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Definitions of Genetic Testing

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Aim

The document from an European Commission Expert Group (25 Recommendations on the Ethical, Legal and Social Implications of Genetic Testing, 2004) establishes, as its very first recommendation, the need to define explicitly what is meant by *genetic testing*, whenever the term is used, and the need to develop a consensus definition that is globally applicable.

That document suggests that a definition should be developed globally by several public and private bodies involved (including the World Health Organisation, the Organisation for Economic Co-operation and Development, the European Commission, the International Federation of Human Genetic Societies, and the International Conference on Harmonisation), and states that the EC should take initiative.

The expert group used for its recommendations a broad definition for genetic testing, i.e. any test that yields genetic data, unambiguously revealing underlying DNA information, either germ-line or somatic and where the nature/technology of the test is not important, but the information derived.

In spite of including information on somatic cell mutations in its broad definition, and acknowledging its importance for identification of disease mechanisms and pathways, disease classification and identification of targets for new medicines, the expert group addressed in its recommendations only data related to transmissible germinal changes, pertaining to heritable diseases or traits.

The need for an agreement of a common definition was also identified at the meeting with EU Member States representatives. The network with Member States should also be seen as a follow up of the expert group.

The present document results directly from that recommendation and aims at contributing to the discussion of such consensus definition and of its applicability. It also aims at comparing the definitions provided by a number of organizations with the recommendations they issue and/or the practices they pursue.

Scope

We have been reviewing definitions of genetic testing mainly from international or trans-national organizations, and national and international associations of professionals, consumers and industry, but also from many other public and private entities at the academic, medical, laboratory, ethical, legal and societal level, including scientific societies and lay organizations. We have included, for comparison and for completeness, documents from some of the most authorized experts in the field.

We have identified 78 institutions/organizations. We have finished analysing the 153 documents collected (mainly online) for definitions of genetic testing (and other related definitions). A total of 65 organizations have been reviewed for their definitions. These include *European Organizations*: European Commission, Council of Europe, CoE-CDBI, European Parliament, IPTS-JRC; *Genetics Professional Organizations*: IFHGS, ACMG, ESHG, ESHRE, ASHG, CORN, SACGHS, Association of Genetic Nurses & Counsellors, UK; HGAC; HGSA; NSGC; UKGTN; American Board of Genetic Counselling; Nuffield Trust; *International/Transnational Organizations*: OECD, WHO, UNESCO, WMA, HUGO, CIOMS; International Soc. Nurses; *Patient/Consumers Organizations*: EuropaBio, Genetic Alliance; EPPOSI: Eurodis; GIG; GeneWatch; *Regulating Agencies*: CDC, ICH, HGC, FDA; *National Institutions*: NIH (SACGT), NCI; *Insurance Organizations*: NAHU; *Human Rights Associations*: ACLU; DPI; *Medical Pathologists Organizations*: CAP/AMP; RCP; *Ethics Organizations*: ACGT, Nuffield Council for Bioethics; European Churches Commission; EGE in Science and New Technologies; SIBI; *Professionals Health Organizations*: Health Council of the Netherlands; British Medical Association; American Society of Pediatrics Committee in Bioethics; AMA; ICMR; NHGRI; *Pharmaceutical Industry*: ABPI, GSK; Roche; Genzyme; *Research Funding Agencies*: Wellcome Trust; MRC,UK; *Prominent Authors*: Peter Harper; Neil Holtzman; *Other Organizations*: EJHG, HGP; Gene Tests; Parliamentary Office of Science and Technology (POST); President's Commission for the study of ethical problems in Medicine and Biomedical and behavioral research Feb 1983.

We now intend to analyse a few other organizations associated with these main groups, search for other organizations, like Law Professional Organizations and look for more recent documents from all the organizations above mentioned (see Table 2). We also plan to analyse all documents reviewed with NVIVO 7 software.

Background

We are living in the Genetic era, cloning, genetic testing, the sequencing of the human genome are now part of everyone's vocabulary and reality. However, these sudden developments are equally astonishing and frightening. Most people although amazed, feel that don't know enough about them. And intelligible concepts are necessary to calm society and improve health care. Thus, these accomplishments must be understood by everyone particularly by health professionals and patients.

Since the year 2000, when an initial sequencing of the human genome was completed, new discoveries promised new developments in the prevention, diagnose and treatment of numerous diseases.

This hasty progress carries several ethical questions and raises complex debates about the social, economic and legal consequences. Reflection is required so these new technologies can be used to the profit of health improvements. (Ref)

As referred before, in response to the new genetic reality, the European Commission Expert Group wrote a document entitled *25 Recommendations on the Ethical, Legal and Social Implications of Genetic Testing, 2004* where established, as its first recommendation, the need to define explicitly what is meant by *genetic testing*, whenever the term is used, and the need to develop a consensus definition that is globally applicable.

The fact is, nowadays, only specific groups understand the implications of genetic services, those are the groups directly implied by these services - health professionals and patients. (Ref) Nevertheless, as the expert group explains, these services will be part of National Health Services and public and health professionals need to be certain about the implications and the concepts associated with genetic services and genetic testing.

An EuroGentest work-package was created in this context in an attempt to respond to these developments.

As referred in the next section (obstacles and limitations), during the EuroGentest Workshop Unit 3, 21-22 September that occur in Porto, European experts debated the theme and realized that a consensus definition was probably impossible to achieve. This is due to the fact that different contexts demand different definitions.

Meanwhile the necessity to clarify the message is a reality that urges to respond.

The present document intends to present different definitions of Genetic testing (or related definitions) and to identify trends, differences and ideas presented by national international, health, patient and genetics associations.

Obstacles & Limitations

While there is a consensus about the need of clearness, the creation of a global definition of Genetic Testing, seems to divide experts in the area.

During the EuroGentest Workshop Unit 3 (Porto, 21-22 September 2006), a complex debate occurred dividing opinions about the obligation and importance of developing a new working definition. As some experts pointed out, there is a risk of creating just one definition in a universe of several others.

Another question has to be raised; there are numerous different contexts where genetic testing may have different meanings and implications. Should we develop a group of definitions? Or, perhaps, after the Porto meeting, we ought to select a new approach for

this work. Instead of another definition or group of definitions (context dependent), we should concentrate in collecting a list of factors that should be included in any definition of genetic testing.

Preliminary analysis

The definitions currently used for genetic testing are extremely variable, as expected. Nevertheless, there seems to be some patterns as to the items and areas that are covered, as well as to the aim with which they are produced (e.g., patient interest groups and consumers *versus* insurers, genetics organizations *versus* pathologists associations, ethical bodies *versus* commercial labs, etc.). In one area, legislation, are definitions more inconsistent than in any other, and too often at stake with one another.

Definitions range from the strict view of being synonymous to DNA-based testing, to any source that can provide unambiguous genetic information (thus covering some instances of ‘non-classic’ *genetic* tests, physical examination in some cases and family history). In spite of its variable nomenclature and phrasing, most types of DNA testing, particularly if related to a heritable disorder, performed in a medical context, and either in affected persons, or a healthy individual or foetus, seems to gather some consensus.

Items variably included in the definition of genetic testing are linked to the methods used for testing or to derive genetic information, its purpose, and the material analyzed:

- DNA-based testing ± cytogenetics and biochemical data
- Mendelian fully-penetrant traits ± susceptibility genes
- disease testing ± drug response
- testing for medical conditions ± identity forensic testing
- germline ± somatic mutations
- direct mutation detection ± linkage analysis
- clinical ± research purposes
- individual data ± family history
- patients, families, or population screening
- variable life-cycle timings (PGD and prenatal)
- various methods and target materials

The definition of genetic testing relies heavily on the concept of genetic information. We have thus tried to list first possible sources of genetic information (Table 1).

As referred before, Table 2 shows some of the prestigious and authoritative organizations and authors that are being surveyed for definitions of genetic testing. We then provide an overview of the wide variability among definitions given by these organizations or individuals, according to our interpretation of which of the previous items are covered or not in those definitions (Table 3). The definitions used are given and referenced as an appendix.

We have tried to analyse also, in the form of comments, the intent and the purpose for which those definitions were made (very often, working definitions with very specific aims are produced). For the Table 2 and for the proposal of a consensus definition,

however, the actual content (not the intent) of each definition was taken into consideration (as if they were to be used out of the context in which they were cited). Nevertheless, this work had to rely, to a certain extent, on the interpretation we have made of that definition. Whenever available, explanatory notes or examples following a definition were used for the analysis of its content.

While some sources are concerned with and try to define genetic testing, others are clearly more interested in genetic information, i.e., more with the results or the information extracted, than with the methodologies used to derive it. Thus, patients and civil rights associations, as well as ethical and legal organizations, tend to use broad definitions of genetic testing (information), while insurers and non-genetics professional associations tend to prefer narrower definitions.

Table 1.
POSSIBLE SOURCES OF GENETIC INFORMATION

Subjects

- individuals
- foetus and embryo
- family
- population

Targets

- gene mutations (pathogenic)
- gene polymorphisms (allelic variants)
- other polymorphic variations in DNA (anonymous sequences)

Genetic and other materials (chromosomes, genes, gene products and phenotypes)

- chromosomes
- nuclear and mitochondrial DNA
- RNA and cDNA
- proteins and metabolites
- haematology and clinical chemistry (routine blood tests)
- imaging and physiological exams
- physical exam and personal history
- family history
- population background or ethnicity

Cellular level

- germ-line
- somatic

Methods of DNA-based testing

- linkage analysis
- sequencing
- mutation detection (various methods)

Purpose and context of genetic testing (medical and non-medical applications)

- context – clinical or research
- application – medical, epidemiological/public health, forensic, over-the-counter/self-administered
- purpose – medical condition, identity testing (zigosity, paternity, immunological, criminal)
- health status – affected patients; relatives at risk, prospective parents and other healthy persons
- motivation – medical diagnosis/prognosis, counselling healthy persons, self-administered
 - medical diagnosis and prognosis – diagnostic, presymptomatic, susceptibility, pharmacogenetics, prenatal diagnosis, population screening
 - counselling healthy persons – carrier state for AR or XL traits, presymptomatic, susceptibility, pharmacogenetics
 - self-administered – paternity, (diagnostic, presymptomatic, susceptibility, pharmacogenetics)

Table 2. ORGANIZATIONS SURVEYED FOR DEFINITIONS OF GENETIC TESTING**European Organizations**

- ✓ European Commission
- ✓ Council of Europe - CM
- ✓ CoE - CDBI
- ✓ European Parliament
- ✓ IPTS – JRC

International/Transnational Organizations

- ✓ UNESCO
- ✓ WHO
- ✓ OECD
- WMA
- HUGO
- FIGO
- ✗ International Soc. Nurses
- World Bank
- CIOMS

Professionals Health Organizations

- RCP
- ✓ British Medical Association
- American Society of Pediatrics Committee in Bioethics
- ✓ AMA
- ✗ ICMR Indian Council Medical Research
- ✓ Health Council of the Netherlands
- ✓ NHGRI
- ✓ US National institutes of Health and Department of Energy

Regulating Agencies

- ✓ HGC, UK
- ICH
- EMEA
- FDA
- ISO
- ✓ CDC

National Health Institutions

- ✓ NIH
- ✓ NCI

Genetics Professionals Organizations

- IFHGS
- ✓ ESHG
- ✓ ASHG
- Assoc. Genetic Nurses & Counsellors, UK
- ESHRE
- ✓ HGAC Hum Genetic Advisory Com
- ✓ HGSA Hum Gen Soc Australia
- NSGC Nat Soc Genetic Counsellors
- ✓ UK Genetic Testing Network
- ✗ Nuffield Trust
- Clinical Genetics Com., Royal College
- ✗ American Board of Genetic Counselling
- American College of Medical Genetics
- ✗ CORN (Council Reg. Networks Gen.Serv.)
- ✓ SACGHS

Medical Pathologists Organizations

- RCP
- ✓ CAP/AMP

Law Professionals Organizations

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Ethics Organizations

- ✓ Nuffield Council of Bioethics
- European Churches Commission
- EGE in Science and New Technologies
- ICB
- Scientific Com., Int. Soc. Bioethics (SIBI)
- ✓ ACGT

Insurance Organizations

- ✗ NAHU

Patient/Consumers Organizations

- EPPOSI
- Eurordis
- ✓ EuropaBIO
- ✓ Genetic Alliance
- Alliance - Europe
- ✗ Genetic Interest Group
- GeneWatch

Human Rights Association

- ACRU
- ✓ ACLU
- ✗ DPI

Other Organizations

- ✓ HGP
- Orphanet
- EDDNAL
- ✓ GeneTests
- EMQN
- ✓ EJHG

Research Funding Agencies

- Wellcome Trust
- ✓ MRC, UK

Pharmaceutical Industry

- ✓ Association of the British Pharmaceutical Industry (ABPI)
- Glaxo, Smith and Kline
- Novartis
- ✓ Roche
- ✗ Genzyme

- | | |
|---|---|
| ✓ | Checked, definition included |
| ✗ | Checked, only related definitions found |
| ○ | Checked, no definition found |
| ■ | No documents found at the moment |

Table 3. Items covered by various definitions of genetic testing

	Context			Type of testing										Phenotypes			Mutat.	Object					
	Medical applications	Scientific research	Non-medical applications	Diagnostic testing	Presymptomatic testing	Disease predisposition testing	Drug response	Carrier testing	Prenatal testing	PGD	Population screening	Paternity testing	Criminal identification	Mendelian traits	Genetic predispositions	Other polymorphic traits	Somatic mutations (vs. germinal only)	Chromosomes	Genes/DNA	Specific gene products	Routine blood tests	Physical exam	Family history
EC	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	○
CoE	+	○	○	+	+	+	○	+	+	+	+	○	○	+	+	○	○	+	+	+	+	+	+
CDBI	+	+	○	+	+	+	+	+	+	+	+	○	○	+	+	○	○	+	+	+	○	+	+
IPTS	+	○	○	+	+	+	+	○	+	+	+	○	○	+	+	○	○	+	+	+	+	+	○
ESHG	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	+	+	+	+	+	+
ASHG	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	+	+	○	○	○
OECD	+	○	○	+	+	+	+	○	+	+	+	○	○	+	+	○	○	+	+	+	+	+	○
WHO	+	○	○	+	+	+	+	+	+	+	○	○	○	+	+	○	○	○	+	○	○	○	○
UNESCO	+	+	○	+	+	+	+	+	+	+	+	○	○	+	+	○	○	+	+	+	○	○	○
CDC	+	○	○	+	+	+	+	○	+	+	○	○	○	+	+	○	+	+	+	○	○	○	○
NIH	+	○	○	+	+	+	+	+	+	+	+	○	○	+	+	○	+	+	+	+	○	○	○
HGP	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	+	+	+	○	○	○
Genetic Alliance	+	+	○	+	+	+	○	+	+	+	+	○	○	+	+	○	○	+	+	+	+	○	○
Nt.Cancer Inst. (US)	+	○	○	+	+	+	○	○	+	+	○	○	○	+	+	○	+	○	+	○	○	○	○
NAHU	+	○	○	+	+	+	+	+	+	+	+	○	○	+	+	○	+	+	+	+	○	○	○
ACLU / NTFCLW	+	○	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	+	+	+	+	+	+
CAP	+	○	○	+	+	+	○	+	+	+	+	○	○	+	+	○	○	+	+	○	○	○	○
ACGT	+	+	○	+	+	+	+	+	+	+	+	○	○	+	+	○	○	+	+	+	○	+	○
Nuffield	+	+	○	+	+	+	+	+	+	+	+	○	○	+	+	○	○	+	+	+	○	+	+

+	– includes	+	– may include
○	– does not include	○	– may not include
∅	– excludes explicitly		

Discussion

Items usually included in the definition of genetic testing

Definitions of genetic testing were found to include (1) usually: medical applications, diagnostic, presymptomatic and complex disease testing, prenatal diagnosis and PGD, Mendelian traits and genetic predispositions, and DNA-based testing; (2) only sometimes: drug response, carrier testing, population genetic screening, somatic mutations, cytogenetic tests, RNA and other metabolites; and (3) rarely: non-medical applications, scientific research, identity testing, other polymorphic traits, routine blood tests, physical exam and family history.

Clues for discussion of definitions of genetic testing

In order to define genetic testing, we need beforehand to define clearly what a ‘test’ is (“*uses an assay for a particular purpose, puts assay into a context*”, Ron Zimmern). Can we include subsidiary exams, physical examination and family history as particular forms of a genetic *test*, in cases where they can provide unambiguous information (at least with the same predictive value of most DNA-based tests)?

It is also clear that it is the information derived, not the testing methods used that will be important for any consensus definition. This should address the predictive value of the information, and include sources of genetic information other than DNA-based testing.

On the other hand, there seems to be a need for context-dependent definitions (e.g., insurance and reimbursement policy; legislation for data protection and discrimination, ethical recommendations; genetics and other professionals guidelines; somatic vs. germinal mutations).

The question rises, then, if it will ever be possible to have *a* consensus definition of genetic testing. Could we have and propose 2-3 ‘contextual’ definitions, instead?

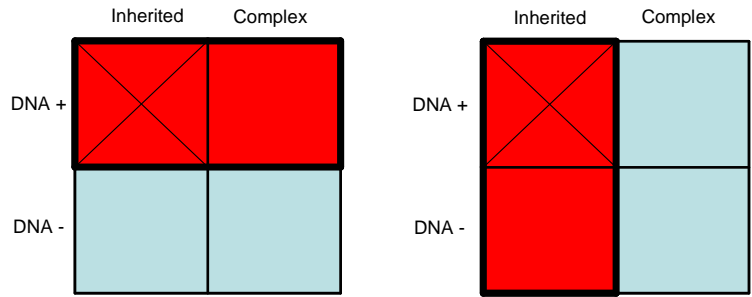
It may also be important for this purpose to make a distinction between genetic information and DNA-based information. Some of these questions are graphically displayed in Fig. 1.

Finally, when addressing a definition of genetic testing, should we not address also other related definitions (e.g., genetic screening, diagnostic, predictive, presymptomatic, pharmacogenetics/pharmacogenomic tests)?

We are planning to survey EuroGentest participants about these questions, using a questionnaire that is being revised for that purpose.

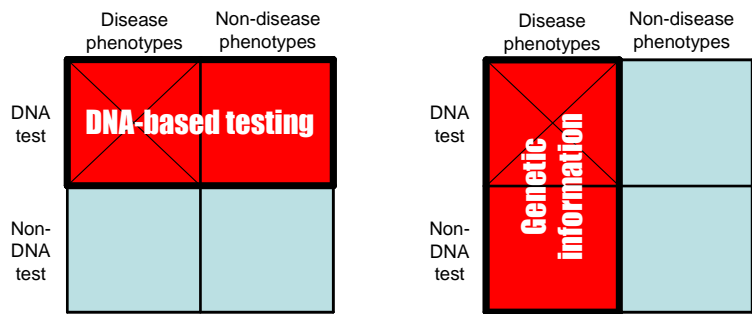
It would also be interesting to compare also definitions contained in the legislation of European (and other) countries, what will be done at a later time, together with Unit 2.

What is genetic testing?



Based on idea by Ron Zimmern

Genetic testing?



High predictive value genetic testing

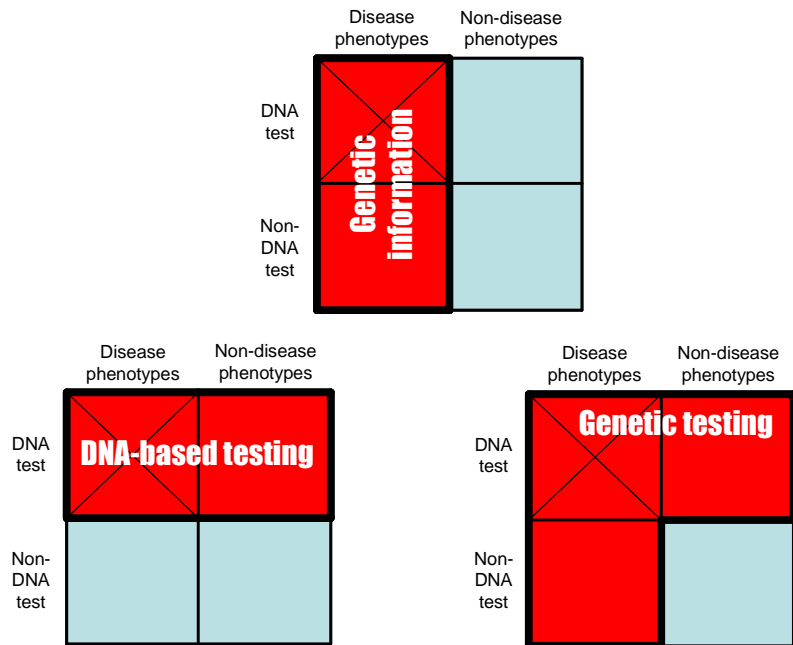


Fig. 1. Models for discussion of definitions of genetic testing

Appendix**Definitions, positions and statements used***European organizations***European Commission (STRATA Group on Genetic Testing)**

Genetic test: A broad definition was used for genetic testing, i.e. “any test that yields genetic data”. Any test which yields genetic data. More specifically a genetic test detects the presence or absence of, or change in, a particular gene or chromosome, including variants or other inherited polymorphic traits that are not necessarily diagnostic of disease. They also include biochemical tests for gene products such as enzymes and other proteins.

Genetic data or information relate to inherited or acquired properties that are transmitted during cell division and that affect subsequent generations of offspring (“germlinal genetic data”) or cells and tissues (“somatic genetic data”). Genetic data comprise: data describing structural properties of DNA (nucleotide sequence or chemical modifications of nucleotides); or data describing properties of other biological markers (RNA, proteins, metabolites, other biological constituents) that are the direct consequence of the underlying DNA template’s structure.

Medical genetic testing: The application of genetic testing to derive information relevant to healthcare: disease risk, prediction, disease diagnosis, disease prognosis, disease treatment and reproductive choices.

Non-medical genetic testing: The application of genetic testing for all purposes that do not have a medical aspect, mainly for the purpose of identification, e.g. paternity and forensic testing, or the identification of the presence of animal and plant materials.

Biochemical genetic test: The analysis of human proteins or other molecules predominantly used to detect gene products showing genetic variations or mutations.

Diagnostic test: A test providing primarily information about an existing condition and its prognosis. However, it is possible. Although uncommon, that a test applied to diagnose a particular disorder may provide predictive information about another disorder.

Pharmacogenetics: The study and understanding of the genetic variation between individuals underlying differential response to drug treatment (efficacy or adverse reactions).

The term comes from the words pharmacology and genetics and describes the interaction of pharmaceuticals and genetics.

Like other forms of genetic testing, the concept of pharmacogenetics encompasses the use of information encoded in patient’s DNA to help predict their responses to medicines and thereby enhance the effectiveness and safety of medicines for individual patients.

It is important that pharmacogenetics is not confused with genetic testing for rare monogenetic disease diagnosis or prediction.

References:

- *25 Recommendations on the Ethical, Legal and Social Implications of Genetic Testing:* http://ec.europa.eu/comm/research/conferences/2004/genetic/pdf/recommendations_en.pdf
- *Ethical, Legal and Social Aspects of Genetic Testing: research, development and clinical applications, STRATA Group on Genetic Testing, 2005:* http://europa.eu.int/comm/research/conferences/2004/genetic/pdf/report_en.pdf]

European Commission

Prenatal screening consists in the extended application of risk assessment procedures to populations of pregnant women rather than to individuals.

Prenatal screening raises additional ethical issues namely in terms of public health policy.

Preconceptional testing or screening allows individuals to be aware of specific genetic risks to their offspring. It could involve the development of simple-to-use genetic testing kits, which raise ethical issues regarding the management of information by the individuals.

Preimplantation diagnosis (PID) consists of analysing the genetic components of very early embryos *in vitro*. This allows the transfer of embryos of a particular sex or genotype to the woman's uterus, thereby greatly reducing the need to consider termination of pregnancy for couples at risk of transmitting genetic diseases. PID is currently at the experimental stage of clinical trials. Compared with PND, PID, which requires *in vitro* fertilization raises additional ethical question.

Genetic testing in this context means the use of a scientific test to obtain information on some aspects of the genetic status of a person, indicative of a present or future medical problem. In this context of employment, "genetic testing" incorporates "genetic screening" and "genetic monitoring".

Genetic screening in this context means the use of a scientific test to determine whether a person possesses particular variant forms of one or more genes in his/her genome.

Genetic monitoring in this context means the examination at regular intervals, for chromosomal abnormalities in samples of cells from a person who may be at risk, in their employment, of exposure to agents which cause genetic damage.

Non-DNA based genetic screening – the definition of genetic screening need not be restricted to tests carried out directly on an individual's DNA (...) For the purposes of this Opinion, any test that evaluates specific genes or gene products that may be indicators of a persons genetic status are considered to be Genetic Tests.

Family medical histories – as family medical histories can provide information on a person's genetic status, which may have predictive value for future health as significant as laboratory performed genetic test, these are included within our definition of **genetic tests**.

References:

- *Ethical Aspects of Prenatal Diagnosis (Opinion of the Group Advisers on the Ethical Implications of Biotechnology to the European Commission):*
http://europa.eu.int/comm/european_group_ethics/gaieb/en/opinion6.pdf
- *Opinion on the Ethical Aspects of Genetic testing in the Workplace (The European Group on Ethics in Science and New Technologies to the European Commission) July 2003 (EGE):* http://europa.eu.int/comm/european_group_ethics/docs/avis18EN.pdf

Council of Europe - Committee of Ministers

Genetic testing and screening can be carried out at different levels, such as on chromosomes, genes (DNA), proteins, organs or a given individual, and can be complemented with aspects of the family history. The essential distinction between **genetic diagnosis and genetic screening** is that the latter is not initiated by the individual who is its subject, but by the provider of the screening service. For the purposes of this Recommendation, the term "**genetic tests for health care purposes**" refers to tests which serve: to diagnose and classify a genetic disease; to identify unaffected carriers of a defective gene in order to counsel them about the risk of having affected children; to detect a serious genetic disease before the clinical onset of symptoms in

order to improve the quality of life by using secondary preventive measures and/or to avoid giving birth to affected offspring; to identify persons at risk of contracting a disease where both a defective gene and a certain lifestyle are important as causes of the disease. The term "**genetic diagnosis**" refers to tests carried out to diagnose a presumed ailment on an individual or several members of a family in the framework of a family study; the term "**genetic screening**" refers to genetic tests carried out on a population as a whole or a subset of it without previous suspicion that the tested individuals may carry the trait.

Any **genetic testing and screening** procedure should be accompanied by appropriate **counselling**, both before and after the procedure. Such counselling must be non-directive. The information to be given should include the pertinent medical facts, the results of tests, as well as the consequences and choices. It should explain the purpose and the nature of the tests and point out possible risks. It must be adapted to the circumstances in which individuals and families receive genetic information. Everything should be done to provide, where necessary, continuing support for the tested persons

Reference:

- *Recommendation R(92)3 of the Committee of Ministers to Member States on Genetic Testing and Screening for Health Care Purposes, 10 Feb 1992:*
<http://www1.umn.edu/humanrts/instreet/coerecr92-3.html>

Council of Europe - Steering Committee on Bioethics (CDBI), 2003

The provisions of this section apply to **genetic tests** on a living person or materials removed from a living person performed in order to diagnose a genetic disease or disorder and/or to determine whether the person possesses one or more genetic traits which may lead that person to develop a disease or a disorder in the future or may result in a disease or disorder if transmitted to that person's progeny or which are relevant to medical treatment. **Predictive genetic tests:** Tests which are predictive of genetic diseases or disorders or which serve either to identify a person as a carrier of a gene responsible for a disease or disorder, or to detect a genetic predisposition or susceptibility to a disease or disorder may be performed only for health purposes or for scientific research linked to health purposes. **Genetic screening for health purposes:** The provisions of this section apply to specific tests offered for health purposes in an authorised programme, to an entire population or section of a population in order to identify asymptomatic persons with an increased risk of developing a genetic disease or disorder or transmitting such a disease or disorder to his or her descendants.

Reference:

- *Working Party On Human Genetics (CDBI-CO-GT4), Working document on the applications of genetics for health purposes, 2003:*
[http://www.coe.int/t/e/legal_affairs/legal_co-operation/bioethics/activities/human_genetics/INF\(2003\)3E_Wkgdoc_genetics.pdf](http://www.coe.int/t/e/legal_affairs/legal_co-operation/bioethics/activities/human_genetics/INF(2003)3E_Wkgdoc_genetics.pdf)

Council of Europe - Steering Committee on Bioethics (CDBI), 2005

Genetic tests: (A - scope not limited to tests aiming at obtaining health related information, but including also for example behavioural and performance tests) Tests involving analysis of human biological samples and aiming specifically to determine genetic characteristics of a person which are transmissible to his or her descendants. Analysis refers to chromosomal analysis, DNA or RNA analysis, or analysis on any other elements enabling to obtain information which are equivalent to those, in determining genetic characteristics transmissible to descendants. The

Protocol does not apply to genetic tests carried out on the human embryo or foetus; genetic tests carried out for research purposes; genetic tests carried out for identification purposes.

or (B - scope limited to tests aiming at obtaining health related information) Tests involving analysis of human biological samples and aiming specifically to determine health related genetic characteristics of a person which are transmissible to descendants. Analysis refers to chromosomal analysis, DNA or RNA analysis, or analysis on any other element enabling to obtain information which are equivalent to those, in determining genetic characteristics which are transmissible to descendants. The Protocol does not apply to genetic tests carried out on the human embryo or foetus; to genetic tests carried out for research purposes; to genetic tests carried out for identification purposes.

Proposal from the Secretariat for the Explanatory Report. The notion of “genetic test” is based here on two elements: its method and its objective. It is to be understood as a procedure including removal of human biological material, where relevant, as well as the analysis of personal information obtained therefrom. This procedure involves analysis of biological samples and aims specifically to determine [health related] genetic characteristics of a person which are hereditary or acquired at embryonic stage, or which appear during lifetime but affect gametes and therefore are transmissible to descendants.

The Protocol also covers further use of tests results, including in fields other than health. The analyses of biological samples are most often cytogenetic analyses on chromosomes, or molecular analyses concerning DNA, RNA or products of expression of genes. However, tests using any other method of analysis on biological samples enabling to obtain information which are equivalent to those obtained by the methods referred to here above for the determination of [health related] genetic characteristics transmissible to descendants are also considered to be covered by the Protocol. [This would exclude tests aiming to obtain information on pathological genetic modification acquired during lifetime by only certain somatic cells due for example to external factors in the environment.] This would exclude as such collection of genetic information through family history.

The Protocol covers any genetic test carried out on a person whether leaving or dead, or on human biological material, [in particular] in the fields of health, employment and insurance. This includes diagnostic, predictive or healthy carrier tests as well as pharmacogenetic tests. Genetic tests offered in the framework of a genetic screening programme are also covered.

The Protocol does not however cover [genetic tests on the human embryo and foetus], genetic tests carried out for research purposes and genetic tests carried out for identification purposes such as filiation or for forensic inquiries, when not for medical purposes.

Genetic services - The goals of these services are to respond to the needs of individuals and families wishing to know whether they are at risk of developing or transmitting a disease or disorder with a genetic component, or who are faced with such disease or disorder. This includes in particular providing information and genetic counselling, carrying out genetic testing and interpreting results, ensuring care for the person concerned and their family, namely preventive care, as well as the training of persons involved in genetic services.

Predictive test - The expression “predictive test”, in accordance with Article 12 of the Convention on Human Rights and Biomedicine, refers to a test which is predictive of genetic diseases or which serves 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. The predictive nature of the information obtained with predictive genetic testing, the psychological impact of knowledge of genetic risk for the person concerned, the possible implications for family members, and the often difficult decisions to make for the person concerned, including where appropriate in relation to procreation choices, make appropriate genetic counselling particularly important for such tests. This also applies to any other test with similar consequences for procreation choices or important implications for family members.

Genetic counselling - The notion of “genetic counselling” is to be understood here as a communication and support process aiming to enable individuals and, where appropriate, families, to make informed choices with regard to a genetic test and its implications.

It includes the obligatory provision of information prior to requesting consent or authorisation as required in paragraph 1. It also includes an offer of support before and, if appropriate after the test, to the person concerned allowing him or her to “handle” the implications of the test and its results, including, where appropriate, communication to family members of information relevant to their health, or procreation choices.

Genetic counselling is an individualised and non directive process taking into account, in particular, the psychological and familial context of the person concerned and involving an exchange between him or her and the person providing the counselling. This support process may therefore vary in form and extent depending on the test considered but also on the particular significance of the information that the test is likely to provide for the person concerned or for members of his or her family.

Reference:

- CDBI (2004) 14 REV2 - Draft Protocol on genetic testing: revised proposals [**Restricted**]

European Parliament

Pharmacogenetics - determining differences in individual reactions to drugs

Pharmacogenomics – development of customised drugs – “personal pills”

Genetic tests - many tests have already been developed to identify or confirm rare genetic diseases. However, whereas until a few years ago there were only a handful of genetic tests for a small number of hereditary diseases, today, as a result of the impetus provided by academic and commercial laboratories, there are tests for cystic fibrosis, Huntington’s chorea, muscular dystrophy, and, moreover, a great many non-hereditary degenerative diseases – the symptoms of which can appear in youth or adulthood – such as, for example, diabetes, cancer, cardiovascular diseases, high blood pressure, and Alzheimer’s disease. Genetic tests give incontestable prognoses where some diseases are concerned but in many other cases reveal no more than a predisposition that can be influenced by external factors such as environment, diet, and lifestyle. Genetic tests can be carried out for various purposes:

– **postnatal diagnostics** is used to diagnose a disease, determine the probability that an infant will develop a given disease, the onset of which does not occur until later in life, and detect genetic alterations that increase the predisposition to some illnesses such as certain tumours and cardiovascular disorders;

– **antenatal diagnostics** is used to diagnose a genetic disease or condition in a foetus;

– **preimplant diagnostics**, an alternative to antenatal diagnosis, is used to diagnose a genetic disease or condition in an embryo before it is implanted in the uterus (it is an application of *in vitro* insemination).

Embryonal chromosome analysis using the technique of **preimplant genetic diagnosis (PGD)** makes it possible to ensure that embryos will not be implanted if they have abnormal chromosomes and cannot survive. PGD enables selected, i.e. undeformed, embryos to be implanted and avoids the abortions that might otherwise follow a conventional antenatal diagnosis at an advanced stage of pregnancy (after the third month in the case of amniocentesis). It offers an alternative to the normal antenatal diagnosis methods, especially in cases where parents are at high risk of having a child with severe genetic diseases. It can be used to detect many single-gene disorders. Data and reports relating to the findings of PGD are compiled at world level. The PGD Consortium, a body which works in collaboration with the European Society of Human Reproduction and Embryology (ESHRE), published the most recent findings last summer. Over 200 babies have been born with the aid of this technique (see papers read by Professors Devroy

and Hovatta at the temporary committee meeting of 27 March 2001). PGD has undoubted advantages over conventional antenatal diagnostic techniques, in which diagnosis is carried out in about the third month of gestation, whereas PGD enables an eight-cell embryo to be analysed when it is as little as three days old. Conventional techniques require samples consisting of many cells, whereas in PGD the diagnosis can be confined to just a few (from one to three). Furthermore, the findings resulting from conventional techniques are not known until a couple of weeks after the tests, whereas the findings of PGD are available within about two days (see paper read by Prof. Devroy at the temporary committee meeting of 27 March 2001).

Merely from the above description of the technique it is plain to see that PGD entails different ethical implications from conventional diagnostic techniques for a couple who decide to have an abortion in the light of the diagnosis. PGD methods have prompted disquiet on account of the possibility that people might want 'made to measure' children with particular traits such as intelligence or a gift for music. However, leaving aside the possible objection that ethics has yet to address these questions, it is technically completely impossible to identify such characteristics in embryos (see paper read by Prof. Hovatta on 27 March 2001).

Gene therapy - Gene therapy is designed to correct anomalous gene function. It is termed somatic gene therapy when it is used on body cells (blood, organs, etc.) – the main applications are in oncology, cardiovascular medicine, and the treatment of genetic diseases – and the genes inserted will not be passed on to succeeding generations. It is termed germinal gene therapy when it is practised on reproductive cells (oocytes and spermatozoa) or embryos. In this case the change will be passed on to offspring.

Genetic medicine - Unlike gene therapy, genetic medicine does not act upon or permanently alter cell functions. Most of the new medicines are aimed at more easily reachable targets, generally proteins and enzymes on the surface of a cell or in its cytoplasm. They will be more efficacious but have less potent side effects and will act on the body in a much more selective way. Doses will be personalised on the basis of pharmacogenetic tests (papers by Prof. Neri and Mr Goodfellow – meeting of 26 April 2001). Backed by knowledge of the patient's predispositions, these medicines will prevent the disease rather than curing the symptoms.

Pharmacogenetics - Pharmacogenetics studies how genetic differences influence the variable reactions of individual patients to drugs administered to them (papers by Prof. Neri and Mr Goodfellow – meeting of 26 April 2001). The ultimate goal will be to devise a personalised therapy.

Genetic data - Genetic data are regarded as highly specific information. They can reveal important facts not just about the person examined, but also about the members of his or her family and, in the final analysis, have a great impact on individual lives and lifestyles, not least as regards decisions to have children. The legal framework for data protection covers matters such as confidentiality, anonymity, commercial exploitation, access to information, insurance, employers, and so forth. It might be necessary to update Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

Predictive genetic tests - 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 Convention on Human Rights and Biomedicine 1997 – similar definition-based on)

Reference:

- *Report on the ethical, legal, economic and social implications of human genetics, Temporary Committee on Human genetics and other New technologies in Modern Medicine (European Parliament, 2001)*
http://europa.eu.int/comm/research/biosociety/pdf/pe_genetics.pdf

IPTS-JRC

Genetic testing (working definition) is used to identify variations in the DNA sequence that correlate with a disease or higher risk to develop a disease. This type of test can be used for diagnosis before any symptoms of disease are recognisable and to determine the personal risk for certain multifactorial diseases. Thus, the results of genetic testing can have far reaching effects on an individual's life.

There exist slightly different definitions of “genetic testing”, regarding the comprehensiveness of what is subsumed under this term. Against the background of reported problems in the field of genetic testing, the working definition used by OECD is adopted for further discussions: “*Genetic testing is testing for variations in germline DNA sequences, or for products/effects arising from changes in heritable sequences, which are predictive of significant health effects.*” The study targeted only molecular DNA testing for diagnosis of hereditary diseases, excluding other types of diagnostic tests, such as cytogenetics or biochemical testing. Pharmacogenetics falls also beyond the scope of the study.

Genetic tests as defined above can be applied serving the following purposes:

Diagnostic testing: This is the most common reason for a request for a genetic test triggered by a patient presenting clinical signs or symptoms suspected to have a genetic cause. In this case, the test is performed to confirm, refine or exclude a clinical diagnosis. In many cases the test is widely used as an exclusion test with a low probability of a positive diagnosis (an example is a test for fragile-X disease on children with learning difficulty).

Predictive testing: To estimate the risk to a person with no symptoms of developing a genetic disorder in the future. Usually two forms of predictive testing are distinguished, presymptomatic and predisposition testing: **Presymptomatic testing** looks for a mutation (or alteration) in a healthy individual, which, if present, will almost certainly lead to occurrence of symptoms. This type of testing is most applicable to adult-onset genetic conditions like Huntington's chorea. Adults may have no symptoms of disease at the time of the test but there might be a suspicion of high risk of inheriting a genetic condition from a parent. A minority of individuals in this situation seek predictive information through a genetic test.

Predisposition testing looks for gene mutations that provide a probability of occurrence of the disorder (e.g. mutations in the genes BRCA 1 and 2 provide certain susceptibility for breast cancer, but a positive test result does not indicate a 100% risk of developing breast cancer). Many common human diseases – cardiovascular disease, diabetes, atopy, Alzheimer disease – appear to be multifactorial, i.e. are susceptible to a number of genetic *and* environmental influences. The search for the genetic components of these conditions is currently a major research undertaking, with enormous commercial implications.

Carrier testing: Clarification of presence of a gene mutation for a recessively inherited or X-linked disorder that will not affect the person but could eventually affect his/her relatives. The test result might be important for reproductive decisions. Carrier testing in children where the test has no implication for their own health has been controversial with many geneticists arguing that the possibility of testing should be delayed until an age when a child can give informed consent for the test.

Prenatal testing: Clarification if the foetus carries certain mutations or alterations responsible for hereditary diseases. Prenatal testing for Down syndrome and related conditions usually results from increased risk either because of maternal age or following a pregnancy screen by ultrasonography or a biochemical test of the mother's blood. Prenatal diagnosis for single gene disorders is comparatively rare. It is mainly requested where parents are at high risk and have direct experience of a serious genetic condition in their own child or in a close relative. A close liaison between obstetric and genetic services is desirable since parents may choose to end pregnancies shown to be at high risk of a genetic condition after a test. **Genetic screening:** Predictive testing, prenatal testing and carrier testing can also be offered systematically at the population level. Genetic screening may be concerned with the general population or with sub-

populations defined on the basis of their risk. Population screening programs are usually decided on and organised by health authorities at the national or regional level. The only well-established screening programmes are newborn screening programmes: Testing of new-born shortly after birth for specific disorders such as phenylketonuria, galactosemia, congenital hypothyroidism. Biochemical genetic testing of newborn infants is recommended for some monogenic conditions and is carried out in specialist neonatal screening laboratories.

Preimplantation genetic diagnosis (PGD) follows an in vitro fertilisation procedure. Genetic testing is carried out on one or two cells removed from the early embryo. Embryos shown by the PGD test not to have a genetic mutation for the condition examined are then implanted in the uterus to attempt to establish a pregnancy. The scope and range of testing in the context of this study were circumscribed to diagnosis of health effects but there are many other common applications of these techniques.

Pharmacogenetics, which refers to the identification of DNA variants (polymorphisms) that are related to the variability in drug response, is amongst these other applications of genetic testing with a potentially massive expansion. Adverse drug responses currently account for many hospitalisations and deaths per year. On average in Europe, up to 7% of hospital patients receiving medication experience severe side effects and it is thought that pharmacogenetic testing could reduce this incidence and may contribute to the development of individualised prescription of medicines, or the assurance of the ‘right medicine for the right patient’.

Another type of **DNA-based testing** is carried out for *disease sub-typing*, for example in oncology laboratories to characterize different types of cancer. The mutations that are under investigation in these cases are most often so-called somatic changes, which arise in a specific tissue, causing a clone of cells to proliferate. These techniques are also used in the *identity testing* for forensic and criminal law applications, to establish or disprove paternity and to confirm family relationships in immigration applications.

This type of testing is currently widespread and occurs in both the public and private sectors. Areas of related activity that are economically important and share technologies include genetic testing in non-human areas to promote *animal health and food safety and regulation*, for example testing for permissible levels of genetically modified organisms in food products. Performing a molecular genetic test is a complex process comprising multiple steps: the assignment of the correct indication for sampling, administrative steps, the sample analysis and the writing of a correct and informative report.

Genetic counselling is a communication and educational process to inform the patient and family members on benefits and risks of genetic tests, the limitations and meaning of results. It is meant to inform but also to help the individuals and their families to cope with information gained from testing (including psychological and social implication). Counselling is extremely important considering the wrong or exaggerated expectations connected with genetic testing often reported in the media. Genetic tests are often perceived as being a very accurate method of predicting the future health status of an individual, but depending on what is being tested the accuracy of predicting the future health status might vary profoundly.

The role of the counsellor is critical in giving this information to the patient. The quality of genetic testing cannot be considered isolated from either the type and quality of laboratory reporting, or the quality for the counselling that the patient receives pre-and post-test.

Genetic testing services include not only the actual technical performance of a genetic test at the lab bench but also the referral system, the accuracy of test results and their correct reporting, proper handling of samples and data (in terms of informed consent and privacy) and also pre and post-test counselling. When discussing quality and harmonization, all these aspects should be taken into consideration (Nys, H et al, Genetic testing patients’ rights, insurance and employment. A survey of regulations in the European Union, 2002, European Commission:Brussels p.154).

Reference:

- *IPTS-JRC and ESTO, Towards quality assurance and harmonisation of genetic testing services in the EU, 2003: <http://www.orpha.net/docs/genetictesting.pdf>*

International/Transnational Organizations

UNESCO

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

Human genetic data: information about heritable characteristics of individuals obtained by analysis of nucleic acids or by other scientific methods.

Human proteomic data: Information pertaining to an individual's proteins including their expression, modification and interaction.

Biological samples: Any sample of biological material (for example blood, skin and bone cells or blood plasma) in which nucleic acids are present and which contains the characteristic genetic make-up of an individual.

Genetic screening: Large-scale systematic genetic testing offered in a programme to a population or subsection thereof intended to detect genetic characteristics in asymptomatic people.

Genetic counselling: A procedure to explain the possible implications of the findings of genetic testing or screening, its advantages and risks and where applicable to assist the individual in the long-term handling of the consequences; It takes place before and after genetic testing and screening.

Genetic counselling should be non-directive, culturally adapted and consistent with the best interest of the person concerned.

References:

- *International Declaration on Human Genetic Data, 2003: http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_PRINTPAGE&URL_SECTION=201.html (modified from ACGT and NCB)*

UNESCO

Genetic counselling provides the link between genetic technologies, several of which have been acquired through the Human Genome Project, and patient care. It can be defined as a communication process which involves diagnosis, explanation and options.

Definitions of genetic counselling. The definitions given concur that it is a communication of information about diagnosed genetic conditions, in a way which allows to make a decision, as autonomous as possible, and safeguarding the emotional and ethical character of the person who asks for the consultation. While defined as based on a physician-patient relationship in many countries, the complexity of genetic counselling has led to a new profession of genetic counsellors who are not physicians, especially in North-America.

- **UNITED STATES OF AMERICA:** A communication process which involves diagnosis, explanations and options (as in all medical consultation). In genetic counselling there is a stronger need for detail, especially in the explanations and options, for which empathetic and emotional support are an essential part. Counsellors are involved in the ethics of the "people's right to know".

• **UNITED KINGDOM:** Counselling entails precision of diagnosis, the estimation of risks, and a supportive role to ensure that those who are given information are able to benefit from it and from the interventions that are available.

• **ITALY:** The objective, methods and indications of genetic consultation are:

Objective: to provide information to patients (and/or blood relations of a patient) at risk of contracting a disease that may be hereditary on:

- consequence of pathology in question
- probability of contracting and transmitting it
- possibility of keeping it in check and treating it

Methods:

- construction and analysis of pedigree
- calculation of the risk of recurrence (Mendelian or empirical)
- estimation of the consanguinity coefficient
- more specific analysis

When is counselling indicated:

- known or presumed illness in patient or family
- congenital malformation
- mental retardation
- consanguinity
- recurrent miscarriage, infertility

• **CHILE:** A medical process of communication between a physician and a consultant (counselee) where scientific knowledge, data and facts are exchanged in order to provide a framework to understand the genetic problem of the patient and the family.

• **ARGENTINA:** Better called "genetic advising" - a useful tool in preventive medicine.

• **ZAIRE:** Information on eventual pathology, not therapeutic but predictive.

References:

- *Genetic Counselling - UNESCO 1995:*
http://portal.unesco.org/shs/en/file_download.php/e5ec8f48c2de32a26171790bbdda05ec_counsellingCIB3_en.pdf]

World Health Organization (WHO) - 1

Genetic testing: DNA analysis to determine the carrier status of an individual; to diagnose a present disease in the individual; or to determine the individual's genetic predisposition to developing a particular condition in the future.

DNA genetic testing involves the analysis of DNA in order to determine the presence of a gene associated with a particular disease. In general, there are four kinds of genetic tests: **Carrier testing** determines if the person tested, who does not himself have the disease, carries a gene for the disease. If two carriers have a child together, there is a high probability that their offspring will have the disease. **Prenatal testing** determines whether a foetus is affected with a genetic abnormality causing a particular condition. Embryos may also be tested during in vitro fertilization before being surgically implanted into the womb; this is called pre-implantation diagnosis. For technical reasons, the latter method is not widely practised. **Diagnostic testing** determines

whether the tested individual in fact has a particular genetic condition or a genetic predisposition for acquiring the condition later in life. **Predictive testing** determines the presence in asymptomatic individuals of an abnormal gene that will lead to a disease in the future, or of a genetic predisposition for acquiring the condition later in life, in interaction with environmental factors.

Reference:

- *Genetics, genomics and the patenting of DNA Review of potential implications for health in developing countries*, WHO 2005: <http://www.who.int/genomics/FullReport.pdf>

World Health Organization (WHO) - 2

Genetic Counselling is the provision of accurate, full and unbiased information in a caring, professional relationship that offers guidance, but allows individuals and families to come to their own decisions. Counselling is essential before any genetic testing is carried out and should continue afterwards if the results entail choices for the person and family tested.

Genetic Counselling should be available to all, and should be as non-directive as possible.

Genetic Counselling - Non-directive counselling has two major elements. The first is the provision of accurate, full and unbiased information that individuals and families may use in making decisions. The second is an understanding, empathic relationship that offers guidance and helps people to work towards their own decisions.

In non-directive counselling, the professional avoids purposely slanting information that may lead people to do what the counsellor thinks best, individuals and families must depend on the counsellor as a source of accurate information, and usually have no way of discovering when information is biased. Non-directive counselling does not mean presenting information and then abandoning individuals and families to make their own decisions without help. Most people may want to talk with someone who will listen to their concerns, help them to express and understand their own values, and help them to work towards their own decisions. Non-directive counsellors do not tell people what to do; decisions are those of the individuals and the families. The counsellor should, as much as possible, support all decisions.

Genetic Screening refers to tests offered to a population group to identify asymptomatic people at an increased risk from a particular adverse outcome. Examples are phenylalanine screening for phenylketonuria in newborn babies, as the use of maternal serum biochemical markers in pregnant women to screen for fetuses with Down syndrome. In all cases, individuals whose screens indicate that they are at risk must be offered a definitive diagnostic test.

Genetic Testing is the analysis of the status of a particular gene. A genetic test may establish:

- a) A specific diagnosis of a genetic condition in a symptomatic individual;
- b) The certainty that a particular condition will develop in an individual who is asymptomatic at the time of the testing (presymptomatic diagnosis), or c) the presence of a genetic predisposition to develop a particular complex disease such as cancer or cardiovascular disease.

Presymptomatic testing refers to identification of healthy individuals who may have inherited a gene for a late onset disease, and if so will develop the disorder if they live long enough (e.g. Huntington disease).

Susceptibility testing identifies healthy individuals who may have inherited a genetic predisposition that puts them an increased risk of developing a multifactorial disease, such as heart disease, Alzheimer disease or cancer but who, even so, may never develop the disease in question.

Presymptomatic testing in the absence of therapeutic options should be available if the following conditions are met:

- a) The information provided by testing will be used to prevent harm to the person tested, or to spouse, family, prospective children or others.
- b) The person is fully informed about the limitations of testing, including possibilities of uninformative results and inability to predict exact age of onset or (sometimes) severity of symptoms.
- c) The person (or legally authorized representative) is mentally capable of giving consent.
- d) Testing is accompanied by a counselling programme of appropriate length and intensity for the disorder.

Prenatal diagnosis of genetic disorders and foetal anomalies has expanded significantly for hundreds of conditions through DNA analysis of foetal cells and the increased use of ultrasound and maternal serum biochemical screening (amniocentesis). The purpose of prenatal diagnosis is to rule out the presence in the foetus of a particular medical condition for which the pregnancy is at an increased risk. This information is provided to the couple to assist in their decision-making process regarding the available options, such as carrying the pregnancy to term, preparing for a difficult delivery and for special newborn care, or terminating the pregnancy. Genetic counselling is particularly important prior to prenatal diagnosis and, after a result indicating an affected foetus, to secure fully informed choices.

Genetic information has the unusual character of being both individual and familial; it can provide important details about the health status of the patient, but often suggests something about the health status of blood relatives.

References:

- *Proposed International Guidelines on Ethical issues on Medical Genetics and Genetic Services – WHO 1998:*
<http://www.who.int/genomics/publications/en/ethicalguidelines1998.pdf>
- *Quality and Safety in Genetic testing: An Emerging Concern (WHO):*
http://www.who.int/genomics/policy/quality_safety/en/print.html

OECD (Ad-Hoc Working Definition)

Pharmacogenetics refers to the identification of genetic mutations and of polymorphisms involved in or responsible for variability in drug response, including drug metabolism and disposition and the development of what is often described as “the right medicine for the right patient”.

The terms “**pharmaco-genomics**” and “**pharmaco-genetics**” are often used interchangeably. However, **pharmaco-genomics** refers to the application of molecular tools to R&D, including, but not limited to, differential gene expression (DGE), proteomics, tissue immunopathology and histopathology, etc. **Pharmaco-genetics** refers to the identification of genetic mutations and polymorphism involved in or responsible for the variability in drug response including drug metabolism and disposition and the development of what is often described as “the right medicine for the right patient”.

(What is genetic testing?) There are several possible interpretations and definitions of genetic testing. In order to delineate the issues to be discussed at the workshop, the OECD steering Group changed with the organization of the workshop developed the following *ad hoc* working definition and related explanatory notes:

Genetic testing is testing for variations in germ line DNA sequences, or for products/effects arising from changes in heritable sequences, which are predictive of significant health effects.

Genetic counselling provides individuals and families with an inherited disorder with accurate, full and unbiased information and offers support in the decision-making process (Ad Hoc Committee on genetic Counselling (1975), “Report to the American Society of Human genetics”,

Am. J. Genet. 27, pp 240-242. T.M. Marteau, B.B. Biesecker (1999), "The future of genetic counselling: An international perspective", *Nature Genetics*, Vol. 22, No 2, pp. 133-137.). It is a complex process, which stands in opposition to eugenic principles and seeks to help families to cope with the diagnosis of an inherited disorder, to face its implications and to make decisions on the basis of their medical and non-medical options. As genetic testing is involved in the diagnosis of inherited disorders, counselling becomes an integral part of it; it aims at encouraging the autonomy of those involved and reducing the adverse consequences of testing. The need for counselling derives from: *i*) the peculiarities of genetic information, as compared to other biomedical tests, particularly in terms of its predictive and complex character; *ii*) the gap between the ability to diagnose and to treat an inherited disorder; *iii*) the social value attributed to heritable characteristics; and *iv*) the psycho-social and ethical problems often arising in testing situations. Counselling is traditionally performed by healthcare professionals specifically trained to use procedures different from those in everyday clinical practice.

Reference:

- OECD, *Genetic Testing: Policy Issues for the New Millennium*, Organisation for Economic Co-operation and Development, 2000;
http://www.oecd.org/document/16/0,2340,en_2649_37407_1895632_1_1_1_37407,00.html
- Ronchi E: *Genetic Testing – the OECD Agenda, Brussels 2004*:
<http://ec.europa.eu/research/conferences/2004/genetic/pdf/ronchibrussels.pdf>

International Society of Nurses in Genetics (ISONG)

Genetic information refers to any information about a person that identifies inherited traits or characteristics, or genetic alterations that are acquired during a person's lifetime.

References:

- *Privacy and confidentiality of Genetic Info: the role of nurses (ISONG 2005)*
http://www.isong.org/about/ps_privacy.cfm

Professionals Health Organizations

British Medical Association Board of Science

Screening is a public health service in which members of a defined population, who do not necessarily perceive that they are at risk of, or are already affected by, a disease or its complications, are questioned or offered a test. The aim is to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications. (UK National Screening Committee at www.nsc.nhs.uk - go there now - accessed September 2004)

A distinction needs to be made between **genetic screening** and **genetic testing**.

Screening involves testing members of a population for a disorder for which there is no prior evidence of the condition, although they may be part of a higher risk group, such as Ashkenazi Jews who are at risk of developing Tay Sachs disease (National Institute of Neurological Disorders and Stroke, www.ninds.nih.gov - accessed January 2005).

Testing relates to those who know that they are at risk, such as people belonging to families that may carry high penetrance genes associated with breast cancer, or with a history of Huntington's disease. (National Institute of Neurological Disorders and Stroke, www.ninds.nih.gov - accessed

January 2005). Genetic testing can mean carrying out a genetic test for a condition, such as Alzheimer's (National Institute of Neurological Disorders and Stroke, www.ninds.nih.gov - accessed January 2005). and coronary heart disease. (HS Diabetes, heart disease and stroke (DHDS) prevention pilot project, www.nelh.nhs.uk/screening - accessed January 2005) It can also be testing for a genetic disease, which may or may not involve identifying the genetic makeup. Examples include cystic fibrosis (Cystic Fibrosis Trust, www.cftrust.org.uk (accessed January 2005) and sickle cell disease. (Sickle Cell Society, www.sicklecellsociety.org (accessed January 2005) Genetic screening raises specific concerns where a hereditary condition is being tested for, as it will have implications not only for the individual, but also for family members.

Predisposition testing may show lower levels of risk. While this does not resolve issues of uncertainty about developing the disease, it may be useful where changes can be made to reduce the chance of developing the disease, for example lifestyle changes relating to heart disease.

Presymptomatic genetic testing, which establishes whether a disorder will develop, raises few concerns where effective medical intervention is available.

Genetic testing may identify people as carriers of a genetic mutation, and while not actually suffering from the disease themselves, the discovery would have implications for their children, siblings and relatives of childbearing age.

Preimplantation genetic diagnosis (PGD) is 'a technique which involves the genetic testing of embryos created *in vitro* for deleterious heritable genetic conditions which are known to be present in the family of those seeking treatment and from which the embryos are known to be at risk' (Human Fertilisation and Embryology Authority, www.hfea.gov.uk - accessed December 2004)

Pharmacogenetics is the study of how a response to a drug is influenced by genetic makeup (Royal Society, www.royalsoc.ac.uk (accessed January 2005), Wolf C R, Smith G & Smith R L (2000) Science, medicine and the future: Pharmacogenetics. *BMJ* **320**: 987-90).

References:

- *Population screening and genetic testing*
[http://www.bma.org.uk/ap.nsf/AttachmentsByTitle/PDFscreeningbriefingsecond/\\$FILE/ScreeningBriefing2.pdf](http://www.bma.org.uk/ap.nsf/AttachmentsByTitle/PDFscreeningbriefingsecond/$FILE/ScreeningBriefing2.pdf) (August 2005)

American Medical Association

Genetic testing usually refers to the analysis of DNA to identify changes in gene sequence (deletions, additions, or misspellings) or expression levels. Genetic testing can also refer to biochemical tests for gene products (proteins) and for microscopic analysis of stained chromosomes. Genetics testing still is in its early stages, so both patients and experienced physicians may need guidance when it comes to navigating this new and emotionally complex territory.

How is genetic testing used clinically?

- **Diagnostic medicine:** identify whether an individual has a certain genetic disease. This type of test commonly detects a specific gene alteration but is often not able to determine disease severity or age of onset. It is estimated that there are >4000 diseases caused by a mutation in a single gene.
- **Predictive medicine:** determine whether an individual has an increased risk for a particular disease. Results from this type of test are usually expressed in terms of

probability and are therefore less definitive since disease susceptibility may also be influenced by other genetic and nongenetic (e.g. environmental, lifestyle) factors.

- **Pharmacogenomics:** classify subtle variations in an individual's genetic makeup to maximize a drug's effectiveness and safety.

Genetic testing is performed for the following reasons:

- conformational diagnosis of a symptomatic individual
- presymptomatic testing for estimating risk developing disease
- presymptomatic testing for predicting disease
- prenatal diagnostic screening
- newborn screening
- preimplantation genetic diagnosis
- carrier screening
- forensic testing
- paternal testing

Gene testing involves examining a person's DNA for some anomaly that could cause or increase the risk for a disease or disorder. The DNA usually is taken from cells in a sample of blood or occasionally from other body fluids or tissues. In addition to studying chromosomes or genes, genetic testing in a broader sense can also include biochemical tests for the presence or absence of key proteins that signal aberrant genes.

Pharmacogenomics is the study of how genes affect the way individuals respond to drugs. In this report, the term pharmacogenomics refers to products that use any variety of biomarkers for diagnosis, drug prescription, or patient treatment. These biomarkers can include differences in the DNA, RNA, alleles, and single nucleotide polymorphisms (SNPs) among patients. This definition also includes all technologies that involve gene therapy, gene expression, proteomics and bioinformatics.

References:

- *Genetic Testing* <http://www.ama-assn.org/ama/pub/category/9178.html> (updated July 2005)
- *Basic Genetics* (updated June 2005) <http://www.ama-assn.org/ama/pub/category/4646.html>

Indian Council Medical Research (ICMR)

Somatic cell gene therapy is the only method that may be permissible for the purpose of preventing or treating a serious disease when it is the only therapeutic option. It should be restricted to alleviation of life threatening or seriously disabling genetic disease in individual patients and should not be permitted to change normal human traits. However, rapid advance in science necessitates periodic review of guidelines in this area. This includes evaluation of safety and efficacy of DNA vaccines and transgenic foods as well

References:

- *Ethical Guidelines for Biomedical Research on Human Subjects – 2000* <http://www.icmr.nic.in/ethical.pdf>

Health Council Netherlands

Prenatal testing - amniocentesis, chorionic-villus sampling (CVS), and tests on foetal blood from the umbilical cord - can be used to determine the sex of a foetus, or to detect chromosomal abnormalities or an increasing number of metabolic disorders (Royal College of Physicians. Prenatal diagnosis and genetic screening. Report. Londen 1989).

Germline-cell gene therapy involves the correction of one or more genes in cells which form part of the germ line, that is, egg and sperm cells, and the totipotent cells of the pre-embryo.

Genetic counselling is a communication process which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to 1) comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management; 2) appreciate the way in which heredity contributes to the disorder, and the risk of recurrence in specified relatives; 3) understand the alternatives for dealing with the risk of recurrence; 4) choose the course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards, and to act in accordance with that decision and 5) make the best possible adjustment to the disorder in the affected family member, and/or to the risk of recurrence of the disorder. (Health Council Report: Gezondheidsraad. Ethiek van de erfelijkheidsadviesing. Den Haag 1980)

The main purpose of **genetic counselling** is to provide clients with the information they need to make the choices appropriate to their beliefs and circumstances. Clients usually ask questions related to their potential offspring; the information they receive covers a wide range. This may include the diagnosis of the condition about which guidance is sought, the prognosis, the risk that a child - whether a first or subsequent - will be handicapped, the treatment available for particular conditions, and the options open to the client.

- The options generally are:
- to accept the risk (or perhaps certainty) that a child will be born with a handicap;
- to seek abortion, if prenatal testing reveals an abnormality;
- to opt for artificial procreation (insemination using donor sperm, or in vitro fertilization using a donor egg) ;
- to decide not to have (more) children, and perhaps to adopt.

Carriers - those not themselves affected but able to transmit the condition to their offspring

Genetic screening may involve chromosome testing, be carried out to determine the presence of mutations directly, or it may involve biochemical examination of substances indicating the presence of a mutation or a heightened risk of congenital abnormalities or hereditary disorders. In addition, ultrasound scanning can be used at the prenatal stage to detect anatomical defects in the fetus.

The committee understands '**genetic screening**' to mean any kind of test performed on people for the systematic early detection or exclusion of a hereditary disease, the predisposition to such a disease or to determine whether a person carries a predisposition which may produce a hereditary disease in their offspring. In the following pages, the committee provides a further explanation of this definition, and of the boundaries which were drawn during the preparation of this report.

The committee understands 'early detection' to mean: the search for disease, predisposition or carrier status in those who have not (yet) been led to seek medical aid because of physical signs, symptoms or anxiety. In the case of carriers, detection occurs at a time when there are still

opportunities for genetic counselling, or further tests, with regard to reproduction. In screening it is the care system which takes the initiative with regard to detection. The committee understands ‘**screening**’ to mean determining in advance those who are eligible for early detection (the target group) and approaching this group in a systematic way. Here, ‘systematic’ is taken to mean that (in principle) every member of the target group is specifically invited to take part in (or is expressly informed concerning the opportunities offered by) early detection of the disease, predisposition or of carrier status.

The definition of **genetic screening** therefore has the following distinguishing characteristics:

- hereditary disease, predisposition or carrier status
- no reason for those involved to seek assistance
- systematic approach to the target group.

All of these characteristics must be present before the term **genetic screening** can be used. In the committee’s view, characteristics such as the organisational form, the scale involved, the place where early detection is actually carried out and the question whether it is a new or a previously accepted part of the health service) are not of overriding importance for the definition. In any case, such characteristics can vary from one screening programme to another. Therefore, screening need not take the form of large scale population testing.

The committee acknowledges that even the definition selected here is still not totally sound. By way of illustration: From the viewpoint of public health, a comprehensive publicity campaign which causes virtually all members of the target group to request early detection has the same implications as issuing individual invitations to the members of a target group. The character and the extent of such publicity campaigns tend to obscure the distinction between individual requests and making an offer. The committee sees the express provision of information as constituting an offer. Another point is that genetic testing in relatives (necessary in order to respond to individual requests for genetic counselling) can also be included within the definition. In the field of genetics, it would appear to be difficult to draw clear borders between individual genetic testing, genetic testing within families, and genetic screening. These show considerable similarities in terms of the desired effects (enabling people to make meaningful choices), the possible risks and the conditions for good implementation and supervision. As a result, within the framework of this report, the committee has opted for an overly broad interpretation of the concept of genetic screening rather than an overly narrow one. This means that the committee has also included in its deliberations the family testing as currently performed in clinical genetics centres. However, this in no way implies that the committee feels that the status of such family testing should be changed in any way whatsoever. It is simply that the committee views family testing from a different perspective to that usually adopted by the medical profession. The profession sees family testing as constituting individual medical aid, while it views screening as studies involving (large parts of) the population. The committee considers that screening is not necessarily (by definition) a large scale activity while family testing is not necessarily a small scale undertaking.

The committee will return later on (7.2) to the matter of the relationship between the concepts of ‘genetic screening’ and ‘population screening’ (within the context of the Population Screening Act) and to the role played by family testing.

There is yet another reason for applying a broad interpretation of the concept of genetic screening. Screening during the prenatal phase involves the use of ultrasonography, which also detects non-hereditary foetal defects. It is the committee’s view that the search for such defects (which is irrevocably linked to this technique) also falls within the scope of this report.

The State Secretary also requested that consideration be given to testing for non-hereditary disorders. The committee thinks that, from the viewpoint of the technology used, there is actually very little difference between the early detection of hereditary diseases and of diseases lacking a hereditary component. Exceptions to this are certain factors which play a part in infectious diseases. Thus, when examining the question of genetic screening, problems could (in principle) be encountered which are involved in other types of disorders. However, the objectives and the social implications of genetic screening often extend much further, since such screening can also

have repercussions for others (in this instance for descendants or for other members of the family). This is something which genetic screening has (to some extent) in common with the detection of infectious diseases such as tuberculosis or AIDS. However, the committee has not studied the special aspects and specific implications associated with the detection of infectious diseases. Since it considers the investigation of genetic screening to be a complex matter in itself, the committee will restrict itself to this topic in the present report.

Pre-implantation genetic diagnosis (PGD) is the examination in vitro of an embryo (or an egg cell prior to fertilisation) in order to exclude a genetic condition in case a very high risk of that condition is known. PGD can only be used in combination with in vitro fertilisation (IVF).

References:

- *Heredity: Science and Society* (HCN 1989)
www.gezondheidsraad.nl/pdf.php?ID=7208&p=1;
- *Genetic Screening – A Report of a Committee of the Health Council of the Netherlands* (19 December 1994) www.gezondheidsraad.nl/pdf.php?ID=1221p=1;
- *Pre-implantation Genetic Diagnosis* (Health Council of the Netherlands, 2006):
<http://www.gr.nl/adviezen.php?ID=1333&highlight=genetic>

National Human Genome research Institute (NHGRI)

Genetic test -The analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers and establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn and carrier screening, as well as testing in high-risk families, are included. Tests for metabolites are covered only when they are undertaken

with high probability that an excess or deficiency of the metabolite indicates the presence of heritable mutations in single genes. Tests conducted purely for research are excluded from the definition, as are tests for somatic (as opposed to heritable) mutations, and testing for forensic purposes.

References:

- *Promoting Safe and Effective Genetic Testing in the United States* (2005)
<http://www.genome.gov/10001733>

National Institutes of Health and Department of Energy task force

Definition of genetic tests - "The analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect inherited disease-related genotypes, mutations, phenotypes, or karyotypes, for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn, and carrier screening, as well as testing in high risk families, are included. Tests for metabolites are covered only when they are undertaken with high probability that an excess or deficiency of the metabolite indicates the presence of inherited mutations in single genes" (*Task Force on Genetic Testing. Promoting safe and effective genetic testing in the United States. Final report. Baltimore: Johns Hopkins University Press*)

References:

- *Genetic Testing and public policy_ Neil Holtzman 1998*
http://www.findarticles.com/p/articles/mi_m0999/is_n7134_v316/ai_20440211/pg_1

Regulating Agencies

Human Genetics Commission (HGC), UK - 1

Personal Genetic Information: may be defined as any information about the genetic makeup of a person. This information may be derived from a sequence of the components (the nucleotides, the As, Ts, Cs and Gs of the genetic code) that make up the DNA molecules in the chromosomes which are found in almost every cell in our bodies. There is also DNA in the mitochondria (small independently reproducing organelles found in most cells which power the chemical machinery of the cells). The chromosomes together with the mitochondria and other biochemical structures provide our biological inheritance –our genome- which is transferred from generation in the egg and sperm.

Genetic Testing in Medical Practice. In the medical context, genetic testing may be undertaken as part of the process of treating or advising an individual patient. There are four forms of genetic test in this category:

- 1) **Diagnostic genetic testing** – use of genetic testing in individuals with symptoms to aid in his or her diagnosis, treatment and management.
- 2) **Presymptomatic genetic testing** – Primarily carried out in healthy people or those without symptoms to provide information about that individual's future health, with respect to specific genetic (also called inherited or Mendelian) diseases. Such a test result may indicate that the individual has a high likelihood of developing the disorder or of excluding it. Presymptomatic testing is most frequently used in late onset dominantly inherited diseases such as Huntington's disease.
- 3) **Carrier testing** – Used to detect individuals who possess a single copy of a gene which follows a recessive pattern of inheritance (e.g. cystic fibrosis, sickle conditions or thalassaemia). Individuals who are carriers will not develop the inherited disease but if they have children with another carrier these children have a one in four chance of developing the disease.
- 4) **Susceptibility tests** – gene variants have been discovered which are associated with common diseases such as Alzheimer's disease and diabetes. While the associations between carrying the gene variant and developing the disease do not appear to be close enough to make predictive testing useful, it is likely that increasingly genetic tests for such variants will be used to target drug treatments to those most likely to benefit from them. This rapidly growing field of genetically targeted drugs is known as pharmacogenetics.

Reference:

- *Whose hands on your genes? – HGC (Nov 2000):*
http://www.hgc.gov.uk/UploadDocs/DocPub/Document/business_consultations2maintext.pdf

Human Genetics Commission (HGC), UK - 2

We have define direct genetic testing as any test to detect differences in DNA, genes or a chromosome that is not provided as part of a medical consultation.

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

We received a number of interesting responses on this point, which we might loosely categorize as follows:

- **Narrow** – the definition should be confined to direct information about gene sequences from DNA or RNA tests or protein analysis that directly relates to gene sequence. Most of these responders felt that the public were concerned about DNA/gene tests and that oversight should recognise this no matter if it was somewhat illogical to single such tests out from other health testing services. Some felt that broadening the definition would make any oversight cumbersome and would inevitably delay matters.

- **Broad** – the definition should cover all direct and indirect tests that give information about genetic conditions. The rationale for this seemed to be that indirect testing could be as significant as direct DNA tests and that by its nature indirect testing may be more prone to variations in analysis or interpretation. There was also a linked view that limiting oversight to DNA tests would create a loophole that might encourage the unrestricted proliferation of indirect testing methods.

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

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

Therefore for the purposes of our report we will define genetic tests as: **a test to detect the presence or absence of, or change in, a particular gene or chromosome, including an indirect test for a gene product or other specific metabolite that is primarily indicative of a specific genetic change**

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

We also note the similar, but more detailed and comprehensive, definition of a genetic test adopted by the SACGT. It made clear, however, that *“tests that are used primarily for other purposes, but that may contribute to diagnosis of a genetic disease ... would not be covered.”* In our previous report we also noted the US Bill on genetic discrimination (as an example of recent US legislation) which defined genetic tests as *“the analysis of human DNA, RNA, chromosomes, proteins and metabolites that detect genotypes, mutations or chromosomal changes”*

Genetic test: A test to detect the presence or absence of, or change in, a particular gene or chromosome (including indirect tests for a product indicative of a specific gene change in a person).

Genetic counselor: In the UK, a non-medical health professional providing genetic counselling in a clinical setting. Genetic counselling is a communication process between the counsellor and the individual or family which deals with the medical and other issues associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family.

Genealogy test: Genetic tests used in the study of family history and descent.

Paternity test: A test which uses DNA analysis to determine whether a man is the biological father of a particular child.

Pharmacogenetics: The study of how people respond differently to drugs due to their genetic makeup, in terms of both how well the drug will work and what side effects the person might suffer.

Pharmacogenetics: where people were tested for a likely response to a particular drug before being given that drug whether as part of a research study or to help with prescribing decisions. While still at an early stage, the potential use of pharmacogenetics raises a range of social, ethical, legal and economic issues

References:

- *Genes Direct: Ensuring the effective oversight of genetic tests supplied directly to the public* - March 2003 (HGC):
http://www.hgc.gov.uk/UploadDocs/DocPub/Document/genesdirect_full.pdf
- *Our Genes, Ourselves: Towards appropriate genetic testing* – Third Annual Report of the Human Genetics Commission 2003:
<http://www.hgc.gov.uk/UploadDocs/DocPub/Document/HGC%203rd%20Annual%20Report,%20final%20PDF.pdf>

Human Genetics Commission (HGC), UK - 3

Prenatal screening tests can help identify women who are at increased risk of having a baby with a disorder. Those women identified at increased risk are then offered a *diagnostic test*.

Diagnostic tests can tell a woman if the baby has a chromosomal abnormality such as Down's syndrome, or a genetic disorder like cystic fibrosis.

Prenatal screening is a public health service which offers pregnant women a test to see if the baby is at significant risk of having a particular disorder such as Down's syndrome.

Prenatal diagnosis is a type of test which is person and condition specific that aims to provide a diagnosis of the particular condition the baby might have.

Genetic counsellors are specially trained professionals who generally come from medical or nursing backgrounds and have first hand knowledge of genetic disorders and their impact.

Prenatal genetic diagnosis (PND) is a type of test which is person and condition specific and aims to provide a diagnosis of the particular **genetic** condition the baby might have.

Preimplantation genetic diagnosis (PGD) is a technique where embryos created outside the body by IVF can be tested to see if they have a genetic disorder. One or two cells are removed for testing from the embryo at the 6-10 cell stage (day 3 of development). Implantation into the woman's uterus will generally only be attempted for embryos without the genetic disorder.

PGD is currently being offered for three major categories of disease including: to determine the sex of the embryo with the aim of avoiding sex-linked disorders such as Duchenne muscular dystrophy; to identify embryos with single gene disorders such as cystic fibrosis; and to identify embryos with chromosomal disorders, where a technique called fluorescence in situ hybridisation (FISH) can be used to identify or confirm abnormal chromosomal rearrangements.

Reference:

- *Choosing the Future: Genetics and Reproductive Decision Making* – July 2004:
<http://www.hgc.gov.uk/UploadDocs/DocPub/Document/ChooseFuturefull.pdf>

Human Genetics Commission (HGC), UK - 4

Prenatal screening is a public health service that offers pregnant women a test to see if the baby is at an increased risk of having a particular disorder such as Down's syndrome.

Prenatal diagnosis is an individual procedure that aims to provide a diagnosis of a particular condition that the baby might have.

To identify the genetic father of a fetus, a DNA sample from the man (or men) in question is required for comparison with the fetal sample. Concerns have been raised about "**fatherless**" **paternity testing** in this context. Fatherless testing is when a DNA sample from the supposed father is used without his knowledge or consent.

PGD was developed in 1990 in the UK. It uses assisted reproductive technology (ART) to create a number of embryos in the laboratory. These embryos are usually created by fertilising the woman's egg with her partner's sperm, but occasionally donor gametes are used. The fertilised eggs are allowed to develop in an incubator for 2 to 3 days until they consist of about 8 cells. At this stage, 1 or 2 cells are removed from the embryo and tested for the specific genetic condition for which the embryo is at increased risk, enabling the embryos from which they were removed to be identified as affected or unaffected. The couple can then elect to place in the womb 1 or 2 embryos that are predicted to be unaffected, so allowing them to embark on a pregnancy that is at very low risk of the condition.

PGD was originally developed for use by couples who know they are at increased risk of having a child with a genetic disorder but do not wish to consider prenatal diagnosis and the possible subsequent termination of a pregnancy. Other potential uses are now emerging. These include testing for a pre-disposition to cancer, late onset and lower penetrance conditions, and the creation of so called 'saviour siblings'. These would be selected to have the same tissue type as an existing brother or sister affected with a disease, and donations of their umbilical cord stem cells or a bone marrow transplant could be used to treat that sibling.

Reference:

- *Making Babies: Reproductive decisions and Genetic Technologies – January 2006:*
<http://www.hgc.gov.uk/UploadDocs/DocPub/Document/Making%20Babies%20Report%20-%20final%20pdf.pdf>]

Human Genetics Commission (HGC), UK - 5

Another key difference in the various regulation is the meaning given to "**genetic testing**" and "**genetic information**". Some regulation construes "genetic testing" very narrowly, whereas other regulation defines it more inclusively.

For example, the Swedish Agreement restricts the definition of **genetic testing**, for the purposes of the agreement, to presymptomatic, predictive, and susceptibility testing.

In contrast, legislation enacted in South Carolina and Maine provide that a **genetic test** is any laboratory test for determining the presence or absence of genetic characteristics in an individual.

Moreover, legislation such as the *Medical Checks Act* does not define either genetic testing or genetic information because such definitions are not relevant to the application of its provisions. Accordingly, it is not really possible, or indeed appropriate, to isolate the definitions of such terms for the purpose of comparison, as each must be read and understood in its context; that is, in terms of the aims and purpose of the legislation (or policy), and in light of the terms of other provisions.

Definition of 'Genetic Testing' - For the purposes of the agreement, '**genetic testing**' means:

- genetic tests carried out prior to the appearance of symptoms;
- genetic tests carried out for predictive purposes; and
- genetic tests carried out in order to demonstrate or exclude the possibility of people being genetically predisposed to a hereditary disorder or disease that manifests itself only in subsequent generations.

For the purpose of the agreement, "**genetic testing**" means "a genetic diagnosis of inherited predispositions in the genes and chromosomes in those instances where the predisposition has not yet given rise to a sickness" (Swedish Insurance Federation, "Agreement on limiting the use of information derived from genetic testing during risk evaluation of life and sickness-benefit insurance", 24 September 1997, pg2), i.e. presymptomatic genetic testing.

In March 1999, the Human Genetics Society of Australasia (HGSA) issued a short set of guidelines on genetic testing and privacy. The guidelines distinguish between three categories of **genetic testing**:

- **diagnostic testing**, for the benefit of a person who is already symptomatic or for whom treatment is required;
- **carrier testing**, where the implications are usually for reproductive choices; and
- **predictive testing**, where the test predicts the onset of a disease at some future time.

The Report also specifies that in assessing which genetic tests are appropriate for children, the nature of the test is a crucial consideration. (**Joint Statement, p.3.**) For this purpose, it is necessary to distinguish between the types of genetic test currently available, namely:

- (1) Tests for preventable or treatable diseases;
- (2) Tests for serious childhood diseases;
- (3) Tests for adult-onset diseases for which no treatment or preventative action is available in childhood;
- (4) Tests indicating a pre-disposition to a common adult-onset disorder for which some general preventative measures may be taken in childhood;
- (5) Tests for behavioural traits;
- (6) Tests for carrier status and other conditions that may impact on the child's future reproductive decisions;
- (7) Tests that parents request without any direct relation to treatment or reproductive options of the child; and
- (8) Tests performed solely for the benefit of another family member.

Reference:

- *Protection of Genetic Information: An International Comparison (HGC-Sep 2000):*
http://www.hgc.gov.uk/UploadDocs/DocPub/Document/international_regulations.pdf

International Conference on Harmonisation (ICH)

Genotoxicity tests can be defined as *in vitro* and *in vivo* tests designed to detect compounds which induce genetic damage directly or indirectly by various mechanisms.

Reference:

- *Note for Guidance on Genotoxicity: a Standard Battery for Genotoxicity Testing (1997)*
(ICH): <http://www.emea.eu.int/pdfs/human/ich/017495en.pdf>

CDC (Center for Disease Control)

Genetic testing - Processes or methods used to analyze human DNA, RNA, genes, chromosomes, proteins, or metabolites in order to detect mutations, chromosomal changes, karyotypes, phenotypes and/or expression pattern variation. Although most **genetic testing** is used for diagnosing rare genetic disorders, a growing number of genetic tests have population-based applications, including carrier identification, predictive testing for inherited risk for common diseases, and pharmacogenetic testing for variation in drug response. These tests and other anticipated applications of genomic technologies for use in screening and prevention have the potential for broad public health impact.

Carrier – An individual who possesses a mutant allele but does not express it in the phenotype, either because of a dominant allelic partner or because the mutation is nonpenetrant.

Diagnostic test – A test performed to determine the presence or absence of a specific medical condition.

Genet Therapy – An experimental procedure aimed at replacing, manipulating, or supplementing nonfunctioning or malfunctioning genes with healthy genes.

Genetic counseling – The educational process that helps individuals, couples, or families to understand genetic information and issues that may have an impact on them.

Genetic predisposition – A genotype that increases the risk but is insufficient to result in disease. Impaired expression expression of alleles at other gene loci and/or environmental factors are neededbefore disease appears.

Genetic screening – testing a group of people to identify individuals at high risk of having or passing on a specific genetic disorder.

Genetic testing - Analyzing an individual's genetic material to determine predisposition to a particular health condition or to confirm a diagnosis of genetic disease.

Screening test – A test designed to identify subjects who are at sufficient risk of a specific disorder to benefit from further investigation or preventive action, among those who have not sought medical attention on account of symptoms of that disorder.

References:

- *Draft Genetic Test Review - Cystic Fibrosis Glossary:*
www.cdc.gov/genomics/gtesting/ACCE/FBR/CF/CFGlossary2.htm
- *Genomics and Population Health – CDC 2005:*
<http://www.cdc.gov/genomics/activities/file/print/2005report/fullReport.pdf>]

National Health Institutions

NIH (SACGT) (also NHGRI task force) (same as NIH-DOE-ELSI report)

A **genetic test** is an analysis performed on human DNA, RNA, genes and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition.

A **genetic test** also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable for acquired genotypes, mutations or phenotypes. The purposes of these genetic tests include predicting risks of disease, screening of newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families or populations. Tests that are used primarily for other purposes, but that may contribute to diagnosing a genetic disease (e.g. blood smear, certain serum chemistries), would not be covered by this definition. Also excluded from the definition are tests conducted exclusively for forensic identify purposes.

Genetic tests can be performed for a number of purposes. Moreover, a test can be used in more than one way, such as when a test used for diagnostic purposes is also used to predict risk of disease.

Preimplantation diagnosis is used following *in vitro* fertilization to diagnose a genetic disease or condition in a preimplantation embryo.

Prenatal diagnosis is used to diagnose a genetic disease or condition in a developing fetus.

Newborn screening is performed in newborns in state public health programs to detect certain genetic diseases for which early diagnosis and treatment are available.

Carrier testing is performed to determine whether an individual carries one copy of an altered gene for a particular recessive disease. Recessive diseases occur only if both copies of a gene that an individual receives have a disease-associated mutation; thus, each child born to two carriers of a mutation in the same gene has a 25-percent risk of being affected with the disorder.

Diagnostic/confirmatory testing is used to identify or confirm the diagnosis of a disease or condition in an affected individual. Diagnostic testing may also be useful to help determine the course of a disease and choice of treatment.

Predictive testing determines the probability that a healthy individual with or without a family history of a certain disease might develop that disease.

Presymptomatic testing refers to predictive testing of individuals with a family history. Historically, the term *presymptomatic testing* has been used when testing for diseases or conditions such as Huntington disease where the likelihood of developing the condition (known as penetrance) is very high in people with a positive test result.

Reference:

- *Enhancing the oversight of genetic tests: Recommendations of the SACGT, Secretary's Advisory Committee on Genetic Testing, June 2000:*
[\[http://www4.od.nih.gov/oba/sacgt/qtdocuments.html\]](http://www4.od.nih.gov/oba/sacgt/qtdocuments.html)

National Cancer Institute - USA

Genetic Testing - Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder.

Genetic Analysis - The study of a sample of DNA to look for mutations (changes) that may increase risk of disease or affect the way a person responds to treatment.

Genetic Counseling - A communication process between a specially trained health professional and a person concerned about the genetic risk of disease. The person's family and personal medical history may be discussed, and counseling may lead to genetic testing.

Genetic Marker - Alteration in DNA that may indicate an increased risk of developing a specific disease or disorder

Genetic Susceptibility - An inherited increase in the risk of developing a disease.

Reference:

- *Dictionary of Cancer Terms:*
http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=46128

Genetics Professionals Organizations

ESHG (PPPC – Insurance and Employment Paper)*

Need for definition: Insurance contracts laws state that the contract must be written up in utmost good faith otherwise the contract may be void. This means that the applicant is under an obligation to reply honestly, without withholding information. But if the definition of what can be considered genetic information is not clear, how can an applicant reply honestly and how can an insurer ask specific questions which are relevant to risk assessment? There is a need then for

clear definitions of terms used in genetics, insurance and employment, so that different professions and their clients have a common understanding of the issues. A **genetic test** is a test of anything that is, or potentially can be, inherited according to Mendelian laws. This covers not only DNA, RNA, and chromosome analysis, but also protein truncation test and clinical examination of a patient for a Mendelian condition that is diagnosable in that way. But does the test result have predictive value for the subject or family members? If the answer is no, there are no special features. If it is predictive for the subject but not the family, it is ethically similar to several other medical tests. Only if there are also implications for the family is there a special case. It is also important to distinguish between research and clinical genetic tests. A lot of people's worries concern tests for disease susceptibility, and these are almost always part of research, but only clinically validated tests should be considered for insurance purposes. Legislation without a precise definition of these terms may confuse insurers and applicants when underwriting or renewing an insurance policy. There is a need for clear definitions of the terms used in genetics and insurance, for the transparency of the process by which genetic information is incorporated into insurance decisions, and for ensuring that genetic information is not used to the detriment of other family members. There is a broad consensus that insurance considerations should not unduly influence the uptake of appropriate clinical care, which may increasingly involve genetic tests. There is also a broad consensus that applicants should not be asked to undergo genetic tests, in order to obtain insurance.

Presymptomatic testing identifies healthy individuals who may have inherited a gene for a late-onset disease and if so will develop the disease if they live long enough. Multifactorial diseases are frequent and most likely triggered by specific combinations of functional DNA polymorphisms interacting with the environment in ways that are subject to behavioral changes.

Susceptibility testing identifies healthy individuals who may have inherited a gene that puts them at increased risk of developing a multifactorial disease, although these individuals may never develop the disease in question. In these situations, the most that the genetic test can do is to show a propensity to a disease. (Evans JP, Skrzynia C, Burke W: The complexities of predictive genetic testing. *BMJ* 2001; 322: 1052– 1056. Holtzman NA: Are we ready to screen for inherited susceptibility to cancer? *Oncology* 1996; 10: 57– 64)

Genetic testing classifies people into those who have the mutant gene and those who do not have it. Now, a mutant gene is not a disease. Genetic disorders show different degrees of severity and diverge with respect to the age of onset. Some genetic disorders affect people with nearcertainty but others not. Predictions are therefore complicated by these phenomena.

Clear definitions of the terms used in genetics and insurance should be developed, so that different professions and their clients have a common understanding of the issues. In these recommendations, the term genetic information (of which genetic tests are a part) refers to: information that derives from the variation between people that exists in their chromosomes or DNA, or information that is being used to infer that a specific genetic variation or genetic influences might be present. The former includes cytogenetic and DNA test results and very specific biochemical changes, whilst the latter category of genetic information includes family history, clinical diagnosis, imaging, clinical chemistry test results, etc.

References:

- *ESHG: Genetic information and testing in insurance and employment: technical, social and ethical issues – Recommendations of the ESHG: Eur J Hum Genet (2003) 11, Suppl 2, S11–S12: <http://www.nature.com/ejhg/journal/v11/n2s/pdf/5201116a.pdf>*
- *Godard B, Raeburn S, Pembrey M, Bobrow M, Farndon P, Aymé S: Genetic information and testing in insurance and employment: technical, social and ethical issues. Eur J Hum Genet (2003) 11, Suppl 2, S123–S142: <http://www.nature.com/ejhg/journal/v11/n2s/pdf/5201117a.pdf>*

ESHG (PPPC – Genetic Services Paper)

In the 1980s, the general objective of **genetic services** was more precisely defined “to help people with a genetic disadvantage to live and reproduce as normally and as responsibly as possible”

(WHO: Report on Community Approaches to the Control of hereditary Diseases)

Nowadays, the aim of a **genetic service** is often seen as to respond to the needs of individuals and families particularly their wish to know whether or not they are at risk of developing a genetic disorder or of bearing an affected child. A primary responsibility in genetic counselling is to provide information as accurate as possible on diagnosis and chance or recurrence within the family.

Genetic counselling has been defined as a communication process, which deals with the human and psychological problems associated with the occurrence, or risk of occurrence, of a genetic disorder in the family. This process involves an attempt by one or more appropriately trained persons to help the individual or the family to (1) understand the medical facts, including the diagnosis, the probable course of the disorder and the available management; (2) appreciate how heredity contributes to the disorder and the risk of recurrence in specified relatives; (3) understand the options for dealing with the risk of recurrence; (4) choose the course of action which seems appropriate to them in view of their risk and their family goals and act in accordance with that decision; and (5) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder. (Fraser FC: Genetic Counselling, Am J Hum Genet 1974).

Presymptomatic and predictive testing: It has been demonstrated that it is in the category of presymptomatic and predictive testing that most of the difficult issues involving genetic testing lie.³³ It should be noted that the term ‘presymptomatic testing’ is best reserved for those situations where an abnormal test result will almost inevitably lead to development of the disease at some point in later life, whereas the term ‘predictive testing’ covers a broader range of situations in which the risk of a disorder occurring is substantially increased or reduced, but without necessarily implying any degree of certainty.

(Harper PS, Clarke A: Genetics Society and Clinical Practice. Bios Scientific Publishers: Oxford 1997)

References:

- *ESHG: Provision of genetic services in Europe: current practices and issues – Recommendations of the ESHG. Eur J Hum Genet (2003) 11, Suppl 2, S2–S4: <http://www.nature.com/ejhg/journal/v11/n2s/pdf/5201110a.pdf>*
- *Godard B, Kääriäinen H, Kristoffersson U, Tranebjaerg L, Coviello D, Aymé S: Provision of genetic services in Europe: current practices and issues. Eur J Hum Genet (2003) 11, Suppl 2, S13–S48: <http://www.nature.com/ejhg/journal/v11/n2s/pdf/5201111a.pdf>*

ESHG and ESHRE (PPPC – Genetic Screening Paper)

Definition of genetic screening

(1) Genetic screening may be defined as any kind of test performed for the systematic early detection or exclusion of a genetic disease, the genetic predisposition or resistance to a disease, or to determine whether a person carries a gene variant, which may produce disease in offspring.

(2) Screening may be concerned with the general population or with specific subpopulations defined on some basis other than their health.

(3) Screening for genetic conditions or genetic traits predictive of diseases is a medical act. As the public has trust in the professional duty of care, a compliance effect may be expected when a screening test is offered, whose effect underlines the responsibility of professionals offering such tests.

(4) Genetic screening is distinguished from other types of medical screening by the genetic nature of the disorder that may result in risk implications to family members of the person screened, even though family members may not be, nor perhaps wish to be, included in the screening programme. Genetic screening is also distinguished from other forms of screening because its aim is not necessarily to prevent or treat diseases in the person screened; it may be used for health-related reproductive or lifestyle choices.

In 1975, **genetic screening** had been defined as the search in a population for persons possessing certain genotypes that (1) are already associated with disease or predispose to disease, (2) may lead to disease in their descendants, or (3) produce other variations not known to be associated with disease. (*Committee for the Study of Inborn Errors of Metabolism: Genetic screening: programs, principles and research. Washington, DC: National Academy of Sciences; 1975.*) Today, **genetic screening** may be defined as any kind of test performed for the systematic early detection or exclusion of a hereditary disease, the predisposition to such a disease or to determine whether a person carries a predisposition that may produce a hereditary disease in offspring. With better knowledge of the genetics

In 1998, the WHO has reiterated that the main objective of **genetic screening** is to prevent disease or secure early diagnosis and treatment.

The Council of Europe has also adopted recommendations on **genetic screening** between 1990 and 1994. In these recommendations, genetic screening is defined as ‘a test applied to a defined group of persons in order to identify an early stage, a preliminary stage, a risk factor or a combination of risk factors of a disease’. The aim of screening is ‘to cure the disease or prevent or delay its progression or onset by early intervention’.

The Danish Council of Ethics defines **genetic screening** as ‘the study of the occurrence of a specific gene or chromosome complement in a population or population group’

The Dutch Health Council defines **genetic screening** as ‘any kind of test performed for the systematic early detection or exclusion of a hereditary disease, the predisposition to such a disease or to determine whether a person carries a predisposition that may produce a hereditary disease in offspring’.

Reference:

- *ESHG: Population genetic screening programmes: technical, social and ethical issues – Recommendations of the ESHG. Eur J Hum Genet (2003) 11, Suppl 2, S5–S7: <http://www.nature.com/ejhg/journal/v11/n2s/pdf/5201112a.pdf>*
- *Godard B, ten Kate L, Evers-Kiebooms G, Aymé S: Population genetic screening programmes: principles, techniques, practices, and policies. Eur J Hum Genet (2003) 11, Suppl 2, S49–S87: <http://www.nature.com/ejhg/journal/v11/n2s/pdf/5201113a.pdf>*

ESHG and ESHRE (PPPC – Biobanking Paper)

The American National Bioethics Advisory Commission defined a **DNA bank** as ‘a facility that stores extracted DNA, transformed cell lines, frozen blood or other tissue, or biological materials,

for future DNA analysis'. The same Commission defined a **DNA databank** as 'a repository of genetic information obtained from the analysis of DNA, sometimes referred to as 'DNA profiles'. The genetic information is usually stored in computerized form with individual identifiers'.

Reference:

- Godard B, Schmidtke J, Cassiman JJ, Aymé S: *Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective. Eur J Hum Genet (2003) 11, Suppl 2, S88–S122: <http://www.nature.com/ejhg/journal/v11/n2s/pdf/5201114a.pdf>*

ESHG and ESHRE (PPPC – Reprogenetics Paper)

Prenatal diagnosis (PND) is a diagnostic or pre-symptomatic test carried out on a developing foetus through amniocentesis, chorionic villus sampling, foetal blood sampling, collecting foetal material in maternal circulation, or ultrasound. PND is used to detect a foetus with chromosomal aberration, congenital malformation or disease, or that is at risk for disease and thus offers the parents the opinion to terminate the pregnancy in order to prevent the birth of offspring with genetic and/or congenital anomalies. Couples who have not experienced prenatal testing before, the patients with current infertility, or moral/religious objections, in general opt for prenatal diagnosis (De Die-Smulders et al., 2005)

Preimplantation genetic diagnosis (PGD) was introduced at the beginning of the 1990s as an alternative to prenatal diagnosis, to avoid termination of pregnancy for couples with a high risk of their offspring being affected by a sex-linked genetic disease. At that time, embryos obtained *in vitro* were tested using molecular techniques to ascertain the absence of a Y-bearing sequence, and only female embryos would be transferred. Since then, techniques for molecular and cytogenetic analysis at the single-cell level, including assessment of first and second polar bodies from oocytes or blastomeres from cleavage-stage embryos, have evolved considerably (Sermon et al., 2004)

Techniques for genetic analysis: Polar Body Biopsy; Cleavage Stage Biopsy (most commonly used); Trophoctoderm Biopsy (less used)

PGD vs. PGS (Preimplantation genetic screening): PGD was design for an a priori fertile couple that has a high risk of having an affected child, whereas PGS is provided for an infertile couple to detect certain anomalies of the embryo, which might prevent a successful pregnancy. Indications are hence totally different.

References:

- *ESHG and ESHRE: The need for interaction between assisted reproduction technology and genetics - Recommendations of the ESHG and ESHRE. Eur J Hum Genet (2006) 14, 509-511: <http://www.nature.com/ejhg/journal/v14/n5/abs/5201600a.html>*
- *Soini S, Ibarreta D, Anastasiadou V, Aymé S, Braga S, Cornel M, Coviello DA, Evers-Kiebooms G, Geraedts J, Gianaroli L, Harper J, Kosztolanyi G, Lundin K, Rodrigues-Cerezo E, Sermon K, Sequeiros J, Tranebjaerg L, Kääriäinen H, on behalf of ESHG and ESHRE. Eur J Hum Genet (2006) 14, 588–645: <http://www.nature.com/ejhg/journal/v14/n5/abs/5201598a.html>*

* Documents from *European Journal of Human Genetics*

ASHG

From our perspective, there are problems with the definition of what exactly constitutes a "genetic test" that should require additional oversight. We suggest restricting the definition of **genetic tests** that would require additional oversight to those that test for a particular nucleotide sequence directly or indirectly. This would include all DNA and RNA testing, protein truncation and similar tests of expression that are based on DNA or RNA sequence, and FISH or equivalent kinds of molecular cytogenetic testing. While many genetic diseases can be diagnosed equally well by looking at a gene product, it appears that tests involving nucleotide sequence are the ones that generate particular concern among non-geneticist health professionals and the public, and it is this concern that justifies additional oversight. [ASHG Response to Request for Public Comments on Preliminary Final Recommendations on Oversight of Genetic Testing. May 22, 2000]

The Problem of Defining Genetic Conditions and Tests: Definitions can become important when insurance policies and laws distinguish genetic conditions and genetic tests from other medical conditions and tests. While some conditions (e.g., Tay-Sachs disease) have a virtually purely genetic basis, most genetic disorders involve an interaction between a genetic predisposition and environmental factors. Even single-gene disorders (e.g., sickle-cell disease and cystic fibrosis) have variable expression depending in part on such environmental factors as oxygen tension in the former and nutritional factors in the latter. Similarly, some tests, such as those involving mutation analysis, might seem to be clearly genetic tests, but many others, used to test for genetic disorders, measure gene products or further-removed effects. The latter include many tests that could be considered genetic tests, such as Guthrie spots, which test for elevated levels of phenylalanine, or any X-ray used to diagnose or rule out achondroplasia. The point of these observations is that there is no clear boundary between genetic and nongenetic conditions and tests.

Reference:

- *Genetic Testing and Insurance - background statement. The Ad Hoc Committee on Genetic Testing/Insurance Issues, Am J Hum Genet 56:327-331, 1995:*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7825594

Human Genetics Advisory Commission (HGAC)

Genetic testing - testing to detect the presence or absence of, or alteration in, a particular gene sequence, chromosome or a gene product, in relation to a genetic disorder.

- **Diagnostic genetic testing** - use of genetic testing in a person with disease symptoms to aid in their diagnosis, treatment and management.
- **Presymptomatic genetic testing** - testing of healthy or asymptomatic individuals to provide information about that individual's future risk of certain specific inherited diseases. Such a test may indicate that the individual has a higher likelihood of developing a disorder. Presymptomatic genetic testing is most frequently offered to those thought to be at high risk of autosomal dominant disorders such as Huntington's disease.
- **Carrier testing** - testing of unaffected individuals to determine whether they are carriers of a gene for a recessively inherited disorder (e.g. cystic fibrosis) and are thus at risk of having an affected child.
- **Susceptibility testing** - testing which provides information about a genetic component in a multifactorial disorder. **Multifactorial disorders** are disorders whose genetic components are not the sole cause, but which work with other, often environmental factors, in determining a disease outcome. Multifactorial disorders include many cardiovascular diseases, most Alzheimer's disease of old age and most forms of

diabetes.

The use of genetic testing for biological monitoring (i.e. as a dosimeter to monitor DNA damage due to environmental effects) is not considered in this report.

Genetic screening - a term used to denote application of genetic tests to populations of people, who individually are not at particularly high risk. In contrast, *genetic testing* of individuals is undertaken when there is some specific prior reason to suspect that the person being tested may be at higher than average risk of carrying the gene change being tested for.

References:

- *The Implications of Genetic Testing for Employment*
http://www.advisorybodies.doh.gov.uk/hgac/papers/papers_g/g_03.htm

Human Genetics Society of Australasia

Genetic Counsellor-A health professional with specialised training in genetics and counselling who can provide information and support to individuals or families with concerns about a genetic disorder that may run in the family. Those genetic counsellors who have not completed their training usually denote themselves as Associate genetic counsellors.

The process of genetic counselling is complex as it is a communication process which involves making or discussing a diagnosis, providing accurate information about the disorder and options available to the client, and considering the impact the information has on clients and their families. Harper defines genetic counselling as “the process by which patients and relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and of the ways in which this may be prevented, avoided or ameliorated”. (Peter S. Harper (1998) “Practical Genetic Counselling” Butterworth-Heinemann. Oxford)

Diagnostic test: A diagnostic test is usually ordered by a clinical geneticist to make or confirm a suspected diagnosis, or to exclude a differential diagnosis. A clinical diagnosis or ordering a genetic test is reliant upon the judgement and expertise of the clinical geneticist and is within his/her responsibility. Geneticists may delegate the responsibility of arranging a genetic test to a genetic counsellor with appropriate supervision. A prenatal test may be a diagnostic test when carried out on a developing fetus.

Genetic carrier testing: A test to determine if an individual, with or without symptoms, has a genetic mutation or a chromosome abnormality, which increases the chance of his/her children, having the disorder in question. The term carrier is used with respect to autosomal recessive and X-linked genes and balanced chromosome rearrangements.

Screening tests: Screening tests are non-diagnostic, population-based tests providing the client with a personalised risk. When performed prenatally, screening tests may identify fetal abnormalities or reveal an increased risk of fetal abnormalities. When performed post-natally, the aim of genetic screening is to identify individuals at increased risk of developing symptoms of a disorder in the future, with a view to offering intervention eg, newborn screening. The nature of a screening test should be clearly distinguished from a diagnostic test to the client. Appropriate written and/or verbal information should be provided prior to testing. Support and counselling should be made available to persons receiving a high-risk result so that future options are understood.

Predictive/pre-symptomatic tests: These tests are performed on an individual who has no symptoms of a specific disorder at the time of testing, to determine whether he/she has a mutant gene. If the mutant gene(s) is present the individual is at a increased probability of developing symptoms at sometime in the future. Guidelines for predictive/pre-symptomatic testing for late-onset disorders have been developed by the HGSA.

Research tests: Tests carried out as part of a research study supported by special funding approved by an institutional ethics committee. The NHMRC's National Statement on Ethical Conduct in Research Involving Humans (1999) provides guidelines for genetic testing when performed as part of a research study.

Presymptomatic testing refers to a genetic test performed on a person who has a family history but no symptoms of a specific disorder at the time of testing, to determine whether or not the mutation for that disorder (known to be present in the family) has been inherited.

If the test reveals that the mutation is present, the person is almost certain to develop the disorder at some time in the future, provided he or she lives long enough. Huntington disease, familial adenomatous polyposis (FAP) and myotonic dystrophy are examples of disorders to which the term 'presymptomatic' testing applies.

Predictive testing refers to a genetic test performed on a person who has a family history but no symptoms of a specific disorder at the time of testing, to determine whether or not the mutation for that disorder (known to be present in the family) has been inherited.

If the test reveals that the mutation is present, the person has an increased probability, rather than certainty, of developing the disorder at some time in the future, provided he or she lives long enough. Testing for mutations in BRCA1 and BRCA2 (breast cancer) and MLH1 and MSH2 (colon cancer) are examples of predictive testing. (NHMRC (2000). Ethical Aspects of Human Genetic Testing: An Information Paper. www.nhmrc.health.gov – publications/ethics/human)

There are three categories of **Genetic testing**:

- **Carrier testing**, where the implications are usually for reproduction
- **Diagnostic testing**, for the benefit of the person who is already symptomatic or for whom treatment is required and
- **Predictive testing**, where the test predicts the onset of a disease at some future time.

References:

- Australasian Society of Genetic Counsellors (ASGC) Code of Ethics, 2000
<http://hgsa.com.au/images/UserFiles/Attachments/ASGCCCodeofEthics.pdf>
- HGSA Guidelines for the practice of genetic counseling 1999
<http://hgsa.com.au/images/UserFiles/Attachments/GuidelinesforthePracticeofGeneticCounselling.pdf>
- DNA Presymptomatic and Predictive Testing for Genetic Disorders, December 2002
<http://hgsa.com.au/images/UserFiles/Attachments/PresymptomaticandPredictiveTestingforGeneticDisordersV22005.pdf>
- Privacy Implications of Genetic Test, 1999
<http://hgsa.com.au/images/UserFiles/Attachments/PrivacyImplicationsofGeneticTesting1.pdf>

UKGTN

Genetic tests (which are defined as tests for single gene, germ line disorders where Nucleic Acid is the analyte)

The exact definition of a **genetic test** is still debated but the term *genetic test* should be regarded as a shorthand to describe a test to detect (a) a particular genetic variant (or set of variants), (b) for a particular disease, (c) in a particular population and (d) for a particular purpose. The specification of all these factors are essential for test evaluation since validity will be to a large extent be determined by them.

References:

- *Procedures and criteria for evaluation of genetic testing for NHS service (June 2003)*
<http://www.genetictestingnetwork.org.uk/gtn/UKGTN-information/dossier/mainColumnParagraphs/00/document/BACKGROUND%20INFORMATION,%20GENE%20DOSSIER.pdf>
- *Testing criteria for molecular Genetic Testing*
<http://www.genetictestingnetwork.org.uk/gtn/UKGTN-information/dossier/mainColumnParagraphs/00/document/BACKGROUND%20INFORMATION,%20GENE%20DOSSIER.pdf>

Nuffield Trust

There was general agreement in all the workshops that **counselling** was essential for patients both before and after testing for single high penetrant genes and that it was the predictive power in these circumstances that made it essential. Counselling had to be supportive and non-directive and had to take care to avoid particular courses of action. Before agreeing to a test, patients had to understand their pre-test risks of developing disease and how the test results might alter that risk for themselves and other family members. They would also need to be informed about the range of preventive measures that were available, or, in the case of prenatal testing, of reproductive choices.

Pharmacogenetics was the science by which our knowledge of the individual human genome would explain how drugs affected individual patients, and how as a consequence of this knowledge, physicians would be able to tailor interventions to the particular needs of their patients, both in terms of the choice of drug and its dosage. The individualization of treatment would represent a more refined approach to drug prescribing. At present it was not always possible to predict how a patient would react to a drug, at what dosage level it should be given, how effective it might be, and whether the patient would suffer adverse effects.

References:

- *The Nuffield Trust Genetics Scenario Project - Genetics and Health (May 2000)*
<http://www.archive.official-documents.co.uk/document/nuffield/policyf/gen-00.htm>

American Board of Genetic Counselling

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptations to the risk or condition.

Journal of Genetic Counseling, Vol. 15, April 2006

References:

- *What is genetic counseling?*
<http://www.abgc.net/english/View.asp?x=1683>

CORN (Council of Regional Networks for Genetic Services)

Genetic counseling – A communication process which deals with human problems associated with the occurrence, recurrence or the risk thereof, of a genetic disorder within a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family: (1) comprehend the medical facts, including the diagnosis, the probable course of the disorder, and the available management; (2) appreciate the way heredity contributes to the disorder, and the risk of recurrence in specified relatives; (3) understand the options for dealing with the risk of recurrence; (4) choose the course of action which seems most appropriate to them in view of their risk and the family goals and act in accordance with that decision; and (5) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder. Reassurance that an individual is NOT at risk for the occurrence or recurrence of a disorder is also an inseparable component of genetic counselling.

Genetic diagnosis/evaluation – the process of determining the presence or absence of a condition through physical evaluation and/or laboratory testing. Once a diagnosis has been made, appropriate genetic counselling can be performed and an acceptable treatment plan developed. Diagnostic procedures performed that focus on a foetus are referred to as prenatal services while all others are referred to as clinical services. The clinical evaluation and diagnostic process is typically performed by a physician who is certified by the American Board of Medical Genetics as a clinical geneticist, while prenatal evaluation and diagnostic testing may be performed by an obstetrician/perinatologist, in consultation with genetic professionals as needed.

Genetic screening – A process by which an individual undergoes a procedure and/or test to indicate if they are at greater or lesser risk than the general population for having a specific condition. If a positive screening result is encountered, the individual is typically referred for diagnostic (confirmatory) testing. Current examples of genetic screening include newborn screening for PKU, or maternal serum alpha-fetoprotein screening during pregnancy to identify fetuses with spina bifida or Down syndrome.

Genetics – The branch of biology which deals with heredity and variation: **Human Genetics** – The branch of biology which deals with heredity and variation in the human species; **Medical Genetics** – The application of human genetics to diseases and abnormalities of human development; **Clinical Genetics** – The provision of medical services to individuals, families and populations who have or are at risk for disorders with genetic implications.

Reference:

- *Guidelines for Clinical Genetic Services for the Public's health (Council of Regional Networks for Genetic Services – CORN) 1997:* <http://genes-r-us.uthscsa.edu/resources/pdf/geneticguidelns.pdf>

SACGHS

Scientific and technical advances have expanded our knowledge of genetic contributions to disease and have made possible the development of **genetic tests** that are capable of diagnosing current disease, assessing the risk of future disease and enabling treatment to be tailored to individual genetic variation.

Genetic/genomic tests and technologies - processes or methods used to analyse human DNA, RNA, genes, chromosomes, proteins or metabolites that detect mutations, chromosomal changes, karyotypes, phenotypes and/or expression pattern variation.

Genetic/genomic technologies are applied to tests for germline, inherited, and/or acquired variations in the genome, transcriptome and proteome. Genetic tests generally focus on testing one or a few genes, whereas genomic tests assess larger numbers of genes and sequences up to the context of the entire genome. Throughout this report, use of the terms “genetic test”, “genetic technology”, or some variation thereof implies inclusivity of all genetic and genomic technologies.

Historically, genetic tests have been used to identify germline or heritable variations in an individual’s genome, whether analysing DNA, RNA or proteins. Currently, the term “genetic test” is used more broadly to refer to any test performed using molecular biology methods to test DNA or RNA, including germline, heritable, and acquired somatic variations. As we advance toward genomic medicine, with acquired somatic variations evaluated in the context of an individual’s entire genome variations, the definition of a genetic test will become even broader. Therefore although this report focuses on genetic tests and services with a narrower definition, it is SACGHS’s intention that lessons learned from genetic tests and services be applied to future innovation in clinical care developed using genetic/genomic technologies involving germline inherited and acquired alterations. However, because tests for germline heritable variations have more implications for all blood relatives of an individual patient compared with somatic acquired variations, in some contexts, including but not limited to science policy, testing oversight, and ethical contexts, the narrower definition of a genetic test as a test for a germline and/or heritable alteration, and not for somatic variants, should be used.

Genetic/genomic tests can be used to diagnose a disease, predict future disease, predict risk or susceptibility to disease, direct clinical management, identify carriers of genetic mutations and establish prenatal or clinical diagnosis or prognosis in individuals, families or populations. Genetic/Genomic tests may be used, for example, in preimplantation diagnosis and newborn screening.

Predictive testing determines the probability that a healthy individual might develop a certain disease in the future.

Pharmacogenetic/pharmacogenomic tests are used to determine the likelihood of a person being responsive to a particular drug and/or having an adverse event.

(Genetic/genomic technologies used for nonmedical purposes such as forensic identification or establishing paternity or familial relationships are not considered in this report)

Reference:

- *Coverage and Reimbursement of Genetic Tests and Services – Report of the Secretary’s Advisory Committee on Genetics, Health and Society – February 2006 (SACGHS)*
Department of Health and Human Services – USA
http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf

Medical Pathologists Organizations

College of American Pathologists (CAP)

CAP has defined genetic tests as those which provide information used for diagnosing or predicting an inherited condition or carrier trait. The term "genetic tests" would properly include those used to detect an inherited susceptibility or resistance to a disease. CAP believes that a narrow definition is necessary to target exactly those tests which will generate information that is important enough clinically to warrant counseling patients and their family members as to the risks of diseases. CAP restricts the term "genetic tests" to those that detect classic hereditary disorders that are inherited when a mutation in DNA is transmitted from one generation to another; for example, inheritance of a mutation in the BRCA-1 gene conferring predisposition to breast and ovarian cancer. We would exclude tests, even those that are DNA-based, which target acquired or somatic mutations.

CAP has defined genetic tests as those that are used to detect an inherited condition and that generate information that warrants counseling of patients and their family members. Excluded from this definition are those tests that detect genetic abnormalities that represent acquired or somatic mutations, such as with most cancers. It is worrisome that a broad interpretation of Section 79-I could include tests for acquired mutations (e.g. Her 2/neu) under the ambiguous definition of a genetic test as testing for a "genetic variation linked to a...disability in the individual..."

AMP continues to support the limitation in the definition of a genetic test to inheritable germline variations, and not including somatic variations. If a genetic test is more broadly defined as any molecular biology-based test, then there needs to be a distinction that allows for the discussion of the ethical, social, and regulatory issues specific to inheritable genetic tests, separate from testing for somatic mutations, or DNA and RNA-based infectious disease testing, which do not carry the same ethical and social concerns. We realize that this distinction may not be relevant to the Coverage and Reimbursement Report, but it may be relevant to future reports of the SACGHS.

One specific concern is the inclusion of pharmacogenetics testing in this discussion, since this testing identifies allelic variants that are not associated with disease, but only affect drug metabolism. Only in the presence of an external challenge (drug) will health risks be apparent

References:

- *Paul Bachner, FCAP President: Public Comments on Preliminary Conclusions and Recommendations on Oversight (p.28), 24 May 2000:*
<http://www4.od.nih.gov/oba/sacgt/appendixB.pdf#search=%22%E2%80%A2%09Paul%20Bachner%2C%20FCAP%20President%2C%2024%20May%202000%22>
- *Quality Assurance Standards for Genetic Testing, 8 March 2004:*
http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtl%7BactionOverride%7Fportlets%7FcontentViewer%7Fshow&_windowLabel=cntvwrPtl%7BactionForm.contentReference%7D=statline%7Fgenetic_tests.html&_state=maximized&_pageLabel=cntvwr%7F
- *Public Comment from the Association for Molecular Pathology presented by Mary Steele Williams, 1 March 2005) [AMP comments on Proposed Best Practices for the Licensing of Genomic Inventions - Secretary's Advisory Committee on Genetics, Health and Society*
<http://72.14.221.104/search?q=cache:7MD0H4dAGHwJ:www.amp.org/SACGHS/SACGH%7FS-030105.doc+Public+Comment+from+the+Association+for+Molecular+Pathology+presented+by+Mary+Steele+Williams&hl=en&gl=uk&ct=clnk&cd=1>
- *Comments on the Draft Coverage and Reimbursement, Mark A. Lovell, President, Association for Molecular Pathology, 6 May 2005:*
<http://amp.org/SACGHS/AMPComments.doc>

Ethics Professionals Organizations

...

Ethics Organizations

Nuffield Council for Bioethics

Genetic test - A test to detect the presence or absence of, or change in, a particular *gene* or *chromosome*. This can be done directly, by analyzing the *DNA* of an individual, or indirectly, by examining the products of their *DNA*, such as *RNA* or *proteins*. In some cases, the presence or absence of particular *genes* can be determined by consideration of the family history of an individual, or simply by clinical observation.

Pharmacogenetic test - A test to detect the presence or absence of, or change in, a particular gene or chromosome in order to predict response to a medicine. The test could examine inherited DNA or somatic mutations in DNA.

Pharmacogenetics - The study of the effects of genetic differences between individuals in their response to medicines. These differences may or may not be related to the disease being treated. The research involves comparing the genotypes of individuals who have different responses to a medicine.

Pharmacogenomics - This term is not distinctly differentiated from pharmacogenetics, but implies the examination of whole genomes or substantial numbers of genes in order, for example, to identify putative targets for medicines or to identify large-scale differences in the patterns of gene expression in response to chemical compounds.

Reference:

- *Pharmacogenetics – Ethical Issues*, NCB Sept. 2003:
http://www.nuffieldbioethics.org/go/browseablepublications/pharmacogenetics/report_91.html

NUFFIELD COUNCIL ON BIOETHICS

All forms of **genetic test** aim to identify particular genetic characteristics but approach this in different ways.

Chromosomal tests (cytogenetics) - Microscopic examination of chromosomes from cells in blood, amniotic fluid or fetal tissue may be used to detect the chromosomal changes mentioned above. Until recent years it was only possible to detect large alterations on a chromosome involving many genes, but new techniques are making it possible to detect much smaller defects, allowing disorders involving only a small amount of genetic material to be recognized.

Tests for disorders involving a single gene - Genes cannot be seen using the microscope, so in the past tests for single gene disorders have been largely indirect, involving what the gene produces (protein), or another substance affected by it, rather than the gene itself (see paragraph 2.15). Since the protein is still unknown for the majority of genes, testing for single gene disorders has been very limited until recently.

Direct tests - A variety of techniques have now been developed for identifying important human genes directly. There are two main approaches:

(i) the gene may be isolated if the product (protein) it normally produces is known. This approach was used for the genes involved with the main blood cell protein haemoglobin (important for tests

involving sickle cell disease and thalassaemias). The genes for some metabolic diseases, where a specific chemical defect involving an enzyme was already known, have also been isolated in this way;

(ii) the gene may be isolated if its position on a chromosome is known (**positional cloning**). This approach is increasingly successful in allowing genes to be isolated even when we know nothing about their function or what protein they normally produce. One reason for this success is that detailed **genetic maps** of the different chromosomes are being produced. This approach not only pinpoints the chromosome region where the gene lies, but can provide **genetic markers** (identifiable pieces of DNA) which lie close to the gene, and can enable an accurate test for a genetic disorder to be made even before the gene itself is isolated.

Indirect (biochemical) tests - These tests detect not the gene itself, but some aspect of its function. The most nearly direct are for the specific protein that the gene produces. In a genetic disorder tests may show that the protein is not being made or is present in reduced amount; or it may be altered so that it does not function adequately. Such tests are still important, for example, for abnormalities of haemoglobin (in thalassaemia or sickle cell disease).

Carrier - A healthy individual who has both an abnormal and a normal copy of a pair of genes for a **genetic disorder** or character or characteristic. A carrier of a gene for a recessive disorder will usually remain unaffected through life.

Genetic disease or disorder - Conditions which are the result of alterations in the genetic make-up of an individual.

They may be the direct consequences of defects in single **genes (mutations)**; or in whole **chromosomes**, parts of which may be lost, duplicated or misplaced; or from the interaction of multiple genes and external factors.

Genetic fingerprinting - A technique which enables genetic relationships between close relatives, or the identity of individuals to be established - usually beyond reasonable doubt.

Genetic map - The body of information on the relative positions of **genes** on **chromosomes**. Much of the effort of the **Human Genome Project** is directed towards mapping chromosomes.

References:

- *GENETIC SCREENING ETHICAL ISSUES (December 1993)*
http://www.nuffieldbioethics.org/go/ourwork/geneticscreening/publication_297.html

ACGT (Advisory Committee on Genetic Testing) – Department Health, UK

Genetic Test - A test to detect the presence of, or alteration in, a particular gene or chromosome

Genetic Testing - Testing used to detect the presence of, or alteration in, a gene, chromosome or a gene product, in relation to a genetic disorder.

Reference:

- *Code of Practice and Guidance on Human Genetic Testing Services Supplied Direct to the Public, Sep. 1997:*
<http://72.14.221.104/search?q=cache:7MD0H4dAGHwJ:www.amp.org/SACGHS/SACGH S-030105.doc+Public+Comment+from+the+Association+for+Molecular+Pathology+present ed+by+Mary+Steele+Williams&hl=en&gl=uk&ct=clnk&cd=1>

- *Genetic Testing for Late-Onset Disorders, July 1998:*
<http://www.publications.doh.gov.uk/pub/docs/doh/lodrep.pdf#search=%22genetic%20testing%20for%20late%20onset%20disorders%20genetic%20alliance%22>

Insurance Organizations

National Association of Health Underwriters (NAHU)

NAHU's Position: NAHU supports the prohibition of the use of genetic information in the health insurance underwriting process, provided that the definition of genetic information is limited to DNA, RNA and related gene testing. [Our position statement](#) explains our views in greater detail, but in general we feel that expanding the definition of genetic information to include an individual's personal and family medical history will interfere with normal individual health insurance policy underwriting process. We are concerned that the result of such interference will be higher premiums for the consumer and a greater number of uninsured people.

NAHU supports a definition of **genetic information** that is limited to DNA and related gene testing done for the purpose of predicting risk of disease in asymptomatic or undiagnosed individuals, and which clearly excludes such items as age, gender, and information from physical exams and lab work including items like cholesterol tests, performed to detect symptoms, clinical signs, or a diagnosis of disease.

Reference:

- *Genetic Discrimination:* <http://www.nahu.org/legislative/genetic/index.cfm>
- *Position on Genetic testing 2003* http://www.nahu.org/legislative/Genetic_position.pdf

Patient/Consumers Organizations

EuropaBio

Within this document we define human medical **genetic testing** as the use of a DNA sequence or structure, in direct DNA-based tests or in any other test that provides DNA-specific health information (including cytogenetic and biochemical tests).

Genetic testing by strict definition is any test that yields information about inherited characteristics based on the analysis *in vitro*, (in a laboratory, i.e. outside the human body), of structural properties of DNA, or of RNA, or proteins or other substances (which are a direct consequence of the underlying DNA structure). The broader use of the term, genetic testing, also includes testing of structural properties of DNA or RNA in specific cells, tissues or organs which are acquired during an individual's lifetime, e.g. in certain forms of cancer. The broader use of the term genetic testing is used in this paper.

Medical genetic testing is the application of genetic testing to derive information relevant to health care, as it relates to disease risk prediction, disease diagnosis, disease treatment, and reproductive health.

Non-medical genetic testing comprises the application of genetic testing for all purposes that do not involve a medical decision, mainly for the purpose of identification, e.g. paternity and forensic testing, and identification of the presence of animal and plant materials in foods or other materials

Reference:

- *Human Medical Genetic Testing. A EuropaBio Position Paper (The European Association for BioIndustries-May2004): http://www.europabio.org/articles/article_317_EN.doc*

Genetic Alliance

Carrier testing - The goal of these tests is identifying individuals, or couples, who carry a particular recessive gene allele that would result in a particular genetic condition if a child were to inherit copies of this allele from both parents. "Carrier testing is designed for healthy people who have no symptoms of disease, but who are known to be at high risk of being a carrier for the disorder" (NCI, 1995, p.25)

Genetic testing - examining a sample of blood or other bodily fluid or tissue for biochemical, chromosomal, or genetic markers that indicate the presence or absence of genetic mutations or genetic conditions, including evidence of carrier status or a predisposition to developing a condition which has multifactorial components.

Gene therapy - this refers to a medical procedure that treats a disorder by replacing the faulty gene.

PGD (Pre-implantation Genetic Diagnosis) - this is the testing of a fertilized egg for genetic disorders after in-vitro fertilization, before placing the embryo in the uterus for development.

Predictive gene tests - tests to identify gene mutations that may make a person susceptible to certain diseases or disorders.

Prenatal diagnosis - examining fetal cells taken from the amniotic fluid, the primitive placenta (chorion), or the umbilical cord for biochemical, chromosomal, or gene alterations.

Carrier - an individual who possesses one copy of a mutant allele that causes disease only when two copies are present. Although carriers not affected by the disease, two carriers can produce a child who has the disease. (National Human Genome Research Institute, National Institutes of Health (2000) "Glossary of Genetic Terms")

Pharmacodynamics - the study of how drugs act on the body. (National Institute of General Medical Sciences. National Institutes of Health (1993) "Medicines by Design: The Biological Revolution in Pharmacology" NIH Publication No. 93-474)

Pharmacogenetics - The study of how people respond differently to medicines due to their genetic inheritance. The term has been pieced together from the words pharmacology (the study of how drugs work in the body) and genetics (the study of how traits are inherited). An ultimate goal of pharmacogenetics is to understand how someone's genetic make-up determines how well a medicine works in his or her body, as well as what side effects are likely to occur. In the future, advances gleaned from pharmacogenetics research will provide information to guide doctors in getting just enough of the right medicine to a person--the practice of "personalized medicine."

(National Institute of General Medical Sciences. National Institutes of Health (2000) "What is Pharmacogenetics?" Information)

Gene Therapy - the introduction of a normal, functioning gene into a cell in which that gene is missing or defective. (National Institute of General Medical Sciences. National Institutes of Health (1993) "Medicines by Design: The Biological Revolution in Pharmacology" NIH Publication No. 93-474.)

Genetic Counseling - a short-term educational counseling process for individuals and families who have a genetic disease or who are at risk for such a disease. Genetic counseling provides patients with information about their condition and helps them make informed decisions. (National Human Genome Research Institute, National Institutes of Health (2000) "Glossary of Genetic Terms")

Genetic Screening: Testing a population group to identify a subset of individuals at high risk for having or transmitting a specific genetic disorder. (National Human Genome Research Institute, National Institutes of Health (2000) "Glossary of Genetic Terms")

Reference:

- *Alphabet Soup: Genetics for Genetics Consumers - Terms and Acronyms:*
http://www.geneticalliance.org/ws_display.asp?filter=resources_alphabet_soup

Genetic Interest Group (GIG)

'Genetic information' is taken to mean any data of clinical relevance to the genetic status of an affected or at risk individual. No distinction is made between, for example, family information arising from a counseling session, phenotypic observations made during clinical evaluation or laboratory test results.

Medical genetics is an integrated service comprising clinical genetics and laboratory genetics (molecular genetics, cytogenetics and biochemical genetics). Medical genetics overlaps with most other specialities since mutant genes and chromosomal abnormalities may have pathogenic effects in any organ system and at any age.

References:

- *Confidentiality Guidelines* http://www.gig.org.uk/docs/gig_confidentiality.pdf
Human Rights Agencies

American Civil Liberties Union (ACLU)

ACLU recommends that the appropriate definition of genetic information should cover: "Any information about genes, gene products, or inherited characteristics that may derive from the individual or a family member. This includes, but is not limited to, information regarding carrier status, information regarding an increased likelihood of future disease or increased sensitivity to any substance, information derived from laboratory tests that identify mutations in specific genes or chromosomes, physical medical examinations, family histories, requests for genetic services or counseling, tests of gene products, and direct analysis of genes or chromosomes." (National Taskforce on Civil Liberties in the Workplace)

Reference:

- *Testimony Presented to the Senate Labor and Human Resources Committee (1998):*
http://www.workrights.org/issue_genetic/gd_house_testimony.html

Disabled Peoples International

Gene Therapy

Gene therapy involves making changes to the gene in order to treat a condition.

This could be done by adding a working copy of the faulty gene, by developing genetic-based drug therapy or, as has already been unsuccessfully tried, by imparting a virus into the faulty gene.

There are two kinds of gene therapy:

- Somatic gene therapy - alters the individual gene level.
- Germ line therapy (or human genetic engineering) – alters all the cells in the body, including the reproductive cells and therefore can be passed on through reproduction. This therapy is prohibited in most countries at the moment.

References:

- *Disabled People Speak on the New Genetics*
DPI EUROPE POSITION STATEMENT ON BIOETHICS AND HUMAN RIGHTS

<http://freespace.virgin.net/dpi.europe/downloads/bioethics-english.pdf>
(November 2000)

Other Organizations

Human Genome Project (HGP)

Gene tests (also called DNA-based tests), the newest and most sophisticated of the techniques used to test for genetic disorders, involve direct examination of the DNA molecule itself. Other genetic tests include biochemical tests for such gene products as enzymes and other proteins and for microscopic examination of stained or fluorescent chromosomes. Genetic tests are used for several reasons, including: carrier screening, which involves identifying unaffected individuals who carry one copy of a gene for a disease that requires two copies for the disease to be expressed; preimplantation genetic diagnosis; prenatal diagnostic testing; newborn screening; presymptomatic testing for predicting adult-onset disorders such as Huntington's disease; presymptomatic testing for estimating the risk of developing adult-onset cancers and Alzheimer's disease; confirmational diagnosis of a symptomatic individual; forensic/identity testing.

Reference:

- *Human Genome Project Information: Gene Testing:*
http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetest.shtml

Gene Tests (funded and supported by University of Washington, Seattle, National Library of Medicine, NIH, National Human Genome Research Institute, NIH)

What is Genetic Testing?

A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites in order to detect alterations related to a heritable disorder. This can be accomplished by directly examining the DNA or RNA that makes up a gene (direct testing), looking at markers co-inherited with a disease-causing gene (linkage testing), assaying certain metabolites (biochemical testing), or examining the chromosomes (cytogenetic testing). Selected methodology terms are used in the GeneTests Laboratory Directory. Although genetic testing shares some features in common with other kinds of laboratory testing, in many ways it is unique and requires special considerations.

Points to consider:

- _ Genetic testing may be used for medical management and for personal decision-making.
- _ Genetic test results usually apply not only to the patient but also to other family members.
- _ Genetic testing may be performed in the context of a genetics consultation and should include informed consent, test interpretation, and follow-up medical and psychosocial services as indicated.
- _ Because most genetic disorders are rare, genetic testing is often done only by specialized laboratories.
- _ Intense research efforts in molecular genetics result in the rapid development and availability of new genetic tests; therefore, healthcare providers need to continuously update their knowledge.
- _ In order for genetic testing to yield meaningful results:

- _ multiple test methodologies may be required
- _ other family members may need to be tested
- _ a genetics consultation may be appropriate

These services will entail additional costs.

Diagnostic testing is used to confirm or rule out a known or suspected genetic disorder in a symptomatic individual.

Points to consider:

- DNA testing may yield diagnostic information at a lower cost and with less risk than other procedures ([Clinical Example](#)).
- Diagnostic testing is appropriate in symptomatic individuals of any age ([Clinical Example](#)).
- Confirming a diagnosis may alter medical management for the individual ([Clinical Example](#)).
- Diagnostic testing of an individual may have reproductive or psychosocial implications for other family members as well ([Clinical Example](#)).
- Establishing a diagnosis may require more than one type of genetic test ([Clinical Example](#)).
- DNA testing may not always be the best way to establish a clinical diagnosis ([Clinical Example](#)).

Predictive testing is offered to asymptomatic individuals with a family history of a genetic disorder. Predictive testing is of two types: presymptomatic (eventual development of symptoms is certain when the gene mutation is present, e.g., Huntington disease) and predispositional (eventual development of symptoms is likely but not certain when the gene mutation is present, e.g., breast cancer).

Points to consider:

- Predictive testing is medically indicated if early diagnosis allows interventions which reduce morbidity or mortality ([Clinical Example](#)).
- Even in the absence of medical indications, predictive testing can influence life planning decisions ([Clinical Example](#)).
- Because predictive testing can have psychological ramifications, careful patient assessment, counseling, and follow-up are important ([Clinical Example](#)).
- Many laboratories will not proceed with predictive testing without proof of informed consent and genetic counseling.
- Identification of the specific gene mutation in an affected relative or establishment of linkage within the family should precede predictive testing ([Clinical Example](#)).
- Predictive testing of asymptomatic children at risk for adult onset disorders is strongly discouraged when no medical intervention is available ([ACMG Policy Statement](#)).

Carrier testing is performed to identify individuals who have a gene mutation for a disorder inherited in an autosomal recessive or X-linked recessive manner. Carriers usually do not themselves have symptoms related to the gene mutation. Carrier testing is offered to individuals who have family members with a genetic condition, family members of an identified carrier, and individuals in ethnic or racial groups known to have a higher carrier rate for a particular condition.

Points to consider:

- Identifying carriers allows reproductive choices ([Clinical Example](#)).
- Genetic counseling and education should accompany carrier testing because of the potential for personal and social concerns ([Clinical Example](#)).
- Molecular genetic testing of an affected family member may be required to determine the disease-causing mutation(s) present in the family ([Clinical Example](#)).
- In some situations, DNA testing may not be the primary way of determining carrier status ([Clinical Example](#)).
- Carrier testing can improve risk assessment for members of racial and ethnic groups more likely to be carriers for certain genetic conditions ([Clinical Example](#)).

Prenatal testing is performed during a pregnancy to assess the health status of a fetus. Prenatal diagnostic tests are offered when there is an increased risk of having a child with a genetic condition due to maternal age, family history, ethnicity, or suggestive [multiple marker screen](#) or [fetal ultrasound examination](#). Routine [prenatal diagnostic test procedures](#) are amniocentesis and chorionic villus sampling (CVS). More specialized procedures include placental biopsy, periumbilical blood sampling (PUBS), and fetoscopy with fetal skin biopsy.

Points to consider:

- A laboratory that performs the disease-specific test of interest must be identified before any prenatal diagnostic test procedure is offered ([Clinical Example](#)).
- All prenatal diagnostic test procedures have an associated risk to the fetus and the pregnancy; therefore, informed consent is required, most often in conjunction with genetic counseling.
- In most cases, before prenatal diagnosis using molecular genetic testing can be offered, specific gene mutation(s) must be identified in an affected relative or carrier parent(s) ([Clinical Example](#)).
- Prenatal testing for adult-onset conditions is controversial. Individuals seeking prenatal diagnosis for these conditions should be referred to a professional trained in genetic counseling for a complete discussion of the issues ([ACMG Policy Statement](#)).

Preimplantation testing is performed on early embryos resulting from *in vitro* fertilization in order to decrease the chance of a particular genetic condition occurring in the fetus. It is generally offered to couples with a high chance of having a child with a serious disorder. Preimplantation testing provides an alternative to prenatal diagnosis and termination of affected pregnancies.

Points to consider:

- Preimplantation testing is only performed at a few centers and is only available for a limited number of disorders.
- Preimplantation testing is not possible in some cases due to difficulty in obtaining eggs or early embryos and problems with DNA analysis procedures.

□ Due to possible errors in preimplantation diagnosis, traditional prenatal diagnostic methods are recommended to monitor these pregnancies.

□ The cost of preimplantation testing is very high and is usually not covered by insurance.

Newborn screening identifies individuals who have an increased chance of having a specific genetic disorder so that treatment can be started as soon as possible.

Points to consider:

□ **Newborn screening programs** are usually legally mandated and vary from state to state.

□ Newborn screening is performed routinely at birth, unless specifically refused by the parents in writing. Screening tests are not designed to be diagnostic, but to identify individuals who may be candidates for further diagnostic tests (**Clinical Example**).

□ Many parents do not realize that newborn screening has been done (or which tests were included), even if they signed a consent form when their child was born.

□ Education is necessary with positive screening results in order to avoid misunderstandings, anxiety and discrimination (**Clinical Example**).

References:

- *What is Genetic Testing?* www.genetests.org (Revised 3-19-04)
- *Uses of Genetic testing* www.genetests.org (Revised 3-19-04)

President's Commission for the study of ethical problems in Medicine and Biomedical and behavioral research Feb 1983

Cytogenetics - The study of the structure and function of chromosomes.

Germ cell - A sperm or an egg, or a formative stage of either.

Somatic cell - One of the cells composing body tissues and body organs other than a germ cell.

References:

Screening and Counselling for Genetic Conditions

The ethical, social and legal implications of Genetic Screening, Counselling and Education Programs http://bioethics.gov/reports/past_commissions/geneticscreening.pdf

Parliamentary Office of Science and Technology (POST)

Despite no agreed definition, **genetic testing** generally refers to more direct testing, such as analysis of the structure of DNA (cytogenetic testing) or changes within the DNA sequence itself (molecular testing).

Tests currently available

Genetic tests are used both before and after the appearance of disease symptoms. Tests to diagnose rare inherited disorders, such as cystic fibrosis and Huntington's disease, make up the vast majority of current services. Testing techniques can now also be used to examine non-inherited conditions, for example, analysing acquired changes in cancer tumours. Current uses of genetic tests include:

- diagnosing individuals with rare inherited disorders, where individuals inheriting a specific genetic change will nearly always develop the associated disorder;
- identifying individuals with an inherited genetic change making them at high risk of a small subtype of some cancers, such as breast and bowel cancer;
- characterising leukaemias and tumours by analyzing acquired genetic changes;
- prenatal / neonatal screening of a foetus or newborn baby for conditions such as Down's syndrome;
- examining whether genes are functional, as in tests for blood diseases such as sickle cell disease;
- carrier testing to test for the presence of a genetic change in healthy individuals (such as Fragile X, an inherited learning difficulty) which may have implications for children or their relatives.

Pharmacogenetics

- potential: pharmacogenetics examines the relationship between genetic variation and an individual's response to medicine. It potentially marks a departure from the "one size fits all" approach to prescribing, to one where the results of a pre-prescription genetic test guide subsequent drug selection and dosage levels.

- challenges: age, gender and drug interactions also influence the effect of medicines. Stratifying patient groups according to their genetic profile raises some clinical, regulatory and ethical questions. (Webster et al, *Nature Reviews Genetics*, 5, No. 9 (in Press))

Pharmacogenetics will not impact on all drugs and early identification of relevant targets is needed.

- prospects: many clinical geneticists expect pharmacogenetics to drive the future expansion of genetic testing services. However, a better evidence base is needed and it remains uncertain how the interests of all relevant stakeholders (industry, clinicians, regulators and patients) can be met.

Preimplantation Genetic Diagnosis (PGD) uses in vitro fertilisation (IVF) to create embryos, tests one or two cells from each embryo for the specific genetic abnormality and identifies unaffected embryos for transfer to the uterus. The approach through PGD assists couples at risk of an inherited disorder to avoid the birth of an affected child. The range of genetically transmissible conditions for which testing is possible is continually increasing and examples licensed by the Human Fertilisation and Embryology Authority for PGD include fragile X, muscular dystrophy, Huntington's disease.

References:

- NHS GENETIC TESTING - Parliamentary Office of Science and Technology
<http://www.parliament.uk/documents/upload/POSTpn227.pdf>

- *Preimplantation Genetic Diagnosis (PGD) – Guiding Principles for Commissioners of NHS services*
<http://www.cadasitrust.org/assets/pdf/PGDNHSGuidelines.pdf>

Research Funding Agencies

MRC, UK

Pre-implantation genetic diagnosis - A screening procedure in which a recognised practitioner removes one or two cells from an embryo to test for specific genetic disorders/characteristics before proceeding with embryo transfer.

References:

- *Assisted Reproduction – a safe and sound future, 2004*
http://www.mrc.ac.uk/prn/pdf-assisted_reproduction.pdf

Pharmaceutical Industry

Association of the British Pharmaceutical Industry (ABPI)

Pharmacodynamics The study of the effects of the drug on the body and the mechanisms by which it acts (what the drug does to the patient).

Pharmacogenetics The branch of biology that looks at how an individual's genes affect the way that they react to a particular drug.

Genetic Testing - To detect the presence or absence of, or alteration in, a particular gene, chromosome or a gene product, in relation to a genetic disorder.

NOTE: ACGT's definition of a genetic test is not restricted to a DNA or chromosome test. Many 'biochemical' tests will indicate that a person is likely to have a genetic or familial disorder and these should be treated by RECs as 'genetic tests'.

(a) **Diagnostic Genetic Testing** – Use of genetic testing in a symptomatic individual to aid in their diagnosis, treatment and management.

(b) **Presymptomatic Genetic Testing** – primarily carried out in healthy or asymptomatic individuals to provide information about that individual's future health, with respect to specific inherited diseases. Such a test result may indicate that the individual has a high likelihood of developing the disorder or of excluding it.

Presymptomatic testing is most frequently used in late onset autosomal dominant disorders such as Huntington's Disease.

(c) **Susceptibility Testing** – which provides information about the genetic component in a multifactorial disorder.

(d) **Carrier Testing** – used to detect individuals who possess a single copy of a gene which follows an autosomal recessive pattern of inheritance (see below). Such an individual will not normally develop any disease or disorder but may pass on the gene to his or her offspring.

References:

- *Introduction to the Work of Research Ethics Committees – What Is Involved in Being on a Research Ethics Committee Considering Human Pharmacology*
http://www.abpi.org.uk/publications/pdfs/ethics_web.pdf
- *Personalized Medicine – The Emerging Pharmacogenomics Revolution*

<http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf>

Roche

Genetic testing can refer to several different things. In general, genetic testing is used to learn about human genes. In some cases, we can analyze the parts of a person's genome that relate to their health or the health of their children. Patients need to be aware that genetic testing does have limits. Some mutations may not be identified by tests at present, and for many diseases, genes are only one risk factor and therefore may not tell the whole story.

Genetic testing can also refer to tests on the DNA of infectious agents. These agents may be found in humans or in the environment. The hepatitis B virus is an example of an infectious agent.

Finally, **genetic testing** also refers to using DNA to identify someone. Examples are tests for paternity (fatherhood) and for matching blood and hair found at a crime scene.

Pharmacogenetics is the study of the genetic basis for differences between people in the way they respond to drugs. This information may help in drug research and development. It may also be helpful in prescribing effective drugs in the right amounts to various patients.

Pharmacogenomics is the study of how all of a person's genes (their genome) may affect how they respond to certain drugs.

What are the medical uses of genetic tests?

Medical uses of genetic tests include finding inherited diseases, such as Huntington's disease and sickle cell anemia. People who have the genes for these disorders have a high risk of getting the disease. Therefore, tests may also be used as possible preventative measures for persons at risk.

Tests for some disorders are done when the mother is pregnant or soon after the baby is born. These include Fragile X Syndrome and Down syndrome. (Both these genetic disorders can cause mental retardation.) Genetic testing is also used to advise prospective parents of the risk of having a baby with an inherited disease, such as cystic fibrosis. This type of testing is called carrier testing.

Newborns are also routinely screened for some inherited disorders that may keep them from using certain nutrients. These disorders can lead to severe disabilities if they aren't treated soon after birth. Examples of these disorders include phenylketonuria (PKU), hyperthyroidism and biotinidase deficiency.

Another example is a disorder that causes iron to build up in the body. It is called familial hemochromatosis. Iron build-up can be fatal. Members of families with a history of this disorder can now be tested for the genetic defect. If it is present, they can be followed closely to see if they develop the disease (not all do). If they do get symptoms, they can be treated.

In the future, genetic testing may be used even more to guide doctors and patients in designing the best treatments for each person enabling early treatment and prevention. For example, research is already underway to better understand how genes affect the way a person responds to medications.

What are the non-medical uses of genetic tests?

Genetic tests are commonly used to determine the identity of a person. They are used to identify accident victims. Police use them to test whether tissue (such as blood or hair) left at a crime scene matches up with the suspect's DNA. Genetic tests can also be used to determine paternity

and other family relationships. These tests don't tell any other medical information about the person, though.

What is the impact of genetic testing within Roche?

Genetic testing is done in a laboratory, using cells gathered from inside the cheek or a blood sample. This is called diagnostic or molecular testing.

Genetic testing is also used to advise prospective parents of the risk of having a baby with an inherited disease, such as cystic fibrosis. This type of testing is called carrier testing.

References:

- *Improving healthcare through genetics, genomics and biomarkers _roche*
<http://www.roche.com/sci-improvhealth.pdf>
- *Genetic test in research & healthcare_roche*
<http://www.roche.com/sci-genetictesting.pdf>

Genzyme

Genetic Counselor: A health care professional trained in the field of genetics who reviews a person's family and medical history and determines the risks for possible diseases or conditions. Genetic counselors explain the benefits, risks and limitations of testing options and procedures and facilitate patient decisionmaking regarding these options.

References:

- Genzyme Glossary of terms
http://www.genzymegenetics.com/hcp/prenatal/resources/gene_p_hcp_pre_resources_glos.asp