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### **Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights**

In response to the rapid advancements in genetics and genomics, and within the framework of its work programme for 2014-2015, the International Bioethics Committee (IBC) decided to update its reflection on the issue of the human genome and human rights, building upon the considerable work done on this topic by the IBC in the past, and in particular, taking into account the Universal Declaration on the Human Genome and Human Rights (1997), the International Declaration on Human Genetic Data (2003), and the Universal Declaration on Bioethics and Human Rights (2005). Prior to the 21<sup>st</sup> Session of the IBC and the Joint Session of the IBC and the Intergovernmental Bioethics Committee (IGBC) in September 2014, a concept note was prepared by a small working group of the Committee, providing a preliminary outline of potential areas of reflection for this topic. Members of the IBC, the IGBC, the World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), and the UN Interagency Committee on Bioethics (UNIACB) were invited to submit written comments and suggestions on the concept note. Both the concept note and written submissions were then discussed during the sessions in September 2014. Following this discussion, the IBC established a larger working group to prepare a draft report on the topic, which was discussed during the 9<sup>th</sup> Session of the IGBC in July 2015. The draft report was then revised to take into account the comments of the IGBC. The final draft of the report was further discussed, revised and adopted during the 22<sup>nd</sup> Session of the IBC in October 2015.

**REPORT OF THE IBC ON UPDATING ITS REFLECTION  
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## REPORT OF THE IBC ON UPDATING ITS REFLECTION ON THE HUMAN GENOME AND HUMAN RIGHTS

### EXECUTIVE SUMMARY

The UNESCO General Conference adopted the *Universal Declaration on the Human Genome and Human Rights* in 1997 and the *International Declaration on Human Genetic Data* in 2003. During these last years, genetics made spectacular achievements, which triggered new debates and awareness both of the new opportunities and the ethical responsibilities that stem therefrom. Sequencing DNA has become easier, faster and cheaper. Direct-to-consumer tests, precision/personalized medicine, biobanks, non-invasive prenatal testing, and emerging techniques for engineering gametes and the human genome are among the most challenging developments of today.

With this Report, the International Bioethics Committee updated its reflection on this fundamental and topical issue. Five ethical principles and societal challenges have been addressed:

- **Respect for autonomy and privacy:** an individual's genetic data are among the most "personal" data. They have to be protected;
- **Justice and solidarity:** genetics promises to offer an unprecedented contribution to improve health care. These advancements should be shared with society as a whole and with the international community; any discrimination has to be avoided;
- **Understanding of illness and health:** it might be emotionally relieving or, on the contrary, upsetting for an individual to know about his or her genetic endowment. At the same time, behavioural, social, and environmental determinants of health play a crucial role. Underestimation of the complexity of factors influencing health should be avoided;
- **Cultural, social and economic context of science:** globalization, access to information and growing pluralism strengthens the necessity of deeper reflection on the value, meaning, and direction of science as well as of a legal framework complying with the respect of fundamental human rights;
- **Responsibility towards future generations:** great and specific attention is required in the field of genome editing.

Building on this awareness, the International Bioethics Committee makes the following main Recommendations, which are to be intended as an open list for States, governments, scientists, and all actors of civil society both at the domestic and the international level.

#### **States and governments are called on to:**

- a. Produce an international legally binding instrument to ban human cloning for reproductive purposes;
- b. Agree on a moratorium on genome engineering of the human germline, at least as long as the safety and efficacy of the procedures are not adequately proven as treatments;
- c. Renounce the possibility of acting alone in relation to engineering the human genome and accept to cooperate on establishing a shared, global standard for this purpose, building on the principles set out in the *Universal Declaration on the Human Genome and Human Rights* and the *Universal Declaration on Bioethics and Human Rights*;
- d. Encourage, through the means of national legislation as well as international regulations, the adoption of rules, procedures and solutions, which can be as non-controversial as possible, especially with regard to the issues of modifying the human genome and producing and destroying human embryos.
- e. Adopt legislative and other measures, in order to:

- ensure that quality-assured information be provided with regard to direct-to-consumer tests, including non-medical tests, in order to mitigate risks and avoid misuse;
  - organize health care systems, so that the new opportunities offered by precision/personalized medicine be shared with society as a whole, without becoming a new source of inequality and discrimination;
  - develop a trustworthy form of governance for biobanks and biobank secrecy and harmonize the corresponding rules at the international level;
  - ensure that the new possibilities of genetic screening and in particular of non-invasive prenatal testing comply both with the right to autonomous choices and the principles of non-discrimination and non-stigmatization and respect for every human being in her or his uniqueness.
- f. Consider a revision of the existing UNESCO Declarations: the cogency of principles remains untouched; some applications could need updating.

***The community of scientists and related regulatory bodies are called on to:***

- a. Strengthen and participate in international fora to update research and share information on the efficacy, safety, and consequences of new technologies related to the human genome;
- b. Set and share high quality standards for service delivery in genetics, so that they can be certified and included in legally binding instruments;
- c. Promote the use of genetic tests only for health purposes;
- d. Renounce the pursuit of spectacular experiments that do not comply with the respect of fundamental human rights and universal normative ethical standards and of those with unproven efficacy and safety.

***Media and educators are called on to:***

- a. Raise awareness and promote higher levels of health and scientific literacy, to empower people to make conscious and responsible use of new technologies;
- b. Avoid any sensationalism and encouragement of what is still a mere hope for a future to come, if not a deceptive promise;
- c. Disseminate and strengthen the idea that scientific advancements in biomedicine entail responsibilities, which cannot be left only to market forces of demand and supply to define the line of what should be accepted and allowed.

***Economic actors and for-profit companies are called on to:***

- a. Comply with principles and regulations that ensure the highest standard of quality and safety for consumers and respect for privacy;
- b. Refrain from circumventing restrictions in a particular country, in order to take advantage of weaker rules in other countries and maximize profit.

We are human because of the interplay of many biological, historical, and cultural determinants, which preserve the feeling of our fundamental unity and nourish the richness of our diversity. This is why the human genome is one of the premises of freedom itself and not simply raw material to manipulate at leisure. Scientific advancements in this field are likely to offer unprecedented tools against diseases. Therefore, it is crucial to acknowledge that these opportunities should never become the privilege of the few. What is heritage of humanity entails sharing both responsibilities and benefits.

## REPORT OF THE IBC ON UPDATING ITS REFLECTION ON THE HUMAN GENOME AND HUMAN RIGHTS

### I. INTRODUCTION

1. At the 21<sup>st</sup> Session of the International Bioethics Committee (IBC) and the Joint Session of the IBC and the Intergovernmental Bioethics Committee (IGBC) held in Paris in September 2014, the members and Member States of both committees debated on the ethical issues associated with the human genome and human rights, building on their past work and the reflection elaborated during a preliminary discussion at the 20<sup>th</sup> Session of the IBC (Seoul, June 2013) and at the 8<sup>th</sup> Session of the IGBC (Paris, September 2013).

2. UNESCO has adopted three bioethics Declarations. The Universal Declaration on the Human Genome and Human Rights (UDHGHR), which was adopted by the General Conference on 11 November 1997 and endorsed by the United Nations General Assembly in 1998; the International Declaration on Human Genetic Data (IDHGD), which was adopted by the General Conference on 16 October 2003; and the Universal Declaration on Bioethics and Human Rights (UDBHR), which was adopted by the General Conference on 19 October 2005. These documents form the basis of the IBC's views regarding the rights of individuals and societies as well as the responsibilities of States and researchers related to genetic data and human rights.

3. Article 26 of the IDHGD states that:

UNESCO shall take appropriate action to follow up this Declaration so as to foster progress of the life sciences and their applications through technologies.

While Article 24 of the UDHGHR proclaims that:

The International Bioethics Committee of UNESCO should contribute to the dissemination of the principles set out in this Declaration and to the further examination of issues raised by their applications and by the evolution of the technologies in question.

In accordance with these two articles and in light of rapid advancements in human genetic research in the last decade, the IBC believes that it is timely to update its reflection on the ethical issues arising from human genetic research as an essential step of the follow-up action indicated in Article 25 of the UDBHR. Many challenges have emerged since the adoption of the Declarations. Especially in developed countries but also in the developing ones, recent advancements in the field of biomedical research and medicine have made it easier, faster and cheaper to sequence and analyse not only specific sites but even more the entire human genome, which is at the basis of various ethical concerns. At the same time, other new techniques have evolved such as human cloning for research purposes, spindle and pronuclear transfer to prevent transmission of mitochondrial diseases, gamete formation from somatic cells and genome editing. Among the main concerns that stem therefrom we observe the lack of ethical awareness, as well as of effective national and international regulatory frameworks, with the consequence that unregulated actions, even though only in some countries, become automatically allowed.

4. Building on these preliminary observations, the Report will focus on selected areas considered of major interest. For every area of reflection, it will provide a brief description of the recent discoveries and of their applications, of the ethical challenges associated with it, and of some practical recommendations, bearing in mind the principles enshrined in the existing Declarations. The selected fields are the following:

- a. Direct-to-consumer genetic tests and non-health care related analysis;
- b. Precision/personalized medicine;
- c. Biobanks;

- d. Non-invasive prenatal testing;
- e. Emerging techniques for engineering gametes and editing the human genome.

## **II. ADVANCEMENTS IN HUMAN GENETICS AND BIOMEDICINE**

5. Following the completion of the Human Genome Project in 2000, an unprecedented technological development has resulted in reduction of the price of determining human genomic sequence by several orders of magnitude. The speed of obtaining a complete human DNA sequence has increased dramatically as well. The combination of lower costs and increased speed brought sequencing of individual patients' genomes into clinical medicine as a diagnostic procedure to detect mutations responsible for certain diseases. This includes both monogenic diseases and complex, heterogeneous 'common diseases' which can gradually be classified into subgroups. Concomitant development of bioinformatics tools for genome analysis and the possibility to link this information with data on an individual's health, environmental exposure and lifestyle have created the 'big data' challenge. Functional analysis of genomic sequences has also revealed epigenetic regulations that modify the expression of the DNA sequence throughout the life of an individual and add to the complexity of genomic information and human diversity.

6. A particularly troublesome outcome of the rapid advances in genome analysis, boosted by the remarkable price reduction, is the creation of a global web-based market for direct-to-consumer (DTC) tests for medical and non-medical applications, driven also by the promotion of these services in poor as well as rich countries. This market is based on the individuals' right to know information regarding them and undergo genetic testing for whatever purpose they consider valid, for example DNA analysis to determine their own or their children's ancestry. In many cases, the tests' results advertised on the internet are not based on scientific evidence. Yet such analyses are offered to suggest a tailored diet, exercise program, face cream etc. In some countries appropriate agencies can intervene when these tests approach health related matters, though offers on the international market are difficult or impossible to regulate on the national level. Moreover, there are so far no effective approaches to regulate the sequencing applications according to consumer protection law. The fact that the companies performing the testing collect personal information that they may exploit for their own benefit, with little guarantee on the respect of individual privacy, is another important matter of concern.

7. The progress of genetic and biomedical research has introduced a new concept, 'precision medicine' (PM) or 'personalized medicine', which is gradually being introduced into health care. This development is faced with the challenge of integrating and interpreting the enormous amount of data ('big data') derived from genetic and other molecular analyses, and from health records, including medical imaging, as well as different types of health-related environmental and lifestyle information. Such research has revealed that in most cases diseases result from an interplay of multiple (even hundreds of) factors. The results have a statistical value which is often difficult to apply to an individual; they are imprecise, and limited to the type of information about whether a person can be said to have a lower than normal or increased risk for a disease. This type of information is difficult to interpret, to communicate and to apply in daily healthcare. Some mutations are directly life-threatening, others may only become a risk factor in later life, yet others increase the risk for a given disease, or decrease the risk for other diseases (e.g. sickle cell disease and malaria). Many other variations cannot be interpreted in a meaningful way because they are new or have only rarely been found and nobody knows yet what they mean. Convergence of big data and PM is favoured by the fact that the same companies offer these services through different subsidiaries.

8. The impact of technological development associated with genomics is not restricted to sequencing. A number of technologies can be involved (already or potentially) in human reproduction, such as human somatic cell nuclear transfer into an enucleated oocyte, spindle

or pronuclear transfer for preventing mitochondrial diseases in offspring, and derivation of gametes from induced pluripotent stem cells (iPSC). What was only a theoretical possibility a few years ago has now become scientific reality and could enter the area of human clinical application in the near future.

9. New experimental tools make it possible for scientists to insert, remove and correct the sequence of genes, opening up the possibility of treating, or perhaps even curing, certain single-gene disorders such as beta-thalassemia and sickle cell disease, and certain forms of cancer. If these procedures are refined and their safety to patients is established, they would enable the long-awaited success of somatic gene therapy. In several countries somatic gene therapy has received ethical and regulatory acceptance because the genetic changes induced are not passed on to the next generation. It is exactly the potential application of these technologies to germline modification, either for therapeutic purposes or for purposes of enhancement of particular characteristics of an individual that has raised the concerns of ethicists and scientists. As a result, there have been calls for a moratorium on such technologies, at least until their safety and long-term consequences are better understood. Some countries banned germline modifications in humans whereas others do not impose legal bans, but have administrative or ethical rules ('soft law') prohibiting such experiments on gametes and embryos.

## **II.1. Ethical challenges**

10. As outlined above, genetic analyses are becoming cheaper, faster, more comprehensive and, with regard to prenatal testing, non-invasive. Furthermore, genetic tests are being offered more and more for non-medical purposes and the boundary between medical and non-medical use is blurring: commercial endeavours are increasingly flourishing, with companies earning profits through performing genetic tests for customers for almost everything. This has to be kept in mind when considering the impact of genetic interventions on ethical issues like autonomy and privacy, justice, solidarity, the understanding of illness and health, the context of science, and the responsibility towards future generations. None of these ethical issues are new, but technical progress in genetics brings deeper challenges and new requirements for regulations to protect individuals. On the other hand, freedom of research and freedom of individuals should not be inhibited by too many strict regulations.

### *II.1.1. Respect for autonomy and privacy*

11. An individual's genetic data is considered personal data. Therefore, such identifiable data have to be protected from access by unauthorised persons as well as from possible misuse. As a general principle, only the person tested has the right to decide, whether she or he wants to know or not to know about her or his genetic makeup, whether someone else may get access to this information and for what purposes genetic data are to be processed and used. With regard to genetics, autonomy as a fundamental feature of the human species leads to the right to self-determination, which obtains its value as an ethical principle from its role in living a good life according to one's own beliefs.

12. Information about one's own genetic make-up can be helpful for preventing and treating diseases. However, in some cases it can also cause anxiety, uncertainty and become a significant moral burden. In order to actually decide autonomously the person has to get validated and reliable information about the test, its possible outcomes and consequences. The lack of proper genetic counselling, uncertainty as to the reliability of the test results and problems with understanding and interpreting such results may have a detrimental effect on the quality of the decision-making process. Counselling without the influence of commercial interest is an important prerequisite for fostering adequate awareness and especially DTC tests pose major challenges here.

13. In order to give an *informed consent* for a genetic test, the individual has to understand the potential impact of the results on her or his life, considering at least the most significant aspects. Differentiations are relevant with regard to:

- a. The nature of information: whether it may be health-related as well as affect lifestyles (e.g. sports or cognitive talents) or be of no relevance to lifestyles or health.
- b. The probability of occurrence of a phenotype if a particular genotype is present; the concept of risk factor should be clearly explained.
- c. The probable time when a phenotype will occur, e.g. with regard to late onset of health disorders.
- d. The severity of an expected health disorder.
- e. The possibility of prevention or treatment, and
- f. The technical reliability and scientific validity of the genetic test.

14. The problem of incidental findings and findings that are difficult to interpret is becoming more significant due to increasing use of high-throughput sequencing in medical practice. It is an issue of debate whether the right to know encompasses the right to be informed about incidental findings. Newborn screening programs which utilize this type of sequencing also may struggle with this problem. Qualified disclosure and regulation policies for various clinical and research settings are important to respect autonomy, but also to avoid harm, to allow scientific and medical progress and to encourage the sharing of possible benefits.

15. Autonomy in genetics cannot only take into account the person being tested. There are necessary implications for relatives and communities as well, who may share the same or similar genetic status. Is there an overarching right not to know and / or not to disclose, or can there be situations where family members have to be informed, e.g. when a severe disease can be prevented or treated, or when diagnosis of a serious disease can only be made when another family member is also tested?

16. Further problems arise with regard to individuals who cannot give consent to be genetically tested. A lot of legal instruments exist to protect the welfare of these individuals with legal representatives being one of them. However, all these instruments cannot protect the unborn child from being genetically tested in a comprehensive way, taking into account that the unborn child has a different moral and legal status in different countries. There is a lively controversy about the right of the child, especially the unborn child, to have its future right not to know, its right to an open future and its right to privacy preserved.

17. Sufficient information about the genetic makeup can challenge the individual to not only understand its significance meaningfully, but also to behave accordingly. Good health literacy therefore becomes an important prerequisite for autonomous decisions and behaviour. This pertains to accessing, understanding, appraising and applying health information. The scope of personal responsibility is constantly growing; what formerly would have been fate now might be considered as the result of responsible behaviour and this might have implications for justice as well.

### *II.1.2. Justice and solidarity*

18. Genetics might contribute to a better health care in several ways. For example, personalized medicine promises better outcomes and lowers the burden for specific diseases like some types of cancer. However, although genetic techniques are becoming increasingly less costly, they still require a lot of resources which some health systems cannot afford and can challenge other important areas and dimensions of human life and social determinants of health, such as protection of the environment and the improvement of working conditions. With regard to justice in health care and participation in progress, these gaps remain a major challenge within and among countries.



19. Huge inequalities in the distribution of wealth are obviously a barrier to sharing the benefits of scientific progress and its applications according to fundamental human rights. Education is also a matter of justice: persons with a lower education level and lower health literacy are denied the information which is required to exercise their freedom and autonomy.

20. In thinking of the distribution of responsibilities another issue arises: the possibility of behaving in a health-promoting way upon knowing one's genetic make-up might lead to social expectations of individuals living accordingly. Genetics itself has the potential to contribute substantially to this trend, mainly due to the – often unconscious and erroneous – perception of its deterministic character. If a person does not live in a health-promoting way, either due to a lack of health-literacy or due to the choice of a different lifestyle, the community might blame her or him for causing a disease and deny support to fight disease and suffering. Instead of sanctions, incentives can be introduced, e.g. by granting discounts or rebates of premiums charged for health insurance to encourage health promoting behaviour. This could result in discrimination and stigmatization of those who do not live a health-promoting lifestyle.

21. Discrimination and stigmatization on genetic grounds can also occur outside the health sector (e.g. non-medical insurance or work place). Even racism could be fostered, and be that only on the basis of erroneous or even unintentionally misinterpreted data. High sensitivity and attention as well as effective measures to prevent and promptly fight such developments are necessary.

22. Effects of discrimination and stigmatization can also occur with regard to prenatal and preimplantation genetic testing. The consequence of detecting a genetic abnormality is very often not a therapeutic intervention for the unborn child, which may be simply impossible. Even though some diagnoses have led to treatment in utero, the more likely consequence is resorting to abortion or discarding the embryo. Erroneous or misinterpreted results could lead to the destruction of healthy and normal embryos or fetuses. The introduction of non-invasive prenatal diagnosis is being increasingly implemented as a routine measure during early stages of pregnancy, especially in countries with an established system of technique-based pregnancy care. This could have a major impact not only on reproductive freedom, but also on the perception of disability and on societal solidarity with disabled people and women who give birth to them.

23. Justice and solidarity between countries is a priority in this field as well as in many others. This is especially true for lower and middle income countries which might contribute to scientific progress through participation in scientific and medical research without having the possibility to benefit from the results, because the health care system cannot afford implementing appropriate genetic services.

24. This kind of scientific knowledge, inasmuch as it is immediately related to what has been defined “heritage of humanity” in Article 1 of the UDHGHR, raises immediately the question of understanding it as a *common* good, to which *open* access should be therefore guaranteed. This question involves obviously the rethinking of the scope of informed consent (how broad or narrow the consent should be as both may have major implications), and raises the issue of confidentiality and data protection, as well as the problem of equitable sharing of research results between all participants. At the same time, however, it calls upon the international community, governments and researchers to address the very complex issue of the looming conflict between the right to have access to scientific knowledge and other relevant principles, starting with the patents for protection of intellectual property.

### *II.1.3. Understanding of illness and health*

25. The increasing knowledge about the impact of genetic factors on diseases and disabilities may have different consequences. On the one hand, it may be beneficial and emotionally relieving for an individual to know about genetic influences on her or his disorder, which formerly was believed to be caused by her or his own behaviour and faults. It

may be a relief for a family to learn – after having visited dozens of doctors who examined the child again and again without finding an explanation – that the child’s disease is caused by a genetic mutation. Furthermore, it is hoped that knowledge of genetic influences may lead to the development of therapeutic or preventive interventions for hitherto untreatable diseases. On the other hand, an overestimation of the genetic influence on the phenotype of a person, called genetic determinism, may lead to an underestimation of other biological as well as behavioural, psychosocial and environmental factors. This would result in a failure of the research to identify the real causes of the disease and would be a loss of opportunity for the individual. The responsibility of scientists and clinicians to explain the importance and the limits of genetics to the whole public is particularly important here.

26. As whole genome sequencing is becoming increasingly easy to perform, in parallel with the technical possibilities of integrating huge amounts of information on other biological parameters to get risk profiles for the manifestation of diseases at later phases in life, what can happen when people learn about their future risks should be taken into account. Of course, this knowledge may be beneficial. However, some problems need highlighting. Apart from the problem that information on risk profiles and disease prediction, especially of multifactorial diseases, is hardly evidence-based, the healthy individuals, knowing of a higher risk for some diseases, may already perceive themselves as being ill. Knowledge of a greater risk can be especially burdensome when there is no available preventive or therapeutic intervention and it has detrimental effects on the individuals and their family.

#### *II.1.4. Cultural, social and economic context of science*

27. Science, research and medical practice take place and develop in a particularly fast-evolving context: phenomena such as globalization, access to information and the multicultural melting-pot pose several new challenges. As a consequence, some cultural, social and economic aspects of scientific advances introduce a new tension between two poles that could be summarized as follows.

28. On the one hand, the logic of scientific and technological progress induces a rapid change, leading some people to imagine that everything that is technically possible should be achieved. This process is hard to control: no ethical standard or legal body appears to be capable of containing it. Such a phenomenon is intensified due to a radical conception of autonomy, according to which any medical progress should be at the disposal of patients, who are turned into consumers (clients). Several aspects of medicine, which previously asked “Where does it hurt?”, have been transformed into a practice of “What would you like?” and respond to the logic of demand and supply.

29. On the other hand, humankind is aware that any technological advance does not guarantee human progress *ipso facto*, in so far as it may go against the dignity and the equality of all human beings. In general, it is admitted that science, including basic research which is not possible without the freedom of researchers, must be regulated by ethical considerations and practiced within a legal framework respectful of fundamental human rights. The strength and success of the scientific method is based upon its quantitative approach, which sets aside the underlying purpose of things and beings and therefore does not by itself provide value, meaning and direction. When technical and scientific capacity reaches a new threshold (for instance, the possibility of introducing a genetic mutation into the genome of a human being), the ethical problem arises: what to do or not do, so that human beings remain human beings and achieve the best of their development? Global science requires an interdisciplinary and global update of the idea of human nature based on the progress of life sciences, social sciences, and ethical-philosophical thought.

30. In order to cope with this situation, several factors have to be taken into account. In particular, the following three factors:

- a. Ethics is not simply a matter of individual morality but it involves society as a whole. Therefore, technology cannot be justified only by individual freedom or consumer demand that goes with it: it must also pursue the common good. This societal dimension of ethics is paramount.
- b. Technical and scientific progress and research should not be idealized as if they were free from any uncertainty. With respect to the human genome, for instance, it is unrealistic to imagine that its integral deciphering can deliver the secret of the person involved. On the contrary, the genome entails a dynamic process, which extends over the entire social life of individuals. The belief that we can simply dismiss uncertainties would lead us towards an unreal 'ideology of promise'. Hence, caution is required when considering achieved results.
- c. Science tends to become more accessible to citizens. This is also a driver of many and complex developments. Over the last years, the status of patients has changed profoundly: they enjoy more autonomy and are more involved in the decision-making for their medical treatment. New media, the internet and free access to medical publications, as well as the large amount of information readily available, contribute to amplify this change, which has been called 'participatory medicine'. This involvement entails great opportunities and some concerns. The issue of determining the quality of information provided via the internet is an illustrative example. The advantage of the internet in its wide accessibility even beyond national borders is also its pitfall.

31. Article 3 of the UDBHR underlines that the interests and welfare of the individual should prevail over the *sole* interests of science or society. Misconception of this Article should be avoided, according to which attention is focused uniquely on individuals, technical solutions are considered under their exclusive responsibility, and society is exonerated from its responsibilities and from requirements of social solidarity, as if individual biology, starting with the genetic profile, would dictate only rules for individual adaptability to social conditions and to the environment. This is what happens, for instance, when oocyte cryopreservation is proposed to allow a woman a rapid professional career and possibly a pregnancy at an older age instead of developing a system of day care and assistance for working mothers. The equal development of the human being, both personal and social, should guide the use of technical and scientific progress, leading to more humanity, more solidarity and a harmonious development of human life in all of its dimensions: biological, psychological, sociological, and spiritual.

#### *II.1.5. Responsibility towards future generations*

32. Reproductive choices with regard to genetics are an issue of ongoing controversy. While some people claim that parents have the right to make far reaching choices concerning their offspring, including the use of genetic information obtained from the early stages of pregnancy, others hold that they should refrain from genetic testing of their future children if it is not necessary for their health. Some people underline the responsibility of parents to strive for the best possible health of their children even by intervening in their genes, whereas others stress the right of every human being to have an unmanipulated genetic make-up, so that nobody is due to choices of other human beings with respect to their biological starting configuration if it poses no risk of developing a disease of particular severity.

33. Thus, the responsibility to future generations is important because it respects the rights of those coming into life later on. It is also important for our social relationships, for a society in solidarity and for justice between all peoples to keep in mind that the respect for the dignity of every human being entails the duty to refrain from making her or him a mere instrument for the fulfilment of the wishes and preferences of others.

34. Germline genetic interventions were the subject of science-fiction novels and scientific theoretical debate, but considered non-executable. That has changed recently, even though the effectiveness, safety and harmlessness of these procedures are far from being warranted at the present time. This new reality calls upon experts, governments and all citizens to consider all the possible consequences on human rights and fundamental freedoms as well as on the future of humanity itself. Here it is very important to be aware of the uncertain and highly variable functional state of the genome. We cannot be sure of the long term effects of the introduced changes.

## **II.2. Institutional and transnational framework of genetic research**

35. As the implications and reach of biomedical and genetic research have extended beyond national borders, it has become necessary to address the corresponding ethical issues through international instruments and standards for the conduct of such research. However, differing social and cultural sensitivities among countries have made the articulation and implementation of universal norms challenging. International organisations have therefore developed an ethical framework for the conduct of genetic research in the form of declarations, guidelines and reports. This framework is especially important for countries which do not have national or institutional instruments in place for genetic research.

36. This section will focus on the ethical framework that has been developed by UNESCO, WHO (World Health Organization), WMA (World Medical Association), CIOMS (Council for International Organizations of Medical Sciences), and CoE (Council of Europe). These international instruments stressed the special nature of our genetic heritage, and attempt to set limits on the applications of human genetic research based on the human rights paradigm.

37. Issues arising from human genetic research are summarized below based on the following documents:

- a. UNESCO: UDHGHR (1997), IDHGD (2003), UDBHR (2005);
- b. WHO: *Review of Ethical Issues in Medical Genetics* (2003);
- c. WMA: *Statement on Genetics and Medicine* (2005, revised in 2009);
- d. CIOMS: *Declaration of Inuyama on Human Genome Mapping, Genetic Screening and Gene Therapy* (1990) and *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002);
- e. CoE: *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* (1997).

### *II.2.1. Consent*

38. The various international instruments are in agreement that prior voluntary informed consent without undue inducement should be obtained before conducting any human genetic research or testing. However, exceptions may be made if there are compelling reasons consistent with domestic law and international human rights law. During the consent taking process, the prospective participants should be informed of their rights, and provided with the objectives, benefits, burdens and expected results of the research. One of these rights includes the ability to withdraw from research at any point of time. This right may only be subject to narrow exceptions.

39. For research involving those lacking mental capacity, consent should be obtained from a legal representative, based on the best interests of the person undergoing research or on a direct health benefit, and if there is no research alternative of comparable effectiveness with research participants able to consent. Research which does not offer potential health benefit may be allowed provided that it does not expose the participant to more than minimal

risk, and only if the research is expected to contribute to the health benefit of other persons in the same category. Prospective participants should be engaged in the decision making process, and their right to refuse to participate as well as to withdraw from the research should be respected. In the case of minors, their opinions should be taken into consideration as a determining factor in research participation, and the weight of which should be in proportion to their age and degree of maturity.

#### *II.2.2. Research Findings*

40. The right of the individual to decide whether or not to be informed of the research results and consequences of genetic examination should be respected. The right to know does not apply to research on data that is irreversibly anonymized or to data that does not lead to specific findings concerning the individual. Where appropriate, the right not to be informed should also be extended to identified relatives who may be affected by the results.

#### *II.2.3. Privacy and confidentiality*

41. All the international instruments uphold the individuals' right to privacy and confidentiality, including their genetic data. The instruments also state that genetic data should not be disclosed to third parties without the individual's consent. To protect the confidentiality of an individual's genetic characteristics, the human genetic data and biological samples collected for research should normally be anonymized. Even when such data or biological samples are anonymized, specific precautions should be taken to ensure the security of the access to the data or biological samples. If the research requires the identification of the human genetic data and biological samples, the privacy and confidentiality of the individual should be protected according to domestic law and the data should not be kept in an identifiable form for longer than is necessary to achieve the relevant research purpose. For genetic test results that may have implications to family members, the persons tested should be informed during the consent taking process that they are encouraged to discuss these implications with them. In cases where failure to disclose the results involves a direct and imminent threat to the life or health of a person, some legal instruments allow the physician to reveal the results to third parties, provided there is prior discussion with the participant. It is also desirable that physicians consult their ethics committee prior to revealing these results to third parties.

#### *II.2.4. Non-discrimination and non-stigmatisation*

42. Individuals, families, groups or populations should not be discriminated against or stigmatized on the basis of their genetic characteristics. Population-based genetic studies and behavioural genetic studies should therefore be treated carefully and appropriate measures taken as the information published could lead to discrimination or stigmatization of certain populations or communities. To avoid discrimination and stigmatization, education with adequate norms and information about the objectives of research could be the most prudent avenue to reassure the public and correct their misconceptions about genetic research and techniques.

#### *II.2.5. Benefits versus burdens*

43. There is a need for an assessment of benefits and burdens before conducting human genetic research. Ideally, it would require maximizing direct and indirect benefits and minimizing any possible material and moral burden for research participants and other affected individuals. Research should only be allowed for the benefit of humankind and its results should not be used for non-peaceful purposes such as bioterrorism or purposes which infringe human dignity such as eugenics

#### *II.2.6. Sharing of benefits*

44. All the international instruments stress the need for sharing of benefits between countries, and especially with developing ones. The formulation of measures to enable developing countries to build the capacity to undertake research and have access to other benefits such as quality health care, the provision of new diagnostic and therapeutic modalities stemming from research and support for health services are encouraged, as well as international dissemination and free flow of scientific information and knowledge. The commitment to foster scientific and cultural cooperation is emphasized, especially between industrialized and developing countries for the developing countries to build up their capacity to participate in generating and sharing scientific knowledge. Finally, transnational health research should be responsive to the needs of host countries, and the importance of research contributing to the alleviation of urgent global health problems should be recognized.

#### *II.2.7. Intellectual property and patents*

45. The human genome in its naturally occurring state should not be used for profit, for example by patenting it. It is important to observe that the reference exactly to the *natural* state does not exclude in principle patent claims on *methods* of manipulating genes as well as on DNA in which the order of the nucleotides has been altered. All the more so, this normative statement cannot be extended automatically to the applications derived from this knowledge. As a consequence, many cases have been discussed in the Courts. The most famous one is probably the case concerning BRCA1 and BRCA2 genes, whose mutations confer a high risk for breast and ovarian cancer: after a long and contradictory sequence of decisions, the US Supreme Court reaffirmed in 2013 that isolated human genes may not be patented.

#### *II.2.8. Germline modification*

46. Due to uncertainties on the effect of germline modification on the future generations, such interventions have been strongly discouraged or legally banned in many countries. There are exceptional cases where interventions on the genome may be undertaken only for preventive, diagnostic or therapeutic purposes, and only if the aim is not to introduce any heritable modifications in the genome.

#### *II.2.9. Genetic counselling*

47. Non-directive genetic counselling should be offered before and after the conduct of genetic tests or screenings, which may have health implications for the person tested. This is necessary as genetic test results may be ambiguous and subject to differing interpretations. Thus, it is important that medical students and physicians, as well as bioethicists are trained in the field of genetic counselling, particularly relating to pre-symptomatic diagnosis of diseases. There are many principles underlying genetic counselling: respect for persons and families; full disclosure to individuals and families of relevant health information; protection of the privacy of the individuals and families from being discriminated and stigmatized by third parties; and informing the individuals of their ethical duty to inform blood relatives that they may be at genetic risk, or inform a spouse if a future child is at genetic risk.

### **III. SELECTED AREAS OF APPLICATION**

#### **III.1. Direct-to-consumer (DTC) tests and non-health care related analysis**

48. DTC genetic tests are accessible directly by any individual, without involving a medical professional. It is the individual who addresses and deals with the service provider directly, usually through a website. At times a medical professional may be approached after the test results have been received by the service user. This consultation may have different

purposes, in particular: a clarification of the meaning of the results; some advice on how to make use of them; responses to the worries that these results cause.

49. Generally the decision of taking a DTC test expresses the desire of the individual to satisfy curiosity about possible predisposition to certain illnesses, often prompted by known family backgrounds and antecedents. Rarely are these tests solicited as a way of providing a second medical opinion. DTC tests cover a broad range of genetic variants, associated more or less with genetic illnesses. In technical terms, they are a genetic study that goes far beyond analysing mere single gene variants or mutations associated with monogenic diseases because they analyse various genetic factors as well as variants associated more or less with multifactorial disorders including genetic susceptibility

#### DTC tests and medicine as consumer goods

50. The practice of DTC tests contributes to create the ‘commercialization of medicine’, something which changes not only the relationship between patients and healthcare professionals but also between the individual and the healthcare system. Modern society, especially in the more developed nations, might well be characterized by promoting the consumerism of individuals and incentivizing economic growth. Health has not been left out of this trend. More and more often, healthcare services are seen as just another consumer good. Even the information gathered thanks to DTC tests, has acquired an economic value. It allows DTC companies to sell services and treatments that are considered best at maintaining health or, in the case of illness, at preventing or curing it. Information can also be sold to third parties in particular under the guise of therapeutic research.

51. Many tests are also available for non-medical reasons. The problems that stem therefrom are of the same nature as DTC tests performed in the medical domain. Moreover, the non-medical tests can be both more pervasive (as one does not have to be ill to consider taking them) and more difficult to regulate. The information sought by customers and offered by providers ranges from tests for single non-medical conditions (e.g. caffeine sensitivity or soft or hard ear wax) to those offering analysis of the ethnic origins. Some tests are aimed at more complicated analyses such as genes which are ‘markers of skin aging’ to help prepare (and sell) the best anti-aging creams; and various metabolic and muscle markers to provide guidelines for personalized diets and/or physical activity.

52. DTC tests represent a business sector which crosses nations’ borders, requiring that problems be approached at the international level. Prohibition will not prevent individuals from easily jumping border restrictions through their access to websites, courier and sample transport services. DTC is a paradigmatic example of the globalization of healthcare services that makes national regulations overwhelmingly insufficient.

#### Lack of validity and clinical application of polygenic testing

53. DTC tests also encompass diseases which are multifactorial, a fact that contrasts sharply with clinical genetic testing for a single gene disorder. A lot of the offered DTC tests check only several of the very many genes potentially involved in the tested condition and the variations of some genes are not enough to determine, for instance, whether someone will have diabetes, or a stroke. In general, for most conditions for which tests are available the analysed genes are but the tip of an iceberg, and the result can only say very little about relative risk on the basis of these genes, without knowing anything about the other genes or risk factors such as diet or environmental conditions. People might be carriers of the variant without ever developing the disease and others could be affected by the disease without having the genetic variants known to be associated with susceptibility to the disease. The large number of factors associated with events in an individual’s life makes the targets announced by some DTC vendors in terms of the prediction and prevention of multifactorial diseases illusory.

### III.1.1. Ethical challenges

54. At least two fundamental rights are involved in an individual's solicitation of a DTC test. First, it can be said that such a step fits well with the right to health, to the extent that such genetic tests could be a possible way to protect one's health, taking advantage of the advances of biomedicine. Secondly, DTC tests could be approached in the context of the right to free personal development, to the extent that one of the reasons that give rise to their use lies in the desire of the individuals to be able to make decisions about their personal, family and professional future. Thus, as the request for a DTC test consists of an expression of the individual's rights, any limitation has to be based on strong grounds, otherwise running the risk of infringing them.

55. Limits may either be intrinsic or extrinsic. Referring to the former, it has to be reaffirmed that the individuals must have adequate and correct information, in order to make truly independent use of their rights. If there is any form of defect in the capacity of the individuals to exercise their will, it could otherwise be argued that the limitation is due to the lack of foundation for the exercise of freedom itself. It is therefore vital to assess the quality of information that is usually supplied by the service providers. As to the extrinsic limits, the individuals' freedom may be limited by conflicting either with the rights and interests of third parties, namely family members, or with general interest.

56. From the perspective of respect for autonomy, any measure unjustly limiting individual freedom may well be deemed paternalistic (patronizing, overbearing), to the extent that it imposes on the individuals what is considered as best for them. However, such a measure may not be deemed paternalistic when it aims to provide a remedy for the lack of information regarding the consequences of the decision made by the individual. It has to be stated, for instance, that some test results, without the further benefit of contextual information regarding family background and lifestyle habits, lack clinical relevance.

57. In many cases, the individual's autonomy and independence is seriously compromised, as companies that offer such services are not offering clear or adequate information about the true worth of the results of these tests in a diagnostic or predictive sense. Therefore it may happen that these tests do not represent any real benefit for individuals and lack scientific evidence of their safety and efficacy. When these tests represent a danger, the principle of non-maleficence itself should be invoked to prevent harm before it occurs.

58. The individual's autonomy might also be limited due to the risk of causing harm to third parties, i.e. family members who could find their right not to know affected. Genetic diagnosis and predisposition towards developing an illness in the future are data which belong not only to the individual, but also to the close family members and communities, as this information can have an impact on them.

59. A different yet relevant infringement of autonomy may be the consequence of the possibility to order a DTC test for a sample taken on someone else and without their knowledge. This is particularly true for paternity tests, but also for many other situations, where someone (an employer, an insurance company) may have an interest to acquire information on someone else's genetic endowment. Thus the autonomy of the person *giving* the tested sample is simply dismissed, together with her or his interest.

60. The principle of justice is also of concern. These tests do not merely represent personal decisions without any other consequence. They tend to have an impact on the public health system, as it is extremely common that 'consumers' resort to it in order to resolve their doubts originating from DTC test results. Therefore, public resources may well be diverted, and thus affect sustainability and equality of healthcare services.



### *III.1.2. Practical recommendations*

61. Such difficulties and the fact that DTC tests are offered within an environment of a globalized market cannot exonerate their practice from complying with ethical and legal principles and rules. Genetic counselling, through which the individual will be adequately informed about the value and use of the test results, is the first, necessary step to avoid the risk of causing harm either to the user or third parties. In this perspective, the role of public authorities is essential to promote campaigns to inform citizens about the real or unfounded scientific basis of DTC tests and raise appropriate awareness.

62. The main responsibilities to meet both at the domestic and the transnational level can be summarized in three points:

- a. evaluate the analytic and clinical validity as well as the clinical utility of these tests;
- b. promote and enforce clear regulations on the information to be supplied to possible users of these services;
- c. provide appropriate counselling whenever a DTC test is solicited. This may not be possible to implement everywhere, but at least sound information about the test and the meaning of its results should be obligatory for the test provider.

63. Regulations and consumer protection laws should also be in place for non-medical DTC tests, so that only validated tests can be sold and, once again, that their use cannot be detrimental to others. The more vulnerable the individuals, the stronger the protection should be. It is very important, for instance, to not test minors without a medical reason and proven scientific basis for genetic factors supposedly associated with lifestyles. DNA testing of children to select a sport for them is another example of what should not be done, as it could easily lead to limitations of autonomy, overload of expectations or, on the contrary, to stigmatization.

### **III.2. Precision/personalized medicine (PM)**

64. Next generation sequencing and genome analysis are central to the emerging concept of PM, which aims at comprehensive appraisal and analysis of individual patient data over time through integrating multiple disciplines including mathematics and biology. Applications already exist, particularly in the field of oncology. An example of an important immediate benefit to patients is the possibility of finding the correct dosage of the right drug at the right time as well as preventing loss of chances due to ineffective drug or harmful side effects. Genomic analysis can also be used to improve diagnosis with earlier intervention and more efficient management of the patient's condition and to monitor the response to the treatment and make an early detection of residual disease such as circulating tumour cells, thus preventing a relapse or allowing early treatment of it.

65. Development of PM is especially based on understanding of the individual's genetic makeup. This requires development of a constantly updated clinical decision support software, as no single doctor can understand the secrets of the 3,000,000,000 base pairs of genetic information of their patients. PM is the result of a more general integration of personal biological and health data, that aims to make medicine not only precise but also predictive, preventive and participative to make it finally personalized medicine. This goal requires identification and monitoring of multiple biological parameters of the individual, which may lead to a customized treatment for a given patient.

66. Having in-depth knowledge of an individual's genetic make-up will also be an advantage when making a decision on whether to choose a patient for inclusion or exclusion in a clinical trial. The ability to detect those who can profit most from a test can increase the security of patients from adverse events, and allow more – and cheaper – trials to be conducted.

#### *III.2.1. Ethical challenges*

67. The first ethical concern is the respect for privacy. Access to personal data, including the personal genome and health records, may accelerate the understanding of the physiopathology of many diseases, which may lead to prevention and new treatments. Genomic data being the easiest way to identify an individual, however, the accessibility to these data, their security and the rights of individuals to know at any time what is done with their DNA sample or its sequence are essential, even if the collection is done with their informed consent. PM programs may allow private companies to create a novel business model using the information they may extract from the collected data. Several recent examples illustrate this tendency of genomic information extracted from cohorts being sold to pharmaceutical companies.

68. Another ethical issue is the cost and affordability of PM. Hopefully the cost of customized treatment should decrease and the proper use of treatment may in the long term lead to considerable savings in healthcare, as there will be fewer inappropriate or ineffective therapies. However, we are at an early stage in applying PM: its cost is still relatively high, and providing equitable access to it may be difficult even within a single country, due to various levels of health insurance or access to information. It would be unethical if a person was found to be suitable for a treatment, but could not afford it. In any case, the predictive aspect of genomic data is currently a matter of promise and very few gene mutations or variants are really informative. Cost-benefit analyses are needed to ascertain which procedures have clinical utility and validity and for what diseases. Moreover, it is very important to remember that the development of precision medicine, however promising it may be, should not take place at the expense of neglected diseases such as rare diseases and tropical diseases.

69. Another problem lies with the communication of valid, actionable data to the patient, which can be used to determine treatment, make lifestyle changes or allow the individuals to make informed decisions pertaining to their well-being if no treatment is possible, as still is the case for a number of genetic diseases. This is more a question of training of medical personnel and giving patients access to genetic counselling, considering also the rights of the other members of the family when a genetic variant which entails some risk is detected.

70. Protection of patients is also an issue. There are basic concerns regarding the potential consequences, particularly the psychological effects, for patients who are found to be unsuitable for a certain treatment if no efficient alternative exists or are non-responsive towards a PM based treatment. Anticipation of such situations and an appropriate medical environment must be developed. The right of the patient to refuse analyses also needs to be considered.

### *III.2.2. Practical recommendations*

71. The pharmaco-genomic data associated with a given drug must be incorporated into its prescription label, to help create the optimal possible treatment decision for the patient. Specific regulatory standards, analysis strategies, reference materials and new monitoring tools have to be developed. Regulatory agencies should be entrusted with matching them and checking the validity of various sequencing platforms, so that their reliability can be assured.

72. Reimbursement policies and health care systems need to be redefined to suit the changes that PM can produce. There are many factors that ought to be thought of: the efficacy and the interest of assorted genetic tests among the whole population; cost-effectiveness in relation to benefits; the specificity of payment systems in the context of rare diseases; the way to redefine a 'shared risk' insurance to include the impact of the newer notion of 'individual risk factors'. The specific implications for some ethnic groups should also be considered. Moreover, genetic data should not be misused by employers or insurers.

### **III.3. Biobanks**

73. Development of genomics research is based on storage of samples and data derived from patients and collected for diagnostic and research purposes in large sample collections (biobanks). Systematic collection of human samples and data provides the foundation for basic and clinical research towards better stratification (subgrouping) of diseases, according to the specific profile of the disease, allowing the development of new approaches to prevent and treat diseases and for development of new drugs and companion diagnostics (theranostics). Analysis of biobanked human samples has come to stay as part of medical practice and is very likely to increase substantially in the future. The IBC has already addressed the role of biobanks and some of the related ethical issues in its *Report on the Principle of Non-Discrimination and Non-Stigmatization*, finalized in 2014.

### *III.3.1. Ethical challenges*

74. A major challenge of biobanking involves the informed consent. It should be stressed that participation in a biobank must be voluntary. In newly established biobanks, sample donors are required to sign an informed consent form specifying the objectives of the research. However, it is essentially impossible to give donors specific information on the potential future use of their samples and data stored in a biobank as new technological advances are likely to provide totally new approaches regarding analysis of old samples and so a change of research on these samples. This is why informed consent, building on the premise of the respect for individual autonomy and self-determination, can also entail consent for a broader future use of the samples and data. Even more problematic are samples from cohorts dating from the pre-consent era as these samples with tens of years of follow-up data are very valuable for research, and yet only an oral consent or a presumed consent is available.

75. As huge numbers of samples are often required to study the relationship between diseases, environment, nutrition and lifestyle, it is essentially impossible to ask hundreds of thousands of donors for re-consent every time a new experiment is considered. This obstacle must not lead to an abuse. Commercial companies selling DTC genetic tests often obtain very 'soft' consent for research purposes and use personal data and the collected DNA, within the framework of a service already paid by the consumer, for their own benefit.

76. Protection of the confidentiality of data is a challenge when it can remain available also for authorized re-use. It is likely that biobank-derived genetic information will gradually become part of routine health records and be treated as part of other confidential health information. In some countries specific biobank legislation has already taken such situations into consideration and allows the transfer of old diagnostic samples to biobanks. Public announcements are used to inform donors of their right to opt out, i.e. to withdraw their samples and data from the biobank. Other countries may have transitional provisions for such legacy issues. Another danger of biobanks aimed at specific ethnic populations is that of stigmatization if genetic particularities are found. To maintain public trust in biobanks clear rules should be in place for the protection of individuals to make secure the way of storing and sharing the biobank materials, whether DNA, cells, tissue or information.

77. A practical question is how much protection of genetic data – a truly unique identifier of every human being – is needed. To access biobanked samples and data, complicated access policies and user authorization processes are put in place together with scientific and ethical review of such research projects carried out on samples.

78. Another ethical problem of using biobanked samples for large scale sequencing stems from 'incidental' findings which may in the future be of considerable medical importance for the individual. Considering that whole genome sequencing is now easier and cheaper to perform, incidental findings will be less and less unexpected. Several questions emerge, including:

- a. Is it necessary or interesting to analyse every DNA variation?

- b. Is it necessary to disclose everything?
- c. Who should receive the information: the patients, their physician, their family?
- d. When to disclose?

At least two positions have been voiced. The American College of Medical Genetics and Genomics (ACMG) argued for disclosure when the genetic variant is clearly linked to a disease, especially when steps can be taken to reduce the risk. European associations and the Presidential Commission for the Study of Bioethical Issues of the US recommended anticipation: patients should be told before testing that variation unrelated to the condition being tested for might be found and they should decide in advance whether or not they want to be told about any such unexpected discoveries. If an individual has chosen not to be informed of incidental findings this should be respected, even if such findings could be of considerable importance for the medical professionals in charge of the patient's treatment. If such information is stored in the medical records, it could be taken into account at a later stage if a need arises and with prior consent of the patient. Article 10 of the *International Declaration on Human Genetic Data* also stresses the right of the patient not to know the results of a genetic test. As it has already been underlined in paragraph 14 of this Report, the many and complex questions related to incidental findings are an issue of debate.

79. The perception of one's DNA sequence as determining the fate of an individual appears to be changing with the overall increase in genetic information, people's understanding of the benefits of genetic testing in medical practice and the availability of DTC tests. Individuals interested in knowing about their genetic makeup and inheritance contribute to the Personal Genome Project, which was founded in 2005 in order to publicly share genomic, health and trait data of a great number of volunteers throughout the world. The goal of this project is to widen scientific knowledge of the human genome and its relations to the environment of the individual and to learn about ways of interpreting the big data of high throughput sequencing. This type of Citizen or Participatory Science is opening up scientific research projects, including genetics, to volunteering non-professional laypersons who are increasingly empowered to collect their medical information and even to analyse it. This is one example of what is referred to as Participatory Medicine. In some way, this trend is fostered by the secrecy of the pharmaceutical companies and academic medicine about the results of their research, so that individuals with rare diseases are using the existing resources like the internet and Citizen Science to find out more about their conditions and diseases and share this knowledge.

### *III.3.2. Practical recommendations*

80. It would be challenging to include all existing biobanks in an international registry with clear rules for access and sharing, in particular for cross-border and industrial access, because there are too many of them and have statuses that are too diverse. However, this type of registry should be implemented. The rules governing data confidentiality and ethical review should also be harmonized.

81. For broad informed consent (as mentioned in paragraph 74) to be morally acceptable it is essential that participants are ensured of a trustworthy form of governance involving among others a strict protection of personal information and research data (which is not necessarily incompatible with the use of research data for future research purposes). A strict framework for biobanks should satisfy the following requirements:

- a. It must apply for the whole duration of existence of the samples and data from the time when the samples are acquired and the related data are collected.
- b. It must restrict the processing and transfer of samples and related data for the duration of their existence to the purposes of scientific research.
- c. It must guarantee that personal information is inaccessible to all non-research third parties and ensure this by appropriate prohibitions on use.

- d. It must enable and at the same time guarantee the use of anonymized and pseudoanonymized samples and data in accordance with their intended use and their further transfer for this use alone.
  - e. Personal samples and data may be transferred within the domain of science only to the extent that this is necessary for research purposes.
82. The model of governance for a biobank should at least specify:
- a. How samples are stored (quality control);
  - b. Who has access to the bank (ensuring privacy);
  - c. Property rights of the patients and other people who provided samples;
  - d. The conditions for allowing secondary use of samples or the results of their analysis;
  - e. The conditions of scientific and ethical evaluation of requests for secondary use (and among which: the way in which it would be determined if this secondary use falls within the scope of the original consent);
  - f. Who can use samples for secondary use and how competition for samples among researchers is settled;
  - g. Whether commercial companies have access to the biobank and the norms for this use;
  - h. What secondary findings will be returned to the donor;
  - i. How donors can remain informed of future use of their samples or the results of the analyses stemming from their samples
  - j. In case of storing and/or using specimens and/or data in a country other than the one in which the samples were taken, the model of governance for a biobank should at least specify:
    - (i) How the interests of the country of origin and sample donors are taken care of in the governance of the biobanks;
    - (ii) Under what circumstances the material is returned to the country of origin;
    - (iii) How resulting benefits are shared.

#### **III.4. Non-invasive prenatal testing (NIPT)**

83. In recent years, new screening tests have been developed to identify chromosomal and genetic abnormalities of embryos and fetuses. These tests are non-invasive, making use of DNA from the embryo or fetus circulating in the mother's blood. The development of this technique started with a test for trisomy 21, than added trisomy 13 and 18 as well as chromosomal aberrations. Since recently, microdeletions and duplications can be examined as well, though their clinical relevance is often not known. For research purposes, already the whole genome of the unborn was sequenced. These new tests represent a technical breakthrough, but have also a significant ethical relevance.

84. Prenatal screening encompasses the entire array of medical tests that all pregnant women – depending on institutional and financial accessibility – qualify for during pregnancy. This is distinct from tests that may be indicated for some individual pregnant women in the context of looking for a specific abnormality that has already affected a child in their family. The latter cases constitute an individual diagnostic process and not population based screening.

85. Screening for chromosomal abnormalities is at present a stepped procedure: the first step is called a 'combined' or 'first-trimester test', which is performed at a pregnancy term of eleven to fourteen weeks. It combines ultrasound with biochemical examinations from maternal blood. So they are non-invasive as well, though typically the notion NIPT is only used for the new genetic tests for circulating DNA. Pregnant women in whom the combined

test indicates an elevated risk of a child with an abnormality are offered follow-up testing to determine whether the foetus has indeed a chromosomal abnormality. This is done using amniocentesis (at fifteen to eighteen weeks) or chorionic villus sampling (at eleven to fourteen weeks). Amniocentesis and chorionic villus sampling are invasive procedures during which cells are harvested from the amniotic fluid or the placenta. This is associated with a small but not negligible risk of miscarriage.

86. In several countries NIPT, at present, is offered as a second screening test to pregnant women diagnosed with an elevated risk due to a positive combined test. The advantage is that pregnant women receive a rapid, reliable and almost always reassuring (negative) test result. An invasive test would only follow in the event of an unfavourable (positive) NIPT result, because a final diagnosis is needed if the pregnant woman is to consider terminating the pregnancy. This strategy with NIPT as second screening test can significantly reduce the number of invasive procedures. Once the validity of NIPT will be established in the general population, the question whether NIPT should be used as first-line screening test – instead of the combined test – will arise. Indeed some already recommend NIPT as an alternative to the combined test within the context of screening programmes.

#### *III.4.1. Ethical challenges*

87. Population screening is defined as the offering of medical investigations to people who have no symptoms or other reasons to seek medical care for the conditions that are the target of the investigation. Screening is only justified if the usefulness of the intervention has been proven, and the advantages for the participants clearly outweigh the disadvantages. For most forms of screening, this means that health gains may be achieved through timely treatment or prevention. This also applies to prenatal screening programmes for infectious diseases and blood group antigens.

88. The situation is different when the purpose is not health gain but to decide, according to many domestic legislations, whether to carry a pregnancy to term, as it may be the case with serious foetal abnormalities. If they carry to term, it allows those involved to prepare for the birth of a sick or disabled child. If they do not, they avoid giving birth to a sick or disabled child. No matter how difficult or painful, many pregnant women and couples feel it is important to be given the choice. Prevention as a social objective, focused, for example, on reducing care costs for people with congenital conditions or disabilities, cannot be the goal of such screening. That would imply a discriminatory practice that sends the message that these people are unwelcome in society. Of course, these possible effects should be discussed in the overall context of ethical reflection on all prenatal diagnostic methods and not only with regard to NIPT.

89. The potential ethical disadvantages of NIPT can be summarized as routinization and institutionalization of the choice of not giving birth to an ill or disabled child. The disadvantage of a simple, safe test may be that participation is considered self-evident and presented as such by care providers, especially when financed by health insurance. This may lead to pregnant women (and their partners) not fully realising that the test results may leave them with a major and possibly extremely difficult decision. Ironically, the introduction of a test that may bring informed choice to more pregnant women may undermine this goal in practice, if NIPT is used without thinking enough about the impact. Furthermore, there is the risk that pregnant women with a positive result don't await the validation of the result through invasive diagnostics, but immediately choose to abort the embryo or foetus, without adequate counselling about the relevance of the detected abnormality. Also women may feel pressured to submit to such screening. They might be stigmatized if they refuse to take the test.

90. A widespread use of NIPT, namely as general screening in order to detect abnormalities, followed by an abortion, is perceived by some people as an evidence of the will to avoid permanent pain in a lifetime, by others as a sign of a situation of the exclusion

society gives to people affected by this illness, meaning indirectly that certain lives are worth living, and others less. The absence of or the insufficient health, education and protective structures for these people in many countries must also be underlined for the definition of health policies in this regard.

91. Another risk lies in the cultural prejudices of preferring a child of the male sex, the sex of the baby being one of the characteristics that can obviously be discovered by NIPT. As this test can be carried out at a very early stage of the pregnancy it would be difficult, even impossible for doctors to forbid the communicating of sex to the parents, and especially at a time when many countries have liberalised abortion. This could lead to a selection based on sex, which is against ethical values of equality and non-discrimination.

92. In addition, a widespread use of NIPT to analyse more and more genetic features up to the entire genome would mean that the complexity of data would lead to a significant increase of false-positives, requiring a confirmation by invasive tests or of abnormalities whose relevance is not known at all, but this unknown might lead the parents not to take any risk. Hence the following paradox: the number of invasive diagnostics would rise because of the use of the NIPT that should precisely be diminishing the use of invasive diagnostics. Given that the sequencing of the genome in many cases only enables one to determine the probability of developing an illness, a difficulty arises: how to establish an accurate relation between the gravity of the foreseen illness and the probability of it appearing? Must a weak probability of developing an illness later be considered as a major or a minor risk? Access to such tests, especially if they are not correctly interpreted, is anxiogenic; how will parents live with the knowledge that the child has the probability of developing a serious illness that may never develop?

#### *III.4.2. Practical recommendations*

93. Many fear that the widespread use of NIPT as general screening may induce 'eugenic' use, even when the state is not involved. The adding up of a lot of individual choices to the 'acceptability' of aborting certain kinds of embryos or fetuses brings forward a societal phenomenon, which resembles a kind of eugenics in the search for a 'perfect child'. It is therefore important to develop a framework that on the one hand acknowledges the right of an individual to make autonomous choices, and on the other hand ensures what is enshrined in articles 6 and 2 of the UDHR: that no one shall be subjected to discrimination based on genetic characteristics and that individuals should be respected in their uniqueness and diversity.

### **III.5. Emerging techniques for engineering gametes and editing the human genome**

94. A number of new techniques have emerged with the potential to dramatically change the possibility of intervening on human genetic material: somatic nuclear transfer, induced pluripotent stem cells (iPSCs), spindle and pronuclear transfer, gamete formation from iPSCs and genome editing.

#### *Somatic nuclear transfer*

95. Somatic nuclear transfer is a technique that has been used for cloning numerous species of animals: the most famous case was the sheep Dolly in 1997. This technique is based on extracting the genetic material (the nucleus) from a normal somatic cell (not a germ cell so not an egg or a sperm) and introducing it into an oocyte (egg cell) of the same species from which the nucleus has been previously removed. The reconstructed oocyte is induced to develop and is implanted in the uterus of a female mammal of the same species. The success rate of this technique is not high. Dolly was the one successful outcome of almost 300 attempts, whereas for mice, for which there are more data than for any other mammal, it is about 1%.

96. Since the birth of Dolly, somatic nuclear transfer has been successful for many mammals, but its use for humans was more a theoretical possibility and an ethical problem than anything else. Two terms were introduced: cloning for research purposes and cloning for reproductive purposes. The aim of the former was to obtain early stage embryos, which would never be implanted but could serve as the source of embryonic stem cells, which could be used for various purposes in regenerative medicine. The second term is self-explanatory: the aim of the process would be to obtain an embryo that would be implanted and would lead to the birth of a baby that would be the clone or the genetic copy of another human being. Human cloning for research purposes was first done in 2013.

#### Induced pluripotent stem cells

97. The discovery of a new method for producing stem cells with the capacity of producing any cell of the human body without having to destroy embryos led to a great deal of enthusiasm. iPSCs are produced through the introduction of several special genes into normal somatic cells. The capacity of iPSCs to be a substitute for normal embryonic stem cells (ESCs) is a topic of debate. Comparisons between ESCs, iPSCs and embryonic stem cells obtained from cloning for research purposes showed that there may be quite a number of differences between iPSCs and ESCs, and fewer differences between cells obtained after somatic nuclear transfer and ESCs.

#### Mitochondrial diseases – methods to avoid passing them to the next generation

98. Mitochondria are organelles of human cells, they have their own DNA (mitochondrial DNA) and are passed only from the mother to her children – paternal mitochondria are destroyed in very early embryos. The mitochondrial DNA does not contain many genes (37 genes in comparison with more than 22,000 genes in the nucleus), but it can contain mutations, which cause a number of diseases, most often involving nervous tissue and muscle, and can lead to blindness, deafness, diabetes and many other diseases with a variety of symptoms. No treatment for these diseases is known. Within a given cell, not all the mitochondria bear a mutated gene. Most mitochondrial diseases become symptomatic when the percentage of mitochondria carrying the mutated gene exceeds a certain threshold, which depends on the mutation and the tissue. In contrast to diseases caused by mutations in nuclear genes, prenatal and pre-implantation diagnosis (though it has been successfully used) does not always give fully reliable results. Moreover, for at least one of the more common mitochondrial diseases, a form of blindness, the percentage of mitochondria carrying a mutated DNA is 100% in most persons affected with this disease so it is always passed on to the next generation, though for this particular disease women are often asymptomatic.

99. Maternal Spindle Transfer (MST) and Pro-Nuclear Transfer (PNT) are two IVF based techniques which have the potential of preventing transmission of maternally inherited mitochondrial disorders caused by mutations in the genes of mitochondria. For MST, nuclear DNA from an egg cell (coming from a woman who is carrier of mutations) is transferred into a donor's egg cell from which the nucleus is removed and consequently which brings healthy mitochondria and the reconstructed cell is then fertilised. For PNT, the nuclear DNA is removed after the egg of the woman with faulty mitochondria has been fertilized and is then transferred into a donor's fertilized egg, after removing the nucleus from the latter. MST does not involve the destruction of donor embryos because transfer is performed before fertilization.

100. Recently a different method has been tried in mice to modify mitochondrial genomes in oocytes without resorting to donor eggs and using a genome editing technique addressed at mitochondrial DNA, which gave promising results.

#### Gamete formation from iPS-cells



101. Successful derivation of egg and sperm precursor cells from mouse embryonic stem cells (ESCs), so called ‘artificial gametes’, has been performed in several laboratories, and more recently this has also been achieved with human cells. Recently, it has been shown that artificial gametes can be produced in mice also from induced pluripotent stem cells (iPSCs). These findings demonstrate not only that iPSCs are developmentally similar to ESCs, but also that somatic cells from adult tissues can produce gametes in vitro, that is, if they are reprogramed into iPSCs. These procedures promise numerous new possibilities for stem cell research and the techniques of assisted reproductive technology. Couples would be able to use in vitro fertilization to have a genetically related child, without the need for gamete donors. However, the technique that is successful in mice may not necessarily work in humans. In addition, major technical challenges still remain. Current results produce primordial germ cells (created in vitro from stem cells) which must be converted into mature sperm and or in eggs by transplanting them respectively back into testes and ovaries. Furthermore, both iPSCs and ESCs frequently pick up chromosomal abnormalities, genetic mutations and epigenetic irregularities during culture.

### Genome editing

102. A new technique of genome editing using a bacterial system, called CRISPR-Cas9, has recently been introduced offering the possibility of inserting, removing and correcting DNA with relative simplicity and efficiency, unrivaled so far. As we explained in § 9, the application of this technology to the germline raised serious concerns within the scientific community itself since its discovery. In April 2015 a group of scientists from China published the results of applying this technique to human embryos obtained from in vitro fertilization but carrying abnormalities preventing their further development. The technique turned out not to be very effective and caused numerous inserting errors.

#### *III.5.1. Ethical challenges*

103. Gene therapy could be a watershed in the history of medicine and genome editing is unquestionably one of the most promising undertakings of science for the sake of all humankind, even though it must also be noted that there are only few diseases for which the abnormality of one single gene is a necessary and sufficient condition. Gene therapy cannot provide the quick fix for the vast majority of diseases, which depend on many genes as well as environmental factors and lifestyles.

104. At the same time, this development seems to require particular precautions and raises serious concerns, especially if the editing of the human genome should be applied to the germline and therefore introduce heritable modifications, which would be transmitted to future generations. Also the debate on using and manipulating gametes outside the human body, prompted by the advent of the IVF technology, has been completely renewed and made more challenging after performing the first human ‘cloning’ of an embryo, after the experiments on spindle and pronuclear transfer to prevent mitochondrial diseases and after those to produce ‘artificial gametes’ from iPSCs.

105. As it happens in the case of different sorts of drugs or treatments, *safety* is the unquestionable condition for application to human beings. This is all the more so when the object of investigation is an intervention which is likely to have significant effects on the life of individuals who could be considered ‘designed on demand’ by someone else without their consent, and transmit their genome modifications to future generations. Many scientists claim that little is known about gene interactions and the possible unintended consequences of modifying the human genome. By eliminating some harmful predisposition, other problems may result and impose other risks potentially as serious as the ones we were able to eliminate upon individuals and the human species itself.

106. The destruction of embryos implied in some of these techniques revives the well-known controversy on the principle of *respect for human life* and the related issue of the

status of zygotes, embryos, and fetuses. Here, consensus is impossible to attain. On the one hand, there are those who support the argument that the threshold of the ‘right to life’ is reached only *at some point* of the development of human life, depending on several considerations on the progressive acquisition of essential characteristics, traits, and abilities as well as the necessity to balance this principle with the one protecting the mother’s self-determination. On the other hand, there are those who contend that unconditional respect is due *from the very beginning*, building on the observation that embryo development is an ongoing process as well as a strong notion of the sanctity of life. Even the most widespread religions do not share the same position.

107. *Dignity* is another matter of ethical concern. Article 1 of the UDHGHR states 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”. The well-known definition of the human genome as “the heritage of humanity” in a symbolic sense immediately follows. According to UNESCO’s definition of the world heritage, generally applied both to monuments and natural sites, this is to underline the outstanding value of what should be *protected* and *transmitted* to future generations. Nature is often understood as a limit to human freedom. At least in this case, building exactly on Article 1 of the UDHGHR, the argument is made that it should be rather considered as its premise, so that interventions on the human genome should be admitted only for preventive, diagnostic or therapeutic reasons and without enacting modifications for descendants, as affirmed in Article 13 of the Oviedo Convention. The alternative would be to jeopardize the inherent and therefore equal dignity of all human beings and renew eugenics, disguised as the fulfilment of the wish for a better, *improved* life.

108. The issue of dignity is strictly related to the issue of *justice*. The prohibition to get financial gains from the human genome in its natural state, enshrined in Article 4 of the UDHGHR, has already triggered very complex legal disputes. Once we recognize the human genome as the heritage of humanity, the unavoidable consequence is the sharing of possible benefits resulting from scientific research, without distinction, among others, of legal systems and economic conditions. Differences of the former underline the differences of ethical evaluations and traditions that prevail in different communities and countries, including those related to the concepts of parenthood and family, which explain the different ways of considering the several techniques for manipulating and combining gametes. The latter also remind us of the necessity for new technologies to fill in the gaps of inequality as to the access to the most advanced opportunities of health care. The looming risk is to make them deeper.

### *III.5.2. Practical recommendations*

109. Medical reasons should always remain a mark not to overstep. The goal of eliminating terrible diseases can only be a shared one and gene therapy could also help reduce the controversies on the principle of respect for life, as it could be a way to address the cause without raising the issue of deciding on the life itself of the foetus or embryo that carries it. On the contrary, the performance of spectacular achievements without any sound medical reason, especially when it raises relevant problems of safety as well as serious ethical concerns, is to be discouraged – for instance by not giving access to public resources – and in some cases even prohibited. Research on the possibility of cloning human beings for reproductive purposes remains the most illustrative example of what should remain banned all over the world.

110. The international community of scientific researchers should be entrusted with the responsibility of assessing and ensuring the safety of procedures that modify the human genome. A thorough and constantly updated investigation on all the consequences of these technologies is required.

111. The goal of enhancing individuals and the human species by engineering the genes related to some characteristics and traits is not to be confused with the barbarous projects of eugenics that planned the simple elimination of human beings considered as ‘imperfect’ on an ideological basis. However, it impinges upon the principle of respect for human dignity in several ways. It weakens the idea that the differences among human beings, regardless of the measure of their endowment, are exactly what the recognition of their equality presupposes and therefore protects. It introduces the risk of new forms of discrimination and stigmatization for those who cannot afford such enhancement or simply do not want to resort to it. The arguments that have been produced in favour of the so-called liberal eugenics do not trump the indication to apply the limit of medical reasons also in this case.

112. Scientific research is a global endeavour, as the market for its applications is global. Therefore, what becomes legal in one single country becomes allowed. Society has been used to several kinds of ‘medical tourism’ related to assisted reproductive technologies and surrogate motherhood, just to mention the most debated examples. It is important for States and governments to accept the principle of a shared global responsibility when the engineering of the human genome is involved. The race to be the first should be avoided, especially when germline modification is proposed.

113. The ethical debate on producing and destroying human embryos for some relevant human good continues. Procedures that are as ‘non-controversial’ as possible on this point should always be encouraged: contraception rather than abortion; use of the so called adult stem cells or induced pluripotent stem cells (iPSCs) rather than embryonic stem cells. New techniques to prevent and treat diseases should be investigated and developed according to the same priority. This approach should also be considered, as much as possible, in national legislations and international regulations and guidelines while respecting the human rights to freedom and safety.

#### **IV. FINAL RECOMMENDATIONS**

114. These recommendations are to be understood as complementary and interrelated.

115. In a symbolic sense, as stated in Article 1 of the UDHGHR, the human genome is “the heritage of humanity”. Abiding by this definition, it is acknowledged that the advancements of science and technology in this field entail a global responsibility, which has to be met not simply by States and governments, but by the international community as a whole. Otherwise, the ‘demand’ for some product, service or achievement will always find a space where the corresponding ‘supply’ remains or becomes legal. This is also to underline the risk that it could be essentially the market, which is as global as science, which would decide what possibilities are worth realizing and draw the line on what is ‘acceptable’ or not. Ethical principles should always guide genetic diagnosis and interventions.

116. States and governments, especially in relation to editing the human genome so that genetic modifications would be passed on to future generations, should renounce the possibility of going into it alone within their own legal system. Retaining their freedom to adopt more detailed and even stricter national regulations, they are called on to boost the idea of shared global standard-setting and regulation, building on the universally accepted principles enshrined in the UDBHR: human dignity; autonomy and individual responsibility; respect for vulnerable people and personal integrity; privacy and confidentiality; equality, justice and equity; non-discrimination and non-stigmatization; respect for cultural diversity and pluralism; solidarity and cooperation; social responsibility for health; sharing of benefits; protection of future generations; protection of the environment, the biosphere and biodiversity.

117. The importance of a discussion involving scientists and bioethicists to reflect at the global level on the consequences of new technologies relating to the human genome is crucial. The United Nations, through its several agencies and bodies and other possible procedures of consultation and evaluation of the advancements of research, should be

responsible for making fundamental normative decisions. The precautionary principle should be respected, ensuring that substantial consensus of the scientific community on the safety of new technological applications be the premise for any further consideration.

118. Against this background, the IBC reaffirms the necessity for a ban on human cloning for reproductive purposes and recommends a moratorium on genome editing of the human germline. There is no medical or ethical argument to support the former. As to the latter, the concerns about the safety of the procedure and its ethical implications are so far prevailing. A special case of debate is posed by the novel techniques for the prevention of mitochondrial DNA disorders. Once again, it is essential to have reliable international scientific fora to ensure – as it is recommended also in the key conclusions of the in-depth Report of the Nuffield Council on Bioethics on this topic – that these procedures “are adequately proven to be acceptably safe and effective as treatments” before considering them for use in human beings. Even among scientists, an agreement on the threshold of what could be considered as “acceptably safe and effective” has not yet been reached. At the same time, acknowledging the existence of different perspectives and normative standards, the debate remains open on the *ethical* acceptability of these techniques.

119. Many issues, especially those related to the respect for human life at its very beginning, remain controversial. The IBC suggests applying the method of the largest possible inclusion: those procedures should be encouraged that are ethically ‘non-controversial’, that is respectful as much as possible of the different sensitivities and cultural traditions. National legislations and international regulations and guidelines ought to be framed accordingly.

120. DTC tests and new generation sequencing techniques, including whole genome sequencing, require raising awareness and higher levels of health literacy and education for professionals, patients, research participants and all citizens. Protection is no longer possible only through rights and duties in the patient-doctor-relationship, but requires an independent empowerment of the user, who needs to have sufficient information and access to appropriate counselling.

121. Service delivery in genetics should always be quality assured, accredited according to high quality standards and officially certified. The same pertains to websites which provide information about genetics. A regulatory agency framework should be implemented for DTC tests, guaranteeing autonomy, privacy and unbiased information, and the absence of misleading advertisement for the sake of financial gain. Having in mind the difficult nature of the results of genetic analyses, especially in the case of diseases with multifactorial traits or new variants with unknown impact on the individual, special training is needed for people communicating them. Doctors should know about the role of genetics in diagnosis, therapy and prevention of diseases.

122. The difference between medical and non-medical use of the new technologies remains crucial. Any future work, research, and research application in the non-medical fields should respect human rights and dignity. Therefore, enhancement techniques, which have long since been a matter of special concern in sports, also deserve deep reflection and precaution. Benefits resulting from advancements in human genetics, inasmuch as they have an impact on health protection and health care, for instance through precision and personalized medicine, should be considered as content of the fundamental right of every human being to enjoy the highest attainable standard of health regardless of whatever distinction, which entails – among others – the right to have access to quality health care and medicines. However scientific progress should not deepen inequalities within and among countries nor be used for discriminating against individuals or groups.

123. Considering the growing implementation of biobanks and the problem of big data, biobank safeguards should be internationally implemented and international guidelines and standards continually updated to protect research participants from violation of their autonomy and privacy and to foster preparedness to participate in research. States must

give priority to public biobanks and must promote laws and contracts between private biobanks and citizens that take into account justice and equity in benefit sharing. An international public registry of DNA mutations and variants should also be implemented.

124. Those who cannot decide that they wish to know the results of genetic testing, including for example healthy children, should not have that information imposed on them. Children should only be tested when it is for the purpose of their better medical care or that of their close relatives.

125. The widespread use of genetic screening and in particular of NIPT may foster a culture of ‘perfectionism’ or ‘zero defect’ and even renew some ‘eugenic trends’, with the consequence that it could become more and more difficult to accept imperfection and disability as a part of *normal* human life and a component of the diversity we are all called on to acknowledge and respect. The anxiogenic effect is also to be considered. The right of an individual to make autonomous choices is to be made consistent with the right not to be subjected to discrimination or stigmatization based on genetic characteristics and the duty to respect every human being in her or his uniqueness.

126. New genetic technologies may not become available on a large scale in LMICs soon. However, to harness the benefits of genomics, LMIC governments should begin to develop national genomics policies that will address human and technology capacity within the context of their national economic and sociocultural uniqueness.

127. With the rapid advancements in genetics, deepening and updating of ethical reflection are a never-ending commitment. Probably, some revision of existing declarations should also be considered. The cogency of the principles is untouched. The scope of possible applications is changing and widening every day. First of all, this is a task to perform for UNESCO, building on its well-established, pivotal role as a global forum for global bioethics and relying on the contribution of its institutional and expert bodies. At the same time, this responsibility should be taken on by all international agencies working in the field.

128. We are human because of the interplay of many biological, historical, cultural determinants, which preserve the feeling of our fundamental unity and nourish the richness of our diversity. The international community, States and governments, scientist, actors of civil society and individuals are called upon to consider the human genome as one of the premises of freedom itself and not simply as raw material to manipulate at leisure. At the same time, considering that scientific advancements in this field are likely to offer unprecedented tools against diseases, it is crucial to acknowledge that these opportunities should never become the privilege of few. What is heritage of humanity entails sharing both of responsibilities and benefits.

## BIBLIOGRAPHY

Council for International Organizations of Medical Sciences (CIOMS): *Declaration of Inuyama on Human Genome Mapping, Genetic Screening and Gene Therapy*. Available at: [http://www.cioms.ch/publications/guidelines/1990\\_texts\\_of\\_guidelines.htm](http://www.cioms.ch/publications/guidelines/1990_texts_of_guidelines.htm). Accessed 11 February 2015.

CIOMS: *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Available at: [http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf). Accessed 11 February 2015.

Council of Europe (COE): *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*. Available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm>. Accessed 11 February 2015.

Nuffield Council on Bioethics: *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review*. Available at: [http://nuffieldbioethics.org/wp-content/uploads/2014/06/Novel\\_techniques\\_for\\_the\\_prevention\\_of\\_mitochondrial\\_DNA\\_disorders\\_compressed.pdf](http://nuffieldbioethics.org/wp-content/uploads/2014/06/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf). Accessed 22 August 2015.

UNESCO: *International Declaration on Human Genetic Data*. Available at: <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genetic-data/>. Accessed 11 February 2015.

UNESCO: *Universal Declaration on Bioethics and Human Rights*. Available at: <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/bioethics-and-human-rights/>. Accessed 11 February 2015.

UNESCO: *Universal Declaration on the Human Genome and Human Rights*. Available at: <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights/>. Accessed 11 February 2015.

WHO: *Review of Ethical Issues in Medical Genetics*. Available at: [http://www.who.int/genomics/publications/en/ethical\\_issuesin\\_medgenetics%20report.pdf](http://www.who.int/genomics/publications/en/ethical_issuesin_medgenetics%20report.pdf). Accessed 11 February 2015.

World Medical Association (WMA): *Statement on Genetics and Medicine*. Available at: <http://www.wma.net/en/30publications/10policies/g11/index.html.pdf?print-media-type&footer-right=%5Bpage%5D/%5BtoPage%5D>. Accessed 11 February 2015.