

Presidenza del Consiglio dei Ministri



**GENETIC SUSCEPTIBILITY TESTING AND
PERSONALISED MEDICINE**

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CONTENTS

Members of the ad hoc Joint Group.....	p.3
Foreword.....	p.4
SECTION ONE: SCIENTIFIC ASPECTS OF SUSCEPTIBILITY TESTING IN MULTIFACTORIAL DISEASES OF ADULTS AND THE CONCEPT OF PERSONALISED MEDICINE.....	p.8
I.GENETIC RESEARCH AND GENETIC TESTING.....	p.9
II .THE CLINICAL USE OF GENETIC SUSCEPTIBILITY AND PREDICTIVE TESTS.....	p.14
SECTION TWO: RULES FOR GOOD CLINICAL PRACTICE,GENETIC COUNSELLING,DEONTOLOGICAL,BIOETHICAL AND LEGAL ASPECTS.....	p.24
Notes.....	p.46
References Section One.....	p.53
References Section Two.....	p.63
ATTACHMENTS.....	p.71
1.Prof.C.Petrini: Review of Institutional Documents on Genetic testing at International, European and Italian level.....	p.72
2.Text of the Agreement between the Government, the Religions and the autonomous Provinces of Trento and Bolzano on “Implementation of the Guidelines for medical genetics activities”.....	p.87
3.Report on the activity of medical genetics in Italy: Italian Society of Human Genetics, Year 2006.....	p.91
4.Extract of the Rules regulating Health advertising licenses: currently genetic tests fall within medical devices.....	p.95
5.Documents on Genetics published by the NBC and the NBBLSC.....	p.96
GLOSSARY.....	p.98

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FOREWORD

In 1999 the National Bioethics Committee (NBC) published “Indications for genetic testing” and the National Committee for Biosafety and Biotechnology (now known as the National Committee for Biosafety, Biotechnology and Life Sciences, NBBLSC) published the “Guidelines for genetic testing”.

While the two documents were conceived independently, the general “inspirations” for each are remarkably similar: each aimed to clarify the nature and medical applications of the tools made available by genetics, though with a different emphasis on the choice and treatment of the issues generated by the relatively young “discipline” that was then evolving rapidly in both theoretical and practical terms.

The first document aimed primarily to provide a framework for the use of the new tools of genetic research within medical, personal, family and social settings, bearing in mind not only theoretical knowledge but also the maximum protection of human rights. Particular emphasis was therefore placed on bioethical aspects and issues of national and international law.

The second document was similarly attentive to these aspects but adopted a more analytical approach to the practical and laboratory aspects of tests, seeking to define the exact “indication” for their use and focusing on the absolute need for quality in their performance, providing guidelines for laboratories and physicians for the protection of potential users. The National Bioethics Committee subsequently explored the issue of pharmacogenetics and pharmacogenomics in an extensive study of the cultural and historical relationships between genetics and drugs and of recent procedures for analysing the responses to drugs in different types of human genetic disorders. The analysis included broad bioethical and legal considerations on the relationships between personal rights and the scientific and industrial development of new drugs (“From pharmacogenetics to pharmacogenomics”, CNB, 21 April, 2006).

Reasons for proposing a new document on the application of genetics to the protection of human health in the field of multifactorial diseases.

The inspiration, style and choice of contents of these documents are still valid; however, the development of human genetics in what is now known as the “post-genomic” age has brought to light new problems and made available different techniques, the objectives have been further honed and, above all, huge resources of information regarding the human biological makeup have been acquired.

Without delving into the fascinating history of modern genetics, it is sufficient here to recall that in the second half of the last Century advances in genetics permitted the identification of an increasing number of monogenic and Mendelian familial diseases and the mapping of their genetic factors to specific chromosomal regions. Studies of twins and pedigree analysis had strengthened the conviction that important hereditary, i.e. genetic, factors were involved even in some of the most frequent complex human diseases such as diabetes mellitus, heart disease, a majority of mental disorders and numerous tumours.

These diverse disorders were considered “polygenic”, reflecting the assumption that several genes – at different levels – are responsible for their onset.

There then began a search for the specific genes involved and their mechanisms of action.

F. Collins and V.A. Mc Kusick (2001) recall how the successful mapping of the gene involved in Huntington’s disease to chromosome 4 in 1983 fuelled the hope of success in identifying the genes responsible for many more complex polygenic diseases.

Thus was born the “Human Genome Project”, founded on – and rendered operational by – huge advances in the necessary sequencing technology (Collins F.S. et al., 1993; 1998).

In June 2000 an international consortium established in the USA, Great Britain, France, Germany, Japan, China and Canada, together with a private Company, Celera, jointly announced the completion of the “Human Genome Project”, that is the sequencing of 3 billion base pairs, launched amid much enthusiasm, but also considerable uncertainty and controversy, in the early 1990s.

Respected geneticists had foreseen the positive “spin-offs” of such a complex operation on the practice of medicine, where it would substantially enhance two fields of research already being investigated – albeit with great difficulty – using traditional techniques: the relationship between the genome and the clinical manifestation of numerous common human diseases; and the response to drugs at the molecular level of cells and tissues. The development of these lines of research would, over the years, not only increase our understanding of the mechanisms of action of genes on the human organism in conditions of equilibrium with environmental factors (good health) and under the modifying effects of endogenous and exogenous pathogens (disease), but also lead to the possibility of evaluating the measure of and possible differences in individual responses to an identical stimulus, correlated with the uniqueness of each genetic profile (polymorphisms, etc.).

With this end in sight the very concept of the gene underwent a change. The discovery of segments that have a regulatory action rather than coding for RNA molecules or proteins led to the generalisation of the concept of the gene; it was no longer to be considered as one, but as a series of genomic sequences that cooperate to code products with potentially identical functions (Gerstein, 2007).

This leads to a strategy of “**personalised medicine**” based not only on millennium-old knowledge of the “phenotypic variability” of health/illness indices well known to clinical medicine, but on the still virtually untried possibility of directly understanding individual variations in the association between an individual’s genetic makeup, environmental factors, lifestyle and life history. The purpose of this is to obtain data “from source” (to be compared with phenotype data), to aim for improved “prevention” in relation to health risk factors, to enable a better choice of drugs and to prevent the risks (at times serious and even life-threatening) of an abnormal susceptibility to a particular drug or drugs (Collins F.S., 1999; Collins F.S. and Mc Kusick V., 2001; Bumol T.F. and Watanabe A.M., 2001; Nathan D. et al., 2001; Baron A. and Scarpa A., 2002)).

Ten years have elapsed since then and much has been achieved and reported in a vast number of publications. Nonetheless, some researchers express a certain disappointment regarding the results obtained so far, even

though the “strategists” of the new approach to medicine based on the fine association between genetic makeup, environment and molecular reactions to pathogens had predicted that, however intense the research, no clinically concrete results would be achieved before 2020.

Notwithstanding this, the first decade has seen the publication of a number of positive results that can already be applied for diagnostic or therapeutic purposes: an example in the field of diagnostics is the test for the HER2 human epidermal growth factor receptor that identifies patients who may benefit from the anti-tumour drug trastuzumab; in the field of therapy, the identification of variants of cytochrome P 450 and other genes in turn integrated by non-genetic factors (Borgiani et al., Pharmacogenomics, 2009) that are a risk factor for persons taking ordinary doses of the anticoagulant warfarin, for whom sensitivity testing is routinely indicated. Of greatest concern is the haste with which the market has produced and distributed “tests” whose clinical efficacy – in the sense of offering a greater “positive” contribution than that of tried and tested phenotype tests – is still unproven.

Some experts have pointed to the uncertainty of results (particularly their repeatability) associated with current GWA (genome-wide association) techniques (Jarvis J.N. and Centola M., 2005).

Finally, the offer of direct-to-consumer diagnostic tests frequently disregards both the professional genetic counselling required by international regulations and bioethical considerations such as the protection of confidentiality, privacy, the familial dimension of genetics, the right “not to know” and protection against discrimination and stigmatisation that, in a moment of enlightenment, were made an integral part of the “Genome project” from which the concept of personalised medicine arose.

About this document

On the basis of the above considerations the two Committees – which have continued during the last decade to cooperate (albeit while submitting separate documents for examination and approval by their respective general assemblies) in addressing some of the problems raised by genetics, such as the issues of “Genetic data banks”, “Consent to donate biological samples for purposes of genetic research”, “Protection of the confidentiality of personal data and insurance”, and examining and commenting on international documents¹ – recognised the need to produce a document devoted specifically to “predictive and susceptibility testing”. In the years under consideration these tests have not only developed at an increasing and at times tumultuous pace, as just recalled, but they have, by their very nature, provoked contrasting psychological reactions in the attitudes and major decisions of those involved that are at times out of proportion to the value of the information they provide.

These tests claim to be able to determine an individual’s risk of contracting one of many – mostly chronic – polygenic diseases, thus inspiring confidence in consumers who are unaware of the real “state of the art”. The two Committees feel it is their duty to reflect on the real value today, and for the foreseeable future, of developments in genetic research for medical-health purposes and to inform the public. Studies based on GWA analysis are not always of proven efficacy and in any case their interpretation calls for mature discernment. Research today is focused on these tests but there is debate as to the clinical validity of the information they can provide for the purposes of

“personalised medicine”, the strategy that has been chosen for the future development of healthcare systems, including prevention.

These aspects need to be evaluated in order to determine both the ethical correctness of professional conduct and the efficacy of provisions put in place to protect individuals undergoing the tests. They thus involve considerations of clinical bioethics and biolaw, bearing in mind the duties imposed on governments by various national and international organisations to ensure the provision of proper information to the public and the protection of health and basic rights.

The present document comprises two sections divided into brief chapters: the first section addresses scientific questions, both theoretic and operational (Chapters I,II); the second addresses more strictly bioethical aspects (Chapters III,IV), including issues of professional ethics, and concludes with comments and recommendations (Chapters V, VI).

The Annexes examine in greater detail specific issues that are important for understanding the proposed text but which cannot be included in the main document for reasons of space. These comprise: a careful albeit summary review of international, European and Italian legislation on these issues; a report on the current state and possible future developments in the field of genetics in Italy by the Italian Society for Medical Genetics (2007 census); a brief bibliography; a glossary of technical terms used in this highly specialised field; a list of previous documents on genetics published by the CNB and the CNBBSV.

SECTION ONE

SCIENTIFIC ASPECTS OF SUSCEPTIBILITY TESTING IN MULTIFACTORIAL DISEASES OF ADULTS AND THE CONCEPT OF PERSONALISED MEDICINE

I . GENETIC RESEARCH AND GENETIC TESTING

Introduction: classification of genetic tests

Over the past 20 years the application to humans of genetic research has produced one key translational result: the transfer of knowledge to clinical practice, in the form of genetic tests. According to one definition, “genetic testing is the analysis of a specific gene, its product or function, or other DNA and chromosome analysis, to detect or exclude an alteration likely to be associated with a genetic disorder” (Harper, 1997).

However, given that genetic tests are not necessarily limited to analysing pathological conditions, the influential UK Human Genetics Commission² (2009) recently defined genetic tests as tests “to detect the presence or absence of, or a change in, a particular sequence of DNA, gene or chromosome or a gene product or other specific metabolite that is primarily indicative of a specific genetic change”.

This definition is currently used to describe several wide-ranging tests performed primarily, but not exclusively, by the medical profession. These vary according to the specific objective and include: diagnostic tests; pre-symptomatic tests; carrier testing; pharmacogenetic tests; susceptibility or predictive tests; behavioural and lifestyle tests; nutrigenetic tests; phenotype tests; ancestry tests; genetic relatedness tests.

Diagnostic tests are performed on subjects with a particular medical condition, often transmitted through simple or Mendelian heredity (e.g. Duchenne Muscular Dystrophy), or forms of dysmorphism caused by chromosome disorders (e.g. Down Syndrome) or genomic disorders (e.g. Williams Syndrome); they are used to confirm a clinical hypothesis or to support a clinical diagnosis, to subclassify a disease and to establish genotype-phenotype correlations (i.e. between the genetic make-up and overall morphological and functional traits) with a view to defining the aetiology of the condition. They are generally performed to improve genetic counselling and occasionally to orient treatment.

Pre-symptomatic tests are performed on asymptomatic subjects from families with late-onset autosomal dominant disorders (e.g. Huntington’s disease, adult polycystic kidney disease, spinocerebellar ataxia, myotonic dystrophy, etc.). Individuals with mutations in these disease genes will, if they live long enough, develop the correlated disease.

Carrier tests theoretically involve the whole population, given that everybody is heterozygous (healthy carrier) for a small number of genes that can, if mutations are present, cause diseases that can be transmitted from one generation to the next. These tests are used in several contexts: 1, screening for mutations that are common in a population (e.g. thalassaemia, cystic fibrosis) and that imply a risk for the children of heterozygous parents; 2, to test the relatives of patients with autosomal recessive disorders (which occur in subjects who possess two mutated genes) with an incidence equal to or lower than 1:10,000 (carrier frequency \leq 1:50); unaffected siblings of patients with these disorders are 66% likely to be heterozygous and, because of the high frequency of the mutation in the population, if they marry a person who is not genetically related their theoretic reproductive risk is \leq 1:300 (e.g. spinal

muscular atrophy); 3, to characterise female members of families in which X chromosome-linked recessive disorders are transmitted; these subjects are potentially at risk of being heterozygous and genetic testing in association with genetic counselling can determine their reproductive risk (e.g. haemophilia).

Pharmacogenetic tests predict how well an individual will respond to drugs and the risk of adverse effects (e.g. the gene for thiopurine methyltransferase defines the response to 6-mercaptopurine, a drug used to treat leukaemia).

Predictive or susceptibility tests determine the presence of susceptibility or resistance to complex common diseases (so-called multifactorial diseases, caused by the interaction between genes and the environment) in a particular individual in comparison with that of the general population (e.g. susceptibility to type 2 diabetes or to Crohn's disease, an inflammatory intestinal disorder).

Behavioural and lifestyle tests provide information about an individual's behavioural propensities, physical and cognitive capacities and response to certain environmental conditions, with the aim of assisting individuals to modify the outcome by elective changes in behaviour (e.g. HLA testing to determine sensitivity to beryllium, a metal used in several types of industrial processing).

Nutrigenetic tests provide information on how an individual metabolises food (e.g. genes involved in the metabolism of lipids, fatty acids, sugar, aminoacids).

Phenotype tests provide information about how a person's phenotype is conditioned by their genotype (e.g. the correlation between specific mutant alleles on the LAMNA/C gene and distinct clinical pictures).

Genetic relatedness tests define the percentage of genes shared by persons who are possibly genetically related (e.g. biological paternity and maternity).

Ancestry tests establish an individual's relatedness to a specific ancestor or ancestral group and how much of his or her genome is inherited from ancestors from particular geographical areas or ethnic groups.

Genetic identification tests define the probability that a sample or trace of DNA recovered from an object or other material belongs to a specific person.

This classification is only a general guide. Some prenatal tests can be considered diagnostic (e.g. identification of the G380R mutation in the FGFR3 gene in a foetus with an ultra-sound image suggesting rhizomelic dwarfism, which genetic testing will classify as achondroplasia), while others can be classified as pre-symptomatic (e.g. identification on the trophoblast of a mutation in the FMR1 gene, which leads in postnatal life to the most common form of fragile X chromosome mental retardation in sons of heterozygous mothers). Similarly, the testing of families at risk of developing breast tumours associated with the BRCA1 gene should be considered as identifying a mutation that may lead to a clinical condition over the lifetime of women exposed to the risk. In fact, the gene's penetrance – in other words the lifetime likelihood of developing the tumour – is about 70%, meaning that this can be classified as a predictive test (given that it identifies a different level of susceptibility from that of the general population). However, the term predictive is usually used only to define tests that identify the genetic component of multifactorial disorders, which are due to the interaction between the additive effects of several genes and the environment. Behavioural and lifestyle tests and nutrigenetic tests are effectively a form of predictive or susceptibility testing

(given that they are applied to complex traits), while phenotype tests can be considered diagnostic (they are applied to simple traits). Lastly, relationship tests, such as ancestry and genetic relatedness tests can be considered in the same way as those intended to characterise individual variability.

The difficulties attached to examining such a complex matter are associated with what is nowadays a widely accredited hypothesis, namely that there is no such thing as a simple phenotype or a simple disease. As Dipple and McCabe (2000) appositely noted: “With the accumulation of detailed information about the mutations in “single-gene” disorders, geneticists have observed that the primary mutant gene product is embedded within a highly complex system in which a multiplex of genetic polymorphisms, additional nonallelic mutations, and environmental influences represent the differences between individuals”.

Decoding complexity

The sequencing of the human genome and the impressive evolution of technology that enables the rapid and relatively economical analysis of an entire genome hold the promise of wide access to the decoding of individual genomic profiles and, in theory, to identifying the constitutional variations that affect our susceptibility to diseases and influence our lifestyles.

This scenario had already been foreseen at the end of the 1800's by William Osler, a well-known Canadian physician who realised that “if it were not for the great variability among individuals, medicine might as well be a science and not an art”, anticipating the axiom that there are no diseases, just sick people. Progress in genetics has confirmed the concept of “variability” intuited by Osler at a time when DNA and its extraordinary variability were as yet unknown, as were the epigenetic effects of external factors. In the mid-1900s the American genetist Francis Collins wrote “Virtually all diseases have some genetic basis”, and that identifying their mechanisms was a research priority (Collins, 1995).

Technological development and “molecular strategy in predictive medicine”

The notion that common diseases and, generally speaking, complex phenotypes are caused by the interaction between the additive effect of mutant genes and the environment was essentially founded in the past on mathematical models based on a normal statistical distribution (so-called bell curve, or Guassian function)³ of genetic and environmental susceptibility factors within the population under consideration.

However, while this criterion allows us to calculate the *average* susceptibility of a group of subjects on the basis of the incidence of a particular pathology, it cannot measure the susceptibility that counts: the *individual* susceptibility, defined as the variable interaction between an individual's genetic makeup and the environment - which together form the phenotype.

Today this is accomplished through Genome Wide Association studies, which aim to define the biological basis of complex traits using a series of molecular strategies that form the basis of “predictive genetic medicine”. In recent years genome research has documented numerous associations between specific chromosomal loci and complex disorders. These studies are

based essentially on data from the *International Human HapMap Project* (2007) and on the possibility of using a genetic variation at one locus to predict, with a high degree of accuracy, a variation at an adjacent locus. Given that the human genome contains about three billion base pairs, the haplotypic structure of our genome allows us to analyse common variations associated with the risk of a given disease by genotyping approximately one million carefully selected markers present in the genomes of thousands of cases (the probands) and controls. The use of these protocols has permitted the identification of common variants (present in over 5% of the population) that carry a very low risk of disease, usually 1.2-5 times higher in subjects with the variant than in those without it.

Given the increasing spread of this technology it is appropriate to add a few considerations.

Before GWA studies can be performed the specific disease or complex trait to be investigated must be selected. The chances of success increase in parallel with the sensitivity and specificity with which the chosen phenotype can be diagnosed or measured. To achieve this objective it is necessary to recruit samples from thousands of controls. These tests depend on a complex methodology that is indispensable to provide statistical support for the existence of associations which must then be duplicated in independent studies before they can be considered as proof. Thus the number of samples enrolled in each study (thousands/tens of thousands) is of critical importance, given that the genetic component of the complex system under consideration may be relatively insignificant. The quality of all the clinical data (probands and controls) must also be of a high order, including data concerning environmental factors and lifestyles.⁴

About 600 GWA tests have been performed, involving more than 150 disorders and complex traits and confirming significant associations with about 800 SNPs⁵. Nonetheless, known polymorphisms contribute only minimally to the genetic variants correlated with these phenotypes (Hardy and Singleton, 2009)⁶ and, in particular, the average risk associated with each variant has been calculated as 1.33. For example, it has been estimated that “approximately 93,000 SNPs are required to explain 80% of the population variation in height” (Goldstein, 2009). It has been suggested that the hereditary control of complex phenotypes is due to rare variants with a prevalence of less than 5%, which may have a more marked effect than more common ones analysed using currently available technological tools (Kraft and Hunter, 2009). The modest effect of these common variants on complex phenotypes is thought to be associated with evolution and to reflect the efficiency of natural selection on the increase in variants associated with complex diseases in the population.

For this reason some researchers have questioned the clinical utility of GWA studies based on today’s technology. Others, in contrast, are more optimistic and emphasise that their main objective is not to predict individual risk but rather to identify the biologic pathways underlying polygenic diseases and traits (Hirschhorn, 2009). Some studies of complex diseases are actually rediscovering genes that have for some time been implicated in these processes. For example, 11 of the 23 genes involved in controlling lipid levels code for lipoprotein, lipase and other key lipid metabolism enzymes that have been studied for many years using other procedures. About one fifth of the approximately 90 loci associated with type 2 diabetes mellitus (DM2) or with lipid levels, obesity or height correspond to mutated genes in correlated

Mendelian disorders. GWA studies have thrown light on the importance of specific genes that code for the action sites of drugs such as sulphonylurea (in DM2 studies), statins (in studies of lipid control mechanisms) and oestrogens (in bone density studies), suggesting that this type of research could in future lead to more finely targeted therapies for common diseases. Other GWA studies have found a correlation between complex disorders and new and previously unsuspected metabolic pathways. For example, genetic variations associated with age-related macular degeneration have confirmed the role of specific components of the complement system, while studies of chronic intestinal inflammatory disorders, and Crohn's disease in particular, have shown the importance of autophagy and interleukin-23; height studies have demonstrated the role of genes encoding chromatin proteins and the hedgehog pathway (a gene family coding for inductive signalling during embryogenesis), especially a secreted protein that establishes the fate of cells during development.

Finally, although most of the data now available have a modest effect on our ability to predict complex disorders and explain only a small part (5-10% on average, although data from the heart project [www.cuore.iss.it] enable us today to estimate the ten-year risk of myocardial infarct with an accuracy of more than 30%) of their heritability, this limited predictive potential is no smaller than that commonly used to calculate risk using non-genetic clinical tests such as LDL cholesterol levels or prostate-specific antigen.

It is possible that as our understanding of the genetic loci potentially associated with a specific disease risk increases, so will the possibility to correlate expected risk with real risk. Nonetheless, this correlation is only one of the reasons that make understanding genetic risk important. It should not be forgotten that the use of these tests presupposes respect for three axioms that are often neglected:

- 1) no susceptibility test should be performed unless it is known what to do with the results;
- 2) of approximately 20 tests performed with a specificity of 95% at least one is a false positive;
- 3) the complete sequencing of an individual's genome is therefore estimated to contain at least 6000 errors.

The clinical value of any test depends, moreover, primarily on the possibility of associating particular variants with an improvement in the clinical outcome. It is thus a dynamic process that is constantly being revised and in which progress is marked by the results of scientific research.

To conclude, although susceptibility testing for most complex phenotypes appears premature for almost all the diseases investigated (Edelman and Eng, 2009), this state of affairs could change over the next few years. Studies of the biological basis of complex traits remain essentially a matter of research, given that, with a few rare exceptions, predictive or susceptibility tests have no clinical application. On the other hand it seems increasingly probable that the most common diseases are caused by the cumulative effect of genes, the individual effect of each of which carries a very modest risk of contracting a disease (very low penetrance) but that this risk becomes considerable when it is combined with numerous, or even multitudinous, others.

II – THE CLINICAL USE OF GENETIC SUSCEPTIBILITY AND PREDICTIVE TESTS

Susceptibility and predictive tests in the health market: the category of “unpatients”

The bioethicist George Annas (2000) imagined that decoding the human genome would identify the DNA molecule as a sort of medical record. He also anticipated that before this objective could be achieved a few questions would need to be answered, including: who is authorised to create the ‘CD’ of an individual’s genetic information? Who will store it? Who will have control over its use? In what way could this CD be considered to contain sensitive medical information? Ten years or so later the expected scenario seems within our grasp. Not only has the objective of bringing down the costs of sequencing the human genome and, therefore, of making it available been achieved but, above all, the technology required to process large volumes of biological samples is available to numerous laboratories and consumers are under increasing pressure from the health market, which is trumpeting the presumed predictive and preventive potential of these tests.

The sequencing of the genomes of celebrities such as the geneticists James Watson (one of the discoverers of the DNA double helix) (Wheeler et al., 2008) and Craig Venter (one of the two coordinators of the projects that sequenced the human genome) (Levy et al., 2007) set the stage for the era of “personalised medicine” and created huge expectations in public opinion. A small fraction of Watson’s sequence has not been made public but Venter’s whole sequence of 23,224 genes and variable regions has been, and includes polymorphisms that imply his potential susceptibility to antisocial behaviour, alcoholism, coronary disorders, hypertension, obesity, insulin-resistance, left heart hypertrophy, acute myocardial infarct, lipase lipoprotein deficiency, hypertriglyceridaemia, ictus and Alzheimer’s disease (Levy et al., 2007).

Despite this, Craig Venter is not a particularly unlucky individual. His genomic sequence is merely an example of the “imperfect genome” shared by all members of the human race. Each individual chosen at random is known to be heterozygous for a significant number of mutations (44% of Venter’s genes were found to be heterozygous for one or more variants). A small number of these mutations affect genes responsible for rare diseases (most of which are transmitted via Mendelian mechanisms), while several hundreds of thousands of variants affect genes associated with complex diseases, acting on the phenotype with a small additive effect that combines with the environmental component (multifactorial heredity).

The concept of multifactorial heredity is also supported by the first sequencing of a subject of Asian origin, whose genes were found to contain more than 56% of the polymorphisms known to be associated with a risk of Alzheimer’s disease, 15% of those associated with diabetes, 10% of those associated with hypertension, 9% of those for Parkinson’s disease and 63% of those for tobacco addiction (Wang et al., 2008).

The scenario revealed by the sequencing of these genomes and the potential impact on the concept of health of “genetic prediction” based on the sequencing of individual genomes had been foreseen a decade earlier by

Jonsen et al. (1996), who anticipated the pressing problem of the presence on the medical stage of “unpatients”. Even then it was clear that the imminent possibility of testing for susceptibility to common disorders would lead millions of asymptomatic individuals “to sweep into the world of medicine”. For the authors of this article, *unpatients* are a new class of person within the world of medicine: they are not “patients” in the classical sense, as they have no symptoms; they are individuals who share genetic predispositions, who could live in the expectation of the hypothetical appearance of some sign of disease, organise their lives around visits to the doctor or laboratory tests, and end up feeling ill or even developing psychosomatic symptoms.

Without denying the importance of our genomic profiles and their ability to condition our future quality of life, it must be reiterated that our health/disease status is not defined only by our DNA but also by the interaction between DNA and the environment. This point is exemplified by the case of identical (monozygotic) twins who share the same DNA but in whom phenotype differences are amplified during their lifetime. This is because the complex regulation of the genome is strongly affected by the environment and effectively triggers differences at the functional level of the genome (Choi and Kim, 2007). These mechanisms form the foundation of a new discipline, known as “epigenetics”, which is evolving rapidly and which studies any chemically activated regulatory activity of genes that does not bring about changes in the DNA code but which can modify the phenotype of an individual and/or progeny (e.g. DNA methylation). These epigenetic events alter physical access to the genetic code of complex molecules delegated with gene expression, thereby altering the functional level of genes.

The commercialisation of genetic tests and direct-to-consumer marketing

Today it is extremely important to emphasise certain aspects of the commercialisation of genetic tests and the growing trend to sell them via internet. It may therefore be useful to recall the criteria to be borne in mind in order to ensure that each test is properly evaluated. These are:

1) its analytic validity: the ability to identify the desired genotype. Because the quality of any test depends directly on the quality of the laboratory that performs it, this criterion reflects the importance of choosing a laboratory with the specific expertise required;

2) its clinical validity: the ability to identify a phenotype using classical parameters of specificity, sensitivity, positive predictive value and negative predictive value.

The possibility to use the web to create a “service” providing free information and genetic testing direct to consumers appeared already in the ‘90s. The marketing strategy was based on the benefits to the community to be achieved through the expansion of genetics: on the one hand consumers would benefit by being able to satisfy their thirst for knowledge about their genetic profiles autonomously and independently of the diagnosis of a genetic disease; on the other hand the economy would benefit from the knock-on effects on research institutes (in the preparation of tests), on the expansion of sales outlets (e.g. pharmacies) and on laboratories and specialised physicians.

There was no lack of opponents of the proposal to encourage access to tests performed without a specific medical prescription and by non-accredited laboratories.

Some of this opposition was directed at “commercialisation” *per se* (i.e. the pursuit of profit), even when it was acknowledged, at least in Anglo-Saxon countries where genetic research was being most actively pursued, that most of the economic burden was being sustained by private sector companies (Cook, Deegan et al., 2001; Holtzman et al., 1999) keen to recover at least some of their investments through sales of the reagents for performing the tests. Some arose from concern that direct access to testing would lead to distortions both in the demand for tests and in their interpretation (Kodish et al., 1997).

A survey by Caulfield and Werzt (2001) indicated that between 1985 and 1995 there was a sixfold increase in the number of organisations interested in the unregulated commercialisation of tests.

Notwithstanding strong criticism of these initiatives from experts in the field, the calls for caution have to date been unable to halt the commercialisation of predictive or susceptibility tests that have frequently not been properly – if at all – scientifically validated and which are offered without any regard for the protocols or rules of caution that the medical profession should adopt when evaluating new diagnostic and technological developments (Offit, 2008). There are dozens of internet sites selling whole genome tests (e.g. 23andMe, Knome, DeCODE Me) or tests to determine susceptibility to complex diseases (DNA Direct, Genelex, Health Test Direct, Mygenome, Navigenetics, Pro-DNA, Proactive Genetics, Smart Genetics), or even to detect a genetic propensity for sports (23andMe) or the metabolic profile on which to base one’s diet (so-called Nutrigenomics: e.g. Inneova, Sciona, Suracell) or, finally, to help choose the most suitable beauty cream (so-called dermogenetics: Virginia Skin Clinic) or the partner with the most “compatible” DNA profile (ScientificMatch).

A better understanding of what is being sold to and bought by innocent consumers can be obtained by examining a meta-analysis of the most important association studies published between 2000 and 2007, which compared the genotypes of persons with common diseases with those of a general population control group (Janssens et al., 2008)⁷. The study concluded that there is insufficient scientific evidence to support the use of genomic profiling to measure the genetic risk of common diseases or to develop personalised diet or lifestyle recommendations for disease prevention. In perfect agreement with these results, the US Government Accountability Office (GAO) performed a retrospective study of results produced by private companies regarding risk prediction for a number of pathologies such as hypertension and prostate tumours: separately tested samples gave contradictory results that varied from below-average to average to above-average risk for a single sample. As well as a high error margin, this study also underlined inadequacies in communicating the results as well as the making of false claims regarding the predictive or curative properties of the tests.

The following considerations can be deduced from this already complex and still unregulated state of affairs:

- the decision to seek a genetic test is often dictated not by medical concerns but by pure intellectual curiosity, occasionally coupled with “informational exhibitionism” (circulating one’s genetic profile on the net: Gurwitz and Bregman-Eshet, 2009).

- it is not at all clear at the moment whether the market for direct-to-consumer genetic testing can properly be considered legal: in Europe the additional Protocol on genetic testing “for medical purposes” (Strasbourg, 2007) requires that tests be conducted under “individualised medical supervision”. It is easy to claim – as some companies do – that direct marketing via internet is not “for medical purposes”(!) but “for purposes of knowledge and culture”, which would not, however, be allowed by a strict interpretation of the Oviedo Convention;

- considerable concern has been expressed regarding the “quality” of tests conducted in this way and the possible consequences (Hunter et al., 2008; Van Ommen et al., 2008; Kaiser, 2007; Blow et al., 2007), which may be not only medical, but also moral or even biolegal, in connection with insufficient safeguards for privacy, if unauthorised archives (data banks) are established, or if the recruitment of individuals is not properly regulated and consent not properly obtained;

- different interpretations have been proposed for the “ownership” of a sample once the response has been given via internet.

To sum up, it must be acknowledged that the whole issue of the scientific and clinical validity of tests obtained through this “freedom of personal initiative”, as well as of their usefulness in medical terms, needs to be more carefully examined and regulated in the interest of relations between scientific progress and society (Patch et al., 2009).

Although only a few states (in Europe, Austria and, to some extent, the United Kingdom) have to date embarked on a process of regulation, some are proposing the urgent introduction of procedures for self-regulation by companies engaged in direct-to-consumer genetic testing along the lines of the current European guidelines which, in the case of predictive tests, call for genetic counselling – in every case and regardless of the procedure used⁸.

Others believe that the proposal for self-regulation is an evasive tactic adopted by the companies concerned and that it is intended to delay the introduction of legally binding regulations.

For the sake of intellectual honesty it should be mentioned that there is yet another point of view that holds that direct-to-consumer testing is better able to ensure privacy and carries a lower risk of the disclosure of information concerning an individual’s genetic profile; then again, there are those who fear that minors will be subjected to tests that would not normally be authorised without valid consent.

Finally, there are those who hold that facilitating the performance of tests via the internet is a stimulus to enhance intra-family “solidarity”, which it is held would materialise when information that is “useful” for the health and well-being not only of one individual but also of relatives is exchanged among family members over the internet (e.g. for nutritional tests, etc.).

Future prospects for personalised medicine and evolution of the concept of the general practitioner

As well as by the various limitations mentioned above, including those deriving from our fragmentary knowledge of the biological bases of diseases and complex traits, “personalised medicine” is also complicated by the difficulty of unravelling the relationships between genotype and phenotype caused by epistasis (gene-gene interactions), and by other factors such as gene-

environment interactions and locus heterogeneity (Moore and Williams, 2009). Most research into the effects of genetic associations on large groups of individuals have not yet sufficiently investigated these aspects.

The spread of genomic testing is in any case destined to highlight further the medical aspect of an individual's life and will probably bring additional changes to the role and figure of the physician. Advances in laboratory medicine and in technological instruments have already over the last 50 years transformed the profession of general practitioner; as increasing numbers of tests become available, there is a growing tendency to prescribe these rather than to visit patients and talk things over with them. The genomic era risks further transforming the role of the physician, who will perhaps become a "genomicist", in other words someone whose job is to interpret the sophisticated data processed by highly technological devices (Guttmacher et al., 2010).

In some countries this issue has been amply debated. At the moment it seems that general practitioners are unable to comprehend the effective significance of biological progress and thus to transfer the information and data produced by genetic research to clinical practice. However, it is plain that in future physicians will have to extend their knowledge of genetics, as it is unthinkable that the impact of this discipline on health can be handled only by specialists in genetics. It is probable that over the coming years the "general practitioners", "physicians in charge" or "family doctors" as they are variously known, will figure more prominently in the field of "clinical genetics" than the "genetic physician" (Rantanen et al., 2008), bearing also in mind how inopportunistly this issue has erupted onto Italy's cultural scene⁹.

The establishment of a network of integrated services combining professionals from different fields is gradually gaining ground as a rational means of satisfying varying requirements and solving the issues associated with differences in medical specialisations.

In countries where this approach has been adopted (e.g. the United Kingdom and some US states) the primary care sector – where there was initial reluctance to consider the practical basics of genetics as a necessary "component" of everyday practice – has acknowledged that it is their responsibility to identify individuals and families who may carry genetic risks (Emery and Hayflick, 2001; Suther and Goodson, 2003; Frezzo et al., 2003). In one pilot study, nursing staff trained to gather data for pedigree construction were able to overcome initial fears of inadequacy (Tempest et al., 2005). When geneticists and specialists in different fields have cooperated (offering patients an integrated assessment when necessary, as in reproductive or paediatric medicine or in oncology) this has been found to offer the best results for individuals seeking information regarding their genetic history. With this model of integration the practice of counselling (Donnai et al., 2000) provided by experienced and sensitive geneticists can and must become more accessible when necessary.

From pharmacogenetics to pharmacogenomics: current knowledge and future prospects

As noted in the foreword to the detailed paper published by the CNB, *From pharmacogenetics to pharmacogenomics* (21 April 2006), to which the reader is referred for further information, several definitions of

“pharmacogenetics” and “pharmacogenomics” are to be found in the literature. For the former there appears to be broad agreement: “pharmacogenetics is the study of the genetic causes of individual variations in drug responses, including safety, efficacy and drug-drug interactions”. As such the objective of pharmacogenetics is the development of personalised therapies.

In the case of “pharmacogenomics” there is no universally accepted definition. For some it is a mere practical evolution of pharmacogenetics in the wake of advances made, particularly as a result of the sequencing of DNA, and is defined as “the study of the genome and its products (including RNA and proteins) insofar as it correlates with the discovery and development of new drugs” (Pharmacogenetics Working Group). For others there is a conceptual difference between pharmacogenetics and pharmacogenomics: the source of variations in drug response studied in pharmacogenetics is of a “structural” nature and therefore represents a static comprehensive individual trait, whereas pharmacogenomics studies a second – “functional” – source of variation, in other words one associated with the expression of genes in different tissue cells. While the former source is not tissue-specific, the latter is, making it a changeable element of dynamic variability in the response to endogenous and exogenous stimuli (Consortium on Pharmacogenetics).

Pharmacogenetics can more generally be defined as the discipline that “deals with the genetic basis of individual variations in drug response” while pharmacogenomics is charged with transferring this new knowledge of the human genome to the discovery and development of new drugs and personalised therapies. The genetic polymorphisms that underlie the diagnostic, susceptibility and predictive tests examined in the present document also underlie pharmacogenetic and pharmacogenomic testing.

At this point the concept of “genomic biomarker” needs to be clarified, as its meaning is different from that of a susceptibility test. The International Conference for Harmonisation (ICH) classifies the genomic biomarker separately as “a measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions”

Genomic markers may thus have different roles, being considered prognostic, predictive or pharmacodynamic (Cazzola and Novelli, *Pulm Pharmacol Ther.*, 2010), so that the specificity of genetic tests as the sole parameter of significance appears insufficient and reference must be made to the validation and qualification of the genomic biomarker (a roadmap to achieve this is described in Novelli et al., 2009, *Public Health Genomics*).

In practice, there are three ways in which polymorphisms can affect drug response: the way in which a drug is metabolised by an organism (pharmacokinetics); the way in which the protein receptor for a drug is modified (pharmacodynamics) and the process in which a particular polymorphism (in combination with a broader correlation between genes and environment) influences the “risk” of triggering a disease pathway.

It is readily apparent from this summary description that this branch of pharmacology has a considerable “potential”, in both informational and operational terms, for medical practice and for the pharmaceutical industry, starting from the empirical, “bedside” realisation that the administration of an identical dose of an identical drug to different individuals does not always produce identical effects and that these may vary in both their efficacy (from

maximum to none at all) and in their safety (presence or absence of side-effects, which may be toxic and even fatal).

While the causes of this variability in drug response are certainly many – including biological (individual traits) and environmental (from the type of disease to nutrition, lifestyle, etc.) factors – it has now been proven that some can be inherited, and it is precisely this aspect that is addressed by pharmacogenetics (Pignatti, P.F., 2008; Daly, A.K., 2010). At this point a more detailed look at these issues is advisable.

1. *The use of pharmacogenetic testing in clinical practice*

From the point of view of medical practice the development and use of pharmacogenetic tests (Buchanan et al., 2002) aims to:

- increase the efficacy of treatment and reduce the risk of adverse effects of specific drugs;
- eliminate the precautionary test phase that is currently obligatory for drugs, allowing them to be administered promptly and enhancing the safety of treatment;
- reduce treatment costs by avoiding the administration of drugs that subsequently prove not to have the desired effect in particular patients;
- permit the recovery of experimental molecules that have produced adverse effects in some patients in order to identify patients to whom they should not be administered and separate these from patients for whom the molecules proved helpful.

Other useful spin-offs comprise

- guidelines to adapt the dose of the drug to the individual;
- the possible development of alternative treatments tailored to individual genetic profiles (particularly if equally effective);
- criteria to improve the classification of both diseases and drugs on the basis of their mechanisms of genetic action (e.g. the enzymes involved, etc.).

In recent years, and particularly since 2007, numerous GWA studies in the fields of both pharmacogenetics and pharmacogenomics have been published (for a review: AK Daly: *Genome-wide association studies in pharmacogenomics*, Nature Reviews Genetics, 11: 241-246, 2010). These studies aimed to identify loci/genes of potential interest in the response to drugs such as warfarin and acenocoumarol (cumarin-based anticoagulants), interferon- α (used to treat hepatitis C), clopidogrel (a thienopyridine class antiplatelet agent), methotrexate (an antimetabolite and antifolate used in the treatment of tumours and autoimmune diseases), thiazide (a diuretic), interferon- β (used to treat multiple sclerosis), anti-TNF drugs (biological drugs used to treat arthritis), methylphenidate (an amphetamine analog used in the treatment of ADHD), iloperidone (an atypical antipsychotic used in the treatment of schizophrenia), citalopram (a non-tricyclic selective serotonin reuptake inhibitor (SSRI)), various drugs used in the treatment of leukaemia and minimal change disease, and various molecules with antidepressant effects. Genes and loci of potential interest in controlling the response to these drugs were identified only for some of these molecules (warfarin, acenocoumarol, interferon- α , clopidogrel, methotrexate, thiazide). Other GWA studies have investigated the genetic basis of susceptibility to adverse reactions and identified genes associated with simvastatin (an active ingredient indicated for the treatment of hypercholesterolaemia) and flucloxacillin (used to

treat *Staphylococcus aureus* infections), while no significant molecular evidence was found for etoposide (a topoisomerase II inhibitor used to treat cancer), ximelagatran (an anticoagulant), bisphosphonate (bone resorption inhibitor), iloperidone and other antipsychotics. These studies are particularly important in the light of evidence that approximately 100,000 deaths each year in the USA can be attributed to adverse drug responses. As an example, undesired effects are reported in 1-10% of subjects treated with 6-mercaptopurine (an immunosuppressive); in 5-8% of those treated with tricyclic antidepressants or abacavir (a reverse transcriptase inhibitor used in the treatment of AIDS) and ximelagartran (an anticoagulant); in 10% of patients taking carbamazepine (a key molecule in the treatment of epilepsy); in 5-50% of subjects taking warfarin and in 30-40% of those receiving the anti-cancer drug irinotecan.

To date the biological mechanisms underlying the response to therapeutic molecules have been identified in only a limited number of cases. In most of these cases only one gene (major gene) is responsible for the related effect. Some of these studies have made it possible to develop genetic tests to define an individual's response to a specific molecule and thus to identify the most appropriate drug and its optimal dose. However, because of the difficulties involved in recruiting the large numbers of subjects being treated with the same molecules that are necessary for GWA tests, a significant leap in our knowledge of interactions between an individual's genome and the environment/drug can be achieved only through international cooperation programmes. One problem that will certainly complicate the interpretation of results from pharmacogenetics research is the use of cocktails of drugs, which makes it difficult to distinguish the effect of individual drugs on the genome.

2. The pharmaceutical industry

So far as the pharmaceutical industry is concerned, the development of pharmacogenetic tests is directed primarily to identifying "critical" regions of an individual's genome that are important for regulating the health/disease status and can lead to further research in the fields of both pharmacogenetics (e.g. the action of the enzyme CYP2D6 in metabolism of the tricyclic antidepressant amitriptydine, used in psychiatry) and pharmacodynamics (structure of receptor proteins, for example).

It is believed that the spread of genetic testing can foster the development of new drugs and enhance the potential for cures; at the end of the last century a mere 483 molecules were available for use as drugs (Drews J., 2000; Peet, N.P. and Bey, P., 2001), today it is estimated that between 5,000 and 10,000 proteins could potentially become targets for pharmacogenomics.

Progress is expected in the fields of cancer, psychiatric and cardiovascular diseases and asthma. It is hoped to expand the inventory of tailor-made drugs, meaning not so much the absolute "personalisation" of drugs as the division of patients into sub-groups according to their genetic profiles and/or type of response to a drug.

This "strategy" – which has a certain appeal – is not, however, without reservations, both in industrial terms (the fragmentation of user samples implies the synthesis of very finely targeted molecules for each group; this adds to the costs of research, which in turn are inevitably passed on) and in bioethical terms (the possible emergence of new classes of patients who do not respond

to drugs, giving rise to new categories of “orphan drugs”; the possibility of discrimination against difficult-to-cure patients and the relative impact on care).

To date at least 100 drug-associated tests have been approved by the regulatory agencies, at least 30% of which involve cancer drugs.

The interpretation of pharmacogenetic and pharmacogenomic tests is still a complex matter, requiring knowledge of both exogenous (e.g. alcohol or tobacco consumption, etc.) and endogenous (gender, age, co-morbidities, ethnic group, genetic makeup, etc.) confounding factors.

The statement inserted by the US Federal Drug Administration (2007) in the patient information leaflet for the Bristol-Meyers-Squibb drug warfarin seems sensible and could be applied as a general rule: “The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes”.

3. Bioethical aspects of pharmacogenetic and pharmacogenomic tests

This area of pharmacology appears full of hope and promise, provided that the related technology is used appropriately and by qualified professionals. At the same time, however, it poses questions of a bioethical nature.

In the first place there is the question of insufficient information given to operators, which leads to failure both to administer the proper test and to choose the most suitable drug, thereby exposing patients to a risk of adverse side-effects or of a missed benefit when drugs tailored to an “average” population are administered to the minority of subjects who are either non-responsive or hypersensitive to them. We are not talking here about a “classroom hypothesis” but about real events that will certainly become more frequent in the coming years as pharmacogenetics research advances and which could even lead to legal proceedings.

These shortcomings can be remedied by extending and intensifying medical training in the field of pharmacogenetics.

It has also been pointed out that pharmacogenetic tests include “secondary information”, which goes beyond predicting the response to a specific drug and may generate other genetic information about the patient and his/her family (Roses A.D., 2000), thereby permitting: differential prognosis and diagnosis of diseases; alternative therapies; risk evaluation for blood relatives or descendants of the subject tested (Netzer C., Biller-Andorno N, 2004).

There are areas where aspects of pharmacogenomics overlap with more general bioethical issues involved in the genetics of common diseases such as some tumours with a genetic component, and the same rules of properly informed and deliberate consent to undergo a test that apply in the case of pharmacogenetic tests should also be applied here (Van Delden J. et al., 2004).

It is also expected that the individual’s interest in protecting his or her health from possibly very high risks of an “intolerance” to drugs will prove the most effective way of “deflating” the fear that personal genetic data may be used improperly and lead to better and more widespread training in the storage and treatment of sensitive data.

However, concerns have also been expressed that the real “risk” of pharmacogenetics may in fact turn out to be the variations in drug response, in other words the potential to create a class of individuals who cannot benefit from safe and effective drugs because they do not “fit” any of the drugs placed

on the market and who will have to be treated with traditional drugs tailored to a much broader reference population, which are less effective and probably carry a greater risk of adverse effects.

This possible trend would violate the principle of equity and could pave the way to justifying forms of social stigmatisation or discrimination, although such concerns appear somewhat premature in the present European climate.

In conclusion: pharmacogenetic and pharmacogenomic tests are one of the “positive” technological spin-offs of the sequencing of the human genome, but the possibility of transferring them to clinical practice calls – first and foremost – for reproducible evidence that they are really effective; for quality certification of the laboratories performing them; for the dissemination of knowledge among both health operators and consumers; for the definition of a satisfactory cost-benefit ratio that takes into account the interests not only of industry but also of consumers – particularly the social cost of possible discrimination.

SECTION TWO

RULES FOR GOOD CLINICAL PRACTICE, GENETIC COUNSELLING, DEONTOLOGICAL, BIOETHICAL AND LEGAL ASPECTS

III - RULES FOR “GOOD CLINICAL PRACTICE” IN THE PROVISION OF GENETIC TESTING AND GENETIC COUNSELLING

1. Genetic Counseling

Marked by the diversity of its reference models and objectives, the history of genetic counselling has evolved in parallel with changes on the socio-cultural and political stage and advances in knowledge of human genetics and molecular biology (Rose N., Novas C., 2000).

For the first half of the last century, under the influence of the “eugenic” movement that gained ground primarily in certain European and North American countries, genetic counselling was presented above all as a public education strategy aimed at improving the biological “quality” of populations, including through reproductive selection. This view changed radically after the second World War, as the issue gradually distanced itself from the “public health” model in which the interests of the community prevailed over the rights and sanctity of the individual, with its overtones of mass eugenics.

In 1975 the American Society of Human Genetics (Ad Hoc Committee on Genetic Counselling, 1975) adopted a definition of genetic counselling that gained international recognition and is still valid: “Genetic counselling is a communication process which deals with the human problems associated with the occurrence, or the risk of an occurrence, of a genetic disorder in the family. This process involves an attempt by one or more appropriately qualified persons to help the individual or family to: 1) comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management; 2) appreciate the way heredity contributes to the disorder (...); 3) understand the alternatives for dealing with the risk of occurrence; 4) choose the course of action which seems to them appropriate (...); 5) make the best possible adjustment to the disorder (...) and/or the risk of recurrence of that disorder.”

This definition of genetic counselling still holds good: however, while up to now genetic counsellors provided medical-genetic information and psychological support above all to individuals or couples preparing to make reproductive decisions in situations of risk (birth of an affected child, risk of late-onset disorders, diagnosis of genetic disease in a family member or partner), from now on they face new challenges generated precisely by the susceptibility tests and personalised medicine that are the subject of the present document.

Increasing numbers of individuals will wish to learn about their predisposition or resistance to multifactorial pathologies or the suitability of specific therapies. It is no longer a matter of determining a “certain” risk of a particular disease, but of communicating highly complex concepts relating to the “probabilistic” nature of the data generated by these tests. The problem is therefore to decide what level of genetic counselling is needed to enable the individual to comprehend these concepts and the best way of communicating them.

The organisation of genetic counselling, with a focus on Italy

Because of the lack of properly qualified professional operators and also with a view to reducing costs to their health services, some European countries are tending to develop different levels and organisational procedures for professional genetic counselling in relation to the different types of test, while maintaining the possibility to vary the form and duration of counselling in accordance with counselees' effective needs. All the national, European and international documents that lay down guidelines or recommendations for genetic counselling consider it indispensable or even imperative both before and after presymptomatic, susceptibility or probability tests¹⁰.

The person-to-person oral communication of preliminary information accompanied by informative material is also considered obligatory for other types of test such as those to identify healthy carriers, so that the individual can express doubts and reservations and ask for any clarification that he or she thinks necessary. Counsellors should be able to reply exhaustively in clear and easily comprehensible terms, to discuss in depth the motives for requesting a specific test, to explain the reality of the expectations concerning a test and, when necessary, the clinical uselessness of a test for the individual requesting it, even to the point of advising against it.

In Italy genetic counselling is entrusted to specialists in genetic medicine or to persons with an equivalent degree, who may be supported by other competent professionals such as specially qualified clinical psychologists. The organisation of genetic services is regulated by the Guidelines laid down by the State-Regions Conference¹¹.

In other European countries such as the United Kingdom pre-test genetic counselling may occasionally be provided by other professionals (genetic nurses) operating within the health service, provided they are properly qualified for such a delicate task (House of Lords, 2009).

This is because some of the problems involved in genetic counselling may call not only for professional expertise on the part of the counsellor but also for personal sensitivity¹².

National and international guidelines all reiterate not only the fundamental importance of ensuring respect for individual rights, including the right to decide autonomously whether or not to undergo a test (and in the former case, whether or not to know the result), freedom from pressure from third parties and the strictest respect for confidentiality (OECD, 2007), but also the fundamental criterion for offering genetic testing within the public health system: its proven scientific validity and clinical utility (article 6 of the Additional protocol concerning genetic testing for health purposes of the Council of Europe, 2008), as well as the stipulation that it may be performed only after fully informed consent has been freely given by the interested party.

1. Practical regulatory principles concerning the supply of genetic tests

The personal consequences for individuals undergoing genetic testing are related not only to the type of test and the information it can provide but also to personal and family circumstances. In practice (as already noted) pre-test genetic counselling is not always provided, but the provider of tests cannot fail to take account of both the type of test requested and its impact on the

person concerned. Some tests, particularly those concerning specific hereditary disorders, should be offered only if accompanied by pre- and post-test genetic counselling, in accordance with national and international guidelines: clear and consistent information should also be provided when tests of minor import are purchased via internet or performed in authorised private laboratories.

Even where testing for susceptibility to common disorders is concerned, it is evident that the products sold should comply with certain minimum requisites, namely:

a) Producers of genetic tests must comply with the legal provisions and voluntary codes of practice that regulate advertisements for tests. Advertising should indicate the characteristics and limitations of tests offered without emphasising any unproven usefulness. Any statements concerning their utility should include a reference to scientific evidence supported by published peer-reviewed articles.

b) The management must ensure that the standards of quality are sufficient to protect those being tested and their families. The laboratory technician must attend to the criticality analysis of the tests used in terms of sensitivity (frequency of a positive result when a disease is present) and specificity (frequency of a negative result when no disease is present), and verify (with the aid of internal standards and other criteria) the reliability of the data obtained. These criteria apply to all types of laboratory test but are particularly important in the case of genetic tests, which have a much greater impact than more routine types of test. Individual reactions depend above all on the personality of the person undergoing the test and on understanding the result and its implications. The intensity of the emotions aroused in the individual and in the family will depend not only on broad interindividual differences but also on the quality of the information provided and the general context within which each test is performed. These issues become more acute when an individual applies directly to a diagnostic laboratory without the mediation of a specially qualified physician.

c) When a consumer applies to a laboratory (or via internet) for a test without a medical prescription, he or she must be informed of the need to consult a medical geneticist both prior to the test, to explain its utility, and after the test, to clarify the meaning of the result and to ascertain that the consumer fully understands it.

d) Only validated genetic mutations should be used for diagnostic testing. Anyone who provides a test must be able to produce scientific evidence demonstrating the sensitivity of a particular marker for a disease. The risk of becoming ill or of developing specific conditions or characteristics must be calculated according to standard statistical procedures accepted throughout the scientific community and the algorithms used must be available for consultation. The information laid before the consumer prior to the test must be relevant, intelligible, accurate and appropriate and must include an explanation of the scientific basis of the test¹³.

e) Certain fundamental principles of medical ethics (professional ethics) must be observed, i.e.:

1) genetic data are sensitive and maximum protection of the security and confidentiality of their treatment must therefore be guaranteed, in line with regulations governing the protection of privacy and, at the interpersonal level, with the principles of confidentiality¹⁴;

2) genetic tests may be performed only after the person to be tested has given informed consent in writing. Consent is considered “informed” only after the individual has received all the relevant information in such a way that he/she is able to comprehend the risks, benefits, limitations and implications involved;

3) genetic tests may not be performed on persons who are unable to give informed consent in writing unless the test is in their interest and is authorised by their legal representatives. Tests that are not in the direct interest of minors must be postponed until they reach majority and are able to give consent on their own account;

4) testing may not be carried out on biological samples obtained through deception or theft or in any circumstances in which the subject tested did not give consent;

5) in regulating genetic testing a distinction should be drawn between medical objectives and general health protection on the one hand and other objectives such as determining the status of family members on the other, in which latter case the interests may be balanced differently.

Some practical rules that derive from these general principles are:

- Clinical records containing personal data and genetic information that could be linked to an identifiable individual must be compiled so that personal and clinical data are held separately and procedures for confidentiality must be followed for the filing and storing of such information;

- Health service operators must take special care to maintain confidentiality in communications among themselves regarding data relating to a specific individual.

These requisites form the key to confidentiality and operators should be continuously reminded of them; monitoring should also be continuous and, where necessary, operators should be reprimanded.

IV – ETHICAL-LEGAL AND BIOETHICAL ASPECTS

At this point the following aspects need to be examined:

1. the ethical-legal issues implicit in a request, made either spontaneously or at the request of another person, to undergo a genetic (susceptibility/probability) test in relation to polygenic disorders should be distinguished from those relating to participation in population screening programmes or other forms of genetic research (e.g. prenatal medicine);
2. autonomy and the right to “self-testing”;
3. relations with families;
4. bioethical aspects of provisions for protecting confidentiality and privacy in relation to susceptibility and probability testing of adults;
5. issues of evident discrimination/stigmatisation that prejudice an individual’s “moral personality”;
6. the right “not to know”;
7. issues of legal medicine.

These issues are widely debated in every study of the applications of clinical genetics and effectively represent the core of bioethical considerations in this field.

The following paragraphs address some key general considerations, with a focus on specific aspects of susceptibility/predictivity testing for polygenic disorders in adults.

1. FUNDAMENTAL BIOETHICAL AND LEGAL PRINCIPLES INVOLVED IN ACCESS TO GENETIC COUNSELLING AND TO GENETIC TESTING

The peculiar process of communication between an individual and an “expert” regarding the use of so-called susceptibility/probability tests to determine whether or not genetic risk factors are present may in practice be initiated in three ways: at the direct request of an individual; because the individual has been advised by a family physician or specialist; or because the individual is already in possession (probably via internet) of the results of a genetic test obtained directly from a laboratory (possibly linked through internet to some organisation) and wishes to discuss with an expert the meaning and prognostic value of the response. This document refers only to adult counselees.

The first ethical-legal issue is to establish the precise position of the individual undergoing a test in this context as opposed to participating in a genetic survey involving the general population. In operational terms this testing process involves the direct and personal interest of an individual and should not be confused with population screening, although this distinction is not always made correctly.

In any case access to individual testing or to screening to identify one’s genetic traits is always governed, so far as the individual is concerned, by the *principle of autonomy*¹⁵, the motivations and consequences of which may occasionally echo the principles of *solidarity* and *responsibility* to others. The special importance of these principles is considered by many to be absent in

the case of biochemical data derived from more routine tests (genetic exceptionalism)

Informed consent to undergo a genetic test

The *act of consent* that follows genetic counselling summarises the information received and affirms the subject's informed decision to undergo a test: it must also specify the sampling procedure and the type of test to be performed for the agreed purpose.

Correct and exhaustive information must be communicated during a personal interview with a trained counsellor (independently of the simultaneous provision of paper and electronic documentation on the meaning of the test); information based solely on widely available material without direct personal contact with a counsellor is not considered sufficient, at least in the case of predictive testing (see Section III concerning the Convention of Oviedo, 1997, and the Additional Protocol concerning genetic testing for health purposes, 2008).

Consent must be free of constrictions. The free determination either to undergo a test or not to undergo one has effects that have to be responsibly evaluated.

In the first place consent involves rights. An individual who undergoes a test has the right, among others: to receive and disclose the data acquired freely and without pressure; to ascertain the veracity of the information concerning the test to be carried out or already performed; to decide which personal data can be disclosed (directly or indirectly) to others in the event that he/she undergoes the test but decides to exercise the right "not to know".

It nonetheless also involves responsibilities. An individual who undergoes a test has responsibilities to him/herself, such as a duty to consider carefully the motives behind his/her desire to know the results, as well as to foresee the potential personal effects of those results such as, for example: serious depression following the revelation of a predisposition to progressive diseases; anxious debate as to whether to accept or refuse changes in lifestyle as a precautionary measure; awareness of the risks involved in having children and the effects on other people.

Also implied in a decision to undergo genetic testing are other duties, such as the sharing of the results with family members indicated by the geneticist as being most "at risk".

In short, there can be no moral rejection of the "relational dimension" of autonomy, in which the concepts of solidarity and responsibility imply, at the very least, an understanding – prior to undergoing a test – of the immediate consequences of the test as well as, if possible, of the broader impact that the decision effectively involves (Niebuhr H.R., 1978; Terrel White M., 1999).

The peculiar value of the counselling service offered to the individual is thus to guide him or her along the path of self-awareness so that he or she is capable of making a decision and accepting its consequences.

Possible subsequent use of samples taken for purposes of personal testing after a proband accepts a counsellor's invitation to take part in a screening and/or research programme

There is a tendency both in the literature and in practice to separate counselling and research activities and to restrict the use of samples to the test requested by the proband and his/her physician. However, circumstances may arise in which the rare clinical profile of a case or the results of a test performed for clinical purposes assume an "added value" for the purposes of scientific progress; when this happens the counsellor – particularly if he/she operates within a scientific research institute such as a university – may inform the individual concerned.

It is evident that even in general terms the relationships, the information provided and the guarantees involved in consent are all more complex when an individual consents to take part in research or to be included in research trials already under way or in ongoing population screening programmes.

Without here going into a detailed analysis of the various aspects of research in genetics, it is as well to make it clear that any person who takes part in research performs a commendable social act, overcoming widely held reservations concerning the safeguarding of personal data and the improper use of an individual's genetic makeup, bearing in mind that – as is inevitably the case for many areas of research – the relevant data have to be preserved for future use and cannot be destroyed immediately after the clinical test has been concluded.

In the legal transition of the individual from someone who has requested a genetic test to a participant in more complex research that has possibly already been approved by an Ethics Committee, the consent previously given for clinical purposes is no longer considered sufficient: special and more elaborate formulas for consent are needed, of a quasi-contractual kind, even though no compensation is envisaged for the testee (principle of free donation of biological material similar to that of a "license").

The conditions governing the use of biological material should therefore be treated separately¹⁶.

It is a widely held opinion that both the drawing of a clear distinction between data and initiatives resulting from routine clinical examinations and those deriving from carefully defined genetics research programmes planned and approved by Ethics Committees, and compliance with appropriate procedures to ensure the upholding of human rights can only benefit the progress of genetics and enhance public confidence in geneticists [Clayton E.W. (2003); Hunter E and Caporaso N (1997); Dean J et al. (2000); Kerzin-Storarr L et al. (2002); Pullman D and Hodgkinson K (2006,etc.)].

2. AUTONOMY AND THE "RIGHT" TO SELF-TESTING

It has already been recalled that for some time now certain tests have been placed on the market either through direct sales in pharmacies without a medical prescription (although it should be emphasised that tests sold over the counter in pharmacies must have obtained prior authorisation from the Ministry of Health), or directly on internet.

These direct sales initiatives usually take for granted the "autonomy" (self-determination) of the individual, who is presumed to be "mature", in other words

– particularly after reaching majority – able to evaluate the benefits and risks of expressing or withholding consent. They have even been considered as the supreme interpretation of the principle of privacy (meaning the maximum protection of reserve and “going it alone”), a concept deeply entrenched in the self-healthcare approach in several areas of medicine.

The question is not only whether all individuals are capable of correctly completing the testing procedures but whether they are capable of comprehending/evaluating the results (Gevers S., 1999).

To dismiss this problem as “his/her own business” – in other words as involving only the person making the decision, as some would argue – is not enough, even in a bioethical view that is sensitive to the relational dimension of the personality and takes account of the prerequisites to be met before any decision in this delicate field can truly claim to be “informed”.

Of equal delicacy in our opinion is the position assumed in some states (partly in consideration of the economic “productivity” of the medical genetics sector): abstention from any serious attempt at “specific” regulation of the free marketing of genetic tests, which (even in Europe, in an Act of the European Parliament and of the Commission of the European Union) are treated simply as *in vitro* diagnostic medical devices.

The fact that a test can easily be performed at home does not exempt us from taking account of the nature of the possible disease or the potentially serious significance of the result for the individual and his/her family members.

To treat a genetic test in the same way as any “*in vitro* diagnostic medical device”, while not denying the semantic precision of the wording, carries a real risk that – in some quarters – genetic counselling will be eliminated, to the detriment of those undergoing tests.

In addition, undergoing a test that may be performed by a non-accredited laboratory is in itself an additional risk that the individual may – often unconsciously – take in regard to the quality of the result.

These arguments and the objective complexity of some diagnoses were behind the solution provided in Article 8 of the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes (which came into force in 2008), which states that a person who in any manner undergoes or performs a genetic test for predictive purposes must have access to appropriate genetic counselling. This unusually assertive phrasing for an international convention directed at governments leaves no room for doubt.

In conclusion, it is recognised that European Conventions on the free circulation of goods cannot be overridden and consequently the direct sale of some genetic tests cannot be absolutely forbidden, nor can consumers be barred from buying them freely. At the moment, though, some room for manoeuvre is allowed to governments, not only to interpret the Convention and the genetic protocol in such a way as to specify tests that require both a medical prescription and genetic counselling, but also to regulate the advertising of such tests directly to the public.

Nonetheless, other tests should be recognised as being “specific” in the sense implied in binding European regulations (see the Convention of Oviedo and the Additional Protocol just mentioned) and the susceptibility/pre-symptomatic tests dealt with in the present document are clearly among them.

For a real and credible implementation of the precautionary regulations established by the Council of Europe, the decision to place genetic tests within

the generic category of “in vitro diagnostic medical devices” should be reviewed and a separate category (albeit linked to the general framework) should be created, with its own identity, thus bringing the provisions of Article 8 of the Protocol into the ambit not only of the Council of Europe but also of the European Union and national regulations.

3. GENERAL RELATIONS BETWEEN PROBANDS AND THEIR FAMILIES

It is now accepted that genetic diseases do not concern only the affected individual but are family disorders (Sorenson, 2003) and several surveys have attempted to ascertain both how families react to learning the genetic makeup of one of their members and how the “testee” interacts with the family in varying environmental and cultural settings.

It would seem consistent with the concepts both of a family and of shared responsibility between partners in matters of reproduction that a decision to undergo a genetic test should be communicated to family members, at least where tests for “healthy carriers” are concerned. However, various factors may prevent compliance with these principles¹⁷: nor is it even clear that they should apply to susceptibility testing.

In the case of tumours the general objectives of counselling for persons requesting a test are the same as those pursued when testing for other pathologies, although some specific objectives are (obviously) different, just as the procedures followed are different¹⁸. One important issue is that of informing family members of “positive” results of testing for a tumour risk that may affect them. This should be addressed during the pre-test counselling and every effort should be made to encourage the proband to adopt a course of “responsibility” and solidarity within the family, although the counsellor will usually go no further than to suggest the advisability of this approach¹⁹.

In every case the proband has the right to request and to be granted respect for confidentiality and privacy on the part of family members, if he/she thinks this is advisable.

4. PROTECTION OF CONFIDENTIALITY OF INFORMATION AND RESPECT FOR PRIVACY

Fear that the passing of genetic information to other people, albeit family members, may (at least potentially) cause either immediate or future harm to an individual is reported in the literature to be fairly widespread in some countries, less so in others.

It is also one of the most hotly debated bioethical issues involved in genetic testing. Only a few comments can be made here.

The notion of “confidentiality”

The existence of a relationship of confidentiality between physician and patient has been known for thousands of years, although its interpretation has changed over the centuries. Today the more frequent sharing of medical information among different people – a consequence partly of increasingly “specialised” medicine and partly of the use of computers to record data – has fuelled the public’s fear that failure properly to protect the confidentiality of

information regarding an individual's genetic makeup could more easily lead to discrimination.

Almost all the international or national documents that ban discrimination on the basis of a person's "genetic makeup" (e.g. Article 10 of the Convention on Human Rights and Biomedicine and Recommendation R(97)5 on the Protection of Medical Data) refer explicitly to confidentiality and urge maximum respect for it.

Nonetheless, ignorance of these proscriptions – or lack of confidence in their implementation – means that a sizeable percentage of the population fears abuses, particularly where the hiring of employees is concerned. Families are also affected by this lack of trust, as they are seen as possible, albeit unwitting, sources of leaked medical information.

It is useful when examining these issues to draw a distinction between **confidentiality** and **privacy**, as this is not always clear. An individual or an institution that fails to prevent the unauthorised disclosure of information to third parties is guilty of breaching a patient's confidentiality and trust: if, on the other hand, third parties acquire medical records or certificates without authorisation, the privacy to which the patient is entitled is breached (Beauchamp T.I. and Childress J.E, 2001).

All those who are privy to information classified as confidential are bound by the notion of confidentiality; this includes family members and the physician/genetic consultant if, as is usually the case, such is the will of the person communicating the information.

The "duties" regarding respect for confidentiality and the possible consequences of violating it are nonetheless different in legal terms.

a. Confidentiality of information given to healthcare operators

The notion of confidentiality applies to all information confided by a patient to a physician (or other health operator) – entrusted, in other words, in the legitimate expectation that it will not be divulged to other parties without explicit authorisation from the patient.

The greatest possible respect for the principle of confidentiality is justified in bioethical terms on various grounds. From the consequentialist point of view it can be seen as the necessary prerequisite of the patient/physician relationship to prevent the disclosure of information eroding the patient's faith in the – moral, at least – trustworthiness of the physician; or as dismantling the barrier that the patient might erect in order to conceal from the physician delicate but necessary elements of his or her medical history.

It can also be seen as an act of reciprocal respect for the autonomies of both patient and physician, which in the course of therapy converge with reciprocal loyalty and transparency.

Or it can be considered as enshrining the principle of "non-maleficence" on the part of the consultant vis-à-vis the counselee.

That said, there are circumstances in which the physician must also bear in mind the "*broader sense of responsibility*" of his profession towards persons who, as a result of information concerning a single patient, find that they too are also genetically "at risk" of some particularly serious disease or harm to their health that can be avoided if timely measures are taken.

The subject who has undergone the test should similarly sympathise with those unknowingly exposed to the risk of contracting a disease which, if

they were aware of it, could be prevented or possibly cured; he or she should therefore be willing not to block the passing on of information.

b. Intrafamily confidentiality

On this point the comments regarding interfamily communication are again valid.

The literature has recently placed more emphasis on the need to work towards a “point of mediation” between the different needs that the good geneticist/consultant has to balance (e.g. Lucassen A; Parker M, 2004; Forrest L et al., 2007; Weijer C, 2000, etc.): on the one hand are the needs of the family and, on the other, those of the proband who can be helped by the consultant to adopt an open and altruistic attitude. Currently available data show that when information is given only to family members with whom the proband has solid emotional ties, the risk of information leaks is very limited (Hughes C et al., 2002; Metcalfe A et al., 2008)²⁰.

3. DISCRIMINATION AND STIGMATISATION

Today there is widespread legal and ethical condemnation of discriminatory conduct or stigmatisation based on a person’s genetic makeup, at least in theory. In practice, however, this is a matter where exceptions and divergent interpretations abound, particularly in the fields of employment and – in some contexts – also of insurance, business and trade.

However, some authors have observed – particularly in countries with strongly liberalist-leaning economies – episodes of “job selection”, “high school selection”, “missed promotion to managerial roles with greater responsibility”, etc. on the basis of genetic assessments of adults; these involved mostly susceptibility and probability tests for organic disorders, but also for genetic psycho-attitudinal, psychological and psychiatric tendencies (where there is still controversy concerning their effective usefulness).

The question becomes even more complex when insurance is involved²¹, although the issue of a lack of health or life insurance does not arise in European states that have universal healthcare services. It could, though, be relevant in relation to additional health insurance policies with private profit-making organisations.

At the moment the parties have an understanding and there is essentially a national moratorium on the use of genetic data for insurance purposes: evidently the insurance companies have not yet acquired experimental proof regarding genetic tests to warrant abandoning the current rules, based substantially on the use of actuarial tables of survival and disease incidence, and embracing more “personalised” risk formulas.

Apart from forms of insurance-related discrimination – which can in any case be variously disciplined – other more subtle forms of discrimination and stigmatisation are fairly widespread throughout society and are far more difficult to eradicate.

There is general recognition that overcoming “genetic discrimination” depends essentially on education and it is hoped that increased broad-mindedness will – albeit gradually – develop as genetic testing becomes more widespread²².

4. THE RIGHT “NOT TO KNOW”;THE RIGHT “TO KNOW”

Already in the 1970s Hans Jonas underlined in one of his better known essays a devastating novelty in ethical theory on the subject of cloning: the emergence of a new “moral right” to ignorance of one’s future, invoked in defence of the free construction and definition of the sense of self. Because new biomedical discoveries and technologies are challenging the respect for “the right of every human life to find its own way and be a surprise to itself” (Jonas, 1974).

Alongside the right to informational self-determination – seen as expressing personal autonomy – recent decades have seen a gradual consolidation of the “right not to know” information concerning one’s health, including genetic predispositions, as a possible requisite for freedom in self-education. The combined pressure of information-age obligations and those of a health service in crisis could call this right into question and transform it into a synonym for irresponsibility and egoism.

Lori Andrews and Dorothy Nelkin are critical of this trend, pointing out that doctors and jurists are already talking of a right for everybody to know his or her genetic makeup in order to make appropriate lifestyle choices (Andrews, Nelkin, 2001)²³.

In practice the conflict between the right to know and the right not to know arises mainly when the disease concerned is either highly likely or certain to appear at a time when the proband is much older than when the diagnosis is made (e.g. tumours in some families or Huntington’s disease, etc.), while the psychological and conflictual repercussions are far less marked when the test aims to identify a susceptibility. While the risk of transmission to first-degree blood relatives of Mendelian (monogenic) diseases is in the order of 25-50%, the risk for the same relatives of contracting multifactorial diseases is much lower (mostly 3%, with some exceptions). This is because the hereditary component of complex traits is linked to the interaction of common mutations, each of which has a small or very small effect on the disease. The problems posed by genetic susceptibility tests are very specific and have not yet been properly addressed from the bioethical point of view.

While in the case of genetic tests the right not to know is ensured by a simple refusal to undergo the test, experience of genetic counselling indicates that sometimes the decision not to know the result of the test is reached in the interval between the actual test and communication of the result. Or a person may accept to undergo a test – requested by the geneticist as being necessary or advisable – as a gesture of responsible consideration for a family member on condition that he or she is not told the result.

To conclude this brief chapter on the key bioethical aspects surrounding genetic testing it is worth recalling that all national and supranational guidelines or “codes of good conduct” for the use of genetic procedures and technology in health research and therapy include among the ethical and legal guidelines not only the criterion of proven clinical utility of the test but also the need to respect the “right to be informed” and the “right not to be informed”, both of which are considered basic human rights.

5. ASPECTS OF LEGAL MEDICINE

Without here examining all the possible questions of civil and criminal law that could arise in the event of a patent failure to respect the above principles – which merit separate attention – we can assume that legal medicine will become involved when material or formal errors are made in the performance of tests, when genetic counselling is lacking or fails to meet the standards of competence, diligence and prudence, or when there is a breach of confidentiality or privacy.

That said, the following should be noted:

1. The first problem from the point of view of legal medicine is to evaluate the appropriateness of the tests administered in each case, bearing in mind all personal, clinical, family and other circumstances. The document published by the National Committee for Biosafety, Biotechnology and Life Sciences²⁴ dedicated ample space to the additional qualitative requisites that should be scrupulously observed, some of which have already been mentioned. Firstly there are the technical and organisational requisites and quality standards that laboratories have to adhere to before obtaining authorisation to operate in the field of genetics²⁵, bearing in mind that genetic tests, in common with other forms of medical diagnostics, are subject to technical errors above all, though not exclusively, where rare diseases are concerned. Considering the low predictivity of most of the tests used to identify complex diseases, their use does not seem, for the moment, to warrant undue concern in medico-legal terms.

All managerial staff of genetics laboratories, including the director, must be specialists in genetic medicine or equivalent (second level public sector executive physician or biologist with documentary proof of professional skills in the specific activities of the laboratory). Medical genetics facilities must follow regional and national guidelines and ethical principles (National Committee for Biosafety and Biotechnology, National Bioethics Committee, Italian Society of Human Genetics²⁶, etc.) and submit to national and/or European quality controls.

2. The often uncontrolled spread of genetic testing, particularly pre- and post-natal tests, which are useless and potentially harmful (as repeatedly reported in the literature), is a source of considerable concern and of legal problems, and susceptibility testing seems to be following a similar trend. With direct access to testing, an individual who has been tested will be assailed by uncertainties and doubts when facing a diagnosis almost always without counselling from a specialist or anyone else to clarify the meaning of the response. Obviously, any harm suffered by a patient who has received no or incomplete information can be laid at the door of the person or persons who – through negligence, imprudence or inexperience – failed to provide proper counselling.

3. There are many potential situations of liability for genetic counsellors: from failure to comprehend the problem under consideration to underestimation of the risk of occurrence (particularly regarding the birth of malformed or otherwise genetically affected children), to failure to consult with other professionals in order to build a more complete picture of the case in terms of case history and prognosis, to giving the interested parties incomplete information concerning the effective objectives of the planned test in regard to the “genetic risk” of complex diseases, bearing in mind that such tests are not a

horoscope and can only provide information on an individual's predisposition to a given pathology that may or may not develop, depending on the occurrence of numerous exogenous environmental factors, habits and interactions with other genes, given that, as repeatedly emphasised, these are multifactorial disorders.

4. An individual who refuses to undergo a test may do so as a direct consequence of receiving too little information, or of receiving so much and such detailed information as to be deterred. Incomplete or inexact information can become a serious matter for the specialist in legal medicine, and even more so for the courts if there has been harm to the patient or to family members. A still young and healthy person may test positive for a predictive test carried out after receiving only superficial genetic counselling and without exploring the clinical records of his or her family: in such cases the response could trigger a worrying anxiety syndrome, perhaps with panic attacks, leading to the continuous repetition of tests to exclude the presence of the pathology in question, or even to preventive mutilation of the organs that could one day host the feared pathology (e.g. bilateral mastectomy in cases of positive BRCA1 testing).

5. Another possible source of legal disputes is the failure of the counsellor to respect the right not to know the results of a test, as provided in international documents (Unesco, Convention of Oviedo, etc.)²⁷. According to jurists (Cirillo²⁸), the decision not to be informed is part of "the general principle of respect for human dignity", "above all in those cases where prior knowledge of a disease would only lead to an anticipation of suffering, without real advantages in terms of therapy"²⁹.

6. Effective measures to safeguard information that, if disclosed, could lead to drastic consequences are thus necessary also from the point of view of legal medicine, particularly in employment or insurance contexts where discrimination against an individual for reasons of genetic makeup is a possibility or where the individual's social relations could be compromised³⁰.

7. Discrimination in employment and in the workplace is a special concern. Until a few decades ago an individual's suitability for employment was seen in terms of productivity and the possible repercussions of working on health were of scant interest³¹, to the extent that the law provided for a medical check-up to verify that the individual possessed the "*special requisites of resistance to the action of the noxious agents to which he will be exposed*". A form of preventive dismissal was even proposed to safeguard health, with no effective provision to guarantee wages, as in the case of workers exposed to lead: "*after a maximum period of employment every worker shall be temporarily dismissed, after which he may be reinstated*"³².

The motivation for this approach was probably the need to avoid paying compensation for damages rather than to protect workers' health. Some fear that predictive genetic tests will result in a return to the past, through the use of specifically targeted pre-employment medical tests by the designated occupational health physician (Article 16 of Legislative Decree 626/1994)³³, who may discover that, as a result of exposure to specific physical, chemical or biological agents (genotoxicity, see Glossary) that will determine a particular phenotype at some future time, an employee is at risk of contracting a work-

related disease. At the moment it is not possible to select future employees on the basis of whether or not they may spontaneously contract a disabling disease as not only is the physician not required to perform such investigations but even it were possible to do so the information thus acquired could not be used; in all western countries only the “current” state of health can be legally investigated. Resolution A2-237/88 of the European Parliament confirmed that before a worker can be asked to undergo genetic tests he or she must be properly informed and must give consent, which can be revoked at any time without the need for justification and without prejudice to employer-employee relations.

V – REMARKS AND CONCLUSIONS

In concluding these considerations, it must be acknowledged that the results of genetic research can help us to comprehend the biological basis of each individual's uniqueness in both biological and clinical terms by giving us the tools to decode that which, at the molecular level, both unites and distinguishes human beings. Genetics has played a major role in banishing the concept of "race" and in demonstrating that discrimination based on skin colour or ethnic origins has no biological foundation. It should, in the same way, help us to reach a more mature attitude towards people with disabilities. Genetics has also shown us how to recognise a series of hereditary and acquired DNA mutations that cause diseases and to develop more effective and appropriate forms of action. There is nonetheless no doubt that what still remains to be discovered vastly exceeds what we already know. The relatively small number of genes in comparison with the number of products encoded by our cells gives some idea of how fragmentary is our understanding of the way genes function during prenatal development and in adulthood, and of how they interact among themselves and with the environment. Notwithstanding the availability of high throughput technology, it is unthinkable that all the relevant data can be acquired in a short space of time³⁴.

The question that arises is therefore: what are the current potential clinical applications of the knowledge acquired so far?

The British Human Genetic Commission (2006) has declared that not only scientists but all professionals involved in various ways in disseminating scientific knowledge have a responsibility not to overestimate the potential of new and developing techniques. In line with this cautious approach, it is likely that the clinical impact of genetic testing, and particularly of Genome Wide Association studies (GWA) to define the hereditary component of complex phenotypes, will increase, especially where the prediction of individual disease risk and the identification of new therapeutic targets are concerned. But it should immediately be made clear that the possibility to predict the risk of becoming ill is desirable most of all if effective measures are available to treat the disease, in other words when the "clinical value" of a predictive test correlates directly with the subsequent availability of therapeutic measures, their efficacy, safety and cost. Genomic tests to identify common disorders and quantitative phenotypes are generally at an early stage of development, given that only a modest percentage of the results achieved have been translated into clinical practice. This is mostly cutting-edge research that aims to define the clinical criteria, statistical models and tools necessary to decode the biological basis of these diseases.

The information obtained is in any case an important point of departure that promises new discoveries based on sequencing the genome and on the functional analysis of firstly animal and then human models with a view to identifying effective applications in clinical medicine.

What is the expected impact on the community?

It has to be acknowledged that while biological knowledge is making exceptional advances, research into other aspects involved in the uses of genetics and their impact on society seems to proceed much more slowly. In

the vacuum created between knowledge acquired and our ability to comprehend its significance and draw up appropriate regulations, proposals are being made and measures taken that, quite simply because they involve a discipline directly linked to humans, cannot fail to have ethical and legal implications. If we look at what biological progress has given us and what it promises to offer in the immediate future, we must take a longer view of genetics and its spin-offs that goes beyond the definition attributed by early researchers, namely that of a discipline “that studies heredity and mutations”. Today we need to see beyond this genetics-centred view and seek a general, epigenetic and interdisciplinary perspective that does not ignore the associated ethical, legal and social effects.

What are the possible negative effects of genetic testing?

One of the dangers that has been pointed to is that the growing importance attributed to so-called “predictive medicine” may obscure its objective, which is to improve the quality of life of individuals, and that it may become a more or less occult process of medicalising our whole lives, with risks divided according to age brackets and “risk” situations being tackled with an obsessive recourse to drugs in a numbing state of constant alarm. Faced with these problems, the relationship between our genetic and our biographic identities acquires a central role; in other words, between our generally unknown (except to some degree during illness) biological makeup and the perception that each individual has of him or herself and that is built up over a lifetime through social interaction and lifestyle choices made along the way.

Because the confidence of being socially acceptable depends increasingly on conforming to the dominant model of bodily efficiency, health and physical and psychological “normality”, the knowledge of a genetic predisposition to develop specific disorders and to see oneself – and be seen by close friends and relatives – as a subject “at a declared risk” and thus different from the commonly held concept of “normality” could impact on the development of an individual’s sense of self and self-esteem.

The issue of genetic characteristics is also important in relation to the discrimination and stigmatisation that could result from the results of a test. Although in the West there has been some legislative progress in the battle to prevent and suppress such incidences, there has been little effective change in practice. While discrimination is less frequent, at least in some sectors, even in today’s liberal-democratic and well-meaning societies the stigma is still latent, albeit often downgraded from the level of a conscious spoken word to that of practical behaviour and body language: witticisms, lapses, gestures, various deliberate reactions that reveal discomfort around persons identified as possessing an imperfect or “different” body compared with one that is normal and socially acceptable (this is even more apparent in relation to persons labelled as “differently able”).

A discerning attitude to “new genetics” and appreciation of its benefits

In the final analysis presymptomatic and susceptibility genetic tests need to be viewed rationally, using mature discernment that avoids non-appealable judgements regarding fate, rejects narrow determinism and instead, when possible, encourages the potential for measures to restore physiological equilibrium. An ethical judgement of a decision to know or not to know the results of a test must be made on a case-by-case basis within a framework of

flexible rules and answers that carefully weigh the peculiarities of each actual case, which calls for the guidance of an experienced genetic counsellor.

To sum up this document, we can state that:

a) Given the difficulty for an individual with no specific knowledge to assess his/her own genetic “risk” situation, there is a need for “genetic counselling”, by which is meant the process of communication that will help the individual to comprehend the nature of possible genetic diseases and the risk that they will occur/recur, to evaluate the social, medical, psychological and family implications of his/her genetic makeup and to adapt to them as well as possible.

b) For this reason genetic counselling should be seen as an integral part of testing, in accordance with the indications expressed in numerous international, European and Italian documents.

c) Because genetic disorders involve all kinds of medical and surgical specialisations, genetic counselling needs to call on various areas of professional expertise: it must also ensure that the freedom of the consumer to make decisions is accompanied by full awareness that the astonishing growth of genetics in terms of its capacity to analyse the genome is only very rarely paralleled by an equivalent capacity to treat or prevent genetic disorders.

d) Genetic counselling needs to foster an alliance between scientific knowledge and its dissemination through both specialised publications and the popular media in a manner that is sensitive to the human aspect that should inform all activities, including the protection of personal health.

The development of pharmacogenetics, and in particular of pharmacogenomics, holds great promise. The possibility of using appropriate biomarkers to test sensitivity to a drug (possibly chosen from a selection of molecules available for the therapy in question) in order to identify the most effective and least risky for each individual has become a key objective, including from the point of view of the “safety” that every human being asks of technology for the protection of life and health.

In this regard, advances in “personalised medicine” – which in our opinion should come about through humanely responsible research – are to be hoped for and pursued.

Nonetheless, beyond this albeit important objective is a more general issue: that of nurturing a more mature and better informed scientific culture. In this context, it is to be hoped that **government authorities will promote campaigns to inform the public about the human genome, its characteristics, advances in human genetics and genomics, particularly in the field of multifactorial disorders caused by low penetrance variants, and the proper use of data; and that these campaigns will be directed not only to the general public but also to the education system as a whole.**

VI – RECOMMENDATIONS

The documents prepared by the CNB-CNBBS (2008) and by the CNB, “Dalla farmacogenetica alla farmacogenomica” (2006) conclude with a series of bioethical recommendations that reassume the positions of the CNB on the issues dealt with in greater detail in the present document. The reader may also refer to these general recommendations. Here we illustrate only those that are particularly important for the correct use of genetic susceptibility tests, in other words tests that may be requested in order to diagnose multifactorial disorders, which comprise the majority of human pathologies and are probably caused by low penetrance variants in several genes, each of which by itself has only a very small effect.

1. Attention should be paid to the risks involved in the improper use of genetic testing by consumers if adequate measures are not taken to limit their availability in the open market and if the provision of genetic counselling is not ensured both prior to testing and afterwards to interpret the results.

In this regard and in agreement with the arguments put forward by both international and Italian researchers it is felt that tests with high predictivity should be requested, performed and discussed under the responsibility of a specialised genetic counsellor, while tests with low predictive value may be more easily “liberalised”, provided that adequate information is provided beforehand and that counselling by specialised health personnel is also available³⁵.

2. Particular attention should be paid to health personnel and training, not only for operators in the field of genetics and in laboratories, but also for general physicians in sectors that will increasingly be called upon for initial advice concerning diseases with a more evident genetic component; the training of super-specialists will also be necessary. It must also be remembered that different forms of training in genetic counselling are needed according to whether complex or simple disorders are being addressed; in other words the training will need to be very specialised.

In the light of the increasing demand for more varied tasks that these facilities will likely face in the near future, it is perhaps time to review medical genetics services, as well as to provide for adequate professional cooperation above all on the part of general physicians, for which current training programmes will need to be upgraded. Given that genetic diagnostics has become a multi-disciplinary field, this training – in keeping with that introduced in other European countries – should involve not only personnel engaged in these specific services but also physicians and specialists from different clinical fields operating in other national facilities. Training for persons prescribing genetic tests, particularly susceptibility tests, will involve changes in the curricula of medical faculties in order to respond to these needs, as has been recognised in other countries (McNally E., Cambon-Thomsen A. et al., 2004). It will also be necessary to provide permanent opportunities for physicians already employed in the national health service voluntarily to increase their knowledge of genetics, particularly in practical terms³⁶.

3. Campaigns to inform and educate the public on the use of genetic counselling and genetic tests are particularly important and should therefore be arranged, promoted and regulated as a matter of urgency.

A more direct and urgent objective (particularly within the European Union) is to improve the public's ability to choose, as "consumers". It has been amply demonstrated in the Group's work that Europeans today are increasingly pressured by the health market and urged by deceptive promises of achieving optimum management of their personal "biological risk" to buy genetic tests offered directly on internet. This practice will probably become more widespread and can be countered only by a thorough "counter-information" campaign at several levels to scale down the expectations of potential users and prepare general physicians to be more aware of the meagre or negative reliability and appropriateness of most of these tests, as well as of the risks associated with their use and of the need to guide patients.

4. In the light of the above, the following recommendations can be made for the correct use of direct-to-consumer genetic susceptibility tests:

- because advertising is creating an inappropriate demand for testing and much of it is deceptive, all forms of advertising should comply with international standards and guidelines;

- as the predictive value of numerous common mutations associated with multifactorial disorders is below the standards required for their use in clinical practice, all the ethical, legal and social implications should always be taken into consideration;

- the current supply of genetic tests without medical control could create a series of problems that may have negative effects on health resources on account of the increase in demand for clarification from clinical geneticists, not to mention the possible negative consequences on consumers' health. Only tests that offer guarantees of quality and are relevant for health and for prevention should be offered.

- genetic tests without a medical prescription should never be performed on minors.

5. Concern for the increased availability of genetic susceptibility tests sold direct to consumers is felt in many other countries and both governments and private enterprises operating in the sector are being urged to draw up international rules to regulate the market so as at least to contain the possible damage: it is therefore to be hoped that coordination of inter-European policies regarding the genetics and genomics of multifactorial disorders can be enhanced in full recognition that the incentive for profit clearly contrasts with the "systematic doubt" of scientific research and with the caution required when translating new biomedical technologies into clinical practice.

6. With regard to Italy, there is a need to reorganise and extend the practice of genetic counselling.

In this regard, the fact that while the number of genetic tests performed by authorised – though not always accredited – laboratories is rising, genetic counselling was provided in only 13% of cases is of particular concern.

It is useful to reiterate the importance, when arranging counselling, of involving clinical specialists in the pathology being investigated. This cooperation could be extended and enhanced by more formal kinds of teamwork; if the clinical geneticist and the person performing the test (laboratory manager) are not the same individual their respective roles should also be more clearly defined, given the different professional training and functions involved.

7. At the same time the accredited facilities will have to be validated. With regard to public or private sector genetic testing facilities that are accredited or operate within the national health service, the provisions of the “Agreement between the Ministry for Health, the Regions and the autonomous Provinces of Trento and Bolzano on Guidelines for medical genetics activities” adopted by the permanent Conference for relations between the State, the Regions and the autonomous Provinces of Trento and Bolzano on 15th July 2004 and the subsequent Agreement between the Government, the Regions and the autonomous Provinces of Trento and Bolzano on the Document defining the “Implementation of the Guidelines on medical genetics activities” adopted on 26th November 2009 will have to be fully implemented.

In particular it is considered necessary to reorganise and coordinate diagnostics services in order to achieve greater equity and a more rational distribution of supply throughout the country. It should also be possible to set up a continuous system to monitor laboratories for the purpose of evaluating their compliance with the specific quality standards required by the Guidelines.

Notes

¹. Publications on genetics by the National Bioethics Committee and the National Committee for Biosafety, Biotechnology and Life Sciences are listed in the Bibliography.

². The advisory body of the British government on how new developments in human genetics impact on people and healthcare.

³. The best known model is that proposed in the mid-twentieth century by Falconer (1967), known as the “susceptibility” or “threshold” model, based on the assumption that the phenotype depends on the combined action of the environment and genes, particularly common mutations or polymorphisms. The latter define the genetic component of the complex system – heritability. Today GWA technology is providing growing evidence of the interaction between mutated genes and the environment in the etymology of some diseases.

⁴. The first step consists in genotyping the genomic SNPs (single nucleotide polymorphisms), using commercially available chips. The data are then checked for quality and “cleaned”. In this stage, for example, samples from ethnically distant subjects are removed and adjustments are made on the basis of inter- and intra-cohort variations. SNPs that pass this stage are tested for an association with the disorder or trait being studied. The statistical “P” value is fixed $\leq 1 \times 10^{-8}$ in order to reduce the percentage of false positive results. The SNPs or loci are then selected to be replicated in a separate sample, if possible the same sample used for GWA analysis or a broader one. The loci are selected solely on the basis of the statistical significance, or on the combination of statistical significance and biological plausibility. The number of SNPs selected may vary in relation to the initial design or to the availability of resources. Replication of the results may confirm or exclude an association with the specific disease, or it may evidence an association that does not exceed the established statistical threshold. Data that prove an association are verified by means of other genotyping procedures on independent cohorts. All the transcripts in the region being examined are analysed, all variations are mapped and those associated with the disease are identified, the effects of the disease being defined at the biological and functional levels.

⁵. See Hindorff LA, Sethupathy P, Junkins HA, et al. *Potential etiologic and functional implications of genome-wide association loci for human diseases and traits*. Proc. Natl. Acad. Sci. USA 2009; 106:9362-7.

⁶. See Hindorff LA, Junkins HA, Manolio TA, NHGRI Catalog of published genome-wide association studies (accessed June 7, 2010, at <http://www.genome.gov/gwastudies>).

⁷. This study examined polymorphisms tested by 7 companies offering complex trait diagnostic services: specifically, 69 polymorphisms in 56 genes. No meta-analyses were available for 43% of the genes tested. For the remaining 32 genes, the study involved 260 meta-analyses that examined 160 unique polymorphism-disease associations, only 60 of which (38%) were found

to be statistically significant. Even the 60 significant associations studied, which involved 29 different polymorphisms and 28 diseases, were generally modest (odds ratios 0.54-0.88 for protective polymorphisms and 1.04-3.2 for risk variants). Genes in cardiogenomic profiles, moreover, were more frequently associated with non-cardiovascular diseases and though two of the five polymorphisms used to define the osteogenomic profile did show significant associations with disease, the associations were not with bone diseases.

⁸. The free commercialisation of genetic tests was the subject of repeated discussions during preparation of the “Additional Protocol to the Convention on Human Rights and Biomedicine, on Genetic Testing for Health Purposes”.

Some delegations insisted on the need for a medical prescription in all cases; others were more inclined to favour free access to services offering tests, with the consumer assuming direct responsibility for any consequent psychological and medical effects.

With no possibility of attaining the quorum of a two-thirds majority and, above all, in recognition of the fact that genetic tests are classified by international commercial regulations as “medical devices” and as such enjoy unregulated commercialisation, the Protocol, after describing the requisites for all services and tests, states:

“Article 7 – Individualised supervision

1. A genetic test for health purposes may only be performed under individualised medical supervision.

2 Exceptions to the general rule referred to in paragraph 1 may be allowed by a Party, subject to appropriate measures being provided, taking into account the way the test will be carried out, to give effect to the other provisions of this Protocol.

However, such an exception may not be made with regard to genetic tests with important implications for the health of the persons concerned or members of their family or with important implications concerning procreation choices.”

The text is thus clear in setting limits to some personal choices when requesting and – equally –performing particularly important tests. It remains to be seen how the different European governments will implement these indications.

⁹. A press release from AGI of 30 November 2009 noted that “from December myGeneSis, an innovative genomic testing and counselling service based on DNA tests, will be accessible in Italy; it will initially evaluate risk in the area of cardiovascular disorders, diabetes, osteoporosis and the major degenerative diseases. The service was presented in Florence during the 26th SIMG (Italian Society of General Medicine) Congress, and will involve general physicians as the fundamental figure of reference for families. After taking a simple saliva swab, the physician will transmit the patient’s genetic sample to the GenHealth laboratories in Florence for testing and after only a short interval the report will be returned to him/her via a panel of consultants specialised in different fields so that the physician can advise the patient regarding the correct precautionary measures in respect of any disorders potentially revealed by the test. The report will indicate an objective percentage of risk or protection in regard to the diseases investigated and will enable the patient to take proper precautions and adopt suitable lifestyle and nutritional behaviours, as well as to

take any preventive action necessary such as personalised diagnostic tests, check-ups, nutritional supplements.”

A report of the Agenzia di Sanità News of 11 March 2010 informed readers of the availability of nutrigenetics tests via the internet, together with the arrangement of appropriate counselling by specialised personnel.

¹⁰. See the Protocol to the Convention of Oviedo concerning genetic testing for health purposes.

¹¹. The text of the guidelines specifies that counselling sessions concerning diagnostic, presymptomatic or susceptibility testing or tests to identify healthy carriers should generally, albeit in their different ways, be considered as a complex process of communication with the following aims:

a) to provide complete, accurate and impartial *pre-test* information that includes not only clarification of the genetic component of a disorder and the meaning, limitations, reliability and specificity of the test in question (which may even call for the acquisition of additional data concerning the counselee’s family tree), but also an indication of possible therapies; the counselee should also be informed concerning the procedures and scheduling of both the test itself and disclosure of the results, as well as the implications of possible outcomes for existing and future children and for other blood-relatives, possible psychological and social advantages – and risks – that may be encountered should the result confirm the presence of a mutation;

b) provide correct *post-test* explanation of the result and, where this is positive, support for individuals who must come to terms with the short and long-term implications of the outcome and make difficult decisions on the basis of the medical and non-medical options available;

c) in the case of diagnostic tests, offer the support necessary to accept the implications of a hereditary disorder and to adjust to it in the best possible way.

¹². These situations concern the counselee’s autonomy and are dealt with in the section covering bioethical aspects.

Some examples include:

a) Counselling individuals from the different ethnic groups that have become more numerous in countries with high rates of immigration. Should counsellors need to know not only the particular genetic aspects associated with specific ethnic groups but also the cultural backgrounds?

b) When a counselee is willing (and therefore does not refuse) to undergo testing, not directly for personal reasons but because it may benefit a family member, but wishes to exercise his or her right “not to know”, should counsellors act as intermediaries with responsibility for the case?

c) The possibility for a counsellor to disclose test results to family members of tested persons when this is considered urgently necessary but the individual concerned, even after being directly informed and urged to cooperate, does not intend to inform his/her family. This is one of the most controversial issues involved in genetic counselling; can the solution be justifiably left solely to the moral sensitivity of the geneticist?

d) The plausibility of a request by a counsellor to an individual requesting a test or who has already been tested, to examine other family members in order to define more precisely or confirm a particularly complex diagnosis. The advisability for a counsellor to accept a request to be tested by a minor who is

nonetheless of an age to comprehend fully the significance of his/her genetic status (Duncan A. et al, 2005; Malpas P.J., 2008)).

¹³. It is recommended that the informations provided cover appropriately the following issues: the role of genes in physiological and pathological conditions; their ability to condition the phenotype; the techniques used to analyse them; the respective roles of genetic and environmental components, including lifestyle, on health, disease and phenotypes; specific information on the test in question; its accuracy and limitations; the analytical and clinical validity of the markers analysed; information on the results expressed as statistics, for example the definition of relative and absolute risk, so that the consumer is able to understand the result; information concerning the measures to ensure the confidentiality of personal data and the safe storage of biological samples, including the duration of storage, the method of conservation and possible transfer to other laboratories; the possible use of the biological sample for other purposes, the transfer of personal data to third parties and the related conditions; the procedures for handling and resolving complaints from consumers; the procedures for releasing the results and possible availability of post-test genetic counselling; the possibility that the results may provide indications concerning degrees of kinship. In addition, the possible results of the test and the nature of decisions that the consumer may have to face should be clearly explained.

¹⁴. On this point see the Code concerning the protection of personal data (Legislative Decree No.127/2001), in particular the indications of the Information Commissioner and the section of this document dealing with "Confidentiality and Privacy" in the chapter on bioethics. These ethical-legal indications are based not only on numerous documents drawn up by the profession (usually in the form of guidelines) but also on international declarations (see for example the "Universal declaration on genetic data" issued by UNESCO in 2003 and the Protocol to the Convention on Human Rights and Biomedicine of the Council of Europe of 2008, which is dealt with more fully in the annexes to this document.

¹⁵. In Europe, especially, even the earliest texts published by the Council of Europe (Recommendation 934 (1982) of the Parliamentary Assembly on genetic engineering; R.151 (2001) on the protection of the human genome; the Euroscreen Group (1994-1997) of the European Commission, etc.) clearly indicate the voluntary nature of access to testing. This may be replaced, for medical reasons, by consent given by a legal representative if the individual concerned is not capable of expressing consent in person. The Convention on human rights and biomedicine agreed by the Council of Europe (Oviedo, 1997) and, above all, the Additional Protocol to that convention concerning genetic testing (2008) regulate this issue.

See also Chadwick R.,1998: *Genetic screening and ethics: European perspectives*, in J. of Medicine and Philosophy 23/3, 255-273, 1998.

¹⁶. These few comments are not intended to cover the whole issue of participation in genetics research, which is addressed in greater depth in the Joint Committee's document: "Collection of biological samples for purposes of research: informed consent", Rome, February 2009.

¹⁷. For example, an adult who fails to inform his/her closest family members in advance of the decision may be motivated either by personal reasons he/she does not wish to share or, on the contrary, by "altruistic"

motives such as the desire to avoid disrupting the family's peace of mind (Vernon et al., 1999).

In the case of testing for BRCA 1/2, in particular, the decision to undergo the test is usually shared only with a few trusted family members (Green et al., 1997).

With regard to the sharing of results with family members by a subject who has autonomously and discreetly undergone a test without previously informing them, where the test has revealed a high degree of susceptibility or the probability of contracting a disease, two types of behaviour have mostly been observed: either the individual considers the issue a strictly personal matter and thus not to be disclosed; or it is considered suitable to be disclosed only to some family members but not to others.

This conduct appears more frequent where testing for susceptibility to tumours in women is concerned and – if the information is given to a sister – is associated with less psychological stress in the person undertaking the test and with the possibility of receiving more effective psychological support.

The sharing of information regarding the results of testing with minor offspring is less frequent (Wagner-Costalas et al., 2003).

¹⁸. Because of the impossibility of addressing this issue more completely here, see specialist publications.

¹⁹. Some counsellors offer to be present with the proband when the information is communicated to family members; if the proband consents to the information being disclosed but does not feel personally able to communicate it, some counsellors may offer to inform the family physician, who can then inform the family of the diagnosis: other authors suggest that the local "Cancer prevention service" should be called upon, if there is one.

²⁰. One very special case is that of revealing the existence of a risk when adolescent children (aged 13-17) are involved and a parent who is either affected or destined to become affected with a disease such as Huntington's disease must attempt to ensure that the child can "incorporate the information into his own identity" (Malpas P.J., 2006), thereby avoiding the disastrous effects on their relationship that would ensue were the information to reach the child, even accidentally, from another source (Sobel S. and Cowan C.B., 2000,2003). (Issues regarding this age bracket are not addressed in the present document, but we underline their importance nonetheless).

According to Metcalfe A. et al., 2008, who studied these issues, the disclosure by parents to children of particular genetic situations within the family involves serious emotional problems for which adequate professional support is lacking.

²¹. For further reading, see "Genetic testing and insurance" published by the joint CNB and CNBBSV on the 20th of October 2008; also the works of Raithathan and Smith R., 2004 and Feiring E., 2009. The Steering Committee on Bioethics of the Council of Europe has initiated a broader study of genetic discrimination that could in some countries arise from access to genetic testing.

²². This issue is addressed in the Conclusions to the present document.

²³. If we examine individual cases, respect for both rights could become aporetic for reasons other than those mentioned. The spread of cultural attitudes in favour of planning personal lifestyle choices on the basis of information concerning one's "genetic body" could clash with the explicitly expressed legal protection of the right not to know or to keep in ignorance. This is borne out by the emergence in international documents concerning genetic information and the respective powers of the interested parties of a new and legally significant category: the "biological group". This term is used to refer to the intrinsically intersubjective nature of genetic data, defined as being shared by a multitude of subjects and as such potentially accessible to all those belonging to the same genetic lineage, regardless of the wishes of the person to whom they refer directly. In this case the scales could tip towards the right to know, seen as part of the right to health (as has already happened) rather than towards the right to privacy and, perhaps at some future date, the right not to know. At this point it is recognised that precisely because we are talking about information of a predictive nature it is difficult to guarantee a "veil of ignorance" for those not wishing to be worried by knowing their biological risk status even when the person requesting the test undertakes not to communicate the results, as his or her subsequent behaviour could effectively reveal them (Rodotà S., 2003; 2006).

²⁴Report of the Working Group, 19th of May, 1998.

²⁵.Genetic laboratories perform specific tests (cytogenetics, molecular genetics, biochemistry, etc.) to identify diseases on a genetic basis and can be integrated as departments. They must have a regional or supraregional catchment area. These recognised specialist laboratories are regulated at national level (firstly by the Decree of the President of the Council of Ministers of 10/2/1984 and subsequently by Presidential Decree of 14/1/1997) and are located throughout the country. The management of genetics laboratories and access to the executive levels of management are regulated by Legislative Decree 502/1992 and subsequent amendments and additions).

²⁶. See the Agreement between the State and the Regions.

²⁷. Article 5(c) of the UNESCO Declaration on the human genome states that "the right of each individual to decide whether or not to be informed of the results of a genetic examination and the resulting consequences should be respected." The Convention of Oviedo on Biomedicine has a similar declaration in Article 10(2).

²⁸. F.M. Cirillo: "La progressiva conoscenza del genoma umano: tutela della persona e problemi giuridici connessi con la protezione dei data genetici" (Advancing knowledge of the human genome: personal protection and legal problems concerning the safeguarding of genetic data) in *Rivista di diritto civile*, 2002, p.410.

²⁹. The Information Commissioner and Article 33 of the Italian Code of Medical Ethics (2006) confirm the right to refuse to be informed: "the documented desire of the patient not to be informed or to delegate another person to be informed must be respected". Barni observes that the subject's wishes must be respected, but that the refusal cannot be considered absolute "on account of the existence or possible emergence of major medical liabilities".

³⁰. It is worth recalling the raising of insurance premiums in France for parents of disabled children, considered carriers of some unspecified genetic “defect”, as well as an episode that occurred in 2003 in Germany: a young teacher seeking open-ended employment was rejected when it emerged from her tests for admission that her father had developed Huntington’s disease, as a result of which she had a high risk of developing the same disorder. “Predetermination” could be claimed in similar cases, reducing individuals to a mere genetic identikit, a sort of fatalism “that weighs on the individual as a predetermined and unchangeable ontological condition that can obliterate any role of individual will” (Piccinni A., 2008).

³¹. Checcaglini G., Roggi M., Rossi M.: *Test genetici predittivi e idoneità al lavoro: il rischio di un ritorno al passato?* (Predictive genetic tests and suitability for employment: the risk of a return to the past?)

³². Commessati G., *Individualità e intossicazione saturnina* (Individuality and saturnine intoxication), *Il Lavoro*;1905: 11-15.

³³. Health surveillance regulations: 1. Health surveillance is carried out in the circumstances provided for in current regulations. 2. Surveillance as per (1) is carried out by the occupational health physician and comprises: a) *preventive tests to determine the absence of counterindications for the job to which workers are assigned, for the purpose of evaluating their suitability for the specific tasks*; b) periodic tests to check the state of health of workers and judge their suitability for specific tasks. 3. The tests as per (2) include risk-associated clinical, biological and diagnostic tests as the occupational health physician deems fit (Thomas T).

³⁴. Nonetheless, as already stated clearly in previous documents published by the CNB (e.g. “Orientamenti bioetici per i test genetici” – 19, IX,1999; “Dalla farmacogenetica alla farmacogenomica” – 21, IV, 2006) and by the CNBBSV (e.g. “Linee guida per i test genetici”, Roma 1999) this does not imply a “reductionist” approach in which the complex of genes, in their interaction, amounts to “determinism” of their actions on living structures, rendering them impermeable to counter-actions by environmental variants which, in the case of humans, include those produced by cultural evolution.

³⁵. Tests for known polymorphisms associated with the more common disorders are considered “low predictivity” tests.

³⁶. The mixed Group does not wish to conceal the extent and difficulty of the organisational and practical commitment that this implies and advises adopting tried and tested regionally-based models for limited numbers of applicants, managed by available teaching facilities.

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ATTACHMENTS

1. Prof. C. PETRINI¹: REVIEW OF INSTITUTIONAL DOCUMENTS ON GENETIC TESTING AT INTERNATIONAL, EUROPEAN AND ITALIAN LEVEL.

2. TEXT OF THE AGREEMENT BETWEEN THE GOVERNMENT, THE REGIONS AND THE AUTONOMOUS PROVINCES OF TRENTO AND BOLZANO ON “IMPLEMENTATION OF THE GUIDELINES FOR MEDICAL GENETICS ACTIVITIES”.

3. REPORT ON THE ACTIVITY OF MEDICAL GENETICS IN ITALY: ITALIAN SOCIETY OF HUMAN GENETICS, YEAR 2006.

4. EXTRACT OF THE RULES REGULATING HEALTH ADVERTISING LICENSES: CURRENTLY GENETIC TESTS FALL WITHIN MEDICAL DEVICES.

5. DOCUMENTS ON GENETICS PUBLISHED BY THE NBC AND THE NBBLSC.

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ATTACHEMNT 1

Carlo Petrini

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1. Institutional documents on genetic testing: a summary

Numerous national, international and supranational institutions have drawn up and published documents on the subject of genetic testing. Governments, parliaments, national bioethics committees, professional associations, scientific societies and international organisations have all made declarations. These pronouncements consist of: regulations, deontological codes, guidelines, declarations, recommendations, treaties, conventions, opinions and more. Some are binding; others, while not binding, nonetheless represent references that cannot be ignored, given the authority of the issuing institutions. The following paragraphs contain a brief description of some of them: section 4 lists the more significant.

It should be borne in mind that while numerous documents address the ethical implications of genetic testing, those that deal specifically and exclusively with the ethical aspects of predictive tests are less numerous. The issues involved in predictive tests are addressed mostly in documents that also treat other aspects of genetic testing.

This is not an exhaustive description; its aim is not to give a complete list of all the documents but to select and provide a brief introduction to the most significant. Its purpose is to provide a panoramic view showing how in most cases the different documents express concordant evaluations. A chronological list that includes documents not presented in the body of this paper is given in the appendix.

A) *United Nations – UNESCO*

On 11 November 1997 the United Nations Educational, Scientific and Cultural Organisation (UNESCO) adopted the “**Universal Declaration on the Human Genome and Human Rights**”¹, which was adopted in turn by the General Assembly of the UN on 9 December 1998. This Declaration is not legally binding, but member states were invited to promote the principles it set out (Article 22). Article 1 declares that “The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity”. On the specific question of genetic testing, Article 6 states that “No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity” and Article 7 declares “Genetic data associated with an identifiable person and stored or processed for the purposes of research or any other purpose must be held confidential in the conditions set by law”.

On 16th October 2003 the General conference of UNESCO adopted the “**International Declaration on Human Genetic Data**”². This proclaims the general principles for the respect of human dignity and the protection of human

rights and fundamental freedoms in the collection, use and storage of human genetic data, with particular emphasis on informed consent.

B) Organisation for Economic Cooperation and Development

Other international documents have also defined more operational criteria.

Among the most important of those adopted in recent years are the “Guidelines for quality assurance in molecular genetic testing”, which the OECD adopted in May 2007. These contain a series of recommendations to governments and other authorities involved in the management of genetics services. The “general principles” laid down in the Guidelines state that:

- “Applicable legal, ethical, and professional standards should be respected in the practice of molecular genetic testing;
- Molecular genetic testing should be delivered within the framework of healthcare;
- All molecular genetic testing services should be provided and practised under a quality assurance framework;
- Informed consent to test should be the norm and should be obtained in compliance with applicable legal, ethical, and professional standards;
- Pre- and post-test counselling should be available. It should be proportionate and appropriate to the characteristics of the test, the test limitations, the potential for harm, and the relevance of test results to individuals and their relatives;
- Personal genetic information should be subject to privacy protection and security in accordance with applicable law;
- The benefits of cross-border exchange of patient samples and personal information for molecular genetic testing should be recognised,
- The use, storage, transfer and disposal of patient samples collected for molecular genetic testing should be subject to applicable legal, ethical and professional standards;
- Advertising, promotional and technical claims for molecular genetic tests and devices should accurately describe the characteristics and limitations of the tests offered”³.

C) Council of Europe

The Council of Europe first addressed the issue of genetics in the 1970s: both the Parliamentary Assembly and the Committee of Ministers have produced numerous documents on the subject. In 1983 the Ad Hoc Committee of Experts on Bioethics (CAHBI) was charged with drawing up guidelines for biomedical research, including genetics. In 1992 the Committee became a statutory organ and took the name Steering Committee on Bioethics (CDBI), and was responsible for the adoption of a number of resolutions by the Committee of Ministers. The need for member states to provide regulations for access to genetic testing was clearly expressed already in the 1990s in the **Recommendations R(92)1⁴ and R(92)3 of 10 February 1992⁵**, concerning genetic testing respectively within the framework of the criminal justice system and for healthcare purposes. Both recommendations offer a number of definitions: Recommendation R(92)1 states that “DNA analysis” refers to “any procedure” for the analysis of DNA.

In 1993, at the request of the Committee of Ministers, the CDBI began to prepare a text for a “**Convention on Human rights and Biomedicine**”⁶ with the aim of agreeing basic bioethical principles in Europe. The document was open to signature by the states at Oviedo on 14 April 1997.

After stating that “The interests and welfare of the human being shall prevail over the sole interest of society or science” (Article 2) Chapter IV is dedicated to the human genome. It states a number of general principles (including the rejection of “any form of discrimination against a person on grounds of his or her genetic heritage”) as well as more specific provisions. Article 12 stipulates that “tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling”. The need for genetic counselling is repeated in all the key documents that address this issue.

Among recent documents, the “**Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes**”⁷ approved by the CDBI in June 2007 is of particular significance. The protocol is an addition to the “Convention on Human Rights and Biomedicine” approved by the Council of Europe and deals more fully with the principles outlined in the Convention. Both documents have the status of international treaties. Unlike other texts of a purely indicative nature, the Protocol is binding on the countries that signed and ratified the Convention. The Additional Protocol was adopted by the Committee of Ministers of the Council of Europe on 7 May 2008 and opened for signatures on 27 November 2008. It establishes general criteria for the performance of genetic tests and defines principles for the quality of genetic services, for informed consent and for genetic counselling. Particular importance is attached to the increasing proliferation of commercial genetic tests, as well as to criteria for the performance of genetic tests on persons unable to give consent. It also addresses the issue of protection of personal data.

D) European Union

The issue of genetic testing has been addressed in different documents by the European Union. On the 24th of February 2003 the “**Statement by the European Group on Ethics in Science and New Technologies on advertising genetic tests via the internet**”⁸ was approved. This stated that “the information currently being offered is likely to be misleading and incomplete, particularly in view of the limited level of predictability of diseases linked to test results in the case of multigenic traits. Often, there are not sufficient guarantees that genetic data sent for such tests have been collected in compliance with the regulations applying to data subjects’ consent (...). Genetic tests can be harmful without proper advice and counselling (...). Consequences of genetic testing for both individuals and society should be assessed carefully. Given the peculiar features of genetic data, fundamental rights may be violated, in particular equality rights. Both individuals’ health and confidentiality of health data may be jeopardised. Advertising of genetic tests tends to convert them into commodities and to give

rise to a demand for genetic testing which may result in disruption of social and personal relations”.

Subsequently, on the 6th and 7th of May 2004 the European Commission organised a congress in Brussels to stimulate “a reflection on the ethical, social and legal implications of genetic testing”, which in turn gave rise to a document containing 25 recommendations⁹. These are divided into three major sections dedicated respectively to an analysis of the general background, the implementation of genetic testing in healthcare systems and genetic tests as instruments of research. A prefatory document to the recommendations, “Ethical, legal and social aspects of genetic testing: research, development and clinical applications”¹⁰ describes and explains in detail the considerations underlying the recommendations, sums up the state of the art in the development and use of genetic tests in Europe and puts forward the points of view of the different participants in the Group. The first recommendation points to the need for universal standard definitions agreed by all public and private bodies (“any official statement or position should precisely refer to an explicit definition of the terms used or topic addressed”). Subsequent recommendations note, among other things, how the media give distorted views of genetic tests, in particular by over-emphasising their predictive potential. It is significant that the working group puts forward a number of arguments for the inappropriateness of the notion of “Genetic Exceptionalism” (the sentiment that genetic data are different from other medical data): the members of the group consider that many of the features held to make genetic data “exceptional” are not exclusive to genetic data.

E) National Bioethics Committees

Several National Bioethics Committees have addressed the issue of genetic testing. The following two examples have been chosen from opposite extremes in chronological terms: one of the first and one of the most recent opinions on the subject.

The French **Comité Consultatif National d'Éthique pour les Sciences de la Vie et de la Santé (CCNE)** was among the earliest committees to draw up specific documents concerning predictive tests. Its “Opinion” no.46, approved in 1997, addressed the ethical aspects of genetics and predictive medicine¹¹. The Committee describes how the identification of a large number of human genes could fuel “the illusion that perfect knowledge of an individual’s genome could open the door to a person’s real self and to his or her destiny (...), a concept that is both scientifically unacceptable and ethically dangerous” given that it ignores the multitude of factors “external to genetic determinism”.

The Portuguese **Conselho Nacional de Ética para as Ciências da Vida** is one of the most recent National Committees to have addressed the issue of predictive genetic tests. In its Opinion on Direct Marketing of Genetic Tests to the Public (56CNECV/208: Opinion on direct marketing of genetic tests to the public)¹², the Portuguese Committee proposes a series of recommendations similar to those found in other documents on the same issue, repeating the need for: transparency and thoroughness (principle 1), availability of information prior to the performance of a test (principle 2), quality assurance in the laboratories (principle 3), regulation of laboratories and procedures (principles 4 and 5), instruments for checking compliance with rules (principles 6 and 7), training of laboratory personnel (principle 8), cooperation between

regulatory authorities of different states (principle 9). The importance that tests should be offered only for medical purposes (principle 10) and that proper counselling should be provided during and after testing (principle 11) is also stressed. The Committee also invites caution regarding false expectations created by commercially available tests (principles 12, 13,14).

2. Brief outline of regulations regarding genetic testing in Europe

This section offers some information on regulations applying to genetic testing in a few European countries other than Italy.

Two introductory comments are necessary:

The first is that this document does not claim to be either complete or up to date. Its objective is to offer a summary of tendencies in regulations designed to address the key problems posed by genetic tests, using examples. As this is not the place for a nation-by-nation analysis, only some have been selected. No specific selection criteria were applied; rather, an attempt has been made to provide examples from different areas of the continent, from the north, the south and the eastern countries that have recently joined the European Union.

It should also be borne in mind that the extremely rapid development and increasing proliferation of genetic tests mean that many countries are having to update their regulatory frameworks. In many nations the regulations are therefore under review, or a review is planned in the near future. The purpose of this selection is thus not to offer the reader an updated list of regulations in each nation, or to provide a source for consultation, but rather to point to the key aspects addressed, using some examples. For this reason, and because the present document is intended to be non-technical and informative, there is no detailed bibliography listing all the documents quoted: the examples have been chosen arbitrarily.

The second introductory comment regards the fact that regulations applying to genetic tests generally address issues that are common to various types of test, rather than specific categories such as susceptibility tests, the object of the present document. Much of what follows thus applies also to other types of genetic test and not only to susceptibility tests.

In **Austria** the regulatory framework for genetic testing is defined by the “Genetechnology Act, BGB1 no. 510/1994”, which applies to predictive, presymptomatic and diagnostic tests. The regulations cover all the relevant aspects: the quality requisites of the tests and of the facilities that offer them, the preservation of biological samples, etc. The issue of the different fields in which data may be used are also addressed: insurance, legal, employment. The regulations are particularly severe in the legal field, the intention being to avoid abuse. The use of genetic tests is not allowed when preparing insurance or employment contracts.

In **Belgium** the genetic test sector is regulated by a series of provisions, particularly the “Arrêté Royal du 14 décembre 1987 fixant les normes auxquelles les centres de génétique humaine doivent répondre”, the “Loi du 22 mars 1999 relative à la procédure d’identification par analyse ADN en matière pénale”, the “Loi du 28 janvier 2003 relative aux examens médicaux dans le cadre des relations de travail”, and the “Circulaire du 21 juin 2007 relative aux

modifications intervenues dans la réglementation en matière de séjour des étrangers suite à l'entrée en vigueur de la loi 15 septembre 2006". Additional decrees identify a limited number of centres authorised to perform the tests and lay down rules for the use of genetic tests for legal purposes. Insurance companies and employers are not allowed to use genetic tests to select clients or employees.

In **Denmark** genetic testing is regulated through a framework of laws that govern the entire national health service: the 2005 Health Act also applies to genetic tests, and especially to patients' rights. More specific provisions also exist regarding the use of genetic data in the insurance and employment fields. Section 3a of the "Act on insurance agreements and pension funds" amended on 19 June 1997 bans the use by insurance companies of data concerning a genetic predisposition to possible pathologies. Similarly, Act 286 of 24 April 1996 bans the use of genetic data by employers when hiring personnel: genetic tests can be used only to check the health status of workers possibly exposed to risks. In Denmark about twenty national health service centres have been authorised to perform genetic tests: each is subject to periodic quality controls, both internal and external, under the responsibility of a specialist (usually an expert in clinical chemistry).

Finland has no specific provisions governing genetic testing, but centres that perform these tests are subject to quality controls. More generally, many aspects of genetic testing are regulated less by specific regulations than by respect for international codes and guidelines. The use of genetic tests when hiring employees is also forbidden in Finland.

Several provisions regulate genetic testing in **France**, including the decree of 23 July 2000 concerning the conditions for prescribing and performing genetic tests and the so-called "laws of bioethics" of 29 July 1994 and 6 August 2004. Title I of Chapter II of the first book of the Civil Code (amended by Law No.94-653 of the 29th of July 1994) distinguishes between "the genetic study of a person's characteristics" and "the identification of a person by means of his/her genetic fingerprint". Article 16-10 of the Civil Code states that "the genetic study of a person's characteristics cannot be accomplished except for medical purposes or for scientific research" and that "the consent of the person must be obtained prior to undertaking the research". Article 16-11, par.1 of the same code states that "no person may be identified by his/her genetic fingerprint except within the ambit of a judicial enquiry or pursuant to instructions imparted by a legal authority, or for medical purposes, or for scientific research". The law of 4 March 2002 concerning the rights of the sick and the quality of the health service added to the Civil Code an article (16-13) that establishes that "no-one may be subjected to discrimination on grounds of genetic characteristics". This statement is also found in the penal code, in the labour code, in article L 1141-1 of the public health code, in article L 133-1 of the insurance code and in article L 932-39 of the social welfare code. The regulation of bioethics is currently under review and the new code is expected to be adopted during 2010. While the present document was in preparation an intense consultation campaign was under way in public ("États généraux de la bioéthique") and in parliament ("Mission parlementaire d'information sur la révision des lois de bioéthique") prior to adoption of the new

regulations. Among other contributors to the debate was the Académie Nationale de Médecine with its report “Diffusion et validation des tests génétiques en France”, adopted on 8 December 2009. Current provisions cover the different types of genetic tests authorised in France, namely: individual tests performed under medical prescription, certain prenatal tests, some tests for research purposes, five tests as part of screening programmes (hyperphenylalaninaemia, congenital adrenal hyperplasia, sickle-cell anaemia, cystic fibrosis, congenital hypothyroidism) and tests prescribed by the judiciary.

Like France, **Germany** is one of the nations in which the rapid evolution of technology and knowledge has recently led to a review of the provisions regulating genetic testing. On 24 April 2009 the Bundestag approved the Gendiagnostikgesetz (Human Genetic Examination Act, GenDG). A brief summary of the situation as it was may help comparison with the new regulations. Prior to adoption of the new law Germany had no single set of regulations for genetic tests: some aspects were addressed separately in various provisions, while others were in effect not explicitly regulated. A form of indirect regulation did exist, however, particularly through the Gemeinsamer Bundesausschuss (Federal Joint Committee) whose job is to establish the requisites for providing key health services. A similar situation obtained for the use of genetic data for insurance purposes or in hiring employees. In the absence of specific regulations, reference was made to various self-regulation codes, for example to avoid genetic data becoming grounds for discrimination. In this regard the Gesamtverband der Deutschen Versicherungswirtschaft e V. (German Insurance Association) had adopted a code that committed insurance companies not to use genetic tests when stipulating contracts. Authorisation and quality control were likewise not covered by specific provisions: facilities planning to offer genetic tests did not require an authorisation as such but procedures existed for approval and control through professional medical associations and a federation of hospitals and health centres.

The new regulations approved on 24 April 2009 came into force on 1 February 2010. They introduce stricter rules for the performance of genetic tests, which only physicians are authorised to perform. The regulations cover many types of test: paternity tests, preimplantation diagnostic tests for medically assisted procreation, the use of genetic data by persons hiring employees and by insurance companies. The circumstances in which genetic tests are allowed or forbidden are defined. Prenatal testing is allowed only if it is performed “for medical reasons” associated with specific pathologies that may develop and become a health risk in infancy. Testing for pathologies with late onset, such as breast cancer or Alzheimer’s disease, is prohibited, as are tests to identify possible desirable physical features of a foetus. Tests on adults are authorised only “after careful counselling and explicit consent of the subject concerned”. Employers are forbidden to ask workers to undergo genetic tests except in the case of jobs involving health risks for which monitoring is required, such as some types of processing in the chemical industry. The German regulations forbid insurance companies to request genetic tests and allow them to consult the results of tests already carried out only when stipulating policies for sums in excess of 300,000 euro.

The authorisation of laboratories performing genetic tests in **Lithuania** is not compulsory. However, laboratories that have been granted authorisation

in accordance with procedures laid down by the Council of Ministers enjoy a series of advantages, with the result that most such facilities are certified. Certified laboratories are required to comply with certain quality requisites established in 1997 in the “Law on medical treatments”, which was amended in 2001 in regulation no.133 (of the Council of Ministers) and in 2002 in regulations no. 75 (of the Welfare Ministry) and no. 77 (of the Council of Ministers). Some laboratories are members of an external quality control system established by the European Molecular Genetic Quality Network (EMQN). The use of genetic data is not regulated by specific provisions. However, some aspects are covered by specific regulations: the Law on Medical Treatments (1997), the Law on Personal Data Protection (2000), the Law on Research in Human Genetics (2003) and various regulations issued by the Health Ministry: no. 14/13 of 2004 concerning pregnancy and neonatal age; no. 311 of 2003 on potential donors of gametes for medically assisted procreation among others. These provisions include a ban on the use of genetic tests in an employment context when hiring personnel and by insurance companies.

The last decade has seen the publication of numerous documents on the subject of genetic testing in the **United Kingdom**, including during major initiatives for the promotion of research and applications. The Scottish Parliament, the National Assembly of Wales and the Northern Ireland Assembly have all addressed the issue.

Within the National Health Service (NHS) there are about 25 centres specialising in genetics, many of them linked to specialised clinical facilities.

The UK Genetic Testing Network (UKGTN) has been in operation since 2002, with the key objective of promoting equitable access to genetic testing. Laboratories that are members of the network must comply with precise quality criteria. Within the UKGTN tests are assessed for scientific quality and clinical usefulness before they are made available.

The same year saw the establishment of two National Genetic Reference Laboratories (Manchester and Wessex) which promote specific research, training and technical-scientific evaluation programmes.

In 2003 the Department of Health published a white paper entitled “Our inheritance, our future – realising the potential of genetics in the NHS” and simultaneously announced the investment of about fifty million pounds to promote the proper use within the NHS of new genetic tests as they become available.

On the 7th of July 2009 the House of Lords Science and Technology Committee published two long reports (totalling almost a thousand pages) under the title “Genomic medicine”. The reports provide an in-depth examination of the problems associated with “genomic medicine” and put forward proposals and recommendations for the different fields based on advances in technology and scientific knowledge: scientific research, application of research to clinical practice, the role of the health service, public participation, ethical issues, the role of computerisation, training, commercialisation, and more besides.

On 8 September 2009 the Human Genetic Commission (HGC) published a document entitled “A common framework of principles for direct-to-consumer genetic testing services. Principles and consultation questions”. This document contains a series of recommendations to protect individuals using

genetic tests, with emphasis on the transparency of information given to consumers and due care in obtaining informed consent. The document was made available for public consultation until 6 December 2009. The final version, taking into account the comments received, is to be prepared during the first half of 2010.

In general, all countries have established some basic requisites, which are also dealt with in professional ethical codes: informed consent as a right of the person undergoing a test and as the duty of the specialist performing it; the right to protection of personal data; the right to refuse to be informed of the results of a test; the rejection of any form of discrimination on genetic grounds. Not all nations have specific regulations on accreditation and quality control for facilities that perform genetic tests: however, control mechanisms of various types are in place virtually everywhere in accordance with national and international documents, recommendations and guidelines. To avoid abuse, the insurance, legal and professional sectors are those most regulated.

3. Some notes on Italy

Among the most recent reference points in Italy mention must be made of the **“Guidelines for medical genetics activities” adopted on the 15th of July 2004 by the Permanent Conference for relations between the State, the Regions and the autonomous Regions of Trento and Bolzano**¹³. This document identifies medical genetics facilities as specialised structures delegated to care for cases of genetic pathologies and defines their activities as distinct from those of other clinical specialisations. The document indicates criteria for the provision of medical genetics services by public and private sector facilities and by laboratories. To implement the Guidelines a Ministerial decree of 8 May 2007 established the “Commission for Genetics in the National Health Service”, one of whose tasks was to define the criteria for the certification and accreditation of medical genetics facilities. The document prepared by the Commission¹⁴ was adopted in the Agreement between the State, the Regions and the autonomous Regions of Trento and Bolzano as “Implementation of the guidelines for medical genetics activities” on 26 November 2009¹⁵.

The ethical and deontological problems posed by genetic tests are also addressed in a number of deontological Codes. Article 46 of the **“Code of Medical Ethics” of the National Federation of the Orders of Physicians, Surgeons and Dentists** (FNOMCeO) addresses the issue of predictive tests and states: “No physician may carry out genetic or predictive tests for insurance or employment purposes unless express and conscious consent has been given by the interested party, who is the only designated recipient of the information. Genetic and predictive tests may be performed only in centres complying with the structural and professional requisites laid down in current national and/or regional regulations”¹⁶.

With regard to the confidentiality of personal data, the **Provision of 22 February 2007 “General Authorisation for the processing of genetic data” by the Italian Authority for the Protection of Personal Data**¹⁷ defines principles, limits and guarantees that apply to the treatment of genetic data.

The Provision applies to all persons who handle genetic data: physicians, public and private sector health facilities, medical genetics laboratories, pharmacists, research agencies and institutes, psychologists and assistants, technicians, defending counsels and, exclusively for the purposes of family reunification, diplomatic or consular officials.

The **Italian Authority for the Protection of Personal Data** calls for the implementation of specific procedures to ascertain without any possible doubt the identity of a subject from whom biological material is collected and requires that this information be held separately from the biological material from the very moment it is collected.

Informed consent is a basic requisite: anyone who handles genetic data is required to ask for consent, which must be in writing and revocable. In accordance with the Provision the interested party must be informed of the objectives pursued, the results obtainable, the length of time for which the data and the biological samples will be stored.

Genetic data and biological samples contained in data banks must be handled using coding technology and the data should be retrievable only through the use of meticulous authentication procedures. The Provision provides that biological samples and genetic data cannot be held for longer than is strictly necessary to attain the objectives for which they were collected and used.

Genetic data cannot be circulated and the results of research can be made public only in aggregate form.

The **Italian Authority for the Protection of Personal Data** also repeats the ban on the use of genetic data by insurance companies and by employers when hiring personnel.

In the case of genetic tests on unborn children, the Provision provides that consent be given by the mother and, if the test can identify the onset of paternal pathologies, also by the father.

The initial authorisation granted by the **Italian Authority for the Protection of Personal Data** was in effect from 1 April 2007 to 31 December 2008 and has been extended twice: up to 31 December 2009¹⁸ and subsequently up to 30 April 2010¹⁹.

4. List of international and supranational institutional documents

The following is a list of the main documents referring to genetic testing published by international and supranational agencies. They are grouped according to the agency of origin and, within each group, in chronological order.

Organization for Economic Cooperation and Development (OCSE)

Organization for Economic Cooperation and Development. 2000. Genetic testing. Policy issues for the new millennium.

Organization for Economic Cooperation and Development. 2007. Guidelines for quality assurance in molecular genetic testing.

United Nations Educational, Scientific and Cultural Organization (UNESCO)

UNESCO: International Bioethics Committee. 1994. Report on genetic screening and testing.

UNESCO: International Bioethics Committee. 1995. Genetic counselling.

UNESCO: General Conference. 1997. Universal Declaration on the Human Genome and Human Rights.

UNESCO: International Bioethics Committee. 2000. Report on Confidentiality and Genetic Data.

UNESCO: General Conference. 2003. International Declaration on Human Genetic Data.

Europe

Council of Europe

Council of Europe: Parliamentary Assembly. 1982. Recommendation 934 (1982) on Genetic Engineering.

Council of Europe: Committee of Ministers. 1984. Recommendation no. R (84) 16 concerning notification of work involving recombinant deoxyribonucleic acid (DNA).

Council of Europe: Parliamentary Assembly. 1986. Recommendation 1046 (1986) on the Use of Human Embryos and Foetuses for Diagnostic, Therapeutic, Scientific, Industrial and Commercial Purposes.

Council of Europe: Parliamentary Assembly. 1989. Recommendation 1100 (1989) on the Use of Human Embryos and Foetuses in Scientific Research.

Council of Europe: Committee of Ministers. 1990. Recommendation No. R (90) 13 on Prenatal Genetic Screening, Prenatal Genetic Diagnosis and Associated Genetic Counselling.

Council of Europe: Committee of Ministers. 1992. Recommendation No. R (92) 3 on Genetic Testing and Screening for Healthcare Purposes.

Council of Europe: Committee of Ministers. 1992. Recommendation No. R (92) 1 on the use of Analysis of deoxyribonucleic acid within the framework of the criminal justice system.

Council of Europe: Committee of Ministers. 1994. Recommendation No. R (94) 11 on screening as a tool of preventive medicine.

Council of Europe: Parliamentary Assembly. 1994. Recommendation 1240 (1994) on the protection and patentability of material of human origin.

Council of Europe 1997. 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.

Council of Europe: Parliamentary Assembly. 2001. Recommendation 1512 (2001) on protection of the human genome by the Council of Europe.

Council of Europe. 2002. Additional protocol to the Convention on human rights and biomedicine concerning transplantation of organs and tissues of human origin.

Council of Europe. 2008. Additional protocol to the Convention on human rights and biomedicine concerning genetic testing for health purposes.

European Union

European Parliament (Temporary Committee on Human Genetics and Other New Technologies in Modern Medicine). 2001. Report on the ethical, legal, economic and social implications of human genetics.

European Parliament and the Council of the European Union. 2004. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

European Commission. 2004. 25 Recommendations on the ethical, legal and social implications of genetic testing.

European Commission. 2004. Ethical, legal and social aspects of genetic testing: research, development and clinical applications / Human genetic testing: what implications? (Conference on the ethical, legal and social aspects of genetic testing. Brussels. 6-7 May 2004)

Council for International Organizations of Medical Sciences (CIOMS)

Council for International Organizations of Medical Sciences. 1990. The declaration of Inuyama. Human Genome Mapping, Genetic Screening and Gene Therapy.

World Medical Association (WMA)

World Medical Association. 1987. World Medical Association Statement on genetic counselling and genetic engineering.

World Medical Association. 1992. World Medical Association Declaration on the Human Genome Project.

World Medical Association. 2005. Statement on genetics and medicine. Adopted by the WMA General Assembly, Santiago, 2005.

World Health Organization (WHO)

World Health Organization. 1998. Proposed international guidelines on ethical issues in medical genetics and genetic services.

World Health Organization. 1998. Statement of WHO expert advisory group on ethical issues in medical genetics.

World Health Organization. 2000. Statement of the WHO expert consultation on new developments in human genetics.

World Health Organization. 2003. Review of ethical issues in medical genetics.

Notes to Attachment 1

¹ United Nations Educational, Scientific and Cultural Organization (UNESCO). Universal declaration on the human genome and human rights. 11 November 1997.

http://portal.unesco.org/en/ev.php-url_id=13177&url_do=do_topic&url_section=201.html.

² United Nations Educational, Scientific and Cultural Organization (UNESCO). International declaration on human genetic data. 16 October 2003.

http://portal.unesco.org/en/ev.php-url_id=17720&url_do=do_topic&url_section=201.html.

³ Organisation for Economic Co-operation and Development (OECD). OECD Guidelines for quality assurance in molecular genetic testing. 2007. <http://www.oecd.org/dataoecd/43/6/38839788.pdf>

⁴ Council of Europe. Recommendation R (92)1 of the Committee of Ministers to member states on the use of analysis of deoxyribonucleic acid (DNA) within the framework of the criminal justice system. 10 February 1992.

<http://wcd.coe.int/com.instranet.instraservlet?command=com.instranet.cmdblobget&instranetimage=573811&secmode=1&docid=601410&usage=2>.

⁵ Council of Europe. Recommendation R(92)3 of the Committee of Ministers to member States on genetic testing and screening for healthcare purposes. 10 February 1992.

<http://wcd.coe.int/com.instranet.instraservlet?command=com.instranet.cmdblobget&instranetimage=573883&secmode=1&docid=601492&usage=2>.

⁶ Council of Europe. Convention for the protection of human rights and dignity of human being with regards to the application of biology and medicine: Convention on human rights and biomedicine. 4 April 1997. <http://conventions.coe.int/treaty/en/treaties/html/164.htm>.

⁷ Council of Europe. Additional protocol on the Convention on Human Rights and Biomedicine concerning Biomedical Research. Strasbourg: Council of Europe; 2005. <http://conventions.coe.int/treaty/en/treaties/html/195.htm>.

⁸ European Group on Ethics in Science and New Technologies on advertising genetic tests via the internet. 24 February 2003.

http://ec.europa.eu/european_group_ethics/docs/statement_ege_advertising_genetic_en.pdf.

⁹ European Commission. The 25 recommendations on the ethical, legal and social implications of genetic testing. Conference on the ethical, legal and social aspects of genetic testing. Brussels, 6-7 May 2004).

http://europa.eu/comm/research/conferences/2004/genetic/pdf/recommendations_en.pdf.

¹⁰ European Commission. Ethical, legal and social aspects of genetic testing: research, development and clinical applications (Conference on the ethical, legal and social aspects of genetic testing. Brussels, 6-7 May 2004).

http://ec.europa.eu/research/conferences/2004/genetic/pdf/report_en.pdf.

¹¹ Comité Consultatif National d'Éthique pour les Sciences de la Vie et de la Santé. Avis 46. Avis et recommandations sur "Génétique et médecine: de la prédiction à la prévention". Rapport. 30 Octobre 1995. www.ccne-ethique.fr/docs/fr/avis046.pdf.

¹² Conselho Nacional de Ética para as Ciências da Vida. Parecer sobre venda directa de Testes Genéticos ao público. 56/CNECV/2008.

www.cnecev.gov.pt/nr/ronlyres/e05fc1fd-51e5-462f-be0a-df3bbe59f9e7/0/p_056cnecev.pdf.

¹³ Conferenza Permanente per i Rapporti tra lo Stato, le Regioni e le Province autonome di Trento e di Bolzano. Accordo tra il Ministro della Salute, le Regioni e le Province autonome di Trento e di Bolzano sul documento recante: "Linee-guida per le attività di genetica medica" (Accordo ai sensi dell'articolo 4 del decreto legislativo 28 agosto 1997, n. 281. Repertorio atti n. 2045). 15 luglio 2004. *Gazzetta Ufficiale della Repubblica Italiana* - Serie generale, n. 224, 23 settembre 2004.

¹⁴ Ministero del Lavoro, della Salute e delle Politiche Sociali (Dipartimento della Qualità, Direzione Generale della Programmazione Sanitaria, dei Livelli Essenziali di Assistenza e dei Principi Etici di Sistema). Commissione Ministeriale per la Genetica nel Servizio Sanitario Nazionale. Relazione. 2008. www.ministerosalute.it/imgs/C_17_publicazioni_908_allegato.pdf.

¹⁵ Conferenza Permanente per i Rapporti tra lo Stato, le Regioni e le Province autonome di Trento e di Bolzano. Accordo tra il Governo, le Regioni e le Province autonome di Trento e Bolzano sul documento recante "Attuazione delle linee guida per le attività di genetica medica" (Lavoro, Salute e Politiche Sociali). Accordo ai sensi dell'articolo 4 del decreto legislativo 28 agosto 1997, n. 281. Repertorio Atti n. 241/CSR del 26 novembre 2009.

¹⁶ Federazione Nazionale degli Ordini dei Medici Chirurghi e Odontoiatri (FNOMCeO). Codice di deontologia medica. 2006.

www2.fnomceo.it/PortaleFnomceo/downloadFile.dwn?id=60474&version=0.

¹⁷ Garante per la Protezione dei Dati Personali. Provvedimento 22 febbraio 2007. Autorizzazione generale al trattamento dei dati genetici. *Gazzetta Ufficiale della Repubblica Italiana* - Serie generale, n. 65, 19 marzo 2007.

¹⁸ Garante per la Protezione dei Dati Personali. Deliberazione 19 dicembre 2008. Differimento dell'efficacia dell'autorizzazione al trattamento di dati genetici rilasciata il 22 febbraio 2007. *Gazzetta Ufficiale della Repubblica Italiana* - Serie generale, n. 15, 20 gennaio 2009.¹⁹ Garante per la Protezione dei Dati Personali. Deliberazione 22 dicembre 2009. Ulteriore differimento dell'efficacia dell'autorizzazione al trattamento di dati genetici rilasciata il 22 febbraio 2007. *Gazzetta Ufficiale della Repubblica Italiana* - Serie generale, n. 11, 20 gennaio 2010.

ATTACHMENT 2

Agreement between the Government, the Regions and the autonomous Provinces of Trento and Bolzano on "Implementation of the guidelines for medical genetics activities" (Labour, Health and Social Policies)

Agreement pursuant to Article 4 of Legislative decree no. 281 of 28 August 1997.

Register of Acts no. 241/CSR of 26 November 2009

THE PERMANENT CONFERENCE FOR RELATIONS BETWEEN THE STATE, THE REGIONS AND THE AUTONOMOUS PROVINCES OF TRENTO AND BOLZANO

In the session of this day, 26 November 2009:

HAVING REGARD TO Articles 2 para 2(b) and 4 para 1 of Legislative Decree no.281 of 28 August 1997, which charge this Conference with the task of promoting and ratifying agreements between the Government and the Regions in implementation of the principle of loyal cooperation, in order to coordinate the exercise of their respective responsibilities and perform activities of common interest;

HAVING REGARD TO the Agreement between the Ministry for Health, the Regions and the autonomous provinces of Trento and Bolzano regarding the "Guidelines for medical genetics activities" ratified by this Conference in the session of 15 July 2004 (Register no. 2045);

HAVING REGARD TO the note received on 30 January 2009 in which the Ministry of Labour, Health and Social Policies, for the purposes of finalising a special agreement in this Conference, forwarded a document entitled "Implementation of the guidelines for medical genetics activities"

HAVING REGARD TO the letter dated 4 February 2009 in which the document in question was circulated to the Regions and autonomous Provinces;

WHEREAS, as agreed during the relevant technical meeting held on 3 March 2009 the Tuscany Region, interregional coordinator for health, distributed a document regarding the proposals by the Regions and autonomous Provinces to amend the document in question;

BEARING IN MIND that, during a further technical meeting held on 28 May 2009, the representatives of the Ministry of Labour, Health and Social Policies reserved the right to forward a new version of the proposed agreement;

WHEREAS the matter in question, entered on the agenda of the session of this Conference on 29 October 2009, was postponed at the request of the Regions and the autonomous Provinces;

HAVING REGARD TO the final version of the proposal for agreement transmitted by the Ministry of Labour, Health and Social Policies on 11 November 2009;

HAVING REGARD TO the letter of 17 November 2009 with which the final version was transmitted to the Regions and autonomous Provinces;

HAVING REGARD TO the note of 18 November 2009 in which the Tuscany Region, interregional Coordinator for Health, expressed a favourable technical opinion regarding the final version of the proposal for agreement;

HAVING ACCEPTED, during today's session, the assent of the Government and of the Presidents of the Regions and of the autonomous Provinces;

RATIFIES THE AGREEMENT

Between the Government, the Regions and the autonomous Provinces, as follows:

WHEREAS

- Legislative Decree no. 502 of 30 December 1992 and subsequent amendments and, in particular, Article 10, establishes the routine adoption of the method for the control and review of the quality and quantity of the services to be developed in accordance with the organisational models and information flows of the provider; and Article 8-octies provides for the Regions and local Health Units to put in place a system to monitor and control the definition of and compliance with the contractual agreements of all the interested parties, as well as the quality of care and the appropriateness of the services offered;

- The Presidential Decree of the 14th of January 1997 "Approval of the Act of guidance and coordination of the Regions and autonomous Provinces of Trento and Bolzano regarding the minimum structural, technological and organisational requirements for the practice of healthcare activities by public and private sector facilities" defines the activities of evaluation and quality improvement in methodological terms and establishes that the general requisites required of public and private facilities include possession of a series of processes and procedures for the management, evaluation and improvement of quality;

- The Decree of the President of the Council of Ministers of 28 November 2001 "Definition of Basic Levels of Healthcare" indicates the need to identify in-patient and out-patient diagnostic workups and treatment courses;

- the Presidential Decree of 7 April 2006 "Approval of the 2006-2008 National Health Plan" identifies the objectives to be attained in order to implement the constitutional guarantee of the right to health and other social and civil rights in regard to health, and in particular para. 3.3 sets out to create a system for cooperation between different Health Systems through the establishment of referral centres to address the problems associated with rare diseases and pathologies requiring highly specialised care;

- the Agreement between the Ministry of Health, the Regions and the autonomous Provinces of Trento and Bolzano regarding the "Guidelines for medical genetics activities" ratified by this Conference in the session of 15 July 2004 (Register no. 2045) has approved the "Guidelines for medical genetics activities";

- the Ministerial Decree of 8 May 2007 establishes the "Commission for Genetics in the National Health Service" for the purpose of implementing the guidelines for genetic medical activities approved by the State-Regions Conference on 15 July 2004, lays down the criteria for the institutional certification and accreditation of Facilities for Medical Genetics, defines the Medical genetics activities that permit the best use of the resources available to the National and Regional Health Service by providing appropriate indications concerning the use of genetic tests and determining the forms of linkage with the rare diseases network, defines the indicators and evaluates the commissioning, as well as the overall economic assessment of medical genetics activities, establishes the rules for the publication and promotion of

genetic testing and genetic counselling, and publishes recommendations based on scientific evidence regarding medical genetics;

- it is intended to follow up the indications contained in the Commission's document, particularly with regard to implementation of the Guidelines for medical genetics activities approved in the Agreement;

IT IS AGREED

1. Considering that genetic tests are an important diagnostic tool involving a preliminary clinical assessment of the indications for their performance and a subsequent interpretation of their results with the involvement not only of the individual undergoing the test but also of family members, the Regions undertake to:

- promote and adopt diagnostic-care workups in accordance with scientifically validated guidelines (with particular reference to the "Guidelines for medical genetics activities", 2004) that include appropriate pre- and post-test genetic counselling and the provision of comprehensive and exhaustive information to patients and family members. These workups, based on solid scientific evidence, must aim to guarantee the appropriateness and quality of the services provided;

- implement systems to monitor the services that are able, using suitable indicators, to define the clinical and healthcare impact of the activities, their appropriateness, efficacy, efficiency and safety, in order to be able to measure the work volume of facilities and the quality in organisational, management, professional and technical terms;

- launch a genetic activities plan that identifies the optimum geographical distribution and characteristics of accredited facilities and their adequate organisational setup, in order to channel cases towards facilities and operators able to guarantee an adequate work volume combined with constant updating of know-how and technology;

- adopt where these are not provided in the relative regional regulations, procedures for the accreditation of facilities offering medical genetics services (laboratories and clinical facilities) that include specific criteria, including the acceptance of external quality controls and certification mechanisms;

- integrate medical genetics services into healthcare networks already operating in the same fields on a regional and interregional basis (with particular attention to rare diseases, maternal-paediatric care and oncological diseases),

1. The Ministry, the National Health Institute, the Regions and the autonomous provinces of Trento and Bolzano, supported by Scientific Associations – and in particular by the Italian Society for Human Genetics (SIGU) – undertake to ensure that;

- the public is properly informed, through institutional and other media, of the use and efficacy of genetic tests, in order to avoid their improper use;

- the public receives information that is always correct and up-to-date concerning the limitations and the obligations imposed by current provisions regarding the treatment of data of a genetic nature;

- internationally validated institutional websites are identified to assist in the circulation of correct information and to permit access to accredited and/or certified facilities.

The present document in no way modifies the basic levels of healthcare pursuant to the Decree of the President of the Council of Ministers of 29 November 2001 and does not determine any additional expense, being limited to identifying appropriate procedures for the proper provision of medical genetics services within the National Health Service.

THE SECRETARY

THE PRESIDENT

ATTACHMENT 3

Genetic testing in Italy

Italy is the only country that can boast the monitoring of genetic testing since the 1980s and, more recently, the overall monitoring of the activities of medical genetics facilities. The surveys were carried out by the Italian Associations of Medical Cytogenetics (AICM) and of Medical Genetics (AIGM) until the end of the 1980s and since 1998 by the Italian Society of Human Genetics (SIGU).

The 2007 census of Italian medical genetics facilities was entrusted by the SIGU to the Mendel Institute (Dallapiccola et al, 2009) and followed three years after the preceding census (Dallapiccola et al, 2006): its aim was to describe the demand for and supply of genetic services performed by these facilities in Italy.

The 2007 census involved University Institutes, Institutes of Care and Scientific Research (IRCCS), Hospitals, local health centres, National Research Council laboratories and private laboratories. Data were collected between May and September 2008 by means of a self-administered on-line questionnaire; the information covered the type and general details of each structure, cytogenetic, genetic-molecular and immunogenetic diagnoses and clinical activities (genetic counselling), as well as the procedures for quality management and for assessing the appropriateness of certain tests. The facilities questioned were those already registered in earlier censuses (updated each year) and others recruited via internet or which participated spontaneously thanks to a national campaign through scientific conventions, the SIGU website and word of mouth. The results are estimated to cover at least 95% of the facilities operating in Italy.

The 2007 census recorded the activities of 388 laboratories for cytogenetic, molecular genetic and immunogenetic diagnosis and 102 facilities for clinical genetics operating within 278 structures (including 83 hospitals, 72 universities, 45 private facilities, 38 IRCCS, 29 local health centres) which, at the time of the census, employed a total of 2,748 people.

Of the 278 facilities questioned, 108 were accredited with the National Health Service (39%) and 62 (22%) were in the process of applying for accreditation. With regard to quality management, 79 (28%) facilities were certified in accordance with ISO-9001 regulations and 31 (11%) were in the process of being certified; 27 (10%) were accredited in accordance with ISO-15189 and ISO-17025 regulations and 37 (14%) were in the process of accreditation. Only 96/278 (34.5%) facilities had taken part in external quality assessment procedures.

The total number of genetic tests performed in 2007 was about 560,000, including 311,069 cytogenetic tests (148,380 post-natal and 162,689 prenatal) and 227,878 molecular genetic tests (215,551 postnatal and 12,327 prenatal) and 20,813 immunogenetic tests. Over the same period a total of 70,154 persons received genetic counselling.

All the data collected confirmed a decreasing trend in all types of activity from the north of Italy to the south and islands. For example, 46% of cytogenetics laboratories were situated in northern regions, compared with 20% in the south and 11% in the islands: the picture was similar both for molecular genetics laboratories, with 50% in the north and 22% in the south, and for clinical genetics facilities, 55% of which were located in the north and 17% in the south. While 64% of the facilities operating in the north were certified for quality control, the figure for the south was 12%.

The 2007 census confirmed a factor that had emerged in the 2004 census, namely that a plateau had been reached in regard to invasive prenatal diagnoses. In effect, the number of prenatal cytogenetic diagnoses (127,919, of which 101,750 on amniocytes, 25,691 on trophoblasts and 478 on foetal blood) was only slightly higher than the number recorded in 2004, indicating that in 2007 more than one pregnancy in every 5 in Italy had been monitored using an invasive technique.

The overall number of molecular tests (227,878) revealed a significant increase compared with 2004 (190,610), although this increase was less marked than in other European countries. The number of disease genes analysed, fewer than 500, was low in comparison with the general diagnostic capacity of about 1,500 genes. In addition, 67% of the molecular diagnostic tests concerned 10 disease genes and 91 out of 201 molecular genetics laboratories (45%) had performed fewer than 500 tests during 2007; 61 out of 171 cytogenetics laboratories (35%) had performed fewer than 1,000 tests.

The number of prenatal molecular tests (12,327) was only apparently lower than that recorded in 2004 (20,342), due to the fact that one private facility that handles a significant portion of these tests (mostly services 'bought' by couples not at risk simultaneously with cytogenetic tests) did not take part in the census. One thousand and four diagnoses of genetic deafness were found to be commercially driven, as were 848 of X-linked mental retardation and 340 of Duchenne muscular dystrophy. The same applied to 1,276 prenatal tests to identify Y chromosome microdeletions (the consequences of which are limited to male infertility) and 14 prenatal paternity tests.

Of particular significance were the results of studies focusing on 6 diseases used to define the appropriateness of tests. Only 2.82% of tests for Williams syndrome (deletion of 7q11.23), 3.34% of those for DiGeorge/velo-cardio-facial syndrome (deletion of 22q11.2), 4.17% of tests for fragile X mental retardation (FMR1 gene) and 8.83% of tests for Angelman syndrome (anomalies in the 15q11-13 region) were positive. These figures underscore the urgent need to invest in clinical training for those prescribing genetic tests.

Requests for testing to identify susceptibility to complex diseases appears still limited to a small diagnostic niche; exceptions to this rule are the over 65,000 tests relating to 7 genes in which mutations may lead to a risk of thrombophilia and the more than 27,000 tests involving the major histocompatibility complex (HLA), which in any case account for about 37% of all molecular diagnoses performed in 2007.

A separate mention should be made of the introduction and application to diagnostics, in some laboratories, of new technological platforms. The year 2007 saw the performance in 24 laboratories of 1,443 postnatal and 393 prenatal cytogenetic diagnoses based on array comparative genomic hybridisation (high resolution genomic tests). The use of these techniques in prenatal diagnosis is especially interesting, bearing in mind that no guidelines are yet available and that the intrinsic features of these tests, which often analyse common genomic variations, call for extreme caution in their interpretation, given that many of the variations are not associated with pathological clinical manifestations. The popularity these tests are gaining underscores the excessive casualness with which translational technologies are invading the health market, suggesting the desirability of dedicated studies by scientific societies, as well as highlighting the need for greater vigilance by the supervisory authorities.

The total number of genetic counselling cases recorded in 2007 was low in comparison with the volume of laboratories' diagnostic activities. Only 11.5% of chromosome tests and 13.5% of molecular genetic tests were accompanied by genetic counselling. These figures are virtually unchanged in comparison with those of the preceding census and show how little attention is paid in Italy to national and international guidelines.

The results gleaned from the 2007 census permit the following conclusions to be drawn:

- there is a marked decline in the activity of medical genetics facilities from the northern regions towards the south and islands;
- the increase in the number of genetic tests is relatively small in comparison with trends in other countries;
- the number of diagnostic laboratories continues to rise without justification and the total (388) is higher than that of any other country with a similar population; the need to rationalise the costs of diagnosis and to improve quality suggests that an overhaul of the diagnostics network should be carefully considered;
- the number of facilities that are certified/accredited in accordance with ISO regulations (about 40%) is low, as is the number of facilities that have taken part in external quality control programmes;
- prenatal diagnosis using invasive techniques (amniocentesis, villocentesis, cordocentesis), has reached a plateau in Italy, with an average of more than 1 pregnancy in 5 being monitored;
- more than two thirds of total molecular genetic tests concerned 10 genes, suggesting that the reorganisation and coordination of services should be seriously considered;
- molecular tests for genes associated with susceptibility to complex diseases (which are often of little or no clinical relevance) are still less frequently requested in Italy than in other countries, especially the USA;
- the use of new high-resolution technological platforms (e.g. some arrays), which have already invaded the delicate field of prenatal diagnoses, should be carefully monitored, and indicates a need for scientific Associations to draw up agreed guidelines and for oversight authorities to supervise the rationality and reliability of their use;

- the appropriateness of tests as evaluated by reference to six diseases shows that physicians have great difficulty making the right clinical diagnosis even when relatively common genetic disorders are involved;

- the use of genetic counselling in association with genetic tests (<13%) was scant, out of line with the recommendations contained in national (State-Regional Conference, 15 July 2004) and international (OECD, 2007) guidelines.

ATTACHMENT 4

Medical devices

Advisory Committee for the granting of licenses to advertise health products

The Committee of experts was established by Article 201 of the health code and its composition is currently disciplined by Article 4 of Presidential Decree no.86 of 14 May 2007; the committee is the advisory body of the Ministry of Labour, Health and Social Policies with responsibility in the field of advertising all the following health products:

- medicines
- medical/surgical devices
- mineral waters
- veterinary medicines
- all means of prevention or treatment advertised as such

GENERAL

Advertising of health products
(Article 21 of Legislative Decree no.46 of 24/2/97)

Application for authorisation to advertise health products must be submitted, complete with revenue stamp, by the manufacturer or the person responsible for the marketing of a product and must include exhaustive information regarding the producer, the product to be advertised, the type of advertising and the media to be used. Applications should be addressed to:

Ministero della Salute
Dipartimento dell'Innovazione
Direzione Generale dei farmaci e dei dispositivi medici – Ufficio II
Via Giorgio Ribotta, 5
00144 Roma

One of the following advertising media should be indicated:

1. Short film for tv or cinema
2. Radio spot
3. Daily newspapers or periodicals
4. Outlet poster: shop window sign, display, flier, brochure distributed in pharmacies
5. Billboards, posters
6. Other

ATTACHMENT 5

Documents on genetics published by the NBC

- Dalla farmacogenetica alla farmacogenomica (From pharmacogenetics to pharmacogenomics) (21 April 2006)
- Terapia cellulare del Morbo di Huntington attraverso l'impianto di neuroni fetali (Foetal neurone implants as cell therapy for Huntington's Disease) (20 May 2005)
- Parere del CNB sulla bozza di Protocollo sulla genetica umana (Opinion of the CNB on the draft Protocol on human genetics) (6 March 2002)
- Considerazioni etiche e giuridiche sull'impiego delle biotecnologie (Ethical and legal considerations on the use of biotechnology) (30 November 2001)
- Protocollo europeo sulla ricerca biomedica (European protocol on biomedical research) (19 November 1999)
- Orientamenti bioetici per i test genetici (Bioethical guidelines for genetic testing) (19 November 1999)
- Parere su "Convenzione per la protezione dei diritti dell'Uomo e la biomedicina" (Opinion on the "Convention for the protection of human rights and biomedicine) (Council of Europe) and Bozza preliminare di dichiarazione universale sul genoma umano e i diritti umani (Preliminary draft universal declaration on the human genome and human rights)(UNESCO) (21 February 1997)
- Progetto genoma umano (Human genome project) (18 marzo 1994)
- Documento sulla sicurezza delle biotecnologie (The safety of biotechnologies) (28 May 1991)
- Terapia genica (Gene therapy) (15 February 1991)

Documents on genetics published by the NBBLSC

Year 2006:

- Biotecnologie Bianche (White biotechnology) (5 May 2006)
- Bionanotecnologie (Nano biotechnology) (2006)
- Biotecnologie industriali (Industrial biotechnology) (December 2006)
- Metodologie per la corretta informazione e comunicazione sulle biotecnologie e le scienze della vita (Procedures for correct information and communication regarding biotechnology and life sciences)

Year 2005:

- Linee guida per lo sviluppo delle biotecnologie in Italia (Guidelines for the development of biotechnologies in Italy)
- Studio delle possibilità di modifica normativa sul prelievo coattivo di materiale biologico ai fini della determinazione del DNA e dell'istituzione dell'Archivio Centrale del DNA a fini forensi (Study of possible regulatory amendments regarding forced collection of biological material to test DNA and the establishment of a Central DNA Archive for legal purposes)

Year 2003:

- Protocolli tecnici per la sperimentazione in regime di sicurezza delle attività di ricerca e di sperimentazione riguardanti gli OGM in campo agricolo (Technical protocols for safe experimentation and research regarding GMOs in agriculture)

Year 2002:

- Infrastrutture e network di eccellenza a livello europeo nel campo della biosicurezza e delle biotecnologie (European infrastructures and networks of excellence in the fields of biosafety and biotechnology)

Year 1999:

- Parere sull'attuazione della Direttiva 98/44/CE sulla protezione giuridica delle invenzioni biotecnologiche (Opinion concerning EU Directive 98/44/EC on the legal protection of biotechnological inventions)

Year 1998:

- Aspetti regolatori della terapia genica: guida ai produttori e agli utilizzatori (Regulatory aspects of gene therapy: guide to producers and consumers)
- Linee guida per test genetici (Guidelines for genetic testing)

Documents on genetics published by the Ad Hoc Joint Group

- Test genetici e assicurazioni (Genetic testing and insurance) (20 October 2008)
- Raccolta di campioni biologici e le biobanche: consenso informato (Collection of biological samples and biobanks: informed consent) (July 2009)

GLOSSARY

Achondroplasia - A form of rhizomelic dwarfism (1:25,000) caused by an autosomal dominant mutation in the FGFR3 gene.

Adult onset polycystic kidney disease – Autosomal recessive disease that usually becomes clinically apparent in adults; it has a frequency of approximately 1:1000, is heterogeneous with two principal known loci; it consists in progressive degeneration of the kidney and formation of cysts, sometimes extending to other organs.

Allele - An alternative form of a gene that occupies the same position on a pair of homologous chromosomes.

Association - The occurrence of a particular allele in a group of individuals with a greater frequency than can be readily explained.

Autosomal trait - Linked to non-sex chromosomes.

Autosomal inheritance - Transmission of a trait or of a disease through a gene located on a non-sex chromosome.

Autosome - Any of the 22 non-sex chromosomes.

Bacteriophage (phage) - A virus that infects bacteria.

Band - Chromosome region of a lighter or darker colour than adjacent regions, highlighted on chromosomes treated with specific dyes or after chromosome denaturation; also the dark area at autoradiography representing the localisation of alleles on a gel.

Base - the hydrogen base of nucleic acid molecules (A=adenine, T=thymine, U=uracil, (C=cytosine, (G=guanine).

Beta thalassaemia - Hereditary haemoglobinopathy marked by reduced beta chain production, present in certain geographical areas, notably the Mediterranean and the Indian sub-continent

Carrier - A male or female who is heterozygous for a recessive gene or for a balanced chromosome translocation, or a female who is heterozygous for an X-linked mutation.

Cascade screening - Identification of carriers of a recessive mutation or autosomal dominant gene, females heterozygous for X-linked recessive mutations, or carriers of balanced chromosome rearrangements through systematic testing of a family.

CentiMorgan (cM) - The unit used to measure map distances, corresponding to 1% recombination.

Chorion (chorionic villi) - The structure that covers a fertilised egg, the villous portion of which becomes the placenta (see trophoblast).

Chromosomal aberrations (chromosomal mutations) - Anomalies in the number or structure of chromosomes, visible under the microscope; these may affect germinal or somatic cells, leading respectively to constitutive or acquired pathological phenotypes.

Chromosome - A dark, thread-like structure in the cell nucleus, composed of DNA and chromatin and that carries genetic information.

Chromosome analysis - The study of the number and structure of chromosomes.

cM - Abbreviation for centiMorgan.

Common disease - Pathology that occurs frequently in the population (e.g. cancer, coronary disease, diabetes, etc.).

Compound heterozygote - Person who has an autosomal recessive disease caused by two different allelic mutations.

Congenital - A genetic or non-genetic anomaly present at birth.

Consanguineous mating - Between persons who have one or more ancestors in common.

Consanguinity - The relationship between relatives.

Contiguous gene syndromes - Disorders caused by the deletion (or duplication) of genes that are physically close on the chromosome.

Continuous traits - A trait, such as height, that is present in a range of observations or phenotypes in the population and is presented by every person, in contrast to discontinuous traits, which are found on an “all or nothing” basis, i.e. they are present only in certain persons.

Counselee - A person receiving genetic counselling.

Crohn's disease - Chronic inflammatory disease of the intestine.

Cystic fibrosis - Autosomal recessive hereditary disorder due to a mutation in the CFTR gene; the intestines, pancreas, liver and lungs are variously affected.

Cytogenetics - Branch of genetics concerned with the study of chromosomes.

Cytoplasm - The part of the cell that contains the nucleus, the endoplasmic reticulum, mitochondria, etc.

De novo mutation - A genetic mutation that is not inherited.

Deoxyribonucleic acid - See DNA.

Diploid - Of a cell that has two sets of haploid chromosomes; the normal state of somatic cells, in which the diploid number (2n) is 46.

Discontinuous (trait) - An “all or nothing” trait, e.g. cleft palate, unlike a continuous trait, e.g. height.

Discontinuous traits - Traits that obey the “all or nothing” law (e.g. harelip), in other words they are present only in certain persons, unlike continuous traits (such as height).

Disease gene - A gene that is responsible for a hereditary disease.

DNA - Deoxyribonucleic acid: nucleic acid present in chromosomes, in which genetic information is coded.

DNA probe - Sequences, usually marked with radioactive isotopes, used to identify a gene (e.g. genomic or cDNA probes).

Dominant - Trait that is expressed also in heterozygotes.

Down syndrome - Clinical condition linked to chromosome 21 trisomy.

Duchenne muscular dystrophy - Muscular disease linked to the X chromosome that affects 1:3500 males on average and reduces life expectancy.

Dysmorphology - The science of malformations.

Dystrophin - Product of the DMD gene.

Empirical risk - Risk of recurrence of a multifactorial disease.

Enzyme - A protein that acts as a catalyst in biological systems.

Epistasis - Phenomenon in which the effect of one gene is modified by the action of one or several other genes that are often called modifier genes.

Eugenics - The “science” that promotes the improvement of hereditary qualities in a population or species.

Euploidy - Condition of a cell or an organism characterised by a number of chromosomes corresponding to an exact multiple of the haploid set.

Exon - Region of a gene that is not excised during transcription; forms part of mature mRNA and is thus part of the primary structure of gene products.

Expression - Variation in the degree of externalisation of a phenotype of a particular gene.

Familial colonic polyposis - A disease that predisposes to cancer of the intestine, caused by an autosomal dominant mutation; primitive lesions are polyps that tend to degenerate.

First-degree consanguinity - Genetically closest relatives, sharing 50% of their genes (e.g. parents-offspring, siblings).

FISH (Fluorescent In Situ Hybridisation) - Cytogenetic diagnostic technique that uses single-strand DNA sequences, marked with a fluorochrome, that bind specifically to complementary sequences on chromosomes and can be recognised using an UV light microscope.

Gamete - Germ cell (spermatozoon or oocyte) that contains a haploid (n) number of chromosomes

Gene - A part of the DNA molecule of a chromosome that directs synthesis of a specific polypeptide chain.

Gene therapy - Treatment of hereditary disorders through the addition, insertion or substitution of one or more genes in normal cells.

Genetic code - Triplets of DNA nucleotides coding for different amino acids.

Genetic counselling - The service that offers information concerning genetic disorders, their diagnosis, mechanisms of onset, the risks of occurrence or recurrence and options to contain or prevent them.

Genetic heterogeneity - Phenomenon whereby a genetic disease is caused by many different allelic or non-allelic mutations.

Genetic susceptibility - Hereditary predisposition to develop a disease, due not to a single genetic cause but to a complex interaction between different genes (polygenic heredity).

Genetic variance - Phenotypic variation due to the presence of different genotypes in the population.

Genome - All the genes in a cell.

Genomic DNA . The full complement of DNA contained in chromosomes.

Genotype - Genetic makeup of an individual.

Haemophilia - Disease characterised by blood coagulation deficiency caused by little or no production of a clotting factor. The two most common forms, haemophilia A and B, are linked to chromosome X and are caused respectively by deficiency in factor VIII and factor IX clotting factor.

Haemoglobinopathy - A hereditary disease of haemoglobin.

Haploid - The condition of a cell that contains half the set of chromosomes of a somatic cell: in humans the haploid number (n) present in normal gametes is 23.

Haplotype - Variants in DNA sequence on a particular chromosome near to a locus of interest.

Hemizygous - The male genotype; males have only one X chromosome.

Heritability - The percentage of total variability of a trait attributable to the genetic component rather than to the environmental component; in other words, the hereditary component of a complex trait.

Heterozygote - A person who has two different alleles at a specific locus, on a pair of homologous chromosomes.

HLA (Human Leukocyte Antigen) - Identifies tissue antigens.

Homologous chromosomes - Chromosomes that appear during meiosis and contain the same loci

Homozygote - A person who has identical alleles at a specific locus on a pair of homologous chromosomes.

Human genetics - Branch of genetics that studies aspects of direct interest for humans, including medical genetics and differences in human beings.

Human genome project - An internationally coordinated effort to map and sequence the entire human genome.

Huntington's chorea - An autosomal dominant neurodegenerative disease, usually with adult onset, caused by expansion of a CAG triplet on the HTT gene.

Inborn error of metabolism - Hereditary defect of metabolism that causes an anomalous deficit in the production or synthesis of an enzyme.

Insulin-dependent diabetes mellitus - Diabetes controlled by using insulin, usually with early onset, known as Type 1 diabetes.

In vitro - Literally "in glass", i.e. in the laboratory.

In vivo - Literally "in a living organism", i.e. in a normal cell.

Karyotype - The array of chromosomes in a cell.

Kb - Abbreviation of kilobase.

Kilobase - 1000 base pairs.

Late onset - Defines phenotypes not present at birth, which become evident in adulthood.

Law of segregation - Each person has two genes for a particular trait, only one of which is transmitted to offspring at each conception.

Linkage - Synonymous with association between genes, loci, markers; when two loci are physically very close on the chromosome they tend to be transmitted together in gametes.

Linkage disequilibrium - Tendency of two or more alleles at closely linked loci to be together more frequently than expected.

Locus - The location of a gene on a chromosome (plural *loci*).

Low penetrance - Dominant gene that is not manifest in a percentage of heterozygotes.

Major histocompatibility complex or HLA - Genes on chromosome 6 that code for cell surface antigens that are important in organ transplants.

Malformation - Primitive structural defect of an organ or part of an organ caused by a developmental anomaly.

Mapping/Chromosome mapping - Localisation of a gene or of a sequence of DNA to a specific chromosome or region.

Maternal or mitochondrial inheritance - Transmission of a mitochondrial trait, exclusively through the mother.

Mb - Megabase, corresponding to 1 million bases.

Medical genetics - Branch of genetics that studies the hereditary bases of diseases.

Mendelian inheritance - Inheritance that follows the laws of segregation and independence proposed by Mendel.

Messenger RNA - Single-helix molecule complementary to one of the strands of double-helix DNA that is synthesised during transcription and transfers information from the nucleus to cytoplasmic ribosomes and acts as a template for protein synthesis.

Microdeletion - Small chromosome deletion that is apparent on chromosomes amplified in the prophase or using molecular cytogenetic techniques (FISH).

Mitochondrial DNA (mtDNA) - Genetic material contained in the mitochondria that codes for enzymes involved in reactions that supply energy; mutations in mtDNA are the cause of disease.

Mitochondrion - A structure in the cytoplasm of cells that is responsible for cell respiration.

Mosaicism - Describes a person who has two or more cell lines originating from a single zygote.

Mucoviscidosis - Term formerly used to describe cystic fibrosis.

Monofactorial (monogenic) - Trait controlled by a single gene.

Multifactorial disease - Common disease considered secondary to the additive effect of polymorphic mutations and the environment.

Multifactorial inheritance - Inheritance controlled by more than one gene with additive effects (polygenic) and by the environment.

Mutagen - Chemical or physical agent that increases mutation rates, causing permanent DNA modifications.

Mutant - Gene that has been changed or mutated.

Mutation - Modification of the genetic makeup, whether affecting a gene or the number or structure of a chromosome; mutations that occur in gametes are hereditary, those of somatic cells are non-hereditary.

Myotonic dystrophy - Disease marked by difficulty in muscle relaxation; frequency is about 1:10,000; there are various forms, the most common being Steinert's disease, an autosomal dominant form caused by a repeat of a CTG triplet in the DMPK gene.

New mutation - A mutation of a gene that is not inherited.

Non-paternity - The biological father is not the person indicated.

Non-polyposis colorectal cancer - Familial cancer in which those at risk of developing the tumour have no polyps and the tumour is not preferentially proximal or right-sided.

Nucleotide - Elementary structure of nucleic acids; each nucleotide consists of a nitrogenous base, a sugar and a phosphate group.

Nucleus - Cell structure containing the chromosomes and the nucleolus.

Obligate heterozygote - Heterozygosity at a locus in the offspring of a homozygote; heterozygosity in the daughter of a hemizygous father, caused by a recessive X-linked mutation.

Oligonucleotide - A chain of a few nucleotides.

Penetrance - The percentage of heterozygotes for a dominant mutation that express a trait.

Pharmacogenetics - Branch of genetics that studies genetic variations in drug metabolism.

Phenocopy - Condition caused by environmental factors that resembles another genetically caused condition.

Phenotype - The (physical, biochemical and physiological) aspect of a person, due to the interaction of the genotype with the environment.

Pleiotropy - Multiple effects of a single gene.

Polygenes - Genes that contribute a small additive effect to a polygenic trait.

Polygenic inheritance - Genetic contribution to the aetiology of diseases caused by more than one gene.

Polymorphism - A common mutation with a population frequency $\leq 1\%$.

Polypeptide - Organic compound consisting of three or more amino acids.

Predictive test - Test to measure the susceptibility or resistance of a person to a disease (usually with late onset) in relation to the average of the general population.

Preimplantation diagnosis - In vitro identification of the genotype of a hereditary disease in the product of conception, before implantation.

Prenatal diagnosis - Tests performed during pregnancy to determine whether the embryo or the foetus has inherited a genetic disorder.

Presymptomatic diagnosis - Tests to determine if a person has inherited a gene disorder, before clinical symptoms are present.

Presymptomatic test - Tests to determine if a person has inherited a disease gene before clinical symptoms appear.

Prevalence - The percentage of persons who at a given moment and in a specific population present a particular trait.

Proband (index case) - An affected individual who draws medical attention to a family.

Probe - A marked fragment of single-stranded DNA that hybridises to DNA to enable identification and localisation of complementary sequences in different DNA fragments.

Prokaryote - An organism that does not have a cell nucleus.

Protein - Complex organic compound consisting of hundreds or thousands of amino acids.

Recessive - Of a trait that is expressed only in homozygotes.

Relative risk - The frequency with which a disease occurs in the presence of a specific marker in comparison with the frequency of the same marker in the general population, in other words among healthy persons.

Rhizomelic dwarfism - Dwarfism characterised by short limbs.

Ribonucleic acid - See RNA.

Ribosomal RNA - RNA molecule that helps bind mRNA and tRNA to ribosomes; together with protein molecules, forms the ribosome.

RNA - Nucleic acid present in the nucleolus and ribosomes.

Teratogen - An agent that causes congenital anomalies in the embryo or foetus in the developmental phase.

Thalassaemia intermedia - A less severe form of β -thalassaemia that requires less frequent transfusions.

Thalassaemia major - Hereditary haemoglobinopathy caused by a deficit in synthesis of one of the globin chains.

Thalassaemia minor - Hereditary haemoglobinopathy caused by a deficit in production of one of the globin chains.

Transfer RNA (tRNA) - Transfers activated amino acids from the cytoplasm to mRNA.

Trisomy - Aneuploidy, or an abnormal number of chromosomes in a pair of homologous chromosomes.

Screening - Identification in a population of subjects who have a disorder or are carriers of a disease gene.

Segregation - Separation of alleles at meiosis so that each gamete contains only one of each pair of alleles.

Segregation analysis - The study of how a disease is transmitted in a family in order to establish the heredity model.

Sequence - Set of DNA nucleotides; in the field of congenital malformations, it describes deficits that occur as cascades of events secondary to an initial primitive factor.

Sex chromosomes - The chromosomes that determine sex (XX in the female, XY in the male).

Sex-linked inheritance - Disease caused by a mutation on a gene on a sex chromosome.

SNP (Single Nucleotide Polymorphism) - Polymorphic variation of a single DNA nucleotide that occurs every 500-2500 base pairs.

Somatic (cells) - Non-germ cells.

Somatic mutation - A mutation limited to non-germ cells.

Spinal muscular atrophy - Mostly autosomal recessive diseases of the anterior horn of the spinal cord, leading to progressive muscular atrophy: the age of onset varies widely (often immediately after birth).

Spinocerebellar ataxia - Heterogeneous group of degenerative diseases, caused mostly by autosomal dominant mutations, that become clinically evident with age and consist in neurological symptoms dominated by lack of movement coordination.

Spontaneous mutation - A *de novo* mutation.

Sporadic - Said of a disease that affects only one person in a family.

Structural gene - A gene that codes for a protein.

Syndrome - Complex of signs and symptoms associated with a specific disorder.

Type 2 diabetes - Non-insulin-dependent diabetes, or adult onset diabetes, marked by hyperglycaemia in the context of insulin-resistance and relative insulin deficiency.

Threshold - Concept used to describe discontinuous multifactorial diseases; identifies subjects who are above an empirically defined limit and develop the pathology in question.

tRNA - RNA molecule involved in transferring amino acids during the translation process.

Trophoblast - Tissue that encloses the embryo at the start of pregnancy and gives rise to the placenta (equivalent to chorionic villi); it is collected for first trimester prenatal diagnosis.

Ultrasonography - Use of ultrasound imaging technology to visualise objects, e.g. foetal development.

Variant - Allele present in less than 1% of the population.

Virion - An infective viral particle.

Williams' syndrome - Condition that is clinically marked by dimorphisms and psychomotor retardation caused by deletion of 26/28 adjacent genes from the 7q11.23 region of chromosome 7.

X-linked trait - A trait carried by the female sex chromosome.

Zygote - Fertilised egg.