REPORT

ON BANKS OF BIOLOGICAL MATERIAL OF HUMAN ORIGIN (BIOBANKS) IN BIOMEDICAL RESEARCH

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The present report discusses the key-points of the debate which developed in recent years around banks of human biological material (biobanks). The great importance of biobanks for research and the serious emerging bioethical questions have began to attract the attention of the research community in our country as well. The issue is closely linked to the management of genetic data (see related earlier Commission report) in so far as – as we are going to demonstrate – biobanks also collect this kind of information. Therefore, certain aspects are already covered by that discussion.
Next we will attempt to demarcate the scope – to avoid confusion with other collections of human biological material (I), describe the major international examples of biobanks (II) and pinpoint the main ethical (III) and legal (IV) dimensions of the issue.

I. Definition

The term biobanks refers to collections of biological specimens which are linked to the personal information of the specimens' donors. The biological specimens include tissues, cells, blood or DNA extracted from them. Personal information includes, in addition to the donor's identity, genetic information extracted from the specimens and medical data. This may often include genealogical information or information on the donor's lifestyle (dietary habits, smoking, consumption of alcohol, exposure to pollutants).

Although the term "biobank" was coined relatively recently, collections of biological specimens for medical or research purposes are quite common. Biological samples collected and stored in the context of (a) academic research on genetic diseases, (b) clinical records for diagnostic purposes, (c) population research to study genetic variation, are but a few ordinary examples of such collections.
The "novelty" of biobanks in the context of medical research lies in collecting large numbers of specimens as well as genetic information extracted from these specimens and, first and foremost, in constantly updating the database with the donors' medical and/or social information.

The combined study of genetic and other types of data aims at identifying the genetic basis of complex phenotypes of – mostly – medical interest such as the onset of disease (a) due to mutations of several genes with varying gravity of symptoms depending on the type and number of mutations carried by the individual, (b) which is manifested only in conjunction with the appropriate environmental factors, or/and (c) in relation to patient response to a given pharmaceutical treatment. The identification of these factors is based on finding correlations between the genetic data and the

information on the medical phenotype under investigation (e.g. hypertension). Correlations are established by way of statistical analyses and, to be reliable, a significant number of initial specimens is required from which the information was extracted. Besides, according to an essential rule of reliability, the correlation must be identified only in the group of individuals carrying the phenotype in question (e.g. hypertension) and be found missing in the group of individuals not carrying the phenotype.

The results expected from biobank research will hopefully be able to predict that certain individuals with a specific genetic make up (and/or lifestyle) are more likely to develop a disease as compared with the rest of the population, and to indicate specific preventive measures for the members of vulnerable groups. The results of genetic tests make sense only in the context of groups of persons because of the epidemiological nature of these studies and cannot lead to "individualized" interpretation except and only if combined with genealogical data from the donors. Nevertheless, the fact that a link persists between the genetic data and the personal information of the donor, brings to mind the genetic tests for hereditary diseases, where this link is indispensable (in order to inform accordingly the person under examination) confounding the distinction between the collective and individualized nature of results. The only instance where the "collective" character of the results may be amenable to an "individualized" interpretation, is when biobanks have access to the genealogical data of participants. So, when a biobank is developed primarily for research purposes, the results concern one or more groups of people and can be "individualized" only under certain conditions. By contrast, when a biobank is developed primarily for diagnostic purposes, the results are individualized.

At any rate, the interest for public health of the results expected from these research projects combined with the volume of specimens required to draw reliable conclusions led some countries to start collecting and analysing specimens from national population samples and some countries with existing large collections to focus on genetic analyses on already available specimens.

II. Examples of the most important biobanks of national or local scope

▪ In December 1998 the Icelandic Parliament passed the Health Sector Database Act. This Act granted to DeCode Genetics, a private company, exclusive rights for the development of two databases. One were to be comprised of the medical records of all Icelanders (approximately 270.000 people) and the other one of biological specimens (DNA) from volunteers in order to investigate more than 50 diseases. The same Act provided for linking the two databases to each other and to another existing database with genealogical information from 600.000 Icelanders, virtually the total sum of the people who ever lived on the island. Under this Act, the government reserves the right of access to the database of medical records for the purpose of policy-making in the area of public health and deCode reserves the exclusive right of commercial exploitation for a period of 12 years. The Act endorses the presumed consent of Icelanders to have their medical data recorded in the first database but enables those who wish to exclude them to declare so (opt-out). Records of medical data available since 1915 would be collected from medical centers all over Iceland. Not much time later, in 2000, the Parliament passed the Act on Biobanks which lays down the operation terms of the second database (biological specimens). Though it provides for

the informed consent of volunteering donors of biological specimens, this Act also adopts the presumed consent of donors to allow recording of their current biological specimens or those collected in the past in the context of clinical diagnostic analyses. However, it enables those who wish to be exempted to do so by filing an application (opt-out). In all cases of opt-out, applicants only get that no more specimens will be obtained from them but may not pursue the removal of already recorded information. To this date, it is estimated that approximately 80.000 individuals (7%) chose to apply for an opt-out from the first database.

The criticism against the Icelandic database regards mainly three points: (a) the rules on presumed consent, (b) the exclusive exploitation of data by a private company, and, (c) the approach to the management and protection of the Icelanders' personal data.

▪ In June 2000 Singapore launched its Gene Program with the aim to identify new genes and their molecular targets which contribute to the onset of high incidence diseases in the population such as liver cancer. The Program intends to develop a big database that will also contain health information of Singapore's population. The variety of population (of Chinese, Indian and Malay origin) is hoped to help identifying variations relating to the geographical/ethnic origins of patients in regard to their response to specific pharmaceutical treatments.

▪ In December 2000, Estonia created its own biobank following the proposal of a non-profit research foundation (Genome Center Foundation). The Estonian biobank was established by the Human Genes Research Act. Its aim is to link the genealogical, medical and genetic data of the 75% of the population and to include about one million specimens. According to the law, participation in the biobank project is voluntary and consent may be revoked at all times in which case the biological sample of the donor is destroyed. The Act grants the exclusive commercial exploitation of the biobank for a period of 25 years to the company Egeen whose sole shareholder for the time being is the public research foundation that suggested its creation. Already to this date, specimens from 10.000 donors have been collected. Within the next two years, the program developers expect to collect 100.000 specimens.

▪ In 2002 Britain laid the foundations for the development of the British Biobank. They set themselves the aim of collecting no less than 500.000 specimens from volunteers aged 45-69 whose genetic data will be combined with medical data and information on lifestyle. The British biobank is different from the ones mentioned so far not only because it focuses attention on a particular age group but also because it aims at a regular medical follow up of the volunteers for 10-15 years. The ultimate goal of researchers is to identify genes predisposing for disease. In order to achieve a representative sample of the British population among the 500.000 volunteers, random selection methods will be used to include people from every geographical region. Then, the selected persons will be summoned by their family practitioners, receive information about the study and be invited to participate. The British biobank is financed by the Ministry for Health, the Medical Research Council and the non-profit foundation Wellcome Trust. The biobank will be supervised by an independent ethics board. The specimens will be analyzed by certified laboratories and the biological material will not, as a rule, be sent to third parties. By way of exception, biological specimens may be sent to third parties if the genetic analyses to be carried

out are protected by third party patent holders. Access to data is open to researchers of public and private agencies whose projects are approved by the independent board.

▪ Since January 2003 Sweden has been implementing the Biobanks in Medical Care Act. The Swedish Act covers the collection, storage and processing of biological specimens. The Act requires prior informed consent for every specific use of specimens. For every new use, the donor has to re-consent. By way of exception, the initial consent covers the use of specimens in research if the project is approved by an ethics committee. Consent may be revoked at all times in which case the specimen is destroyed and the data is dissociated from the personal information of the donor (anonymized). By this Act, Sweden endeavours to capitalize on the available collections of biological specimens in its territory. A typical example is the UMEA blood collection of 100.000 biological specimens. This collection extends as far back as 1985 and covers 60.000 people from northern Sweden with additional medical records and information on their way of life. The UMEA biobank is financed by the company Umangenomics who has exclusive rights of commercial exploitation. The company is a spin-off of UMEA University and the local medical care authorities. University researchers enjoy unhindered access to the biobank's specimens.

III. Concerns regarding biobanks

The development and use of biobanks raises questions of security and confidentiality of the data of participants due to the unprecedented programmed collection of specimens. Also, the fact that the results of research conducted in the context of biobanks pertain to groups of people raises issues of discrimination and/or stigmatization of these groups based on genetic criteria, geographical and/or ethnic origin or social behaviour (e.g. dietary habits). In addition, the ownership (public or private) of the specimens and of the data linked to them and the involvement of profit-making organizations in the exploitation and, sometimes, the creation of biobanks for research together with the development of new and efficient pharmaceutical compounds give cause for concern. Finally, the recognition of the need to control and supervise their operation has led several countries to adopt a statutory framework to ensure normal operation and win social acceptance for these research projects (see IV, 2, b below).

A question that has dominated the discussion on biobanks and continues to cause confrontation is the participants' consent; associated with it is the fact that future analyses of the biological specimens included in a biobank are not necessarily known at the moment the specimens are obtained. The reason for which the total number of analyses cannot be known in advance has to do both with the swift pace of scientific progress in genetics and the range of scientific hypotheses that may arise during research. Thus, in actual terms, the information given prior to consent cannot cover all the potential uses the specimen may undergo in the future.

The ensuing question is whether the initial consent must be so broad as to cover all future uses or whether consent should be given for a specific use and re-consent be sought for every new use that is significantly different from those planned initially. The majority argue in favour of broad consent since the nature of research is such that if consent is required for every new use, research will be brought to a (administrative) standstill. Therefore, if our society finds it desirable that biomedical research be

carried out on such a population range, it would be burying our heads in the sand not to recognize the need for a broad donor consent. With the exception of Iceland which opted for presumed consent, all the other projects are based on voluntary participation. So, as long as the medical purpose of studies is ensured there is no reason for specific consent. Why should someone who accepted to participate in a study on hypertension would decide not to participate in a study on asthma?

By contrast, others argue that broad consent amounts in fact to bypassing the procedure of consent infringing the requirements of current medical ethics. They believe, accordingly, that when a new use of the biological specimen is planned the donor must be informed anew in order to decide whether they want to participate or not. According to the proponents of this view, respect for individual autonomy is an inviolable principle. Besides, the requirement to re-consent ensures the social acceptance of research and (indirectly) operates as a means of social control.

Similar arguments are put forward with regard to the potential use of specimens harvested for medical diagnostic purposes (e.g. prior to a biopsy operation) when parts of the unused specimen are stored in the collections of laboratories. In most cases, these specimens are stored in order to be available for future medical uses by the same donor. Given that the initial donor consented to a specific test and was not informed about the potential use of the specimen for a different purpose later on, at issue is whether re-consent is required for the new use.
Historically, the endorsement of "free specific and informed consent" by the medical research community aimed at protecting fundamental individual rights, especially in the aftermath of the Nazi atrocities committed during World War II. As some people argue, the context of this consent, however convenient because we are familiar with it, is not necessarily relevant to the debate on biobanks. The reason is that the research method followed in the context of biobanks focuses on (genetic and other) parameters pertaining to groups of persons. Therefore, the emphasis on consent distracts the discussion away from the question of development or/and exploitation of biobanks which is of collective nature and constitutes a public health issue[1].

The common point of reference shared by those who value consent, be they proponents of broad or specific (and renewable) consent, is the principle of personal autonomy. They consider, accordingly, that the decision to participate is made by the individual and as such cannot be anything other than voluntary. On the other hand, those who view consent as a peripheral issue and stress the collective and public interest nature of biobanks believe, on the basis of the solidarity principle, that members of society have an obligation, at least a moral one, to facilitate this kind of research projects. They recognize, however, that in modern (western) societies, the principle of solidarity does not enjoy the support that would allow the effective execution of so large-scale research projects. Be that as it may, they think that this is the proper basis for a wide public debate on biobanks.

[1] According to the proponents of this view, the novelty of biobanks lies precisely in that they serve the general interest, be it public health (as here) or public order (see forensic DNA banks).

IV. The legal dimension

One may distinguish two sets of legal issues with regard to biobanks: a) questions concerning the relationships between biobanks and the State, and, b) questions regarding the relationships between biobanks and individuals. The former have to do with the public interest served by biobanks and, through it, the State's interest in the creation and operation of biobanks; the latter pertain to the protection of the fundamental rights of those whose data are stored in the biobank.
Naturally, the two sets are connected but they can be discussed separately.

1. The relationships between biobanks/the State

a) Defining public interest

The ultimate goal of the collection and processing of medical, genetic and social information in a biobank is to better protect public health. This is how a specific public interest may be defined and how State intervention can be justified as a consequence. This statement does not mean, however, that all such collections are equally important for public health. Obviously, only collections reflecting a representative sample of the population which are able to yield reliable results are relevant.
The State may intervene by facilitating the development of private biobanks mainly in two ways: by granting access to the information collected by public organizations for their own purposes (e.g. medical or social personal records kept in public hospitals or social security funds) or by granting rights of exclusive commercial exploitation of the research results. In case the biobank is a public law entity (as in Estonia) the right of commercial exploitation of its products is vested in the State.
State licensing is another manifestation of public interest. By certifying compliance with certain operation terms in advance, a license ensures a level of quality of provided services which is indispensable for the protection of public health and of the rights of individuals whose situation is particularly at stake here (see II). In theory, a private biobank might be free to operate without a license in the context of economic freedom; but then, there would be no guarantee for its services: the State could act only *ex-post* by imposing sanctions as with any other economic or social activity, ultimately ignoring the specific public interest the biobank is supposed to serve.

b) The Greek legal context

Protection of citizens' health as an expression of public interest calling for State attention is enshrined in art. 21(3) of the Constitution. This clause safeguards a social right which is activated specifically as the legislator may think fit depending on the available financial resources. This right provides the main ground for the organization of the NHS.
In the issue at hand, the wording of the constitutional clause is wide enough to cover agreements between the State and private actors wishing to develop a biobank – in return for rights of commercial exploitation – provided, to all intents and purposes, that these rights are compatible with a certain improvement of services in the area of public health (e.g. rationalization or saving NHS resources). All the more so, when it is the State itself that steps in to develop and run biobanks with public funds.

Having said that, the State's interest in biobanks has an additional sense, that of the State as custodian of fundamental rights (art. 25(1) of the Constitution). Indeed, any collection and processing of personal information poses *de facto* increased risks for certain individual freedoms and constitutional principles (value of human being, principle of equality) which lends weight to the role of the State as defined in this constitutional clause.
The conclusion that may be drawn from the above is that in the context of the Greek Constitution, the development and operation of biobanks would justify the adoption of specific legislation because of the double public interest. No to adopt legislation in this case would create legal uncertainty. In addition to the potential forms of cooperation between the State and private actors and the issue of commercial exploitation of the research results, this legislation should also provide for the protection of the fundamental rights of those whose information is used in the biobank. These issues will be discussed next.

2. The relationships between biobanks/individuals

a) The rights at stake

The collection and processing of various categories of personal information in a biobank, information pertaining indeed to the core of personality, raise the issue of the appropriate protection of this information due to its sensitive nature in the context of the corresponding fundamental right (art. 9 of the Constitution). In particular, one of the safeguards of medical data is the medical duty of confidentiality (arts 13, 14, Act 3418/2005 – "Code of Medical Ethics").
On the other hand, the goal of serving citizens' health is translated into specific individual benefits for each and everyone which means strengthening the social right to health. The simultaneous existence of these two rights calls for special arrangements so that one does not cancel the other.
It must be noted, at this point, that these rights are also relevant to the implementation of the principle of equality. In fact, even if adequate protection of personal data can be ensured – in the sense that no-one may access the identity of donors – the fact that it is linked to specific population groups may engender illegitimate discrimination, either favourable or unfavourable, impacting on the exercise of individual rights.
Moreover, aside from these two principal rights, there are others which must also be taken into consideration in regard to the scientists and sponsors who develop biobanks. These are: freedom of research (art. 16(1) of the Constitution) and economic freedom (art. 5(1) of the Constitution) as well as the more specific derivative rights, especially patent rights.

b) Legislative experience (comparative law)

Protection of personal data is specifically regulated in all known biobanks. The example of Iceland, however, was met with criticism both on the technical issue of inappropriate protection of the identity of donors as well as on the legal issue of consent (discussed earlier). In particular, the general rule of prior express informed consent for the collection and processing of such data was abandoned on this occasion and the question is whether presumed consent, even if accompanied with information, is adequate with regard to the purpose of the biobank.

In Estonia, the law requires prior consent and encryption of identity. A second level of encryption protects data from third party access: a specific license is required for that. Also, discrimination in labour and social security relationships based on genetic data and its link to medical information obtained from research is prohibited.
In the example of the British biobank, its statutes provide for withdrawal of (prior) consent and a prohibition of "transfer of biological specimens" to third parties. Access is allowed to information, e.g. for the development of new diagnostic methods, but not to the identity of donors.
Unlike Estonia which granted the right of exclusive commercial exploitation of the products of the biobank to the company EGeen for a period of 25 years, whose shares are nevertheless owned by the State, in Iceland similar rights were granted to DeCode, a purely private company, for a period of 12 years for a price. This concession by the State – and the creation of a monopoly – was challenged on grounds of illegitimacy (although it was brought about by law).

c) The Greek legal context

The collection and processing of information that may be of interest to a biobank is governed by the special provisions on sensitive data in the sense of Act 2472/1997 (art. 7) in all cases where the identity of the person the data pertains to is or may become known. In principle, collection and processing are allowed by authorization of the Data Protection Authority[2].
The issue of the origin of the information collected by a biobank must be treated separately. If this information is obtained from (genetic or other) tests conducted in the biobank itself (or by a third party on its behalf), the donors must be informed accordingly and give their consent for harvesting of related biological specimens pursuant to art. 5 of the Oviedo Convention, in addition to the consent required for the specific processing (collection of information) pursuant to art. 7 of Act 2472/1997.
When this information originates from already existing collections (hospitals, social security funds, private practices, diagnostic labs, etc.), its transmission and processing for different purposes in a biobank requires specific informed re-consent. By way of exception, re-consent is not required only when the identity of the donor is not disclosed to the biobank or is safely encrypted by the latter[3]. Prior authorization of the Authority is always required[4]. Physicians may disclose information protected by the duty of confidentiality to biobanks if the donor specifically agrees to that (art. 13 (4) CME).
The processing of information stored in a biobank is governed by the general rule of art. 10 Act 2472/1997 which lays down strict conditions to ensure the confidentiality and security of any such processing. The key-person in this respect is the one responsible for processing who must fulfil specific duties – also vis-à-vis the Data Protection Authority. The law does not expressly require that all relevant research projects go through ethics control but the Authority may impose such requirements[5].

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[2] Namely, biobanks do not qualify for the exception of art. 7 A (d) of Act 2472/1997.

[3] See exception (f) art. 7 Act 2472/1997 which allows processing "for exclusively research or scientific purposes" provided the anonymity of data and the protection of personal data is ensured. In our case, these conditions must be met by the biobank, especially data encryption.

[4] See arts. 7 and 8 of Act 2472/1997.

[5] Under art. 7 (3) Act 2472/1997. In the example of the British biobank, ethics control is entrusted to a special committee.

Freedom of research for biobanks is basically determined by the above framework. Biobanks are also obliged not to hinder access to the results of research to third parties outside the framework of protection of sensitive personal data. Thus, third parties may be allowed access only if informed consent was obtained from the donors[6]. Naturally, biobanks are free to communicate any research findings not disclosing the identity of donors to third parties.

In the context of economic freedom, a private biobank would normally be entitled to find commercial uses for the results of its research by applying for patents (if they are "inventions" in the sense of p.d. 321/2001) or by negotiating deals (e.g. with pharmaceutical companies, etc.). It must be noted that, in principle, the State does not hold any rights on the personal data stored in collections of public agencies which may, therefore, be used by biobanks, neither on the results of the biobank's research. Any entitlements to the data are owned only by the donors who are free to use them even for profit. Indeed, our legislation does not regulate the commercialization of such data in so far as it does not encroach on the rights of third parties or violate the Constitution (particularly, the value of human beings) or morality (art. 5(1) of the Constitution, arts 178, 179 CC). As long as this framework remains in place, donors may exchange consent for specific economic advantages which are ultimately borne by the biobank.

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[6] In the context of labour relations, however, it is not always possible to obtain consent. See Guideline 115/2001 of the Data Protection Authority on genetic data at work.

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