The wide variation of definitions of genetic testing in international recommendations, guidelines and reports

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Received: 12 January 2012 / Accepted: 6 February 2012 / Published online: 25 February 2012
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Abstract In spite of being very commonly used, the term *genetic testing* is debatable and used with several meanings. The diversity of existing definitions is confusing for scientists, clinicians and other professionals, health authorities, legislators and regulating agencies and the civil society in general, particularly when genetic testing is the object of guidelines or

Electronic supplementary material The online version of this article (doi:10.1007/s12687-012-0084-2) contains supplementary material, which is available to authorized users.

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legal documents. This work compares definitions of genetic testing found in recommendations, guidelines and reports from international institutions, policy makers and professional organizations, but also in documents from other stakeholders in the field, as the pharmaceutical industry, insurers, ethics bodies, patient organizations or human-rights associations. A systematic review of these documents confirmed the extreme variability existing in the concepts and the ambiguous or equivocal use of the term. Some definitions (narrower) focus on methodologies or the material analysed, while others (broader) are information- or context-based. Its scope may range from being synonymous of just *DNA analysis*, to *any test that yields genetic data*. *Genetic testing* and *genetic information*, which may be derived from a range of medical exams or even family history, are often used interchangeably. *Genetic testing* and *genetic screening* are sometimes confused. Human *molecular genetics* (a discipline) is not always distinguished from *molecular biology* (a tool). Professional background, geographical context and purpose of the organizations may influence scope and usage. A common consensus definition does not exist. Nevertheless, a clear set of precise definitions may help creating a common language among geneticists and other health professionals. Moreover, a clear context-dependent, operative definition should always be given.

Keywords Definition · Genetic test · Genetic information · Screening · Soft law · EuroGentest

Introduction

Genetic tests have been used for several decades, but their applications have increased enormously as the human genome was being deciphered. While other promises of the

Human Genome Programme, as *personalized medicine*, still lay far ahead, the number and volume of genetic tests increased dramatically since 1998 (Ibarreta et al. 2004) while substantially changing our medical practice (particularly in the fields of medical genetics, reproductive medicine and oncology).

At a time when whole-exome and whole-genome sequencing are emerging as daily medical applications, the interpretation of the term *genetic testing* is still debatable and a matter of confusion, due to its many possible meanings and variable usage. During this process, we noticed that definitions of “genetic testing” may be centred on the material used (e.g. DNA, chromosomes) or the methods applied (e.g. DNA analysis, cytogenetics), or based on the context and purpose of the test or the information derived (Sequeiros, 2010).

The same term may extend from the narrow definition of a DNA-based laboratory analysis, to the much broader concept of *genetic information* that may be derived by many different methods (including a wide range of conventional subsidiary medical exams or, on instances, a physical examination, or a family history). This wide diversity of existing definitions of *genetic testing* (and related terms) is confusing to geneticists and other professionals, as well as health authorities, legislators and regulating agencies, the public and the media and will thus bear on the quality of democracy.

The European Commission (EC) invited a multidisciplinary, independent, expert group to discuss genetic testing, through 2003–2004, including scientists and academicians with different backgrounds (law, philosophy, ethics and medicine), representatives from the industry and patient organisations, from various national backgrounds within Europe (EC Expert Group 2004a). The group agreed on the “25 Recommendations on the Ethical, Legal and Social Implications of Genetic Testing”, which address the implementation of genetic testing in healthcare systems and its use as a research tool (EC Expert Group 2004b).

As its first recommendation, this document established the need to define explicitly what is meant by *genetic testing*, whenever the term is used in *any official statement*, but also the need to *develop globally* (by *all respective public and private bodies involved*) a *consensus definition*. Those bodies were to include the World Health Organisation (WHO), the Organisation for Economic Cooperation and Development (OECD), the EC, the International Federation of Human Genetic Societies (IFHGS) and the International Conference on Harmonisation (ICH). The recommendation also stated that the EC should take initiative. The need for an agreement of a common definition was also identified at an informal network of the European Union (EU27) Member States, which met twice in Brussels, as a follow-up of the EC expert group. This network led to an EU-

wide survey on national legislation and activities in genetic testing (Matthiessen-Guyader 2005).

As a result, “EuroGentest—Harmonizing Genetic Testing in Europe”, an EC-funded FP6 Network of Excellence (www.eurogentest.org), was asked to prepare such a *consensus definition*. A dedicated *work-package* within EuroGentest Unit 3 (“Clinical Genetics, Community Genetics and Public Health”) started to compare definitions actually used by a number of organizations, including the ones mentioned by the EC Expert Group (2004b) and others.

This work led to two preliminary background documents on definitions of genetic testing contained in international recommendations and professional guidelines (Sequeiros and Guimarães 2008) and in legal documents (Varga and Sequeiros 2008). A survey of EuroGentest participants and users of its website was also conducted for their interpretations and opinions about the feasibility of having a consensus (Pinto-Basto et al. 2010). A study of the definitions of genetic testing in international and European (EU27 and national Member States) legislation and other legal documents is presented separately [(Varga et al. 2012), this number]. All this provided evidence for the proposal of a decision-framework and a set of definitions to be considered when regulating genetic testing (Sequeiros 2010).

This study derives from the first background document (Sequeiros and Guimarães 2008). Its major goal was to compare the definitions provided in recommendations and reports from international institutions, professional guidelines and other documents from policy makers, patients’ organizations and human rights associations, the pharmaceutical industry, insurers and other stakeholders in the field of genetic testing. It aims at contributing to the discussion about the need and possibility to achieve a consensus definition, as stemming from the recommendation of the EC Expert Group (2004b).

Materials and methods

Search for definitions of genetic testing

We conducted a systematic retrospective review (2005–2011) for existing definitions of genetic testing in documents produced by a number of international institutions, but also many other public and private entities at the academic, clinical, laboratory, industrial, ethical, legal and societal level. Definitions (in English or official translations) were extracted mainly from recommendations, best practice guidelines, statements, reports and other documents from (1) international or transnational and European institutions, (2) national health institutions, regulators and funding agencies, (3) health professional and scientific societies (of genetics and others), (4) pharmaceutical industry and insurers

associations, (5) genetics and other lay associations, (6) human rights associations, public policy and national ethics committees and (7) other genetics-related organizations and programs. The collection was finalized by 31 December 2011.

Methods, sources and purposes of acquiring genetic data

Terms employed (either exactly, synonyms or related terms) to identify and classify definitions related to tests and exams (1) performed in individual subjects at various stages of the life cycle, in families or in the population; (2) studied by different methods; (3) using a variety of genetic and other materials that may provide genetic data information; (4) to detect genetic changes of variable nature; (5) in germinal or somatic cells; (6) for a variety of purposes and different contexts; in (7) medical and non-medical applications (Table 1).

Terms used for the search

Although the focus of this work was on definitions of “genetic testing”, we also considered in this search terms related (such as *genetic information*, *genetic screening*, *genetic counselling*, etc.) and different synonymous or overlapping names for various types and contexts of genetic testing (such as *diagnostic*, *predictive*, *presymptomatic*, *predisposition*, *susceptibility*, *pharmacogenetics*, *carrier*, *heterozygous*, *identity*, *forensic* and *paternity* testing and *prenatal* and *preimplantation* diagnosis); several variations of these terms were also used.

Items covered by definitions of genetic testing

To compare the scope of the different definitions of genetic testing contained in recommendations, guidelines, statements, reports and other documents identified from the institutions and organizations surveyed, the first task of all this work was to list, based on our own experience and common knowledge, all the items that could possibly define the scope of genetic testing; 24 items were identified, regarding (A) the broad purpose of testing: (1) medical applications, (2) biomedical research or (3) human non-medical applications (e.g. forensic genetics or ancestry studies); (B) specific type of testing: (4) diagnostic testing (in affected patients, either for confirmation of a clinical diagnosis or for excluding specific genetics diagnoses), (5) presymptomatic testing predictive for late-onset Mendelian diseases (usually dominant, with high penetrance), (6) disease predisposition–susceptibility tests (claimed to be predictive of genetic predispositions to late-onset complex diseases with multifactorial inheritance), (7) pharmacogenetics (to predict response to therapeutic drugs, including adverse reactions or to adjust drug dosage), (8) carrier testing (detection of heterozygotes for Mendelian recessive diseases (including cascade family

Table 1 Possible sources of human genetic data

1. Target
Embryo
Foetus
Newborn
Children
Adults
Immortalized cell line
Post-mortem material (slides, paraffin blocks, cryopreserved)
Family
Population or population subgroups
2. Method
Cytogenetics (incl. molecular cytogenetics)
Molecular genetics (linkage analysis, sequencing, other methods of mutation detection)
Biochemical genetics
Clinical pathology
Physical phenotyping
Family history
3. Object (chromosomes, genes, gene products and other 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
Pedigree information
Population background or ethnicity
4. Nature of genetic variation
Chromosomal anomalies (numerical, structural)
DNA mutations (pathogenic)
Transcribed gene polymorphisms (normal allelic variants)
Untranscribed variants in DNA (anonymous sequences)
Epigenetic changes (DNA methylation, histone (de)acetylation and methylation)
5. Cell level
Germline (inherited)
Somatic (acquired)
6. Context
Type of disease—Mendelian, mitochondrial, complex inheritance
Health status—affected patients; relatives at risk, prospective parents and other healthy persons
Medical purpose—diagnosis, response to treatment, prognosis, counselling, prevention
Supervision—medical prescription, direct-to-consumer
7. Application (medical and non-medical)
Clinical
Epidemiological and public health
Biomedical research
Population structure
Forensic (civil or criminal identification)
Ancestry

screening), (9) prenatal diagnosis, (10) preimplantation genetic diagnosis (PGD), (11) population (genetic) screening (for the whole population or large population groups at an increased risk, e.g., particular ethnic groups, pregnant women or newborns), (12) paternity testing (or other family relationships, as MZ vs. DZ twins or, rarely, maternity testing), (13) identity testing (often independently of family relationship, either for forensic criminal purposes or civil identification, as with missing persons, unknown human remains or body parts); (C) human genetic diseases and other phenotypes: (14) pathogenic mutations for hereditary (or Mendelian, rare) diseases, (15) complex diseases—genetic (multifactorial) predisposition to common diseases or (16) polymorphic traits (at the DNA, protein or other level) for non-disease traits; (D) origin of mutations: (17) somatic mutations (mainly cancer genetics) vs. inherited (germline) constitutional mutations; (E) biological material: (18) non-human vs. human; and (F) the object of testing (biological material or other sources of genetic data): (19) human chromosomes (cytogenetics), (20) human genes/genomic DNA (molecular genetics), (21) specific gene products (RNA or cDNA studies and biochemical genetics for proteins or metabolites), (22) (other) subsidiary exams (as clinical pathology tests in blood or urine, electrophysiological tests, imaging, etc.), (23) physical exam or (24) family history and pedigree drawing.

Dissemination, discussion and further analysis

The results from the analysis of the definitions contained in these documents were presented at the workshops organized by Unit 3, to which several experts were invited, as well as at the general assemblies of EuroGentest and its external advisory board (2006–2010). During this period, five versions of a background document were posted on the EuroGentest website and comments were received. That led to further analysis and reshaping of the discussion and conclusions for this article.

Limitations of this study

Due to its nature, this study was limited to documents written in English. Though this is not expected to have limited the number or contents of most of the documents from international institutions (those of greatest interest), it certainly has affected representativeness of national organizations and introduced a bias towards documents from the European Union (EU27), the UK and the USA. National institutions from other continents are, thus, under-represented or not represented at all.

Websites are in constant change; thus, some of those visited earlier during the study period are no longer available, have changed address, or are now available to members

only. Some of the organizations considered have a broad or undefined scope and/or mixed stakeholders, which made them difficult to classify (Table 2). Though we have tried to reproduce the exact definitions and the relevant text when a clear definition was not provided (all available as [Electronic supplementary material](#)), discussion of the scope of the definitions was subject to interpretation (Table 3), mainly when the documents gave no indication of the purpose or the specific context in which the test was done.

Results

Organizations surveyed and documents identified

The organizations surveyed, which were selected because of the goals they pursued or their field of action (with a potential link or impact on genetic testing activities), are shown in Table 2. Usually, only the main organizations were considered, but not their sub-groups or committees (e.g. the European Group of Ethics (EGE) in Science and New Technologies of the EC, the CDBI-Steering Committee of Bioethics of the Council of Europe or the Clinical Genetics Committee (CGC) of the Royal College of Physicians (RCP) in the UK (Tables 2 and 3). Often, some organizations dissolved or were replaced by others (e.g., the US Congress President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 1978–1983); changed name and/or scope (e.g. the CAHBI-Ad hoc Committee of Experts on Bioethics at the Council of Europe became, in 1992, the CDBI); or merged with other ones (e.g. the CGC was subsumed, in 1998, into the Joint Committee on Medical Genetics of the RCP, Royal College of Pathologists and British Society for Human Genetics). In the [Electronic supplementary material](#), all details about authorship are provided in those cases.

Many organizations had no documents relating to genetic testing: such were the cases of the International Organization for Standardization (ISO), European Medicines Agency (EMA) (formerly EMEA-European Agency for the Evaluation of Medicinal Products), American Board of Medical Genetics (ABMG) or American Civil Rights Union (ACRU), among others (Table 2).

Other organizations or institutions produced documents related to or containing the term “genetic testing”, but never defined it in a precise and concise fashion, or as a descriptive text: Some examples are the Council for International Organizations of Medical Sciences (CIOMS), the Human Genome Organisation (HUGO), the International Federation of Human Genetics Societies (IFHGS) or the European Organisation for Rare Diseases (EURORDIS) (Table 2).

Table 2 Organizations surveyed for definitions of genetic testing

International Organizations^a <ul style="list-style-type: none"> ✓ WHO ✓ UNESCO ○ CIOMS ✓ OECD ■ World Bank ✓ CoE European (EU27) Institutions^b <ul style="list-style-type: none"> ✓ European Commission ■ European Council ■ Council of the EU × European Parliament ✓ IPTS (EC JRC) Regulating Agencies^c <ul style="list-style-type: none"> × ICH ■ ISO ■ EMA (EU27) ✓ HGC (UK) ✓ UKGTN (UK) ✓ FDA (US) ✓ CDC (US) ✓ CLIA (US) ✓ AHRQ (US) <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <ul style="list-style-type: none"> ✓ Definitions of 'genetic testing' found × Only definitions of related terms ○ Documents, but no definitions found ■ No documents relating to genetic testing </div>	Scientific and Professional Genetics Organizations^d <ul style="list-style-type: none"> ○ IFHGS ✓ ESHG (Europe) ○ ESHRE (Europe) ○ ENGNC (Europe) × BSHG (UK) ○ AGNC (UK) ✓ HGAC (UK) ✓ ASHG (US and Canada) × NSGC (US) ✓ ACMG (US) ■ ABMG (US) × ABGC (US) × CORN (US) × HGSA (Australasia) Other Genetics Organizations^e <ul style="list-style-type: none"> ✓ HGP ○ HUGO ○ ORPHANET ○ EDDNAL ✓ GeneTests ○ EMQN ✓ EuroGentest (E27) 	National Health Institutions^f <ul style="list-style-type: none"> × Health Council (NL) ✓ SACGHS, NIH (US) ✓ SACGT, NIH (US) ✓ NHGRI, NIH (US) ✓ NCI, NIH (US) Health Professionals Organizations^g <ul style="list-style-type: none"> × WMA ○ FIGO × ISONG × RCP (UK) × BMA (UK) ✓ AMA (US) × ICMR (India) Clinical Pathology Organizations^h <ul style="list-style-type: none"> × RC Pathologists (UK) ✓ CAP (US) ✓ AMP (US) Research Funding Agenciesⁱ <ul style="list-style-type: none"> ○ Welcome Trust (UK) × MRC (UK) Pharmaceutical & Biotech. Industry^j <ul style="list-style-type: none"> ✓ EuropaBio (EU27) ✓ ABPI (UK) ○ Glaxo, Smith and Kline ■ Novartis 	<ul style="list-style-type: none"> ✓ Roche × Genzyme Insurance Organizations^k <ul style="list-style-type: none"> × NAHU (US) Patient/Consumers Organizations^l <ul style="list-style-type: none"> × DPI ○ EPOSI (EU27) ○ EURORDIS ✓ Genetic Alliance ■ International Genetic Alliance ■ EGAN × GIG ○ GeneWatch Policy, Ethics and Religious Org.^m <ul style="list-style-type: none"> ○ SIBI ✓ POST (UK) × Nuffield Trust (UK) × Nuffield Council on Bioethics (UK) ✓ ACGT (UK) ✓ ELSI, NIH & DoE (US) ✓ PCSBI (US) ○ CEC ■ ICB Human Rights Associationsⁿ <ul style="list-style-type: none"> ■ ACRU (US) × ACLU (US)
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^a WHO – World Health Organization (www.who.int), UNESCO – United Nations Educational, Scientific and Cultural Organization (www.unesco.org), CIOMS – Council for International Organizations of Medical Sciences (www.cioms.ch), OECD – Organisation for Economic Co-operation and Development (www.oecd.org), World Bank (www.worldbank.org), CoE – Council of Europe (www.coe.int)

^b European Union (EU27) Institutions (europa.eu) are the European Parliament, European Commission (EC), European Council, Council of the EU and Court of the EU; EC JRC – Joint Research Centre, IPTS – Institute for Prospective and Technological Studies, Seville (ipts.jrc.ec.europa.eu)

^c ICH – International Conference on Harmonization (www.ich.org), ISO – International Organization for Standardization (www.iso.org), EMA – European Medicines Agency (www.ema.europa.eu), HGC – Human Genetics Commission (UK) (www.hgc.gov.uk), UKGTN – UK Genetic Testing Network (www.ukgt.nhs.uk), FDA – Food and Drug Administration (www.fda.gov), CDC – Centers for Disease Control (www.cdc.gov), CLIC – Clinical Laboratory Improvement Advisory Committee (www.cdc.gov/clia), AHRQ – Agency for Healthcare Research and Quality, US Department of Health and Human Services (www.hhs.gov)

^d IFHGS – International Federation of Human Genetics Societies (www.ifhgs.org), ESHG – European Society of Human Genetics (www.eshg.org), ESHRE – European Society of Human Reproduction and Embryology (www.eshre.eu), ENGNC – European Network of Genetic Counsellors and Nurses (www.engnc.org), BSHG – British Society of Human Genetics, AGNC – Association of Genetic Nurses and Counsellors (UK) (www.agnc.org.uk), HGAC – Human Genetic Advisory Committee (www.hgc.gov.uk), ASHG – American Society of Human Genetics (www.ashg.org), NSGC – National Society of Genetic Counsellors (www.nsgc.org), ACMG – American College of Medical Genetics (www.acmg.net), ABMG – American Board of Medical Genetics (www.abmg.org), ABGC – American Board of Genetic Counseling (www.abgc.net), CORN – Council of Regional Networks for Genetic Services (www.kumc.edu/gen/prof/corn.html), HGSA – Human Genetics Society of Australasia (www.hgsa.org.au)

^e HGP – Human Genome Project (www.ornl.gov/sci/techresources/Human_Genome/home.shtml), HUGO – Human Genome Organisation (www.hugo-international.org), Orphanet – The Portal for Rare Diseases and Orphan Drugs (www.orpha.net), EDDNAL – European Directory of DNA Diagnostic Laboratories (www.eddnal.com), GeneTests (www.genetests.org), EMQN – European Molecular Genetics Quality Network (www.emqn.org), EuroGentest – Harmonizing Genetic Testing across Europe (www.eurogentest.org)

^f Health Council (NL) (www.gezondheidsraad.nl/en), NIH – National Institutes of Health (www.nih.gov), SACGHS – Secretary's Advisory Committee on Genetics, Health, and Society (oba.od.nih.gov/SACGHS), SACGT – Secretary's Advisory Committee on Genetic Testing, NHGRI – National Human Genome Research Institute (<http://www.genome.gov>), NCI – National Cancer Institute (www.cancer.gov)

^g WMA – World Medical Association (www.wma.net), FIGO – International Federation of Gynecology and Obstetrics (www.figo.org), ISONG – International Society of Nurses in Genetics (www.isong.org), RCP – Royal College of Physicians (www.rcplondon.ac.uk), BMA – British Medical Association (www.bma.org), AMA – American Medical Association (www.ama-assn.org), ICMR – Indian Council Medical Research (icmr.nic.in)

^h RCP – Royal College of Pathologists (www.rcpath.org), CAP – College of American Pathologists (www.cap.org), AMP – Association for Molecular Pathology (www.amp.org)

ⁱ Welcome Trust (www.welcome.ac.uk), MRC – Medical Research Council (www.mrc.ac.uk)

^j EuropaBio – European Association for Bioindustries (www.eurobio.org), ABPI – Association of British Pharmaceutical Industry (www.abpi.org.uk), Glaxo, Smith and Kline (www.gsk.com), Novartis (www.novartis.com), Roche (www.roche.com), Genzyme (www.genzyme.com)

^k NAHU – National Association of Health Underwriters (www.nahu.org)

^l DPI – Disabled Peoples International (www.dpi.org), EPOSI – European Platform for Patient Organisations, Science and Industry (www.eposi.org), EURORDIS – European Organisation for Rare Diseases (www.eurordis.org), Genetic Alliance (www.geneticalliance.org), International Genetic Alliance/Alliance – Europe (www.intga.org), EGAN – Patients Networks for Medical Research and Health (www.egan.eu), GIG – Genetic Interest Group (www.geneticalliance.org.uk), GeneWatch (www.genewatch.org)

^m SIBI – International Society of Bioethics (www.sibi.org), POST – Parliamentary Office of Science and Technology (www.parliament.uk), Nuffield Trust (www.nuffieldtrust.org), Nuffield Council on Bioethics (www.nuffieldbioethics.org), ACGT – Advisory Committee on Genetic Testing (www.dh.gov.uk), ELSI – NIH & Dep. of Energy Work Group on Ethical, Legal and Social Implications (www.genome.gov), PCSBI – Presidential Commission for the Study of Bioethical Issues (www.bioethics.gov), CEC – Conference of European Churches (www.cecurope.org), ICB – Institute of Catholic Bioethics (icbioethics.com)

ⁿ ACRU – American Civil Rights Union (www.theacru.org), ACLU – American Civil Liberties Union (www.aclu.org)

Finally, other documents did not contain the term genetic test or testing, but only related terms such as specific types of genetics tests or referred to genetic counselling (in the context of testing), as was the case with the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Human Genetics Society of Australasia (HGSA) or the American Civil Liberties Union (ACLU) (Table 2).

Overall, we defined 84 organizations and collected 163 documents related to genetic testing, produced by them. Among these, 109 documents (from 56 organizations) contained definitions on genetic testing or related terms and texts (Table 2). In [Electronic supplementary material](#), all organizations are listed, together with the names and sources of the documents selected and the definitions and other relevant text they contained.

Types of definitions

Very few of the documents examined had a *working definition*. A good example of a document with a clear working

definition at its very start is the Council of Europe's (CoE 1992) "Recommendation No. R (92) 3 on Genetic Testing and Screening for Health Care Purposes", which states that

"For the purposes of this Recommendation, (a) 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."

Furthermore, this document also states clearly that diagnostic tests are just one type of genetic testing and clearly separates *genetic screening*:

Table 3 Scope of definitions of genetic testing by some organizations

	A. Broad purpose			B. Specific type of testing										C. Phenotypes			D. Som. mut.	E. Non hum.	F. Object							
	1. Medical applications	2. Biomedical research	3. Non-medical applications	4. Diagnostic testing	5. Presymptomatic testing	6. Disease predisposition testing	7. Pharmacogenetics	8. Carrier testing	9. Prenatal testing	10. Preimplantation genetic diagnosis	11. Population screening	12. Paternity testing	13. Identity testing	14. Pathogenic mutations for hereditary diseases	15. Complex diseases	16. Polymorphic traits	17. Somatic mutations (vs germinal only)	18. Non-human DNA/RNA (bacteria, viral, fungal pathogens)	19. Human Chromosomes	20. Human Genes/DNA	21. Specific gene products	22. Subsidiary exams	23. Physical exam	24. Family history		
WHO ¹	+	+	○	+	+	+	○	+	+	+	○	○	○	+	+	○	○	○	○	+	○	○	○	○	○	
UNESCO ²	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	○	+	+	+	○	○	○	○	
OECD ³	+	○	○	+	+	+	+	+	+	+	○	○	○	+	+	○	○	○	○	+	+	○	○	○	○	
CoE ⁴	+	○	○	+	+	+	+	+	○	○	○	○	○	+	+	○	○	○	+	+	+	+	○	○	○	
CoE ⁵	+	+	○	+	+	+	+	+	+	+	○	○	○	+	+	○	+	○	+	+	+	+	+	+	+	
EC ⁶	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	+	+	+	+	○	○	○	
EGE ⁷	+	○	○	+	+	+	+	○	+	+	+	○	○	+	+	○	○	○	+	+	+	+	○	+	+	
JRC-IPTS ⁸	+	○	○	+	+	+	○	+	+	+	+	○	○	+	+	○	○	○	○	+	○	○	○	○	○	
HGC ⁹	+	○	+	+	+	+	+	+	+	+	○	+	+	+	+	+	○	○	+	+	+	○	○	○	○	
UKGTC ¹⁰	+	○	○	+	+	○	○	+	+	+	○	○	○	+	○	○	○	○	○	+	○	○	○	○	○	
CDC ¹¹	+	○	○	+	+	+	+	+	+	+	+	○	○	+	+	○	+	○	+	+	+	○	○	○	○	
AHRQ ¹²	+	○	○	+	+	+	+	+	+	+	○	○	○	+	+	○	+	+	○	+	○	○	○	○	○	
ESHG ¹³	+	○	○	+	+	+	+	+	+	+	+	○	○	+	+	○	○	○	○	+	+	+	+	+	+	
ASHG ¹⁴	+	○	○	+	+	+	○	○	+	+	○	○	○	+	+	○	○	○	○	○	+	○	○	○	○	
ACMG ¹⁵	+	○	○	+	+	+	+	+	+	+	○	○	○	+	+	○	○	○	○	+	+	+	○	○	○	
HGP ¹⁶	+	○	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	○	○	+	+	+	○	○	○	
GeneTests ¹⁷	+	+	○	+	+	+	+	+	+	+	+	○	○	+	+	○	○	○	○	+	+	+	○	○	○	
EuroGentest ¹⁸	+	○	○	+	+	+	+	+	+	+	+	○	○	+	+	○	○	○	○	+	+	+	+	+	+	
SACGHS ¹⁹	+	+	○	+	+	+	+	+	+	+	+	○	○	+	+	○	+	○	+	+	+	○	○	○	○	
SACGT ²⁰	+	○	○	+	+	+	+	+	+	+	+	○	○	+	+	○	+	○	+	+	+	○	○	○	○	
NHGRI ²¹	+	○	○	+	+	+	○	+	+	+	+	○	○	+	+	○	○	○	+	+	+	○	○	○	○	
CAP ²²	+	○	○	+	+	○	○	+	+	+	○	○	○	+	○	○	○	○	○	+	○	○	○	○	○	
AMP ²³	+	○	○	+	+	+	○	+	+	+	○	○	○	+	+	○	○	○	○	○	+	○	○	○	○	
EuropaBio ²⁴	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	○	+	+	○	○	○	○	
Roche ²⁵	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	○	+	○	+	○	○	○	○	○	
Genetic Alliance ²⁶	+	○	○	+	+	+	+	+	+	+	+	○	○	+	+	○	○	○	○	+	+	+	○	○	○	
POST ²⁷	+	○	○	+	+	+	+	+	+	+	○	○	○	+	○	○	+	○	+	+	○	○	○	○	○	
Nuffield ²⁸	+	○	○	+	+	○	○	+	+	+	+	○	○	+	○	○	○	+	+	+	+	+	+	+	+	
ACGT ²⁹	+	+	○	+	+	○	○	+	+	+	+	○	○	+	○	○	+	○	+	+	+	○	○	○	○	
ELSI ³⁰	+	○	○	+	+	○	○	+	+	+	+	○	○	+	○	○	○	○	+	+	+	○	○	○	○	

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

“(b) 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, (c) 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. (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.)

This is particularly important as, very often, diagnostics tests and genetic screening are not classified as specific types of genetic testing, or, even worse, are not distinguished from each other.”

Another example of a clear working definition is that of the OECD Guidelines for Quality Assurance in Molecular Genetic Testing (OECD 2007):

“This Recommendation applies to quality assurance of molecular genetic testing offered in a clinical context.

It addresses genetic testing for variations in germ line DNA sequences or products arising directly from changes in heritable genomic sequences that predict effects on the health, or influence the health management, of an individual. It focuses on molecular genetic testing for the diagnosis of a particular disease or condition and predictive genetic testing often carried out before any clinical signs of the disease or condition appear. It is relevant to tests for heritable DNA variants that predict the response profile of an individual to a drug or course of therapy and that affect susceptibility to disease, patient prognosis, counselling, treatment and family planning. It does not address testing carried out only for research purposes.”

A particular type of a working definition (concerned with validity, for test evaluation in the *Gene Dossiers*) is the one provided by Mark Kroese (2005) in a document to a meeting of the steering group of the UK Genetic Testing Network (UKGTN):

“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.” (This definition was first given in Kroese et al. (2004)).

Many other documents contain more or less extensive definitions of genetic testing and/or list specific types of testing and related terms. Still others have no clear definitions, but provide long explanations of what they mean by genetic testing and/or related terms (see [Electronic supplementary material](#)).

Scope of definitions

Definitions collected ranged from the strict view of being synonymous to *DNA-based testing*, to *any source that can provide genetic information*, thus covering as well some instances of “non-classical” *genetic* tests, physical examination and family history.

An example of the former is that found in a WHO document (2005; p.78):

“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”.

Also, the UKGTN (2008; p.13) provides one of the strictest (and most concise) definitions found (although the

network had been extended to some cytogenetics labs, in 2006):

“...testing for germ line disorders where nucleic acid is the analyte.”

In the UNESCO (2003; p.41) International Declaration on Human Genetic Data, for example, the concept is enlarged to include conventional cytogenetics and biochemical genetics testing, in addition to DNA or RNA 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”.

Some documents, well focused on their goals, opt to exclude explicitly some types of tests (e.g. somatic mutations, cytogenetics) or context (e.g. biomedical research, forensic genetics), as is the case with the working definition of the OECD (2007; p.8), cited above, and others as CAP’s (2000; end of §2nd of “Definition of Genetic Testing”):

“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.”

Another type of working definitions is that of the US Food and Drug Administration (FDA 2007; p.3), where the “definition” consists in accentuating the context by resorting one specific type of test to the point it is no further considered a *genetic test*:

“II. Pharmacogenetic Testing versus Genetic Testing: Therefore, a pharmacogenetic test target population will typically be composed of candidates for a particular therapeutic. Target populations of genetic tests, on the other hand, will usually be composed of those who are suspected of having, or are at risk of developing, a particular disease or condition.”

At the extreme of the scope is, e.g. the EC Expert Group (2004b; p.8), who provided a very broad definition for genetic testing (though the work focused mainly on genetic data transmissible at the germinal level, pertaining to heritable diseases or traits, and not on somatic genetic data):

“i.e. ‘any test that yields genetic data’. 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')."

The Committee of Ministries of the Council of Europe (CoE 1992; p.2) extends its definition to the exam of organs and individuals, *complemented* by family history:

"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 European Group on Ethics (EGE) (EC 2003; p.6) provides one good example of a definition broadening even further the scope, by adding in *family history* as a "genetic test":

"In so far as family medical histories can provide information on a person's genetic status, which may have a predictive value for future health as significant as a laboratory performed genetic test, these are included within our definition of genetic tests." ... "The EGE's opinion also views the analysis of family history as a genetic test, again in so far as it reveals characteristics of an individual's genetic disposition."

In a concise sentence, the ESHG (Godard et al. 2003) provided one of the broadest possible definition, in the background document for recommendations on genetic information and testing in insurance and employment (ESHG 2003):

"Genetic testing classifies people into those who have the mutant gene and those who do not have it."

Tackling also with insurance, the ASHG (2000), in a practical manner (because of the possible need for "additional oversight"), suggests restricting the definition of *genetic tests* 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."

Though, some time before, the ASHG-appointed Ad Hoc Committee on Genetic Testing/Insurance Issues (ACGT 1995) had been forced to conclude that:

"...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."

Misused genetic terms

Often, *genetic testing* and *genetic screening* are not distinguished (Sequeiros, 2010). For instance, the EGE (EC 2003, p.5) states that:

"In the context of employment, 'genetic testing' incorporates 'genetic screening' and 'genetic monitoring'."

The National Cancer Institute (NCI undated) of the US NIH provides a "dictionary of cancer terms" where *genetic testing* and *genetic analysis* are different entries with different meanings, both centred on prediction, where the major differences (most probably unintended) are actually that the first mentions DNA variants and the second includes only mutations; and this one encompasses pharmacogenetics, whereas the first one does not:

"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."

Finally, we provide a particularly illustrative example of the great confusion that may be found among some established use of the terms *genetic test* or *genetic testing* (and even *molecular genetic test*), in the definitions of the ECRI Institute Evidence-based Practice Center for the US Department of Health and Human Services (AHRQ 2010; p.1):

"In this report, we use the term 'molecular test' (MT) interchangeably with the term 'molecular genetic test'. We adopted the definition of molecular genetic test recommended by the Genetic Work Group of the Clinical Laboratory Improvement Advisory Committee. The Work Group defined a genetic molecular test as 'an analysis performed on human DNA or RNA to detect heritable or acquired disease-related genotypes, mutations, or phenotypes for clinical purposes' (Tabar 2005). According to this definition, cytogenetic tests, which are performed on human chromosomes, and biochemical genetic tests, which analyze human proteins and certain metabolites, are beyond the scope of this report. However, molecular cytogenetic tests (e.g. the tests using the fluorescence in situ hybridization (FISH) technology) in which analyses cross both the

chromosome and the DNA levels are included in this report. In this report, we also consider a test performed on pathogen (e.g. bacterial, viral or fungal) DNA or RNA as a molecular test, if the purpose of the test is to diagnose an infectious disease caused by the pathogen in human.”

The Clinical Laboratory Improvement Advisory Committee of the US CDC (CLIA 1998; p.3) definition, cited above by the AHRQ (2010), is a good example of emphasis on methodology (this being an organization concerned with laboratory quality), not on information content. The definition of CLIA, cited above by AHRQ, is actually of “*molecular genetics and cytogenetics tests*” (taken together); CLIA distinguishes only between these and “*biochemical genetics tests*” (CLIA 1998; p.3, and [Electronic supplementary material](#)). But the AHRQ then departs from the definition cited to add also molecular tests of pathogens in human infectious diseases.

Definitions of genetic information

Some organizations prefer to use the term *genetic information*, though in some instances confusing it with genetic testing. For instance, the National Association of Health Underwriters (NAHU 2002) 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 that it should clearly exclude 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.”

At the other extreme, the American Civil Liberties Union (ACLU 1998) recommends a definition of *genetic information* covering:

“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.”

A similar stand is taken by the UK Genetic Interest Group (GIG 1998), defining genetic information as:

“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.”

Discussion

Comparison of contents and scope of definitions

Using the items listed in Table 1, we compared in table-format the scope of various definitions (as interpreted by us) provided by 30 well-known organizations (Table 3). These include some examples of all the various types of organizations, indicated in Table 2, and of different geographic and professional backgrounds. Some similarities, as well as some striking differences can be observed. More importantly, the wide variation of definitions and of their scope is well apparent, sometimes even among similar or closely related organizations.

In our interpretation, the definitions of genetic testing found (Table 3; [Electronic supplementary material](#)) covered unequivocally always diagnostic and presymptomatic DNA-based testing for germline mutations, i.e. medical applications in hereditary diseases. In over 80% cases, carrier testing, prenatal diagnosis and PGD, susceptibility testing for complex diseases and population genetic screening were also covered. Chromosomes (conventional cytogenetics) and gene products (biochemical genetics) were unequivocally covered in 67–70% of those definitions.

The research context and non-medical applications, somatic mutations, pharmacogenetics and forensic genetics testing were included only in 17–30%. Non-human DNA for infectious diseases, physical examination and family history were covered only in 7–10% of the definitions.

Variability with the type of organization and among similar organizations

Nevertheless, there seem to be some patterns as to the items and areas that are covered, as well as to the aim with which they were produced (e.g. patient interest groups and insurers; or genetics and clinical pathology associations) (Table 3).

It was also obvious that some documents were concerned with and tried to define genetic testing in the strict sense of the analysis of genetic material (chromosomes, DNA and/or gene products), while others were clearly more interested in the concept of genetic information (i.e. with the contents of the information extracted), than with the methodologies used to derive it. Thus, lay associations, human rights

organizations and ethicists and policy-makers tended to use broader definitions of genetic testing/information, while insurers and non-geneticists or organizations dealing with laboratory quality assurance tend to prefer much narrower definitions. The actual definitions can be found (together with their references) in the [Electronic supplementary material](#) provided.

There may be also some geographic differences, among similar-purpose organizations, with a tendency for broader definitions to being used by the European Union institutions and narrower ones in the USA (but also some UK entities).

The use of the term *genetic test* may apply to human genetic material only, up to pathogens as bacteria, viruses or fungi (diluting the distinction between *molecular biology*, as a laboratory tool, and human *molecular genetics*, as a discipline and specialty), as can also extend from the analysis of nucleic acids only, up to physical examination and family history (merging the concepts of *genetic testing* and *genetic information*).

Items specifically excluded or inadvertently omitted

Some possible items were excluded from a definition (in our interpretation) almost certainly without any specific intention: This may have been the case with cytogenetics for the Guidelines on Ethical issues on Medical Genetics and Genetic Services of the WHO (1998) (“*the analysis of the status of a particular gene*”); or with *carrier testing* in a definition in the website of the American Society of Human Genetics (ASHG website: http://www.ashg.org/education/genetic_testing.shtml) (“*to determine if someone has a genetic condition or is likely to get a specific disorder*”).

Others items were, however, explicitly excluded for clear operational reasons: Such was the case with PGD and prenatal diagnosis, in the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes (CoE 2008), or with somatic mutations in cancer and pathogens in human infectious diseases, for the USA Association for Molecular Pathology (AMP 2005).

Items more frequently included in definitions of genetic testing

Though the difference between medical and non-medical applications is frequently mentioned in definitions of genetic testing, the important distinction between *clinical* context and *research* is rarely made. Pharmacogenetics and susceptibility testing for complex disorders are sometimes inadvertently or purposefully not covered in definitions of genetic testing. Forensic genetics and testing for cancer somatic mutations are areas that are or may be considered too different to be included in many definitions and documents.

Only twice was the definition of (medical applications of) genetic testing used to encompass also the analysis of pathogens for human infectious diseases, i.e. the use of non-human genetic material (AHRQ 2010; Roche, 2005).

Genetic testing versus genetic information

A frequent confusion made is between the terms *genetic testing* and *genetic information*. In fact, several sources do not distinguish between *genetic testing*—the actual analysis with a particular purpose and using specific methodology—and *genetic information*—the data or content derived from a medical exam, regardless of its type, methods and material used, requiring an interpretation to put it into context.

But, the definition of genetic information, itself, can vary from being synonymous of DNA-based testing (NAHU 2002), to any information about inherited characteristics that may have been acquired by any methodologies, including physical and laboratory medical examinations and family information (ACLU 1998; GIG 1998).

The fact is that, as stated before by the ACGT (1995), “*there is no clear boundary between genetic and nongenetic conditions and tests*”.

Conclusions

In spite of variable nomenclature and phrasing, most types of DNA testing, if related to a heritable disorder (germline mutations), performed in a medical context, either in affected persons and healthy relatives, embryos and foetuses, seem to be covered by all definitions.

Other than that, “genetic testing” is a very ambiguous and equivocal term, often used (as well as its subtypes) in a very imprecise way. It is often confused with *genetic screening*, a very specific term in medical genetics, and it is not always distinguished from the potentially broader *genetic information*. In spite of the previously established goal, our work shows that it is unlikely that a common consensus definition can be achieved.

A clear set of precise definitions (e.g. of “laboratory-based genetic testing”, “clinical genetics testing” and “genetic information”) is needed to create a common language among clinical and laboratory geneticists, other health professionals, legislators, regulators, policy-makers and other stakeholders; this will impact on transparency and accuracy of legislation and on the quality of democracy.

A clear context-dependent, working, definition should always be applied, whenever the term *genetic testing* is used. In particular, in case of guidelines or legislation, a clear explanation of what is the scope of the document should be required.

Acknowledgements This work was produced as part of the European Commission financed (FP6) Network of Excellence, EuroGentest—Harmonizing Genetics Testing across Europe. We thank all members and experts, particularly those of former Unit 3 (Clinical Genetics, Community Genetics and Public Health), as well as the members of the External Advisory Board who provided helpful comments at meetings and the general assemblies of the network. We are particularly grateful to Ron Zimmern of the PHG Foundation, Cambridge, UK, for helpful discussions.

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Reference to the sources of the documents from where all the definitions analysed were extracted (including those compared on Table 3) is made in the [Electronic supplementary material](#).