

Presidenza del Consiglio dei Ministri



**COLLECTION OF BIOLOGICAL SAMPLES FOR
RESEARCH PURPOSES: INFORMED CONSENT**

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1. Reasons for the working group's initiative

One of the most important problems for those working in the field of scientific research with biological material, is to establish the limits and methods within which it is licit to preserve samples for a time longer than that necessary to achieve the aim for which the sample was collected, and if it is legitimate to also use samples for purposes different from those initially identified. In fact, it frequently happens that scientific research institutes preserve collections of biological samples which, with the progress of the research, could be useful for new studies. It is important to consider the variety of the situations that occur, according to whether the samples are collected (or obtained) anonymously, or whether they are deposited anonymously (irreversibly breaking the link between the sample and the subject's data), or whether they are still identifiable (but always through protection codes). The working Group put together by the National Bioethics Committee (NBC) and the National Committee for Biosafety, Biotechnologies and Life Sciences (NCBBLs) decided to offer a further "synthesis" on the topic, so that the two Committees can express an "opinion" about this issue, which will contribute to the harmonisation process of the informed consent used by Italian biobanks instituted for research purposes, and which will help to define the position of Italy within the European project *Biobanking and Biomolecular Resources Research Infrastructure* (BBMRI), which aims at creating a European network of biobanks that use standardised procedures. Finally, the working group intends to propose a format that allows people to express, by donating a biological sample, an attitude of solidarity towards other people, including future generations.

2. Definitions

In this document, the collections of biological samples or biobanks are defined as: "*non profit-making service units, aimed at the collection and the preservation of biological material used for diagnosis, studies on biodiversity and research*" (1), accompanied by the protection that the Council of Europe asks the health authority to exercise, defining biobanks as: "*non profit-making institutions which are officially licensed by national health administrations, or recognised by the competent authorities, and must guarantee the processing, preservation and distribution of the material*" (2).

In addition, we refer to the definition that can be found in the 2006 Recommendation number 4 by the Council of Europe, according to which a biological bank, in order to be a genetic bank, must necessarily be, as well as a place to store materials, also an archive of personal, medical, lifestyle and

genealogical data that can be linked to the samples and updated (3). The recommendation also anticipates the possibility of future research, as biobanks are established in order to provide for projects not yet defined in the study's rationale. For this reason, the Council recommends its member States to adopt an approach that aims at including, with official recognitions, the highest number of collections.

3. Biobanks in biomedical research

Many common illnesses, like for example Alzheimer's, asthma, arthritis, cancer, cardio-vascular diseases, diabetes, hypertension, obesity, Parkinson's disease and psychiatric disorders, are due to complex conditions that not only cause individual suffering, but represent a burden for society in terms of healthcare costs and economic productivity. Fully treating these diseases remains elusive because they do not originate from a single defect, but they are the result of a great number of effects, often additive, deriving from a genetic predisposition, lifestyle, the environment.

These diseases are estimated to represent, in our country, over 70% of all illnesses, causing over 80% of all premature deaths (4). For this reason, a more precise classification, based on biological proof, would improve the state of knowledge, making the treatment of these diseases quicker and cheaper, it would lower the incidence of side-effects to the treatments, it would lead to more efficient clinical trials and to new parameters for prevention and the promotion of health.

The study of complex pathologies requires comparing a great number of subjects affected and not affected by specific pathologies or exposed and not exposed to specific environmental factors (case-control). Biological material collections, or biobanks, together with the clinical information associated to the individual are, therefore, an indispensable instrument to elucidate the molecular mechanisms and the causal *pathways*, genetic or environmental, and to translate biomedical research into improvement of care.

Chronic, slow progression diseases are a direct and indirect burden on our country's economy. If biobanks based research will lead to direct improvements in the treatment and prevention of illnesses, we can foresee an important economic impact in terms of a decrease in healthcare costs and an increase in productivity, due a healthier population.

Biobanks based research will give raise to new synergies between industry and public research institutions, reinforcing our Country's ability to compete in the healthcare industry. In addition to the final objective of preventing and treating complex illnesses, a short term benefit will derive from the new and more effective diagnostic methods. In fact, molecular diagnostics, a new discipline that uses "omic" technologies in order to understand illnesses and help the individuals at risk, is one of the fastest growing sectors of the healthcare industry.

In addition, biobanks represent a fundamental instrument of research in the field of rare illnesses. There are by now numerous cases in which research on genes that can cause diseases, accelerated thanks to the existence of biobanks, leading to a better understanding of pathogenic mechanisms, to the development of new diagnostic instruments and to the planning of therapeutic strategies.

In order to achieve the abovementioned socio-economic benefits, large collections of biological material are being created. Amongst these, significant initiatives come from the English UK DNA biobank, which intends to collect samples from 500,000 people, the Estonian Biobank and Genetic Variation, the Norwegian Biobank for Health, the French Biobanque de Picardie; at the European level: EPIC, European Prospective Investigation into Cancer and Nutrition, which collected 370,000 samples in nine countries participating in the study. A similar project has also been initiated in the USA by the National Human Genome Research Institute.

These biobanks combine the biological material of ill and healthy patients, with data on their state of health, nutrition, environmental risk factors, demography, socio-economic variants and lifestyles.

4. The European framework

The European Commission financed numerous collaboration projects and networks involving biobanks like EUROBIOBANK (5), GenomeEutwin (6), in the fifth framework programme; ENGAGE, EUHEALTHGEN (7), COGENE and PHOEBE (8), in the sixth; in the seventh. *Biobanking and Biomolecular Resources Research Infrastructure* (BBMRI) (9), has the objective of creating a network of European population biobanks or dedicated to specific diseases, within which the participants will be called to adopt shared standardised procedures for the acquisition, categorisation, preservation and distribution of the samples. BBMRI also intends to develop shared guidelines for the ethical-legal aspects concerning the collection, the preservation and the use of the samples. This European project requires that the participating biobanks are connected to the European network through national coordinators who, within their own country, will finance the national network and propose any eventual legal interventions that should become necessary: The National Committee for Biosafety, Biotechnologies and Life Sciences (NCBBS) is, in agreement with other European partners, the national coordinator of the network of Italian biobanks participating in the European project.

5. Existing Italian networks

In Italy, Telethon financed a project for the creation of a national network of genetic biobanks (<http://www.telethon.it/ricerca/servizi.asp#dna>). Currently the network includes 7 research centres which collect, preserve and make available to the scientific community, relevant samples for the research on genetic diseases. Similarly, Alliance against Cancer (<http://www.alleanzacontroilcancro.it>), the association of the Oncology Comprehensive Cancer Institutes is creating a network of biobanks of cancer cells and tissues. The Health Minister, with the Ministerial Decree of the 21st of July 2006 (published in Official Journal: number 183 of the 8th of August 2006), gave Alliance Against Cancer the task of developing a “unified national network and international collaborations”, with particular reference to a European collaboration. Alliance Against Cancer decided to participate to the preparatory phase and developmental phase of the European Biobanking project, included

in the priorities of European infrastructures identified by the *road map* of the *European Strategy Forum for Research Infrastructures*.

Other initiatives for the creation of a network of biobanks have been undertaken by the National Centre for Biological Resources, with the aim of instituting a network in the Liguria Region and by the Foundation Cassa di Risparmio di Trento e Rovereto, for the creation of a bank of human tissues and blood, called Trentino Biobank. Significant is also the presence of Italian biobanks in European and international networks.

Currently, apart these networks, in Italy there are many researchers who, within specific research protocols, often collect biological material in public research establishments, hospitals, Local Health Agencies, etc. Generally these are small groups and have a low level of organisation. The structures dedicated to this purpose are in fact lacking in specialised personnel and sufficient funds to bring the installations in line with rigorous regulations, in order to guarantee the quality, the safe storing of the samples, their distribution and the computerised management of data, as by law, in order to protect privacy. In addition, the use of preserved samples is limited to the research group that requested them.

Aware of this situation, the National Bioethics Committee, in 2006, hoped: "...for a preliminary census of the collections of biological material and of the tissue banks already existing today within state and private institutions in Italy and the possible founding of a National Register"(10).

6. Ethical-social aspects

Recent public debates on topics like stem cells, animal cloning, DNA banks, highlight the probability that bad communication could cause misunderstandings and damage the public image of science. The harmonisation process, necessary in the European infrastructure, of the ethical and legal aspects, offers a unique opportunity to improve communication between scientific, medical and legal disciplines, and between the scientific community, healthy donors and patients.

European aspects of information and consent

Both at the international and at the European level, the regulation (legislation, authoritative groups of specialists) of biobanks focuses our attention, first of all, on the distinction between biobanks for therapy and transplants and biobanks for research. The distinction is significant from a legal point of view, as it highlights the different "aims" of the collection and use of the material in the two types of biobanks. In fact, this distinction involves the need to use two informed consents, different in content.

Specifically, the Recommendation of the Council of Europe on the use of human biological material for biomedical research purposes, still today the only organic document that regulates the use of human biological material, defines models of informed consent according to the type of biobank under consideration (3). This use has been anticipated in medicine and other healthcare disciplines, but not in applications of a different nature that are external to healthcare issues.

Current international literature identifies four models, presented in the table (11).

Model of informed consent	Definition
Broad consent	Allows the use of biological specimens and related data in immediate and future investigations of any kind at any time
Partially restricted consent	Allows the use of biological specimens and related data in specific immediate research and in future investigations directly or indirectly associated with them
Multi-layered consent	Requires several options to be explained to the research subject in a detail form
Specific informed consent	Allows the use of biological specimens and related data only in immediate research, forbids any future study that is not foreseen at the time of the original consent

Information to potential donors

Internationally, particularly in Europe, the essential elements of the information to the donor/patient – to be recorded with analytical methods in the documentation of the consent or dissent given – are: voluntary participation, eventual transferral of the samples to another bank, or to research groups different from the original one, the possibility or the exclusion of a return of information to the donor about the outcomes of the research, (exclusion that can happen when the investigation of the genetic material does not have a “clinical” significance), indications about the possible consequences for the donor or is/her family members of the results of the genetic analysis, the possibility of making the samples anonymous or of identifying them with a code; the measures adopted for the protection of personal data; the possibility for the donor to withdraw, at any moment, his/her consent; the destiny of the samples in case the donor withdraws consent or the biobank closes; eventual commercial possibilities of the research (including depositing patents) and potential reimbursements of incurred costs, as well as the donor’s participation to the possible diagnostic/therapeutic benefits deriving from the research.

The information disseminated and the initiatives of education to solidarity by donating biological samples for research

The awareness that biological banks are fundamental resources for the advancement of scientific knowledge in biomedicine is stressed by the fact that, in many contexts, the start of many biological collections is no longer linked to the initiative of single researchers, but organised by governments (12-14).

With regards to this, we highlight the need to consider, with concrete measures, the protection of particular interests, including healthcare interests, of populations and/or groups that offer their contribution to the implementation of collections and/or banks of biological data and tissues.

The genetic material or data preserved in biobanks is doubly relevant: it can be used both for the donor/patient's direct interest, as well as for a more general research purpose (13-16), as it can not only predict individual sensitivity to a normal or pathological manifestation, but it can have a significant impact on the family group and even extend to future generations, acting beyond the restricted group to which the person belongs, and in this way assuming a cultural value. In fact, the investigation on biological and genetic material in particular, can shed light on the understanding of the etiopathogenesis of many illnesses that affect large groups of people.

The double value, public and private, of the genetic data, supports and reinforces the idea of creating biological banks, adequately disciplined by clear norms of law for future studies and of putting in place measures able to make the scientific value of collecting samples known, in view of a free disposition educated to civil solidarity.

International management of samples and data: concession for use and donation

According to the old international custom, the overall discipline about this topic is called "tissue donation" (and cell donation, in some documents) in analogy with the donation of organs for transplant.

In the relationships established between the person who wants to do a voluntary and "supererogatory" action – for moral reasons, for the benefit of society - and biobanks, we can identify, at least in theory, two options: real donation, definitive and irreversible; a form of concession for use under certain conditions.

The information/consent regulates the options.

The working Group believes that it is important – both in principle and with regards to policies – that these aspects are looked at in more depth and regulated.

Keeping, for the moment, the general denomination (currently in use internationally and nationally) of donation, the Committees highlight that the donation of biological material has many moral values: it is an act that can benefit other people now or in the future; it is an act of forethought in case of future personal need (for particular clinical conditions) and it is a contribution to biomedical research in view of both new knowledge and better medical treatments. For all of these reasons, donation must always be intended as a free, informed, gratuitous act that can be withdrawn, in view of the current international prevailing interpretation of agreed concession for use.

The donation can happen in life but – with special care and guidance of the extent of use provided by the donor – also after death. In this case, it is important to decide in advance – regulations – national criteria that allow it, both in "early declarations of intent" and in the decisions that are eventually the responsibility of legal representatives, or of that family member who is acting as support assistant or is chosen as the family representative.

In conclusion, the donation expresses an attitude of solidarity towards other contemporary people and future generations, as stressed in the document by the National Bioethics Committee: *"More than in the rights of the individual, and within the respect of private life, biobanks could become tools in a new form of solidarity between groups and generations, based on a voluntary*

sharing of samples and information, for a common resource that must be available on a basis of rules of democratic participation” (10).

This vision is stated also in the Oviedo Convention, which stresses the importance of the use of medical progress for the benefit of present and future generations (12), as in the Universal Declaration on the Human Genome by UNESCO, adopted in 1997, which qualifies the human genome: “in a symbolic sense, it is the heritage of humanity”.

If the reasons described – which aim at increasing scientific knowledge – stress the need to plan and consolidate biological banks in our Country, the same reasons lead us to recognise that it is appropriate to exercise an ethical evaluation not only on the statutes of each biobank, but also of the research that is carried out in them.

In synthesis, it seems necessary to adopt a system of procedures that makes potential donors able to choose in full conscience, to withdraw, to access their own data, to have the guarantee of their destruction if requested. These procedures, in view of the social need for the preservation of biological material, require a broader informed consent for the sample’s use and the destiny, which goes well beyond the agreement to the removal and that clearly illustrates the intent to preserve the collected material. The predisposition to a solidarity donation, which must be plainly stated in the informed consent, will necessarily be accompanied by information about people’s right to withdraw their samples. The possibility to withdraw, means allowing donors to express their consent more happily: in fact, this opportunity increases their trust in scientific research, thanks to the perception of a better transparency and of an indirect involvement in the research objectives. This effect of trust will be visible in the medium and long term (18).

Experience has shown that trust is obtained when the donor is informed of all the conditions that can be vital to the decision to consent or refuse the donation and of the setting up of tools that can certify the transparency of the activity of biobanks. Biobanks, used for research purposes, require the control of an independent organisation, like the Local Ethics Committee, to ensure the respect of the ethical and legal regulations in force.

Some organisational aspects of biobanks

Referring, for a broader analysis of the topic, to documents previously published on this issue by the NBC and the NCBBLs and to the numerous international contributions (OCSE for example; Nuffield Foundation, German Bioethics Committee...), here, and for the purposes of this document, we simply highlight that the scientific potential of biobanks cannot be fully exploited if their use is limited to isolated, pre-defined research projects. Although it remains the donor’s prerogative to limit his/her consent to a single project, donors should be able to give their consent for a rather general use of their samples for biomedical research, including genetic research, if it is coherent with the first use.

Biobanks – with the collection of related data – must, in conclusion, achieve optimal conditions of collection and management, coherent with the resources available. It is evident that, in order to establish them, it is necessary to inform the public and involve the people we want to take a census of and enrol. Therefore, the process will have to be transparent, fixed by a management statute/regulation which will be made public – but suitable to

support correct scientific processes and sustained by information given to the right participants and carried out by specialised personnel. The Authority's directives for the protection of personal and sensitive data on The Protection of Personal and Sensitive Data (legislative decree 196/2003), the Authorisation to the treatment of genetic data with procedures regarding the setting up and functioning of biological banks for research purposes (February 2007), the Guidelines for the treatment of personal data in the clinical trials of medicines (August 2008) state that patients should be informed and give their consent for the use of personal data and, therefore, this can interfere also with the use of samples.

A more explicit clarification – although it does not involve in vivo medicine trials but the use of preserved biological samples - seems appropriate in order to protect personal data, but to in the same way support scientific research which, in some sectors, necessarily requires the coordination of the laboratory data with the clinical data – existential of the person (eventually repeated in time).

From a legal point of view, currently the management of the samples is complex because the problem of the “ownership” of the sample has not been tackled and in general we prefer to talk about responsible maintenance and safeguarding of the sample when faced with purposes that are different from direct diagnostic/therapeutic ones. In the current situation, the Committees believe that in the great majority of cases the samples belong to the donor, who makes them available – allowing their use according to the consent given – in the spirit of solidarity, towards future benefits deriving from the research (if possible personal but in any case shared by the community); they hope however that the option of real and irreversible donation can be received favourably, as clarified above.

7. Historic collections

Many researchers use human biological samples taken from archives of pathological anatomy, in particular, from histopathology and cytology laboratories which, processing smears, biopsy and surgery samples for diagnostic purposes, can collect fresh tissue during their routine dissection procedures. In this way, the samples can be preserved, after being adequately catalogued, for diagnostic and research purposes. Checking the sample's origin and nature is therefore entrusted to specialists in anatomic pathology, who certify the sample's conformity to the biobank's requirements.

In laboratories of pathological analysis, there are tissue archives fixed in formalin and enclosed in paraffin, which represent scientific goldmines to explore with modern genomic, transcriptomic and proteomic techniques. These archives (paraffin slabs), taking into account the obligation to preserve the tissues undergoing a diagnosis (the minimum conservation period must be 20 years for histological material – slides and slabs), are considerably large, representing an inheritance of inestimable value for the scientific community. With regards to these samples, on which today is often possible to carry out a genetic analysis, it will be necessary to create regulations that exceed the current directives, in order to allow their use for research purposes, not only in the Institution of Pathological Anatomy they belong to, but also in collaborative studies. In fact, in the majority of cases there's no informed consent for the use

of the samples for research purposes and, very often, it is no longer possible to ask the donors' consent, because they have in the meantime passed away.

In the 26 screening laboratories for metabolic diseases, recognised by the Regional authorities, there are blood micro-samples on tissue paper (Guthrie spot) and only a small amount of them has been used for the screening of some hereditary metabolic diseases. These samples are a fundamentally important biological bank for prospective studies in genetic research. In fact, in some of these Centres, the samples have been preserved even for twenty years, before being destroyed, on the basis of a non-verified interpretation of the Authorisation to the treatment of genetic data in procedures regarding the setting up and functioning of biological banks for research purposes (Authority for the treatment of personal data, February 2007). Instead, Guthrie spots can provide fundamental elements for genotype-phenotype correlations, especially with regards to complex diseases, and supply indispensable information about the "weight" of genetic factors in comparison to environmental ones. In this case, we could ask the consent of the respective donors (newborns at the time) in order to analyse some susceptible genes and verify, today, their impact on the subject's state of health. Other countries, not having at their disposal this Italian inheritance, are creating similar banks, which will become useful in 20-30 years (United Kingdom, Sweden, Estonia, etc.).

It seems therefore desirable that the historic collections of samples removed for diagnostic purposes and preserved for scientific interest, are not managed according to current criteria. The "historic" collections would be lost to research if we asked, according to the current criteria, an informed consent for their use. Therefore, we propose that the local ethics Committee could allow the use of historic collections, when such use does not affect the donor's interest with regards to the protection of personal data, and his/her anonymity is ensured, as recommended by the Council of Europe (3). The local ethics Committee should, in this case, take into account the following criteria:

- 1) that the research is in the general interest;
- 2) that the research is carried out under the responsibility of the institution that first collected the sample;
- 3) that the research is less effective, or is not possible, without the identification data of the subject from whom the sample was taken;
- 4) that the donor has not expressed an objection;
- 5) that the confidentiality of personal data is guaranteed.

8. Informed Consent

Taking up again, in this paragraph, arguments already put forward in paragraph 6, with regards to the ethical-social aspects of "information", the Committees have examined with particular attention the elements relative to the "consent".

As a premise, we recall that – at the national level – the National Bioethics Committee has recognised as an adequate model of informed consent the "*partially restricted consent*", a consent that allows the use of biological material (and the related data) for the purposes of the specific research for which the collection began and for future purposes linked to it in a more or less direct way (10).

The Committees stress that informed consent is a fundamental requisite in biomedical ethics, so much so that all documents on this topic highlight the need and importance of it (19-21).

With regards to informed consent, the Declaration of Helsinki by the World Medical Association in article 24 recommends that: *"In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed."* (22).

The Committees have no difficulty in agreeing with what has been stated by some, that is, that in research with biological samples there can be a conflict between the need to adequately protect the subjects (from risks, from an improper use of personal information and from other damages) and the researchers' need to have sufficient flexibility to carry out the research, otherwise it becomes impossible to progress in our scientific knowledge (23).

They believe however that the directives already emerged internationally and nationally are sufficient, if translated into clear rules, to overcome the abovementioned difficulties – both for the so-called "donations" occurred in life and after death.

As already stated, in the case of deceased people, the consent can be "explicit", but also "presumed". However, if the party concerned objected while alive, no retrieval of tissue may take place, with the exception of judicial proceedings. Furthermore, if there has been no explicit expression of will and the applicable system is that of "presumed" consent, the doctor responsible must ensure as much as possible that relatives of the deceased, or those legally representing him/her, have the opportunity to express the deceased person's wishes (24).

The informed consent must cover the entire process undergone by the sample, and therefore include the phases of collection, preservation, use and transferral to other researchers or institutions.

(A complete discussion of the requisites of informed consent can be found in the presentation by Dr. Carlo Petrini, attached to this document).

The requisites of informed consent

A) Informed consent is an essential requisite for the collection and preservation of biological material. It must be voluntary and free from coercion.

B) Information given before the request of consent must be clear, truthful, precise and formulated in a way that does not give false hope.

C) The consent must be expressed in writing. If this is not possible, adequate procedures must be set up in its place, and the relative documentation must be preserved.

D) In general, the subject should always be guaranteed the possibility of withdrawing consent at any moment.

E) The consent expressed for a diagnosis and/or a treatment must be seen as distinct from the consent to scientific research.

Consent for studies or research using biological material

1) The collection and the preservation of biological samples can be carried out only if the subject expresses a free and informed consent, except in case of particular needs (public health needs that are above individual rights, legal measures, and others).

2) The collection of samples must occur for specific and clearly identified purposes, unless the sample is made anonymous.

3) The anticipated length of time for a sample to be preserved in a biological bank must be stated, unless the removed sample is considered not suitable for storage in the bank (this is a legal obligation, according to the "Authorisation to the Processing of Genetic Data" of February 2007).

4) In case an eventual commercial exploitation of the research with biological samples is foreseen, the donors must be clearly informed. The subjects must also be made aware that they will have no right to the potential profits.

Compulsory options of consent/refusal in the informed consent

> Availability to provide consent for any future anticipated research that has been clearly indicated.

> Availability to provide consent for future research linked to the condition for which the sample was initially collected, as long as the subject is contacted again; a new and specific request of consent is formulated; the research is approved by an ethics committee.

> Availability to provide consent for future research linked to the condition for which the sample was initially collected, as long as the research is approved by an ethics committee.

> Availability to provide consent for future research, even if not linked to the condition for which the sample was initially collected, as long as: the subject is contacted again; a new and specific request of consent is formulated; the research is approved by an ethics committee.

> Availability to provide consent for future research, even if not linked to the condition for which the sample was initially collected, as long as the research is approved by an ethics committee.

Procedures of samples collection to be taken into account

* The ethics committee must be consulted also when there is no obligation to do so according to national legislation. The ethics committee has a very important role, especially in evaluating research that involves minors or other categories that cannot, for physical or legal reasons, express their consent.

* The samples collected from minors or from subjects who are unable to express their consent can be used for experimentation only if:

> The research is directly linked to the subject's clinical condition.

> The legal representative has expressed a valid consent.

- > The risks for the subject are minimal.
- > In the case of adult subjects, about whom there are doubts regarding their ability to express a valid consent, adequate tests to assess their capabilities are carried out.
- * The sample for which the subject participating to the study/research expresses his/her consent to removal must be considered donated.
- * Subjects participating to the research must be offered no financial or other type of incentives to encourage the donation. It is only allowed to reimburse eventual costs (for example travel costs).
- * Biological samples must not be the object of a sale.
- * The collection of samples, the management of biobanks and any procedure must be carried out by qualified and competent personnel.
- * The information gained from studying the samples must be divulged in the terms consensually agreed before the collection.
- * The biological samples and data must be adequately protected to avoid intrusions and unauthorised access (also according to the **Technical Specifications Regarding Minimum Security Measures, Articles 33 to 36 of the Code** for the protection of sensitive data attached to the legislative decree 196/03).
- * The transferral of data and samples between different centres must be carried out only after individual consent.
- * Various aspects of a correct management of personal data and samples collected in biobanks are the object of regulations about the protection of personal data, and they must be referred to. To comply with this regulation, it is necessary to introduce in the informed consent forms a specific section dedicated to the “treatment of personal and sensitive data” and ask for a consent specifically with regards to this (which is different from asking consent to participate to the study with or without biological material), adding to the informative note the rights reserved to the subject, according to article 13 of legislative decree 196/2003).

9. Conclusions

Many studies on informed consent highlight the fact that people generally want to control whether their samples are used for research purposes, but also that the majority of these people is happy to donate samples. The model of informed consent elaborated by the NBC and the NCBLS respects this will, informing donors of the use intended for the biological material and the information related to it, as well as guaranteeing that the correct procedures are adopted in order to protect personal data. The proposed model for informed consent allows us to strike the right balance between social interest and the protection of personal information, by not putting the collective interest before individual interests. The consent model proposed for the “donation” does not contradict the respect for the guidelines found in the Italian recommendations and in the Oviedo Convention, which in article 2 states: “The interests and welfare of the human being shall prevail over the sole interest of society or science” (12).

In particular, the Committees:

1. agree with the general formulation of “Recommendation number 4-2006” by the Council of Europe.

2. stress that the donation of biological samples for research purposes, and for the preservation in biobanks or collections, cannot be carried out for financial gain.

3. believe that it is important to stress what has already been stated in the NBC’s Opinion (2006) regarding the usefulness of a census of the collections of biological material and of tissue banks existing today in state and private institutions, in order to create a National Register.

4. feel that there is a current need to establish, in Italy as well, a number of biological banks in line with a regional programme, disciplined by clear laws that also include the coordination with a local Ethics Committee, which would ensure the respect of the ethical regulations in force for the protection of the person concerned, and confirm the need to put in place measures aimed at making the scientific value of collecting samples known, in view of the free disposition of the educated person to civil solidarity.

5. the Committees recommend that donors are given in any case, in writing, clear, truthful, precise information, formulated in a way that does not give false hope, so that they are able to exercise their free will with regards to the use of their biological samples.

6. propose the adoption, in the necessary discipline of information and informed consent to the concession and use of biological samples and related personal data (so-called “donation”) different forms, according to the use anticipated for the sample and/or the data agreed with the donor (so-called “broad, partially restricted, multi-layered, specific consent”).

7. believe that the presence of a geneticist in the local Ethics Committees is necessary, in case the research submitted to the opinion of the local Ethics Committee has to be carried out on preserved samples with a genetic interest.

8. the Committees, with regards to the legal regulations concerning samples, propose that the samples belong to the donors with the general formula of “concession for use”, or are considered as “explicit and irreversible donation”, on the basis of a choice expressed by the donor in writing, confirming in any case the principle of gratuity and the prohibition of personal discrimination. In the cited hypothesis of the option indicated as “concession for use”, the possibility for the person concerned to have control over his/her own samples and information must be ensured, as well as the right to withdraw the consent initially given.

9. the Committees propose to draw up regulations on the basis of which the local Ethics Committee can allow – after a motivated request by the researchers – the use of historic collections when such use does not affect the interests of the untraceable living donor with regards to the protection of personal data, and his/her anonymity is ensured, in line with what has been recommended by the Council of Europe (3).

10. finally, the Committees stresses that, highlighting the social value of the research with biological samples, individual rights are not overlooked. On the contrary, proposing an adequate system for the protection of individual rights through the informed consent, they promote personal interests and social interests at the same time.

The proposed model of informed consent is only applied to the collection of biological samples for research purposes.

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Steering document on the standardised consent form model

Introduction

Informed consent is essential in the relationship of trust between doctor/researcher and study participant who is the donor of biological material (patient or healthy subject). It regulates the transfer of information and biological material from the donor to the doctor/researcher or to his/her representative and it details its possible uses.

The use of the biological samples and of the information about the donor is necessary for both diagnostic and therapeutic reasons in ordinary clinical practice, but also during experimentations and research.

For a correct use by those collecting, preserving, studying and disseminating the information obtained from these samples, it is necessary for the donor to completely understand, at the moment of signing the informed consent form, the purposes, uses and relative restrictions.

The informed consent form must:

a) guarantee the collector and those accessing the biological material preserved in biobanks that the data and information have been legally acquired;

b) inform and guarantee the donor of the correctness of the preservation and use intended for the biological material and the related information.

Finally, the informed consent form must anticipate:

a) the use of the biological material and the related information by third parties

b) the possibility for the donor to demand that the unused samples and related information are destroyed

c) that the criteria to avoid the donor's "potential identification" are followed. (Any sensitive data arising from the analysis of the samples dictated by a study protocol cannot be communicated to a third party outside of the study, or published, therefore circulated, except in aggregated form. The result relative to a single case can be published, for scientific purposes, but being very careful not to give "accessory" indications (that is, other information) which, with a reasonable use of methods and techniques can allow, even potentially, with good probability, an identification of the subject).

Therefore, the purpose of this document is to identify and categorize the various parts that constitute the informed consent model, in order to allow us to combine them in different ways, according to the purposes for which it is requested. The document's main elements are:

a) identification of the donor and of the collector

b) identification of the reasons for the collection

c) identification of the place, duration and methods of preservation

d) reversible and irreversible anonymisation of the samples

e) ways to protect the donor

In the standard form, the dotted lines refer to attached lists/documents that identify the content/type of information/material given or collected.

Consent model: general part

Project's title

Creation/expansion of a bank of biological material for research on.....

Research purposes

The techniques available today and those that will be developed in the future, can help to better understand these illnesses and consequently, to improve their treatment.

This is the reason why we intend to create/expand a biobank of biological samples of, which would facilitate access to samples, in quality, in order to allow the development of research and of diagnostic and therapeutic instruments for patients affected by that illness.

However, we will not achieve this objective if the donors/patients and their relatives will not donate blood and tissue samples, to be preserved in appropriate conditions, in order to be able to use them in future research.

Procedures

If you accept to take part in this project, a sample of: (*specify, blood, tissue*) will be preserved and the information relative to the sample will be included in a database, available to researchers.

If you agree, the collected samples (for diagnostic purposes and/or therapeutic interventions; for scientific research purposes) will be preserved in the biobank, a public biobank that provides services of collection, preservation, categorisation, use and distribution of biological samples outside of the institution

Your samples will be used for this project's specific purposes and for all research of this type which, directly or indirectly, is connected to those purposes (*describe in general the area and the potentially related secondary uses*).

This activity will be developed in line with the directive on the protection of personal data and in accordance with ethical regulations, internationally accepted, and all research will be supervised by an Ethics Committee that will ensure the respect of the abovementioned directives and regulations.

Your collaboration is voluntary and free. You are free to withdraw from these studies at any time and without giving any reason. No type of discrimination will be made towards you in case of withdrawal. You can ask, at any time, for the samples and the related data to be destroyed or made irreversibly anonymous.

Access to clinical data

Researchers could have the need to access your clinical data to gather information necessary to the completion of the research project.

The identification of samples

The confidentiality of the samples will be guaranteed, as they will be labelled with a code. The samples will be preserved, coded/encrypted in and manipulated anonymously by researchers. However the donor/patient could be identified by a code, the access to which is restricted to the person responsible for the safety of the data. The decoding will be carried out only by the person responsible for the safety of the data (*specify: Name*) or by a person designated by him/her.

Consent for tissues that are destroyed (*leftovers*)

You need to undergo a surgical procedure to and we ask your consent to study the tissues that will be removed during surgery; tissues that are normally destroyed. The study does not affect the medical treatment or the surgical procedures. We ask your consent to preserve and use your samples for future studies.

Duration of the preservation

The samples will be preserved for an indefinite time (*specify: Institution and biobank*) under the responsibility of (*specify: researcher responsible or person in charge of the biobank*), unless the donor/patient gives different instructions.

- " indefinite time
- " time necessary to (*specify*)

Benefits

This is an altruistic donation, for which the donor will not have any financial gain. The information obtained could be useful for you or for your relatives. We hope, on the other hand, that the results obtained by its use will allow us to improve our knowledge of this type of illness and can be beneficial to the whole of society.

Physical risk

You will not be exposed to any physical risk associated with the collection of samples, seen as they have already been removed (during the course of your treatment, for a biopic assessment, etc.)

(in case of a healthy donor, describe the possible physical risk associated to the collection of the sample, as, for example, bleeding when taking a blood sample)

Protection of personal data

The creation of a biobank involves the existence of a file containing all your personal and medical data. This file will be set up according to the instructions of the Authority for the Protection of Personal Data (legislative decree 196/2003) and, when applicable, the Authorisation to the processing of genetic data for procedures regarding the setting up and the functioning of

biological banks for research purposes (Authority for the treatment of personal data, February 2007).

Both the information given and the results of the research will be confidential. The information will be *(describe the safekeeping system)*.

The results of the research will be published anonymously and in aggregated form, so that it will not be possible to identify the donor.

Communication of the results

The results of the research that concern you will not be communicated to your family members or doctor, unless you give specific authorisation to do so.

" I authorise the communication of the results that concern me to

" I do not authorise the communication of the results that concern me to any third party

The scientific results obtained will be published on the biobank's site. If these results have a potential impact on your health, do you want to be informed by a doctor?

" YES, in all cases, even if there are no new treatments or preventive measures available

" YES, only if there are new treatments or preventive measures available

" NO

Person to contact

In case you need further information on the development of the research project or want to communicate a change of address, you can contact *(name, surname, job description and work times)* at the following number.

Signature of the Operator collecting the consent

Signature of the Donor or support Administrator or legal representative

Date

Consent model: specific part

Part I

Identification of the donor and of the person responsible for the collection of the samples

The undersigned Born in on the and resident in declares to consent to the donation and preservation of biological material at and to have been sufficiently informed by (a) about the reasons and the risks of the removal carried out by (a) The methods of information were (b)

I have been told that all personal data collected will be handled in accordance with legislative Decree number 196 of the 30th of June 2003, (personal data protection Code, also known as consolidated text on privacy).

Identification of removed biological material and of the purposes of the collection

The biological material that is being removed is (c) and is collected through (d) by (e)

The biological material is collected for the following purposes:

scientific research, the purpose of which is clarified in the attachment/

scientific research, the purpose of which is not already defined/

quality control/

In case collected material is destined for destruction

The collected material is the result of the removal of tissues during surgery. This material is generally destroyed as special hospital refuse

o) I consent to the material being preserved for future studies

o) I do not consent to the material being preserved for future studies

o) I consent to this material being used for future studies related to the purposes of the original research

Use of samples

The coded/encrypted samples could be used in other research projects with the approval of an Ethics Committee. Can we preserve your samples and use them in other research projects?

" YES

" NO

In order to be able to use your samples in a new research project, the objectives of which are different from those for which the consent was originally requested, a new consent could be necessary. In this case, do you want to be contacted to express a new consent?

" YES

" NO

Can your samples be used in research that requires the distribution of samples to other researchers, including those outside of this institution?

" YES

" NO

Identification of the preservation's place and methods

The collected biological material is preserved for (f), in premises used for this purpose in (g) under the responsibility of (h)

I declare that I sufficiently understand and accept what stated above and described in detail in the attached form.

I also declare that I have been informed and accept that, for study purposes exclusively, my sample or a part of it (percentage) can be sent to external, collaborating groups, identified in the protocol, or to technical centres for *service* operations.

The fate of personal identification data

My identification data (*i*) are available, together with the biological material, for the uses declared in previous paragraphs. They will be:

- "destroyed" "kept for the entire time required by the identified scientific research

- "destroyed" "kept at the end of the procedure of quality control

- "destroyed" "kept for the entire time my samples will be preserved in the biological bank

I declare that I understand the correlation that, by choice, there will be between my identification data and the biological material donated by me in line with the Authority's directives for the protection of personal data; a correlation described in detail in the form attached.

Fate of biological and clinical data

My biological data (*j*) and my clinical data (*k*) are available together with the biological material for the use declared in paragraph "*Identification of removed biological material and of the purposes of the collection*".

They will be:

- "destroyed" "kept for the entire time required by the identified scientific research

- "destroyed" "kept at the end of the procedure of quality control

- "destroyed" "kept for the entire time my samples will be preserved in the biological bank

Part II: Modification of the donor's will

Possibilities of information about the use of biological material

I am aware of my right to be informed on request about the purposes for which my biological material is used, and:

"I decide to take advantage of it

"I decide not to take advantage of it at the moment, but to do so eventually in the future

The person responsible to whom I have to address my request is And the method I have chosen to use is (*l*)

I declare that I accept what stated here and described in detail in the attached form.

Possibility of being informed of any results obtained concerning my health

In case I decide to maintain the link between my identity and the clinical-biological data related to the removed material, I am aware of my right to be informed of the results obtained analysing my material/biological data if they concern my health and

"I decide to take advantage of it

"I decide not to take advantage of it at the moment, but to do so eventually in the future

In case of affirmative choice, the way in which I want to be informed is (b)

I declare that I accept what reported here and described in detail in the attached form.

Possibility of withdrawing identification data

In case I decide to maintain the link with my personal identification data, I am aware that I can, at any time, withdraw my authorisation by communicating it to: NAME SURNAME ADDRESS (Responsible for the processing of personal data according to legislative decree 196/2003)

And the method I have chosen to use is (b)

I declare that I accept what reported here and described in detail in the attached form.

Withdrawal of informed consent

In case I decide to withdraw my consent to the donation of biological material, the person responsible to whom I have to address my request, is and the method I have chosen to use is (l)

In this case, I will be asked if:

- o) I intend to eliminate also any personal identification data related to the removed biological material;
- o) I intend to eliminate also any clinical/biological data related to the removed biological material or it must be destroyed;
- o) I consent to the remaining biological material, removed and unused, to be used completely anonymously.

I am aware that it will not be possible to destroy the information obtained previously and used in aggregated form for scientific publications, research outcomes and relative patents, and that these will not be linked ever again with my personal data and my identity.

I declare that I accept what reported here and described in detail in the attached form.

Receipt of informed consent and relative attachments

I declare that I have received a copy of these forms (list) and of the relative attachments (list) signed by the undersigned and by the persons responsible.

Dr. (specify the name) explained to me the nature and outlook of the research project. I completely understand the consent form. I have had the chance to ask questions, which have been exhaustively answered.

After careful reflection, I have reached the decision to participate to this research project without any attempts of persuasion by the personnel responsible.

Signature of the operator collecting the consent

Signature of the donor or of the support Administrator or of the legal Representative

Donor's name and surname

Address

Telephone number

e-mail

(a)

- 1) Generic doctor or specialist
- 2) Professional nurse authorised to remove the sample
- 3) Coordinator of the experimental project/researcher in charge

(b)

- 1) Writing to be kept by the donor

(c)

- 1) Tissue sample
- 2) Blood sample
- 3) Bodily fluid sample (plasma, saliva, amniotic liquid, spinal liquid, internal or external secretion, etc... To specify in the attachment)

(d)

- 1) Standard procedure of tissue removal without need for sedation
- 2) Standard procedure of tissue removal after partial or general anaesthetic
- 3) Standard procedure of blood sampling
- 4) To specify in the attachment

(e)

- 1) By authorised medical-healthcare personnel
- 2) By the generic doctor
- 3) By the specialist doctor
- 4) By competent personnel belonging to the research group

(f)

- 1) Limited time (*specify days, months, years*)

2) Indeterminate time

(g)

- 1) Internal laboratory of analysis
- 2) External laboratory of analysis
- 3) Biobank

(h)

- 1) Director responsible for the research project
- 2) Principal investigator
- 3) Person in charge of the biological bank

(i)

Name, date of birth, address (and place of residence if different), telephone number, tax code.

(j)

Age, gender, ethnical group, weight, height,

Habits and lifestyles:

- dietary habits
- consumption of alcohol, smoking, narcotic substances, drugs, homeopathic products, etc...
- other, to specify in the form attached

(k)

- No-one
- In case of possible or ascertained, current or past pathologies, specify which ones with a documented diagnosis and the therapies undergone or still under way.
- In case of previous treatment with document the type of response
- State of health at the time of the removal, certified by a full medical record.

(specify)

- 1) If the test has come up positive for any infective diseases
- 2) If, in the course of the studies, any alterations of specific analytical data commonly associated with cancer have been identified.
- 3) If the results identify the presence of genic alterations that can be linked to a greater risk of curable pathologies and/or pathologies for which there is some form of prevention that improves its prognosis.
- 4) If the results identify the presence of genic alterations that can be linked to a greater risk of pathologies for which there is no cure and/or prevention.
- 5) If factors that can affect the wellbeing of my progeny have been identified.

6) Other, to be specified in the attachment.

(f)

- 1) Mail address
- 2) Telephone number
- 3) E-mail address

**INFORMED CONSENT FOR THE COLLECTION, PRESERVATION AND USE OF
CELLS AND TISSUES IN BIOLOGICAL BANKS FOR RESEARCH PURPOSES:
*ETHICAL ASPECTS***

MIXED GROUP DOCUMENT
NATIONAL BIOETHICS COMMITTEE / NATIONAL COMMITTEE FOR BIOSAFETY,
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Preliminary notes

- This document tackles ethical questions with regards to the informed consent for the collection, preservation and use of biological samples for research purposes. However, other problems of ethical relevance, raised by biological banks, are not tackled, if not in some of their aspects that are connected to the issue of informed consent.
- In order to draw up the document, we referred to the literature on this topic, but especially to institutional documents (laws, regulations, declarations, recommendations, treatises, conventions, deontological codes, guidelines, etc.). A list of the institutional documents is reported in appendix 1.

1. Introduction

1.1 The importance of biological banks and their dissemination

From 1998, numerous biological banks of large dimensions have been proposed and often created, to the point of involving the population of entire nations (for a list, with a comparative synthesis, also in the form of a synoptic table, see, for example, K. J. Masken's review "Navigating an ethical patchwork – human gene banks" [1, 2]).

1.2 The importance of informed consent

Informed consent is a fundamental requirement of biomedical ethics. All documents on this topic highlight the need and importance of it [3, 4, 5].

In the Declaration of Helsinki, the World Health Association already recognises in the first article that: "medical research involving human subjects includes research on identifiable human material and data". With regards to informed consent, with article 24 it is established that: "In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspect of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisals. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed" [6].

1.3 Conflict of values

In research with biological samples, there is a clash between the duty to adequately protect subjects (from risks, improper use of personal information and other damages) and the researchers' need to have sufficient flexibility to carry out the research, otherwise it would be impossible for scientific knowledge to progress [7].

This clash is at times seen as a contrast: often researchers feel stifled by rules that they judge excessively onerous and restrictive.

At the root of this tension there are also very serious theoretical problems, which have been debated for decades by bioethicists, jurists, scientists and other experts.

Therefore, solutions must be found to satisfy both needs: the protection of individual rights and public benefit. It is indispensable that these solutions respect ethical principles. It is also important that this respect is perceived by the public, whose trust must be encouraged.

2. About “genetic exceptionalism”

Before tackling the specific topic of the consent to collection, preservation and use of biological samples in biobanks, some preliminary considerations about the so-called “genetic exceptionalism” seem appropriate.

The term “exceptionalism” was introduced in biomedicine in 1991 by R. Bayer with regards to the HIV infection, referring to the actions carried out for the treatment of AIDS, different from other infections [8]. The expression, which referred to privacy issues, the protection of personal data, discrimination, stigmatisation, was then applied to genetics [9].

If we reject “genetic exceptionalism”, and therefore we consider the genetic data as any other sensitive data, specific provisions will not be necessary (at least in theory, whilst some will still be needed practically, because of the nature of the sample). If instead we accept “genetic exceptionalism”, a more in depth reflection is needed.

As we know, the Authority for the Protection of Personal Data, in line with the directives already adopted [10], anticipates specific regulations for the handling of genetic data, more restrictive than those adopted for other medical-biological data [11, 12, 13, 14].

In specialised literature, the debate on the opportunity of protecting genetic data more than other types of personal data, we find two contrasting, extreme positions (in favour and against exceptionalism) [15].

Summarising schematically, we can say that the debate focuses around three main questions:

- Is it possible to neatly separate genetic information from other personal medical-biological information?
- Is genetic information naturally susceptible to more violations of privacy and of individual interests compared to other information?
- Are there suitable ways of processing genetic information differently from other information?

In the document “The 25 recommendations on the ethical, legal and social implications of genetic testing” [16] by the European Commission, recommendation number 3 states:

- “genetic exceptionalism” should be avoided, internationally, in the context of the European Union and at the level of its Member States. However, the public perception that genetic testing is different needs to be acknowledged and addressed;
- all medical data, including genetic data, must satisfy equally high standards of quality and confidentiality;

- in order to track the evolution of public perception of genetic testing and to identify issues for future debate:

- further research on ethical and social perceptions of genetic testing is necessary and should be promoted by the European Commission and by national bodies;

- questions relevant to genetic testing should be included in pan-European surveys such as the Eurobarometer”.

Recommendation number 10 of the same document states that: “genetic data of importance in a clinical and/or family context should receive the same level of protection as other comparably sensitive medical data”.

Some legislations in fact consider genetic data together with other types of medical data [17].

However, there are some strong reasons for giving genetic data particular protection. We can easily identify both general reasons, which refer to the significance and the peculiar value of the genetic make-up, as well as to more operative reasons, which consider the consequences of using genetic data. With regards to the first level, it will suffice to recall that in the “Universal Declaration on the Human Genome and Human Rights”, adopted on the 11th of November 1997, in article 1 UNESCO states that the human genome [18] “in a symbolic sense, it is the heritage of humanity”. Still UNESCO, in the premises of the following “International Declaration on Human Genetic Data”, adopted on the 16th of October 2003, although “recognising that any medical data, including genetic data and proteomic data (...) must be handled with the same standards of confidentiality”, highlights that “human genetic data have a special status, on account of their sensitive nature since they can be predictive of genetic predispositions” [19]. As exemplification of the operative level, we can recall that the English Human Genetics Commission identifies in particular the following reasons [20]:

- the peculiar nature of genetic information, some of which allow us to identify a person and to confirm, or deny or reveal a family connection;

- the possibility of gaining genetic information from very small amounts of biological material (skin, saliva, blood, hair, and other), which in some circumstances is possible to obtain without the subject’s consent;

- the predictive power of some genetic information;

- the possibility that genetic information is used for purposes different from those it was originally collected for;

- the relevance that genetic information could have for some people, amongst which: relatives, insurance companies, employers;

- the importance that some genetic tests could have to identify the susceptibility to rare diseases and to the efficacy of therapeutic treatments;

- the DNA’s stability, which means it can be extracted from samples in biological banks, but also from archaeological finds after a long time.

All this plays in favour of giving particular protection to genetic data [21].

However, and in connection to the transmission of genetic data to our descendants, we cannot overlook family as well as individual rights to genetic information. Particularly explicit in this sense is the English Royal College of Physicians, which states: “Genetic information about every individual must not be considered as personal to that individual, but as a common priority of the people who could share those genes, and who need the information in order to know their genetic make-up. In this case, the prima facie right of an individual to confidentiality

and privacy could be considered less important than others' right to have information regarding themselves" [22]. Similarly, and with specific reference to family interests rather than to the potential collective benefits, in the "UK Human Rights Act" the relationship between individual and family privacy is highlighted, and privacy is defined as a "right to respect for his private and family life" [23].

As we have already said, in Italy legislators have wanted to distinguish the way genetic data is handled from the way any other sensitive data is handled [24], so much so that the expression "sensitive data" was coined. However, we must note that the legislative notion of "genetic data" is absent from Italian legislation: the Authority, in the opinion of the 22nd of May 1999, felt it appropriate to recall the notion presented in the Council of Europe, which includes "all data, regardless of their typology, concerning the hereditary characteristics of an individual or the way these characters are transmitted within a group of related individuals" [25].

According to the writer, rejecting genetic "exceptionalism" seems hard to justify and support, considering the absolutely particular characteristics of genetic data. In fact, they contain information that no other personal data contains. For example, genetic data: allow us to identify family connections; contain information that does not only belong to an individual, but is also relevant for his/her blood relatives; can not only reveal some aspects of our state of health, but also of our person in its totality. However, the recognition of "exceptionalism" does not mean building an insurmountable barrier against the use of biological samples and their related data. We will need to find, each time according to the specific circumstances and situations, the right solutions [26, 27].

1. The content of informed consent

The majority of authors agree with the fact that the procedure for the consent must include the following elements:

- Prerequisites:
 - Competence (understanding and ability to choose)
 - Voluntariness
- Information:
 - Communication from the operators
 - Understanding from the subjects
- Agreement:
 - Decision
 - Authorisation [28].

There are various documents listing the elements that, in general, must be included in the informed consent (directly in informed consent forms or, to avoid weighing down the forms excessively, in attached information sheets, which constitute an integral part of the forms themselves). For an exhaustive list of the information that is necessary to give the subjects participating to clinical trials, and not only with reference to biological samples preserved in biobanks, see, for example, amongst the various documents available, the "International guidelines for biomedical research involving human subjects" by the Council for International Organisations of Medical Sciences (CIOMS), and specifically "Guideline 5. – Obtaining informed consent: essential information for prospective research subjects" [29]. "Guideline 5" is reported in full, in an unofficial translation, in appendix 2 of this document.

In literature there are numerous suggestions of specific models for biological banks, in which the unrenounceable elements that must be included in the informed consent are adapted to the specific case. Some of these suggestions come from taking into consideration numerous models in use in a variety of institutions. For example, amongst the most famous, the work of T. A. Caulfield et al. [30]. Amongst the most authoritative suggestions in Great Britain is the model proposed by the Medical Research Council [31]. In United States, the models proposed by M. Sobel and K. Hansen are widely used [32]. Amongst the most recent models there are, for example, those suggested by C. Portieri and B. Pascal [33] and by E. Salvaterra et al [34].

The Authority for the Protection of Personal Data has identified the elements to include in the information relative to genetic data processing and a model to express consent (with specific reference to genetic data processing).

The elements that characterise the information are also listed in point 5 of the “Directive of the 22nd of February 2007. General authorisation to genetic data processing” [35] as well as in points 7 and 8 of the “Guidelines for personal data processing in the clinical trials of medicines. Deliberation number 52. 24th of July 2008”. This last deliberation is particularly significant for this document and will be repeatedly referred to in the parts following. The deliberation also includes an example of “Information and expression of consent to personal data processing” which is also applicable to biological samples [36].

Informed consent must cover all the procedures undergone by the samples, and therefore include the phases of:

- collection,
- storage,
- use.

Following, we report the elements that, we believe, should be part of informed consent:

- Indicate:
 - ✓ The sample’s place of storage.
 - ✓ The size of the biobank.
 - ✓ Eventual other centres involved (in case of experimentations).
 - ✓ The name of the person in charge.
 - ✓ Sponsor and founding (if applicable).
- Specify if the sample is removed for a diagnostic assessment, therapeutic treatment or exclusively for scientific research purposes.
 - ✓ In the first two cases specify:
 - If the sample is:
 - Part of ordinary removals for diagnostic or therapeutic purposes.
 - Additional to ordinary removals.
 - Which procedures are part of the diagnostic or therapeutic practices and which ones are part of the experimentation.
 - ✓ In the third case specify:
 - Importance of the research.
 - Context of the research.
 - Current state of knowledge.

- Research purposes.
- Expected outcomes.
- Expected duration of:
 - Research.
 - Subject's participation (if different from that of the research).
- Procedures followed.
 - Specify the anticipated risks and discomforts, as well as eventual compensation in case of damage.
 - Specify the expected benefits, distinguishing:
 - ✓ Benefits for the subject.
 - ✓ Benefits for other subjects and for the advancement of knowledge.
 - Describe eventual alternative procedures, distinguishing:
 - ✓ Advantages.
 - ✓ Disadvantages.
 - Specify that:
 - ✓ Participation is voluntary.
 - ✓ An eventual refusal to participate does not lead to any penalisation.
 - ✓ It is possible at any moment, without being penalised, to:
 - Withdraw consent.
 - Ask for the destruction of the samples.
 - Ask for the destruction of personal data.
 - Offer the possibility of receiving or refusing information about the results obtained and confirmed.
 - Indicate the possibility that the results become the object of scientific publications, presenting the data in anonymous and aggregated form.
 - Specify if it is possible that the clinical information emerging will be useful for the subject and, if so clarify:
 - ✓ How the subjects will be informed.
 - ✓ The possibility of asking not to be informed.
 - Specify that the sample will not be used for commercial purposes and that, if any financial benefit will come from the research, the subjects will have no right to them.
 - Indicate the people that can be contacted for eventual clarifications or requests.
 - Summarise the ways in which privacy will be protected, in line with legislative decree 196/2003 and with the measures following it, specifying:
 - ✓ Which personal information are collected.
 - ✓ Which measures are adopted for the protection of sensitive personal data.
 - Indicate the methods with which samples and personal data will be transferred to other centres for research purposes (if applicable).

With regards to the last two points, relative to the protection of personal data, it is important for the information and informed consent forms to be drawn up taking into consideration what the Authority for the Protection of Personal Data prescribes in the "Guidelines for personal data processing in the clinical trials of medicines", where it is stated that: "erroneously believing that there is no need to apply the rules of data protection to information linked to the individuals involved in the trial, some promoters invite centres to inform the patients concerned that their data will be passed on by the study's physician to those who commissioned it,

exclusively in anonymous form. This claim, besides being wrong, does not allow those concerned to understand what are the roles actually played by the promoter and by the other subjects, whose collaboration he might eventually use, with regards to data processing. Formulated in this way, the information to individuals participating in clinical trials is, therefore, inappropriate under the Code (article 13); also, it does not allow those concerned to express a conscious intent with regards to the fact that the treatments carried out by the promoter or by other subjects who might collaborate with him (even outside the national territory) concern information that, although coded, as indicated above, can be linked to the people involved. The information to be provided by testing centres to those involved must instead include, even synthetically, but still easily understandable, specific indications about:

- a) the nature of the data processed by the promoter and the possibility that such data will be sent abroad;
- b) the role actually played by the promoter with regards to data processing and the purposes and methods of it;
- c) the subjects or categories of subjects to whom the data may be communicated or who may become aware of them, as persons responsible or in charge;
- d) the exercise of the right of access and other rights with regards to personal data, for the promoter and other subjects who will eventually receive the data (articles 7 and 8 of the Code)” [37].

A very significant problem, concerning a large number of biobanks, also regards the possibility of carrying out, on already stored samples, further research that was not originally anticipated. This aspect is discussed separately in paragraph 7. Obviously the model of informed consent will have to include sufficient information about this as well.

The peculiarities of the research on biological samples and levels of informed consent

To identify the most appropriate ways to inform subjects and to request their consent, it is useful to recall some peculiarities of the research on biological samples.

According to some authors, the subjects who donate samples destined to scientific research cannot be considered “research subjects” in the same way as those who participate in the clinical trials of medicines. In fact, in the first case, as there is no direct intervention on the subject, risks and benefits are indirect.

A further aspect involves the unpredictability of the developments of the research. Studies on biological samples often cover a long stretch of time, during which it is very probable for unpredictable, new elements to emerge, on the basis of which research will be re-directed. Research has therefore, inevitably, an aspect of unpredictability.

These two aspects make it difficult to apply to studies on biological samples the notion of “informed consent” with the exact same meaning adopted in clinical studies.

In clinical practice and in clinical trials in fact, generally the expression “informed consent” is used to indicate a very precise act, free and conscious, by a subject who has been sufficiently informed. In the case of biological

samples, the act has inevitably different characteristics, and for this reason various authors identify different types or levels of informed consent.

For example, P. Lucas identifies three: permission, assent, consent [38]:

- “Permission” is applied when the physical risks are minimal or non-existent and when the individual benefit that can come from it is limited in terms of probability and/or relevance. According to Lucas, studies on biological samples can be included in this category.

- “Assent” comprises and includes permission, but it requires a broader inclusion of all the procedures and associated risks. It is the typical case of many trials that involve limited risks.

- A true “consent”, as an act of mature and conscious agreement, can be attributed to a deeper level, which presumes the assent, and in which individual personality intervenes with conscious choices of altruism, coherent with the values and the way of life that have been personally and freely chosen.

We must however highlight that the expression “assent” is sometimes used with a different connotation, that is, with reference to minors or subjects unable to express consent, and for whom the consent is expressed by those exercising parental Authority or legal representation. However, even for these categories of subjects, if in possession of even only a reduced ability to understand and communicate, it is unanimously recognised that it is our duty to obtain their “assent”, at least in terms of a non-opposition, which has been in some way manifested [39].

1. About the “donation” of biological samples and the social value of the research on biological samples

There is a large amount of literature on the ethical, moral anthropological and social value of the donation.

The issue has been studied in depth by modern sociology, in particular after the studies published by Marcel Mauss in the first part of the 1900s [40].

The “donation” can also have social relevance [41], and therefore it must be accompanied by the respect for the principles of solidarity and sociality:

- In the specific case discussed here, solidarity implies the participation to research with the hope of benefiting others. With regards to this, the literature in English language distinguishes between “benevolent solidarity”, in which the donor can also be one of the beneficiaries, and “altruistic solidarity”, in which only other people benefit from the donation [42, 43].

- The principle of sociality promotes a balance in the distribution of benefits. It is therefore based on distributive justice, and in particular on the moral duty to “equal opportunities” [44, 45].

5.1 The position of some institutions

Samples’ donation has been proposed by a number of institutions.

Here, we report the “Recommendations” expressed in the “Statement on benefit sharing” by the Ethics Committee of the Human Genome Organisation:

- “Whereas
- ✓ we all share a common genetic heritage,
- ✓ there are different definitions of community,

- ✓ communities might have different beliefs about what constitutes a benefit, and
- ✓ genetic research should foster health for all human beings,
- The HUGO Ethics Committee recommends:
 - ✓ that all humanity share in, and have access to, the benefits of genetic research,
 - ✓ that benefits not be limited to those individuals who participated in such research,
 - ✓ that there be prior discussion with groups or communities on the issue of benefit-sharing,
 - ✓ that even in the absence of profits, immediate health benefits as determined by community needs could be provided,
 - ✓ that at a minimum, all research participants should receive information about general research outcomes and an indication of appreciation,
 - ✓ that profit-making entities dedicate a percentage (e.g.: 1-3%) of their annual net profit to healthcare infrastructures and/or humanitarian efforts” [46].

In the Medical Research Council’s document “Human tissue and biological samples for use in research; operational and ethical guidelines” we read: “We recommend that tissue samples donated for research be treated as gifts or donations (...). This is preferable from a moral and ethical point of view, as it promotes the “gift relationship” between research participants and scientists, and underlines the altruistic motivation for participation in research” [47].

5.2. Biobanks as philanthropic organisations

The National Research Council identified in philanthropic organisations (Charitable Trust) a legal structure suitable to manage many of the problems posed by biobanks with regards to safeguarding rights, respecting property, distributing benefits [48].

According to this model, donors formally express their intention to transfer to the organisation the property rights on their samples. The organisation has the duty, by law, to use this right to the advantage of a precise and identified category of beneficiaries.

Various authors saw in the structure of philanthropic organisations a useful and flexible model with a series of advantages, and in particular” [49, 50]:

- The altruism that characterises every donation is respected and enhanced.
- The philanthropic organisation can give the donors an advisory and management role.
- The philanthropic organisation can have more stability compared to private biobanks, the existence of which can depend on market fluctuations.

1. The risks, “minimal risk” and the possibility of identifying the data

Research on biological samples is non-invasive and therefore only poses indirect risks for the subjects, mostly due to eventual improper uses of the information.

For this reason, many believe that all risks due to research on biological samples belong to the category of the so-called “minimal risks”.

The Royal College of Physicians in London compares “minimal risk” to taking a blood sample or to slightly more serious but less probable risks [51].

It is difficult to quantitatively measure “minimal risk”. In the specific case of biobanks, the difficulty is increased by the fact that “minimal risk” is generally defined in relation to indirect risks.

For a judgement about the appropriateness of considering “minimal” the risks deriving from the use of samples in biological banks, it seems fitting to consider the following elements:

- The boundaries of “minimal risk” and the acceptability threshold should always be assessed in relation to the associated benefits [52]. This is definitely important in general and also specifically for biobanks: as in any scientific research, the benefits must outweigh the risks in research on biological samples too.

- The argument of “minimal risk” can easily be considered valid with regards to direct physical risks. However, as we have already observed, in the case of biological biobanks, direct risks are excluded, as there is no direct intervention on the body. There are, however, risks, the impact of which can be considerable with regards to the possibility of spreading sensitive information. In fact, as we already recalled in relation to “genetic exceptionalism”, genetic data, in their own nature, carry very particular information, which does not only involve a single person: in fact, they also indicate links of biological lineage, group links, predisposition to certain pathologies.

- About this, we must also recall that biological samples kept in biobanks are rarely anonymous or anonymised: in the majority of cases they are preserved with identification codes, without irreversibly breaking the link, and therefore it is possible to know the correlation between identification data and subject.

- ✓ With regards to non-anonymous and non-anonymised data, the Authority for the Protection of Personal Data, referring to clinical trials, observes that “Although it is envisaged that the list where patients' names are matched with the corresponding identification codes should only be held by each trial centre, and that the sponsor should in no case become apprised with patients' identities, it is a fact that the sponsor can access, via its own study monitors visiting the trial centres to check compliance with the relevant protocol, the patients' original medical records at the trial centre – under medical supervision – (...); additionally, the sponsor can access, via the same mechanism, the list containing patients' names in connection with the checks on the procedures aimed at obtaining their informed consent (...). It follows that the information related to each patient's identification code is to be regarded as personal data suitable for disclosing the individual data subject's health and – in some cases – sex life” [53]. . For this reason, the Authority stipulates that this information should be protected by all the directives for the treatment of sensitive data, as presented in the “Code for the protection of personal data” [54] and in the specific authorisations that followed it.

- ✓ In the case of anonymous or anonymised information or samples, and also when we deal with large groups, the possibility of finding the subject from which the sample was taken, or from which the sensitive data originated, without the need to use sophisticated algorithms or “probabilistic matching” techniques [55], is not remote. Amongst the examples, there is the case of a statistics expert, sceptical about these arguments, who carried out a test using

In any case, even when the entity of the risks is limited (or their probability scarce) we are not exonerated from the duty to identify, understand and face the risks with adequate and proportionate solutions.

1. “Broad consent” and the problem of the use of biological samples for purposes different from those of the initial collection

7.1. The problem of the use of samples in studies not anticipated initially

Many samples preserved in Italian biobanks were collected in heterogeneous situations, first by the organization of the Authority Guaranteeing the Protection of Personal data and in contexts where the knowledge of the need to carefully and rigorously explain the information and obtain the consent was not always circulated everywhere yet.

This is not only an Italian problem: it is felt everywhere and tackled differently [57]. In an analysis of the norms regulating biobanks’ activity, with regards to eventual subsequent, initially unforeseen uses, it is in fact observed that: “legal comparisons between regulations in different countries are laborious and defy generalisations” [58].

When the samples have been stored without the subject’s consent, or with a very wide consent with regards to eventual future uses, there is therefore the problem of the legitimacy of using the samples [59].

In the case of eventual uses of previously collected samples for initially unforeseen research purposes, the conflict between different needs, which we referred to at the beginning, becomes apparent: protection of personal data, subjects’ autonomy, interests of the research, social interest in the overall development of knowledge, safeguarding of public trust in researchers and institutions.

The practical difficulty is evident: very often, and in particular when a long time has passed between the collection and the eventual use, it is extremely difficult or even impossible to contact the subjects again. On the other hand, the choice that is apparently more respectful of individual rights (that is, using only samples from individuals who can be contacted again and can give a new informed consent) could considerably undermine the validity of a scientific study, as it introduces the bias of selection.

The most obvious solution to try and tackle the various aspects of this problem could be to obtain a “broad” consent from the donors, one that does not preclude the possibility of future research.

However, not everybody feels that broad consent is acceptable, and the suggestions cover all the possible intermediate positions between the two extremes: from the specific consent for a single study to the broad consent for

eventual future studies, unforeseeable at the time of collecting the sample [60, 61].

7.2. Arguments in favour and against broad consent

Generally there are two main arguments to justify recurring to a broad consent [62].

The first is the fact that, for practical reasons, often it is very difficult or even impossible to collect a consent for subsequent research with already collected samples.

The second is the fact that the risks for the donors are extremely limited or even absent.

Other arguments in favour of a broad consent regard also the fact that in some cases, for particular personal or family circumstances, an eventual, further contact could be inappropriate or even damaging for the subject.

The strongest criticism to broad consent is the fact that a generic formula could make the consent meaningless, as, for its own nature, it presumes precise information [63].

7.3. Examples of institutions in favour of a broad consent

7.3.1. Commissions and Committees

“Broad” (or “open” or “generic”) consent has been suggested by influential organisations. The World Health Organisation considers it the “most effective and economical approach” [64].

This position is shared by the ethics committee of the Human Genome Organisations (HUGO) [65], by the European Commission [66], by the National Bioethics Committees of various Countries (for example, a non-exhaustive list is: the Danish Ethiske Råd [67], the French Comité Consultatif National d’Éthique pur les Sciences de la Vie et de la Santé [68], the German Nationaler Ethikrat [69]).

The approach to a broad consent is in line with the “Convention for the Protection of Human Rights and the Dignity of the Human Being with regards to the application of Biology and Medicine: Convention on the Human Rights and Biomedicine” by the Council of Europe [70], and especially with point 137 of the “Explanatory Report” of the same Convention [71], which anticipates, in particular circumstances, the possibility of using biological samples preserved in biobanks without the subject’s consent: “The information and consent arrangements may vary according to the circumstances, thus allowing for flexibility since the express consent of an individual to the use of parts of his body is not systematically needed. Thus, sometimes, it will not be possible, or very difficult, to find the persons concerned again in order to ask for their consent. In some cases, it will be sufficient for a patient or his or her representative, who have been duly informed (for instance, by means of leaflets handed to the persons concerned at the hospital), not to express their opposition. In other cases, depending on the nature of the use to which the removed parts are to be put, express and specific consent will be necessary, in particular where sensitive information is collected about identifiable individuals.”

In Italy the “Convention on Human Rights and Biomedicine” was ratified by law 28 of the 28th of March number 145 [72]. Still today however, the ratification document has not been deposited at the Council of Europe, and it is therefore not formally valid.

This position is also confirmed in Recommendation Rec(2006)4 [73] by the Council of Europe, about research on biological samples of human origin, adopted 10 years after the “Convention on Human Rights and Biomedicine”.

As an example of positions that are particularly open to broad consent by a National Bioethics Committee, we can consider the Danish case. In the already mentioned document titled “Health Science Information Banks – Biobanks”, they express, in fact, a very open position. In the document’s synthesis we read that “The collection of material for biobanks does not require consent for the storage of material extracted in, say, a diagnostic context and its subsequent use for some other purpose (...). If material or information from the biobank is used in a research project, the additional approval of the research ethical committee system is required, though not necessarily the consent of the person from whom that material or information originates”. Specifically referring to banks of biological samples (and not to other types of health archives, which are also the object of the Danish document), in chapter 3 they stress: “Biological banks include collections of human biomaterial stored for diagnostic or research purposes. Common to these biological banks is the fact that, once approval has been obtained from the scientific ethical committee system and in special cases from the individual patients, the material collected is sometimes used for some purpose other than that intended when the material was collected”. In addition, in chapter 4, examining the various aspects of the protection of the individual, the Danish Bioethics Committee states that “Information or material from a biobank can be passed on to, say, a new storage site with other potential applications”. In the sixth chapter, the Danish Ethics Committee stresses that there’s no need to request a specific consent for the eventual move, indicating precisely the uses intended for the sample, but it is sufficient to inform the subject initially that there is the possibility of a move: “By means of general written information, the individual patient should be informed that blood samples, tissue etc. given for diagnostic use may possibly be included in a biobank at a later juncture and used in a teaching context, for research and so on”. The position of the Danish Committee can make us feel perplexed. The most general principles that we can find in the most important documents, in fact, require that consent is given explicitly for any specific use, and that a very generic consent to hypothetical and imprecise uses is not sufficient. According to the Danish Committee, however, the subject’s consent is not necessary to move the samples to other centres or to other research projects, different from those initially specified.

7.3.2. Spanish law 147/2007

Chapter IV of the “Lay de Investigacion Biomedica” [74], approved by the Spanish Parliament on the 3rd of July 2007, is dedicated to biobanks. The law has raised interest also beyond the national boundaries, because it explicitly anticipates the possibility of a broad consent. In the premise it is clarified that the legislative framework is focused on the donor’s consent and on the information that he/she must be given to ensure the validity of the consent. In

article 3, a “biobank” is defined as a “non-profit, public or private institution, which houses a collection of biological samples intended for diagnostic or biomedical research and a technical unit organised with common criteria of quality, organisation and purpose”. Articles 58 to 62 regulate the ways to obtain, preserve, use and transfer samples. The duty to adequately protect single individuals is stated, but there is also an insistence on the needs of modern research, which from the era of genetics has moved on to the era of genomics and now to post-genomics. The law proposes a “flexible, medium” solution between specific consent and broad consent. The law anticipates that the subject can, with the initial consent, express consent also for further research “linked to the one proposed initially” and that this research can be carried out also by a team of researchers different from the one that initially collected the sample. The law does not specify what kind of correlation must exist between the initial research and the following ones.

In addition, the law includes other directives for the use of samples collected for scientific purposes before its coming into effect. In this case, the samples can be used in one of the following circumstances:

- The subject has expressed consent.
- The samples are anonymised.
- In the absence of consent, if obtaining consent involves an “unreasonable effort” (in article 3.i, it is defined as “disproportionate use of time, work or other costs”).

- The subject is deceased or untraceable.

In these cases, the approval of the competent Ethics Committee is needed, which will verify that:

- The research is in the general interest.
- The lack of those data makes the research impossible or less effective.
- There is no explicit objection to the research.
- The confidentiality of individual data is protected.

7.4. The problem of the duration of preservation

The legitimacy of broad consent is inevitably linked to the possibility of preserving the samples also for activities subsequent to that for which they were initially collected.

This issue is also tackled in the “Measure of the 22nd February 2007. General Authorisation for the Processing of Genetic Data” [75] and in the following “Guidelines for Data Processing within the Framework of Clinical Drug Trial. 24th of July 2008”. On the basis of this last document “The data and biological samples related to trial patients must be kept for no longer than is necessary to achieve the purposes for which the data and samples were collected and processed (see section 11(1)e. of the DP Code, and the Garante's authorisation to process genetic data dated 22 February 2007, document no. 1389918). In this regard, the provisions applicable to clinical trials require the key documents related to the trial (including the individual patients' medical records) to be kept by the sponsor and trial centres for at least seven years as from completion of the trial, or else for a definitely longer period in pursuance of the applicable legislation and/or the agreements made between sponsor companies and trial centres (see section 18 of legislative decree no. 200/2007; legislative decree no. 219/2006, annex 1, point 5.2, letter c.; Ministerial decree dated 15 July 1997, *passim*). Generally speaking, the

aforementioned section of the DP Code requires data to be kept by the external entities that collaborate with the sponsor in management and statistical analysis activities for no longer than is necessary to draw up the final trial report and/or publish the trial results (...). Trial sponsors may lawfully use the data and biological samples related to individual data subjects in future studies and researches, also by availing themselves of the external collaborators they had employed for performing the trial, providing the patients were informed adequately thereof beforehand and gave their specific, separate consent in writing (see section 11(1)e. and sections 13, 23, 26 and 99 of the DP Code; see also the authorisation dated 22 February 2007, document no. 1389918)". [76].

Although not explicitly explained by the Authority, the restrictive statement that seems to tie the duration of the preservation of samples to the experimentation for which they were collected, is generally interpreted with some more openness, that is, intending for "experimentation" the "type of experimentation", which is, uses that are linked, for their nature or aims, to the purposes for which the sample was removed and collected.

7.5. Exceptions to consent

Referring to the classical principles of North American bioethics, formulated by T. L. Beauchamp and J. F. Childress, informed consent is directly linked to the principle of Authority [77].

It can be considered a "prima facie" duty. As we know, for "prima facie" duties we mean, according to the definition formulated for the first time by W. D. Ross, that are binding in all circumstances, unless they are in conflict with duties of equal importance in the concrete situation we need to tackle. In this case, according to the author, we should look at "actual" duties, to be fulfilled in the concrete situation and deriving from the balancing that, in the specific case, we can do between "prima facie" duties [78].

According to T. L. Beauchamp and J. F. Childress, the conditions that justify the "balancing" between the value and the lack of fulfilment of "prima facie" duties are:

- "Better reasons can be offered to act on the overriding norm than the infringed norm (e.g., if persons have a right, their interests generally deserve a special place when balancing those interests of persons who have no comparable right).
- The moral objective justifying the infringement must have a realistic prospect of achievement.
- The infringement is necessary in that no morally preferable alternative actions can be substituted.
- The infringement selected must be the least possible infringement, commensurate with achieving the primary goal of the action (...)"

7. 5. 1. The conditions established in Italy by the Authority for the Protection of Personal Data

According to article 110 of the "Legislative decree of the 30th of June 2003, number 196. Code regarding personal data", "the subject's consent to the processing of the data disclosing his/her state of health, finalised to scientific research activities in the medical, biomedical or epidemiological sectors, is not

necessary when the research is anticipated by a legal directive that specifically requires its processing, that is, it is part of a biomedical or healthcare research programme supported by Section 12-bis of legislative decree number 502 of the 30th of December 1992, as subsequently amended, and forty-five days have elapsed since the communication of said activities to the Authority, under section 39. In addition, consent shall not be necessary when, because of particular reasons, it is not possible to inform the people concerned and the research programme is the object of a reasoned opinion in favour of it, by the geographically competent ethics committee as well as being authorised by the Authority also in line with Section 40” [79].

According to point 13 of the “Guidelines for personal data processing in the clinical trials of medicines”, “in the presence of particular and proved circumstances (of an ethical, methodological character or because impossible to organise), from which derives the impossibility of informing the people concerned, the treatment can be carried out also without their consent, provided that the research programme is the object of a reasoned opinion in favour, by the competent ethics committee and the Authority’s authorisation is obtained, which can be issued also with general measures, relative to certain categories of holders or treatments (articles 110 additional Part and 40 of the Code). Consider, for example, some retrospective studies in which time elapsed since the data was collected for analysis, the size of the sample to select and the characteristics according to which the sampling is carried out (for example, a group of people affected by pathologies with a high mortality rate) may reasonably make it impossible to reach the people concerned and provide them with adequate information” [80].

7. 5. 2. The regulations of the United States of America

As we know, the United States refer to the “Common Rule”, that is, a group of federal regulations collected in the “Code of Federal Regulations” (C.F.R.), and in particular to chapters 45 (“C.F.R. 45: Public wellbeing) and 46 (“C.F.R. 46: Protection of human subjects”).

According to the C.F.R., for the research with biological samples, there can be a dispensation to the requisite of informed consent if four criteria are fulfilled:

- 1) the research involves minimal risks for the subject;
- 2) the subject’s rights and wellbeing are unaffected by the dispensation;
- 3) the research cannot be carried out without the dispensation;
- 4) when appropriate, the researcher will give the subjects additional information about the research after their participation [81].

7. 5. 3. Some authors’ proposals

In 1979 A. Meisel [82] identified four categories of exceptions to the need of informed consent: emergency, incompetence, renunciation, therapeutic privilege.

- The emergency exemption is applied in situations of danger, in which the subject cannot have the information or cannot express consent. In emergency situations the subject is considered as temporarily incapacitated to express consent and action is taken in the belief that the subject in danger

- The second situation regards those subjects unable to express consent and it is instead a widespread situation and faced often when wanting to collect, store and use biological samples. In the case of “opt-in” systems, generally subjects unable to express consent are not included, if not in the presence of a valid consent from a legal representative. The “opt-out” system is instead more problematic, as, from an ethical point of view, it has its own legitimisation in the possibility for the subject to receive information and choose freely, and actively, if he/she wants to be excluded. (As we know, “opt-in” indicates the system in which the subject explicitly expresses the intention to participate, whilst “opt-out” is the system which presumes that the subject wants to participate: in this second case, the “silence-assent” is applied and the refusal to participate needs to be explicitly declared. According to some authors, the opt-out system, adopted for example in Sweden, is more appropriate if we want to respect individual autonomy) [83, 84, 85].

- The renunciation to express consent, if freely chosen, does not constitute a violation of autonomy. G. Dworkin in fact observes that “if a patient has consciously and freely asked not to be informed or consulted with regards to the treatments concerning him/her, trying to obtain consent would be a violation of autonomy” [86].

- The so-called “therapeutic privilege” is similar to renunciation, but with a fundamental difference: in this case, in fact, it is not the subject who decides not to be informed, but a third party, who thinks that it is harmful for the subject to give information and ask for information. This is the most problematic situation, in which there could be a conflict between the subject’s autonomy and what another individual considers to be in his/her best interest.

According to Hannson et al. [87], broad consent is an expression of the subject’s autonomy and it is acceptable as long as three conditions are fulfilled:

- Personal information is treated with due discretion.
- The donors have the right to withdraw consent.
- Each new study is approved by the ethics committee.

In the article "Informed consent in medical research: Journals should not publish research to which patients have not given fully informed consent - with three exceptions" [88] L. Doyal reports three arguments raised by some researchers against informed consent:

- The excess of information on purposes, methods, risks, can generate excessive preoccupations.

- Informed consent is certainly necessary when the risk is minimal, especially when obtaining the informed consent could diminish the protocol’s methodological rigour.

- The advancement of knowledge useful to the community can be slowed down unacceptably by an excessive emphasis on individual rights.

According to Doyal such arguments are inadequate, and derive from an old-fashioned form of paternalism. In fact, to these arguments Doyal respectively answers:

- If subjects perceive that they have not been adequately informed on some aspects, the damage that follows and the preoccupation generated in the subjects, can be more than those generated by a thorough initial information.

- The fact that the risks are minimal does not justify not communicating them. The acceptable risk threshold is subjective.
- Compromises between individual rights and collective good are not acceptable.

However, according to Doyal, we can identify three situations in which ethics committees could authorise research without the researchers obtaining informed consent. They are:

- Research with subjects unable to express consent. The exclusion of subjects unable to express consent can in fact involve also the exclusion from eventual benefits as well the impossibility of obtaining useful information for that particular category. The conditions to authorise research on subjects unable to express consent, in the absence of informed consent, are:

- ✓ We can expect important benefits from the research.
- ✓ It must be impossible to carry out the research on subjects able to express consent.
- ✓ The risks caused by the study must be minimal in comparison with the standard treatment.
- ✓ In the case of minors, consent must be obtained from those exercising parental authority or legal representation.
- ✓ The “assent” is requested, to family or those caring for the subject, after having given all the information that would be given to a subject able to express consent. This “assent” is indispensable in the case of therapeutic studies with minimal risk compared to those associated to the standard therapy. (e.g. in the case of emergency treatments).
- ✓ The aims and methods of the research are described at the end of the research to the subjects who in the meantime have regained the ability to express a valid consent.

- Research using only previously recorded clinical data. It is the typical case of epidemiological research from which we expect benefits, for which it is impossible to obtain consent and which does not involve risks and consequences for the subjects. Also, in this case there are minimal requirements to fulfil:

- ✓ The access to clinical data must be indispensable to obtain the results of the research and it is not possible to obtain consent.
- ✓ The research is scientifically valid.
- ✓ The research regards preventive or therapeutic policies or initiatives which will be beneficial to the subjects whose data is studied.
- ✓ Identification data must be removed. If this is not possible, the results must be nevertheless presented so that it is not possible to identify the subjects.
- ✓ The access is limited to specific categories of information, previously approved by the competent ethics committee.
- ✓ The doctor assisting the subject and, according to the type of record and access, the person responsible for his/her care, authorises it.
- ✓ Researchers are informed about their duties with regards to personal data.

- Research with tissues from anonymous donors. The third case in which we can carry out research without informed consent regards samples collected anonymously. This can happen, for example, in the case of residual material after surgery. Obviously, a necessary condition is that the research is in line with ethics principles that must be the basis for all research. This third situation

In appendix 3 we reproduce a summative table proposed by G. Helgesson et al. in the different circumstances that can be hypothesised [89].

According to Helgesson and his co-authors, “genetic analyses of identifiable samples should be permitted without (new) consent. ” as long as the study is not “is not particularly sensitive, and on the condition that (i) strict coding procedures are maintained, (ii) secrecy laws apply to any handling of sensitive information and (iii) vital research interests are at stake, we propose that genetic analyses of identifiable samples should be permitted without (new) consent”. According to Helgesson et al. the proposal to allow, in certain circumstances, research on biological samples without informed consent, is in line with article 138 of the “Explanatory report” to the “Convention on Human Rights and Biomedicine” [90]. The proposal by Helgesson and co-authors has however raised a lively debate [91], and in particular some authors have contested the interpretation given by Helgesson et al. to the position of the Council of Europe. In fact, it has been highlighted that the position of the Council of Europe should be evaluated considering not only the “Explanatory report”, but also articles 21 and 22 of the “Recommendation (2006)4” of the Council, which seems more cautious [92]. In the proposal by Helgesson et al., risks and ambiguities have also been identified (for example in the generic expression “particularly sensitive”), so much so that the proposal is considered “harmful to public trust in scientific enterprise” [93, 94].

1. Subjects who are unable to express consent

The problem of treating subjects and studies with subjects who are unable to or do not have the possibility of expressing a valid consent, for physical or legal reasons, is vast and this is not the place to tackle it in its entirety.

A document on this issue was published by the Higher Institute of Health in 2008 [95] and we refer to it for both a re-examination of the issue, and for operative proposals. In extreme synthesis, the most relevant aspects expressed in the documents by the Istituto Superiore di Sanità’ can be summarised schematically as follows:

- For a long time there has been the tendency to exclude subjects that are unable to express consent from research projects. However, this policy, although focused on an apt protection of the subjects, can be harmful to them: in fact, this exclusion certainly involves the protection from risks, but also the exclusion from eventual benefits of the study and the impossibility of obtaining specific scientific data for that category.
- It is important that, in case of uncertainty about a subject’s ability to understand the necessary information and to express a free and conscious consent, we adopt adequate procedures to quantitatively evaluate, as far as possible, the subject’s capabilities.
- Informed consent is not a bureaucratic instrument. Nevertheless, it also has legal value and must follow formal regulations. For this reason, in the case of subjects who are unable to express consent, only the informed consent expressed by the legal representative or by the support administrator is valid.

- The involvement of the subjects who are unable to express consent in the decision process must in any case, where possible and on the basis of the subject's specific conditions, be encouraged. Their preferences, even if implicitly manifested, must be taken into account and, within possible and reasonable limits, respected.

- Not all sensitive information needs the same level of protection. For this reason, it is necessary that each case is assessed in relation to the circumstances, avoiding generalisations.

A particular case regards deceased subjects, for whom it is not possible to obtain consent or dissent, or opt-out. In these cases, we believe that the use of the sample is legitimate as long as:

- the donor has not express an explicit dissent;
- if the subject's will is unknown, and there is no explicit dissent by his/her family.

1. The communication of results

A delicate and controversial problem regards the communication of results [96].

Also in this case, like in the involvement of subjects who are unable to express consent, we do not propose here an exhaustive analysis, which goes beyond the aims of this document, and which would need multidisciplinary contributions, amongst which, for example, psychological considerations. Without discussing it in detail, we must however refer to the fact that it is appropriate, in the informed consent, to explain the ways in which we intend to communicate the results to the subjects.

The argument must be tackled with particular care. The communication of results, in fact, can create unjustified fears: a relative risk cannot be considered an individual prognosis. In addition, in genetics, not all the information on eventual risks has clinical relevance. At the same time, effective remedies are not available for all risks.

It is therefore evident that quite a few problems are connected to the communication of information, especially when the subjects have not explicitly requested being informed.

From this derives the need for the informed consent form to precisely explain the procedures proposed for the communication of results.

If a study, from which we only expected results of general interest, revealed instead results of individual interest, it would be appropriate to assess case by case, according to the circumstances, the ways to proceed, also requesting the ethics committee's opinion.

2.Considerations and comments

10.1. On scientific quality and respect for basic deontology

It is known that sometimes the tendency to issue increasingly more restrictive directives with regards to the protection of personal data related to

biological samples comes from historically documented abuses [97]. To guarantee the adoption of procedures that are respectful to individuals and at the same time characterised by value and scientific validity, first of all it is necessary that they are given the maximum care by the researchers when drawing up the protocols, as well as a revision by the competent ethics committee [98].

When a subject requests that his/her sample is not used for research purposes (in general, or with particular reference to one or more specific research), it is our duty to always respect that request.

10.2. On individual interests and collective benefits

Reaffirming with conviction the need of an ethics focused on the protection of the single individual, it seems appropriate to highlight the value, even social, of the research: from scientific research derive important discoveries, benefiting single individuals and society.

Personal consent to the preservation and use of biological samples can also have altruistic motivations, as in the case of blood donation or, by some mothers, of umbilical cord stem cells.

The act with which we decide to participate to a research cannot be reduced to the binomial information-adhesion: in fact, it implies more profound choices, coming from a mature and integrated personality, which responsibly and consciously can have also altruistic motivations, and not only aim at his/her own personal benefit.

With regards to this, it can be appropriate to consider the fact that the elements that most typically characterise informed consent (that is: understanding of the information and free and voluntary adhesion) are sufficient to legitimise an intervention, but in reality they do not exhaust the consent.

Therefore, we need to identify, from an ethical point of view, an adequate balance between the protection due to the individual and to his/her sensitive data on the one hand, and the potential benefits offered by scientific research for the advancement of knowledge on the other. The conflict between these two needs cannot be reduced to a conflict of interest between the single donor and the research: donors, in fact, have also an interest in the results of the research.

10.3. On the problem of anonymity

Above, we have mentioned the positions of some authors who believe that it is impossible to guarantee anonymity.

It is however unacceptable that the difficulty of protecting a right is used as an excuse to avoid taking action to achieve that protection.

Anonymisation, with which the link between the sample and the donor's identity is permanently destroyed, can be damaging both to scientific research and to subjects.

In fact, anonymisation can preclude the possibility to confront different types of information, to carry out certain types of reproducibility tests, etc. At the

same time, it prevents the transferral of information, useful to the subject's health, which might eventually emerge during the analysis.

As a result, it does not seem appropriate to recommend anonymisation, except in particular cases.

Coding is, therefore, preferable to anonymisation, in order to guarantee the scientific quality of the study.

10.4. On the problem of broad consent

It is evident and undeniable that, especially in the case of large collections (for example, those deriving from the now numerous national projects, like the UK Biobank or the Estonian Genome Project), which include hundreds of thousand or even millions of samples, and of the related information, it would be impossible to individually contact each subject (some of whom have probably moved, or are dead, or are untraceable for other reasons) before every eventual use. Some also highlight the fact that any further contact with the subjects could be, for the subjects themselves, a nuisance or even a cause for unjustified alarm. For example, according to the UK Human Genetics Commission "many patients very explicitly do not want to be contacted again for such consent" and the procedure of contacting again for each new project "would seriously limit the usefulness of large scale databases of the population" [99]. Therefore, on an exclusively operative level, the argument of the impossibility of collecting consent has its justifications.

It is however necessary to consider a variety of factors in order to evaluate the appropriateness of contacting the donors again: not only the practical means of obtaining consent, but also the nature of the study, the possible personal consequences for the subject who is contacted again, and others.

Certainly, a generic consent, which would allow any research, cannot be suggested and even less accepted.

A solution could be to formulate the consent so that there is a reference to a particular "type" of research conducted at the centre storing the sample, specified in the most precise and limited way possible. In this way, the consent could be valid (and the sample could be preserved) beyond the conclusion of a particular study, in order to later carry out other studies of the same "type" and on the same issue.

The author therefore believes that broad consent is acceptable if:

- Procedures adequate for the coding of the sample are adopted.
- Procedures adequate for the protection of personal data are adopted.

These first two aspects are the object of precise regulations and will therefore be fulfilled insofar as the directives are followed.

- The research objectives are so important that they justify carrying out the research. This aspect should be assessed case by case and it will always be subjected to the opinion of an ethics committee.

- We consider case by case what are the sensitive data involved. Genetic information varies in relevance. Some needs a more restrictive protection, whilst other is less relevant and needs a lower level of protection.

- The results of the research are always presented in aggregated form and never identified.

- Consent is always accompanied by the “opt-out” option for any secondary research. To each subject, we must guarantee the chance to withdraw consent at any time. However, this is not enough: in fact, we must always take into consideration that genetic information always has implications that are not only personal, but also important for families, groups and populations. Therefore there must be other systems in place, as well as withdrawing consent.

- Participants are adequately involved. The participants’ involvement can happen in a variety of ways. For example, before beginning a project, it is possible to have a consultation between participants or divulge information through mass-media. It is desirable that a variety of ways of involving the participants are not alternative, but complementary. It is especially important that there is also a direct participation, for example through the participation of the population’s representatives to the committees, which have the duty to approve the research before it starts.

- There are transparency and control systems in place. Therefore there’s a need for adequate technical, procedural and supervision systems to guarantee the data’s safety. It is also strongly desirable that there are external and independent supervising organisms to oversee that the procedures are carried out correctly.

Giving a “broad consent” therefore does not mean signing a blank cheque. The consent, even if it does not identify a specific study, should in any case indicate the field of studies that it will be legitimate to carry out.

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APPENDIX 1

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APPENDIX 2

GUIDELINE 5. – OBTAINING INFORMED CONSENT: ESSENTIAL INFORMATION FOR PROSPECTIVE SUBJECTS¹

Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:

1. that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;
2. that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;
3. the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;
4. for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;
5. the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;
6. whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;
7. that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;
8. that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case

¹ Council for international Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS and World Health Organization (WHO). Available at: www.cioms.ch/frame_guidelines_nov_2002.htm.

the subject should be informed of, and given, the reasons for such non-disclosure);

9. any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner;

10. the direct benefits, if any, expected to result to subjects from participating in the research

11. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;

12. whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;

13. any currently available alternative interventions or courses of treatment;

14. the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;

15. the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;

16. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;

17. the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;

18. the possible research uses, direct or secondary, of the subject's medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 18 Commentaries);

19. whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);

20. whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;

21. whether the investigator is serving only as an investigator or as both investigator and the subject's physician;

22. the extent of the investigator's responsibility to provide medical services to the participant;

23. that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.

24. in what way, and by what organization, the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);

25. whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;

26. that an ethical review committee has approved or cleared the research protocol.

APPENDIX 3

RECOMMENDED CONSENT ROUTINES FOR RESEARCH ON BIOBANK SAMPLES WHERE NO CONSENT WAS OBTAINED, OR THE CONSENT IS UNCLEAR²

Type of consent	Recommendation
1. No explicit consent was obtained or requested when the samples were collected.	Samples may be used without consent. Use opt-out when feasible. Taking into consideration the research interests, the strict coding procedures proposed, that secrecy laws apply to any handling of sensitive information and that vital research interests are at stake, genetic analyses of identifiable samples should be permitted without obtaining consent, provided that the strict coding measures are maintained.
2. Consent included use for medical research, but was limited to a specific study or specific research and was silent about other research.	Samples may be used without new consent. Use opt-out when feasible. For instance, sample donors consented to the use of their samples for a specific cancer project and for future cancer research. In this case, consent was limited to cancer research in the sense that it only concerned such research. For other kinds of research, no consent or refusal exists. Unless the consent form contained an additional alternative like "I consent also to the use for other kinds of research" (for which the box was not checked) or used a restricting formulation like "... consent <i>only</i> to the use for...", the consent situation for such research is equivalent to the situation described in 1 ^a .
3. Consent included use for medical research, but was explicitly restricted to specific uses different from the present one.	Do not include these samples in research when excluded by previous consent. For instance, sample donors consented to the use only for the original study or only for that and other cancer research. Alternatively, consent was given for research, except for research on, say, diabetes and obesity. These samples should not be used in the excluded kinds of research.
4. Consent followed information specifying that research results of clinical relevance will be reported back to the individual sample donor.	Results reached in research aimed at general questions are not sufficient as a basis for medical treatment; usually a separate intervention study is needed to provide knowledge of utility for preventive or therapeutic treatments for individuals identified with an increased risk. Thus, the value of returning individual results to sample donors is limited and may cause unjustified concern and even harm. In cases where the condition that results to be reported back to sample donor concerns one specific study only, samples may be used without consent for other studies, but the opt-out should be used when feasible. In cases where results to be reported back include future

² Helgesson G, Dillner J, Carlson J, Bartram CR, Hansson MG. See p. 974.

Type of consent	Recommendation
	<p>research, new consent is required—unless researchers are willing to report results to sample donors. If new consent is not obtained and new research is undertaken, a considerable risk exists that research will be carried out on samples from donors who allowed use of their material only on the condition that results would be reported back to them, which would have the unacceptable outcome of going against their expressed will^b. One might also simply exclude samples obtained under consent type 4 from the study (instead of trying to obtain new consent</p>

^aIt might be argued that limited consents should be understood as excluding other research. In this view, consent to, say, a certain cancer study also means 'no' to all other kinds of research using the samples. However, there is no support for such an interpretation. If a consent form concerns participation in a specific study only, and presumptive participants consent to participate in that study, they can certainly do so because they are very positive to all kinds of medical research. Unless they are given the opportunity to express their general attitude toward research, no conclusions about it can be drawn from the consent form.

^bNote that even if previous consent included a clause that results should be reported back, it is not obvious what sample donors want unless the consent form contained alternatives where their preferences could be clearly specified. If the consent form included only one alternative, then consenting sample donors may include both those who allow their samples to be used in research only if results are reported back and those who want to participate in research no matter what (and even those who prefer not to have results reported back, but who find it more important to participate in research than not to have results reported back). If there is only one alternative—in which it is stated that results will be reported back—then these differences cannot be expressed and will therefore not be known.