Special issue

The bioethical and bio-juridical debate regarding the use of biological samples and data for the purpose of genetic research on human health: open problems

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ABSTRACT: Among the categories of personal data, a special status is recognized to genetic information, as genetic identity is a relational identity; personal genetic information is structurally shared with other subjects belonging to the same "biological group" and moreover in this kind of information knowledge and prediction of the risk of getting sick are intertwined. For this reason, biological samples, and the genetic personal data connected to them, are subject to special protection which makes the question of regulating their acquisition, storage, use, distribution and sharing specifically complex. Focusing on this issue of great general bioethical importance, particularly in the current context of the Covid-19 pandemic, the article highlights some theoretical-philosophical problems which underlie, from the very beginning, the bioethical and bio-juridical debate regarding both the status of biological samples donated for genetic research purposes, and the right of sample donors to choose whether or not to know individual results of potential clinical relevance; these issues are explored with special reference to genetic research with minors.

KEYWORDS: Biological samples, genetic information, genetic research with minors, the right not to know

SUMMARY: 1. Introduction – 2. The ethical and legal "status" of biological samples and genetic information – 3. A controversial right: the "Right Not to Know" – 4. Genetic research with minors and the right not to know – 5. Still on "minors": the gap between abstract principles and praxis.

1. Introduction

As a philosopher and bioethicist, I will try to highlight in this article some theoretical-philosophical problems which underlie, from the very beginning, the bioethical and bio-juridical debate regarding both the status of biological samples donated for genetic research purposes, and the right of sample donors to choose whether or not to know individual results of potential clinical relevance. This is an issue of great general bioethical importance,

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particularly in the current context of the Covid-19 pandemic. In the context of the Covid-19 pandemic, numerous biological samples are taken, also in the context of diagnoses and epidemiological investigations, by means of swabs and /or blood samples, as well as in the context of trials for therapeutic purposes. The Italian National Committee for Bioethics has recently produced specific recommendations regarding the use of biological samples in the context of the Covid-19 pandemic[1].
To illustrate the bioethical and bio-juridical framework of the problem, I propose to emphasize only a few significant moments of this ongoing comparison of positions to highlight the reasons for the uncertainties and ambiguities of legislation on a subject that is always *in fieri*[2]. My idea is that even the most recent directives[3] are not exempt due to the difficulty in reconciling the various competing rights and interests in a balanced and generalized way: those of the subjects who donate their samples not to lose control over their use and related personal information / those of the researchers not to have too many constraints / those of patients without effective therapies to accelerate the research and discovery of new life-saving therapies / those of the pharmaceutical industry to realize patents and profits.
In the last part I will consider instead the difficulties encountered by ethics committees when they review the genetic studies of projects that involve the participation of a category of particularly vulnerable subjects: that of the so-called "minors" (newborns, children, adolescents).

2. The ethical and legal "status" of biological samples and genetic information

The ambiguities that still remain regarding the legal status of biological samples used for scientific research and clinical studies have their roots in the centuries-old debate on the status of the human body, always oscillating between dichotomous visions that throughout history have been, depending on the contexts, the subject of multiple philosophical, anthropological, religious, economic, legal arguments in favor of one or the other concept: the body as "me", as subject, as intrinsic value/as

[1] See ITALIAN COMMITTEE FOR BIOETHICS, *Biomedical research for novel therapeutic treatments within the Covid-19 pandemic: ethical issues*, Opinion 22 October 2020, available at http://bioetica.governo.it/en/opinions/opinions-responses/biomedical-research-for-novel-therapeutic-treatments-within-the-covid-19-pandemic-ethical-issues/ (last accessed on June 1st, 2021).

[2] For an analysis and an updated discussion of the legal issues regarding the use of genetic information, see M. TOMASI, S. PENASA, A. O. COZZI, D. MASCALZONI (eds.), *Law, Genetics and Genomics: An Unfolding Relationship,* in *BioLaw Journal-Rivista di BioDiritto,* Special Issue no. 1, 2021, pp. 460, available at http://rivista.biodiritto.org/ojs/index.php?journal=biolaw (last accessed on June 1st, 2021).

[3] *European Union Regulation no. 536/2014 on clinical trials of medicinal products for human use, which repeals Directive 2001/20/EC*; *Regulation* 679/2016 *of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data, as well as the free circulation of such data, which repeals Directive 95/46/EC (General Regulation on Data Protection*); THE COUNCIL OF EUROPE-COMMITTEE OF MINISTERS, *Recommendation to member States on research on biological materials of human origin* CM / Rec (2016) 6; COUNCIL OF INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCE (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, Council of International Organizations of Medical Science (CIOMS), Geneva, 2016, available at https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. These are European and international documents which are binding to very different degrees, but to which I will refer to from time to time in this article regardless of this distinction.

"not-me", as an object of property, as a commodity[4]. These different visions further complicate, giving rise to additional questions, when, in the era of bio-techno-sciences, it becomes possible to break down the body into parts, tissues, cells, products that can live their own extra-corporeal life in time and space, undergo transformations and be used in multiple ways for one's own benefit and/or that of others[5].

Not being able to enter into the merits of a discussion that is continually re-proposed from various disciplinary angles, I will limit myself to considering, in this light, the question of the moral and legal status of biological samples 'donated' for the purpose of research, focusing attention on genomic and postgenomic research and clinical trials. Here a peculiar category comes into play, that of "belonging", which evokes a link of pertinence of the sample to the I of the donor: the "donated" biological sample is something that is both me and not me, because, even if separated from me, it is also always a place of identity, a place of genetic identity, and as such is worthy of particular protection[6]. From a legal point of view, this concept supports the interpretation according to which the subject "donates" his/her own sample in the form of a concession of use under established conditions, that is, to the extent to which consent is given; a formula, which contemplates the right to control the use of the sample, access personal data and their possible correction, together with provision of the possibility to withdraw, at any time, the consent initially given and request the return or destruction of the donated sample. Informed consent must therefore cover the entire path of the sample, including the phases of collection, storage, use and possible transfer to other researchers or institutions and, also,

[4] G. Berlinguer, V. Garaffa, *La merce finale. Saggio sulla compravendita di parti del corpo umano*, Milan, 1996. See also, just to give some examples of a large and articulated debate still underway, L. Andrews and D. Nelkin, *Body Bazaar. The Market of Human Tissue in the Biotechnology Age,* New York, 2001, Italian translation *Il mercato del corpo,* Milan, 2002; M.C. Mazzoni (ed.) *Per uno statuto del corpo*, Milan 2008. Also of interest is the discussion on the licitness or otherwise of the commercialization of parts, functions and products of the human body, which took place in the joint meeting of the Forum of National Ethics Councils (NEC Forum) with the European Group on Ethics in Science and New Technologies (EGE), held in Brussels in October 2010.

[5] In fact, we are immediately faced with an intricate knot of problems which, if on the one hand refer to the more comprehensive concept of the 'person' and personal identity, on the other they are intertwined with very concrete practical interests, of the market and research, regarding the patentability of 'inventions' that incorporate, or reproduce genetic sequences, or human biological materials. The legal status of the human body seems to emerge, however, from this matter, pervaded by ambiguity, even limiting attention exclusively to the scope of European legislation and the comparison between the Oviedo *Convention* and the later Directive of the European Parliament and the Council (98/44/EC) on the legal protection of biotechnological inventions. See, in this regard, M. Tallacchini, *Habeas Corpus? Il corpo umano fra non-commerciabilità e brevettabilità*, in *Bioetica. Rivista interdisciplinare*, vol. 6, no. 4 (1998), pp.531-552. Always in this regard, M. Toraldo di Francia, *Valori costituzionali e "diritto" all'identità personale*, in F. Cerutti (ed.), *Identità e politica*, Roma-Bari, 1996 pp. 113-129, identifying in the continental European constitutional model of the second post-war period, and in the conception of the person as a synthesis of underlying individuality and relationality, the guiding criteria for addressing some of the most controversial issues raised by the innovation of bio-techno-sciences and the evolution of the ethical-cultural perspectives informing today's liberal democratic societies. Along the same lines M. Tomasi, *Genetica e costituzione: esercizi di eguaglianza, solidarietà e responsabilità*, Naples, 2019.

[6] P. Zatti, *Il corpo e la nebulosa dell'appartenenza: dalla sovranità alla proprietà*, in C.M. Mazzoni (ed.), *Per uno statuto del corpo, cit.,* pp. 69-108; S. Rodotà, *Persona e identità genetica*, in G. Bonacchi (ed.), *Dialoghi di bioetica*, Rome, 2003, pp. 19-23.

make clear the possibility or exclusion of a return of information of individual interest to the donor on the results of the research/trial[7].

Without prejudice to the fact that the donation is always to be understood as a free, informed, gratuitous act of social value[8], the question remains open regarding whether or not it is licit, from a strictly bioethical standpoint, to include in the informed consent for genetic studies also the option of an explicit and irreversible donation of one's samples; or rather a broad consent for any future studies not yet foreseeable, which precludes further contacts with the donor and which, in fact, in many cases involves the waiver of any claim of control over the use and fate of one's biological material and related information[9].

The question of the singularity or otherwise of the genetic information drawn from the samples under study with respect to other types of information concerning health cannot be separated from this issue; such singularity would legitimize special protection within the category of the so-called "sensitive" personal data. Despite some discordant voices[10] in most national, European and supranational documents there is agreement on recognizing to this category of data a particularly strong legal status, by virtue of the particular nature of this type of information which, although, it defines the individual in his/her genetic uniqueness, at the same time it puts the individual in relation with other subjects belonging to the same pattern of inheritance[11].

There are two salient aspects of this peculiarity:

i. the presence of a close intertwining between knowledge and prediction, since genetic information allows us to know in advance certain aspects concerning one's biological future, whether in terms of increased susceptibility, compared to the average, to developing certain diseases (or even a resistance to the same diseases), or being predestined to becoming ill and an early death, in the case of monogenic diseases with a variable onset which to date are neither preventable nor treatable;

[7] Italian Committee for Bioethics (ICB) and the National Committee for Biosafety, Biotechnology and Life Sciences, (ICB-CNBBSV Joint Group), *Collection of biological samples for research purposes: informed consent, Joint Opinions ICB/ICBBSL*, 16 February 2009; The Council of Europe, *Recommendation to member States on research on biological materials of human origin, cit.*; Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Health-related Research Involving Humans*, *cit.*

[8] Council of Europe- Committee of Ministers, *Recommendation 2016/6*, cit. For a detailed reconstruction of the regulatory framework of reference for research and experimentation involving human beings, both before and during the pandemic emergency, see L. Palazzani, *Informed consent in biomedical research in the pandemic context. Between bioethics and biolaw*, in *BioLaw Journal – Rivista di BioDiritto*, Special Issue 2/2021, p 3-15.

[9] Both the already quoted *Recommendations on research on biological materials of human origin* and the *International Ethical Guidelines for Health-related Research Involving Humans* recognize as legitimate, albeit with some restrictions, the option of *broad consent* to the storage and use of samples for future research not yet foreseeable. But the reference, in these two documents, seems to relate exclusively to biobanking in known and certified locations and not to sending the samples directly to the large pharmaceutical companies that sponsor the research.

[10] For example, E. McNally, A. Cambon-Thomsen et al., *Recommendations on the Ethical, Legal and Social Implications of Genetic Testing*, *Official publications of the European Communities*, Luxembourg, 2004; Working Group for the American College of Medical Genetics and Genomics, *Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*, in *Genetics in Medicine*, 2013, 15, n. 7, pp. 565-574.

[11] S. Rodotà, *Lo statuto delle informazioni genetiche*, in G. Bonacchi (ed.), *Dialoghi, cit.,* pp. 241-47 and Id., *La vita e le regole. Tra diritto e non diritto*, Milan, 2006.

ii. the fact that genetic identity is a relational identity, as personal genetic information is structurally shared, to some extent, with other subjects belonging to the same "biological group", which is why knowledge of one's own genome may also require the acquisition of information regarding other relatives and/or sharing with them the results of individual genetic analyzes of clinical utility[12].

This peculiarity makes the question of regulating access to such information and its circulation and use even more delicate, especially if one takes into account that the "donated" samples in order to be of use to genomic and post-genomic research, must always be accompanied by a series of data, on the person (age, sex, ethnicity ...), health, lifestyles and living environment, related to the donor. Even in the presence of strict regulations for the protection of sensitive and "highly sensitive" personal information and of standardized procedures for the coding of samples (pseudo-anonymisation, or other solutions), so that direct access to the donor's identity is only reserved to those who are authorized, if there is an explicit and irreversible donation of one's samples, it is difficult to guarantee an adequate level of protection of the data subject's privacy, such as to exclude improper use of samples and data, with possible discriminatory consequences for the donor (for example, in terms of employment or access to goods and services such as health or life insurance)[13].

3. A controversial right: the "Right Not to Know"

Another area in which the discussion on the management of biological samples and related data is open to comparison between different positions is the debate on the legitimacy and possible limitation

[12] On the possible conflicts between the competing interests of persons belonging to the same "biological group", M. TORALDO DI FRANCIA, *La sfida delle biotecnologie: identità, conflitti e nuove forme di discriminazione*, in D. BELLITTI (ed.), *Epimeteo e il Golem. Riflessioni su uomo natura e tecnica in età globale*, Pisa, pp. 276-283.

[13] The issue of the prohibition of genetic discrimination is also at the center of the many regulations and guidelines that have followed one another over time; as regards biomedical research, in addition to *the Convention on Human Rights and Biomedicine* (art. 6 *Non discrimination*), see THE COUNCIL OF EUROPE, *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research,* art. 5, which underlines how the risks of discrimination or stigmatisation cannot be excluded even if the data are anonymised; in the Explanatory Report of art. 4 *Non-discrimination and non-stigmatisation*, of the THE COUNCIL OF EUROPE, *Additional Protocol concerning Genetic Testing for Health Purposes* (2008), the difference between the two concepts is then well clarified: "*The concept of discrimination relates to a difference in the treatment of the person concerned. Yet not all differences in treatment necessarily amount to discrimination [...]The concept of 'stigmatisation' rather relates to the way in which a person or group is perceived on the basis, in this case, of their genetic characteristics, whether these exist or are thought to exist. It takes, in particular, the form of words or acts that negatively label a person or group of persons on account of their known or supposed characteristics*". More recently, again on the prohibition of discrimination or stigmatisation on the basis of genetic characteristics, see article 5 of the *Recommendation on research on biological materials of human origin and Guideline 24 of the International Ethical Guidelines for Health-related Research Involving Humans*. On the problem of the possible discriminatory consequences towards persons and groups, if the applicant request by private insurance companies to be able to use the results of genetic analyzes for the assessment of insurance risk were accepted, cfr. the detailed and still current opinion of the Joint Opinion ICB/ICBBSL, *Genetic tests and insurance*, 20 October 2008, which highlights how, behind the problem outlined, there are broader concepts of the relationship between market and 'privacy', between market and protection the rights of the person in a state of vulnerability.

of the "right not to know", in our case, the right of those participating in research/trials to choose not to know at all, or in part, the results of the genetic analysis of their biological samples, including information derived from the so-called Incidental Findings (IF); that is, from those "incidental" results, of potential clinical relevance, which emerge outside the scope of the original purposes for which the research or trial was conducted and which due to the development of second generation sequencing techniques has become increasingly frequent[14].

As is known, this is a relatively recent right, which follows the recognition of the right to be informed and the achievement of informed consent as a principle of legitimacy for medical intervention[15]. Only in 1997 did the Right Not to Know, characterized as an aspect of personal autonomy, gain its first recognition – to be followed by many others - in the *Universal Declaration on the Human Genome and Human Rights* of Unesco (Article 5) and, in the same year, in the *Convention on Human Rights and Biomedicine* (Article 10) of the Council of Europe. Nevertheless, in the bioethical and bio-juridical debate, the plausibility of the Right Not to Know continues to be a controversial matter due to the continuing lack of agreement on the ethical-philosophical meaning of the concept of "autonomy" and on the rights and/or interests to be protected that derive from it[16].

The most articulated discussion on the subject was developed during the *Symposium From the Right to Know to the Right Not to Know*[17], held in Canada in spring 2014 as a response to the *Recommendations for reporting of incidental findings in clinical exome and genome sequencing*, released one year earlier by the Working Group of the American College of Medical Genetics and Genomics[18], which denied the possibility of exercising the Right Not to Know in the case of genomic sequencing.

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[14] The possibility of incidental results has arisen above all in conjunction with the very rapid evolution of second generation genomic sequencing technologies, which, in recent years, have transformed and accelerated the research and diagnosis of many diseases. While in the past it was possible to analyze only single segments of DNA, new techniques now make it possible to decrypt the entire exome (*Whole Exome Sequencing*, WES), or even the entire genome (*Whole Genome Sequencing*, WGS), including the coding and non-coding sequences of a person (ICB, *Management of "incidental findings" in genomic investigations with new technology platforms*, 17.03.2016). On the problems raised by new sequencing techniques and the management of 'incidental findings', C.G. VAN EL ET AL., *Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics*, on behalf of the ESHG Public and Professional Policy Committee, in *European Journal of Human Genetics* vol. 21 (2013), pp. 580–584.

[15] For an in-depth analysis of the right not to know in a constitutional perspective and in relation to the implications for informed consent, cfr. the recent essay by A. O. Cozzi, *Incidental Findings and the Right Not to Know in Clinical Setting: Constitutional Perspectives*, in *BioLaw Journal-Rivista di BioDiritto*, Special Issue no. 1/2021, pp. 79-109, available at http://rivista.biodiritto.org/ojs/index.php?journal=biolaw&page=article&op=view&path%5B%5D=776&path%5B%5D=646 (last accessed on June 1st, 2021).

[16] Italian Committee for Bioethics, *Managing Incidental Findings*, Managing "Incidental Findings" in genomic investigations with new technology platforms, Opinion, March 17th 2016.

[17] B.M. KNOPPERS, *Introduction from the Right to Know to the Right Not to Know,* in *The Journal of Law, Medicine & Ethics*, Vol. 42, no 1, Spring 2014, pp. 6-10.

[18] WORKING GROUP OF THE AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS, *Recommendations*, cit., then partially revised by the same Board of Directors of AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS, *Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results*, Bethesda, 2014, April 1, https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf (last accessed on June 14th, 2021).

The Symposium, which took place with the participation of scientists, jurists and moral philosophers, marked an important stage in the process of conceptual clarification of the misinterpretations and misunderstandings that had hitherto vitiated the debate on this controversial right and its theoretical presuppositions. In this regard, it emerged that it is precisely these divergent ethical-philosophical interpretations of the concept of "autonomy" which found on conflicting ethical principles both the arguments for and against the recognition of the Right Not to Know. In summary, there are three main interpretations of the concept, which in turn envisage different ideals of what is meant by the expression "autonomous decision" and different, or conflicting, conclusions regarding the regulatory relevance of the Right Not to Know.

For the first ideal, what is of value, and worthy of protection, is non-interference in the most intimate and personal decisions; in this case, autonomy coincides with the personal freedom of the adult and competent individual to decide his/her own life and, therefore, requires a regulatory policy which guarantees these corresponding rights, including the right to refuse to receive information concerning one's own health.

Much more demanding is the interpretation that connects the concept of autonomy to an ideal that requires competent persons, as moral agents, to control the circumstances of their own existence. For this conception, people not only have the right, but also the duty to know as much information as possible about their state of health, including genetic conditions, in order to be able to exercise "self-governance" and make rationally founded decisions, that is, based on all potentially relevant obtainable information for the prudent planning of one's existence. This excludes a priori the possibility of morally establishing the claim of being able to remain in ignorance[19].

But there is also a third conception, often unrecognized, opposite to the one previously illustrated, which links autonomy to an ideal of "authenticity". This interpretation finds, in the philosophical context, its most accredited supporter in Hans Jonas. Already in the 1970s, faced with the accelerated progress of biomedical technologies that seemed to be able to question the "right of each human life to find its own way and be a surprise to itself"[20], Jonas had envisaged the emergence of a new moral right, that of ignorance of one's future; a right which, in certain situations - for example when the information on late-onset genetic diseases currently not preventable or curable is at stake - can present itself as a precondition for the free construction and definition of the self[21].

[19] J. HARRIS, K. KEYWOOD, *Ignorance, Information and Autonomy,* in *Theoretical Medicine and Bioethics*, vol. 22, no. 5, 2001, pp. 415-436. Position maintained by the authors also thereafter.

[20] H. JONAS*, Philosophical Essays*. *From Ancient Creed to Technological Man*, Chicago, 1974, Italian translation *Dalla fede antica all'uomo tecnologico*, Bologna, 1991, p. 251.

[21] The aspect of the 'right not to know' that relates to delicate psychological profiles, of ethical and legal importance, was dealt with in ICB-ICBBSL, *Genetic testing and insurance*, cit. Inescapable is the question of how the knowledge of one's genetic predisposition to certain diseases and this same perception, and being perceived by those closest, as subjects predestined to an inauspicious fate, can reflect on and condition the development of one's sense of self, one's self-esteem and identity, coercing life and relationship choices in advance. On the interest in not knowing genetic information about oneself, due to the possible negative psychological and social consequences deriving from this knowledge, cfr. N. JUTH, *The Right Not to Know and the Duty to Tell: The Case of Relatives,* in *Journal of Law, Medicine & Ethics,* vol. 42, no. 1, pp. 38-52; this article also addresses the issue of the difficult balance between the many interests at stake, individual, family, group, in relation to the question of knowing/not knowing the results of genetic analyzes of possible interest for health or for reproductive choices.

If the second interpretation is incompatible with the recognition of the right not to know, for the other two this right finds instead a foundation - at least as a "prima facie" right, subject to exceptions in particular circumstances[22] - in the negative freedom of the subject in the one case, and in the "existential" freedom of self-determination based on one's values in the other.

However, if we move from the abstract to the factual level of the concrete dilemmas that can arise when researchers and clinicians find themselves having to decide whether or not to communicate the "incidental" results arising from a genetic investigation, the aforementioned concepts do not help to resolve the question of the decision to be taken in the absence of an explicit expression of will on the part of the person concerned to be or not to be informed about this[23]. In these situations, the justification of the Right Not to Know cannot be based solely on the principle of autonomy, as there is no choice; hence the proposal to found the justification of the Right Not to Know also on a different theoretical basis, or rather on the interest in respecting privacy, understood as the separation of the "private" sphere including the individual psychological dimension, not accessible to others except for good reasons, which must always be argued[24].

It is therefore suggested that, faced with the dilemma of whether or not to communicate the unsolicited results of genetic analyzes, the professional in possession of this information (researcher, geneticist ...) should carefully evaluate, case by case and with the help of other consultants, the reasons for communicating /not communicating them to the person most directly concerned, in the awareness that any decision in this regard could also be of interest to others belonging to the same family circle. In this decision, the type of information in question must therefore play a significant role, depending on whether it is data of clinical utility for early prevention, or because there is the possibility of a therapy, or instead, it concerns predictive data for late-onset diseases for which there is currently no treatment but which could prove indispensable in order to make informed reproductive choices, or

On the difficulties encountered, more generally, in the protection of the 'right not to know', in the reshaping of our mutual responsibilities, cfr.r. M. TORALDO DI FRANCIA, *Sviluppo delle bio-tecno-scienze genetiche e cittadinanza,* in *Homo medicus e commodification. Una prospettiva bioetica*, in *Jura gentium*, vol. 17, no. 1 (2020), pp. 187-94. The danger of a loss of relevance of the right to not know was also highlighted by the UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights*, 2 October 2015, available at https://unesdoc.unesco.org/ark:/48223/pf0000233258 (last accessed on June 14th, 2021), which underlines how the possibility of knowing one's genomic constitution can raise the social expectation that people plan and live their lives in accordance with this knowledge. Such an expectation could not only make one lose sight of the importance for health of the multiple social determinants that affect it, but also lead to discrimination and stigmatization of those who do not adopt a "*health-promoting lifestyle*".

[22] E.g. when it comes to information on serious diseases that can be avoided with early prevention, or for which there are effective treatments.

[23] Cfr. M. TORALDO DI FRANCIA, *Genetica Caso 4: Test genetici per malattie a insorgenza tardiva*. *Il punto di vista bioetico; Consenso all'atto medico*, in P. FUNGHI, F. GIUNTA (ed), *Medicina, bioetica e diritto. I problemi e la loro dimensione normativa*, Pisa, 2012, pp 84-90, where this possibility is taken into consideration and possible responses to the dilemma of communication / non-communication to the person directly concerned are examined.

[24] Cfr. J. LAURIE, *Recognizing the Right Not to Know: Conceptual, Professional, and Legal Implications*, in *The Journal of Law, Medicine & Ethics*, cit., pp. 53-63; G. HELGESSON, *Autonomy, the Right Not to Know, and the Right to Know Personal Research Results: What Rights Are There, and Who Should Decide about Exceptions?,* in *The Journal of Law, Medicine & Ethics*, cit., pp. 28-37.

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even predictive data of a disease risk that cannot be quantified at an individual level, or with clinical implications that are still uncertain (the so-called VUS, *Variant of Uncertain Significance*).
Ultimately, however it is justified, the right or interest of adults and "capable" individuals not to know is always considered by its supporters as a *prima facie* right or interest, to be respected in most cases, but which can always encounter limitations in particular situations.

4. Genetic research with minors and the right not to know

The question of respecting the Right Not to Know becomes even more complicated when it comes to research involving the sequencing of the biological samples of a category of subjects to whom special protection is due, that of minors. It being understood that when we talk about research involving minors we must always keep in mind the heterogeneity of this category, which extends from newborns to adolescents on the threshold of adulthood, including subjects with very different physical, cognitive and emotional abilities, there are certain ethical principles that are valid in general for the whole category, first of all the ethical principle of respecting the "best interests" of the minor participating in a research/clinical trial[25]. If this is the guiding principle to be followed also in genomic studies, there is good reason to believe that these interests include not only ensuring minors the possibility of deciding on coming of age whether or not to consent to further conservation-use of their biological samples and data, but also the interest not to know, also defined as the "right to an open future"[26], when the information resulting from the analysis of the samples is not immediately useful for their health[27]. The possible negative effects of such information, for example in the case of the prediction of non-preventable late-onset diseases, include damage to self-esteem, the ability to form meaningful future relationships, the relationship with parents, as well as the loss of privacy and future autonomy. However, the minor's interest "not to know" may, in some cases, conflict with the parents' interest to know the same information to plan their reproductive choices and there is no agreement of views on which of the two interests should prevail in this particular circumstance[28]. What emerges from the bioethical and biojuridical debate on this is, in fact, a clear contrast between two conceptions of the concept of "clinical utility" as a criterion for communicating/not communicating the results of a genetic analysis. On the one hand there are those who still consider valid the classic criteria according to which the clinical utility of an investigation refers to the identification of conditions for which there is immediate availability of treatment, or effective preventive measures; and on the other hand, those who intend to extend its meaning to include information on conditions that do not require immediate medical intervention, or that lack effective treatments, or are not clearly pathological and whose recipients, in terms of the possible benefits to be taken into consideration, involve not only the parties

[25] THE COUNCIL OF EUROPE-COMMITTEE OF MINISTERS,*Recommendation* CM/Rec(2016)6, cit.
[26] J. FEINBERG, *The Child's Right to an Open Future*, in W. AIKEN, H. LAFOLETTE (eds.), *Whose Child? Children's Rights, Parental Authority, and State Power*, Totowa, 1980, pp. 124-153.
[27] See in particular P. BORRY, M. SHABANI, AND H. C. HOWARD, *Is There a Right Time to Know? The Right Not to Know and Genetic Testing in Children,* in *The Journal of Law, Medicine & Ethics,* cit., pp. 19-27.
[28] On the difficulty of balancing the autonomy and interests of the child with the needs and rights of parents C.G. VAN EL ET AL., *Whole-genome sequencing in health care Recommendations of the European Society of Human Genetics,* cit.

directly concerned, but also their family members. In this second perspective, which now seems to prevail, "all the so-called 'actionable' information, i.e., such as to prefigure a decision-making intervention by the person concerned and/or his family members (reproductive decisions, planning of life choices, insurance plans, etc.), are included in the category of information of clinical usefulness and, therefore, to be communicated"[29].

In my opinion, the ethical issue remains open as regards whether or not it is licit to extend the meaning to encompass the parents' need for knowledge for reproductive purposes, needs which, in the case of conflict, can prevail over the protection of the minor's "best interest".

5. Still on "minors": the gap between abstract principles and praxis

Still with regard to the category of "minors", further difficulties can be pointed out relating to the gap between the rights whose protection every research project should guarantee, according to the legislation in force[30], and what in actual fact becomes increasingly difficult to ensure to the participants who donate their samples.

Given that research with minors must comply with all the conditions already provided for "capable" adults (such as, for example, the absence of undue pressure inducing participation, the possibility of withdrawing consent already given at any time, the right to know information of individual interest to health that may derive from research, especially in the case of genetic research[31]), there are additional conditions, supplementary to the informed consent of the parents or legal representative, for this type of study to be considered morally acceptable by the Ethics Committee appointed to undertake the review:

1. research cannot be carried out with comparable efficacy on subjects capable of giving legally valid informed consent;

2. the expected results of the research deliver a real and direct benefit for the minor, or otherwise, the research must have the aim of contributing, through significant improvement in the scientific knowledge of the person's condition, illness, disorder, to obtain results that may be of benefit to other people of the same age group, or who suffer from the same disease or disorder, or have the same

[29] The Italian Committee for Bioethics, *Managing Incidental Findings*, cit.

[30] World Medical Association, *Declaration of Helsinki. Ethical principles for medical research involving human subjects*, 1964 (last revision 2013), available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last accessed on June 1st, 2021).

[31] On the latter point, see The Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research,* cit., Art. 27 "*Duty of care*". The CIOMS Guidelines note that, in the case of genetic research, there is a growing consensus in favor of the duty of researchers to at least provide for the communication of certain types of information deriving from the study, if this is the desire of the donor of the sample. In general, the three main guiding criteria in this regard require that the results have analytical validity, clinical significance and are 'actionable'; it will then be up to the competent Ethics Committee to assess whether or not there is the need to provide genetic counselling contextual to the communication (Guideline 11).

characteristics and the research must entail only minimum risk and minimum burden for the minor involved[32];

3. the opinion of the minor must be taken into consideration as a factor of increasing importance in relation to his/her age and degree of maturity[33];

4. the minor does not object[34].

As for the return of possibly useful information for the health of the minor – there is always reference to genetic research - frequently in the protocols resort is made to the clause regarding the non-clinical purpose of the study in order to deny this right to the person concerned, whereas it would be only right to communicate these data, if requested, especially when the investigation concerns small groups of patients as in the case of investigations on rare diseases.

The ethics committees for paediatric clinical trials also encounter other difficulties when it comes to ascertaining, in the case of studies where there is no real and direct benefit for the donor, that the research involves only a minimal risk for the person concerned, even in terms of his/her right to the protection of privacy; or, again, when they find it necessary to exclude the exercise of direct or indirect pressure on parents, especially when the researcher is also the patient's doctor, or there is a need to recruit "healthy" control subjects for comparison, as often happens in genetic clinical studies with the collection, storage and use of biological samples and related data[35].

As regards, on the other hand, the real possibility of guaranteeing the right to revoke consent already given for present and future research, which provides for the right to request the return or destruction of the donated biological sample and non-use for further studies of the personal information collected,

[32] Still Guidelines 17, of the CIOMS Guidelines, permits, however, the possibility that the competent Ethics Committee approves a 'minor increase' above 'minimum risk', if the scientific and social value of the research is of the utmost importance and it is not possible to achieve the goal in another way.

[33] On the basis of these provisions, the pediatric ethics committees may request the preparation of disclosure-assent forms that are differentiated for the different age groups (7-13; 14-17), in addition to those intended for parents /legal guardian. In the Commentary on Guideline 17 of the *International Ethical Guidelines* it is pointed out that: *"the process of obtaining assent must take into account not only the age of children, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation. As adolescents near the age of majority, their agreement to participate in research may be ethically (though not legally) equivalent to consent. In this situation, parental consent is ethically best considered as "co-consent" but legally, the adolescent's agreement remains assent".*

[34] As stated in the Explanatory Report of the *'Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research*, in the case of newborns and very young children the parents will have to decide taking into account, of course, other factors, while the commentary on Guideline 17 adds that: "*a deliberate objection by a child or adolescent to taking part in research must be respected even if the parents have given permission, unless the child or adolescent needs treatment that is not available outside the context of research, the research intervention has a clear prospect of clinical benefit, and the treating physician and the legally authorized representative consider the research intervention to be the best available medical option for the given child or adolescent. In such cases, particularly if the child is very young or immature, a parent or guardian may override the child`s objections. However, in some situations parents may press a researcher to persist with an investigational intervention against the child`s wishes. Sometimes this pressure is meant to serve the parents' interests rather than the child's. In this case, the parents' decision must be overridden if the researcher believes it is not in the child's best clinical interest to enrol or continue study participation".*

[35] Cfr. M. TORALDO DI FRANCIA, *Note sulla mia esperienza in un Comitato etico per la sperimentazione clinica pediatrica*, in *Forum: Le responsabilità nei confronti della scienza*, in *BioLaw Jounal/Rivista di BioDiritto*, 1/2017, pp. 29-33.

including codified information, it should be noted that in disclosure and informed consents, often clauses are set preventing its enforceability'[36]. While recognizing this right to the parent/legal representative, Sponsors[37] can protect themselves - and this is what often happens when the Sponsor is a large pharmaceutical company with biobanks and analysis laboratories located in several countries – by already warning in the disclosure that it could be unable to guarantee their return-destruction, not only because the samples may have been anonymised, but also because they may no longer be under the Sponsor's responsibility because they have already been released to a third party. In this way, not only is the traceability of the samples lost, with the joint risks of improper use as mentioned above, but the minor is also deprived of the opportunity, on reaching the age of majority, to give new consent to their conservation, transmission, use.

To end on a more personal note, I hope that once we are out of this pandemic thought can be given to what the health emergency has taught us, distinguishing between what is justified to request in times of a pandemic, in the name of a more general common good, and what in "normal" times might no longer be appropriate to recommend, particularly when biomedical research involves minors; I am referring, in this regard, to the request to share with the scientific community, in addition to the results of the studies and the data collected, also biological samples in order to accelerate the achievement of cognitive and/or clinical results of particular relevance[38]. A good compromise, which does not solve all the difficulties encountered, but which, in my opinion, remains the best possible solution, in balancing the rights and the many interests at stake, is to encourage increasingly incisively the establishment of networks of certified public biobanks, regulated by specific procedures for the activities of acquisition, storage, access, use of the samples, and which provide for the transfer of samples to other locations only in exceptional cases. Examples of "good practices" in this sense are not lacking[39], even during the health emergency itself, as in the case of research aimed at studying the genetic variants associated with severe forms of Covid-19 which have preordained the custody of the acquired samples in a certified public biobank; if on the one hand only the DNA or RNA extracted from the samples was sent to external laboratories for genetic analysis, on the other, in accordance with the statements in the attached disclosures of the protocols, the sharing with the community of the results obtained and the data collected[40] was instead foreseen and promoted, subject to guarantees, by other researchers to restrict their use to the study of the causes and consequences of Covid-19.

[36] In today's disclosures there is always a supplement on privacy that refers to the provisions contained in the *Regulation (EU) 2016/679* and, as regards Italy, also to *the Legislative Decree 30 June 2003, n ° 196 Personal Data Protection Code, as amended by Legislative Decree 101/2018 and supplemented by the general authorisations of the Italian Data Protection Authority, for the processing of genetic data and the processing of personal data carried out for scientific research purposes* (see provision no.146 of 2019).

[37] In general, this is multicentre research promoted by large pharmaceutical companies, with offices and analysis laboratories located in other European and non-European countries.

[38] Cfr. L. PALAZZANI, *Informed consent in biomedical research in the pandemic context,* cit.

[39] The reference is to some multicenter studies reviewed by the Paediatric Ethics Committee for Clinical Trials of Tuscany.

[40] In the opinion of the ITALIAN COMMITTEE FOR BIOETHICS, *Biomedical research for novel therapeutic treatments within the Covid-19 pandemic: ethical issues*, cit., data are defined as "a valuable asset" for the advancement of knowledge and it is desirable for researchers to share (data sharing) at every level, also in order to avoid duplication or undersized research.