Presidenza del Consiglio dei Ministri

COMITATO NAZIONALE
PER LA BIOETICA

PEDIATRIC BIOBANKS

11th of April 2014

INDEX

Presentation

The National Bioethics Committee has already made some examination of the general theme of biobanks in previous documents.

In this Opinion, the Committee deals with pediatric biobanks, characterised by the collection of biological samples from minors and aimed at scientific research.

The document, starting with the recognition of pediatric biobanks as a valuable resource for scientific research, addresses emergent bioethical issues.

It upholds the general ethical principles involved in the donation of biological samples (accreditation of biobanks, free donation, protection of privacy), addresses some specific problems with regard to the vulnerability of minors (informed consent of the parents and the child on becoming an adult, the principle of subsidiarity, risk / benefit assessment, the right to know and not to know).

The Committee emphasises that the interests and welfare of the individuals whose biological material is used for research must always prevail over the sole interests of society or science - even more so if they are minors.

To this end, the Committee reiterates the need for normative regulation regarding this field that takes into account aspects of ethical importance: adequate and detailed information (scientific interest of research, protection of privacy, time and place of research) to the parents or the legal representative for purposes of consent which is appropriate whether it be restricted or partially restricted; listening to the will of the minor, in relation to progressive states of maturity, as well as informing the minor as regards the disposal of his biological material by parents and those in charge of biobanks; limitation of the parents' right not to know in cases where the information is trustworthy and useful for the health of the minor in preventive and therapeutic terms; the guarantee of the right to know or not to know, of the minor on becoming an adult and being capable of adequately expressing will.

The Committee also considers necessary the establishing of a supervisory body for the various phases of conservation and management of biological material and the presence of an ethics committee; it recommends appropriate training for the researchers and staff of the biobank; and calls for a census of pediatric biobanks and the possibility of establishing a National Registry.

The working group was coordinated by Prof. Lorenzo d'Avack, who drafted the original text.

Professors Salvatore Amato, Bruno Dallapiccola, Carlo Casonato, Marianna Gensabella, Assuntina Morresi, Laura Palazzani and Dr. Carlo Petrini contributed to the final draft of the Opinion.

The text was discussed and unanimously approved in the plenary session by those present: Profs. Salvatore Amato, Carlo Caltagirone, Stefano Canestrari, Cinzia Caporale, Carlo Casonato, Bruno Dallapiccola, Antonio Da Re, Mario De Curtis, Riccardo Di Segni, Paola Frati, Silvio Garattini, Demetrio Neri, Andrea Nicolussi, Laura Palazzani, Rodolfo Proietti, Massimo Sargiacomo, Lucetta Scaraffia, Giancarlo Umani Ronchi, Grazia Zuffa.

Profs. Luisella Battaglia, Francesco D'Agostino, Marianna Gensabella, Assuntina Morresi, absent from the session, subsequently expressed their approval of the Opinion.

Dr. Carla Bernasconi (FNOVI), Dr. Rosaria Conte (CNR) and Dr. Carlo Petrini (ISS), present and with the right to vote, also affirmed their support. Prof. Monica Toraldo di Francia, absent during the plenary, sent a personal remark.

The President
Francesco Paolo Casavola

1. Preface

In this Opinion, faced with different meanings, for the term biobanks we mean: the operative service Units, assigned to collect, preserve, classify, manage and distribute the human biological materials (cells, tissues, DNA) of individuals or groups of healthy or sick individuals, for biomedical purposes (research, diagnosis, prevention or treatment), inside hospitals or research centres.

It is possible to draw a distinction between two types of biobanks, in connection with their different purposes: depending on whether the biological material is stored for research purposes or for clinical/ therapeutic use, that is, intended for human application. This second type is regulated by specific European legislation (Recommendations 2004/23 EC 2006/17 EC and 2006/86 EC), while for the first, nothing analogous exists yet.

The present Opinion deals with pediatric biobanks, characterised by the collection of biological samples from children and aimed at scientific research. The preservation of human gametes and embryos, which opens different ethical issues, is excluded from present deliberation.

It should be noted that the establishment of biobanks, which collect biological material from both adults and minors, stems from a complex process. At each stage of this process, those acting may be different: the individuals who take the samples, collect the data and information are different from those who manipulate the biological derivatives, label them, encode them, and make them anonymous or identifiable again. Similarly the personnel entrusted with the storage of samples is very often different from the personnel responsible for management of the information regarding samples. Yet another different body of personnel is involved in using the samples for research. It therefore seems appropriate, even more so in the case of biological material collected from minors, to ensure a clear chain of management of the different tasks by setting up a supervisory body in the figure of a guarantor/curator of the procedure responsible for both the proper storage and utilisation of biological material as well as for the management of information, handling relations with families and the minor, on becoming an adult.

This means that all the stages in the process must be regulated in a coherent and responsible manner, taking into account technological advances.

"The collection of biological material - as the National Bioethics Committee (NBC) and the National Committee for Biosafety, Biotechnology and Life Sciences (NCBBLS) were able to observe - together with the clinical information connected to the individual are an indispensable tool to elucidate the molecular mechanisms and causal pathways, whether they be genetic or environmental, and translate biomedical research into improvements in care research based on biobanks will give rise to new synergies between industry and public research facilities, strengthening the competitiveness of our country within the context of health industries. In addition to the ultimate goal of prevention and treatment of complex diseases, a short-term benefit will come from the development of new and more powerful diagnostic tools[1]".

[1] The National Bioethics Committee (NBC) and the National Committee for Biosafety, Biotechnology and Life Sciences (NBBLS), *Collection of biological samples for research: informed consent*, 2009, p. 5.

Despite being a valuable resource for scientific research, biobanks raise bioethical issues, since the archived material is usually associated with the donor's personal and biographical data, including age, sex, ethnicity, and clinical data, such as the place of sampling, the diagnostic procedure, treatment, the natural history of the disease, family medical history, social group membership[2].

The advances in molecular biology have changed over time the nature of biobanks. Biological samples collected have acquired considerable value, both for the researchers and industry. For the researcher this material - tissues, cells, DNA – allows identification not only of the constitutional genomic profile, but also of somatic mutations and to carry out studies that develop more effective diagnostic tools, early detection of people at risk and the development of targeted therapies. These researches have acted as a driving force in the establishment of large biobanks.

While on the one hand biobanks have a significant cognitive and scientific value, which explains their development, on the other they present critical issues for the rights of the individual in the absence of appropriate criteria for management and control. In fact, they are embedded in dynamics in which those who donate biological samples hand over material that carries their genetic identity to be used by researchers for scientific purposes, without necessarily obtaining immediate and direct benefits. Therefore the fundamental ethical problem emerges of balancing on the one hand the need for advancement of scientific research, and on the other the protection of the individuals involved (in particular the right to confidentiality of personal data). The latter are not always aware of the possible implications of certain choices and therefore can not consciously direct the use of the collected material. Besides, whoever donates the sample may fear certain situations at different levels: on the individual level, when the biological sample or data are used for research and purposes different to those consented to by the donor and which are contrary to the donor's values, or when the sample is used for purposes other than research (e.g. insurance companies, employers, etc.); on a commercial level, when the collection of biological material involves rare material that is phenotypically well characterised which comes to have a value in economic terms, rather than for research, with the risk of its being transferred or marketed nationally or internationally; on an international level, when the use of the genetic data of a population, ethnic group, or country, dictated by an economic exchange that is already ethically hard to accept, has little or no return for the donors.

In the past, the samples were generally irreversibly anonymous[3] (obtained without informed consent and without a classification of the donors) and this made it impossible to trace the identity of the donor. Anonymity is in itself reassuring, since it avoids, in fact, possible violations of privacy. Today the

[2] According to the Recommendation of the Council of Europe, n. 4/2006, a biological bank must necessarily contain in addition to the biological materials also “associated personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated”.

[3] The samples can be acquired: completely anonymously (a total lack of reference to the donor); or, in an anonymous manner, for those who carry out research, even if the origin of the sample is known by those who supervise its management (guarantor/curator) using a classification code; or always codified to protect the privacy of the individual, but those actually using it as researchers, have the possibility of opening the code and knowing the donor.

situation has changed: full anonymity remains a possibility, but as an option of the adult individual (expressed in the informed consent form), although the relative ease with which it is possible to sequence the entire genome makes it practically difficult to ensure the anonymity of numerous biological collections. In addition, scientifically, full anonymity may represent for some research a loss in the utility of the material, given the importance for research of the associated information.

The opposite solution is the full identification of the donor. However, the ethical and normative impetus for the need to protect the privacy of the donor, has led to the intermediate model of "controlled" anonymity: the assignment of a code to each individual sample, this code is made known only to certain operators (e.g. the person responsible for the biobank or his immediate collaborators). Therefore there has been a shift from “full” to “partial” anonymity. Upon receipt of explicit donor authorisation, the individual’s identity and personal data are then made accessible to the person who has the key to the connection between the code and the data of the patient. Where it is explicitly permitted, the encryption key enables the donor to receive information regarding research results.

The present Opinion concerns the collection of human biological material obtained from residual parts of samples taken for diagnostic or therapeutic purposes in pediatric contexts and which, as already mentioned, are only intended for research[4]. These samples also include those taken through mandatory newborn screening aimed at the diagnosis and treatment of certain genetic diseases, and carried out using a few drops of blood, when provision is made for storage of residual material after the performing of the tests required by current legislation[5].

There is a lack of attention, in general and particularly in our country, regarding the treatment of the samples taken from minors[6]. The few regulatory

[4] The NBC and NCBBLS, through the drawing up of the documents, *Biobanks and research on human biological material,* 2006, *Guidelines for the establishment and accreditation of biobanks,* 2006, and *Collection of biological samples for research purposes: informed consent,* 2009, have already stressed the importance of biobanks for research purposes as regards the scientific aspect. These documents, have treated many ethical, scientific and legislative issues related to biobanks in general, however, there has not yet been an in-depth treatment of the issue of pediatric biobanks. Take the closely related ethical problems raised in the Opinions of the NBC and NCBBLS, *Long-term storage of residual dot blot spots from neonatal screening,* 2010. As regards the ethical issues that arise from testing and genetic data, one should refer to the NBC Opinion, *Bioethical guidelines for genetic testing,* 1999 and NBC-NCBBLS, *Genetic susceptibility testing and personalized medicine* 2010.

[5] Pursuant to Art.6, paragraph 2 of Law 104/1992 and subsequent implementing decree DPCM 9/07/1999. The Tuscany region has expanded mandatory newborn screening to more than 40 rare metabolic diseases and certain immunodeficiencies such as ADA deficiency. While other regions have their own programs: e.g. Umbria with a memorandum of understanding adopted the program of Tuscany in 2010. Significant is the case of Emilia Romagna, where the resolution of February 1, 2010, no.107 included 24 diseases and has sparked a dispute which from the TAR (Lazio regional administrative court) has reached the ECHR. The disparity between regions is to be overcome by virtue of paragraph 229 of the stability law (2013 n. 147), which provides for extended screening everywhere and which in order to encourage maximum uniformity throughout the country has established a Coordination Centre for newborn screening within the National Agency for regional healthcare services (Age.na.s.) a Coordination Centre for newborn screening.

[6] For a pilot study that outlines a survey of pediatric biobanks at European and Italian level see E. Salvaterra et al., *Pediatric Biobanking: A Pilot Qualitative Survey of Practices, Rules, and Researcher Opinions in Ten European Countries,* "Biopreservation and Biobanking", 2012, 10,

documents[7] lack specific references to minors. And the limited references available are insufficient, as they relate to situations related to a possible diagnostic and therapeutic benefit for the minor, while in the case of pediatric biobanks, as will be pointed out below, the sample is donated and used for research with the predominant philanthropic purposes, regardless of any possible or certain clinical benefit for the donor.

2. Ethical principles for pediatric biobanks

In other documents relating to biobanks in general the NBC and NCBBLS committees have already had occasion to point out certain ethical principles that are fully endorsed for the concession of biological pediatric material and more specifically:

- biobanks must apply for and obtain certification through a transparent procedure approved by a body recognised by the government[8];
- the biological samples belong to the donor and are given under “the general formula of `concession for use` confirming in any case the principle of gratuity and the prohibition of personal descrimination”[9];
- the concession[10] of the biological samples of minors by their parents/legal representative collected in biobanks for research purposes are of great benefit to science and health, however these goals are not to prevail over the rights and interests of individuals involved in the research[11].

More specifically it must now be considered that minors are a particularly vulnerable category, and therefore appropriate protective measures are

1, 29 ff. The datum that emerges is the heterogeneity of practices and the need for homogeneous bioethical and biolegal recommendations.

[7] Regulation of the management of clinical biobanks in the conservation of stem cells from umbilical cord blood for autologous use, conservation authorised only within public facilities devoted to this (Ministerial Decree of 18 November 2009). The procedures for the establishment of bodies responsible for certification of clinical biobanks such as centers for biological resources (CRB) is regulated by the Decree of the Ministry of Economic Development (2006). Law 30.06.2009, n. 85 specifically enacted to establish and regulate a national database of DNA for forensic purposes. To be considered is the *Authorization of the guarantor of privacy on the processing of genetic data* (12 December 2013) and the *General authorization of the guarantor of privacy on the processing of personal data carried out for purposes of scientific research* (12 December 2013) that are also relevant to biobank regulations concerning the use of tissue and archiving of patient data. Even the European regulations cited above, concerning the clinical use of biological samples, never make explicit reference to children, speaking only in general of "people who give authorization on behalf of the donors" (2004/23/EC, art. 2 paragraph 13), but as for consent they refer to national legislation without distinctions for the age of the donor.

[8] NCBBLS, *Guidelines,* cit., 10 et seq.

[9] NBC-NBBLS, *Considerations*, cit., 25 et seq.

[10] In the context of this document, despite noting the correctness of the expression 'concession for use', the word 'donation' is mainly preferred as it is a term used internationally even when referring to minors and moreover it expresses the gratuitous dimension of the act.

[11] Principle reiterated in every opinion in strict accordance with the conventions, EU and international regulations and recommendations (e.g. In Articles 8 and 9 of the General Principles of the *Declaration of Helsinki*, 2013 in the Preamble to the *Rec,* 2006, 4 of the Council of Europe on *research on biological materials of human origin,* in the Introduction of the International *Declaration on Human Genetic Data* UNESCO, 2003; Art. 2 of the *Oviedo Convention*,1997).

required also in the specific case of the concession of biological samples for research. In addition, research involving pediatric biobanks raises different ethical issues to the research using biobanks that collect material provided by adults. In fact, children have limited capability to understand the meaning and implications of the research and to express informed consent, these capabilities are only acquired gradually. On the other hand, although the collection of biological samples is generally associated with the pharmacological experimentation, as previously mentioned, it is neither possible nor appropriate, given their specificity, to apply to pediatric biobanks the ethical principles and legal rules of biomedical research on minors[12].

It should also be noted that the threshold of concern in safeguarding the rights of minors can be placed at variable levels, since the use of biological material is highly heterogeneous.

Therefore, some of the most problematic aspects of pediatric biobanks will be taken into consideration in this document: consent, subsidiarity, the risks/benefits, and return of results[13].

2.1. The consent of parents and the minor/adult

Before any collection of biological material is carried out, it is necessary and of primary importance to have the free and clear consent of the actual donor. And the requirement of biobanks to make use of the consent of participants stems from the fundamental principles relating to biomedical ethics: all documents, agreements and regional and international regulations on the subject emphasise this requirement and its importance.

However, in the case of pediatric biobanks, this prerequisite for various and not marginal aspects raises issues with respect to biobanks collecting material obtained from adult donors given that: a) the material collected does not actually belong to the person granting it, but to another individual, in this case a minor, who comes under the vulnerable individual category; b) minors, until they acquire the capacity of discernment, are able to give informed consent concerning the destiny and future of their biological material.

In the juridical context it is believed that the will and wishes of minors, in view of their best interests, are manifest by the parents or legal representative. The consent of the parents or legal representative must therefore always be declared at the time of the concession of the biological material of the minor/child to the biobank. This should, however, be subject to the information to be given to the minor at the time of the concession of the samples, taking into account the degree of maturity reached by the minor and the ability to understand the information sheet, given that any possible refusal of the minor shall prevail over the consent of the parent/legal representative[14].

It should also be considered that doctrine and legal systems provide for different modalities of consent to the concession of biological samples: "limited consent" to the use of the sample, only for immediate, specified research,

[12] To refer to our regulations: Art. 4 of legislative decree 211/2003.

[13] We will omit discussion of certain customary topics in the context of biobanks such as the status of the detached parts of the human body, the storage conditions of biological materials, the researcher / biobank ratio, biobank certification, the commercialisation of results, etc.

[14] As indicated in the Additional Protocol to the *Oviedo Convention* on scientific research where it is written that, among the conditions to be met in order to conduct research on people who did not have the ability to give informed consent, there is the one regarding non-objection on the part of the subject concerned.

which prohibits use in other studies not provided for at the time of signing; "partially restricted consent", which authorises the use of samples not only for specific current research, but also for future research that is directly related to the initial one; "multi-option consent," which allows to make different choices, all explained to the donor by the biobank; "broad consent", which allows the use of samples for current and future research of all kinds.

In the first three cases, it is expected that donors may have constant control of their own samples and may withdraw given consent at any time, resulting in the destruction of biological samples and related data. Participants must be informed about the content of each individual research project in which the biological samples are used, so as to enable them to evaluate on the basis of knowledge of the project if it is compatible with their moral vision and the goals expected from the research.

In the case of "broad consent", the donor relies on a general information sheet and it is clear that in this way a relationship of trust is established with the biobank, based on the prevailing principle of social solidarity, a reason which in itself justifies the research. An agreement of this type is often called for by researchers in order to have greater freedom in the use of materials and not negatively affect subsequent research on the samples provided.

In view of these various options, the NBC/NCBBLS recognised as an appropriate model of informed consent "partially restricted consent"[15].

In the case of pediatric biobanks, with consent not coming directly from the participant, and given that the concession of biological samples of the minor may not be neutral in its effects, the NBC reiterates, as in another document of the same Committee[16], that the samples should not be rendered anonymous irreversibly and the authorisation of the parents or legal representative should not be "broad", but rather given for a specific research or one directly related to it ("partially restricted consent"), after receiving detailed and full information, so that the giver can assess the aims, duration, place and manner of implementing the scientific project in which the sample is used. Parents, therefore, retain, "control" over the use that is made of the biological material of their child, so as to be able to request an informative report and its destruction following the withdrawal of consent (destruction of both the biological samples and the biographical/associated clinical data).

In addition, parents should be reassured about the management plan and the manner in which the biobank ensures the retention and the "confidentiality" of the collected data. Prohibited access of certain third parties, such as insurance companies[17] and employers should also be made explicit.

Although the Committee insists on the importance of defining these aspects within the context of initial consent, it is nevertheless aware of the difficulty of setting these objectives in a comprehensive way at that time. In fact, the time span of the research is generally long and it is difficult to predict at the moment of giving consent, the possible studies which, after several years could

[15] NBC-NBBLS, *Collection of biological samples for research purposes: informed consent*, 2009, p. 14.
[16] NBC-NCBBLS, *Considerations,* cit., p. 25.
[17] The NBC/NCBBLS in the Opinion *Genetic Testing and Insurance* (2008) stressed the importance of ethics in the context of the use of genetic test results of the principle of non-discrimination, recommending that insurance companies should not ask users to undergo genetic testing, allowing however, the possibility to use the results of genetic tests that have already been carried out, with the consent of the person concerned.

involve the material being re-utilised. This implies that for the proper management and utilisation of the material granted to a pediatric biobank the essential rule, when the minor heads towards maturity, is the loss of importance of the consent given by the parents and the start of a process aimed at listening to the actual adolescent. Those becoming legally of age must have the opportunity to immediately give their consent or, if the research has already begun, renew, modify or withdraw consent to the use of their samples and data in the biobank.

Consequently the head of the pediatric biobank (guarantor/curator) must develop procedures which enable the child on coming of age to be contacted via appropriate means, to obtain adequate information, to be given the opportunity to withdraw or access samples and data and destroying them or delete the registered information. The Committee believes that the data and results of prior research to the eventual destruction of biological samples may be used and published, while respecting anonymity.

The NBC points out that in the context of informed consent it is the responsibility of the biobank to explicitly invoke the duty of parents to inform their child regarding the donation and to maintain contact with the biobank to enable the latter to succeed in the consent.

Also to be considered is the fact that the samples and the information are often transferred - in the context of international and multi-centric research - to other biobanks or different research groups and can be shared with the researchers of other countries (subject to different regulations) so the cancellation of all the information is often complex, if not impossible. In view of the theories that deny the possibility of the dislocation of biological samples of minors, the Committee believes that this should be allowed on the condition that the parents are made aware of this problem at the time of the concession of the biological material, and also the minors themselves when asked for their consent.

A specific problem is the request for informed consent for the use of the biological samples of children with rare pathologies, where the need for research is particularly important. It is important in order to increase the provision of samples in the informative interview that the physicians present the parents/legal representative with the particular significance of this gesture of solidarity, which is essential for the advancement of research for the benefit of other sick children.

However, even within the regulation of pediatric biobanks, there may be exceptions to the continuation of research if there is no expressed will regarding a greater or different use of samples and data compared to the one originally proposed by the parents, or without the subsequent consent of the child. These exceptions are also provided for in the General Authorisation of the Privacy Guarantor in relation to "the processing of personal data carried out for purposes of scientific research" (2012). In the first place, should the processing of data and samples be necessary for conducting studies, with no significant impact on the individual participant, carried out with organic material collected previously for the purposes of protection of public health or for the execution of earlier research projects.

A second exception may be construed when it has not been possible to contact the minor, now adult or the parents, even though reasonable efforts have been made to do so.

In both exceptions authorisations should include the possibility of conducting research with similar goals through the processing of anonymous data or data relating to persons from whom informed consent has been or may be acquired. In addition, these exceptions are admissible unless previously stated otherwise by the actual participants.

However, in these cases, as in all biobanks, research can only be carried out on the basis of a project that has received the approval of the competent territorial ethics committee, which has assessed its scientific appropriateness and ethical acceptability.

2.2. Subsidiarity, risks and benefits

The ethical and legal principles which legitimise scientific research on groups of vulnerable individuals include those that research must be responsive to the health needs and priorities laid down by that category of persons, and that the same research can not be carried out on non-vulnerable persons. In addition, this group should benefit from the knowledge, practices or intervention deriving from the research[18].

It should also be noted that there are established general ethical principles for research on incapacitated persons "with no direct benefit":

- The research project must evisage collective utility;
- The risks and inconvenience to the persons involved should be minimal.

These rules are often cited in the literature for pediatric biobanks. Notwithstanding the already stated differences between scientific research on minors and the collection of biological materials for pediatric biobanks, there is no doubt that the two requirements by way of exception mentioned above are present in this last case treated. The scientific aims of pediatric collection presupposes collective utility and its objective is to enable a significant expansion of medical knowledge on the specific medical condition (e.g. disease) of the group to which the minor involved in the research belongs. The need for scientific research on the biological samples of minors, even if replaceable in some cases with research on the biological samples of adults, in accordance with the principle of subsidiarity justifies the use of the samples collected in pediatric biobanks.

In the present case, therefore, the possibility of a minor to obtain some future medical benefit, not in immediate and specific relation to the time of concession, should not be totally ruled out.

It has been noted, in addition, that minors "benefit" from being generous and supportive to the community, through the choice made by their parents to donate their samples. In this sense, the best interests of the minor would at least partially be represented by the contribution that he provides to the community.

Accordingly, even if a minor does not directly and immediately benefit from the research, it appears justified from the point of view of personal benefit, since it could in future determine some benefit in terms of health to the minor-donor, but also from the ethical perspective, as it is necessary for society.

The other aspect, that of "minimal risk" has been discussed in the context of research, especially on incapacitated persons, and consequently in pediatric biobanks. Primarily, the difference between the two types which jeopardise varying interests should once again be emphasised: health in the first case, in

[18] *Declaration of Helsinki*, Art. 19-20, 2013.

the second the right to protection of personal data. Therefore, it is of primary importance in the context of biobanks to have regulations that guarantee specific protection of privacy, particularly when samples are shared with other researchers not connected to the biobank, which has acquired the sample. Therefore, the preference given to "partial anonymity" through codes both for the samples and the data from a minor is justified for the obvious reinforcement of privacy, unless the use of the biological material or associated data in the "not anonymised" form is in line with the best interests of the actual minor. Once the risk of a breach of confidentiality in its percentage of occurrence is reduced, the limitations in terms of risk to the use of pediatric biological samples tend to diminish. However, it should not be overlooked that if, in general, in the case of biological samples taken from adults the effects on the donor are not significantly burdensome, for children the moment of collection of their samples may have a greater psycho/physical impact resulting in a burden that is not always tolerated and justified in the face of the absence of direct benefits. A potential burden for example may relate to the need for any additional measures to the taking of the sample (taking additional blood or tissue samples etc.). Moreover burdens of another kind may arise from the knowledge subsequently acquired by the minor, on becoming an adult, regarding the type and seriousness of the disease suffered from in the past or some genetic information concerning him which could have a psychological impact on his life.

However, given the general difficulty in the field of research on the incapacitated and minors, to define what risks and inconveniences are minimal and therefore tolerable for the benefit of scientific and social interests, the NBC, instead of referring to fixed and predefined standards, endorses evaluation of the situation, taking into account the context of the study and the particularity of collections by the appropriate ethics committee.

2.3. The Right to "know" and the right "not to know" of parents and the legal representative

Normally biobanks do not communicate to those who have conceded samples the data obtained from the research carried out utilising their samples, except at the express request of the person concerned, as expressed at the time of consent. In fact, in a research context, the results obtained on a sample must usually be validated on other samples. Moreover basic research operates under different conditions compared to traditional laboratory research. It would not therefore be appropriate for the patient's physician to use these results as part of subsequent care, until the study results are not confirmed by subsequent investigation capable of verifying their clinical relevance. Nevertheless, some data obtained from the study of samples can provide useful information on the subject's health (prevention, diagnosis, treatment) or identify genotypic characteristics that may be passed on in the family (significant in the context of procreative choices).

It is now known that as part of the right to self-determination established in our society, both on an ethical and juridical level, with reference to choices in the context of genetic information, there is also the right to remain in "ignorance about one’s future", i.e. the "right not to know." Donation of a biological sample that is immediately completely anonymised is characterised by not asking or expecting anything in return, not wanting to know the next phases and results of the research. This is a possibility as part of the informed consent of adults.

With regard to pediatric biobanks, the Committee believes that the informed consent of the parents/legal representative to the donation of biological samples should explicitly provide for the information sheet to be given, if the research provides sufficiently substantiated, reliable and useful information for the health of the minor on the preventive, diagnostic, therapeutic level or in terms of reproductive health. In this case - in the face of actual and potential benefits - there is the researcher's duty to inform and a right/duty to know on behalf of the parents/legal representative in the interests of the minor[19], even if this entails a burden in terms of costs and on an organisational level for biobanks, as well as a psychological burden for the parents themselves. The parents /legal representative should therefore not be granted the opportunity to express their dissent to being informed and to assert their "right not to know." After concession of the biological material of the child in coded form and this can be traced to the person concerned and how potentially these samples are a possible source of various types of information (medical, biological, genetic, etc..) it is in the interests of parents[20] and of the minor to obtain the informative report concerning the health of the minor, given the possibility to take preventive and curative action in his favor[21]. Those responsible for the biobank should do everything possible to contact the parents or the legal representative of the minor and give them the informative report.

The Committee also considers it necessary that the parents or the legal representative must be informed, even in the case of possible data, not explicitly searched for (so called 'incidental findings', or 'unexpected results'), which highlight genetic diseases with either certain or high probability of late-onset with no current cure (e.g. Huntington's disease). These situations, whilst being infrequent, given the consequential ethical issues, should always be clearly defined as possible and brought to the attention of the parent/legal representative within the context of consent to the donation of biological samples for genetic research.

It will, however, be the duty of physicians to select the relevance of the information and the duty of parents to use this medical data in accordance with the appropriate needs of the minor and to assess when and how to transmit this knowledge to their child.

It will be the latter when an adult, as part of his consent to research to make use of the right to be informed or the right not to know.

In any case, in the context of a return of information, the Committee recommends the help and support of experts as part of an appropriate advice service, given the complexity of the information[22]. The information must be transmitted to parents in an understandable form; the understanding of the communicated results must be verified and, if necessary, psychological support must be guaranteed.

---

[19] This is in accordance with the "duty of care principle" of the Additional Protocol to the *Convention of Oviedo* research (Article 27) and to the Explanatory Report (paragraph 134).

[20] Moreover, the genetic information could be relevant to the parents themselves, for their health and their reproductive choices.

[21] Even the 2006 *Recommendation* 4 of the Council of Europe underlines the risk that may result from the maintenance of the rule of "non-identifiable" or "irreversibly anonymised" material in genetic research.

[22] For genetic counseling it is important to refer to the interaction between genes and environmental factors and the possibility of false-positive or false-negative results.

3. Recommendations

The collections of biological samples present in the pediatric biobanks, are of extraordinary interest for research in biomedicine, in particular biomolecular engineering and in translational research. However, the need to correlate tissue samples and personal data raises the issue of confidentiality and protection of personal privacy. The Committee underlines that the interests and welfare of the individuals whose biological materials are used for research must always prevail over the sole interest of society or science, and this applies all the more if they are minors.

The Committee reiterates the need for legislative regulation on this subject, able to provide guidelines in conformity with the directions that come from European and international papers.

As regards the correct procedures for the acquisition of biological samples from infants and minors, the NBC, while hoping for their donation, believes that the consent of the parents/legal representative can not be broad and irreversible, but fairly restricted or partially limited, filed in written form at the time of taking the biological sample for diagnostic purposes, as a result of detailed information concerning:

- the exclusion of direct commercial purposes for the research and the guarantee that research is carried out in accredited facilities;
- the objectives of the biological sample and the scientific interest in participation in the study;
- the nature of biological materials and the data collected;
- the intended use of the samples and data;
- the measures taken to protect the privacy of the minor and possibly his family and the socio-cultural environment in which he / they belong;
- the times and places of the research (the possible transfer of samples to the facilities /research groups different from the one intended for the sample);
- the financers and the identity of the manager or responsible control body of the biobank and how to contact him/them.

The minor, in relation to his progressive maturity, should be listened to and his expressed will must be taken into account. Moreover, if the research was begun in an earlier period, he must have a way of knowing that he was enlisted and know about the destiny of his biological sample and the possible results emerging from its use so as to be able to confirm or modify or withdraw consent and possibly seek its destruction or the anonymisation of the sample and connected data without being traceable.

At the time of collection of biological samples the operators and/or persons responsible for the biobank are to encourage the parents to inform their children once they are adults, regarding the donation of their biological samples.

The biobank shall make a reasonable organisational effort to recontact minors once they are adults: this operation can also be facilitated by the use of information technologies. This instrument, in accordance with the privacy policy, allows the maintaining of contact between donors and biobanks.

The Committee recommends that biobanks should implement resources and the organisational structure to communicate validated and useful results - with reference to present and future health and quality of life - to the parents and the minor now an adult.

The parents' right not to know is limited in those cases where the information is sufficiently founded, reliable and useful to the health of the minor in preventive and therapeutic terms. Furthermore, the Committee also considers it necessary for parents or the legal representative to also be informed in the case of possible data not explicitly searched for, so called 'incidental findings' which reveal genetic diseases with either certain or high probability of late-onset with no current cure.

The right to know or not to know of the minor, now adult and able to adequately express his will, should be the object of choices within the framework of informed consent.

There must be a supervisory body for the various phases of conservation and management of the biological material and associated information. The model can be represented by a guarantor/curator with the responsibility for both the proper conservation and use of biological material, as well as information management, handling relations with families and the minor when an adult.

It is also necessary for pediatric biobanks to be connected to an ethics committee, capable of assessing the scientificity and ethicality of the research, ensuring observance of the consent and wishes of the minor during his development.

Also recommended is the adequate training of the researchers and staff of the biobank as regards emerging bioethical issues attention to ethical issues would allow for greater protection of minors, helping to build a relationship of trust between donors and researchers.

Despite awareness of the difficulties encountered by repeated exhortations to carry out a census of biological banks and collections of samples present in Italy, the NBC, reiterates the opportunity to establish a National Registry of pediatric biobanks.

Personal remark

A Personal remark signed by Prof. Monica Toraldo di Francia

Whilst agreeing with the general approach and most of the content of the document on pediatric biobanks, I abstained from voting because I dissent on one point, while, however, recognising the great delicacy and complexity: the one on the right/duty of parents to be informed in the event the "research provides sufficiently substantiated, reliable and useful information for the health of the minor in preventive, diagnostic, therapeutic terms or for reproductive health," and even in the event "of possible data not explicitly searched for, (so called 'incidental findings') which reveal genetic diseases with either certain or high probability of late-onset with no current cure (e.g. Huntington's disease)".

I will attempt to explain the reasons for my dissent below:

1) while I have no doubts about the licitness of the limitation of the 'right not to know' of parents, in those cases where there is a real possibility of immediately effective preventive and curative action, I am not so convinced when the data relates to curable diseases of late onset, for which there are no preventive measures of proven benefit. In this eventuality early knowledge of the predictive data would not have clinical utility, while, instead, it would create such anxiety and concern likely to adversely affect family relationships; I also think that, in this type of situation, one should also consider the fact that at stake are the strong vested interests of the pharmaceutical companies for the

minor to precociously begin some kind of drug treatment with the consequent risk of unnecessary preventive 'medicalisation'. Possibly there could be other options, to be included in the information sheet and in the consent forms (which should however be explained, face to face): e.g. asking if one wants to be informed about conditions that may affect decisions about procreation and, with regard to the minor, the possibility of contacting and informing the family paediatrician;

2) Another and even more delicate issue is the one that concerns the so-called 'incidental findings' (IF) highlighting genetic diseases with either certain or high probability of late-onset with no current cure. The bioethical discussion on the categories of IF regarding minors that are always best notified is still ongoing and there is contrast regarding the guidelines on the proper balance between the safeguarding of autonomy and the interests of the minor and the rights-needs of parents to receive (or not receive) information that may be important for future offspring.

While being aware of the good reasons of those who consider it a duty to inform the parents even in the case of data on genetic diseases that are incurable in late-onset, however I believe that the expected benefits from this notification are not sufficient to offset the risk of a potential impairment in the psychological development of the minor and violation of his 'autonomy'. The (obligatory) knowledge of such information would inevitably cause in parents anxiety and psychological stress which have repercussions, even more than in the previous case, on the relationship with the children, a relationship which would be disturbed by the lack of transparency caused by the presence of a dramatic 'secret'. However, should the parents decide to inform the minor, the child would be precluded the possibility of thinking of 'an open future', we should ask ourselves how, self-perception and being perceived by those closest to us, as a person destined to have an unfortunate fate and an early death (compared to the life expectancy of the average person), may reflect on and influence the development of their sense of self, self-esteem and identity, exercising coercion in advance on life choices. In this case the person in question would be not only denied the right to choose for themselves whether or not to know the genetic information about their own health, but may also be more exposed to discrimination and/or social stigma. Moreover, even assuming that the secret may not be revealed and that the person concerned, when of age, may be put in a position to decide autonomously, there would still be additional reasons to question the wisdom of imposing the 'obligation to know'; these additional reasons concern more specifically, the possibility of stipulating insurance, health and/or life policies. Insurance companies in order to adjust premiums based on `objective` risk, have been pressing for a long time also to have access to genetic data of a predictive nature which their potential customers are aware of and they justify their request by referring to the cardinal principle of the insurance contract: that of information symmetry between the insurer and the person insured. If, as has already happened in other European countries, even Italy gave way to the demands of the insurance companies, the families concerned who want to take out a policy for themselves and /or the minor would find a heavy premium surcharge applied or even a refusal to provide coverage.

For the reasons set out above, I consider it to be more appropriate to allow parents the option of being informed or not being informed about IF which identify the presence of genetic alterations correlated with an increased risk of

diseases for which no cure or preventive measures exist and/or the identifying factors which could affect reproductive choices.