

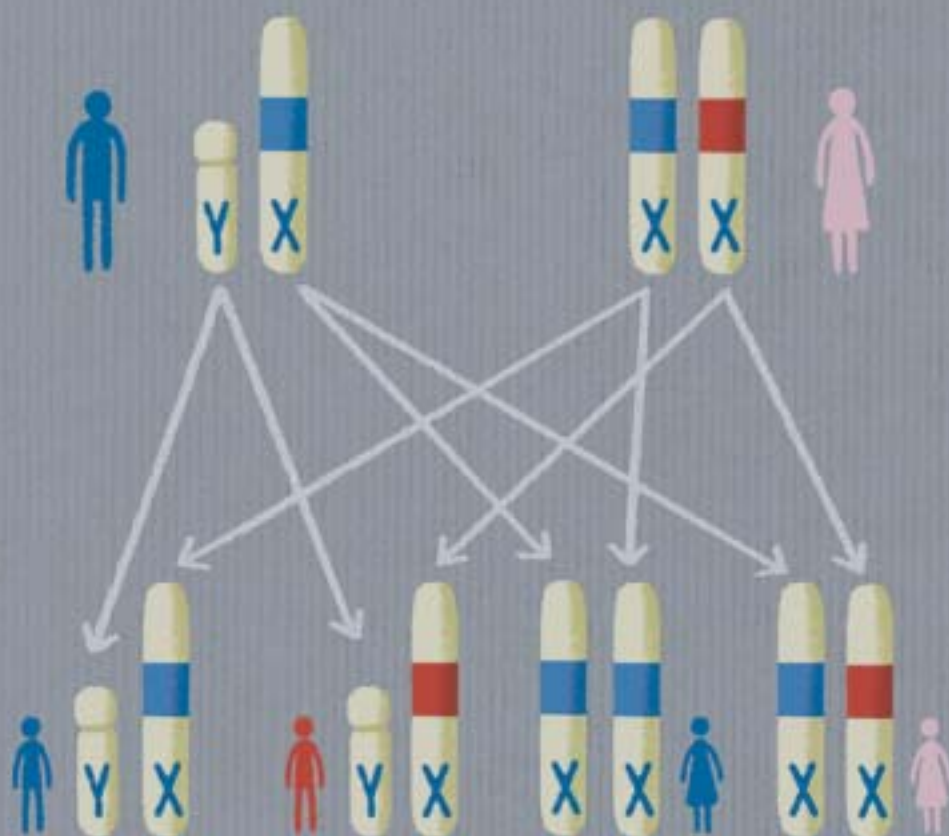


EUROPEAN
COMMISSION

Community research

The Independent Expert Group

Ethical, legal and social aspects of genetic testing: research, development and clinical applications



Interested in European research?

RTD info is our quarterly magazine keeping you in touch with main developments (results, programmes, events, etc.). It is available in English, French and German. A free sample copy or free subscription can be obtained from:

European Commission

Directorate-General for Research

Information and Communication Unit

B-1049 Brussels

Fax (32-2) 29-58220

E-mail: research@cec.eu.int

Internet: http://europa.eu.int/comm/research/rtdinfo/index_en.html

EUROPEAN COMMISSION

Directorate-General for Research
Directorate C – Science and Society
Unit C3 – Ethics and Science
Helpdesk: research@cec.eu.int

For further information on Science and Society,
please refer to the following Internet site:
http://europa.eu.int/comm/research/science-society/index_en.html

Ethical, legal and social aspects of genetic testing: research, development and clinical applications

by

Eryl McNally (chair) and Anne Cambon-Thomsen (rapporteur)

Celia Brazell, Jean-Jacques Cassiman, Alastair Kent,

Klaus Lindpaintner, Paula Lobato de Faria, Detlef Niese,

Henriette Roscam Abbing, Jan Helge Solbakk, H el ene Tack,

Erik Tambuyzer, Thomas R. Weihrauch, Erik Wendel

European Commission contacts:

Barbara Rhode and Maurizio Salvi (secretary to the Group)

Brussels 2004

**Europe Direct is a service to help you find answers
to your question about the European Union**

**Freephone number:
00 800 6 7 8 9 10 11**

LEGAL NOTICE

Neither the European Commission nor any person acting on behalf of the Commission is responsible for the use which might be made of the following information.

The views expressed in this publication are the sole responsibility of the author and do not necessarily reflect the views of the European Commission.

A great deal of additional information on the European Union is available on the Internet.

It can be accessed through the Europa server (<http://europa.eu.int>).

Cataloguing data can be found at the end of this publication.

Luxembourg: Office for Official Publications of the European Communities, 2004

ISBN 92-894-7324-X

© European Communities, 2004

Reproduction is authorised provided the source is acknowledged.

Printed in Belgium

PRINTED ON WHITE CHLORINE-FREE PAPER

Table of Contents

I	Testimony	7
II	Foreword by Philippe Busquin	8
III	Foreword by Eryl McNally	9
IV	Executive Summary	10
	i Approach	
	ii Report	
	iii Summary of the 25 recommendations	
	iv Follow up	
V	Introduction	11
VI	List of Recommendations	14
1	Genetic Testing: State of the art	15
	1.1 Technologies	15
	1.2 Genetic Testing and Screening: current and future possibilities	17
	1.2.1 Diagnostic testing	18
	1.2.2 Diagnostic screening	18
	a) Prenatal screening	18
	b) Neonatal screening	18
	c) Carrier screening	18
	1.2.3 Predictive testing	18
	a) Presymptomatic tests	18
	b) Predisposition tests	19
	1.3 Research approaches for the identification of genes involved in diseases	19
	1.3.1 Population genetics and family analyses	20
	1.3.2 Methodological approaches	20
	1.4 Current provision of genetic testing: market and quality issues	21
2	Stakeholders: prevalent views, concerns and expectations	23
	2.1 Stakeholder groups	23
	2.1.1 Patients and their families	23
	2.1.2 Researchers in basic and clinical sciences	24
	2.1.3 Clinicians and other healthcare professionals	25
	2.1.4 Health authorities, providers and policy-makers	25
	2.1.5 Healthcare industry	25
	2.1.6 Politicians	25
	2.1.7 The public, consumer groups and other public ‘watchdogs’	26
	2.1.8 The disability movement	26
	2.1.9 ‘Non-medical’ interests	26
	2.1.10 Ethics bodies and legal professionals	27
	2.1.11 The media	27
	2.2 Stakeholders in the wider context	28
3	Specific issues underlying the dialogue on genetic testing	28
	3.1 Public perceptions and dialogue	28
	3.1.1 Expectations of patients	29
	3.1.2 Public engagement and communication initiatives in Europe	30
	3.2. Genetic exceptionalism: is medically-relevant genetic data different from other medical information?	31
	3.2.1 The issues at stake	32
	3.2.2 Scientific considerations	32

3.2.3	Information content	33
3.2.4	Is there a policy or regulatory tendency to “Genetic exceptionalism”?	34
3.3	Gender and Ethnicity	36
3.3.1	Gender and genetic testing	36
3.3.2	Ethnicity and genetic testing	37
4	Biobanks as resources and tools for research and development of genetic testing	40
4.1	Data protection and informed consent	41
4.2	The value and sustainability of collections	44
5	Pharmacogenetics	45
5.1	Scientific background	45
5.1.1	What is pharmacogenetics?	45
5.1.2	Pharmacogenetic research	46
5.2	Impact on key stakeholders	46
5.2.1	Healthcare professionals	46
5.2.2	Patients	47
5.2.3	Healthcare providers	47
5.2.4	Pharmaceutical, diagnostic and biotechnology industries	47
5.2.5	Regulatory authorities	48
5.3	Ethical, legal and social considerations	48
5.3.1	Psychological impact on patients	48
5.3.2	The risk of revealing unwanted information	49
5.3.3	The issue of ‘non-responders’ to treatment: creation of rare disease categories and the need for rare medicinal products	49
5.3.4	Data confidentiality	50
5.4	Application of pharmacogenetics	50
5.4.1	Public perceptions and policy	50
5.4.2	Mutual engagement of regulatory authorities and industry to create guidelines and processes for medicine and pharmacogenetic test approval	51
5.4.3	Healthcare provider education	51
6	Research and development of genetic tests	51
6.1	Challenges, needs and duties of test developers	51
6.1.1	Scientific and clinical validation	51
6.1.2	Assessment of clinical utility	52
6.1.3	The need for adequate return on investment	52
6.1.4	The need for legal clarity	52
6.2	Challenges, needs and duties of public health authorities and healthcare providers	52
6.2.1	The need for independent review procedures	52
6.2.2	The need for scrutiny of certain genetic tests	52
6.2.3	The duty to safeguard availability of tests for rare genetic diseases	53
6.3	Rights of individuals and groups involved in genetic testing research and development	53
7	Clinical implementation and use of genetic tests	54
7.1	Challenges, needs and duties of clinicians and genetic counsellors	54
7.1.1	The impact of genetic testing on individuals	54
7.1.2	The importance of professional standards for healthcare professionals	54
7.1.3	The need for professional development and education	55
7.1.4	Informed consent, confidentiality and privacy	56
7.1.5	The duty to provide ‘non-directive’ counselling	56
7.1.6	The duty to disclose actual or potential conflicts of interest	58
a)	Genetic privacy and the duty of disclosure	58
b)	The duty to warn	59

7.2 Duties and rights of individuals undergoing genetic testing	59
7.2.1 The duty to keep informed about genetics	59
7.2.2 The right to know and not to know	60
8 The impact of medical genetic testing on healthcare systems in the EU	61
8.1 Communication, education and information	62
8.2 Policy and regulation	62
8.3 Health economics	63
8.4 Population screening programmes using genetic tests	64
8.5 Looking to the future: new challenges	66
8.6 Genetic testing in the global context	66
9 Reflections on the Group's dynamics and dialogue	67
9.1 How did the Group function and evolve?	67
9.2 Moving on to a larger-scale dialogue and a wider audience	70
Annexe 1 The Group of Experts	97
Annexe 2 Glossary of terms used in the report	104
Annexe 3 Bibliography	111
Annexe 4 List of hearings	121

I Testimony

My name is H el ene Tack

I am 37 years old and married. In 1988, I gave birth to our first daughter. At nine days old she was diagnosed with spinal muscular dystrophy. She passed away three months later. At the time, there was no information and no research on this disease, and there was certainly no question of genetic testing.

We were not ready to give up the idea of having our own children so we decided to take the risk and start again. By that time we knew that we had a 75% chance of having a healthy baby. At the end of 1989, I gave birth to my second daughter but unfortunately she had the same disease. She passed away five months later. After two such unhappy experiences, we were no longer prepared to trust in our luck...

We sought help from patient associations and came across a researcher who was prepared to work on this disease, but he lacked the funds. With the help of the Association Fran aise contre les Myopathies (French Muscular Dystrophy Association) and the funds raised by the T el thon, we found the necessary money – and the gene was localised six months later! The fact that its location was now known meant that we were able to benefit from a prenatal diagnosis. Once again, we were able to look to the future, but at the same time we knew we risked being faced with a difficult choice in the case of a negative result.

But this time we were lucky and we did not have to make a decision. My three following pregnancies were without any problem. I would like to add that the genetic test is carried out at nine weeks of gestation and the results are given three weeks later. During the waiting period, we both lived in anguish as to the result and it was a time which will always remain in my memory. I think it is very difficult to be so desperate for a child, to become pregnant, and yet still not be sure of having a healthy child. However, I will never forget that access to this genetic test allowed me to rebuild my family.

For the last ten years I have been working with the AFM and I have been in regular contact with many families concerned by genetic tests. I feel very strongly about the necessity to reflect on and understand genetic tests so as to be better prepared to accompany the families in their choice, whatever that might be. This is the reason why I chose to be a part of this Group.

Member of the Expert Group on genetic testing

II Foreword by Philippe Busquin

When the news about deciphering the human genome, the so-called "book of life", was announced, news channels predicted that this step in scientific analysis would make it possible to "banish inherited disorders, screen people for their vulnerability to diseases, tailor treatment to an individual's genetic make-up, create thousands of new drugs and extend human lifespan" (BBC, 27 June 2000). Today, only four years later, a range of genetic tests have already been developed and the possibility of genetic testing is profoundly changing the methodologies and strategies in medical therapy and healthcare. The evolving diagnostics and predictive practices are the fruits of continuous advances in genetic research, including that supported by the Research Framework Programmes of the European Commission's Directorate-General for Research.

The technology of genetic testing has enormous potential to develop preventive and predictive medicine. As these medical applications also encompass social, ethical and legal considerations, careful reflection is needed to put an appropriate strategy in place to maximise the potential benefit for healthcare and medical services in Europe.

At present, only a small group of people are sufficiently informed and familiar with the kind of decision-making and consequences that genetic testing entails. They are familiar with these issues because of their professional background, or because they or their families have already been involved as patients. Soon, genetic testing will become part of everyday healthcare systems, and patients and professionals will have to learn to make decisions on the need for a test, as well as to understand its consequences.

When integrating these technologies into the healthcare system, it is important that their application happens within a responsible framework of accompanying measures and activities. Trust and confidence are paramount when developing new testing capacities. In order to help decision-makers at all levels to introduce the necessary requirements rapidly, the Research Directorate-General of the European Commission invited a group of experts from various backgrounds to discuss the ethical, legal and social implications of genetic testing and to propose appropriate actions. The initiative involved the coordination of the various departments which follow the subject from different perspectives.

I am very grateful to Eryl McNally who chaired this outstanding group of representatives from NGOs (patient organisations with an interest in the subject), from the pharmaceutical industry (producing or using genetic tests), and from academia specialised in different fields (law, philosophy and ethics, medicine and biology). I also convey my thanks to the Group, in particular to the rapporteur Dr Anne Cambon-Thomsen who has integrated the different views in a remarkably rich report.

The 25 recommendations that the Group has developed were discussed at a public citizens and stakeholder conference on 6 and 7 May 2004 in Brussels. It is now the right moment to decide what steps should be taken so that this novel technology is able to serve citizens and our healthcare systems.



Philippe Busquin
Commissioner for Research

III Foreword by Eryl McNally

Research into the identification of genes and their mutations causing diseases or inherited disorders has resulted in the availability of molecular genetic tests and their clinical application. It is now the task of decision-makers in Europe to create the appropriate framework of regulation, information and education to guarantee a careful and beneficial application of this promising technology. Consideration of the potential medical, psychological, social, legal and ethical consequences of genetic testing raises the question of how to ensure that the quality, safety and ethical application of genetic tests are guaranteed in Europe and around the world.

The European Commission asked me to chair a group consisting of experts from different backgrounds to negotiate and draw up commonly agreed recommendations. The membership of the Group (see Annex 1) was chosen with the aim of representing different sectoral interests: science, industry, patients, academics, lawyers, and politicians. It soon became clear that any expectation that experts might contribute to the Group's deliberations in a confrontational way because of their different interests, backgrounds or experiences was misplaced. Members were able to engage with the issues in an open-minded way, and to respect the viewpoints of others without abandoning or concealing the specific interests, perceptions and concerns of the sectors they represented.

It also became apparent that people in the Group in fact shared many views, although their different starting points meant that these could be explored through robust discussions and thorough investigation.

Over the past year, the Group has gathered evidence on the state of the art, compiled all the important documents that are available at present, and invited further experts for hearings to which representatives of international organisations were also invited to participate. Having seen all the documentation and heard the views of other experts, the Group produced a draft common report that was thoroughly discussed, then drawn together in its final form by its rapporteur Dr Anne Cambon-Thomson.

The Group considered itself as an experiment in dialogue between various stakeholders and thus also chose to express its views on societal dialogue from that experience.

We can only encourage the European Commission or other decision-making bodies at national or international level to engage further in such a fruitful process. We herewith submit our 25 recommendations as well as the report, to which we also add a glossary which we hope will give everyone, including non-experts, the chance to better understand and evaluate this report. We are looking forward to a broad debate with European and international stakeholders on 6 and 7 May 2004 in Brussels.



Eryl McNally
Member of the European Parliament

*Vice-Chair of STOA
(Scientific and Technical Options Assessment of the European Parliament)
Chair of the STRATA Expert Group*

IV Executive summary

i Approach

Genetic testing is becoming an integral and growing part of healthcare provision and services. In order to ensure the benefit of this innovation for individuals and society at large it is important to implement human medical genetic testing within an adequate framework of accompanying measures and activities. Trust and confidence should prevail when developing new genetic testing capacities. To help decision-makers at all levels to discuss and formulate this framework, the European Commission's Research Directorate-General invited a group of independent high-level experts from various backgrounds to discuss the ethical, social and legal implications of genetic testing and to propose relevant and necessary actions to safeguard the success of this new opportunity.

The Commission's aim was to create a broad European platform for stakeholder dialogue on genetic testing. The Group limited its discussion to issues and perceptions surrounding the application of genetic testing in health research, healthcare and related activities. The Group now submits its consensus report along with 25 recommendations. These documents were used as the basis for discussion at a European Citizen and Stakeholders Conference in Brussels on 6 and 7 May 2004.

The 25 recommendations are also published in a separate volume¹.

ii Report

The report's first two chapters summarise the main points of the state of the art, the views of the various stakeholders, and public perceptions. Chapters 3 to 5 report the current views and the positions of the Group on the specific topics that were discussed – public dialogue, the position of genetic data among all medical information, issues related to gender and ethnicity, 'biobanks' as research tools, and the development of pharmacogenetics. Chapters 6 to 8 address research and development of genetic tests, their clinical implementation and use, and the impact of medical genetic testing on healthcare systems. They underline the challenges, needs and duties of test developers, public health authorities, clinicians and genetic counsellors, and of individuals undergoing genetic testing. Chapter 9 is devoted to the Group's reflections on its own work and its experience of the dialogue. A glossary, bibliography and the list of hearings are given as annexes.

iii Summary of the 25 recommendations

The recommendations encompass a 'code of conduct' applicable to any actor in the field but, where possible, seek more specifically to be considered an "action plan for genetic testing" to be implemented by policy-makers. They are organised into three main chapters: general framework, implementation of genetic testing in healthcare systems, and genetic testing as a research tool.

As a general framework, the Group stresses the need to develop a global consensus definition of genetic data and genetic testing, and to define explicitly terminology used in any official position or statement referring to it.

It strongly affirms that the sentiment that genetic data are different from other medical information ("genetic exceptionalism") is inappropriate. Genetic information is part of the entire spectrum of all health information and does not represent a separate category as such. All medical data, including genetic data, must be afforded equally high standards of quality and confidentiality at all times.

The Group underlines the paramount importance of public information, education and open-minded dialogue involving all stakeholders and allowing constructive exchange of views. The Group considered its own discussions between the different parties as very fruitful and as a successful experiment in productive dialogue between various stakeholders. Consequently, social dialogue and its organisation have also been made a subject of these recommendations.

As a general guideline for many of the topics approached, the Group considers that all stakeholders, including governmental authorities, scientists, healthcare providers, industry and patient organisations, should work together in a partnership approach to optimise future advances in healthcare that may become possible as a result of genetic testing, such as new treatment options and disease prevention.

¹ McNally, Cambon-Thomsen et al., "25 Recommendations on the ethical, legal and social implications of genetic testing", Brussels 2004

Genetic research and its clinical applications should be represented in an impartial way, and realistic expectations should be set as to what they can achieve. Medically relevant genetic testing must be of proven quality, must be considered an integral part of health service provision, and must be equitably accessible, while relevant, clear information must be made available. It should never be imposed and must always be a matter of free personal choice.

The regulatory framework for genetic testing should be further developed by the EU and other international organisations in a way that recognises both the need for new tests and the importance of safety, clinical validity and reliability. Screening programmes for specific sub-groups of the population may be beneficial but also carry risks. Therefore, specific conditions must be set, and evaluation and pilot programmes considered carefully. Appropriate information and non-directive genetic counselling should be made available and, in the case of serious diseases, the offer of specific individualised counselling be made mandatory. Appropriate changes in curricula in order to introduce relevant education and continuous professional development in the area of genetics are suggested. Public concern regarding genetic testing is grounded to some extent in the fear of misuse of genetic data and of inappropriate access to such data by third parties. Confidentiality and privacy with regard to all personal medical data, including those derived from genetic testing, are basic rights and must be respected.

The Group acknowledges the risk of discrimination as a result of genetic testing but notes that fear of discrimination extends far beyond genetics. Such discrimination may affect individuals, families, minorities or larger groups. Analyses and recommendations are proposed in the context of genetic test development and in the conditions set up for the use of these tests, both to ensure fair access and to avoid stigmatisation or stereotyping. For rare but serious diseases for which treatment is available, universal neonatal screening is proposed as a priority.

Although pharmacogenetics is currently still in a mainly exploratory phase, an increase in its application in healthcare is expected, and appropriate measures should be prepared in time for this evolution. The main aim of pharmacogenetics is to help deliver medicines to patients who are most likely to benefit and least likely to experience adverse reactions. Development of an appropriate harmonised legal, regulatory and healthcare policy framework for pharmacogenetics is recommended at EU level, taking into account research, therapy development, and clinical practice. Whether in clinical use or for research, and especially for research using biological samples and personal data, close attention has been given to informed consent, and several recommendations for various situations are proposed.

iv Follow up

The Group does not consider the report and the 25 recommendations as an end in itself but a step towards wider dialogue on genetic testing and related societal issues throughout Europe. The citizen and stakeholders conference held in May 2004 was the first opportunity to add a new dimension to such dialogue, and for the Group to share its experience with others.

The discussion on the 25 recommendations will continue as they have been translated into over 20 languages, including almost all the official EU languages, plus Russian, Chinese, Japanese and Arabic. A post conference report has been published and the public discussion continues on the website:

http://europa.eu.int/comm/research/conferences/2004/genetic/index_en.htm where the video of the conference "Human Genetic Testing – what implications?" is also displayed.

V Introduction

Background

In December 2002, the European Commission's Directorate-General for Research invited an independent high-level Expert Group to discuss the ethical, legal and social implications of genetic testing as a contribution to the Science and Society Action Plan's² aim to establish "a European public dialogue on ethics in science" (Action 30).

The Commission's aim was to create a European stakeholder dialogue on the sensitive issue of genetic testing. Representatives of civil society, including those from patients' groups, together with those of interest groups with opposing views, the healthcare industry and academic experts in the fields of genetics, ethics, law and social sciences, were invited to discuss the ethical, legal and social implications of genetic testing. Such a stakeholder debate could not easily be held directly with the wider European public because of the differences in languages. Therefore, this small group of independent experts³ coming from various national backgrounds was brought together to prepare the topic at a manageable level before entering into a wider citizens' debate.

Genetic testing, and the research and development underlying its application, is still at a relatively early stage of evolution. In Europe, for example, there remains a notable absence of relevant or clear regulations relating to genetic testing, and there are no initiatives or guidelines on how to inform the public, how to improve professional standards, etc. By creating an active dialogue between these different stakeholders, the Group had to discuss points of consensus and non-consensus, aiming always to reach a common position between the members who did not, a priori, share the same opinions on how best to move forward in genetic testing.

This very intense and fruitful discussion has resulted in two different products which can be read and understood separately:

- The "25 recommendations on ethical, legal and social implications of genetic testing" are published in a separate booklet and translated into 19 EU languages plus other major languages⁴;
- The report presented here is a working document that reflects the Group's long and interesting discussions.

The 25 recommendations (summarised in the executive summary) are also integrated in this report, but they are referred to in various places as the Group's broad discussion touched on the recommendations from different angles. The order of the 25 recommendations is therefore not strictly adhered to in the chapters of this report. For orientation, cross-references are given after this introduction. The 25 recommendations are listed under VI with references to the chapters of the report in which they are addressed. Several relate to more than one chapter. For each recommendation, the reference to the chapter where it is discussed most fully is printed in bold. The number of the recommendation is always quoted at the bottom of the box.

The Group's final report is offered as the basis for further discussion by and with the European public. It delivers observations, orientations and policy recommendations, and provides an analysis and synthesis of different aspects of the field of genetic testing identified by the different parties. It should assist interested groups in better understanding the topic and the necessary policy options. However, the report cannot be considered as a fully comprehensive document on the subject as its compilation was very much guided by the intensity of the discussion. It represents the consensus view of this independent Group, unless otherwise indicated.

From the beginning, the Group concentrated on the discussion of genetic testing within the healthcare system and related research. This was important, as all its members were convinced that the new technology could be beneficial to people in Europe, but that accompanying measures are urgently needed to prepare potential users in a sensitive way. Genetic tests in other contexts, such as insurance and employment, were not discussed or were only touched upon briefly. For further explanation of the scope and the intention of the Group's discussions, see chapter 9.

The Group discussed at length the definitions of terms used in the report. These definitions can be found in the glossary in Annex 2 – they also appear in the margins when the expression is first used. However, it should be noted that for many of these terms various definitions are possible depending on the context in which they are used. The report defines genetic testing broadly as: "any test that yields genetic data". The Group stresses the need to develop a global consensus definition of genetic testing and to define explicitly the terminology used in any official position or statement referring to it.

³ See Annex 1 for the composition of the Group

⁴ The 25 recommendations in all languages are available at: http://europa.eu.int/comm/research/conferences/2004/genetic/index_en.htm and can be obtained in print from the European Commission's Research DG on request

Recommendation on the need for standard universal definitions

That:

- a. any official statement or position should precisely refer to an explicit definition of the terms used or topic addressed;
- b. a consensus definition of genetic testing should be developed globally by all respective 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 Genetic Societies, and the International Conference on Harmonisation);
- c. the European Commission should consider taking the initiative on this topic.

See N° 1 of the "25 recommendations" document

The process leading to the compilation of this report is also an example of a new methodology for the study and open discussion of sensitive issues concerning science and technology in Europe. We suggest that this methodology could serve as a basis for further consideration and development in the field of public dialogue when addressing different stakeholders and, at the same time, all Europeans. EU citizens currently speak 20 different languages. In order to achieve a greater understanding and better support for important but culturally sensitive innovations, a more complex and step-by-step approach to public dialogue is needed.

The Group considered its work to be highly demanding. And knowing that the consensus of this small group should also represent the views of the wider public placed a high level of responsibility on each Group member. It was a preliminary experiment on how to prepare consensus in a small group and then expose it, after a thorough internal debate, to the wider public. The public debate with citizens in their own language is a crucial test of whether the recommendations are sustainable in the much wider setting of the complex values of culturally diverse citizens. If successful, the methodology would be able to create greater consensus and trust between different stakeholders in more complex settings than within a nation state.

The final version of the report was printed following the conference, so the conference was still able to influence the final shape of the report. The Group decided only to change minor wordings in the report where they thought that some stakeholders might have misunderstood their position.

The report will now be widely disseminated among interested stakeholders within European and non-European countries. To maximise public access to the document, the electronic version of the report will be included on the Commission's Science and Society web pages in German and French and English.

The initiative of the Expert Group contributed to and enriched the already ongoing discussion and actions on genetic testing within the European Commission's services (e.g. by the Institute for Prospective Technological Studies, the Working Group on Article 29 on data protection, and the European Agency for the Evaluation of Medicinal Products) and its activities (e.g. those carried out under the Strategy on Life Sciences and Biotechnology).

Today, it may be even more important that all the other competent international organisations (Council of Europe, OECD, UNESCO, WHO), as well as the national authorities dealing with these topics, take on board some or all of these recommendations according to their competences, and take them forward in the context of their own work. These organisations were regularly invited to the public hearings organised by the secretary of the Group Dr Maurizio Salvi of the "Ethics and Science" unit in DG Research. They were also invited during the conference to give some indications of what they could contribute to the promotion or implementation of the 25 recommendations. The extensive documentation compiled for the Group is also displayed on the Science and Society web page (http://europa.eu.int/comm/research/science-society/index_en.html)

VI List of recommendations

The 25 recommendations on the ethical, legal and social implications of genetic testing

General framework

1. Need for universal standard definitions see **Introduction** and Annex 2
2. Germinal and somatic genetic testing see chapter **9.1**
3. "Genetic exceptionalism" see chapter **3.2**
4. Public information and education see chapters 3.1.2, 7.2.1 and **8.1**
5. Public dialogue see chapters **3.1.2** and 9.1

Implementation of genetic testing in healthcare systems

6. Medical genetic testing and its context see chapters 1.2, **3.1.1**, 7.1.2 and 8.1
7. Quality assurance see chapters 1.4 and **8.2**
8. Population screening programmes see chapter **8.4**
9. Genetic counselling see chapter **7.1.5**
10. Data protection: confidentiality, privacy and autonomy see chapters 3.2, **4.1**, 7.1.4 and 7.2.2
11. Protection from discrimination see chapters 3.2 and **3.3**
12. Ethnicity and genetics see chapter **3.3.2**
13. Gender issues and genetics see chapter **3.3.1**
14. Social, cultural and economic consequences see chapters **8.3** and 8.5
15. Professional development see chapters **7.1.3** and 8.1
16. Partnerships and collaborations see chapter **2.1.2**
17. Regulatory framework and criteria for test development and use see chapter **6.2.2**
18. Rare diseases see chapters 1.4 and **6.2.3**
19. Pharmacogenetics see chapter **5**

Genetic testing as a research tool

20. Existing and new 'biobanks' see chapter **4.2**
21. Collections of human biological material and associated data and their uses see chapter **4.2**
22. Cross-border exchange of samples see chapter **1.4**
23. Informed consent see chapters 3.3.2, 4.1 and **7.1.4**
24. Samples from the deceased see chapter **4.1**
25. Consent procedures for children and vulnerable individuals in human genetic research see chapter **7.1.2**

The full text is displayed in the chapter printed in **bold**.

1 Genetic testing: state of the art

The understanding of human genetics has progressed steadily over the last few decades. The completion of the Human Genome Project is only one example of the new knowledge. The results of these findings are now being translated into clinical applications including diagnostics and therapies, and into the development of new concepts in predictive medicine.

The discovery of human genes, and of their variants potentially related to pathologies, predisposition, behaviour or physical characteristics, opens up new avenues for diagnosis, preventive healthcare and disease monitoring for rare genetic disorders. Sometimes these pathways are opening up for the first time, but more often they will serve more common chronic degenerative conditions and common disorders with a multifactorial pathology.

Technologies related to genetics are also enhancing our understanding of disease mechanisms and pathways, and of how medicines work in general. These developments have already had an impact on health systems and healthcare delivery, and this impact promises to become more substantial.

1.1 Technologies

Genetic testing and screening allow inherited variants in the genetic information stored in an individual's genetic material to be identified.

Human genes can exist in a number of different forms, known as **alleles**. All human cells, apart from sperm and egg cells, contain two copies of each gene – one inherited from the mother and one from the father. The two copies can be identical or different alleles. Sperm and egg cells contain only one copy of each gene, which is then passed on to the offspring.

The existence of different alleles for the same gene, known as polymorphism, is perfectly normal. Alleles first develop through chance variations of existing genes – a process called 'mutation'. Once established in a population through inheritance, they may contribute to individual characteristics like eye or hair colour. Some abnormal or mutated alleles, however, can be responsible for genetic disorders.

In some cases, the presence of only one abnormal allele is sufficient for the development of a disorder. The allele is then said to be dominant and there is a 50% chance that each of his/her children will inherit the dominant allele from an affected parent. Huntington's chorea, a disease affecting the nervous system, is an example of a dominant genetic disorder.

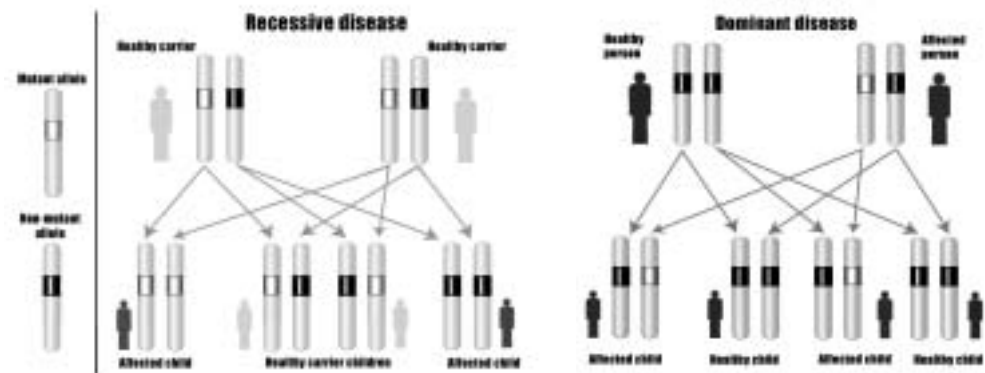
If two identical copies of the abnormal allele are necessary for the disease to develop then it is said to be recessive. If an individual has only one copy of the recessive allele, he/she will not develop the disease but may pass the abnormal allele on to his/her children. Such individuals are called carriers. Only when both parents are carriers is there a risk of their children developing the disease. In this case, each child has a 25% chance of inheriting two recessive alleles and therefore of being affected by the disorder. Cystic fibrosis is a recessive genetic disorder.

■ Allele

One of a number of different forms of a gene. Each person inherits two alleles for each gene – one allele from each parent. These alleles may be the same or may be different from one another.

Figure 1 shows how recessive and dominant genetic disorders can be passed on from one generation to the next.

(Source: "Tests génétiques", Repères collection, Inserm, July 2003)



■ DNA

Deoxyribonucleic Acid. A nucleic acid that is the main constituent of the chromosomes of all organisms (except some viruses). DNA is self-replicating, plays a central role in protein synthesis, and is responsible for the transmission of hereditary characteristics from parents to offspring.

■ RNA

Ribonucleic acid. A nucleic acid similar in structure to DNA that is found in the cell nucleus and cytoplasm. RNA transfers genetic information from DNA to the cytoplasm and plays a key role in protein synthesis and other cell activities.

■ Chromosome

A grouping of coiled strands of DNA and other accompanying molecular structures containing an organism's genes and found in the nucleus of cells. Sexually reproducing organisms have two copies of each chromosome, one from each parent. Humans have 23 chromosome pairs.

A number of different methods are used to investigate the composition of genetic material, like **DNA**, **RNA** and their products, such as proteins, carbohydrates and lipids, and to detect the presence of abnormal genetic variation. These include:

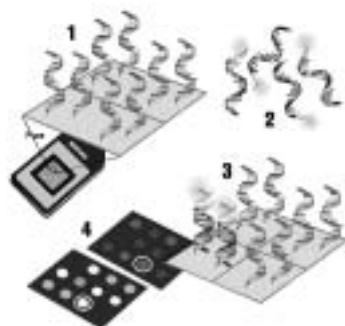
- Cytogenetic analysis – the study of **chromosomes** (the structures inside the nucleus which carry genetic material) and chromosome abnormalities;
- Molecular analysis – the analysis of DNA or other nucleic acids;
- Biochemical analysis – the analysis of proteins or other biological molecules;
- Immunochemical analysis – the identification of a protein or other molecule by its immunological reaction to antibodies.

These different methods can be used individually or in combination. A biochemical analysis may, for example, show that a particular protein is present in a cell. That protein may be known to be the product of a gene variation. However, to identify precisely the specific gene variation present, a second method such as molecular analysis of the DNA may be used.

Using one or more of these methods, genetic testing can yield different types of information such as:

- Confirmation or exclusion of the diagnosis of a specific disease;
- The magnitude of the risk of developing a disease or of adverse reactions to treatments and environmental factors;
- The magnitude of the risk that biological descendants will inherit a defect.

While the methods mentioned above are the basic tools used in genetic testing and screening, ongoing genetic research on the human genome requires much larger-scale technology. The large amount of information resulting from the sequencing of the human genome necessitates high-throughput technologies which can rapidly examine large amounts of genetic material, and the extensive use of computers to analyse the associated data (bioinformatics). Microarrays are one of the commonest high-throughput technologies used in genetic testing.

Figure 2: A microarray

(Source: "Tests génétiques", Repères collection, Inserm, July 2003)

1. The surface of each **microarray** is divided into a number of tiny squares, each of which receives a number of copies of different DNA sequences associated with a known gene, or gene variant.
2. Fragments of mRNA, another molecule corresponding to the active genes in the cell being analysed, are isolated and 'marked' with a fluorescent substance.
3. The RNA solution is poured on to the microarray and the fragments of mRNA fix themselves to their corresponding DNA sequence.
4. The fluorescent markers on the mRNA show where the active genes are present.

Certain rare collections of DNA samples, used to study the association or linkage of genetic variation with disease, and its inheritance pattern within a particular family, may constitute non-renewable resources only available to a limited number of laboratories. Technologies to amplify DNA, providing many copies from one original DNA sample, are now being used in a growing number of research and diagnostic applications to enable more researchers to have access to such material. Whole **genome** amplification methods are also being used to generate the large amounts of DNA that may be required for genetic testing.

1.2 Genetic testing and screening: current and future possibilities

Genetic testing can be performed on individuals as well as core or extended families. The term screening is usually reserved for systematic testing for inherited genome modifications of the members of defined populations or high-risk population sub-groups. As the relevant high-throughput technology improves and its cost decreases, it will also be possible to screen the genome of individuals for a series of inherited variants.

Since the composition of an individual's chromosomes and DNA are fixed at fertilisation (except in lymphocytes), most tests can be done at any stage of life, either before birth (pre-implantation and prenatal diagnosis) or after birth (neonatal and adult screening and testing). Nevertheless, in most genetic testing centres the testing of children is, and will be, strictly limited to those cases in which a diagnosis is important for disease management or therapy.

Genetic testing is, or should be, carried out in specialised laboratories under the supervision of skilled laboratory technicians and trained geneticists. Tests are either performed using scientific protocols developed in-house, or by using diagnostic kits – standardised packages of components and instructions provided by manufacturers of diagnostics. For many genetic tests, diagnostic kits do not yet exist, so a large number of tests are still being carried out using protocols developed in the genetic testing laboratory itself, based on published scientific literature or other in-house protocols⁵.

Although molecular genetics and genomics have developed rapidly over the past decade, it is important to bear in mind that genetic information has been used for many years in medicine, even before the

■ **Microarray**

A glass (or plastic) slide on to which thousands of small DNA molecules (or fragments of other biological molecules) are attached at fixed locations, known as 'spots'. Microarrays allow comparison of gene expression between two different samples of biological material.

■ **Genome**

An organism's set of chromosomes, containing all of its genes and associated DNA. The sum of all the genetic material present in each cell in an organism.

■ **Fragile X**

A genetic condition resulting from a mutation of the FMR1 gene located on the X chromosome causing a wide range of mental impairment, from mild learning disabilities to severe mental retardation. It is the most common cause of genetically inherited mental impairment.

■ **Down's syndrome**

A genetic condition that causes delays in physical and intellectual development occurring in approximately one in every 800 live births. Individuals with Down's syndrome have 47 chromosomes instead of the usual 46. It is the most frequently occurring chromosomal disorder.

■ **Phenylketonuria (PKU)**

A rare genetic metabolic disorder characterised by an inability of the body to utilise the essential amino acid, phenylalanine, contained in protein foods. It results in mental retardation and other neurological problems when treatment is not started within the first few weeks of life.

■ **Hypothyroidism**

A disorder affecting the thyroid gland which produces a hormone needed for normal growth and development. Only certain forms of the disorder are inherited.

era of molecular genetics. Examples include blood group typing before transfusion, and assessment of human tissue compatibility before transplantation to avoid rejection.

The following major categories of genetic testing or genetic screening can be distinguished:

1.2.1 Diagnostic testing

Using one of the technologies cited above, the genetic information of an individual is probed for defects or variants in one or more genes to confirm or exclude a specific disease diagnosis. In the same way, carriers of genetic defects can be identified. These tests are usually done for diseases with a strictly genetic basis, either before or after birth. Postnatal cytogenetic tests, based on the study of the chromosome, represent about 35% of the workload of genetic laboratories, while molecular tests account for about 40%. The remaining 25% of the workload comes from prenatal tests.

In some centres, multiple prenatal tests using the same biological sample are offered for cystic fibrosis, **fragile X** disease, **Down's syndrome** and thalassaemia. Carrier tests are offered separately for cystic fibrosis, fragile X disease or thalassaemia, but attempts are being made to combine tests for these different diseases. (See Annex 2 for a full description of these diseases.)

When the causative genetic variation is known, biochemical and cytogenetic testing is often complemented by molecular testing to ensure a more accurate diagnosis. After precise identification of the genetic variant in a family, testing for this variant can also be used in carrier testing of family members or in prenatal diagnosis.

1.2.2 Diagnostic screening

The following types of screening are included in this category:

- a) **Prenatal screening** for major chromosome and neural tube defects is routinely done in most countries using serum tests combined with ultrasound imaging. Confirmation of the diagnosis is carried out using cytogenetic methods involving chromosome analysis.
- b) **Neonatal screening** for treatable diseases such as **phenylketonuria** (PKU) and **hypothyroidism** is available in all EU countries, mainly through use of low-cost biochemical tests on blood spots taken from new-born babies (known as Guthrie card tests). For other diseases, like **galactosemia**, screening procedures vary. Neonatal screening for cystic fibrosis has recently been implemented in some countries. In these cases, molecular testing is used to confirm the biochemical test.
- c) **Carrier screening** for cystic fibrosis is recommended and performed in the US, but is not yet being implemented in most European countries, except in cases of male infertility. It has been introduced in the UK and is under consideration in a number of other countries, including France and the Czech Republic.

1.2.3 Predictive testing

The tests in this category cover a broad range of diseases and acquired conditions and can lead to the prediction of the future health status of an individual. However, the dividing line between strictly inherited and acquired conditions is not always clearly defined. Two different groups of predictive tests can be distinguished, based on the nature of the information resulting from them:

a) Presymptomatic tests

The presence of defects in certain specific genes or gene products creates an almost 100% risk of developing a particular disease later in life. Huntington's chorea, Hereditary Polyposis Coli carcinoma (a form of hereditary colon cancer), some rare forms of Alzheimer's disease, and some forms of familial hereditary thyroid carcinoma are the diseases most frequently tested for in **genetic centres** under this category, representing about 5% of their present workload.

b) Predisposition tests

- i) This category includes tests for other disorders in which defects in a single major gene are considered to increase substantially lifetime risk of developing the disease, such as hereditary breast/ovarian carcinoma and HNPCC (**hereditary non-polyposis colon carcinoma**). In addition, it includes tests for the combined presence of a series of inherited variants of genes or gene products, which increase the risk of developing a particular disease, moderately or significantly – including common multifactorial diseases and **traits** such as psychiatric disease, cardiovascular disease, diabetes, rheumatoid arthritis, and osteoporosis. With the exception of some tests for genes involved in hemochromatosis, blood clotting or cardiovascular diseases (e.g. Factor V Leiden, and Angiotensin Converting Enzyme), which still require further development, very few clinically useful tests are currently available for this category of disease although some commercial diagnostic kits are on the market. As our knowledge about these diseases increases, this group of multifactorial diseases could potentially become by far the largest target for genetic testing in the future.
- ii) Pharmacogenetic tests, which determine the predisposition of individuals to react differentially to drugs, can also be placed in the group of predisposition tests. For some medicines, pharmacogenetic research will ultimately result in doctors being able to select the medicine that is most likely to benefit a particular patient and/or the dose that is most appropriate. At present, pharmacogenetics is not a widespread clinical practice. However, many pharmaceutical companies today routinely include genetic and genomic analyses in clinical medicine development. The topic of pharmacogenetics is covered in full in chapter 5.
- iii) Tests for monitoring disease outcome and possible complications are also finding an important application in the diagnosis and/or prediction of the evolution of early disease stages (e.g. in particular cancers). A growing number of applications are slowly moving into clinical practice.

It is clear that as our understanding of the function of all the DNA sequences that make up the human genome increases, other possibilities for testing and screening will become available, leading to an increase in the accuracy and predictive power of the tests. Indeed, modulators of gene expression – other genes, non-coding DNA sequences, proteins involved in the three-dimensional organisation of the DNA or acquired but heritable modifications of the DNA – will be identified. As a result, most of today's simple tests will have to be complemented with tests allowing more precise predictions of the risks of developing a particular disease, its likely progression, and its phenotypic characteristics.

Proof of **clinical utility** and subsequent validation of all genetic tests are prerequisites before their implementation into clinical routine.

See also recommendation on medical genetic testing and its context (N° 6)

1.3 Research approaches for the identification of genes involved in diseases

The human genome contains approximately 30 000 genes, and the DNA located between these genes, rather than the genes themselves, constitutes the largest part of the genetic material. Only 0.1% of the genome varies from one person to another. This corresponds to one variation in every thousand nucleotides among the 3 billion nucleotides making up the DNA of the human genome.

The human genome could be compared to a huge multi-storey car park. In each parking space there is either a car, a lorry, a bus or a van, depending on the space available. These vehicles represent the genes. For any given parking space, there is always the same type of vehicle, but it could be a different colour, have a different type of engine, or have added features, for example. These different 'options' are equivalent

■ **Galactosemia**

A rare genetic metabolic disorder resulting from the absence of the enzyme needed to convert galactose, a by-product from the digestion of dairy products, into glucose.

■ **Genetic centres**

Academic centres where genetic clinics, diagnostic laboratory facilities (genetic services) and research are concentrated in one structure.

■ **Hereditary Non-polyposis Colorectal Cancer (HNPCC)**

A genetic condition resulting in an increased tendency to develop colorectal cancer. Mutations in one of five genes are now known to be responsible for most cases of HNPCC.

■ **Trait**

A distinguishable feature or characteristic that can be linked to a genetic marker.

■ **Clinical utility**

The impact of a test on clinical decision-making, and medical or health economic outcomes.

■ **Genetic marker**

A gene, or other identifiable portion of DNA, which can be located on the chromosome and which exhibits enough variation between individuals for its inheritance to be traced.

■ **Genetic component of disease**

The genetic part in the cause(s) of a disease. Several factors may influence the occurrence or development of a disease. Some of them may be of a genetic nature. Their relative importance in the disease process may be variable. A disease can be caused by one gene (monogenic disease) or depend on several genetic factors (multigenic disease). When genetic and non-genetic factors are involved, it is referred to as a multifactorial or complex disease.

■ **Population genetics**

An investigation of the genetic variations – polymorphisms and mutations – which exist between individuals in one or several populations. It looks at their distribution in populations and their consequences at the population level.

to polymorphisms. This image helps to explain how each of us has a particular combination of features which make us biologically unique even though the general characteristics of our genomes are shared.

If a specific variation in DNA sequence has a known location on a chromosome, it is called a **genetic marker**. Such markers constitute important tools for studying the **genetic component of diseases**. The number of genetic markers that can be used for studying genome variation is rapidly increasing as knowledge of the genome progresses. These variants are often related to the function of genes. They may play a role in the development of common diseases and in the responses of individuals to treatment. They may also give clues for the development of new medicines. Data on genome variation is therefore of primary relevance, not only to academic and medical geneticists but also to biotechnology and pharmaceutical companies. The availability of automated molecular techniques and bioinformatics tools makes large-scale screening for variants from small amounts of biological material much easier and faster.

Before a genetic test is developed, the genetic basis of a particular disease needs to be well understood. Different conceptual research approaches, including the study of **population genetics** and genetic epidemiology, are necessary. These disciplines rely on the use of human biological samples and population, family and/or clinical data.

1.3.1 Population genetics and family analyses

Genetic differences between individuals also result in genome variation across populations. The distribution of genetic variation varies according to population and geographic origin. The discipline of population genetics investigates the genetic characteristics of populations and how populations differ genetically from each other.

Genetic epidemiology investigates genetic risk factors, their contribution to the cause of a particular disease, and/or the interaction between genetic factors and the environment that may influence the development or course of that disease. Studies in genetic epidemiology form the basis for the localisation and subsequent identification of the genes involved in diseases, and may precede the understanding of their functions. Prevalence of diseases in populations, and frequency of relevant genetic markers are essential for the assessment of disease risks associated with these genetic markers. Knowledge of the population distribution of the variants involved in diseases is also crucial to the commercial development of genetic tests. It allows developers of genetic or pharmacogenetic tests to detect the most relevant variation in a gene in a given population, where numerous variants of that gene exist. Population-based research is therefore essential for optimised design and application of genetic testing.

Genetic epidemiology is performed on population data or on family data. The discovery of the gene involved in a specific disease has often relied on the study of large families which include several cases of the same disease, along with good associated clinical data and samples to enable testing of genetic markers. Analysing numerous families maximises the power of the genetic analysis. Knowing the geographic/ethnic origin of the families allows the distribution of genetic variation across populations to be taken into account.

1.3.2 Methodological approaches

There are two main methodological approaches to discovering genes involved in diseases. The “gene candidate approach” consists of testing a small number of previously identified genes with known variations. This method assumes a good hypothesis for the implication of the gene variation in the disease process. The “genome screen approach” does not rely on a prior specific hypothesis and consists of testing a large number of genetic markers distributed over the genome. The regions of the genome with a high probability of containing genes of interest for the disease in question are localised in a step-by-step approach by identifying which genetic markers are good disease indicators.

Both types of study require large collections of genetic material to be available from individual patients affected by the disease, from their families, and from groups of unaffected individuals for comparison (see chapter 4). For both approaches, relevant data on family structure, ethnic origin, medical and environmental information must be available on those individuals

1.4 Current provision of genetic testing: market and quality issues

The quality of genetic testing services, including accuracy of test results, proper handling of samples and data (in terms of informed consent and privacy) and also pre- and post-test counselling, is of the utmost importance and should be considered as an ethical issue in its own right. With samples increasingly transported across borders within Europe, as indicated by recent surveys (OECD⁶, or the EU-funded Eurogenbank project⁷), quality control needs to be tackled at a European level.

Recommendation on cross-border exchange of samples

That:

the European Commission evaluates the need for, and the feasibility of, developing harmonised standards for the research use of human samples and associated data (including informed consent issues), taking into account relevant international conventions on cross-border exchange of samples.

See N° 22 of the "25 recommendations" document

At present, genetic testing is a small-scale activity compared to the market for testing in general pathology, microbiology or clinical chemistry. **Molecular genetic testing** in Europe is thought to account for approximately 200 000 – 300 000 clinical reports from some 300 centres at a cost of €65-97 million.

The demand for genetic testing has increased substantially over the last few years. A recent report⁸ clearly shows that the number of tests performed in many European countries has doubled or tripled since 1997. To further illustrate this, some recent figures for Italy are given in Table 1:

Table 1: Genetic testing in Italy: a survey of the situation in 2002

	Number/%	Increase per year
Diagnostic laboratories	306	n.a. (not available)
– Cytogenetics	159	n.a.
– Molecular	147	n.a.
– Accredited	24%	n.a.
Cytogenetic tests	230 000	17%
Molecular tests	164 000	19% (43% of which prenatal)
Genetic counselling given with the tests	20%	n.a.

(Courtesy of the Italian Society of Human Genetics)

⁶ OECD (2001)

⁷ Hirtzlin, I. et al. (2003)

⁸ Ibarreta D., Balzi E. et al. (2003)

■ **Molecular genetic test**
A genetic test that involves the analysis of DNA or other nucleic acid.

A confident prediction is that the genetic testing sector will grow rapidly over the next ten to 15 years and spread beyond the small number of specialist genetic centres now active. This is already taking place in the US. Market structures are expected to change according to demand and more private laboratories and companies will offer genetic testing. This situation presents an opportunity to influence quality assurance standards at an early stage of the field's development.

This is particularly important as recent figures for Europe⁹ indicate that a substantial number of technical and clerical errors are still being made in test results and clinical reports, suggesting that a major effort towards improving quality assurance of the different aspects of genetic testing will be necessary, including the development of reference materials.

Current efforts to harmonise the quality of genetic testing services in Europe (through external quality schemes and proficiency testing) are fragmented, and information about the provision of quality services in EU countries is not available. There are also no procedures in place to guarantee that information contained in the numerous medical genetic databases and bioinformatics tools used in diagnostics conforms to quality standards. Analytical and clinical validation of tests is only available on a limited scale and requires input from relevant experts at the European level.

At the same time, issues pertaining to patient rights and informed consent, to the effect of gender on testing, and to the effect of patenting on the availability and costs of tests, may have a major impact on the provision and quality of the tests. Some of these dimensions did not receive adequate discussion and documentation during the Group's work.

A consistent regulatory framework assuring a high standard of quality control for genetic testing services, including a system of accreditation of genetic testing laboratories, needs to be developed. However, any regulatory framework should take into account that rare diseases require specific attention regarding provision and quality assurance of genetic testing services. Because of their very low prevalence in the population, genetic tests for rare diseases are unlikely to be converted into diagnostic kits, and will remain **'home-brew'** tests – i.e. based on methods developed in-house. Nevertheless, these need to be quality-assured and performed by accredited laboratories. It is essential to establish a European or even intercontinental network to enable patients, wherever they are, to access appropriate test results for rare diseases. Networking laboratories is likely to be the only way to assure high-quality provision at minimum cost by achieving a sufficient volume of tests for efficient service delivery in expert centres, and a minimum number of laboratories for quality-assurance schemes to be viable.

■ **'Home-brew'**
Tests or research
protocols developed
in-house and
not available
commercially.

See also recommendation on rare diseases (N° 18)

Genetic testing is clearly not being developed for the benefit of those who do it, but the retention of high-value jobs in this and related sectors (such as *in vitro* diagnostics, pharmaceutical development, laboratory equipment and instrumentation) is nevertheless an issue that needs to be addressed. Europe must develop and maintain genetic testing capabilities through the public sector, industry and public-private sector partnerships. Quality genetic services may have large economic potential, including for small and medium-sized biotechnology companies, and will help to ensure European competitiveness in this area.

European society will benefit from genetic testing as it develops. The keys to developing genetic testing as a service industry will be its reliability, throughput, turn-around time, accuracy and cost. Quality assurance is at the heart of maintaining customer confidence in this type of industry. Service providers that fail to implement quality assurance are likely to suffer unacceptable rates of diagnostic error,

increased medico-legal costs and a diminished market share as their reputation suffers. Inappropriately low quality puts patients at risk and results in unacceptable costs for healthcare systems. Competition in this market is already significant, and quality assurance systems standardised by self-regulation or authority-imposed regulations are required not only to eliminate 'pirates' offering inferior quality for the more lucrative tests but also a 'level playing field' for both European and other international public and private-sector service providers.

See also recommendation on quality assurance (N° 7)

2. Stakeholders: prevalent views, concerns and expectations

The successful development and use of genetic tests is dependent on the interests and concerns of a wide range of stakeholders being recognised and responded to constructively. Failure to take this into account will result in a loss of confidence by certain stakeholders and could lead to an interruption in the developmental pathway that a **diagnostic test** follows from innovative scientific idea to clinical utility.

2.1 Stakeholder groups

The following groups may have a legitimate interest in the development and use of genetic tests:

- Patients and their families
- Researchers in basic and clinical sciences from the public and private sectors
- Clinicians and other healthcare professionals
- Healthcare authorities, providers and policy-makers
- Healthcare industry
- Politicians
- The public, consumer groups and other public 'watchdogs'
- The disability movement
- Non-medical interest groups (insurers, employers, etc.)
- Ethics bodies and legal professionals
- Media

In addition to the above stakeholders, the Group also discussed regulatory agencies for pharmaceutical and device development and approval.

Whilst many of the interests and concerns of these groups overlap, others are specific to single stakeholder groups.

2.1.1 Patients and their families

Patients at risk from a disease with a significant genetic component, and their families, have a direct interest in the development of, and access to, genetic tests. In classifying the 'utility' of any given test, a number of questions come to mind. These relate to the information potentially available from the test in question, whichever way this is accessed (by DNA analysis, examination of chromosomes, or clinical examination, for example).

Before suggesting a diagnostic test, it is necessary to consider the salience of the information to be revealed to the family – the power to discriminate between those at risk or affected by the condition in question,

■ **Diagnostic test**
A test providing information primarily 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.

■ **Predictive**

Indicative of a particular condition that is not clinically evident at the time of testing, i.e. that causes no clinical signs or symptoms, and that is only discernible based on the genetic test.

■ **Genetic polymorphism**

Natural variations in a gene, DNA sequence, or chromosome that are not necessarily associated with adverse effects on the individual and occur with fairly high frequency in the general population.

■ **Genetic disease**

A disease that has its origin in changes to the genetic material, DNA. Usually refers to diseases that are inherited, although some forms of cancer also result from DNA mutation.

■ **Alkaptonuria**

A rare inherited disorder resulting from an enzyme deficiency that leads to a build up of homogentisic acid in the body. It can cause premature osteoarthritis. The urine of affected people turns black.

■ **Genetic test**

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.

and those who are possibly carriers or not affected. Into this, it is important to factor familial perceptions about inheritance patterns within their families (“In our family it works like this ...”). There are also the implications of the test results for the individual and the wider family to consider. These may be clinical, relating to the likely development of the disorder, familial, where the family dynamic will be altered by the revelation of the existence of a genetic disorder, or societal. The individual and the family’s ability (or their perception of their ability) to function in society will potentially be altered by knowledge of their ‘genetic status’. This may have particular importance for various cultural, religious or ethnic groups.

Whether a test is used for diagnostic, **predictive**, predispositional or for some other reason is also an element that needs to be considered, particularly as the information from the test may have different implications for each family member, depending on their proximity to the individual first identified as affected.

The consequences of a genetic test on the individual can also be affected by the person providing the test result. There is evidence, for example, that obstetricians tend to be more direct than clinical geneticists, whilst other clinicians may concentrate on the immediate clinical implications, neglecting the familial aspect.

In situations concerning a mutation for a highly penetrant gene with a high probability of causing disease, the decision to be tested may be taken with a view to benefiting others (such as children) where the result can be used to establish the likelihood of future offspring carrying the same gene mutation. The result may also help parents to understand why their offspring are affected and may lead to a consequent reduction in feelings of guilt or blame.

2.1.2 Researchers in basic and clinical sciences

Notwithstanding the huge advances in our knowledge of genetics, there are still many common conditions, such as migraine, asthma, diabetes and heart disease, which involve genetic predisposition and which cannot be tested for reliably and effectively. Genetic testing for susceptibility to these disorders will eventually cover a larger field than diagnosis of diseases directly caused by mutation of a single gene.

Since the description of the first **genetic polymorphisms** (recognition of ABO blood groups in 1900), and the discovery of the first **genetic disease (alkaptonuria)** in 1908, fundamental research in molecular genetics has led to numerous discoveries resulting in new **genetic tests**. For example, technology for amplifying DNA, developed in 1985 (see chapter 1.1) has increased the feasibility of using genetic techniques in various applications immensely. Genetic tests have largely developed from both basic research and large international genome exploration programmes.

Developing these tests and bringing them to the point where they can be produced clinically or commercially requires skilled individuals willing to make a commitment to this field. This, in turn, means they must have a reasonable expectation of being able to make a long-term career in this area of research. Insecurity and lack of opportunity for personal and professional development will result in many researchers being diverted to other areas.

For effective development of new tests and products, there must be a productive interchange between academic scientists and those from industry. Sometimes it can seem that academics are relatively powerless in influencing commercial decisions on the development of new tests and products. A framework for transparent collaboration is recommended.

Recommendation on partnerships and collaborations

That:

- a. the European Union stimulates and supports partnerships between stakeholders;

b. a framework for transparent collaboration between industry and academic scientists be established.

See N° 16 of the "25 recommendations" document

2.1.3 Clinicians and other healthcare professionals

Healthcare professionals must have the appropriate skills and knowledge to appreciate the significance and the salience of the information to be revealed from a genetic test. Awareness of the availability of a test is the starting point – which, in a rapidly changing field, raises issues of continuing professional development. If the professional does not know that a test is available, the chances of a family receiving it are inevitably considerably reduced.

The necessity of a test being administered or interpreted by a medical doctor, rather than another professional, may vary between healthcare systems in different countries¹⁰.

2.1.4 Health authorities, providers and policy-makers

Predicting the future demand for tests and the mix of skills and resources required to meet this demand in a timely, cost-effective and efficient manner requires sensitive planning and forecasting techniques. Genetic testing services are often small-scale consumers of resources compared with other areas of healthcare. If insufficient attention is given to genetic testing service delivery at a sufficiently senior level in the healthcare planning hierarchy, progress and access to tests may be limited. Different types of genetic tests can have very different levels of clinical impact. Diagnostic genetic tests or highly predictive genetic tests for a number of monogenic diseases can be of extreme importance for very few people, while susceptibility tests which constitute only one of many different elements to evaluate either a risk for, or the presence of, more common diseases, but which have little clinical utility, may be applicable to many more people.

In healthcare systems struggling to adopt innovations whilst controlling expenditure, there can be a temptation to consider the use of genetic testing or screening as an economic tool – using the predictive power of genetic tests to determine eligibility for treatment and/or the allocation of scarce resources. Where such an approach is suggested, the rationale for adopting it must be robust, transparent and open to challenge, and have the patients' interests in mind.

2.1.5 Healthcare industry

Prior to investing in the development of diagnostic kits for genetic testing and/or the setting up of commercial testing services, companies must have a reasonable expectation that the test or service will be bought and used. To ensure survival, private companies need to be profitable. In this context, products only needed by a very small population (like those for rare diseases) are less likely to be of commercial interest and therefore less likely to be developed.

Whilst no guarantee of uptake by healthcare systems can be given (indeed, such a guarantee may be inappropriate), there needs to be a robust and transparent mechanism allowing the development and supply of such products and services to healthcare systems and the families they serve. Any such mechanism needs to take into account issues of quality (see chapter 1.4) and intellectual property rights.

2.1.6 Politicians

Genetic testing is a potentially sensitive issue. The questions of whether or not to develop genetic testing, under what circumstances, how quickly, and under what type of regulatory regime all have a political

dimension. Creating an environment in which the inputs from different stakeholders – commercial, professional and public – can be balanced and evaluated is a key political skill. With respect to genetic testing, a balance needs to be struck between the extent of regulatory intervention required and the need for innovation (which rarely prospers in a tightly regulated environment).

2.1.7 The public, consumer groups and other public ‘watchdogs’

Genetic testing may evoke both optimism and excitement, or anxiety. Public perception of genetic testing is affected by civil as well as medical uses: the forensic application of DNA databases for the pursuit of criminals enjoys quite high levels of support in most European societies, whilst anxieties about other uses, such as insurance or employment, may jeopardise the acceptability of genetic testing programmes. These perceptions, whether based on fact or not, will affect the opportunities available to develop and use genetic testing, as well as other research relying on the use of human genetic data, and illustrate the need for balanced public education and awareness programmes.

Watchdog and consumer concerns focus on the protection of the individual or of specific groups and the need to avoid the consequences of abuse that could arise from the misuse of genetic test results.

It is important to note that the vast majority of the general public have no direct experience of genetic testing or do not perceive the genetic dimension of a number of common tests (blood group typing being the most common). Their understanding is shaped to some extent by what they see in the media – both factual and fictional. However, if their direct experience increases, which is likely if the practice of drug prescription linked to genetic diagnostics (pharmacogenetics) becomes more widespread in the next few years, then attitudes may change significantly.

The attitude of the public toward genetic technologies is also likely to be strongly influenced by the reaction of the scientific community and other professionals to their concerns, and how confident people are that their best interests are being respected.

2.1.8 The disability movement

While many patient and family support groups are in favour of genetic testing, the disability movement often takes a broadly oppositional stance to genetic testing. This is based on an analysis that sees disability as a social rather than a medical problem, calling for disabled people to be embraced as part of the wide diversity of humankind. There is a fear that genetic testing will result in a resurgence of eugenics, questioning disabled people’s right to life, and an increase in pregnancy termination among families expecting a child deemed to be other than ‘normal’.

The disability movement fears that the medicalisation of disability, and the absence of any input from disabled people to the counselling of parents-to-be, could create subtle pressure to terminate affected pregnancies as part of a wider programme to cut healthcare costs by reducing the number of births of disabled babies.

Whether or not the worst-case scenario evoked here could ever become a reality is an open question. However, the perception that genetic testing might be used in this way is real and cannot simply be dismissed as misguided.

2.1.9 ‘Non-medical’ interests

Genetic testing is of interest in a number of non-medical contexts. The interest of insurance companies in using genetic test results as a tool for stratifying risk and adjusting premium levels accordingly has been extensively discussed elsewhere¹¹. In most European countries, there seems to be strong public

opposition to the use of genetic test results for this purpose, based on the sentiment that the information would serve the profitability of private companies, rather than the consumer.

Despite the absence of evidence for the current use of genetic testing as a screening tool in the context of employment in Europe, there is a fear that genetic tests will be used for this purpose. This is particularly prevalent with regard to stigmatised conditions such as psychiatric disorders (“You’re not mad now, but we know you will be”), cancers with a high genetic component, like some breast cancers, or chronic, expensive conditions. Whilst there may be some grounds on which it might be legitimate to use genetic tests in employment contexts (for example, when a clear and substantial link to significant third-party risk can be demonstrated), these are few, and certainly much less common than is sometimes assumed to be the case, as underlined in Opinion 18 of the European Group of Ethics in Science and New Technologies report on ‘Ethical aspects of genetic testing in the workplace’¹².

2.1.10 Ethics bodies and legal professionals

Ethics committees, whether local (research ethics committees, for example), national, European, or international, play a role in shaping public opinion through the provision of balanced opinions for debate, of advice to authorities, and by influencing practice. Their multidisciplinary and independence are especially important. It is desirable to have a clear definition of the role of each kind of committee. Currently, the number and role of such bodies varies between countries.

Through the examination of relevant research protocols, the research ethics committees shape the way ethical issues are dealt with in science. Although this is not specific to genetic testing and related research, they do play an important role in genetics (see chapter 3.2).

The legal dimension is of paramount importance in the general landscape of the human rights framework and the application of health law that is also applicable to the area of genetic testing (see chapter 3.2.4). The Group underlines the importance of the education of professionals involved in genetic testing, both in ethics and in relevant legislation.

2.1.11 The media

Genetics and genetic testing are ‘hot topics’ for both fictional and non-fictional media channels, and they have an important role to play in forming public perceptions of genetic testing. Virtually every citizen, in the developed world at least, will be exposed to the media on a daily basis.

Whilst it might be assumed that the role of non-fictional media is to inform (and possibly even educate), this is, in fact, a secondary goal, and often one which comes a long way behind the primary one of entertaining the reader or viewer. Failure to entertain will result in consumer ‘turn-off’, with a consequent loss of revenue, and a lost opportunity for the reader/viewer to engage with the issues.

To capture and retain public engagement, the organs of the media must respond to the reality of public involvement. Thus the reporting of events will tend to emphasise controversy at the expense of consensus, and exaggerate progress or threat.

The media will also tend to fixate on issues which create good copy, such as the use of genetic testing in insurance – even when these are only directly relevant to particular sub-populations – without drawing distinctions between the general and the particular. The need to work to tight deadlines, and the self-referential culture of media outlets tends to make stories self-perpetuating as reporters and researchers will often use their own or other media archives as a source to confirm their own working hypotheses. As a result, there is a tendency to overplay the power of DNA-based testing with “Genetic breakthrough”-type headlines which are not always justified.

¹² European Commission European Group on Ethics in Science and New Technologies (2003)

Genetics is also a driver in literature (e.g. *Brave New World*), television drama and film (e.g. *Gattaca*). Here, the emphasis is generally on the deterministic power of DNA, with the power of environmental, lifestyle or therapeutic interventions to alter or moderate the effect of the genetic ones either ignored or minimised.

Of course, the media are not solely responsible for the public presentation of genetic information. Other stakeholder groups, whether industrial, academic, political or voluntary, are to a greater or lesser extent adept at using the media agenda to their own advantage.

2.2 Stakeholders in the wider context

Genetic testing is subject to a wider public and political debate about the relationship between the individual, the family, the community and society, and the role of science, industry, politics and the law in framing the context in which we operate as individuals and as citizens, able to assimilate and manipulate information derived from scientific advances.

In structuring the consideration of genetic testing issues it is important to give due weight to opinions expressed by different stakeholder groups. It would not seem unreasonable that 'proximity' to the issue ought to be a significant factor. Individuals and families for whom the outcome of a genetic test may impact on major decisions have a stronger claim to be heard than those further removed from the issue. Parents wishing to avoid the birth of a child with a severe genetic disorder should not be made to feel guilty about their decision. Nor should they be expected to shoulder responsibility for a wider societal 'good' that may be derived from "the need to maintain diversity".

Genetics, and the impact of genetic testing in particular, can act as a 'lightning conductor' for concerns about bigger issues such as the power of government and industry and the relative powerlessness of the individual. Widespread ignorance of, for example, existing regulatory frameworks and the activities of interest groups (often coming together in unusual partnerships such as the coalition between the disability movement, some church groups, the anti-abortion lobby, and environmentalists on some genetic issues) leaves the public feeling unsure and vulnerable. Opinion surveys reveal a decline in trust in governments and industry although, in general, public confidence in the medical profession remains high – but even here the nature of the relationship is changing and if trust were to be undermined substantially it would be hard to restore.

3. Specific issues underlying the dialogue on genetic testing

A number of specific issues were given particular attention by the Group and made the subject of extensive discussion and documentary research. They are discussed in this chapter and in chapters 4 and 5.

3.1 Public perceptions and dialogue

Any discussion of genetic testing that is not confined to narrow scientific or technical issues, such as reliability or validity, must at some level take account of public perceptions. Even consideration of clinical utility is dependent to some extent on the ability and willingness of patients to understand and make use of the information that a genetic test provides in order to reach an informed decision with regard to the options open to them.

The multiplicity of issues at stake for the different groups described in the preceding chapter makes the context for any debate on genetic testing a complex one. Alongside patients', and their families', hope for

a cure, the other drivers of the debate – ostensibly a scientific one which ‘ought’ to be evidence-based – are more often to do with factors which have little to do with the small print of quality science. Rather, it is the large print of the media’s need to entertain, to shift copies, make money and satisfy the shareholders, the academic’s need to secure a research grant, an industrialist’s desire to obtain the next stage in funding their product development from shareholders or venture capitalists, a politician’s need to satisfy voters, or an NGO’s goal as an agent of change on behalf of its constituency, which shapes and colours the debate.

In this complex and volatile climate, patients and their families have to sift through the mass of information, and often-conflicting advice, before making an informed decision about genetic testing and its results.

3.1.1 Expectations of patients

Whilst the information provided to patients by clinicians will clearly be of key significance in enabling them to understand and use test results, it is rarely the case that patients will be totally naïve with regard to the potential impact of genetic test results on their health choices. Much more likely will be the case that, prior to consultation with the professional, the patient will have formed an opinion about the potential power of the genetic test to shape their present and/or future health, and the decisions they can make as a result (see also chapter 2.1.1).

A central issue in developing the perceived relevance of genetic testing to the patient’s experience and opportunities will be the answer to the question “Who is asking for the genetic test to be done, and why?”. Other key questions include who will be responsible for interpreting the test result (both in the laboratory and in the clinical consultation with the patient) and who will be responsible for any ongoing support. The patient and family will need to be able to call on a complex mix of clinical, counselling, scientific and technical skills and expertise in order to make an informed choice as to whether or not to be tested, and how to use and respond to the information resulting from it, if this is revealed.

If it is the patient requesting a test then there is likely to be a reason originating in their previous medical history – or that of their family. They may already have experience of genetic disease or reason to suspect that it is something about which they need to be concerned. In such a case, the decision is likely to be at least partially informed and realistic, taken in a clinical context with access to medical support.

If it is a physician requesting a test, reasons may be varied. In the context of a clinical genetic consultation, the decision to test will probably have been preceded by counselling, a record of family history being taken into account and possibly the scrutiny of the medical records of other family members. Even in countries where clinical genetics is a well-established specialist field, requests for DNA analysis that originate from geneticists amount to less than half of the total requested. Other clinicians may or may not appreciate the full implications of a request for DNA testing and the possible impact on the individual or family. Dialogue between physicians and patients and the process of obtaining informed consent may not always be sufficiently robust.

There is also the possibility that testing is offered in the context of a public health screening programme – such as prenatal screening for Down’s syndrome or neonatal screening for **cystic fibrosis**. Unless care is taken to ensure that good practice is followed, the routine nature of these procedures is likely to minimise opportunities for discussion between patients or families and professionals. In these situations, the family’s understanding and appreciation of what is proposed will be formed by their prior knowledge and the public context for genetics in their society or culture.

Finally, there are the enthusiasts who, driven by a belief in the value and power of genetics, undertake testing in the expectation that the outcomes will inevitably reveal something of value for them or for society – even if the research evidence is still weak and needs confirmation. The initial perception that

■ Cystic fibrosis

An inherited disorder caused by more than 1 000 different mutations of the cystic fibrosis gene. Symptoms can include production of an abnormally thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections, but vary from person to person due to the large number of different mutations possible.

BRCA 1 (a gene variation which increases risk of breast cancer) was 80-90% penetrant is an example of this. Although true for particular groups, such as the Ashkenazic Jews, the premature generalisation of this information to the wider population was later discovered to be unfounded. This enthusiastic attitude may be found in any group of stakeholders. Premature generalisation or unrealistic expectations are issues that all stakeholders can help reduce in their own spheres, but the media may have a particularly important impact here.

Against this background, a number of programmes and events, aimed at different sectors of the population, have been developed to promote dialogue, and an evidence-based appreciation of the scientific and social challenges presented by genetics.

Recommendation on medical genetic testing and its context

That:

- a. medically relevant genetic testing be considered an integral part of health service provision;
- b. medically relevant genetic testing never be imposed and always be a matter of free personal choice;
- c. comprehensive information about the availability of genetic tests be freely available from a range of reputable sources including public authorities, physicians, and patient groups;
- d. national healthcare systems ensure that genetic testing will be accessible equitably to all who need it.

See N° 6 of the "25 recommendations" document

3.1.2 Public engagement and communication initiatives in Europe

Public engagement and societal confidence in the beneficial application of genetic testing will be enhanced by robust discussion conducted in an open framework in which one 'side' does not try to use its weight to squash the other. Rather than dismissing public anxieties as unfounded and unscientific, these need to be acknowledged and recognised as legitimate even if they are unlikely to materialise. This highlights the critical need for education to raise the knowledge base, and to improve the quality of debate. A top-down deficit model for public engagement is not appropriate as a route to resolving anxieties and concerns about genetic testing, nor should there be an unrealistic pursuit of an unattainable consensus. As surveys have shown, there is a minority in any community whose mindset is fixed, and there is a minority at the other end of the spectrum who do not want to have a view. The majority occupies the middle ground amenable to reasoned argument, provided they do not feel they are being manipulated.

See also recommendation on public information and education (N°4)

There are many initiatives throughout Europe which aim to engage and educate the public in genetics at various levels, and to promote dialogue in society on the associated scientific and social challenges.

- **Belgium:** In 2003, a Citizen's Conference on the subject of genetic testing was organised by the King Baudouin Foundation¹³. Following the conference, a report containing a number of recommendations about genetic services and genetic testing was produced and distributed to the media and to the government. This initiative is now being expanded with a series of conferences and debates on genetic testing, for schools, medical professionals, and the general public.

- **Europe:** The Telethon initiative, which originated in the USA, is now organised in several European countries in the form of an annual television-based fund-raising activity for genetic research. It also provides the opportunity for the stakeholders in genetic research to share knowledge, exchange experiences, get involved in activities, and make contacts. In France, for example, Telethon¹⁴ takes the form of a two-day show with the participation of well-known musicians and TV presenters. Researchers explain different aspects of certain genetic disorders and viewers can see how children and their families cope with these disorders in everyday life.
- **Europe:** In many countries, public debates are now being organised in cafés and other social venues. These events are becoming important milestones in the development of open debate on genetic testing and other related subjects.
- **France:** The "Ecole de l'ADN"¹⁵ (DNA school), initially launched in Nîmes, is now being set up in other parts of France. The 'schools' give members of the public the opportunity to explore the topic of genetics and the related issues at stake through hands-on experiments.
- **France:** Genetic testing is a regular topic for debate at the "Mission d'Animation des Agrobiosciences"¹⁶ – a forum for public debate on biological themes.
- **Pharmaceutical industry:** Roche has produced a CD-ROM on genetics, which has been widely distributed in schools. GlaxoSmithKline has produced a CD-ROM on basic human genetics for use by healthcare professionals.
- **United Kingdom:** The Human Genetics Commission¹⁷ has a patients' panel of approximately 100 people with personal experience of genetic disorders, which it consults regularly on issues relevant to the work of the Commission (genetic testing and reproductive technologies, for example).
- **United Kingdom:** "Genes and You", a teaching pack for 14- to 16-year-olds, produced by the Genetic Interest Group¹⁸, explores genetics in a cross-curricular context focusing on the personal and human aspects of genetics in the national curriculum. It has been distributed to over 8 000 secondary schools.
- **United Kingdom:** 'Theatre-in-education' plays, exploring genetic testing and its implications, have toured secondary schools in the UK. These were commissioned by the Wellcome Trust¹⁹, a biomedical charity.

Recommendation on public dialogue

That:

- a) opportunities for public dialogue between different stakeholders be organised, offering participants equal opportunities for expression;
- b) different formats of dialogue and debate be organised as no single format will fit all purposes and all public.

See N° 5 of the "25 recommendations" document

3.2. Genetic exceptionalism: is medically relevant genetic data different from other medical information?

The Group is aware that the position it takes on the issue of "genetic exceptionalism" differs from a common perception that genetic data constitute a different category of personal medical data.

¹⁴ <http://www.telethon.fr>

¹⁵ <http://www.ecole-adn.fr/>

¹⁶ <http://www.agrobiosciences.org>

¹⁷ <http://www.hgc.gov.uk/cpanel/>

¹⁸ <http://www.gig.org.uk/>

¹⁹ <http://www.wellcome.ac.uk/>

■ **Genetic exceptionalism**

The belief that the particular nature of genetic information gives rise to greater risks or particular risks that are different from other health-related risks.

■ **Huntington's chorea**

(also known as Huntington's Disease) A rare inherited disorder of the nervous system and the brain, characterised by uncontrollable movements. Affected individuals are usually symptom-free until their fourth or fifth decade.

■ **Information content**

The degree to which a positive or negative genetic test result is predictive of the likelihood of a medical condition occurring or not occurring.

■ **Factor V Leiden**

A variant of the protein Factor V, needed for blood clotting, resulting from a mutation in the associated gene. People with Factor V Leiden have blood that has an increased tendency to clot.

3.2.1 The issues at stake

The concern that genetic information may be particularly prone to misuse has fuelled public perception that genetic information is fundamentally different from other forms of medical data, and has led to calls for blanket policies to treat such information differently from all other medical information (“**genetic exceptionalism**”²⁰).

This perception of genetic testing as different or ‘exceptional’ is also the consequence of the fact that until now genetic testing has been carried out primarily for rare, single gene diseases where test results are exceptionally powerful, such as in **Huntington's chorea**, or familial forms of breast and colon cancer, including prenatal diagnosis for these diseases. The information obtained from these tests can indeed have a significant impact on a family and on the reproductive choices of a couple, and may threaten the insurability or employment of an individual in the absence of appropriate protection under the law (see chapter 2.1.9). Increasingly, however, the genetic components of major common and multifactorial diseases (coronary heart disease, asthma, etc.) are being identified and the role of gene variants in these disorders is being understood. Consequently, the possibility for predictive or predisposition testing for these diseases and for pharmacogenetic testing is gradually becoming available.

With these issues in mind, the Group, and others in the life science community, have come to the conclusion that a proper presentation of the status of genetic data identified in genetic tests is needed. Genetic information is not, as such, different from any other personal medical data, and therefore should not be treated differently.

Examples of questions that arise illustrate some of the concerns related to genetics that should be relevant for any medical information with similar characteristics:

- Will the presence of genetic information in the medical record compromise individual liberties, and expose individuals to invasion of privacy, or to discrimination?
- Should healthcare professionals and patients handle genetic testing and predictive data of a genetic disease more carefully than other medical tests and data?
- How can we avoid discrimination by employers of current or prospective employees based on their genetic data?
- How can we avoid discrimination by health insurers and life insurance companies of current and future clients based on their genetic data?

It should be noted that while the concerns generally apply primarily to predictive genetic tests, it seems appropriate to extend this discussion to all genetic tests, since the distinction between the information obtained from a predictive and a diagnostic test is often blurred.

3.2.2 Scientific considerations

Genetic data cover a broad range of predictive and diagnostic medical **information content**, ranging from no or limited clinical significance (for the vast majority of all genetic variants) to low (risk factors in common multifactorial disease, e.g. the clotting **Factor V Leiden** variant in thrombosis), to high (predisposition markers in certain familial diseases, e.g. BRCA 1 and 2 in familial forms of breast cancer) to extremely high (for rare single-gene diseases, e.g. in Huntington's chorea). It should be noted that while such categorisations may be necessary on a pragmatic level, in reality – as everywhere else in biology – genetic data form a continuum and the lack of natural demarcations makes it difficult to clearly distinguish different categories of genetic information. While it is medically and scientifically unjustified to give information resulting from a test with low or non-existent medical information content the same status as a test with extremely high content, and vice versa, this does not mean that all genetic information should be treated

as exceptional and be given a separate status. High and low information content states are also encountered in biochemical, microbiological, and other medical tests, such as blood tests for monitoring cholesterol levels.

Moreover, the information content of any medical data, including genetic data, is highly contextual and dependent on the particular circumstances and the questions applied to them. Thus, a series of genetic markers may hold no predictive information content whatsoever with regard to any health-related issues while, at the same time, its information content with regard to a forensic or paternity examination may be extremely high. This instructs that **all medical data, including genetic data, regardless of its apparent information content, be treated with the same high standards of confidentiality**. This mandate applies to both clinical research and practice and also extends to issues of who has authority to decide on the use of data. It addresses the first two questions raised under 3.2.1 above. The Group believes, therefore, that genetic exceptionalism is both scientifically unjustified and not helpful in addressing ethical and societal issues. At the same time, it acknowledges and respects that this notion currently exists in the public perception of genetic data.

3.2.3 Information content

The current discussion about genetic information is influenced by the perception that all genetic data convey exceptionally high information content with regard to the carrier and his or her relatives (“**genetic determinism**”). This notion, which historically has found reflection in the eugenics movement, understandably causes concern and reservations about genetic tests. However, our physical and psychological characteristics are not simply a consequence of inherited properties but are equally influenced by external factors (environment, lifestyle).

The perceptions regarding the predictive power of genetic tests are not surprising if one considers that the genetic tests to which the public has so far been exposed pertain either to single gene disorders or to paternity and forensic DNA testing. These are distinctly unusual examples as they carry extremely high predictive information content regarding both the carrier and his or her family members, to a degree that is quite atypical among medical tests in general. The public has had little or no exposure to other types of genetic tests. The vast majority of genetic tests will carry information content much more comparable to other predictive medical tests which yield only modest predictive information (e.g. blood pressure measurements). Given this one-sided experience, it is easy to see how what really is a matter of position within a hierarchy of information content is being confused with the genetic nature of the test, leading to the perception that all genetic tests are special.

Specifically, five characteristics are frequently named as particular to genetic tests. All are typical of tests with high information content, but none are unique to genetic tests:

- 1) Strongly predictive of future health: non-genetic factors can also be highly predictive of future health outcomes, e.g. exposure to radiation or certain infections (HIV, SARS);
- 2) Permanent and immutable (i.e. out of personal control): certain environmental exposures, such as to UV radiation or pollution and lifestyle choices (e.g. smoking), can also irreversibly alter risk for certain diseases, such as skin cancer or asthma, respectively;
- 3) Uniquely identifying: fingerprints or other personal data may yield similarly powerful information (note that all require an identified reference sample);
- 4) Informative about family and community members’ health status: non-genetic parameters may carry similarly strong predictive information, e.g. infection with a communicable disease such as tuberculosis;
- 5) Providing unsought information: a cursory physical examination for a cold at the doctor’s surgery may provide information about a malignant melanoma on the patient’s back that is completely asymptomatic, yet possibly already invasive or even metastatic.

■ **Genetic determinism**
The belief in genetic information as a kind of definitive, fatal, unchangeable sort of information.

If we accept that information content is proportional to the potential of misuse, then the public sentiment that currently available genetic tests carry a greater potential of misuse is indeed appropriate, however, not because these are genetic tests, but rather because these tests carry unusually high information content. The importance of information content implies that the discussion should focus on the question of whether special consideration should be afforded not according to the nature of the test, but to carriers of highly predictive medical information, regardless of whether or not this information is genetic in nature.

As with other medical tests (such as HIV), carriers of highly predictive information may need to be afforded special protection. Not recognising this could be damaging and inappropriate. The carefully designed procedures and international guidelines developed at the initiative of geneticists to protect the individual from discrimination and psychological backlash may stand as a model for many other life-threatening diseases, which are often approached in too casual a way. The issue is not whether genetic tests are unique, or whether DNA reveals more information than any other test, but how genetic tests and, for that matter, any medical tests with similarly sensitive information content are applied or should be applied in practice, whether careful preparation of the patient is required, or whether the result will only add medical information needed to treat the patient adequately. Tests with demonstrated lower information content do not require such additional special considerations; the standard protection of confidentiality of medical data must be ensured anyway.

It should be noted that unless the public is reassured that the use of genetic information, regardless of its information content, for purposes of differential treatment or discrimination is not barred, the sentiment of genetic exceptionalism will continue to be reinforced. Only a rational public policy protecting the individual from abusive practices regarding the use of medical and genetic data will stop this self-perpetuating dynamic.

Such rational policies, based on societal consensus, will be required to address the last two questions raised under 3.2.1 above, dealing with tests in the workplace and in the context of insurance.

3.2.4 Is there a policy or regulatory tendency to “Genetic exceptionalism”?

The Group noted that in response to the public’s fear of abuse and misuse of genetic information, for example in employment and insurance, there has been a tendency in public policy to apply specific regulations to the field of genetics.²¹ Recent initiatives from influential international organisations in the field of medical ethics, bioethics and human rights illustrate this tendency:

- The Council of Europe’s Steering Committee on Bioethics (CDBI) has produced a “Working document on the applications of genetics for health purposes” that suggests “the need to lay down a normative framework which allows account to be taken of the rapid development of techniques and knowledge in the field of genetics and developments in the use of applications”²².
- UNESCO’s International Bioethics Committee (IBC) has produced an ‘International Declaration on Human Genetic Data’, which refers, in its preamble, to the sentiment that “human genetic data have a special status... since they can be predictive of genetic predispositions concerning individuals...; they may have significant impact on the family, extending... in some instances on the whole group; they may contain information the significance of which is not necessarily known at the time of the collection of biological samples; and they may have cultural significance for people or groups”²³.

Whilst the Group acknowledges that the fear of abuse and misuse of genetic information is genuine, it feels that these institutional responses to this fear are inappropriate, as abuse and misuse could also occur, and has occurred (example: HIV) with any other medical information. The situation would be managed

²¹ Knoppers B.M. (2003)

²² Council of Europe (2003)

²³ UNESCO (2003)

more sensibly and appropriately through educational efforts and well-founded public policy governing the use of all medical data, including genetic data, and providing adequate protection against misuse.

See also recommendations on data protection: confidentiality, privacy and autonomy (N°10) and on protection from discrimination (N°11)

The Group acknowledged that without doubt a perceived policy tendency to place medical genetic data apart from other medical data is based on strong and noble goals to assure the protection of human rights against the dangers of genetic discrimination, genetic determinism and the violation of genetic privacy. However, the Group underlines that initiatives aimed at regulating genetic data separately from general medical data would create major practical problems in health management since, in many instances, it would be impossible to clearly differentiate between what is 'medical' and what is 'genetic' data. The Group does not support the idea of constructing specific 'islands' in policy or regulatory texts that might fragment and jeopardise the development of a core set of rules concerning medical data privacy and informed consent, and which might delay, rather than support, the prevention of medical discrimination in general, including discrimination based on genetic testing results.

The Group acknowledges that some genetic information, as part of medical information, has specific dimensions which are not necessarily common to all medical information. A framework governing all medical information including, where appropriate, special rules for specific subsets of that information, like certain genetic data, would be more appropriate because it would allow for a more harmonious approach in terms of content and context. Genetic information is part of the entirety of every individual's health information and does not *a priori* represent a separate category, although it may under certain circumstances (e.g. exceptionally high predictive information content). Thus, genetic exceptionalism is inappropriate.

The current public sentiment that genetic information is different is acknowledged. Public experience of genetic testing is largely limited to examples of exceptionally high information content, biasing the perception of the power of genetic data, and possibly maintaining lingering fears of eugenics. Public dialogue to provide factually correct information is imperative.

At the same time, public policy must ensure that safeguards against the inappropriate use of highly predictive medical data include genetic data. Currently generated guidelines, rules, and laws in the area of genetic testing and data ("regulatory genetic exceptionalism") are an understandable response to specific public concerns and historical applications of genetic testing, but are only acceptable as a stepping stone to more comprehensive and inclusive legal and regulatory frameworks that encompass all medical data and testing in a non-exceptionalist manner. Appropriate guidelines should allow evolution to maintain pace with science and public opinion.

Since the information content of any medical data is highly situational and not static, all (private) medical data must be afforded equally high standards of quality and confidentiality at all times.

Recommendation on "Genetic exceptionalism"

That:

- a. "genetic exceptionalism" should be avoided, internationally, in the context of the EU and at the level of its Member States; the public perception that genetic testing is different needs to be acknowledged and addressed;

- b. all medical data, including genetic data, must satisfy equally high standards of quality and confidentiality;
- c. in order to track the evolution of public perception of genetic testing and to identify issues for future debate:
- further research on ethical and social perceptions of genetic testing is necessary and should be promoted by the European Commission and national bodies; and
 - questions relevant to genetic testing should be included in pan-European surveys like the Eurobarometer.

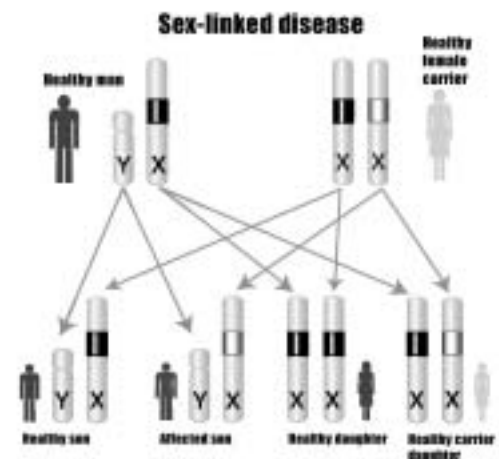
See N° 3 of the "25 recommendations" document

3.3 Gender and ethnicity

3.3.1 Gender and genetic testing

Some diseases are typically inherited in a gender-linked or a gender-limited fashion and can be detected through genetic testing.

In gender-linked diseases, the responsible gene defect is usually recessive, localised on the X chromosome and will mainly affect males. Certain forms of haemophilia are included in this category. Female carriers of the gene defect will usually be healthy or minimally affected by the associated trait. In the small number of diseases where the gene defect on the X chromosome is dominant, the majority of male foetuses may not survive to term, and females will be affected by the disease. A small number of Y chromosome-linked traits also exist, such as spermatogenic arrest which affects male fertility.



(Source: "Tests génétiques", Repères collection, Inserm, July 2003)

■ **Genetic mutation**
A change in the DNA sequence. The term "mutation", as opposed to "polymorphism", is generally used to refer to changes in DNA sequence which are not present in most individuals and are associated with disease (or risk of disease) or those resulting from damage inflicted by external agents (such as viruses or radiation).

■ **Leber's Hereditary Optic Neuropathy (LHON)**
A maternally inherited disorder that primarily affects young men, causing rapid loss of central vision. LHON is inherited through mitochondrial DNA present in the egg cell.

Another class of gender-linked diseases originates in mutations in the mitochondrial DNA. Mitochondria are self-replicating organelles in the cell's cytoplasm which play an important role in metabolism. They contain a small amount of DNA. The large female egg cell contains cytoplasm and hence mitochondria, but the tiny male sperm cell, which needs to be lighter and more mobile, hardly contains any at all. This means that during fertilisation almost all mitochondrial DNA is passed on to the embryo from the mother. As the embryo grows and divides, the new cells make more mitochondria, including mitochondrial DNA copied from the DNA template of the original mitochondria. **Genetic mutations** in mitochondrial DNA can therefore only be passed on from a female to her offspring. Because of the small number of genes found in mitochondrial DNA, the number of disorders linked to mitochondrial inheritance is very small. One example is **Leber's Hereditary Optic Neuropathy** which can cause blindness.

In gender-limited diseases, hormonal as well as other gender-related factors will make one gender more prone to develop a disease. Moreover, one gender may be susceptible to a disease because the disease or the predisposition depends on the presence of a particular organ, e.g. hereditary ovarian cancer.

The differences that exist between men and women in the risk they have of developing a gender-linked or gender-limited disease are well established and do not necessarily create new or unexpected

discriminatory problems. However, there may be gender issues linked to differences in the way men and women experience or perceive genetic testing. For example, prenatal diagnosis, which is typically carried out when a woman is suspected of carrying a foetus at risk of developing a specific disease, will impact both parents quite differently, depending on their presence or absence at the time of the intervention, and their attitude towards pregnancy, giving birth and parenthood in general. A woman's choice to go ahead with having a child at risk of developing a genetic disease may also impact on her relationship with the child's father and her future choices and opportunities.

Males and females generally tend to approach medical problems in a different way. Women are traditionally the 'guardians' of family health. They may take more responsibility for instigating a genetic test in the first place, and the results of genetic testing may bring them extra responsibilities in terms of 'managing' the affected family member's healthcare. The two sexes may interpret the impact of being a carrier or being affected by gene defects quite differently when the risk for their offspring is considered. There may also be differences between the sexes as regards access to medical services, economic independence or autonomy, susceptibility to peer or family pressure, the way they react during genetic counselling, and the way in which they will be interested in implementing preventive measures after a predictive test. Many of these issues have not yet been studied in great detail, however.

Whilst it is important to be aware of the danger of stereotyping particular groups of people, socio-cultural differences may have an impact on women's health choices and the control they have over these choices, particularly where the demarcation of women's and men's roles is particularly well defined. In countries where abortion is not widely available or is prohibited by law, the possible courses of action for pregnant women following prenatal genetic testing may be limited. However, genetic testing can still play an important role in helping such women make decisions about future births.

In certain cultures, sex selection is used to prevent the birth of one sex, usually females. Whilst this type of practice is generally considered unacceptable, it needs to be considered in a particular socio-cultural context, taking into account the pressures women may be under to comply and the possible societal implications if they do not. In recent years, sex selection has also become attractive to families who would like to balance the gender of their children. Many countries forbid the application of such a sophisticated technology for this purpose²⁴.

Recommendation on gender issues and genetics

That:

- a. further studies at EU level address the impact of genetic testing, in particular in societies where women or men are given different rights or privileges;
- b. governments and society be aware of the possible consequences of the application of genetic testing to aid reproductive choice for prospective sex selection;
- c. criteria be established at EU level to ensure that no gender discrimination occurs in the course of, or as a result of, EU-funded research projects.

See N° 13 of the "25 recommendations" document

3.3.2 Ethnicity and genetic testing

The study of population genetics and genetic diversity (see chapter 1.3.1) for anthropological and genetic **epidemiology** purposes started many years before the introduction of molecular genetic tests. Studying the frequencies of specific genetic variants within populations, and comparing them between

■ Epidemiology

Study of the occurrence and frequency of diseases in geographical areas or populations, and investigation of the underlying risk factors for diseases. Genetic epidemiology investigates the genetic risk factors of diseases, their contribution to disease cause, and/or the interaction between genetic factors and the environment that can generate diseases.

populations, has been performed in isolated communities or specific ethnic groups, as well as in more mixed populations.

Although 90% of the genetic variation that exists in the global population of humans is found in every sub-population, certain variations caused by mutation or other mechanisms are more commonly found in people from specific geographic areas or in people with ancestry in those areas. Study of these groups of people can require genetic testing in a very different cultural context, which raises specific issues. Greater knowledge of our genetic diversity across populations emphasises our shared genetic heritage. The Group underlines that genetic tests are inappropriate to determine ethnicity. There is a danger that the power of genetic tests to differentiate between individuals and between groups could be misused.

The categorisation of populations on the basis of cultural and genetic features may lead to stigmatisation or discrimination not only of individuals but of entire groups. This is a source of concern in society. Such issues are especially sensitive with regard to minorities that are often discriminated against for many other reasons. Many diseases with a genetic basis, such as **thalassaemia**, cystic fibrosis and sickle-cell anaemia, are more prevalent in particular groups. A high prevalence of certain genetic disorders in given groups can result in differences in their public profile and a disproportionate distribution of resources relative to their prevalence in the general population, depending on the group's capacity for successful lobbying. Cystic fibrosis research, for example, receives far more funding than sickle-cell anaemia in the US, although it is less prevalent in the population as a whole.

However, knowledge of the characteristics of a population's genetic variation is a prerequisite to many disease studies leading potentially to the development of more appropriate genetic tests for a given population. Recognising genetic diversity within and between populations is different from setting up a hierarchy, but the fear of discrimination remains strong.

The Human Genome Diversity Project (HGDP) marked an historic step with respect to the ethical dimension of global **genetic variation** studies. In 1991, researchers from the US launched the idea of an international initiative to study genetic variation across populations. However, during the design and presentation of the project the populations concerned were not considered as interlocutors by the specialists. This insensitivity provoked strongly negative reactions to the project, mainly from minorities, and led to single-issue pressure groups being able to hijack the agenda for their own purposes. Although an ethical code, which is still used as the basis for ethical conduct in population genetics research, was proposed by the members of the project as early as 1993, the HGDP project was never well accepted by some parts of the public. Several minorities and associations were particularly vocal in their rejection of the project and the controversy was widely reported in the scientific and general media (the "vampire project", etc.)²⁵.

The controversy centred on the possibility that a population's 'genetic richness', represented by its unique genetic diversity, could be exploited without adequate returns to that population. There was also a fear that insufficient measures would be taken to respect the cultural features and beliefs of populations (which may prevent certain populations from participation in research, for example) and to guarantee benefits to populations, such as those in developing countries, already suffering from major health problems.

The issue of benefit-sharing is never a straightforward one. The concept needs to reflect not only the desire to share benefits but also how to do so appropriately. The question of who should receive and distribute the benefits amongst the population also needs careful consideration.

Although the HGDP project, as initially conceived on a global level, has never existed as such and only a rather restricted part of it was ever carried out, it is this project which has had the largest impact on

■ **Thalassaemia**

A group of genetic blood disorders resulting in anaemia. The two main types are called alpha and beta thalassaemia, depending on which of the oxygen-carrying proteins (in haemoglobin) is lacking in the red blood cells. Individuals suffering from thalassaemia usually require frequent blood transfusions.

■ **Genetic variation**

Natural or acquired differences in genes or their products, DNA sequences or chromosomes.

discussions of ethical issues in population studies. This is a good illustration of how public distrust, or the action of self-appointed 'watchdogs', can have significant consequences for scientific projects and the development of a given field.

Recommendation on ethnicity and genetics

That:

- a. genetic tests be clinically evaluated in the populations in which they are to be used;
- b. those who are involved in genetic research, the provision of genetic testing and healthcare policy-making be sensitive to the risks of stereotyping and stigmatisation based on ethnic origin, and recognise and respect ethnic and cultural sensitivities;
- c. minority ethnic groups not be excluded from access to those genetic tests appropriate for them.

See N° 12 of the "25 recommendations" document

In 2001, a new international project, known as HAPMAP, was launched to study specific zones of the human genome implicated in genome variation across populations. Using recently acquired knowledge of genetic markers, the identification of such zones could dramatically increase the efficiency with which the genetic component of many diseases is identified. The first step of the project involves defining this genetic variation across populations. The project has had an integrated ethical, legal and social component right from its conception. Community Advisory Groups have been set up in each area where samples are collected to ensure community consent and the engagement of the populations involved. It is difficult to imagine now that any project having an international audience and addressing one or several minority population(s) could be launched without such a component.

Population genetics studies such as these raise particular ethical questions which mainly concern the implication of a group as a single entity, rather than as a group of individuals, in the research. For example, the traditional role of informed consent as an expression and protection of the autonomy of the person is generally focused on individual consent. In projects involving few individuals or families, the concept of individual consent stands as the only consent pursued. The concept of group consent has been introduced for small communities or populations and was formulated as a protocol in 1993. However, in such projects the question of "who speaks for the group?" becomes an important issue.

See also recommendation on informed consent (N° 23)

Another point to consider is that data relevant for health may be the same as that relevant to more fundamental anthropological studies. However, to be able to identify a genetic variation relevant to health, first one has to identify general genetic variation (as in the HAPMAP project). When describing the aims of a study, it is not always easy to make clear what kind of results will potentially be relevant for the health of the individuals and population in question, and what kind will contribute to the knowledge of the biological history of humanity, without direct interest for health. This complexity of aims is not always easy to explain transparently in different cultural contexts. For example, study of the variation of the cystic fibrosis gene in populations may be very relevant for population history (tracing migration of populations or dating the appearance of mutations) but will also lead to the identification of the specific mutations of the gene prevalent in given populations and which should be tested for in a diagnostic test for the disease.

The high level of ethnic diversity between and within European countries makes ethnicity in the context of genetic testing an important issue for consideration by all Member States. The biological consequences

of this diversity need to be recognised in the provision of healthcare services, and social, cultural and religious sensitivities also need to be taken into account in the planning and delivery of these services (see chapter 8.6). Particular effort may need to be focused on groups which are 'hard to reach' because of cultural segregation. However, it is also necessary to recognise the dangers of making *a priori* assumptions based on cultural traditions.

Genetic testing comes with its own set of technical words and concepts (see Annex 2). Some of this terminology may be difficult to translate accurately. Metaphors are often used to get across concepts, such as risk, related to genetic testing, and those appropriate in one culture may not be so in another. Accurate information on genetic testing should be made available in all languages.

Recommendation on protection from discrimination

That:

- a. data derived from genetic sources not be used in ways that disadvantage or discriminate unfairly against individuals, families or groups in either clinical or non-clinical contexts, including employment, insurance, access to social integration and opportunities for general well-being;
- b. EU-level regulations addressing these issues should be promoted;
- c. timely access to genetic testing should be based on need and appropriately resourced with no discrimination based on gender, ethnic origin, social or economic status.

See N° 11 of the "25 recommendations" document

4. Biobanks as resources and tools for research and development of genetic testing

The participation of patients and populations in large collections of human biological samples and associated data, some of which are referred to as 'biobanks', is an important part of the context of genetic testing today. However, many of the issues related to biobanks extend far beyond genetic testing.

The term biobank is often used, but is not a commonly shared, precise notion. Many kinds of collections may be included in the terminology, in as far as they are made up of human biological samples plus associated personal data which may be used for research activities. The Group has used the following definition: "a biobank encompasses biological samples, plus their related databases, associated with a certain level of access to this material and data for scientific study".

The constitution of a biobank may be necessary for a number of different reasons, depending on the research it serves. These include the need to access a sufficient number of samples for statistical reasons, the need to exchange samples, the need to do multiple testing on the same samples, the need to do repeat testing over time, the multiplicity of interests involved, the complexity of banking and exchange of samples, and the necessity to secure rare samples.

The uses of human genetic material in biobanks are very variable. Samples can be used in population genetics research, identification of the genes playing a role in a specific disease, or clinical research and development of pharmacogenetic tests, for example. Samples can also be conserved to assess the risk of inherited transmission of a specific disease within a family.

A number of different types of institutions may have a biobanking activity, including public hospitals or laboratories, private clinics, medical laboratories, forensic medical services, public research laboratories, private or semi-public associations, charities, and companies in the pharmaceutical, diagnostic or biotechnology industries. There are many small collections but few very large ones. The majority of collections are held by public-sector or charity institutions and function on a not-for-profit basis²⁶.

Biobanks may also include donor tissue banks set up on a commercial basis, using tissue collected from hospitals or extra tissue taken in the margins of a medical research trial, processed for research and sold to research institutions. Exclusive licences are sometimes granted to commercial entities for accessing collections set up as part of a non-profit project, or companies may establish their own collections. Research projects may involve a considerable cross-border flow of data and tissue.

With the rapid development of high-throughput technologies allowing for the screening of very large numbers of samples, and with growing recognition of the important role genetic variation can play, not only in causing rare diseases, but also in the development of common diseases, the responses of individuals to medicines, and the development of new medicines, there has been a tendency to try to constitute large national population collections in various countries (Iceland, Estonia, Latvia, Sweden and the UK, for example), or to investigate sub-populations with defined characteristics (in Italy and Finland, for instance). These collections, considered as national research resources, are usually supported with private funds in combination with public funding, although they are occasionally supported with private funds alone.

4.1 Data protection and informed consent

Much of the discussion in the Group concerning biobanks was centred on the question of the practical application of an ethical framework. The main issues discussed were data protection and informed consent.

Recommendation on data protection: confidentiality, privacy and autonomy

That:

- a. genetic data of importance in a clinical and/or family context should receive the same level of protection as other comparably sensitive medical data;
- b. the relevance for other persons in the family has to be addressed;
- c. the importance of a patient's right to know or not to know be recognised and mechanisms incorporated into professional practice that respect this. In the context of genetic testing, encompassing information provision, counselling, informed consent procedures and communication of test results, practices should be established to meet this need;
- d. these issues are of particular relevance to vulnerable populations whether in the EU or elsewhere in the world.

See N° 10 of the "25 recommendations" document

See also recommendations on informed consent (N° 23)

Of particular importance is consideration of the rules of access to, and level of openness for, exchanges of samples and data between interested parties (research groups, companies, healthcare services). The protection of the rights of people whose samples and data are in the biobanks, with respect to autonomy,

²⁶ Hirtzlin, I. et al. (2003)

■ **Anonymous, anonymised**
See under Identification in Annex 2.

confidentiality and protection of privacy, needs to be assured at the same time as allowing and encouraging research.

Various degrees of identification of the individual sample donors are possible – identified, identifiable, **anonymised or anonymous** (see Annex 2 for precise definitions).

Table 2: Overview of types of sample labelling and level of anonymisation

Sample labelling category	Link between subject identity and sample/ data	Records identifiable for clinical monitoring	Actions possible if subject withdraws consent	Return of individual results to subject	Scope of subject privacy protection
Identified	Yes, directly	Yes	Sample can be withdrawn with immediate effect for any prospective use	Possible	Similar to general healthcare confidentiality
Single-coded (identifiable)	Indirectly, via code key	Yes, via protocol-specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Standard for clinical research
Double-coded (identifiable)	Very indirectly, via two sets of code keys	Yes, via protocol-specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Double code offers added privacy protection over single code
Anonymised	No. Key(s) identifying the link between the data/sample and the identity of the subject is deleted	No	Sample and data are not identifiable. Sample cannot be withdrawn once key is deleted	Not possible	Data/sample not linked to individuals
Anonymous	No	No	None	Not possible	Complete

Adapted from EMEA "Position paper on terminology in pharmacogenetics", November 2002

The ethical issues are different in these various situations. The extent to which informed consent is required can vary depending on the nature of the research, the degree of anonymity, and the question of whether the research may result in new findings of relevance for the health(care) of the donor.

Another factor to consider is that it is not always possible to predict the potential developments in research over time. The issue of informed consent becomes complex in this context. The interest of industrial groups in collected population samples, especially in the context of pharmacogenetic studies on the population frequency of certain polymorphisms, may have been unplanned at the time of sampling for existing collections. Right of access, therefore, depends on further consent or 'anonymisation' and approval of the study by an ethics committee.

There are various forms of consent ranging from detailed express consent, enlarged or broad consent (for a range of broadly defined uses) to presumed consent (where people who do not want to be involved have to voluntarily opt out). The consent could also incorporate the concept of a voluntary sharing of information towards a common good. The most relevant approach may be different depending

on whether collections are archived or are new ones. The specific recommendations of the European Society of Human Genetics on this matter reflect the main views of the Group²⁷. Patients and any other sample donors should have the right to keep control over non-anonymous samples. Workable mechanisms to translate this principle into action need to be developed.

Very large collections, such as the UK Biobank which will include samples and data from 500 000 people, may result in the emergence of new societal dimensions, regarding communication, debate, societal control and the appreciated value of such collections. While group consent, in addition to individual consent, is appropriate for use in small populations and in certain cultural contexts, it is difficult to achieve and may be not adapted conceptually for large populations. A collective democratic debate before the start of a large-scale project and before individual consents are pursued may assist individuals in their decision-making on consent issues. Such large projects provide an opportunity to inform, educate and debate about the use of human tissue samples for genetic testing, thus influencing the attitude of the public towards it.

It is important to assuage public anxiety by reassuring that transparent procedures are used and that protective measures are in place to prevent undesirable effects of participation in genetic research, such as the stigmatisation of specific groups or the misuse of results. However, new perspectives in research with human tissue have brought about shifts in emphasis in the human rights aspects involved. The rights of the individual, as the source of the material, cannot merely be 'translated' into his/her right to confidentiality and to privacy, but must also encompass autonomy and free choice. It is important to recognise that unforeseen direct beneficial uses of the samples or data may appear over time – a test of clinical utility for an individual or for members of his/her family, for example – that did not exist at the time of sampling. Such unforeseen uses should not be ruled out by overly restrictive rules. In the same way, a ruling²⁸ that prohibited the use of samples from the deceased taken without specific consent for such uses would prevent their use to facilitate diagnosis in living relatives.

Recommendation on samples from the deceased

That:

- a. Member States take actions to promote the right of access to samples and data from a deceased person, in the case of overriding interest for blood relatives;
- b. Member States take actions to allow the use of anonymous samples from the deceased for the purposes of genetic research, development of new genetic tests, as well as for teaching purposes.

See N° 24 of the "25 recommendations" document

In certain contexts, human biological samples are considered as parts of the body while in other contexts, as sources of data. When does a genomic sample become data? The concept of human biological material as a 'carrier' of information has emerged. The right of individuals "to know and not to know" has become an important issue alongside the right to physical integrity (see chapter 7.2.2). Whereas physical integrity constitutes the major target of protective legislation in relation to medical research *on* human subjects, the risk of "informational harm" has emerged as a major issue that should be addressed in medical research *with* human tissue.

The Group believes that safeguards should, on the one hand, restrict the likelihood of abuse but, at the same time, allow unforeseen beneficial uses of medical value for individuals or of scientific value for research. The role of review and approval by external independent bodies, such as ethics committees, is critical in such issues.

²⁷ European Society of Human Genetics - Public and professional policy committee, 2002

²⁸ UK Parliament: Human Tissue Bill 2003

4.2 The value and sustainability of collections

It is important to be able to ensure that non-commercial donation and procurement of human tissue continues whilst allowing the development of medical advances by commercial activities based on these samples and the data attached to them. The question of the value of collections in this context is still not often openly discussed. More information on existing and desirable practices would be valuable. Besides recognition of the economic value of a well-organised and reliably documented biobank, standardised indexes to measure the actual use of biobanks could be important parameters to set up.

Recommendation on collections of human biological material and associated data and their uses

That:

- a. the European Commission follow closely relevant activities and developments of the Member States in this field and in the global context;
- b. action be taken at the EU level, in coordination with other initiatives, to follow and address regulatory issues related to collections of human biological material and associated data and their uses.

See N° 21 of the "25 recommendations" document

Similarly, it is important to promote optimal use of the samples for the rapid progress of knowledge, whilst protecting the rights of priority of those researchers who established the collection. It is vital to ensure that the highest quality of sample conservation and management is maintained whilst also allowing easy access.

Depending on the scope and context of individual biobanks (e.g. institutions involved, source of funding, level of access, etc.) their activity may require official recognition and identification, as well as assurance of long-term financial sustainability, particularly as their use and the interests involved may change over time. There is a need for education in 'biobanking' and for guidelines to assure the quality control of collections and of the ethical management of such repositories.

Recommendation on existing and new biobanks

That:

- a. guidelines be developed and coordinated across the EU to ensure that the use of samples, including those from archival collections, is not unduly delayed or impeded, particularly if proper consideration of their level of identification has been taken into account;
- b. action be taken by Member States to ensure that approval by a competent review committee is obtained before research is undertaken;
- c. an inventory of existing biobanks across the EU be created, indicating standards and rules of access, to identify which of their contents may or may not be used for genetic studies;
- d. a system be implemented to evaluate and monitor the current usage of existing biobanks throughout the EU;
- e. the task force on 'biological resource centres' set up by the OECD be followed closely by the European Commission regarding development of standards;
- f. the European Commission closely follows this activity.

See N° 20 of the "25 recommendations" document

There is no consensus on the matter of the existence of ownership of human tissue or genetic data. Ethical issues pertaining to the authority over genetic and non-genetic data, conditions for patenting, commercial use, potential benefit and benefit-sharing are sensitive. Few Member States have well-developed legal frameworks in this field. The Council of Europe is currently working to draw up legislation in the domain of research on human tissue. There is no specific EU legislation on research using or conserving human cells and tissues, although the recently published Directive 2004/23/EC of 21 March 2004 on 'Setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells' is regulating these issues in a clinical context, and the exclusion of research was debated and agreed upon in the European Parliament.

The construction and use of biobanks, whether primarily or secondarily for research use, are important steps in the development of genetic tests but are related to issues that have not been fully addressed by the Group. This area requires specific attention.

The consideration of ethical issues in the context of large-scale biobanks is of primary importance as they relate not only to individual decisions or projects but also to national policies in an international context.

5. Pharmacogenetics

5.1 Scientific background

5.1.1 What is pharmacogenetics?

The reaction of patients to medicines, as regard both their efficacy and their safety, frequently varies from one person to another. Thus, whilst many will benefit from a particular drug, some will not and others may suffer adverse reactions²⁹. The concept of pharmacogenetics encompasses the use of information encoded in patients' DNA to help predict their responses to medicines and thereby enhance the effectiveness and safety of medicines for individuals. Pharmacogenetic research seeks to identify correlations between information from research participants' DNA (**genotypes**, genetic markers) and their response to a medicine. Ultimately, this research will, for some medicines, translate into prescribing information that would help the doctor to select the medicine that is most likely to benefit a particular patient, and/or the dose that is most likely to be appropriate. Pharmacogenetics is not a new concept. However, the increasing knowledge provided by progress in genetics and **genomics** has greatly facilitated developments in this field.

It is important to note that:

- Pharmacogenetic tests developed from this research are intended to help predict response to medicines and not to yield information about the disease, or disease risk.
- Pharmacogenetic tests are expected to enhance safety and efficacy characteristics of a medicine by enabling better prediction of likely outcomes, and are thus expected to improve the benefit-to-risk ratio of a medicine for patients.
- The application of pharmacogenetics to medicines and medical practice will evolve over time rather than present a revolution in medical practice. In most circumstances, application of and consultation about pharmacogenetic information, in the context of other medical information such as the severity of disease and the availability of medicines, will be the domain of practising physicians, rather than of specialist geneticists.
- Each application of pharmacogenetics to healthcare may have unique features for each of the considerations cited above and should therefore be assessed on a case-by-case basis and, if necessary, adapted as new information and technology becomes available. For example, over time, and with the

■ **Genotype**
The genetic constitution of an individual in the genes or genetic markers being studied.

■ **Genomics**
The study of gene expression and regulation usually on a large scale – genes in a given tissue, or the whole genome of an organism, for example. The study of genes and their function.

²⁹ Spear B.B., Heath-Chiozzi M., Huff J. (2001)

necessary supporting evidence, a specific pharmacogenetic test may evolve in clinical application – the test may be applicable for more than one medicine, or be utilised in disease diagnosis or prediction.

- Pharmacogenetics may reduce inequalities in the provision of effective healthcare. Because it is generally not possible to predict patients' responses to medicines, some patients will be treated effectively while others will not. Pharmacogenetics offers the possibility of treating more patients effectively and reducing these inequalities. In addition, pharmacogenetics can improve the basis for decision-making regarding allocation of resources for medicines based on clinically relevant data, further reducing inequities. On the other hand, lack of access to pharmacogenetic tests through the healthcare system could create disparities in the quality of medical care.

5.1.2 Pharmacogenetic research

At present, pharmacogenetic approaches are, by and large, mostly investigational and exploratory. Currently, almost no pharmacogenetic data exists that has been replicated and accepted by drug regulatory authorities and healthcare providers as acceptable for the support of treatment decisions in a clinical setting. It is important that this be clearly explained to patients participating in pharmacogenetic research during the informed consent process. Recommendations regarding the informed consent, as well as the terminology to be used for various levels of encryption of personal data related to the sample, have been proposed by both industry and drug regulatory authorities^{30,31}. Researchers have a responsibility to ensure that identifiable biological samples and data will only be used in accordance with the informed consent, as specified by the EU Data Directive 95.46/EC). The Directive also establishes strict criteria related to data access by third parties.

As pharmacogenetic concepts evolve from exploration towards being used in a clinical setting, the nature of their use in clinical trials will change. For example, for some medicines, later-phase clinical research may be restricted to patients who are more likely to experience therapeutic benefit, if markers indicating the likelihood for such an outcome have been found.

5.2 Impact on key stakeholders

5.2.1 Healthcare professionals

Today's practice of medicine is based on an increasingly detailed understanding of human physiology and pathophysiology, a wide array of diagnostic tests and a variety of treatments. To gain market approval, medicines must be shown to be effective and well tolerated in a defined population of patients. However, it is also true that all medicines are not effective in all patients. Therefore, many medicines are first prescribed to an individual patient, and then evaluated to determine if the patient is receiving the most suitable medicine at the correct dosage. This approach potentially exposes patients to undesirable side effects, without medical benefit, and it produces cost inefficiencies not only in the use of ineffective medicines for individual patients but also in terms of related morbidities and consultation time. With this general model of prescribing, and despite remarkable advances in medicine, many patients are not effectively treated, or experience side effects as a result of their medication. Pharmacogenetics may help physicians prescribe the most appropriate medicine or dose for an individual patient and thereby help to maximise therapeutic outcomes for patients. While pharmacogenetic-like testing is currently required or suggested for only a few cancer medicines (e.g. purine analogs, *imatinib*, *trastuzumab*), physicians are generally unprepared to cope with the likely increase in the use of such testing. Education about pharmacogenetics will need to become part of the standard curriculum in medical, nursing and pharmacy schools, as well as of continued medical education curricula. Only then will physicians be able to make informed decisions and explain these to their patients.

³⁰ EMEA (2002)

³¹ Anderson D.C. et al. (2002)

5.2.2 Patients

The first objective of pharmacogenetic testing is neither diagnosis nor prediction of disease, but determination of an individual's likely response to medicines or to a particular medicine and dose. As a first step, it is important that patients are made aware of the variation that occurs in the response to all medicines and the potential role that pharmacogenetics may play in treatment selection. While medicines do provide significant benefit overall to individuals and society, there are challenges associated with prescribing, including the risk of drug side effects and the outlay for medicines that may not provide therapeutic benefits. Such factors are often not fully appreciated by patients. Secondly, patients must be appropriately informed about the information a pharmacogenetic test will provide to them and their physician, i.e. what the consequences of taking or not taking the test are with regard to treatment options and the likely clinical outcomes entailed in each scenario. In the face of an unfavourable test result, a determination of whether the medicine is nevertheless the best option for the patient would need to be made by the doctor and understood by the patient. In the longer term, it is likely that with increasing knowledge amongst healthcare providers and patients, alongside a gradual introduction of medicines developed using pharmacogenetic information, will come a level of patient awareness that is associated with current medical practices.

5.2.3 Healthcare providers

Assuming constancy in the overall demands on healthcare delivery, the use of pharmacogenetic approaches may result in gains in cost-effectiveness. A reduction in the number of physician or pharmacy visits necessary to find, by trial and error, the proper medication for a patient, or avoidance of adverse events, or prolonged burden of illness, could easily balance the expense of the additional test and, overall, could result in cost savings.

As healthcare systems strive to make better use of finite healthcare resources and establish systems for evidence-based medicine, the utilisation of pharmacogenetics will need to be assessed with regard to:

- Best medical practice;
- Feasibility of operating on longer-term timescales which may be necessary to realise benefits in terms of cost savings for healthcare delivery.

5.2.4 Pharmaceutical, diagnostic and biotechnology industries

Enhancing treatment outcomes for patients and meeting medical needs are the primary business drivers for the industry and, in particular, with regard to research on, and clinical use of pharmacogenetic approaches.

Exploratory work is needed to investigate whether pharmacogenetic approaches are applicable to a new medicine, which may increase upfront the cost of drug development. Ultimately, it is hoped that any increase may be offset by gains in cost-efficiency by the more targeted prescription of drugs, resulting in higher rates of treatment success and a lower incidence of adverse reactions. The impact of pharmacogenetics on the research and development process may therefore include:

- Improving the efficacy, focus, productivity and delivery of research and development by helping to identify, and terminating as early as possible in the research and development process, candidate compounds which are unlikely ever to meet the criteria for medicinal approval;
- Improving the quality of information gained and decision-making throughout research and development, including the post-marketing environment, thereby allowing medicines to remain available to defined patient groups with a favourable **benefit-to-risk profile**;
- The gains provided by developing more medicines that are better targeted to patients and recognised as being more cost-effective by purchasers.

■ **Benefit-to-risk profile**

An expression of the benefits from using a particular therapy or drug compared to its potential adverse effects.

Recommendation on pharmacogenetics

That:

- a. national health authorities play a more active part in encouraging development of the field of pharmacogenetics:
 - by providing particular incentives to enable the development of pharmacogenetic tests and associated therapeutics which are clinically desirable but which may not be economically viable; and
 - by enhancing the possibilities of co-operation between industry, patients, and academia in this field;
- b. an appropriate harmonised legal, regulatory, and healthcare policy framework for pharmacogenetics be developed at EU level, taking into account research, therapy development and clinical practice.

See N° 19 of the "25 recommendations" document

5.2.5 Regulatory authorities

Regulatory authorities are currently actively considering the establishment of a framework for evaluation and incorporation across the R&D process. This includes the encouragement of dialogue and consultation between industry and regulators worldwide^{32,33}.

The pharmaceutical, biotechnology and diagnostic industries and pharmaceutical and device regulatory authorities should continue to work together to move scientific concepts and results into clinical practice and, in parallel, to develop regulatory guidance for all key issues. For example, a global framework is desirable that will facilitate both the exploration of preliminary research findings and the respective pharmacogenetic tests that may be required for their use.

5.3 Ethical, legal and social considerations

The Group acknowledges that ethical, legal and social considerations may arise with regard to private medical information, including pharmacogenetic research and test results. As discussed in the earlier section on genetic exceptionalism, it is important to consider test results on the basis of their information content rather than the nature of the test. A pharmacogenetic analysis guiding the dosing regime for a medicine has a very different impact on a patient than a test which diagnoses or predicts a chronic disease such as HIV infection or Huntington's chorea.

Some of the most frequently cited ethical, legal and social considerations are discussed below.

5.3.1 Psychological impact on patients

Prediction, based on a pharmacogenetic test, that available medicines may not be safe or effective for an individual patient suffering from a serious disease may cause psychological distress. However, administration of an ineffective or unsafe medicine, in the absence of the pharmacogenetic information, is clearly a less desirable option.

Conversely, the prediction of a likely favourable response may have a positive psychological impact and encourage patients to complete courses of treatment and thus gain full therapeutic benefit. It is important to note that while pharmacogenetics may facilitate the identification of patients for whom no highly

³² EMEA (2003)

³³ US Dept. of Health and Human Services (2003)

effective treatment is available, such predictive information is not unique to the application of pharmacogenetics. The potential psychological issues are those generally associated with the prediction of any unfavourable health outcome. Thus, it is critical that pharmacogenetics is not singled out, but that these issues are addressed in a more general debate.

5.3.2 The risk of revealing unwanted information

Although pharmacogenetic tests will not be researched, developed, validated and marketed for the diagnosis or prediction of disease, it is possible that sometimes a pharmacogenetic test may reveal additional information relating to health status or risks. There are two ways in which this might occur. First, in some cases, disease-associated genotypes might be among the genetic factors influencing drug response. Where this is related to the disease being treated, this situation is unlikely to raise ethical issues since the patient is presumably already aware of the disease diagnosis. Secondly, it is conceivable that a pharmacogenetic test may provide information revealing the presence of, or risk of developing, a different disease for which there may be no effective treatment or prevention. If a test is known to have the potential of revealing such information, this should be discussed with the patient, and will then be part of his or her decision regarding the test. The possibility that, at some point in the future, a test result may reveal additional medical information currently not envisioned, may be discussed, but should not be considered as reasonable justification to forego a test that provides important treatment guidance for a current health problem.

A related concern is the possible disclosure of information pertaining to family members as a consequence of pharmacogenetic testing. While such considerations are sometimes relevant with regard to prospective testing for rare single-gene diseases, they are unlikely to be a relevant concern regarding pharmacogenetic tests.

Finally, the "right not to know", generally discussed in the context of highly predictive tests for rare single-gene diseases (see chapter 7.2.2), also applies in principle to pharmacogenetic tests, although the more pragmatic need to find the appropriate medicine will generally prevail.

If a pharmacogenetic test is known to have the potential of revealing secondary health-related information, there may be a number of measures available to help limit the data and preserve confidentiality. For example, it may be possible to avoid using specific genetic variants in the pharmacogenetic test if others can be found with an equally predictive value. A further step may be to limit the reporting of the pharmacogenetic test to the minimum needed for prescribing³⁴.

In general, the benefits of pharmacogenetic testing are likely to outweigh these largely theoretical considerations. Concerns over unsought information are not unique to pharmacogenetic or other genetic tests.

5.3.3 The issue of 'non-responders' to treatment: creation of rare disease categories and the need for rare medicinal products

Concerns have been raised that pharmacogenetics will identify groups of 'non-responders' which may not be large enough to constitute economically viable populations for the development of new, targeted medicines. As a consequence, research and development time would not be invested, and those patients would be left without treatment options. The probability of this scenario is likely to be small and will only occur in instances where there is no appropriate dose adjustment or alternative medicine and the population is very small. Nonetheless, it may be important to consider whether orphan medicine designation should consider the size and prevalence of any pharmacogenetically defined sub-group.

³⁴ Buchanan A., Califano A., et al. (2002)

This is certainly not an argument against pharmacogenetics, as the research does not 'create' responders or non-responders but enables better prediction of outcomes among the patient population. Pharmacogenetics will provide important information relating to the benefit-to-risk ratio of a medicine for individual patients. The physician and the patient will together use the information, along with other medical information such as the severity of disease, alternative treatments, and lifestyle changes, to decide on the most appropriate course of action.

Indeed, it is much more likely that pharmacogenetic approaches will help define research needs and guide the development of medicines that are effective in certain sub-populations of patients (as has already occurred in the field of oncology). Currently, a therapeutic candidate may not be developed if its overall efficacy is limited because a large fraction of patients are showing poor response, or if it is associated with adverse reactions in clinical trials. Pharmacogenetic understanding of efficacy and/or adverse reaction incidence may, in such cases, enable the continued development and regulatory approval of the medicine by selective targeting of patients who are either likely to respond, or not to suffer the adverse reaction.

5.3.4 Data confidentiality

Conceptually, all genetic data are part of the overall spectrum of confidential medical data and cannot be classified as a separate category. The information content of any medical data, including genetic data, is highly contextual and dependent on the particular circumstances and the questions applied to them. All medical data, including genetic data, regardless of its apparent information content, should be treated with the same high standards of confidentiality.

5.4 Application of pharmacogenetics

The application of pharmacogenetics to healthcare improvement has yet to be fully evaluated. The Group supports the development of an appropriate legal, regulatory and healthcare framework for this evolving field in which patient benefits can be maximised and potential risks for the individual reduced. The Group fully supports an open and transparent dialogue in which this can be realised. As science and the discussion progress, and potential applications gradually increase, specific ethical and policy considerations may emerge for debate which should be addressed on a case-by-case basis.

Relevant public policies should recognise that pharmacogenetics – like other forms of genetic testing – is part of the spectrum of confidential information used in medical research and practice and does not represent a separate category. Pharmacogenetics is an evolving scientific area with the promise of significant healthcare benefits, and thus requires thorough research and debate of all medical, scientific, ethical, legal and social issues.

As with any evolving concept and/or new technology, it is important to discuss and debate the potential benefits and risks for all segments of society who are impacted by them. In this regard, it is important to identify and consider any risks which may be unique to the use and application of pharmacogenetic information and which are different from those related to current medical diagnosis and practice. In addition, the possible constraints to realising the potential benefits of pharmacogenetics in healthcare improvement should be addressed by policy-makers and regulators.

5.4.1 Public perceptions and policy

It is important to increase public awareness, education and understanding of genetics and genetics-related concepts and technologies. It is also important that pharmacogenetics is not confused with genetic testing for rare monogenic disease diagnosis or prediction (as employed in medical and reproductive healthcare). The representation of genetic research projects should be balanced and set realistic expectations. Importantly, the public should be aware of the probabilistic nature of most genetic,

including pharmacogenetic, tests and data which convey information about incremental risks and likelihoods. As such, these will need to be clearly distinguished from tests for rare heritable diseases with which the public commonly associates genetic testing. Open communication and debate about real and perceived benefits as well as risks, paired with evidence of appropriate handling of data and samples, will be essential to establish a reasonable level of trust between all major stakeholders. In turn, this will allow the scientific and medical community to conduct pharmacogenetic research and identify applications where pharmacogenetic-guided decision-making can improve health outcomes. In addition, responsibility for accurate dissemination of information must also lie with the media.

In order to gain public confidence, it is important to communicate to the public that almost all aspects of pharmacogenetic research and medical practice are already covered by a comprehensive framework of guidelines and laws governing the conduct of medical research and protecting individual privacy and confidentiality with regard to the use of medical information.

5.4.2 Mutual engagement of regulatory authorities and industry to create guidelines and processes for medicine and pharmacogenetic test approval

The pharmaceutical, biotechnology and diagnostic industries, together with the drug and device regulatory authorities, should work in partnership to move scientific concepts and results into clinical practice and develop, in parallel, regulatory guidance for all key issues. Also, a global framework is desirable that will facilitate both the exploration of preliminary research findings and, in parallel, the assessment and approval of medicines and any pharmacogenetic tests that may be required for their use.

5.4.3 Healthcare provider education

It is likely that the number of medicines that utilise pharmacogenetic information prior to prescription will increase in years to come. It is highly unlikely that there will be a sudden impact on all medicines in all therapeutic areas, and is more likely to be an evolutionary application of knowledge and practice. This will require specific training for healthcare professionals, as part of medical and nursing school curricula, and of continuing medical education programmes. Together with an appropriate healthcare infrastructure across Europe, this will ensure the technology is used optimally for (i) improved therapeutic outcomes for patients, and (ii) the provision of cost-effective healthcare. Calculation of the latter will also require health economists to attain a comprehensive skill set so that clinical outcome data can be analysed appropriately.

6. Research and development of genetic tests

6.1 Challenges, needs and duties of test developers

6.1.1 Scientific and clinical validation

Prior to clinical implementation, a genetic test will have gone through a number of different phases³⁵. In the research phase, the relationships between a genetic alteration and a disease are explored. In the investigative phase, which follows the positive confirmation of an association between a genetic alteration and a disease, the aim is scientific validation, i.e. to assess the reliability and effectiveness of the test to detect genetic alterations, and its utility to the people being tested. Scientific validation of a new genetic test comprises both analytical and clinical validation.

The following precautions should be respected:

- Data should be collected under appropriate investigative protocols and according to relevant guidelines;
- Data should be collected from a representative group of subjects in the study population;
- New formal validation should be sought when a genetic test previously validated for one purpose is used for another;
- Access to well-characterised human DNA or tissue samples should be assured.

These steps comply well with principles laid down in the European *In Vitro* Diagnostic Directive (98/79 EC).

6.1.2 Assessment of clinical utility

In order to establish the clinical utility of a genetic test or screening programme, data are required on the benefits and risks involved in receiving positive and negative test results. From a purely scientific point of view, the best way to proceed in order to safeguard the quality of such data would be to conduct a randomised clinical trial in which half of the study subjects undergo the test, while the control group is assigned to a different intervention, or to no intervention. A less rigorous, but more time-consuming procedure would be to enrol all patients with positive test results who undergo interventions in a registry that is regularly updated with respect to health status and clinical interventions, so that associations between the occurrence of disease and specific interventions can be traced. Such assessment measures are important to ensure that the public will benefit from the envisaged test or screening programme.

6.1.3 The need for adequate return on investment

When the context makes it unlikely that an adequate return on investment is foreseeable within a reasonable timescale, incentives should be provided in order to allow desirable genetic tests to be developed, even when economic return would be absent without such incentives. This may be the case for genetic tests for rare diseases.

6.1.4 The need for legal clarity

Consistency of relevant legal and ethical frameworks within the European Community is important to facilitate the work of European test developers and to enable them to compete with stakeholders in the US and Japan. At present, there is no such common policy within the EU³⁶.

6.2. Challenges, needs and duties of public health authorities and healthcare providers

6.2.1 The need for independent review procedures

When a new genetic test, for a new clinical application, is believed to be appropriate for clinical use it is important that it is reviewed by an organisation or body that is independent of the test provider, as indicated in the EU Directive on *In Vitro* Diagnostics (98/79 EC). National health authorities should take appropriate measures to safeguard the independence and professional capability of such bodies.

6.2.2 The need for scrutiny of certain genetic tests

Some of the genetic tests currently in routine clinical use may not have undergone appropriate validation during test development nor may they have been the subject of independent review before being used in clinical routine. It is therefore important that these tests, whether commercial kits or developed in-house ('home-brew'), are reviewed by appropriate bodies able to determine their suitability for the clinical application for which they are intended, if such information is not available.

Recommendation on regulatory framework and criteria for test development and use

That:

- a. the regulatory framework for genetic testing be further developed by the EU and other international organisations in a way that recognises both the need for new tests and the importance of safety, **clinical validity** and reliability;
- b. all newly developed tests must conform to the standards established before introduction into clinical use, based on a review process by an organisation or body independent of the test developer to ensure that the patient will benefit from the test;
- c. priority setting for the development of accurate genetic tests be guided by the degree of unmet medical need, independently of disease prevalence;
- d. the EC takes measures to facilitate the availability of genetic testing for rare diseases as well as for more common diseases;
- e. the EC actively promotes the regulatory framework on these topics.

See N° 17 of the "25 recommendations" document

■ **Clinical validity**

The clinical performance of a test, based on clinical studies, defining the ability of the test to accurately and reliably identify individuals who have (or will develop) the condition being tested. Also referred to as clinical accuracy.

6.2.3 The duty to safeguard availability of tests for rare genetic diseases

Relevant authorities should take steps to assure that tests for rare genetic diseases, which have been demonstrated to be clinically useful and of sufficient quality, continue to be available if the current supplier decides to discontinue the test, assuming that no other laboratory is prepared to offer it, and/or the methodology is too complex to be readily transferred to other laboratories (see chapter 1.4).

Recommendation on rare diseases

That:

- a. an EU-wide network for diagnostic testing of rare genetic diseases be created and financially supported as a matter of urgency;
- b. an EU-level incentive system for the systematic development of genetic tests for rare diseases be created and financially supported;
- c. for rare but serious diseases for which treatment is available, Member States introduce universal neonatal screening as a priority.

See N° 18 of the "25 recommendations" document

6.3 Rights of individuals and groups involved in genetic testing research and development

In some situations where genetic testing does not directly serve the health interest of the individual, but is performed in another context (research, or testing of human tissue to be used for the healthcare of other patients, for example), there is a possibility that new information is revealed which is of relevance to the individual. This is no different from situations in which non-genetic medical tests are used. If, in such situations, confidentiality and privacy are not sufficiently assured, people may be discouraged from such 'altruistic' behaviour.

If there is a likelihood that new and important information on the health of the research subject or donor will be revealed by the test, this ought to be discussed beforehand as part of the informed consent procedure, in order to allow the individual to make use of his right to know or not to know

(see chapter 7.2.2). Whenever possible, as is the case in certain types of research more widely discussed under the biobank issues (see chapter 4), anonymous samples should be used so as to prevent the revelation of any personal information. Codes of conduct and guidelines may help to resolve difficult problems. Ethical reviews of protocols for genetic research should always take these issues into consideration.

7. Clinical implementation and use of genetic tests

7.1 Challenges, needs and duties of clinicians and genetic counsellors

7.1.1 The impact of genetic testing on individuals

Whilst the legal and ethical implications of a genetic test are very similar to those of any medical test, their impact can be greater than other forms of medical testing because of the sheer number of possibilities of genetic testing. These are expected to increase as methods are developed for rapidly performing a combination of tests at the same time from a single blood or tissue sample.

The issues of concern relating to the impact of genetic testing on individuals are discussed in full in other sections of the report. They stem from a variety of factors including:

- The gap that still exists between genetic testing and the safe and effective follow-up treatment, or other options, that make the test meaningful for the patients (see chapter 7.1.2);
- The relative predictive value of genetic testing. Tests indicating susceptibility for developing an illness which depends on other factors as well may have a limited ability to predict when, how severely, and even whether a person will develop that illness (see chapter 7.1.5);
- The expected future focus on genetic variation in pharmacogenetic testing. Some pharmacogenetic tests may have the potential to provide additional information relating to health status or risks (see chapter 5.3.2);
- The fact that genetic testing has consequences not only for the individual, but also for relatives, including offspring (see chapter 2.1.1);
- The pressure that individuals may be under to take a genetic test and disclose test results to satisfy the demands of relatives or other third parties (see chapter 7.1.6);
- The increased risk of misuse or abuse of the information from genetic tests by third parties, resulting in discrimination and stigmatisation if tests are undertaken prematurely or applied inappropriately (see chapter 2.1.9);
- The potential competing interests of the health benefits and commercial value resulting from research with human biological material and associated data (see chapter 4.2).

7.1.2 The importance of professional standards for healthcare professionals

Professional standards are key elements in the establishment of patient trust. Along with the respect of individual (patient) rights, protection of the individual against misapplication and misuse of any type of personal data is a primary obligation of healthcare professionals. They have a duty to protect the individual/patient against harm as a result of the poor quality of a test or when testing is performed inappropriately. This protection is part of the individual's right to a 'personal sphere' – a virtual buffer to intrusions from the outside world.

A genetic test should be performed or offered only where the expected benefits for the individual outweigh the potential risks. A test should be meaningful, in the sense that follow-up action is available (treatment, prevention, reproductive choices). On the other hand, the offer of a test should not be made out of fear of a liability claim; the interests of the individual to be tested ought to be the primary concern of the specialist. Professional behaviour sometimes requires professional restraint.

See also recommendation on medical genetic testing and its context (N° 6)

In genetic testing, as in other similar types of medical testing, it may be necessary to pay special attention to relevant norms and guidelines when vulnerable people are involved or if the test is performed at a specific moment in the individual's lifespan. Pre-conceptual and pre-implantation testing are less complicated from an ethical and legal point of view than prenatal testing. Some prenatal tests can be controversial. Should they be offered only in situations where there is a medical reason (family history, medical indication of the pregnant woman), or routinely to all pregnant women (screening tests)? A woman's right to free choice may compete with her fear of an over-medicalised pregnancy. Wherever the balance is found, the offer of a routine test should always be based on an assessment not only of the technical factors, but also of the potential for psychological harm.

With minors and vulnerable adults, it is standard practice that a test should only be performed if it serves their best interests. Early childhood testing, for instance, is only indicated for existing conditions which represent an important burden of disease and where preventive measures or curative treatment is available, and effective only if started early. Predictive testing on children is justified only where there is clear evidence that a delay in diagnosis until the child has the capacity to decide will seriously harm his/her health (testing for PKU - Phenylketonuria - being one example). However, susceptibility screening is not justified as the benefit is remote and often uncertain. Carrier screening can also wait until the child can make his or her own decision. A child has a right to an open future.

Recommendation on consent procedures for children and vulnerable individuals in human genetic research

That:

- a. the use of tissue and accompanying data from minors or vulnerable individuals in research be permitted if, in so doing, their interests are served;
- b. specific consideration be given to children's views, the information provided to them, and issues of children's assent and/or consent.

See N° 25 of the "25 recommendations" document

7.1.3 The need for professional development and education

The information available to individuals about genetic or genetics-related tests, and about the implications of a diagnosis and its consequences, is often limited or poorly communicated. More information on diseases, their natural course, available treatment, interpretation of test results, and the impact on future life needs to be made available by healthcare providers to help individuals with the interpretation of their test results. This implies further training and professional development to help healthcare providers cope with this task (see chapter 8.1).

Recommendation on professional development

That:

- a. initial educational and professional requirements be coordinated in all countries of the European Union;
- b. continued professional training be offered for healthcare professionals.

See N° 15 of the "25 recommendations" document

7.1.4 Informed consent, confidentiality and privacy

Public concern over genetics stems mainly from fear of the misuse of genetic information and discrimination. These issues, linked to the management of tissue samples and data, have already been discussed in detail in the section dealing with biobanks (see chapter 4.1).

However, the Group recalls the following:

The appropriate use of genetic testing and genetic information, and the protection of the privacy of the individual in the case of sensitive genetic information is primarily a matter of compliance to professional standards and duties. Sometimes, however, government action may be necessary to protect the individual against abuse and to take all steps to ensure his or her rights are fully respected.

The individual's right to physical integrity, and to a 'personal sphere', are first and foremost protected by the informed consent requirement. In the case of storage and use of tissue left over from a medical procedure, the 'source' of the material has the right to decide about storage and further uses and the right to withdraw consent. The modalities and extent of withdrawal must be precisely explained to the person concerned.

Recommendation on informed consent

That:

- a. the European Commission promotes opportunities for dialogue between stakeholders to support exchange of experience throughout Europe on issues of sample and data use for research, at the individual, family and population level;
- b. the European Commission funds multidisciplinary research into the social, ethical and legal issues related to informed consent procedures for human genetic research and other relevant areas essential for any evolving research in genetics.

See N° 23 of the "25 recommendations" document

7.1.5 The duty to provide 'non-directive' counselling

Genetic counselling is an important activity in current clinical genetics. It gradually expanded in the second half of the previous century, as the achievements of **cytogenetics**, biochemical genetics and prenatal diagnosis enabled more precise diagnoses and risk assessments. In the last 20 years, the availability of molecular diagnostic tools has been responsible for the further spectacular growth of this discipline.

Genetic counselling should be available for anyone who believes he/she might have a genetic problem that may also affect other family members. Counselling requires that the counsellor has acquired a particular set of skills and genetic expertise and that his/her personality is compatible with the requirements of the demanding task of listening and informing about sometimes extremely personal issues.

■ **Cytogenetics**
The study of
chromosomes and
chromosome
abnormalities.

Recommendation on genetic counselling

That:

- a. in the context of healthcare, genetic testing be accompanied by the provision of key information and, where appropriate, by the offer of individualised counselling and medical advice (in the case of highly predictive genetic tests for serious disorders the offer of specific counselling should be mandatory, and patients should be strongly encouraged to take advantage of it);
- b. specific educational programmes on counselling and exchange of experience in the field be organised at the European level;
- c. specific qualifications, and quality standards for those engaged in the provision of specific genetic counselling, whether clinicians or non-clinicians, be established and made mandatory;
- d. appropriate financial means for such training and the subsequent accreditation be made available;
- e. Europe-wide general standards for fundamental principles of genetic counselling be developed by relevant medical professional groups, with due consideration given to patients' views.

See N° 9 of the "25 recommendations" document

The first question the counsellor will address is whether there is indeed a real genetic problem in the family. This will be done by extensive analysis of inheritance patterns in the extended family tree (**pedigree** analysis) and by taking samples for diagnostic laboratory tests – if necessary and possible – for the disease in question. He/she will be aware of the exact meaning and limitations of a test result and will be able to convey this accurately to the person being counselled. Once a diagnosis has been established, the counsellor will inform the individual or family about the risk of recurrence of the defect, the natural history of the disease, if known, the implications and options for reproduction, and the likely social, financial and psychological burden which may result from the disease. Finally, the counsellor should be available to provide continuous and ad-hoc support to those being counselled for decisions they have taken or will take after the counselling. To summarise, the main components of the counsellor's role are: good communication, support, education and information of patients and their families, as well as of other healthcare workers, and skilled interpretation of current research findings. Listening and devoting time, as well as being non-directive, are of paramount importance.

The main goal of genetic counselling is to help individuals or families understand or cope with genetic disease, not to decrease the incidence of genetic disease. In particular, in the context of reproduction, the counsellor should attempt to re-establish reproductive confidence and adopt a non-directive approach, i.e. he/she will leave the decision regarding reproduction and prenatal diagnosis up to the family. This contrasts with the approach historically followed in other medical practices in which advice or recommendations were given as regards treatment or medical intervention. However, it is well aligned with newer, evidence-based medical procedures in which the patient is also educated about the pros and cons of the choice of approaches that can be taken given the established diagnosis. Depending on the country, genetic counselling is provided either by clinical geneticists, or by psychologists, nurses or social workers with the appropriate training in genetic counselling. It is imperative that the counsellors can work in a team setting, since the quality of their service will also be dependent on the additional expertise brought to the specific case by physicians, laboratory personnel, social services, and so on.

In recent years, as presymptomatic and predisposition testing has become a reality (e.g. for Huntington's chorea, breast and ovarian cancer), counselling has become more complex and has had to be extended into a more multidisciplinary approach. Indeed, in an attempt to develop as adequate an approach as possible for predictive testing of Huntington's chorea, given its potentially major impact on the life of

■ Pedigree

A family tree diagram that shows how a particular genetic trait or disease has been inherited.

the individual (and his/her family), guidelines and an experimental protocol, based on broad international consensus, were designed by geneticists, neurologists and family support groups. These protocols involve neurologists, psychiatrists, psychologists and social workers in addition to geneticists. They include a pre-test phase in which the individual and his/her chosen partner are informed about the procedure, about what they can expect from a test result, and what the potential impact of this result can be on their future life. Individuals are given ample time to digest this information and to come to a decision whether to be tested or not. After the actual testing session, which again will provide additional information about the test and its impact, the individual is seen for post-test counselling and the actual result is given, if it is still desired. The post-test counselling session is usually followed by follow-up sessions, six months to one year after the actual test is performed, and can be repeated at the request of the individual. In a number of centres, all such sessions are monitored as part of a scientific research protocol to learn more about these tests and to measure the actual outcome of the procedure with regard to how the individual copes with the situation. Most of these procedures are still in place today and have made predictive testing for this disease almost free of major adverse outcomes. Moreover, this protocol now stands as a model for other hereditary neuro-degenerative diseases as well as for predictive testing in hereditary cancers and other diseases.

■ **Risk (genetic risk)**

The probability that an individual will develop a genetic disease or carry the mutation associated with a disease, or react adversely to a prescribed medicine. Also note the different uses of 'risk', 'uncertainty' and 'ignorance' in this context:

- Risk: quantified probabilities in a defined situation

- Uncertainty: when the situation is defined, but the probabilities of events cannot be quantified

- Ignorance: when the situation is not fully defined.

The most difficult task for the counsellor is to communicate the precise meaning of **genetic risk**. Indeed, an individual's response to information is not only influenced by the information itself but also by his/her pre-existing perceptions and convictions (see chapters 2.1.1 and 2.1.7). The predictive (genetic) dimension of a disease may give it a more dramatic connotation and increase anxiety; emphasising the genetic aspects of a predisposition to disease may even dissuade people from engaging in preventive measures. Different methods – verbal, numerical and graphical – have been developed to communicate risk in an understandable way to the person being counselled, but no consensus exists regarding the most effective way of doing this. Whatever the method, the provision of simple, printed information that can be consulted by the individual after leaving the counselling session has been shown to be essential. Moreover, the existence of genetic support groups for the particular disease or problem, to which the person can be referred will, in many cases, provide information complementary to that given during the counselling session and can provide further support in the understanding of, or the coping with, a genetic problem.

The provision of genetic counselling services is essential for those rare heritable diseases that have a high degree of penetrance – where the predictive information content of testing is high and often almost deterministic. However, a very different situation exists for those genetic variants that are associated with a risk of future disease at a much lower level of predictability, particularly in the area of common complex diseases. Such genetic variants are responsible for a more modest increase in the risk of future disease and their impact closely resembles that of more conventional medical data that have always been handled directly by physicians. The Factor V Leiden mutation, which increases the risk of venous thrombosis three to fivefold, is one example. Advice regarding the above-average increased risk of blood clots in young women carrying the Leiden variant – and who are considering various options of birth control – is handled effectively today by their gynaecologists. In the case of predictive testing for the Her-2 gene variation, associated with reduced survival rates in women with breast cancer, testing and advice on treatment options has always been handled by oncologists.

In future, as more such 'limited information content' tests emerge, the primary physician, or other healthcare professional – rather than a genetic counsellor – will need to provide the necessary advice to the patient. This, of course, will require appropriately trained professionals, and will extend the demands on medical school curricula.

7.1.6 The duty to disclose actual or potential conflicts of interest

a) Genetic privacy and the duty of disclosure

The authority of the individual over the decision to disclose or not to disclose the results of a genetic test in favour of a relative is likely to suffer from the pressure of family interests. Refusal to share information with relatives who may benefit from the information may disrupt family bonds.

As a general rule, the possibility that relatives may have an interest in the information revealed by the test and the ways of dealing with disclosure are discussed with the individual to be tested in a pre-test consultation. There are, however, different legal approaches relating to the passing on of information to relatives. At present, most European jurisdictions, evoking professional secrecy, require the free consent of the individual before relevant personal information is passed on to relatives. Only exceptional circumstances, whereby disclosure could prevent serious harm to the health of the relative, and provided there are no other less-intrusive alternatives with respect to the privacy of the patient, may justify a breach of confidentiality in the doctor-patient relationship, and disclosure of the information by the health professional against the wishes of a patient. In those circumstances, informing the relative that there is a serious indication that genetic testing might be necessary to prevent serious harm to his or her health might be a solution. Unavoidably, such a message puts the relative's right not to know under constraint. This is also the case when a patient decides in favour of disclosure to the relative, and the relative is approached to find out whether he or she wants the information or not. Evidently, with genetic information, individual privacy may give way to the privacy interests of groups of people.

b) The duty to warn

In the United States there is substantial jurisprudence concerning the duty to warn third parties in the case of their health being at risk, despite professional practice guidelines. Fear of liability claims is likely to put even more pressure on professional secrecy, as warning relatives might be viewed as the 'least risky' option. The more individual genetic information is collected, the more physicians could be inclined to pass on relevant information to relatives without bothering about consent and may not limit themselves to applying the principle of duty to warn only as a last resort to avert serious harm.

In other situations, the right to know of one member of the family can come into conflict with the right not to know of another family member. For example, if a deceased grandparent is known to have suffered from Huntington's chorea and his grandchild asks to be tested for carrier status, with a view to making decisions about his reproductive choices, for example, the information that he is a carrier, if that proves to be the case, will also be information about the parent who did not want to know. Such situations are unavoidable but they may, in principle, be resolved if the interest of the person applying for a test is sufficiently overriding.

With the increase in genetic testing possibilities, there is a need for clear guidance, acceptable to all parties involved, on how to deal in practice with competing rights about knowing and not knowing, and how to handle professional secrecy and the protection of privacy.

7.2 Duties and rights of individuals undergoing genetic testing

7.2.1 The duty to keep informed about genetics

One can argue that autonomous choices cannot be made without acquisition of all the information relevant for understanding the situation in which decision-makers find themselves³⁷. Consequently, autonomy implies a duty to keep informed which, in the case of genetic knowledge³⁸, means that people have "a moral duty to know about their genetic disorders in order to be free and autonomous".

³⁷ Rhodes R. (1998); Vehmas S. (2001); Häyry M. and Takala T., eds (2001)

³⁸ Vehmas S. (2001) p. 473

Another argument that could be used to support this claim derives from the notion of 'moral responsibility'. Moral responsibility can be hampered in two ways:

- by coercion and force, or by
- the absence of *crucial* information³⁹.

If these arguments are applied to the situation of prospective parents considering whether to undergo genetic testing before conceiving a child, it seems to follow that in order to act in a responsible way, they ought to get hold of as much relevant genetic information as possible "... and make their decisions on the basis of it without coercion"⁴⁰.

There are several problems underlying these arguments. For example, a couple planning to have a child, and knowing that the woman might be a carrier of a Fragile X gene, may be considered irresponsible in their role as prospective parents if they reject the doctor's advice to undergo testing. Knowing whether the woman is a carrier or not could be considered as information relevant to the couple. However, this argument fails to contextualise the notion of 'relevant information'.

Little is known about what kind of information the prospective parents themselves consider to be relevant in *their* situation. The argument presumes 'relevant information' to have the same meaning for all, i.e. information that makes it possible for prospective parents to go for the 'best' alternative, a healthy child. As observed by several authors⁴¹, this is a contestable presupposition. First, it takes for granted that a disabled child is always worse off. Secondly, it assumes that families with disabled children will always be more burdened (emotionally and economically) than other families. Thirdly, it presumes that the world would benefit more from the birth of a non-disabled individual.

One conclusion that can be drawn from this analysis is that the couple's behaviour could be viewed as *responsible* behaviour. For this to be the case, the decision to decline testing and go ahead with having a child has to be based "on a conscious parental assent to commit to the caring of a future child despite its characteristics"⁴². In such a case, the couple's decision to remain ignorant would be fully reasonable and in accordance with the principle of autonomy.

See also recommendation on public information and education (N° 4)

7.2.2 The right to know and not to know

The broader impact which some genetic testing can have on the individual, compared to other medical tests, has brought about a shift in emphasis from respect for physical integrity to the right to a personal sphere: the right to know and not to know as an expression of autonomy, the right to share confidential information with others, or the right not to share that information.

Genetic testing does not *per se* imply that the normative (human rights) framework applicable in healthcare and related activities should be changed. The application of the norms in practice may, however, need further accentuation and elaboration in order to address specific aspects related to some genetic testing and genetic information.

Real freedom of choice in relation to genetic information with high individual impact sometimes calls for further precision of the application of the legal requirement of informed consent, as well as of the protection of confidentiality and privacy.

39 Vehmas S. (2001) p. 475; Harris J. and Keywood K. (2001) p. 421

40 Vehmas S. (2001) p. 476

41 Häyry M. and Takala T., eds (2001) p 488; Vehmas S. (2001) p. 433-440 and p. 476-477; Bennett R. (2001) p. 468;

Parents E. and Asch A. (1999); Vehmas S. (1999)

42 Vehmas S. (2001) p. 477-478

For instance, it is the level of information content or the severity of the impact of the information which should drive the format of informed consent. With low information content or low impact information, consent may sometimes be presumed or given orally. Only some genetic tests, because of their impact and because of the possibility of pressure from third parties, require express, written informed consent. The aim of the requirement for express informed consent is to ensure that the individual has understood all the implications of a test, including the implications of being a carrier, the implications for reproductive choices and lifestyle adaptation, and also possible societal consequences. It is also – to a certain degree – a procedure to avoid a situation in which an individual takes the decision to be tested under pressure from a relative who needs the information for his/her own sake.

An important issue which needs to be addressed in relation to the right to know is that of possible societal consequences. The issues of societal effects mentioned here are general and also pertain to other aspects dealt with in different parts of this report. Absence of untoward societal effects is one of the requisites for being able to decide freely to know or not to know genetically related information regarding one's health.

The unlimited right of third parties to impose certain genetic tests prior to an employment or insurance contract or to look for existing information of this type, in particular where the test is related to a serious, untreatable late-onset disease, would represent an unjustified infringement to the right to a personal sphere. Such practices could create a serious barrier for the individual wishing to seek medical (genetic) advice, to undergo diagnostic testing, or to participate in screening.

See also recommendations on data protection: confidentiality, privacy and autonomy (N° 10)

8. The impact of medical genetic testing on healthcare systems in the EU

The developments made possible by technologies related to genetics have already had an impact, which promises to become more substantial, on health systems and healthcare delivery. Their impact also has the potential to influence health economics.

The link between diagnosis and therapy will be more specific than previously possible and may allow more accurate predictions about patients' future health, as well as the provision of more effective treatments based on more accurate diagnosis. The healthcare systems of tomorrow will be confronted with the growing demands of the individuals concerned, and of the health professionals, to receive timely information about, and access to, testing and options for prevention and therapy. Government authorities, international organisations, patient groups, healthcare providers, non-government organisations, and industry are all important contributors to the debate regarding the decision processes that will govern information about and access to genetic testing, and its implementation and impact on health systems. Technical, clinical and economic issues, as well as management of real or perceived benefits and risks associated with genetic technologies, will need to be resolved by societal consensus or, in some cases, by political leadership based on foresight and reliable information. Over the coming decade, medical progress related to genetic testing is likely to be evolutionary and gradual, rather than immediate and revolutionary.

Like all medical progress throughout history, developments in genetic testing are accompanied by new societal, ethical, economic, and health policy questions. These need to be addressed in a timely manner and through informed dialogue among a wide variety of stakeholders so that compromise and consensus

solutions are attained before being cemented into healthcare provision and systems. Progress must be guided by the overarching goal of compassion and improvement of the human condition.

8.1 Communication, education and information

While great progress has been made in genetics on the research front, and while appropriate emphasis has been put on bioethical issues, the issues of public understanding, information provision, and education of healthcare professionals and policy-makers about the developing opportunities in genetic testing are lagging behind. Consequently, one of the main challenges faced jointly by healthcare systems and society is providing an improved understanding for the public and health professionals about the possible benefits, as well as the limitations, of the role of genetic testing. This will require communication through multiple channels, including the general and specialised press, public and professional education, and a broad discussion involving society as a whole.

Recommendation on public information and education

That:

- a. materials and resources be developed and made available at the EU, national, and local level to provide information about genetic testing, genetic screening, and pharmacogenetics through a variety of media;
- b. science curricula at all levels (from primary to university level and vocational training) include reference to progress and potential in the field of medical genetics;
- c. national education systems ensure an adequate supply of appropriately trained scientists and teachers, including technicians and clinicians, to ensure that benefits arising from genetic research and genetic testing can be made real and delivered to all EU citizens;
- d. concerted efforts to promote dialogue, education, information and debate be encouraged;
- e. the 'Science and Society' component of the EC research and development framework be further strengthened.

See N° 4 of the "25 recommendations" document

Therefore, one of the main challenges for health systems will be to address the individual's and health professional's information needs, and to build that into the current education system. This means providing flexible healthcare systems in which a more knowledgeable public can manage information and use it for its own benefit, and the direct implementation of education about genetics, including related technologies, consequences, benefits, risks, and counselling skills, into the study programmes for clinicians and other health professionals.

See also recommendations on medical genetic testing and its context (N° 6) and on professional development (N° 15)

8.2 Policy and regulation

It seems clear that the field of human genetic testing will grow, and that the provision of quality-controlled genetic testing services to the medical profession will require accredited service laboratories (commercial and academic). Commercial laboratories and producers of diagnostic kits will play an increasingly important role in the provision of economical, quality-assured genetic testing services. **Analytical performance** and clinical accuracy (i.e. sensitivity and specificity) should be a prerequisite before any

■ **Analytical performance**
The technical performance of a test, including precision (repeatability and reproducibility), trueness (or bias), and accuracy.

new genetic tests are offered for routine diagnosis. A more detailed analysis of these issues has been provided in chapters 1.4 and 6.1.

High-quality provision of genetic testing by laboratories is essential, and a matter of medical ethics. A consistent regulatory framework is necessary to assure a high standard of quality in genetic testing services and a system of accreditation for genetic testing laboratories, whilst taking into account the need to ensure availability and quality of 'in-house' genetic tests for rare diseases.

Recommendation on quality assurance

That:

- a. the European Union institutes a consistent regulatory framework to assure specific standards of quality for all genetic testing services and their providers, including a system of accreditation of genetic testing laboratories;
- b. test providers ensure that information provided is accurate, by conforming with internationally agreed quality standards;
- c. national healthcare systems establish consistent quality requirements for genetic testing.

See N° 7 of the "25 recommendations" document

Such a framework should also prevent premature provision of genetic tests without benefit to the patient (to be judged on scientific and medical grounds by independent experts), and prevent genetic tests being offered that clearly provide a basis for intolerance or stigmatisation, or being misused for racial or social negative discrimination.

Priority-setting for the development of accurate genetic tests, often resource-dependent, should be guided by the severity of the medical need and not by its rarity: it should be independent of the prevalence of the condition. Criteria of likelihood of technological solutions over the short term, and ease of use should also be high on the list.

8.3 Health economics

New genetic tests may allow earlier, possibly preventive, interventions and optimised prescription of medicines and other treatments. However, before their use becomes widespread, society will need to decide how their implementation in predictive and preventive healthcare will work in practice as it may involve reorganisation in some sectors and induce breaking with existing habits, if the potential benefits are to be accessible to all. Patients' access to new genetic knowledge and information will challenge the conventional thinking presently limiting their responsibility with respect to their own health.

Whether these changes will further increase overall healthcare costs is an area of active debate. Some say that there is no reason to suppose that genetic testing will contribute a major cost burden to public health expenditure, but if this is to be the case, its implementation may require substantial change which, historically, is not an easy thing to do in healthcare. An increased understanding of the contributions of genetic factors to various diseases may lead to increasing stratification of patient groups, with smaller groups of patients eligible for certain treatments, or conversely, some diseases which may appear to be different – based on signs and symptoms – may be shown to have similar underlying mechanisms requiring similar therapeutic interventions. It may become necessary to provide economic incentives in order to make the development of treatments for minority groups economically feasible, as is currently the case for 'orphan' medicinal products to treat rare or neglected diseases.

■ **Gene expression**
The process by which a gene's coded information is translated into the structures present and operates in the cell (either proteins or RNAs).

As targeted therapies are developed for life-threatening and severe disorders, including many rare genetic conditions, early diagnosis of these disorders will become extremely important, providing early benefits for the patients before clinical symptoms are irreversible. This would offset the high costs resulting from not treating these patients. Indeed, current care is often as expensive as newly available therapies, including for rare diseases, without even taking the social costs and the benefits healthy people bring to society into account. Cost-effectiveness calculations will also be influenced and weighted by concerns for equity, since genetic testing may send out a message that we are all different, therefore generating new requirements for social solidarity.

Targeting healthcare at those who will benefit the most implies a more efficient use of healthcare expenditure with better health outcomes – on average – for those treated, and a freeing-up of resources, including manpower, for other tasks such as caring for the ageing population. More focus on disease prevention may result in more focus on overall costs and benefits in a holistic approach rather than by department or budget, and may result in higher costs for diagnosis or treatment, while saving on care and on lost working days.

One of the more far-reaching ramifications for healthcare systems of the development of new genetic testing techniques may be the introduction of microchips (microarrays) for the detection of DNA sequences or **gene expression** profiles (which indicate the activity of the genes being studied) in point-of-care application⁴³. An intensive dialogue between national healthcare systems, private insurers, patient groups, and healthcare professionals will be necessary to address and resolve questions of when a particular test is appropriate and how reimbursement should be handled. Research into areas where genetic testing can be cost-effective for healthcare systems should be developed.

The question of whether society can afford the widespread application of genetic testing is an important, but separate issue from that of the value some individuals would put on the information about their health which can be provided by certain tests. These individuals may want to take a genetic test and be willing to pay out of their own pockets to do so.

Recommendation on social, cultural and economic consequences

That:

the European Commission funds more research relating to the impact of genetic testing on the social, cultural and economic aspects of healthcare provision.

See N° 14 of the "25 recommendations" document

8.4 Population screening programmes using genetic tests

Population screening programmes set out to identify the risk of disease or its complications in those individuals who are apparently in good health, and therefore at a time when curative or preventive interventions are still possible. Screening programmes have also to be seen in a socio-cultural and perhaps ethnic context, where the question of "who is screening who and for what" is of high importance. However, screening does have the potential to save lives and improve the quality of life through the early diagnosis of disease.

If no treatment for the disease exists, extreme care has to be given to provide screening tests only to those people really consenting to it and wanting to know the test result. Therefore, the promotion of screening programmes by parties who have a vested interest in the provision of the testing should be carefully investigated and controlled. Nevertheless, screening and testing for incurable or untreatable diseases can be very relevant for families, as it provides them with options for decision-making based on certainty, rather than uncertainty. It is clear that in each individual case, real informed consent is an extremely important condition to allow a patient to make a choice and to be sure that his or her right not to know is respected.

Like other medical testing, genetic testing used for screening carries the risk that false positive or false negative results may seriously impact the patient's health decisions. This is even more relevant for genetic tests because the prevalence of the disease tested for is often very low. Since screening tests are performed on people without present indication of disease, all positive screening test results must be followed up by other, confirmatory tests and by medical consultation before any decisions about management or treatment of the disease can be taken.

Because of fears concerning the potential costs of follow-up in screening programmes, governments tend to be very cautious about recommending screening tests. The costs of screening can be reduced if the sub-population at risk can be identified and tested rather than the whole population (e.g. neonatal PKU screening). This means that if the sub-population is sufficiently well identified by using a variety of risk factors in combination, the test becomes more a diagnostic or a confirmatory test rather than a screening programme, and may be more acceptable to the individuals and for the health systems.

As more epidemiological data about diseases become available, and more genetic tests become reliable and informative, various forms of active screening for increased risk of developing serious diseases will be promoted along with options for treatment and/or prevention.

Examples of screening options include:

- premarital screening for life-threatening diseases like Tay-Sachs
- prenatal and newborn screening for cystic fibrosis
- carrier screening for familial hypercholesterolemia
- extensive newborn screening for metabolic diseases
- newborn screening for risk of developing type I diabetes.

A Danish study⁴⁴ on the economic analysis of prenatal screening for cystic fibrosis indicates that introducing a screening programme will result in a net cost-saving to society, but this conclusion needs further confirmation. Prenatal screening programmes should not increase pressure on individuals to consider abortion as the only option, but should rather be promoted as an element of information and choice.

It is clear that screening programmes and their justification in public health terms need to be fully validated and regularly evaluated, and can only be set up providing strict conditions of quality of testing have been met. Screening programmes could also provide an essential surveillance system for the health of the population – currently lacking – but this potential will depend largely on the specific condition being screened for.

The Group considers that economics should not be the driver of the decision to set up a screening programme.

⁴⁴ Nielsen R. and Gyrd-Hansen D. (2002)

Recommendation on population screening programmes

That:

- a. measures be put in place to ensure that tests are meaningful: the condition screened for must be serious, the test highly predictive, and follow-up actions must be available in terms of healthcare interventions (including reproductive choices);
- b. the relevance of the genetic condition being screened for be validated and regularly evaluated in the framework of the public health context (this may differ from country to country in the EU);
- c. the appropriate medical environment for providing information prior to testing and relevant post-test counselling be in place prior to offering such screening;
- d. pilot programmes be performed prior to the general introduction of the screening;
- e. the economic dimension of envisaged screening programmes should be carefully considered.

See N° 8 of the "25 recommendations" document

8.5 Looking to the future: new challenges

Healthcare systems may face more changes than those currently forecast and discussed above and in other parts of the report. Genetic testing is generating a number of new challenges which relate to the multidimensional consequences for an individual and his or her family. The benefits of genetic testing are relevant to budgets for healthcare, social affairs, economy and public health, and so could lead to increased collaboration between these government departments. In addition, the provision of genetic testing and the potential treatment resulting from it will impose a scrutiny as to what is essential healthcare and should be reimbursed, and what should lead to self-payment by the patient.

See also recommendation on social, cultural and economic consequences (N° 14)

8.6 Genetic testing in the global context

Emerging economies represent 80% of the world's population, but less than 10% of the global economic production – a situation reflected in the current state of their healthcare systems. Any increase in the cost of healthcare and its delivery is likely to widen this gap. Recent and future immigration to and from these nations makes the issue of their specific health needs a rapidly growing and important issue in the European Member States and in North America, in particular. Such immigration contributes to a shift in epidemiological patterns (e.g. a rise in the prevalence of hereditary blood disorders, such as sickle-cell anaemia, and their associated transfusion requirements, and the concomitant burden to properly screen blood supply for risks of HIV and hepatitis B and C infections).

Moreover, the frequency of consanguineous or endogamous marriages in certain populations brings added and specific risks for inherited disease or predisposition to such disease. Socio-cultural differences, such as the close family relations in most populations from developing countries, lead to decisions being taken by the family rather than by the individual. The attitude towards healthcare, including genetic testing, in these populations, and the possible non-acceptance of inherited traits in these families, need to be carefully considered.

9. Reflections on the Group's dynamics and dialogue

9.1 How did the Group function and evolve?

Membership of the Group was chosen with a view to ensuring representation of certain sectoral interests: patients, science, academics, industry, lawyers, and politicians. It very quickly became apparent that any expectation that people would contribute to the Group's deliberations in a consistent and predictable way, because of their particular background and experience, was misplaced. Members were able to engage with their issues in an open-minded way, and could respect the viewpoint of others without abandoning or concealing the specific interests, perceptions and concerns of those they represented.

Scope

The Group had discussions about the scope of the debate and of the report and also about the public to be addressed. It was agreed that it would focus on issues related to human medical genetic testing and tests that are carried out in the framework of research and development.

After initial discussion, the Group members agreed to focus on the current ethical, social, cultural and legal/regulatory challenges raised by potential future scenarios related to human medical genetic testing, including the impact on public health and healthcare systems. The broad areas covered were research and development leading to genetic tests; prioritisation and clinical use of genetic tests; genetic screening programmes; and pharmacogenetic research and tests.

Within this broad framework, particular attention was paid to the following issues which represented areas of shared interest for members of the Group:

- Who are the stakeholders, what are their views?
- Is genetic testing different from other medical testing?
- Population genetics, gender, ethnicity and genetic testing
- Pharmacogenetics
- Impact of genetic testing on healthcare systems
- The role of genetic counselling
- Public perception and public participation (education, information, dialogue)
- The formats for effective debate on genetic testing

Although the Group concentrated on genetic testing as a healthcare tool, it recognises the importance of a number of other areas which were discussed, where appropriate, during examination of other issues, but not addressed as separate topics.

These areas, considered to be outside the agreed scope, include:

- A detailed current state of the art of science and technology
- Gene expression studies and many genomic and post-genomic applications
- Judiciary uses (e.g. criminal, police, forensic uses) and paternity testing
- Fundamental research, such as genome evolutionary studies
- Human gene therapy
- The use of genetic testing in insurance
- The use of genetic testing in employment
- Patenting issues

■ **Germinal genetic data**

Information contained in the DNA of the reproductive cells of the body and transmissible to offspring.

■ **Somatic genetic data**

Information from the DNA contained in any of the cells of the body except the germ cells (sperm and egg) and which cannot be passed on to offspring. Acquired alterations in somatic DNA (i.e. properties acquired after conception) can cause cancer or other diseases.

Some of these areas are either already regulated (e.g. judiciary uses) or were not considered as an integral part of human medicine (e.g. fundamental genome evolutionary studies). Other areas are currently being addressed by other international organisations (e.g. the OECD's work on biological resource centres, the Council of Europe's work on genetics and tissue research protocols, the European Group on Ethics in Science's work on genetic testing in the workplace, the Institute for Prospective Technological Studies' and European Science and Technology Observatory's work on quality assurance and harmonisation of genetic testing services in the EU, and the UNESCO International Bioethics Committee's work on genetic databases).

The Group focused mainly on genetic data transmissible at the **germinal** level, pertaining to heritable diseases or traits, and not on **somatic genetic data** which include genetic variations that are acquired during a person's lifetime, in the context of diseases such as cancer, or through environmental exposure. Somatic genetic mutations take place in cells other than the germinal (sexual) cells and are not transmissible to offspring. Somatic genetic data are subject to increasing interest as tools for identification of disease mechanisms and pathways, disease classification, and identification of targets for new medicines.

The Group believes that important issues are at stake with respect to non-germinal (somatic) genetic testing and that these require more in-depth reflection and investigation.

Recommendation on somatic genetic testing

That:

- a. a specific working group be set up to discuss further issues relevant to genetic testing for acquired genetic properties.

See N° 2 of the "25 recommendations" document

The Group also identified six prevalent perceptions that it considered may influence the general debate on genetic testing:

1. The belief in the possibility of an "*ethically costless*" reduction of risks⁴⁵;
2. *Genetic exceptionalism* – the belief that the particular nature of genetics gives rise to greater risks, or risks which are of different nature to other health related risks;
3. *Genetic determinism* – the belief in genetic information as a kind of definitive, fatal, ultimate, non-changeable sort of information "rather than as probabilistic information to be balanced against other factors"⁴⁶;
4. *Genetic over-generalisation* – the 'failure' to differentiate between different genetic tests, different test results, and different forms of genetic information;
5. *The statistical overestimation of uncertainty*: risk assessment makes part of the uncertainty look less uncertain by quantifying it. However, quantifying uncertainty does not imply its abolishment. In addition, the perception and interpretation of risk can vary a great deal between individuals and the estimation of what figure should count as 'high risk' or what increase in risk is considered necessary to evoke medical concern may vary considerably between health authorities. This may arise as the result of financial considerations, for example;
6. *The obsession with drawing moral lines and boundaries*: the importance of determining boundaries in bioethics is clearly exhibited by the striking frequency of phrases such as: "But where do we draw the line?", "We have to draw a line somewhere", or "Who will draw the line?". Making moral

⁴⁵ Buchanan A. et al., 2002, p.10-11

⁴⁶ Buchanan A. et al., 2002, p.10-11

distinctions is at the heart of *all* forms of ethics, but the act of moral differentiation is described explicitly as line-drawing in medical ethics and bioethics far more frequently and obviously than in other disciplines dealing with ethical issues.

Methodology

The Group met nine times over 15 months and dialogue was maintained throughout this period by a lively exchange of e-mails. The chairperson and the rapporteur acted as the main contact points with the Commission.

Participants made use of their networks, their specific knowledge and also drew upon the results of their earlier work in the field. All participants or sub-groups of them contributed to the work of the Group with an issue paper, reflecting their specific knowledge, and added to the work and final results. The Group also heard a number of presentations from experts, either proposed by members of the Group, or by the Commission with agreement of the Group (see lists of hearings in Annex 4). These hearings included presentations on complementary topics, where expertise was lacking within the Group, or on topics where the Group wanted to hear different points of view on a subject under discussion.

It became apparent that people in the Group shared many views, although their different starting positions meant that these could be explored through thorough discussions and investigation. Some examples of discussions which finally produced a negotiated consensus on principles, but not necessarily on their implementation, were:

- Limiting access to genetic tests through prescription by healthcare systems versus more open access to commercial kits, through the internet, for example;
- The recommendation that setting up neonatal screening for rare diseases when treatment exists should be mandatory;
- Whether the proposition of counselling should be mandatory or not in a number of specific circumstances;
- The modes of consent required in the case of further use of samples from those initially planned (in a biobank, for example);
- The analysis of whether the trend towards genetic exceptionalism actually exists in regulatory or policy domains or is simply a possibility to be aware of.

The quality of dialogue deepened over the time the Group worked together. The necessity to report not only on the best possible recommendations but also on the debate itself stimulated a common understanding and made a number of attitudes explicit.

There were many discussions about the structure and organisation of the report in addition to those about its content. There were no strong differences of opinion between members on the chosen issues, but there were differences in the hierarchy of importance of issues according to the various stakeholders. The differential expression of issues according to the point of view of each member was seen as a factor of dialogue within the Group, although it took some time to establish as a way of working.

The experience of the Group led it to reflect upon what makes a good dialogue. The ingredients identified as being essential to a good dialogue are that it should have a defined scope, be multidisciplinary, be organised transparently, and be carefully designed to involve all relevant and interested stakeholders in an egalitarian fashion. Participants in a dialogue should be encouraged to be open-minded, willing to listen, respectful of others' cultural values, and should treat the dialogue as an exchange of opinions rather than as an opportunity for proselytising. An effective dialogue requires discussion leaders to ensure that all participants in the debate are given equal opportunities to voice their respective positions, and that provision is made for questions and answers.

A growing number of organisations and scientists seem to be willing to get involved in public dialogue, especially in the domain of genetic testing. What is missing is a more shared experience of what sort of dialogue or debate format works best in different contexts. Citizens' conferences, consensus conferences, public debates of different kinds, and web forums are not all equally adapted to the various publics targeted, as there is really no such thing as a 'general public'. There is a growing experience of engineering different forms of debate, yet the classic format of the 'conference–debate' continues to be the most commonly used, although not always very satisfactorily. Television debates with question-and-answer sessions present another option but often highlight only the most sensational or critical aspects of the issues at stake. Local experiences presented in the context of well-established cultural events may capture a different audience but can also generate high-quality dialogue. Students studying genetics in higher education also need an opportunity to debate the ethical issues associated with the subject rather than just being on the receiving end of an information flow.

There is a need for the development of criteria for the evaluation of debating activities and ways of sharing experiences in that domain across the EU and elsewhere. There is also a need to develop tools and methods to promote good dialogue as much as required tools for education. The Group experiment could serve as one of those methodologies.

See also recommendation on public dialogue (N° 5)

9.2 Moving on to a larger-scale dialogue and a wider audience

The Group does not consider the report as an end in itself but as a step towards wider dialogue on genetic testing and related societal issues throughout Europe. The citizens and stakeholders conference (Brussels, 6 and 7 May, 2004) presented a first opportunity to give a new dimension to such dialogue and for the Group to share its experience with others. The discussion continues however, and the ongoing debate can be followed on the following website:

http://europa.eu.int/comm/research/conferences/2004/genetic/index_en.html

Annex 1

The Group of Experts

The Group consisted of 14 experts, including the chairperson and rapporteur, with representatives from politics, civil society (consumer, patient and medical groups), industry, and scientific experts in the fields of genetics, ethics and law. Participants were selected and invited on the merit of their personal experience and their competence. Representatives from the pharma industry were included in the Group as it was hoped that industry at large would submit its present and future practices in research and healthcare applications to the ethical criteria the 25 recommendations require. The representatives from industry who were involved made it clear that they could only speak for themselves. It is hoped however, that companies not involved in this endeavour would also engage in this process.

Participants were proposed by key federations from industrial and scientific bodies working in the field and selected by the services of the European Commission.

The Group respected a balanced geographical distribution and gender participation (30% women).

Group Members

Eryl McNally, UK

Chair, STRATA Expert Group

Member of the European Parliament

Eryl McNally is an MEP for the East of England region. She was first elected in 1994. Since 1999, she has been the Socialist group coordinator on the Industry, External Trade, Research and Energy Committee, having previously been vice-president of the Research, Technological Development and Energy Committee. Her policy interests include world trade, energy and environmental issues (especially renewable energy), and research policy. Eryl McNally is currently the first vice-president of the European Parliament's Scientific and Technological Options Assessment (STOA) and was actively involved in the Parliament's contribution to the European Union's Sixth Framework Programme for Research and Technological Development, in particular the promotion of science and society. Her work in this field included being rapporteur for the Women and Science Report. Mrs McNally was also a member of the D'Avignon high-level group on the future of the Joint Research Centre. More recently, she has been a member of the Commission-led 'Group of Personalities' looking at the creation of a programme for security-related research.

Anne Cambon-Thomsen, France

Rapporteur, STRATA Expert Group

INSERM, Toulouse

Based at Inserm Unit 558 (National Institute of Health and Medical Research) in Toulouse, France, Dr Thomsen is a Director of Research at the CNRS (National Centre for Scientific Research) and leads a multidisciplinary team on 'Genomics, Health, Society', involving human and social sciences in the context of research in epidemiology and

public health. She has an MD, a Masters degree in human biology, and a degree in health ethics. She also leads the 'Genetics and Society' branch of the Toulouse Genopole. Her topics of research encompass human immunogenetics, transplantation, genetic epidemiology of autoimmune diseases, population genetics, and ethics in genetics. From 1985-1997, she directed several research units in these fields.

Dr Cambon-Thomsen is the author of 140 publications and 90 chapters and reports. She is a member of the Advisory Committee for Priority 1 (Genomics and Biotechnology for Health) of the European Union's Sixth Framework Programme for Research and Technological Development and of the advisory scientific board of Genome Quebec. She is involved in a number of activities concerning ethics in health and research, and has been involved in the ethical evaluation of the EU's Fifth Framework Programme projects and a member of an international jury for a 'Society and Genomics' centre in the Netherlands. She is a member of the CCNE (French National Advisory Bioethics Committee) and has been a member of other ethics committees in research and hospitals.

Celia Brazell, UK

GlaxoSmithKline

Dr Brazell is the Genetics Science and Technology Director for Genetics Research at GlaxoSmithKline. In this role she works with research ethics committees, drug/device regulators, policy-makers and healthcare providers to explore the application of genetics to healthcare improvement. Since completing her PhD in neuropharmacology at the Queen's Medical Centre, Nottingham University, UK, she has worked in pharmaceutical research, development and policy with Merck Sharp & Dohme and GlaxoSmithKline.

She is a member of the UK Human Genetics Commission, the UK Department of Health Advisory Group for Genetics Research, and the Council for International Organisations of Medical Sciences (CIOMS) Working Group on Pharmacogenetics and Pharmacoeconomics.

Jean-Jacques Cassiman, Belgium

Centre for Human Genetics, Leuven

After training as an MD specialising in paediatrics, Jean-Jacques Cassiman spent five years at the University of Stanford, CA, US. Since 1984, he has been a Full Professor of Human Genetics and, since 1999, division head of the Centre for Human Genetics in Leuven, Belgium. He is director of the laboratory for forensic genetics and molecular archaeology, and coordinator of EU projects on cystic fibrosis. From 1993-99 he was secretary-general of the European Society of Human Genetics, and has been the liaison officer for the ESHG to the International Federation of Human Genetics Societies since 2002.

He is secretary of EPPOSI (European Platform for Patient Organisations, Science and Industry) and a board member of VIWTA (Flemish Institute for Science and Technological aspects of the Flemish Parliament).

Alastair Kent, UK*Genetic Interest Group*

Alastair Kent is Director of the Genetic Interest Group (GIG) – the UK alliance of charities and support groups for people affected by genetic disorders. GIG's mission is to promote the development of the scientific understanding of genetics and the part that genetic factors play in health and disease, and to see the speedy transfer of this new knowledge into improved services and support for the treatment of currently incurable conditions. Prior to joining GIG, Alastair worked for a number of voluntary organisations on issues concerning policy, service development, and disabled people.

Klaus Lindpaintner, Austria*Roche Genetics and Roche Centre for Medical Genomics*

Professor Lindpaintner's background is in clinical and investigative medicine, in clinical and molecular genetics, and in public health/epidemiology. He has spent the bulk of his time at F. Hoffmann-La Roche setting up mechanisms to implement the use of genomics, genetics, and proteomics, as it applies to pharmaceutical and diagnostics discovery and development in common complex disease indications. In so doing, he has been involved in the ethical, legal, and sociological issues raised by DNA testing and related issues on an almost daily basis over the last four years. Internally, this led to his drafting and getting approval by the company's Board of Directors of a 'Roche Charter on Genetics' that endorses the principles of autonomy, beneficence, non-maleficence, and justice, as well as of solidarity and altruism. Subsequently, he initiated the appointment of an external 'Science and Ethics Advisory Group' that counsels the company in matters related to ethical and legal implications of using DNA testing in its clinical research, and also features representation by the lay community.

In recent years, he has been frequently involved in committees and official advisory groups that have focused on genetic testing and related issues. He is a member of WHO's CIOMS work group on pharmacogenetics, a delegate to the EuropaBio Ethics Committee, a member of the Nuffield Council on Bioethics' Pharmacogenetics Round Table, he has served as a consultant to the Nationale Ethikrat in Germany, and has testified before the European Parliament's Temporary Committee on Human Genetics and New Technologies in Medicine.

Paula Lobato de Faria, Portugal*New University of Lisbon*

Professor Lobato de Faria is a lawyer and Associate Professor of Health Law and BioLaw at the National School of Public Health and in the Faculty of Law at the Universidade Nova de Lisboa (New University of Lisbon). She is also a consultant in ethical-legal aspects to the National Agency for the Fight Against AIDS, and for four years was the coordinator of the National Commission for the United Nations Decade for the Education on Human Rights in the Presidency of the Council of Ministers. She has also worked as a visiting professor in the Department of Health Law, Bioethics and Human Rights at the Boston University School of Public Health.

Author of approximately 60 papers, Professor Lobato de Faria has directed and given different courses, seminars and conferences in Portugal and abroad mainly on patients' rights, the legal aspects of AIDS, medical liability, legal problems of genetics, informed consent, intensive-care ethical/legal questions and health data protection and

confidentiality. Her PhD was on the ethical and legal problems of genetic data. Her work has been published in France by the Presses Universitaires du Septentrion (*Données Génétiques Informatisées – un nouveau défi au droit à la confidentialité des données personnelles de santé*, 1999). She is also author of several articles, published in Portuguese in international magazines, and is currently writing the Portuguese monography on medical law to the *Kluwer International Encyclopaedia of Laws*.

Detlef Niese, Germany

Novartis Pharma

Priv. Doz. Dr Med, Detlef Niese is head of External Relations in Clinical Development and Medical Affairs, Novartis Pharma in Basel. Dr Niese, a licensed pharmacist and physician, obtained a research-based doctoral degree from the Faculty of Medicine, University of Bonn, Germany. He joined industry (Sandoz AG Basel, Switzerland) in 1992 as a Senior Clinical Research Physician, and held positions of increasing responsibility in clinical R&D in transplantation, dermatology and infectious diseases before joining the clinical development management team in 2001. Dr Niese was involved in programmes on organ and cell transplantation (including genetically modified cells), tissue-engineered skin replacement, growth factors, and xenotransplantation for solid organs, bone and cells.

Before specialising in Internal Medicine and Clinical Immunology, he worked for four years as a research fellow in immunogenetics. Between 1980 and 1992, he headed Clinical Immunology and Clinical Pathology at the Department of Internal Medicine, University Hospital in Bonn, Germany providing clinical (in- and outpatient) and laboratory services. He also served as a consultant for immunosuppressive therapy to the university and to major regional hospitals. His primary research interests were the structure and genetics of the MHC (Major Histocompatibility Complex) in man, MHC and disease, autoimmunity and immunodeficiency, specifically in chronic renal failure as well as in HIV infection. Since 1991, Dr Niese has been a member of the Faculty of Medicine of the University of Bonn, Germany.

Henriette Roscam Abbing, The Netherlands

Ministry of Health

Professor Dr Roscam Abbing studied law at the University of Utrecht in the Netherlands. Her thesis dealt with international organisations in Europe and the right to healthcare. She is a legal counsellor to the Minister of Health, on health law and public health issues and is a part-time professor of health law at the University of Utrecht.

Previously, she worked at the Council of Europe Health Division in Strasbourg. She is now the representative of the Ministry of Health at the European Health Committee of the Council of Europe. She also participates in the work of the Council of Europe's Committee on Bioethics and its working group preparing a protocol on genetics. She is co-author of a draft legal instrument on the use of human biological materials and personal data in biomedical research, also for the Council of Europe.

Professor Roscam Abbing is co-editor of the *Dutch Journal on Health Law* as well as of the *European Journal of Health Law*, and a member of the international advisory board of the *Medical Law Review* (UK). She is also a member of the Dutch Health Council, the scientific advisory board on health matters to the Minister of Health. Her present activities concentrate on biotechnology, screening and genetics from the perspective of the inter-relationship between public health, society and law.

Jan Helge Solbakk, Norway*University of Oslo*

Professor Solbakk trained as a physician and a theologian and also holds a PhD in ancient philosophy. Until 1995, he served as Director of the National Committee of Medical Research Ethics in Norway. He is currently Director and Professor of medical ethics at the Centre for Medical Ethics, Faculty of Medicine, University of Oslo. He is also adjunct professor of philosophy of medicine and medical ethics at the Centre for International Health, Faculty of Medicine, University of Bergen. His fields of research are medical ethics, research ethics, philosophy of medicine and ancient philosophy, literature and medicine. He is in charge of a European research project on research biobanks and health registries. Since 1998, he has served as a member of the CDBI-CO-GT4, a Working Party on human genetics at the Council of Europe. In 1999, he served as a member of an expert committee on genetic therapy, set up by the Norwegian Centre for Health Technology Assessment. From 1999-2000, he was chairman of a working party set up by the Ministry of Health and Social Affairs in Norway to issue a report on stem cell therapy. He has been a member of the Norwegian Biotechnology Advisory Board since 2000.

Hélène Tack, France

Hélène Tack's role within the Group has been to represent patients directly concerned by genetically transmitted diseases. She is 37 years old, married and has had five children. She lost her first two children due to a serious genetic disease but was able to benefit from prenatal genetic tests available at the time and, as a result, has three healthy children now.

For the last ten years she has been working with the Association Française contre les Myopathies (French Muscular Dystrophy Association) and has been in regular contact with many families concerned by genetic tests. She feels very strongly about the necessity to reflect on and understand genetic tests so as to be better prepared to accompany the families in their choice, whatever that might be. This is the reason why she chose to be a part of the Expert Group.

Erik Tambuyzer, Belgium*Genzyme Corporation*

Dr Ir. Tambuyzer is Genzyme's Senior Vice-President Corporate Affairs Europe, and a member of the European Management Board of Genzyme Corporation. Having started his professional career at Baxter Health Care in 1977, he pursued his career six years later at Innovi NV (Brussels, Belgium), a technology management and consultancy company. In 1985, he co-founded the biotech company Innogenetics NV (Ghent, Belgium), of which he was General Manager until 1992 when he joined Genzyme Europe.

Dr Tambuyzer is Chairman of the Healthcare Board of EuropaBio, the European Association for Bioindustries, and founder and Chairman of the Ethics Working Group of this association. He is also Vice-Chairman of the European Platform for Patients' Organisations, Science and Industry, EPPOSI, and an adviser to international journals. Dr Tambuyzer is a bio-engineer and holds a doctoral degree in bio-industrial sciences from the University of Leuven (KUL), Belgium. A Belgian citizen, he is married and has three children.

Thomas Weihrauch, Germany*Global Medical Strategy and Relations*

Bayer AG, Pharmaceutical Research Centre

Professor Weihrauch has an MD and PhD in medicine. He is Associate Professor of Medicine, University of Düsseldorf, Germany, and lecturer in internal medicine and therapeutics. He has a specialisation as internist, gastroenterologist, and examiner in clinical pharmacology. He has chaired and participated in a number of industry/government working groups and is an expert in genomics/pharmacogenomics as well as healthcare and health economics issues in medicine, drug safety, innovation, and access to medicines. He is currently Advisor to the German Ministry of Education and Research (BMBF) and co-chairman of the CIOMS VII Working Group (WHO, Geneva).

Erik Wendel, Denmark*European Patient Voice*

Mr Erik Wendel is Secretary-General of the European Patient Voice and executive board member of the Danish Cystic Fibrosis Association. He is co-founder of the European Patients' Forum.

European Commission contacts**Barbara Rhode**

Dr Rhode has a diploma in sociology and a PhD in political sciences. She was responsible for the 'Ethics and Science' unit in the Research Directorate-General of the European Commission. In the 1990s, she was responsible for the accession negotiations to the EU in research for Hungary, the Czech Republic and Slovakia, for science relations with Switzerland, and some ex-USSR countries. She has been working with the EU since 1991. As a national expert, she prepared the social sciences programme for DG RTD.

She has also been a consultant to the UN, an expert for the Council of Europe, and Vice Chair of the German Social Science Committee to UNESCO. In the 1980s, she was seconded by the German Federal Ministry for Science and Technology (BMFT) to a UNESCO East-West co-operation institute in Vienna/Austria, directing East-West research projects on environmental policies, on legal policies, and on the internationalisation of penal law. Dr Rhode was a scientific adviser at the Max-Planck-Institute for International and Comparative Private Law in Hamburg, Germany. She has published scientific papers on economic law and labour law, European environmental policies, international environmental criminal law, environmental ethics, and communications and strategy papers on EU foreign policies in science and technology.

Maurizio Salvi

Secretary to the STRATA Expert Group

Maurizio Salvi holds MDs in modern literature and in philosophy, a postgraduate diploma in bioethics, a PhD in health sciences, and a European PhD in biotechnology. He has lectured in bioethics at the Universities of Rome, Maastricht and Leuven, and has undertaken research on ethical and legal implications of biotechnology for the International Forum of Biophilosophy, the Flemish Institute of Biotechnology, and several research bodies in the EU. Dr Salvi was Director of the human rights and bioethics course at the Interuniversity Centre in Dubrovnik. In 1998, he joined the European Commission with specific responsibility for ethics and bioethics. He has published around 40 papers on ethical, legal and social issues of biomedicine and biotechnology, theoretical biology, ethics, and analytical philosophy.

Annex 2

Glossary of terms used in the report

Many of the definitions given below are specific to their use in the context of genetic testing. The terms used in scientific research are in constant evolution as scientific knowledge progresses.

Term	Definition
Biochemical genetic test	The analysis of human proteins or other biological molecules predominantly used to detect gene products showing genetic variations or mutations.
Gene penetrance	In the case of genetic disorders, the probability for an individual carrying a specific gene form or allele to manifest the disease or disorder associated with that gene form or allele. The percentage frequency with which a gene exhibits its effect.
Genetic overgeneralisation	The 'failure' or lack of will to differentiate between different genetic tests, different test results, and different forms of genetic information.
Germinal genetic data	Information contained in the DNA of the reproductive cells of the body and transmissible to offspring.
Identification of samples or data	<ul style="list-style-type: none"> • <i>Identified</i>: those labelled with personal identifiers such as name or social security number • <i>Single-coded</i>: those labelled with a single specific code attributed to protect the individual • <i>Double-coded</i>: those labelled with a second code, providing additional protection of privacy • <i>Anonymised</i>: double-coded samples or data where the key linking the first and second code is destroyed. Can also include previously identified samples or data where the personal identifier has been destroyed • <i>Anonymous</i>: those that do not have any personal identifiers or link with individual identity
Immunochemical test	Identification of a substance, usually a protein, by its reaction to antibodies.
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.
Pharmacogenomics	The study and understanding of differential gene expression in response to drug treatment using DNA profiling techniques.
Phenotype	An individual's characteristics (physical, physiological, etc.) resulting from the expression of the products of genes or from the interaction between genetic and other factors (e.g. environmental, lifestyle).

Annex 3

Bibliography

Documents referred to in the report

- Anderson, D.C. et al., 'Elements of informed consent for pharmacogenetics research; perspective of the pharmacogenetics working group', *The Pharmacogenetics Journal*, 2:284-292, 2002
- Bennett, R., 'Antenatal Genetic Testing', *Theoretical Medicine*, 22, 461-471, 2001
- Buchanan, A., Califano, A., Kahn, J., McPherson, E., Robertson, J., and Brody, B., 'Pharmacogenetics: Ethical Issues and Policy Options', *Kennedy Institute of Ethics Journals*, 12:1-15, 2002
- Buchanan, A. et al., 'Pharmacogenetics: Ethical and Regulatory Issues in Research and Clinical Practice'. Report of the Consortium on Pharmacogenetics, Findings and Recommendations, spring 2002
- Council of Europe Working Party on Human Genetics (CDBI-CO-GT4) 'Working document on the applications of genetics for health purposes', February 2003
- Crigger, B.J., 'The "vampire project"', *Hastings Cent Rep*, 25, 2 1995
- EMEA (European Agency for the Evaluation of Medicinal Products) CPMP, 'Position Paper on Terminology in Pharmacogenetics', EMEA/CPMP/3070/01, November 2002
- EMEA CPMP 'Concept paper on Pharmacogenetics Briefing Meetings', EMEA/CPMP/4445/03, 2003
- European Commission, European Group on Ethics in Science and New Technologies, 'Opinion 18 on Ethical aspects of genetic testing in the workplace', July 2003
- European Society of Human Genetics, 'Provision of genetic services in Europe: current practices and issues', *European Journal of Human Genetics*, 11: 900-902, 2003
- European Society of Human Genetics, 'Genetic information and testing in insurance and employment: technical, social and ethical issues', *European Journal of Human Genetics*, 11: 909-910, 2003
- European Society of Human Genetics Public and Professional Policy Committee, 'Data storage and DNA banking for biomedical research informed consent, confidentiality, quality issues, ownership, return of benefits, a professional perspective', EUROGAPP-PROJECT 1999-2000, 1 November 2002
- Fondation Roi Baudouin, 'Lire dans mes gènes?', ISBN 2-87212-403-9, Brussels, 2003
- Green, M.J., Botkin, J.R., "'Genetic exceptionalism" in medicine: clarifying the differences between genetic and nongenetic tests', *Annals of Internal Medicine*, 138, 571-575, 2003
- Harris, J., Keywood, K., 'Ignorance, information and autonomy', *Theoretical Medicine*, 22:415-436, 2001
- Häyry, M. and Takala, T., 'Genetic Information', *Theoretical Medicine and Bioethics*, 22:5, 2001

- Hirtzlin, I. et al., 'An empirical survey on biobanking of human genetic material and data in six EU countries', *Eur. J. Hum. Genet.*, 11: 475-88, 2003
- Human Fertilisation and Embryology Authority (HFEA) 'Summary report on sex selection', UK, November 2003
- Ibarreta, D., Balzi, E., Rodriguez, E., 'Genetic testing: quality assurance issues in research, development and regulations', IPTS Report N° 80, December 2003
- Ibarreta, D., Bock, A.K., Klein, C., Rodriguez-Cerezo, E., 'Towards quality assurance and harmonisation of genetic testing services in the EU', IPTS report 2003
- Leung, A., "The future of the healthcare industry's reputation" in *Health Industry News in Europe*, KHIDI-Europe, 15 July 2002
- Knoppers, B.M., 'Populations and genetics. Legal and socio-ethical perspectives', Martinus Nijhoff, Leiden, 2003
- Nielsen, R., Gyrd-Hansen, D., 'Prenatal screening for cystic fibrosis: an economic analysis', *Health Econ.*, 11: 285-299, 2002
- NIH-DOE Working Group on Ethical, Legal and Social Implications of Human Genome Research, Task Force on Genetic Testing 'Promoting safe and effective genetic testing in the United States. Principles and Recommendations', USA, May 1997
- OECD 'Biological Resource Centres: Underpinning the Future of Life Sciences and Biotechnology', OECD Code 932001041E1, 2001
- Parens, E., Asch, A., 'The disability rights critique of prenatal genetic testing: reflections and recommendations', *Hastings Centre Report* 29: 1-22, 1999
- Rhodes, R., 'Genetic links, family ties, and social bonds: rights and responsibilities in the face of genetic knowledge', *Journal of Medicine and Philosophy*, 23:10-30, 1998
- Spear, B.B., Heath-Chiozzi, M., Huff, J., 'Clinical application of pharmacogenetics', *TRENDS in Molecular Medicine*, 7:201-204, 2001
- *Trends in Biotechnology*, 'Empowering patients with point-of-care testing', June 2002
- UK Parliament Human Tissue Bill, 2003: <http://www.parliament.the-stationery-office.co.uk/pa/cm200304/cmbills/009/2004009.htm>
- UNESCO, 'Preliminary Report on the Possibility of Elaborating a Universal Instrument on Bioethics', SHS/EST/02/CIB-9/5, Paris, November 2002
- UNESCO International Bioethics Committee 'International Declaration on Human Genetic Data', Paris, 2003
- US Department of Health and Human Services, Food and Drug Administration 'Draft Guidance for Industry: Pharmacogenomic Data Submissions', November 2003
- Vehmas, S., 'Newborn infants and the moral significance of intellectual disabilities', *Journal of the Association for Persons with Severe Handicaps*, 24: 111-121, 1999

- Vehmas, S., 'Assent and selective abortion: a response to Rhodes and Häyry', *Cambridge Quarterly of Healthcare Ethics*, 10: 433-440, 2001

Further reading

- Alper, J.S. and Beckwith, J., 'Racism: a central problem for the Human Genome Diversity Project', *Politics Life Sciences*, 18: 285-8, 1999
- Anderlik, M., 'Commercial biobanks and genetic research: ethical and legal issues', *Am J Pharmacogenomics*, 3: 203-15, 2003
- American College of Medical Genetics, 'ASHG/ACMG report: Points to consider: Ethical, legal and psychosocial implications of genetic testing in children and adolescents', *Am. J. Hum. Genet.*, 57:1233-1241, 1995
- Arnott, N., 'Every day new discoveries unlock medical mysteries. How does this affect your family?'. Project of the US Dept. of Health and Human Services, Office on Women's Health, Genetic Counselling, July 1999, <http://www.4woman.gov/editor/jul99/jul99.htm>
- Austin, M.A., Harding, S. and McElroy, C., 'Genebanks: a comparison of eight proposed international genetic databases', *Community Genet*, 6: 37-45, 2003
- Baird, P.A., 'Identifying people's genes: ethical aspects of DNA sampling in populations', *Perspect Biol Med*, 38: 159-66, 1995
- Benitez, O., Devaux, D., Dausset, J., 'Audiovisual document of oral consent: a new method of informed consent for illiterate populations', *The Lancet*, 359:1406-1407, 20 April 2002
- Blatt, R.J., 'Banking biological collections: data warehousing, data mining, and data dilemmas in genomics and global health policy', *Community Genet*, 3:204-11, 2000
- 'Breaking the genetics vicious circle – a cultural breakthrough', *Clinica*, 28 August 2003, www.clinical.co.uk
- Brodwin, P., 'Faultlines in "Bioscience ethics": lessons from the Human Genome Diversity Project', *Am J Bioeth*, 2: 56-7, 2002
- Cambon-Thomsen, A., 'Assessing the impact of biobanks', *Nature Genetics*, 34:25-26, 2003
- Cambon-Thomsen, A. et al., 'Biobanks for genomics and genomics for biobanks', *Comp. Funct. Genom.*, 4:628-634, 2003
- Cancer Research UK, 'A response to "Pharmacogenetics: ethical issues". A consultation paper from the Nuffield Council on Bioethics', London 2003
- Casey, D.K., 'Genes, Dreams, and Reality: The Promises and Risks of the New Genetics' in "Judicature, genes and justice. The growing impact of the new genetics on the courts", *Judicature*, 93(3): 105-11, 1999
- Cassiman, J.J., Kent, A., Miller, G., Miny, P., and Tambuyzer, E., 'Genetic Testing Services in Europe: quality assurance and policy issues', *Journal of Commercial Biotechnology*, 8(2):113-123, 2001

- Caulfield, T. & Outerbridge, T., 'DNA databanks, public opinion and the law', *Clin. Invest Med.*, 25: 252-6 2002
- CCNE. 'Ethical problems raised by the collected biological material and associated information data: "biobanks", "biotheques"' in Opinion 77 (ed. Committee, F.N.C.B.) <http://www.ccne-ethique.fr/english/start.htm>, Paris, 2003
- Chadwick, R. and Berg, K., 'Solidarity and equity: new ethical frameworks for genetic databases', *Nat Rev Genet*, 2: 318-21, 2001
- CIOMS, 'International Ethical Guidelines for Biomedical Research Involving Human Subjects', ISBN 92 9036 075 5, Geneva, CH, (also in http://www.cioms.ch/frame_guidelines_nov_2002.htm), November 2002
- Consumers' Association, 'Genetics and Insurance: unravelling the code for consumers', London, 2003
- Consumers' Association, Response to the Human Genetic Commission's consultation document, 'The supply of genetic tests direct to the public', London, 2003
- Consumers' Association, 'The genetics revolution: getting the policy right for consumers', London 2003
- Council of Europe, European Treaties, ETS n° 164, 'Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine', Oviedo, 4 April 1997
- Dawson, G., 'Human genome, race and medicine', *J Natl Med Assoc*, 95: 309-12, 2003
- Deschenes, M., Cardinal, G., Knoppers, B.M. and Glass, K.C., 'Human genetic research, DNA banking and consent: a question of "form"?' *Clin Genet*, 59: 221-39, 2001
- Doring, O., 'China's struggle for practical regulations in medical ethics', *Nature*, 4:233-239, 2003
- ETC Group (formerly RAFI) communiqué: 'Phase II for human genome research: Human genetic diversity enters the commercial mainstream', January 2000
- European Commission, European Group on Ethics in Science and New Technologies, Opinion N°11 on 'Ethical Aspects of Human Tissue Banking', September 1998
- European Commission Research DG, 'Contribution to the analysis of the positions of trade unions and employers regarding genetic pre-employment tests', EUR 18497 EN, Luxembourg, 1999
- European Commission, European Group on Ethics in Science and New Technologies, 'Genetic Testing in the Workplace - Proceedings of the Round Table Debate' at the Borchette Centre, Brussels, ISBN 92-894-0017-X, March 2000
- European Commission, DG RTD, Quality of Life and Management of Living Resources, 'Genetic Testing: Patient's rights, insurance and employment - A survey of regulations in the European Union', EUR 20446, 2002
- European Commission, European Group on Ethics in Science and New Technologies, 'Statement on advertising genetic tests via the Internet', February 2003
- European Society of Human Genetics, 'Data storage and DNA banking for biomedical research: technical, social and ethical issues', *European Journal of Human Genetics*, 11: 906-908, 2003

- European Society of Human Genetics, 'Population genetic screening programmes: technical, social and ethical issues', *European Journal of Human Genetics*, 11: 903-905, 2003
- Farrelly, C., 'Genes and social justice: a Rawlsian reply to Moore', *Bioethics*, 16 (1): 72-83, 2002
- Firn, D., 'Eat your way to good health', *Financial Times*, 20 February 2004
- Fondation Roi Baudouin, 'Tester l'Humain, les tests de diagnostic génétique et leur impact sociétal', ISBN 2-87212-400-4, Brussels, 2002
- GeneWatch UK, '"Genovations" Genetic Test Kits', July 2002
- Greely, H.T., 'Informed consent and other ethical issues in human population genetics', *Annu Rev Genet*, 35: 785-800, 2001
- Haker, H., 'Ethical aspects of pre-natal genetic diagnostics', *Ethics & Politics*, 1 (1), 2001 http://www.units.it/dipfilo_e_poltica/2001_1/haker.html
- Hannig, V.L., Clayton, E.W. and Edwards, K.M., 'Whose DNA is it anyway? Relationships between families and researchers', *Am J Med Genet* 47: 257-60, 1993
- Harris, J., 'Clones, Genes and Immortality', Oxford 1998
- Harry, D. and Marks, J., 'Human population genetics versus the HGDP', *Politics Life Sciences*, 18: 303-5, 1999
- HGDP 'Model ethical protocol for collecting DNA samples', Stanford USA: Human Genome Diversity Project-Morrison Institute; 1999, <http://www.stanford.edu/group/morrison/hgdp/protocol.html>
- HUGO Ethics Committee, 'Statement on DNA sampling control and access', *Genome Digest*, 6: 8-9 1999
- HUGO Ethics Committee, 'Statement on Human Genomic Databases', December 2002
- Human Genetic Commission, 'Public attitudes to human genetic information', London, March 2001
- Human Genetics Commission, 'The Supply of genetic tests direct to the public' – a consultation document, London, July 2002
- INSERM, 'Tests génétiques', *Repères*, Paris, July 2003
- Joly, Y., Knoppers, R.M., Godart, B., 'Genetic information and life insurance: a 'real' risk?', *European Journal of Human Genetics*, 11: 561-564, 2003
- Kaye, J., 'Genetic research on the UK population – do new principles need to be developed?', *Trends Mol Med*, 7: 528-30, 2001
- Kaye, J. & Martin, P., 'Safeguards for research using large-scale DNA collections', *BMJ*, 321:1146-9, 2000
- Kent, A., 'Consent and confidentiality in genetics: whose information is it anyway?', *J Med Ethics*, 29:16-18, 2003

- Khoury, M.J., 'From genes to public health: the applications of genetic technology in disease prevention', Genetics Working Group, *Am J Public Health*, 86: 1717-22, 1996
- Kivisild, T. et al., 'The genetic heritage of the earliest settlers persists both in Indian tribal and caste populations', *Am. J. Hum. Genet.*, 72:313-332, 2003
- Knoppers, B.M. (ed.), 'Human DNA: Law and Policy: International and Comparative Perspectives. Proceedings of the First International Conference on DNA Sampling and Human Genetic Research: Ethical, Legal, and Policy Aspects', held in Montreal, Canada, 6-8 September 1996, Kluwer Law International, Boston, 1997
- Knoppers, B.M., 'Populations and genetics. Legal and socio-ethical perspectives', 648: Martinus Nijhoff, Leiden, 2003
- Knoppers, B.M., 'Human genomic databases: a global public good?' *Eur J Health Law*, 10: 27-41, 2003
- Lazzarini, Z., 'What lessons can we learn from the exceptionalism debate (finally)?', *J Law Med Ethics*, 29:149-151
- Lee, S., Mountain, J., Koenig, B.A., 'The Meanings of Race in the New Genomics: Implications for Health Disparities Research', *Yale Journal of Health Policy, Law, and Ethics*: 33-75, 2001
- Lock, M., 'The HGDP and the politics of bioethics', *Politics Life Sciences*, 18: 323-5, 1999
- Lucassen, R.P., 'Practical Genetics for Primary Care', Oxford, 1999
- Mason, J.K. and McCall Smith, R.A., 'Law and Medical Ethics', London, 1999
- Matthiessen, L., 'Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human biobanks', European Commission Research Directorate-General, Brussels, 2002
- McGee, G., 'Foreword: Genetic Exceptionalism', *Harvard J Law Technol*, 11: 565-570, 1998
- McPherson, E.C., 'Ethical implications of the Human Genome Diversity Project', *Nursing Connections*, 8: 36-43, 1995
- Medical Research Council, 'Public perceptions of the collection of human biological samples', London, October 2000
- Medical Research Council, 'The UK Biobank: A study of genes, environment and health, ethics consultation workshop', London, October 2003
- Murray, T., 'Race, ethnicity, and science: the haplotype genome project', *Hastings Cent Rep*, 31: 7, 2001
- National Consultative Ethics Committee for health and life sciences, 'Ethical issues raised by collections of biological material and associated information data: "biobanks", "biolibraries"', CCNE Opinion 77, France, 2003
- National Deaf Children's Society, 'NDCS policy statement on genetics and deafness', UK, June 1999
- National Ethics Council, 'Genetic diagnosis before and during pregnancy', Germany, 2003
- National Human Genome Research Institute, 'A brief primer on genetic testing', <http://www.genome.gov>, USA, January 2003
- National Human Genome Research Institute, 'Genetic information and health insurance: report of the task force on genetic information and insurance', <http://www.genome.gov>, USA, May 1993

- National Human Genome Research Institute, 'Genetic information and the workplace', <http://www.genome.gov> USA, January 1998
- National Human Genome Research Institute, 'Genetic privacy and genetic testing', <http://www.genome.gov> USA, January 2003
- NIH-DOE Working Group on Ethical, Legal and Social Implications of Human Genome Research, Task Force on Genetic Testing 'Interim principles', USA, March 1996
- Nuffield Council on Bioethics, 'Genetic screening: Ethical issues', London, 2003
- Nuffield Council on Bioethics, 'Pharmacogenetics: ethical issues – a consultation paper', London, 2003
- Otlowski et al., 'Genetic discrimination: Too few data', *European Journal of Human Genetics*, 11:1-2, 2003
- Parker, M., Lucasson, A., 'Working towards ethical management of genetic testing', *The Lancet*, 360:1685-1688, 2002
- Parker, M., 'Genetics and the interpersonal elaboration of ethics', *Theoretical Medicine*, 22: 451-452, 2001
- Ratcliff, N., 'Marketing genetics: the need for consumer protection', *Consumer Policy Review* (12) 1:8-16, 2003
- Resnik, D.B., 'The Human Genome Diversity Project: ethical problems and solutions', *Politics Life Sciences*, 18: 15-23 1999
- RMGA (Quebec Network of Applied Genetic Medicine) 'Statement of principles on the ethical conduct of human genetic research involving populations', <http://www.rmga.qc.ca> Canada, 2002
- Robertson, D., 'Racially defined haplotype project debated', *Nat Biotechnol*, 19: 795-6, 2001
- Romeo Casabona, C.R., 'Legal implications of genetic testing', *Forthcoming* 2004
- Royal Association for Disability and Rehabilitation, 'Genes are us? Attitudes to genetics and disability' – a survey, London, 1999
- Sabatier, S., 'Report for the Council of Europe's Steering Committee on Bioethics working party on human genetics' (CDBI-CO-GT4), DIR/JUR (97) 13 bis. Strasbourg, 1997
- Smith, M.J., 'Population-based genetic studies: informed consent and confidentiality', *Santa Clara Comput High Technol Law J*, 18: 57-93, 2001
- Solbakk, J.H., Hasan, Homa, S., 'Genetic Tests, Screening and Priorities in Health Care', In Bradley, Peter, Burls, A. (Eds.), *Ethics in Public Health*, 94-105, London, 1999
- Sommerville, A., English, V., 'Genetic Privacy: orthodoxy or oxymoron?', *Journal of Medical Ethics*, 25:144-150, 1999
- UK Department of Health Advisory Committee on Genetic Testing 'Code of practice and guidance on human genetic testing services supplied directly to the public', London, October 1997
- UNESCO, 'Bioethics and human population genetic research', CIP/BIO95/CONF.002/5, November 1995

- UNESCO, 'Draft report on pre-implantation genetic diagnosis and germ-line intervention', SHS/EST/CIB-9/2, Paris 2003
- UNESCO, 'Outline of the International Instrument on Human Genetic Data', SHS/EST/02/CIB-9/3, Paris, October 2002
- Varmus H., 'Genomic empowerment: the importance of public databases', *Nature Genetics*, September 2002
- Weiss, K.M., 'Legitimate and illegitimate views of the HGDP', *Politics Life Sciences*, 18: 334-5, 1999
- Weiss, K.M. et al., 'Proposed model ethical protocol for collecting DNA samples', *Houst Law Rev*, 33: 1431-74, 1997
- WHO, 'Genomics and world health: Report of the advisory committee on health research', Geneva, ISBN 92 4 154554 2 (NLM classification QZ 50), 2002

Annexe 4

List of hearings

The state of the art of genetic testing

Dr João Lavinha

Instituto Nacional de Saude Dr Ricardo Jorge, Lisbon, Portugal

Genetic services

Prof. J.J. Cassiman

University of Leuven, Belgium

DNA chips and genetic testing

Prof. Uwe Maskos

Pasteur Institute, France

Genetic testing and public health

Prof. L. ten Kate

University of Amsterdam, The Netherlands

Genetic testing: a review of OECD activities and future prospectives

Dr E. Ronchi

OECD

Genetic testing and the patients

Mr Y. Poortman

European Alliance for Muscular Dystrophy Associations

Chair EPPOSI, European Platform for Patients' Organisations, Science and Industry

Predictive tests: counselling and psychological impact

Prof. G. Evers-Kiebooms

University of Leuven, Belgium

Legal aspects of genetic testing

Prof. C. R. Casabona

University of Deusto/University of The Basque Country, Spain

Ethical, legal and social implications of genetic testing

Prof. G. Gaskell

London School of Economics, UK

Ethical implications of genetic testing

Prof. S. Holm

University of Oslo, Norway

Testing of the human genome for the development of *in vitro* diagnostic medical devices

Frank Hulstaert

Innogenetics, Belgium

Ethical implications of genetic testing*Prof. D. Mieth*

University of Tubing, Germany

Ethical implications of genetic testing*Stefan Trömel*

European Disability Forum

Genetic testing from the point of view of disabled people

European Disability Forum

Economic implications of genetic testing*Prof. A. Towse*

Office of Health Economics, UK

Ethnic-cultural diversity and genetic testing*Prof. T. Duster*

University of California, Berkeley, USA

Ethics at WHO*Prof. A. Capron*

World Health Organisation

Involving the public in discussion associated to genetic testing*David Bennett*

European Federation of Biotechnology

Observers**World Health Organisation**

Dr Victor Boulyjenkov and Ms Zahra Merali

Council of Europe

Laurence Lwoff

OECD

Elettra Ronchi

GlaxoSmithKline

Andrew Freeman

European Federation of Biotechnology

David Bennett and Daan Schuurbiers

EDMA, Belgium

Donnalea Barber

NV AMGEN SA

Thomas BOLS

F. Hoffmann-La Roche Ltd

Silvia Matile-Steiner

European Disability Forum, Belgium

Sofia Konstantatou

Commission services

SJ, GOPA, RTD DG, MARKT DG, EMPL DG, ENTR DG, SANCO DG, JRC-IPTS DG, EMEA

European Commission

Ethical, legal and social aspects of genetic testing: research, development and clinical applications

Luxembourg: Office for Official Publications of the European Communities

2004 — 93 pp. — 21.0 x 29.7 cm

ISBN 92-894-7324-X

SALES AND SUBSCRIPTIONS

Publications for sale produced by the Office for Official Publications of the European Communities are available from our sales agents throughout the world.

How do I set about obtaining a publication?

Once you have obtained the list of sales agents, contact the sales agent of your choice and place your order.

How do I obtain the list of sales agents?

- Go to the Publications Office website <http://publications.eu.int/>
- Or apply for a paper copy by fax (352) 2929 42758

