Presidency of the Council of Ministers

BIOETHICAL GUIDELINES FOR GENETIC TESTING

19 November 1999

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PRESENTATION

It is a tradition for the National Bioethics Committee (NBC) to accompany its statements with a presentation by the president in office. In the present case, however, also in view of the complexity of the issue and the frequency of the scientific, ethical and legal updates, more than two years were needed to draw up the document which straddled two successive committees: the first one, chaired by Prof. Francesco D'Agostino, whose term expired in December 1998, and the present one, appointed in March 1999. For this reason, a double list of Committee members is attached to the present text.

The the draft work was begun even earlier, by the deputy chairman Angelo Fiore in response to the great significance genetic tests had acquired in the legal sphere, in both penal and civil cases. To his text was added an analysis by Livia Barberio Corsetti on the ethical and deontological problems related to monitoring and genetic screening in the workplace. The working group set up in late 1997 (including, in addition to the above two persons, also Giovanni Chieffi, Isabella Maria Coghi, Vittorio Danesino, Luigi De Carli, Renata Gaddini, Antonino Leocata, Adriana Loreti Beghè, Alberto Piazza and Giulio Tarro) used the bearing structure set up by Angelo Fiori as well as contributions such as Renata Gaddini's reflections on the psychological aspects, and those of Sara Casati and Lucia Galvagni (collaborators) on the ethical aspects and the bibliographic documentation. Coordination was ensured by Alberto Piazza and a first draft of the text received the general approval of the Committee on 18 December 1998.

The new Committee entrusted to Alberto Piazza, who did the job with great sense of commitment and balance, the task of updating the text also in the light of the European Bioethics Convention and the further developments in the bioethical debate. In the meantime, indeed, such topics as the protection of privacy, the risk of genetic discrimination in the insurance field, access to the tests (sometimes excessive, sometimes difficult) and others had emerged and required further study. This was done with the help of the new group composed of Adriano Bompiani, Francesco Busnelli, Isabella Maria Coghi, Luigi De Carli, Angelo Fiori, Carlo Flamigni, Adriana Loreti Beghè (who, together with the collaborator Luca Marini, added a section containing profiles on international and Community law), Demetrio Neri and Anna Oliverio Ferraris. The work of both committees benefited from the essential contribution of competence and creative participation made by Giovanni Incorvati in the NCB scientific secretariat.
The statement on genetic testing was definitively approved by the NBC on 19 November 1999 and, after a purely editorial revision, is now presented in a restricted edition of Sintesi e raccomandazioni, as well as in a complete edition. The document is thus the result of wide-ranging collective work carried out in several stages by different persons, to whom I am profoundly grateful. This is the reason why I would consider it arbitrary to superimpose my own opinions on this work, by actually discussing the merits of the problems.
I merely wish to add that the long period of preparation of this document shows the extent to which the bioethical implications of genetic tests are complex and even contradictory. And that, therefore, this statement, like and perhaps even more than others made by the National Bioethics Committee must remain open to further interpretations and updating.

Rome, 19 November 1999
The Chairman
Giovanni Berlinguer

1. Scope, structure and limits of the present document

The recent advances in genetics, of great scientific and practical importance, are based essentially on molecular biology techniques, all of which raise significant bioethical issues. Some of these emerged in broad outline right from the first few applications of the double-helix model, while others arose with growing knowledge and increasing prospects of practical applications. It may actually be claimed that the broad technological spectrum of molecular biology has played an essential role in shaping the more recent configuration of the bioethical theme.
Among the numerous bioethical problems, that of genetic testing has taken on ever increasing importance in recent times. Genetic testing is defined as the set of tests aimed at:
a) the pre- or post-natal identification of genetic defects in an individual's DNA, believed to be the cause of serious diseases, already in progress or with late onset, or proneness to and/or onset of complex multifactorial pathologies;
b) the typing of DNA regions contained both in the cell nucleus and in the

mitochondria, in order to ascertain the sections that identify each individual or group of individuals on the basis of their genetic constitution.
In the first section of the document, after the introduction of several general concepts related to DNA and the main technologies for manipulating it (biotechnologies), the actual genetic tests are defined and their applications described, both in the field of health promotion and in fields unrelated to the health of the individual or the community. The second section documents the state of the art in Italy, and contains a survey of the structures providing genetic tests and of the current reference legislation. In the third section, a treatment is given, first in general terms and then by specific topic, of the various bioethical implications of the problem. The document is concluded by a chapter on Community and international legislation and a glossary of the main terms used.
Owing to their complexity, genetic tests for research on animals and plants and the problem of gene therapy deserve separate treatment and have been omitted from the present document.

2. Genetic tests and screening

Genetic tests are commonly defined as "the analysis of specific genes, their product or their function, as well as of any other type of study of the DNA or chromosomes, aimed at identifying or ruling out DNA modifications presumably linked to genetic pathologies".
They may be schematically classified into at least six main categories:
A) Diagnostic (or also symptomatic) tests. Designed to confirm a clinical diagnosis or to characterize a pathological condition that is suspect, but not yet brought into objective clinical focus. Several of these tests are used to identify the heterozygotes (or healthy carriers) of common mutations, which signify increased reproductive risk even when the respective partners are heterozygotes for the same mutated gene.
B) Presymptomatic or preclinical tests. Identify a mutation that inevitably leads to the onset of a disease in the course of a lifetime. Tests used for the purpose of prenatal diagnosis are by definition presymptomatic, as are those applied within the same family at risk to identify carriers of genes associated with diseases having a delayed onset (e.g. Huntingdon's chorea).
C) Prognostic tests. The characterization of the various mutations and the subsequent phenotype-genotype correlation often allow the attribution to certain genotypes of clinical patterns having different clinical seriousness and prognostic course. Knowledge of the results of these tests, combined with the clinical symptoms, allows the treating physician to plan less aggressive, more modulated therapies, and is of use to the patient and his/her family.
D) Genetic susceptibility predictive tests. Allows genotypes to be identified which, after exposure to contributing environmental factors or as a result of other causative genetic factors, entail an increased risk of developing a given pathology.
E) Heterozygote identification tests. In the case of several extremely frequent genetic diseases, for example, thalassemia, cystic fibrosis, some mucopolysaccharidoses it is possible to identify heterozygote carriers in the population. These tests, when performed optimally and above all associated with extensive dissemination of

information, result in a decrease in the incidence of the pathology in question.
F) Forensic investigations. The availability of a large number of polymorphic markers that may be detected using comparatively simple techniques and carried out even on tissues in a poor state of conservation allow the determination of paternity or the attribution of biological traces to certain individuals with an extremely high probability of success.

The term individual genetic test is used to emphasize the distinction with genetic screening: the object of the former are individuals or members of families; that of the second are whole populations or part thereof, the component individuals of which, taken separately, are unlikely to be identified as being affected by, or likely to contract, genetically-based diseases owing to the non specificity or absence of symptoms; however, they may benefit from further research or direct preventive measures.

Unlike other laboratory tests, genetic tests have several features that make them peculiar in the field of medical and clinical investigation, namely:

- Genetic testing can be used to identify the risk of contracting diseases in the future; it is unlikely however that this risk can ever become certainty.
- Predictions based on genetic tests cannot always be confirmed by other independent clinical or instrumental evidence. In this case, the prediction will be confirmed only by the onset of the disease.
- The results often compel the couple to face options that involve reproductive choices and include prenatal diagnosis, heterologous insemination, interruption of pregnancy, adoption. These options may clash with the couple's ethical principles or their religious beliefs.
- The test results may provide genetic information related to the future state of health of close relatives of those subjected to the test, regardless of their present state of health.
- For many genetic diseases no effective cures exist, only palliative or containment therapies able to relieve some complications.
- Subjects that, although not yet affected by them, who are identified as being at risk with regard to certain diseases, may suffer psychological stress, be discriminated against, encounter difficulties in their social life, in access to the health or insurance systems, or to employment.
- Membership of a given population may represent a discriminant with regard to diagnosis and the interpretation of the tests.
- Health care personnel with experience of genetic counselling, and the number of public laboratories capable of providing it, are insufficient.

  The genetic screening programmes are normally classified into four categories, according to when the test was performed:
- prenatal (during pregnancy, e.g. Down's syndrome, hemoglobinopathies, etc.);
- neonatal (e.g. phenylketonuria);

- in adolescents (e.g. in the United States and Canada, Tay-Sachs disease carriers);
- in adults (e.g. in Sardinia, pre-marital or pre-pregnancy identification of thalassemia carriers).

The ethically significant objectives of genetic testing and screening are:

- to contribute to improving the health of persons affected by a genetic pathology;
- to allow carriers of a gene that is or will be expressed in a disease to make reproductive choices based on information that is as exhaustive as possible and that will guarantee they have equal opportunity;
- to contribute to relieving the anxiety of families or communities concerning the likelihood of being affected by serious genetic diseases.

3. Scientific research

It is beyond our present scope to emphasize the need for sound scientific research and the rigorous control of genetic testing. The present treatment is limited to examining the possible causes of conflict between the needs of scientific research and the right to privacy exercised by each individual with regard to genetic information concerning him or her.

The most recent legislative dispositions in Italy have taken the needs of scientific research into greater account than in the past by including the simplification or the facilitation of data treatment. Art. 5 of d.lgs. 282/1999 actually excluded the need for consent for the treatment of data liable to reveal the state of health - whenever the aim of the treatment involves scientific research in the medical, biomedical or epidemiological fields - although only "when the research is regulated by a specific law or is part of the biomedical or health research programme provided for in art. 12-bis of d.l. no. 502 of 30 December 1992 as subsequently amended". The d.lgs. 281/1999, which specifically mentions the treatment of personal data for the purpose of scientific research, also makes provision for introducing into the ethical and good practice codes, underwritten in accordance with art. 31 of l. 675/1996, simplified procedures for obtaining consent to obtain sensitive data. It thus appears that these provisions, without prejudice to the need for a specific authorization by the Guarantor, may be applied also to the treatment of genetic data.

It is deemed advisable that, as provided for in the European Union calls for research funding, a part of the funds appropriated in Italy for genetic research should be specifically allocated to the study of ethical problems associated with technical and scientific progress in this discipline and their anthropological and social impact.

4. Genetic counselling

This is structured as a communication process by the medical geneticist. The process is designed to help individuals affected by or prone to a hereditary disease and, in particular, to allow them to understand the nature of the disease, its transmission within the family and the options available as regards family planning and disease management.

Genetic counselling of this type calls for technical, scientific, ethical and psychological

skills that may be applied, on the one hand, to ensuring free and responsible choices can be made by the potential beneficiary/ies and, on the other, by the impartial nature of the information given, the non directiveness of the counsellor.
The potential users of an adequate genetic counselling service should be provided with the tools they need to understand genetic disease; for example, what is meant by monofactorial or multifactorial disease; the meaning of the possible test results; and again, the likelihood of false negative or false positive results being obtained, the meaning of the probabilistic approach to diagnosis, the concepts of predisposition to the disease and risk factor. The results of a single test must always be accompanied by information on the nature of the disease, its seriousness and prognosis, on the existence of an effective therapy, on the genetic mechanisms whereby it manifests itself, and lastly on the extent of the risk of transmission. At the time the results are communicated it is possible to envisage also a further phase of counselling, again in full respect of the subject's desires, aimed at allowing a full and correct understanding of the information obtained. In any case, genetic counselling must always be provided before indicating any genetic tests in a continuous dialogue between potential beneficiary and consultant.

A particularly delicate situation occurs whenever minors or the mentally ill are involved. In such cases, communication must take place simply and gradually, attributing importance to the exchange with the patient, to his/her comprehension of the proposal, as well as to his/her consent to the test, whenever this is advisable. In the case of children and the mentally ill, the communication and the decision to carry out genetic testing is addressed to the parents, relatives or guardians; what is neglected is the relationship with those who are directly involved and the possibility of stimulating in them a gradual development of a decision-making capacity their own is foregone a priori.

5. Genetic testing of gametes and of pre-implanted embryos

Without prejudice to the differentiated ethical positions related to the actual use of medically assisted fertilization techniques, on which the Committee has already expressed an opinion in previous documents (see, for example, Diagnosi prenatali of 18 July 1992, Parere del CNB sulle tecniche di procreazione assistita. Sintesi e conclusioni of 17 June 1994 and La fecondazione assistita. Documenti del Comitato Nazionale per la Bioetica of 17 Febbraio 1995), it should be noted that the continual acquisition of DNA sequences and the identification of new genes make available a growing number of molecular probes that can identify mutations responsible for hereditary and congenital diseases. Diagnosis using non destructive techniques can be performed on the unfertilized egg cell by sampling the polar globule. This technique, although not immune from diagnostic complications intrinsic to the actual chromosomal mechanism during the process of separation, can be used to test above all for the presence of gene mutations, rather than for chromosomal aberrations, as regards both number and structure.
Of course no non destructive diagnostic action can be performed on the zygote. Such action is possible without detriment to the embryo's development starting from the embryo at the stage of 4-8 cells, by means of sampling one or more blastomeres, up

to the blastocyte stage, with the sampling of trophoectodermal cells. Direct DNA analysis may be performed on the material sampled or else chromosomal analysis using suitable molecular probes.
The non invasive approach is of possible interest in determining congenital errors in the metabolism by means of biometric tests carried out in the culture medium in which embryos produced for in vitro fertilization are maintained.
It is important to emphasize the reliability of these tests and the problem of the risks involved, the evaluation of which is linked to that of the risk of medically assisted fertilization. The latter too is dependent mainly ono the process of fertilization and on the transfer to the uterus, rather than on the subsequent manipulations necessary in diagnostic intervention. In the course of the natural process of fertilization the loss of products of conception in the natural process attains values of around 75-80%, which can be as high as 85-90% after fertilization in vitro and transfer to the uterus of a single embryo. Having said this, practically the entire literature reports that the frequency of congenital malformation in children born as a result of assisted fertilization is quite comparable to that found in children born after natural conception.
The obstacles in the way of a perfect understanding of the data are:
a) the fact that the average age of the women treated for sterility is higher than normal and many case histories do not take the different age groups into account;
b) the high percentage of miscarriages (about 30%) and the lack of data on preclinical miscarriages; it must also be pointed out that age is important also in the case of miscarriages, and that very few genetic investigations have been carried out on material from miscarriages;
c) the fact that children born as a result of assisted fertilization are subjected to particularly thorough clinical examinations, which are also certainly more numerous and sophisticated than those performed on children born after spontaneous conception, in whom therefore numerous minor malformations could be missed. It is an even more complex matter to evaluate genetic risk in children born after the intracytoplasmic injection of spermatozoa (ICSI), to which the present document devotes a few remarks. As ICSI is tested directly on man, only time, gradually accumulating data and thorough monitoring will provide reliable answers concerning the true limits and risks of this technique.

6. Diagnosis of predisposition

Increasing knowledge of the human genome brings with it an extension and acceleration of genetic research. In a not too distant future, this research will allow genetic testing to be aimed not only at the diagnosis of a growing number of hereditary diseases but also at the determination of any "genetic predisposition" to polygenic or multifactorial pathologies. The latter, although they cannot be called genetic diseases in the true sense (as they are linked to the existence of exogenous or endogenous environmental factors), are in any case transmitted through inheritance in view of the fact that they preferentially affect subjects with a particular genotype. As a result, techniques will be developed that can detect in both neonates and adults both the predisposition to late onset diseases and to the genetic predisposition to the action of pathogens present in the home or workplace.

A typical example of a disease the onset of which can be comparatively easily predicted by means of a genetic test is Huntingdon's chorea, which is associated with a single and well-known mutation in a specific gene. Researchers have in fact succeeded in identifying both the gene involved in the disease and its location on the chromosome. In subjects with this disease, they also found the presence of trinucleotide sequences repeated a large number of times inside the gene; this fact can be used to predict accurately whether an individual carrier will develop the disease.
It is instead considerably more difficult task to predict the development of much more common diseases, such as several neoplastic processes and a few cardiovascular disorders since mutations in several different genes are involved in their manifestation. It is a known fact that the likelihood of developing cancer of the colon is increased in the presence of a mutation in five different genes, while a mutation in at least two distinct genes leads to the predisposition to breast cancer. The ascertained absence of these mutations does not however absolutely exclude the possibility of the subject subsequently being affected by these tumours. The case of breast cancer is emblematic. One out of ten women in the western world is liable to get this disease by the age of 85, with a mortality of 25% of the women affected. However, only 5% of the breast cancers are hereditary and only 80% of them can be linked to mutations of two genes denoted as BRCA1 and BRCA2. It is thus obvious that specific genetic tests for BRCA1 and BRCA2 will not be able to detect all the conditions of predisposition to breast cancer either in its hereditary forms or, even less so, in its non hereditary forms.

7. Structures and legislation in Italy

The second part of the document describes the number and geographic distribution of medical structures in Italy that operate in the field of cytogenetic and molecular diagnosis, as well as the reference legislative framework. In 1996 there was a total of 174 laboratories, 135 public and 39 private, 83 of which in the North, 39 in the Centre, 35 in the South and 17 on the Islands. A larger number of structures operate in the field of cytogenetics (125) than in that of molecular diagnosis (72). In the year 1996 a total of 24,255 molecular diagnoses (22,479 postnatal and 1,776 prenatal). In 1997 the activity increased by 100%, with a total number of analyses amounting to 48,458 (46,158 postnatal and 2,300 prenatal). The distribution of this activity throughout the national territory reflects the number of laboratories active in the individual regions. The number of molecular diagnoses amounted to 12,340 in 1996 and 29,818 in 1997 in the northern regions and 5,137 and 11,145, respectively, in the central regions and 6,778 and 7,495 in the southern regions/islands.
Overall, in 1996 some 142 diseases (Table 3 in document) had been diagnosed at the molecular level. This number seems large compared with the total number of diseases diagnosed at the molecular level during the same period in Europe (354) in the 280 diagnostic laboratories (including the Italian ones) and listed in the European Directory of DNA Laboratories (EDDNAL). The diseases for which the greatest number of diagnoses have been requested are, as expected, those occurring most frequently in the population, such as thalassemias and hemoglobulinopathies (5,135

diagnoses in 1996), cystic fibrosis (4,742 diagnoses in 1996), chromosome X linked mental retardation (2,790 diagnoses in 1996), muscular dystrophy of Duchenne and Becker (1,689 diagnoses in 1996). The interpretation of this data must not lead us to overlook the probable imbalance between the number of requests for genetic tests even when there is no real need, on the one hand, and the difficulties encountered by those who could benefit from them in finding out about the tests and having access to them, on the other. However, it is pointed out that no certain data are available on this point, nor is any research known to be in progress.
Art. 16 (actually entitled to genetic data) of the recent d.lgs. no. 291 of 30 July 1999 (which contains "provisions concerning the treatment of personal data for the purposes of case history, statistics and scientific research" that specifically regard genetic data: "The treatment of genetic data, regardless of who processes them, is permitted only when specifically authorized by the Guarantor (authority set up under law no. 675 of 31 December 1996: Protection of persons and other subjects in the case of the treatment of personal data, which, within the broad notion of personal data treatment provided by art. 1, para. 2, sub-section b, is without doubt applicable also to genetic tests), after hearing the opinion of the Ministry of Health, who requested the opinion of the Higher Health Council for this purpose. Treatment authorized by the Guarantor may be continued until the issue by the authorization provided for in the present article is issued within twelve months after the data it comes into effect". Consequently, the delicacy of the genetic data issue resulted in further legislative steps to surround the issue of the authorization by the Guarantee Authority with further precautions, as follows:
1) it must be specific and not just issued for the treatment of health data;
2) it is necessary for the treatment of genetic data performed by any subject (and not just that carried out by public bodies);
3) it is subject to the approval of the Ministry of Health (although it is not clear whether this approval is binding or not);
4) it seems to imply a competence concerning the identification of the cases (and thus of the purposes) for which the treatment is allowed.

8. The Human Genome Project

The search for all the genes of the human genome, currently in progress and expected to be concluded by the end of 2005, also raises ethical problems. In the first place there may be a shift in the boundaries of the very concept of individual responsibility: the rapid increase in knowledge concerning the genetic determination of individual character and related behaviour, also at the legal level, opens up a wider range of nuances between liability and non liability, and makes the traditional interpretations even more uncertain.
The central problem accompanying the constantly expanding knowledge of our genes will certainly remain that of genetic discrimination. One of the sources of this danger comes from the admittedly long time elapsing between the prediction or the diagnosis of a genetic (or in any case gene-related) disease and the time in which a suitable therapy can be applied. The specificity of a disease caused or predicted by our gene complement, but incurable, may lead to discrimination against:

a) a healthy individual for whom the prognosis of the disease is made, in the eventuality of this information being accessible to third parties, for example, the individual's employer or insurance company;
b) an individual with the disease, in the eventuality of access to health and social services being differentiated according to the availability of treatment;
c) persons at risk and those already with the disease, because of the scarcity of genetic counselling services in the national health systems in view of the high cost of training qualified personnel.

The Human Genome Project has also aroused other concerns:

- The fear that its results will lead not only to discrimination against groups of individuals but also to their stigmatization.
- The eventuality that, for commercial reasons or for the filing of patent requests, it will not be possible to have fee access to information resulting from new discoveries of the scientific community.
- The reduction of the human being to his DNA sequences, with the attribution of social problems, and other problems specific to man, to genetic causes.
- The elimination of respect for values, traditions and integrity of populations, families and individuals.
- Commitment by the scientific community that is insufficient to plan and conduct genetic research in accordance with protocols and strategies open to the public.

The Human Genome Organization (HUGO), a non-profit international community, of which scientists performing this research are members, has laid down guidelines and procedures to dispel this concern and to ensure that certain ethical standards are maintained. Its recommendations are based on the following four cardinal principles:

- Recognition that the human genome is part of a "heritage" common to the whole of humanity.
- Acceptance of the principles of international human rights.
- Respect of the values, traditions, culture and integrity of those subjected to genetic research.
- Acceptance and upholding of the principles of human dignity and freedom.

These principles, partially developed also in the CNB (1994) document Progetto genoma umano, form an integral part of the Universal Declaration on the Human Genome and Human Rights, adopted by UNESCO in November 1997, in which the wording "common heritage" is attributed a "symbolic" value.

9. Predictive medicine and the right not to know

The most immediate applications of modern genetic knowledge and of the progress made in the analysis of the human genome using molecular biology techniques are related above all to the possibility of performing prenatal diagnosis. The latter is aimed at identifying genetic alterations responsible for specific hereditary diseases, which are manifested at birth or in any case in the neonatal period. In any case, it must be preceded by the phase of genetic counselling, in order to ascertain

the actual effectiveness of the indication, illustrate any accompanying risks and possible error, and the ethical problems involved in the case of positive diagnosis. Much more serious problems are raised by the pre- or post-natal diagnosis based on DNA analysis of late onset genetic diseases, the clinical signs of which will thus appear at the adult age. Prescribing a genetic test at a pre-symptomatic stage would thus be perfectly correct in the presence of a suitable therapy or whenever it was at least possible to modify the course of the disease and to reduce any complications, by means of early medical treatment; it is dubious, to say the least, in all those conditions for which no therapeutic remedy is available. The birth of a modern predictive "molecular medicine" thus calls for an overall reappraisal to be made of the benefits and harm caused by medical science. There is no doubt that each individual has the right to know his/her own genotype; however, the right to know must be accompanied also by the right not to know, especially in those cases in which a prior knowledge of the disease would only anticipate suffering without any concrete advantage in therapeutic terms. The case of families to which individuals affected by the above-mentioned Huntingdon's chorea belong is emblematic. In such cases, familial analysis may run up against considerable difficulties, not only owing to the impossibility of obtaining samples from one or more members of the offspring but also because of the mother's desire to know the degree of risk of disease run by her own foetus but not by herself.

Molecular medicine introduces a new type of approach to the prognostic phase in the patient-physician relationship. Indeed genetic tests identify not so much the presence of a given disease, albeit still in its initial stage of development, but rather the presence of a gene mutation capable of leading to the onset of the disease. This condition may be variously defined in terms of "predisposition", of "proneness", of "potential" or "probable" risk. However, the prognostic indications that may be drawn from such investigations are quite different from those offered by other diagnostic tests, as they identify a "risk" rather than a disease in its early stages.

The capacity to use analysis of the genome in a prenatal period or the genetic makeup of adult individuals to predict that a subject will develop a certain disease or that, while still in perfect health, he/she is nevertheless predisposed to develop certain pathologies, may also involve a high psychological and social cost. The individual may be discriminated against in the various ambits of his everyday life (in the workplace, by insurance companies, or even by his/her own partner) often solely on the basis of a greater probability, not the absolute certainty, that one day he/she may fall ill. It thus becomes necessary to protect the individual from the misuse of genetic information such as to lead to collective discriminating and restrictive behaviour at whatever level that is detrimental to individual freedom and rights.

The very possibility of being able to modify or eliminate part of the genetic heritage deemed to be harmful could produce a fresh impulse for programmes to improve the human race, heirs to a culture of a potential abuse of power that continues to lie dormant in society and that is based on a rigid "genetic determinism" that does not take into sufficient account the important influence of the environment in the determination of the phenotype. Any implementation of such programmes, but also the opposite and equally detrimental demonization of the progress of modern

genetics, can be defeated only by means of correct but widespread information concerning present knowledge, the limits and the effective potential of genetics. From the standpoint of legislative regulation, access to predictive medicine must be provided for subjects of legal age and capable of self-determination. This issue is related to the "right not to know" they are acknowledged as having insofar as it represents the power to prevent knowledge of information concerning them. While the communication of health data to the person concerned, on the basis of art. 23 of l. 675/1996, can only be performed by a physician, information concerning genetic data repeats a situation similar to that of the knowledge of the existence of mortal pathologies or incurable diseases. At the Community level, Recommendation No. R(97) 5 suggests a comprehensive solution regarding the communication of "unexpected discoveries" to persons undergoing genetic testing. The issue has not yet been faced by the Italian legislator: it is however treated in the medical code of ethics (art. 30).

A special hypothesis is related to the genetic information requested from the next of kin of the subject intending to undergo testing. In this case, the right of free self-determination with reference to one's private life is dependent on determinations made by another subject. The problem is thus to decide whether or not there is an obligation to communicate genetic information and the consequences in the case it is withheld. In this connection, it is worth mentioning a very recent statement (one of the first in Europe) made by the Guarantee Authority concerning the protection of personal data: in the case of a woman who underwent genetic testing for the purpose of procreation, the Guarantor deemed that it did not represent a breach of law 675/1996 or the professional secret obligation if the genetic data of a relative (in this specific case, the woman's father) was acquired from clinics or hospitals in the case of refusal or simple omission to give consent. Permission was thus given for the official access to genetic information since the need to protect human life was considered to prevail over the right to privacy.

This type of solution should in any case be extended, also to take into account the configuration of the right not to know whenever it clashes with the opposite interest of third parties such as the legitimate or common-law spouse (which would lead to the exclusion of an unlimited right not to know); and furthermore, in order to address also the problem of the existence of a duty to communicate genetic data to one's partner (this latter problem could involve also the physician treating the subject affected by hereditary disease, with the consequent question of whether to inform the partner of one's patient in view of possible decisions regarding procreation). It should be borne in mind, however, that, above and beyond these particular hypotheses of conflict, the general authorization no. 2198 (point 5) of the Guarantor excludes the communication of genetic data to the family of the person concerned.

10. Oncology

In general, predictive tests for the most common chronic diseases, and particular, for neoplastic pathologies, raise specific problems. Advance information concerning the risk of developing a specific form of cancer can bring significant benefits as far as monitoring and prevention are concerned; however, the knowledge

of future risk can also have important negative effects from the psychological point of view, which do not differ in many respects from those extensively studied in subjects that are seropositive for the HIV virus. For example, operating criteria to allow monitoring of the tests for the presence of the oncosuppressor genes BRCA1 and BRCA2, which are extensively discussed in the present document in connection with breast cancer, are now found in international protocols that are particularly respectful also of the ethical aspects.
The acceptability or not of using predictive genetic tests in the oncological field is essentially dependent on the purpose for which they are performed. They are to be recommended:
a) for a patient with the disease, whenever the genetic diagnosis modifies the treatment and/or allows correlations that enable the course of the disease to be predicted, including diagnosis;
b) for the asymptomatic relatives of a patient, in order to include them in a follow-up programme for the early diagnosis of expected neoplasias, and/or for the purpose of evaluating access to possible prophylactic surgical measures;
c) for an asymptomatic individual, when the genetic diagnosis may lead to a beneficial change of life style and food habits, or to protect him/her from possible risk factors, also of an occupational nature (radioactivity, chemical products, etc.), or in any case to take timely preventive measures.

11. Minors

Parents may be assumed to be responsible for the welfare of their children. Nevertheless, the request for genetic testing may have negative repercussions on children under legal age, which must be acknowledged and discussed with the participation of the rest of the family. Genetic counselling and communication with the minor and his/her family with regard to the advisability or not of performing a genetic test should take the following aspects into account: the evaluation of the potential harm-benefits of the test; the determination of the capacity for comprehension and responsible decision-making of the minor; the protection of the minor's interests.
One of the most widely debated problems is what age and for whom - the minors concerned or their parents - a genetic test is useful. The following recommendations take into account:

A. The impact of the potential benefits and harm on the decision to perform the test

1. A genetic test on children and adolescents is justified only if it implies a timely and certain medical benefit. By medical benefit is meant any type of preventive or therapeutic measure, or diagnostic information in the case of symptomatic minors.
2. In the case of adolescents capable of judging the information they are given, a genetic test could be justified also by substantial benefits at the psychosocial level.
3. If the medical or psychosocial benefits of a genetic test do not come to maturity until the adult age, as in the case of identification of the condition of carrier, or late onset diseases, the test should generally be postponed.
4. If the trade-off between the potential harm and the benefits of the test is uncertain, the principle of autonomy prevails, and the decision of adolescents capable of

thinking for themselves, or else that of their family, should be respected.
5. Whenever the potential harm caused by a genetic test is deemed greater than the possible benefits, the genetic test should be discouraged.

B. The family's involvement in the decision-making process

1. The genetic test should be preceded by genetic counselling and formation work, addressed both to parents and the minors, in a manner appropriate to their degree of maturity.
2. The health practitioner, whose professional duty it is to act in the interest of the minor, must obtain the parents' permission and, depending on the degree of maturity of the latter, the assent of the minor or the consent of the adolescent. He/she should also attempt to ascertain whether the minor's decision was made voluntarily.
3. The request by a minor who is capable of thinking for him/herself to be informed of the results of a genetic test should be deemed to take priority over any request by his/her parents not to reveal the information.

The genetic tests used to diagnose a late onset disease in a minor may inadvertently provide predictive information to the minor's relatives, who are not interested in such information. On the other hand, the identification of a gene that predisposes a minor to a disease could be advantageous to the relatives who may wish to take the test themselves. One of the main bioethical problems is indeed represented by the use of data deriving from genetic tests carried out on the child, for purposes regarding the parents and the family in the broad sense, that is, for purposes that do not benefit the minor directly. The future reproductive choices of the parents may be strongly influenced by a knowledge of the minor's genetic profile, even in those cases in which the genetic counselling services make every effort to provide non directive counselling. The fact that a knowledge of the minor's genetic profile may guide the parents' future procreative choices does not appear to be ethically reprehensible. Nevertheless there are cases on record of minors identified as healthy carriers of Tay-Sachs disease or as born presymptomatic for late onset diseases, as a result of which their parents made choices of social and cultural life that were reductive with respect to what it would otherwise have been possible to offer.

A problem that has social as well as ethical aspects is the decision-making capacity of the minor. Although the age of 18 represents a threshold beyond which the subject is legally recognized as having the capacity to decide, empirical observation shows that the cognitive and moral discernment abilities are subject to gradual development that needs to be evaluated on a case by case basis, according to the personality, family atmosphere and resources available in the environment. Furthermore, numerous special laws, specifically regarding health matters, recognize minors' right to self-determination.

As far as the question of the decision-making capacity of the minor regarding the taking of genetic tests according to Italian legislation is concerned, reference is made to the provisions of art. 2 of d. lgs, no. 282 of July 1999 ("Provisions to guarantee the privacy of personal data in the health field"), which has incorporated art. 23 of l. 675/1996. It would seem at first sight to exclude any capacity for decision by the minor, insofar as he/she is legally incapable of acting. However, a systematic

interpretation of the provision, such that it may be included in a more general context in which a minor who is capable of making existential choices is attributed the power to do so legitimately, should reduce the scope of the law itself: other subjects (who, and this is no coincidence, cannot be reduced to being the sole wielders of parental authority) are authorized to give consent to the treatment only when the minor, owing to his/her age or other causes, is physically or mentally incapable of expressing him/herself.

12. Personality, behaviour and deviant behaviour

The progress made in the knowledge of the genetic components of behavioural traits could lead the parents to make more requests to influence the genotypes of their future children, so as to obtain the desired genotype. The geneticist's task will become even more complex than it already is, at least as far as the characters determined by a single gene are concerned. On the other hand he must allow potential users complete independence in making the decisions concerning their own family, thanks to complete and updated information also concerning the changes that may occur in this information even within short time intervals. On the other hand, he will have to pass on the idea that, even though one or more genes contributing to the determination of a complex character have been identified, a knowledge of the genotype of a single gene has a limited predictive value as far as the phenotype of interest is concerned. Furthermore, it is no easy matter to explain certain concepts to persons who, often anxiously, ask for sure explanations concerning complex problems: neither the limited effects that each gene, taken individually, can have on character; nor the uselessness, from the statistical point of view, of testing the presence of each individual gene, when too little is known about its interactions with the other genes involved.

The genetic differences among individuals in the same population represent a conditio sine qua non for Darwinian evolution to take place. These differences have often been a cause of ideological distortion, because of the frequent tendency to exaggerate their significance. A slight mean difference between two groups for a certain character is interpreted as though all or nearly all the individuals of a group exceed for that character all or nearly all the individuals in the other group. This is rarely the case for genetic characters, whether simple or complex, regarding behaviour or not, that have been measured in man. The tendency of many persons to exaggerate the differences that exist among groups and the discriminations to which this attitude gives rise, have often aroused an opposite, but equally extreme, tendency to claim that these differences do not exist at all. A preferable strategy would be to make a careful assessment of the differences among the groups involved and the predictive capacity - usually rather modest - that they have for single individuals; as well as to encourage public opinion and the press to make a more balanced interpretation of these differences.

The possible discovery of genetic polymorphisms correlated with the development of impulsive and violent behaviour could in future allow the individuals at risk to be identified earlier. The increasing spread of such methods and the development of their diagnostic potential could thus allow judgments of liability and social

dangerousness to be based not only on clinical criteria and psychological tests but also through reference to information obtained from biological studies and molecular genetics investigations. It is thus obvious that genetic research on behavioural disorders raises substantial ethic, legal and forensic problems. The claim that behaviour is the product of free will is actually liable to be challenged by the discovery of factors that, albeit only to a limited extent, can determine individual behaviour. The problem will be to decide when and under what circumstances a genetic test may be admitted.
However, genetic information concerning the predisposition towards deviant behaviour may be accepted in the law court only when it has been fully accepted and validated by the scientific community. In such cases it could allow a choice of therapeutic rather than punitive measures for those having committed acts deemed to be offences.

13. Working activities

The bioethical problems to be considered here partly overlap those considered previously in relation to the genetic diagnosis of disease or pathological predisposition, and partly refer to the possibility of genetic discrimination, in terms of hiring or of career, against employees displaying a greater proneness to certain pathogens. Such discrimination would be even more serious and unjustifiable in the eventuality - fortunately still remote, in view of the technical difficulties and high costs involved - of genetic screening aimed at evaluating whether employees or job applicants are liable to late onset diseases not related to their working activities.
Practical instances have already been described in the vast literature that exists on the subject: one example are the ethical problems raised by genetic screening to detect predisposition for cancer proposed to be performed before taking on workmen to be posted to jobs involving exposure to potentially cancerogenous chemical substances. It is possible that some individuals are genetically more prone to the risk of cancer when exposed to such substances as the respective metabolic variants are capable of reducing any toxicity in different ways and to different degrees.
Once it has been statistically proved that a causal link exists between phenotype and cancer, genetic screening intended to identify any predisposition to illness in the workplace is ethically permissible only if aimed at protecting the worker's health and if it satisfies the following ethical criteria:

a) autonomy of decision: freedom to decide whether or not to take the test, and freedom to choose a compatible job, after complete information has been obtained concerning the nature of the potentially cancerogenous exposure and the limitations of the test;
b) benefits accruing: it is an obvious but often overlooked fact that even before his/her state of genetic predisposition is determined, the worker would obtain greater benefits from not being exposed to the hazard; therefore the employer, before implementing any genetic screening programme, is morally obliged to avoid using cancerogenous substances in the workplace;
c) justice: the distribution of genetic polymorphisms may vary from one population to another and employers could discriminate against groups more likely to develop

diseases.

The following ethical criteria are recommended for the purpose of allowing researchers, on the basis of certain attributes, to identify genetic tests that safeguard the workers' rights. They include: an achievable aim, the active participation of the workforce to be subjected to testing, equal opportunity of access, effective executive protocols, absence of any obligation, informed consent, protection of the subjects' health, access to information, counselling and follow-up services, documentable relationship between test and therapy, protection of the right to confidentiality of the test results.

14. Insurance companies and health services

In the United States, the National Institutes of Health - Department of Energy Working Group on Ethical, Legal and Social Implications (ELSI) of the Human Genome Project, several political movements and part of public opinion itself consider that insurance companies should not have access to genetic information gathered and conserved for diagnostic, therapeutic or research purposes by institutions and health services. Other bodies, such as, in the United Kingdom, the Genetic Interest Group (GIG) itself , a body formed by representatives of individuals affected by genetic disorders, believe on the contrary that such a ban is unrealistic, especially in view of the gradual spread of genetic tests, although they demand that their use in the insurance field be regulated by law. In Europe the legislative scene is still somewhat varied: in Italy, Germany, Spain, Portugal and the United Kingdom there are no laws regulating the use of genetic tests and their results by insurance companies.

Both in Europe and the United States, whereas life insurance is considered a form of investment and a financial operation, insurance against illness, or rather health insurance, aimed at achieving the need-right of health, is certainly of strong social import. The counterposition between health insurance and life insurance that has risen in the United States illustrates the need for all systems based on the interaction between public and private to diversify the regulation of the insurance contract according to the aims pursued.

In particular, in the Italian system, after the socalled 'third' reform of the National Health Service (d. lgs. 229/1999), "health" insurance, as indirect instruments of state action, contributes to the realization of the aims mentioned in arts. 32 and 38 of the Constitution. Since the genetic information are associated with fundamental personal rights, both the public system and the system complementary to it, must guarantee the respect of the inviolable rights of the 'users', in obedience to the principle of equality. The companies managing the Complementary Health Funds must not therefore exclude from their portfolio the more severe genetic risks, denying insurance coverage to those who are more likely to fall ill. Likewise, they must not subordinate to the communication of genetic data the approval of the contract or the determination of the premium. This would be the case if the exercise of the right to the protection of health paradoxically called for the trampling on other rights intrinsic to the latter (the socalled genetic privacy or right not to know).

Similar considerations do not hold, on the other hand, for life insurance, in which the

strictly economic terms of the contract continue to apply. It is perhaps no coincidence that in the USA this form of insurance is regulated by almost exclusively market based rules.
It is recommended that insurance companies for the time being do not take genetic information into consideration, particularly that referring to polygenic and multifactorial diseases - which in any case account for by far the highest relative percentage of pathologies among those requesting insurance - both because of the still incomplete knowledge of the molecular mechanisms underlying their onset, and because of the difficulty of devising actuarial calculation systems for life expectancy and death rate in which this information is taken into account. The estimated risk ascribable to predisposition towards polygenic diseases should in fact be formulated individually, on a case by case basis.
In Italy, the need for the insurance companies to have access to certain sensitive data, and above all, those related to health, has been announced on a number occasions, right up to the most recent parliamentary work preceding the introduction of the much cited law 675/1996, but has always encountered a strong resistance. The general authorization of the Guarantee Authority (replaced by law no. 5/1998) referring to the treatment of sensitive data by banks, insurance companies, brokerage companies, etc. - in particular does not allow genetic data to be processed by subjects exercising insurance activities. Section 5 of authorization no. 2/1998 bans any communication of genetic data, among other things by banks and insurance companies.

15. Identification

The use of DNA polymorphisms for forensic purposes, initially greeted with predictable enthusiasm, was later subjected to a number of reservations concerning both its limits and the causes of error inherent in the techniques used and the lighthearted way extremely delicate inquiries were assigned to laboratories lacking the required experience. In investigations that often have serious consequences, insufficient or inadequate DNA analysis can lead to serious miscarriage of justice in both civil cases (erroneous attribution of paternity) and above all in penal cases; the need is thus strongly felt for an effective quality control and a standardization of methods. Attention is also focused on the problem of identification by means of probability calculus and on that of a correct use of individual genetic characters typed both in terms of reference population and the size of the sample itself.
In some countries, especially in the Anglo-Saxon world, criminal records already exist in which DNA profiles both of subjects definitively convicted of serious offences, especially when habitual, and of subjects that have merely been charged, are included in a central computerized system capable of providing elements of use in comparative verifications in the case of investigations based on biological traces. The establishment of these records has been criticized, although the possible advantages to the prosecution cannot be denied. In the absence of the necessary legal guarantees, the conservation of the genetic profiles and their continual comparison with those obtained from finds made on the scene of the crime, could be detrimental to individual rights and lead to illegitimate presumption based on a kind of genetic

determinism.
As far as Italian legislation is concerned, paragraph four of art. 22 of law 675/1996 considers the hypothetical case of conflict between the defence of the confidentiality of data capable of revealing the state of health (and, therefore, also genetic information) and the request to use them in legal proceedings (not only penal, as in the case of the identification of someone having committed an offence but also civil, for instance, the determination of paternity). The provisions subordinate the treatment of these data to the authorization of the Guarantor, in accordance with a specific ethical code, and above all establish that the treatment must be aimed at ensuring, during a legal proceeding, a right of equal level to that of the person concerned (the point was substantially reiterated and defined more accurately with regard to aims of significant public interest in the field of "disciplinary measures and the preparation of elements of protection at the administrative and jurisdictional level" also by art. 16 of d.lgs. 135/1999).

16. Genetic screening, populations and genetic discrimination

The principal ethical problem to be addressed in this type of investigation is that represented by the criterion of sampling the populations to be investigated: the principle of equality demands that access to screening and the distribution of possible "benefits" from such investigations, albeit in terms of knowledge alone, are guaranteed at least for every group and each population selected. This implies their active and informed participation, as well as the safeguarding of the right to self-determination of all individuals and the respective communities to which they belong through the consent accorded to the performance of genetic tests.
The cultural and social conditions, which vary from population to population, nevertheless make it difficult to pursue any strategy of equal allocation of any beneficial fallout from the investigations. In particular, the developing countries have been involved for years in research in the genetic field; however, the execution of the tests performed in these countries takes place without the previous consent of the populations concerned and with the supervision of the institutions and the competent public authorities (if any). In many of these countries, in which there is often no reference legislation, it is the more or less improvised "representatives" that undertake to give the consent - in relatively uninformed conditions - on behalf of these populations.
Several recommendations emerge from a discussion of these problems:
1. From the ethical point of view it is not correct to propose screenings on which the international scientific community has not expressed sufficiently broad and converging opinions of reliability;
2. Indications must be given concerning the criteria used to select the populations at risk that are to be involved, as well as the degree of reliability of the screening, and the percentage of false positives and false negatives (test specificity and sensitivity);
3. A model of communication with the persons involved must be established which guarantees correct information and allows informed consent to be given;
4. The costs/benefits of screening must be evaluated as well as of other actions that the funding of screening itself might not allow to be carried out;

5. After evaluating the results of the screening, it should be possible to perform further activities of in-depth diagnostic investigation and of therapeutic approach;
6. The genetic information concerning individual persons must remain confidential;
7. All possible measures to prevent the results being used as an instrument of discrimination must be taken;
8. The consent for the screening to be performed must be free and independent of the choices the individual may want or decide to make after being informed of the results;
9. Particularly complex prenatal diagnoses should be carried out in centres recognized as having the required experience. It is recommended that there should be a centralized collection of information on pathological cases by means of structures suitable also for detecting and communicating epidemiological knowledge with potential knock-on benefits for the community at large;
10. In cases of invasive prenatal diagnosis, the choice of method of sampling cannot be separated from other considerations: in particular, it is necessary to plan and maintain a positive trade-off between the risk of miscarriage, or in any case damage to the embryo or foetus, and the genetic risk prompting the diagnosis.

If from population screening to detect the presence of genetic diseases in individuals we proceed to consider the study of populations to identify their genetic make-up, a general ethically significant result emerges. This is represented by the impossibility and uselessness of defining as "beneficial" or "harmful" the "value" of a gene on the basis of an alleged intrinsic property. Rather it is possible to describe the genetic heritage of a community as a function of the presence of different genes and thus on the basis of its genetic variability. The value of the single individual versus the population as a whole does not depend on the quality of the genes but on their specificity, uniqueness and survival. The eugenetic philosophy is thus reversed: not only is there no possibility of characterizing human "races" that are biologically different but internally biologically homogeneous, but the true "improvement" of populations is dependent on maintaining the diversity and safeguarding the genetic richness guaranteed by the simultaneous presence of different genes and cultures. One attitude that has historically always led to genetic discrimination in its basest form, that is, racism, claims that it is in the interest of society to orient the population towards the conservation of "beneficial" genes (positive eugenics) or to the elimination of the "harmful" genes (negative eugenics). This attitude is commonly put into practice by imposing constraints on reproductive behaviour or by the adoption of selective abortion; its justifications differ substantially according to whether it is the result of an autonomous choice, for which a married couple agrees to accept responsibility, or else is aimed at the protection of a public interest, of a good held to be a common one, by the State. This second case - a sort of original sin of the scientific community, which finds a fertile terrain in which to grow in a number of political ideologies - leads to a gross fallacy: that of assuming that it is possible to make significant changes in the frequency of genes held to be harmful within the short span of historical times and events.

17. Community and international law

The Convention on Human Rights and Biomedicine adopted by the Council of Europe on 19 November 1996 and open to the signature of the Member States of the organization on 4 April 1997 at Oviedo, lays down several essential principles:

Art. 10 (Private life and right to be informed) - 1. Each person has the right to the respect of their own private life whenever it is a question of information regarding their own health. 2. Each person has the right to know any information gathered on their health. Nevertheless, the wish of a person not to be informed must be respected. 3. In exceptional circumstances, in the patient's interest, the law may impose restrictions on the exercise of the rights mentioned in paragraph 2.
Art. 11 (Non discrimination) - Any form of discrimination against a person on the basis of their genetic heritage is prohibited.
Art. 12 (Predictive genetic tests) - Predictive testing for genetic diseases, or which allows the subject to be identified as the carrier of a gene responsible for a disease, or else which reveals a predisposition or proneness to a disease, may be carried out only for medical purposes or in research related to the protection of health, and subject to appropriate genetic counselling.

The right to confidentiality of the results of genetic tests is guaranteed also by the Universal Declaration on the Human Genome and the Rights of Man, adopted on 11 November 1997 by UNESCO. The Declaration, although acknowledging the immense future prospects for improving the health of the whole of humanity that may derive from research on the human genome (symbolically defined in art. 1 as "common heritage of mankind", evidences the need, specific to modern democratic society, to reconcile the interest of the community in the development of scientific research with the right of the individual to the protection of his/her own dignity and freedom (art.2). To this end, the Declaration reiterates a number of individual rights aimed, in accordance with the regulations laid down in the national legislation, at ensuring the protection of the persons interested or involved in the gathering and processing of genetic information. The document thereby also acknowledges the need for free and informed prior consent to the performance of research or diagnosis (art. 5, sect. b), the right to know or not to know the results of genetic tests (art. 5, sect. c), as well as the confidentiality of the data obtained (art. 7).
The National Bioethics Committee recommends that these principles be incorporated into the Italian system. The present document is aimed at contributing to their practical application in concrete cases through the development of the debate and its extension to the needs of a society that demands more information, and wants to be reassured, about the effects that scientific progress in the biomedical field can have on the autonomy, benefits and the conditions of equity enjoyed by its members.

18. Conclusions

With regard to such a complex issue as genetic testing, the National Bioethics Committee does not consider it possible to arrive at general ethical conclusions that are valid for all its inner workings and that are not thus reduced to generic statements of principle. It nevertheless focuses the attention on several ethically significant

objectives: in connection with genetic testing and screening , on the subject of genetic counselling, of predictive tests , in the case of complex behavioural characters , in connection with genetic testing in the workplace , the filing of DNA profile for individual identification; and also on certain specific recommendations: on the subject of the Human Genome Project); genetic testing in oncology ; genetic testing of minors; on genetic testing and working activities; on genetic testing and insurance companies ; lastly, on genetic discrimination.