PAPER N. 19
a.a. 2018/2019

Legal issues arising in population-based studies: analysis of property rights implications and governing informed consent procedures through an Italian case study

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Trento BioLaw Selected Student Papers

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Co-funded by the Erasmus+ Programme of the European Union
UNIVERSITÀ DI TRENTO Facoltà di Giurisprudenza

I paper sono stati selezionati a conclusione del corso *BioLaw: Teaching European Law and Life Sciences (BioTell)* a.a. 2018-2019, organizzato all'interno del Modulo Jean Monnet "BioLaw: Teaching European Law and Life Sciences (BioTell)", coordinato presso l'Università di Trento dai docenti Carlo Casonato e Simone Penasa.

Legal issues arising in population-based studies: analysis of property rights implications and governing informed consent procedures through an Italian case study

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ABSTRACT: Population-based studies are an increasingly scientifically relevant tool to investigate the relationship between genetic patrimonies and environmental factors especially in isolated populations such as the one studied in the case study in questions. The paper will analyze the way in which challenges in the regulation of research studies have been overcome by the CHRIS governance outlined in their ethical protocol. In addition, the regulatory framework of the GDPR in relation to informed consent procedure in the field of research will be considered.

KEYWORDS: Population-based study; informed consent; privacy; bio-banking; property rights; GDPR

SUMMARY: 1. Introduction – 2. CHRIS study – 3. MICROS study – 4. Participation to the CHRIS study – 5. How is the study carried out – 6. Informed consent procedure – 7. Privacy and Data management – 8. From Meran Hospital to Bolzano Biobank – 9. Legal issues – 10. Property rights and biological material – 11. Informed consent: issues and developments contained in the GDPR – 12. Conclusion

1. Introduction

This paper introduces a population-based study carried out the most Northern region of Italy. After outlining the aims and procedures that participants undergo, legal aspect of scientific research are going to be analyzed. The relationship between science and law has been increasingly challenging over the last two decades due to astonishing fast developments in scientific knowledge. However multiple problems arise in the regulation of scientific problems due to two reasons: it is firstly impossible to precede scientific developments through legislation and as consequence law has always found itself chasing science by trying to apply tradition legal categories to newly discovered applications. Secondly it is progressively delicate to apply legal notion to research findings. In this paper challenges raised by property rights and privacy concerns are going to be scrutinized.

For the purpose of clarity, definitions of the most relevant terminology will be now provided:

Population based studies «aim to answer research questions for defined populations. Answers should be generalizable to the whole population addressed in the study hypothesis, not only to the individuals included in the study. This point addresses the point of external validity of the findings. Therefore, the valid definition as well as the reliable and valid identification of populations in which research questions for specific populations can be studied is the most important issue in population-based studies»[1].

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[1] A brief but exhaustive definition of population based study: Encyclopedia of Behavioral Medicine https://link.springer.com/referenceworkentry/10.1007%2F978-1-4419-1005-9_45.

Genetic data is defined as «personal data relating to the inherited or acquired genetic characteristics of a natural person which result from the analysis of a biological sample from the natural person in question»[2]. «A population biobank is a collection of biological materials that has the following characteristics: the collection has a population basis; it is established, or has been converted, to supply biological materials or data derived therefrom for; it contains biological materials and associated personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated; it receives and supplies materials in an organised manner»[3].

2. CHRIS Study

CHRIS, Cooperative Health Research in South Tyrol, is a longitudinal population-based study carried out in the region of South Tyrol, more precisely in Val Venosta/Vinschgau. This study is promoted by the Institute of Biomedicine of the EURAC research center together with the South Tyrolean Health care system. The CHRIS study has been approved on 9th April 2011 by the Ethical Committee of the Healthcare System of the Autonomous Province of Bolzano. Its main aim is that of identifying «the genetic basis of common chronic conditions associated with human aging and their interaction with life-style and environmental factors in the general population of south tyrol»[4]. The project is particularly concerned with the study of cardiovascular, neurological, metabolic and psychiatric diseases.

The focus of the CHRIS study rotates around the interaction between genetic heritage and environment: the main environmental factors taken into consideration for the overall assessment are pollution and ordinary life-style such as eating and smoking habits, alcohol consumption and training. On the other hand, genetic patrimonies of a population's section are particularly relevant in order to assess whether the combination between genes and environment might enhance or reduce the probability of contracting a disease. Certain genetic heritages are more inclined to be sensible to environmental factors.

3. MICROS study

Val Venosta/Vinschgau has been previously interested by another population-based study. Even tough, broadly speaking, the valley is located in center Europe on the border between Italy and Austria, the Alps, and in particular this area, has always been mostly isolated. Vinschgau is characterized by multiple scattered and remote villages that have never witnesses waves of immigration or relevant changes in

[2] GDPR n. 2016/679 Recital 34 https://gdpr-info.eu/recitals/no-34/.

[3] Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin and its Explanatory Memorandum, Council of Europe, Chapter V, Article 17(1).

[4] C. Piciocchi, R. Ducato, L. Martinelli, S. Perra, M. Tomasi, C. Zuddas, D. Mascalzoni, *Legal issues in governing genetic biobanks: the Italian framework as a case study for the implications for citizen's health through public-private initiatives*, in *J. of Community Genetics*, 9, April 2018, https://doi.org/10.1007/s12687-017-0328-2.

population composition, therefore the region has drawn the attention of researchers in order to conduct genetic studies on the population. Three villages were selected on the basis of isolation, evidence of old settlement, frequent endogamy rates. More precisely the study has been carried out on the population of Stelvio, Martello, already classified as genetic micro-isolate, and Vallelunga as part of a larger study in the whole region of South Tyrol, the GenNova Project. Studies on isolated populations, such as the one in question, are pivotal for the analysis and discovery of genetic etiology of common diseases, as the «homogeneity of the shared environmental factors and the limited number of recombination events in the DNA make isolates a valuable tool for linkage and association studies»[5].

The population-based study was carried out on adult population, aged 18, composed by 1043 people in Stelvio, 693 in Martello and 339 in Vallelunga[6]. Participants were submitted an interviewer-administered questionnaire, in which several questions were posed regarding their genealogy and family history, overall health condition (precisely questions about cardiology, neurology, psychiatry and others) and lifestyle exposure in particular smoking habits and alcohol consumption. Eventually patients underwent several clinical analyses: anthropometric measurements, respiratory and ultrasound-based bone densitometry tests, blood pressure measurements, collection of urine sample are only few examples. Church records and municipality lists were the main tools used to reconstruct genealogical data. Baptisms, marriages, death record reported information back to early 17th century[7]. Single families were traced back and eventually linked together in order to reconstruct genealogical trees of the three villages.

Data on individuals, such as genetic, genealogical or biological information, was anonymized and to each participant was assigned a unique code associated to questionnaire and specimen. Participants were able to enter a website on which they could monitor and change their participation conditions. Their rights comprised: «non-disclosure clause of personal identifiable data, access by the participant to his/her personal data, right to change or update the personal information provided, study's opt-out clause, guaranteeing that every participant may withdraw at any time from the study, for any reason and without consequences»[8].

This brief introduction to the MICROS study has been included, as it has been the predecessor of the CHRIS population-based study in the same geographical area. It is particularly relevant that the population of the three villages, that took part in the MICROS study in 2002/2003, still resident in the villages of Stelvio,

[5] C. Pattaro, F. Marroni, A. Riegler, D. Mascalzoni, I. Pichler, C. B Volpato, U. Dal Cero, A. De Grandi, C. Egger, A. Eisendle, C. Fuchsberger, M. Gögele, S. Pedrotti, G.K. Pinggera, S.A. Stefanov, F.D. Vogl, C.J. Wiedermann, T. Meitinger, P.P. Pramstaller, *The genetic study of three population microisolates in South Tyrol (MICROS): study design and epidemiological perspectives,* in *BMC Medical Genetics,* June 2007, https://doi.org/10.1186/1471-2350-8-29.

[6] C. Pattaro et. al., *The genetic study of three population microisolates in South Tyrol (MICROS): rationale, objectives, and preliminary results,* cit.

[7] *Ibid.*

[8] *Ibid.*

Martello and Vallelunga, has been highly encouraged to participate to the CHRIS study. The group taking part to the CHRIS study, that had previously been involved in MICROS is now composed by 1259 persons[9].

4. Participation to the CHRIS study

The communication and information phase is pivotal in order to carry out the study, especially to develop and build a relation of trust with the community. The recruitment center is based in Silandro/Schlanders' hospital. The first step is based on an informative campaign which passes through the communication and interaction with local authorities and competent practitioners in the area and reaches the population thanks to local media and public meetings, where the study is extensively introduced to the community.
The population is invited to participate to the study through a letter. Family participation is encouraged as it gives a complete overview on the genetic heritage and it helps the comprehension of disease inheritance mapping. The only threshold established is that only 18+ years old population can participate and they are all identified through publicly available electoral lists[10].

5. How is the study carried out

The active part of the study is carried out in the hospital of Schlanders/Silandro were people, who decide to take part to the population-based study, undergo non invasive clinical analyses. The study is designed to invite up to 10 participants each day, who need to have fasted overnight. After the informed consent procedure is completed, the patient goes through the clinical segment of the study. The procedure includes tremor assessment, blood drawing, urine collection, electrocardiographic analysis, blood pressure measurement, anthropometric measurements[11]. In addition to these analyses, a part of the visit consists in an interview regarding health conditions of the patient, the environment in which he or she lives, his or her eating and general lifestyle habits. Once data submitted by the patient have been elaborated, the person in question receives his or her scientific analysis in order to asses his or her own overall health conditions, however promoters of the study suggest to consult a GP. The participation to the study is completely free and entirely based on the voluntary decision to take part to it. However no financial compensation or reimbursement of potential cost incurred for traveling are provided.

[9] C. Pattaro, M. Gögele, D. Mascalzoni, R. Melotti, C. Schweinbacher, A. De Grandi, L. Fusco, Y. D'Elia, B. Linder, C. Fuchsberger, C. Minelli, C. Egger, L. S. Kofink, S. Zanigni, T. Schäfer, M. F. Facheris, S. V. Smárason, A. Rossini, A.A. Hickis, H. Weiss, P. Pramstaller , *The cooperative Health Research in South Tyrol (CHRIS) study: rationale, objectives, and preliminary results*, in *J. Trans Med*, 2015, https://www.researchgate.net/publication/283980686_The_Cooperative_Health_Research_in_South_Tyrol_CHRIS_study_Rationale_objectives_and_preliminary_results.
[10] *Ibid.*, 2.
[11] C. Picciocchi et al., *op. cit.*

Data of patients, mainly blood urine and dna, are codified and stored in the biobanks of Bolzano and Merano. Data collected are analyzed and filtered according to the terms of participation to which the patient has given consent to. The research group of the institute of Biomedicine, EURAC institute, carries out specific test aiming at identifying risk factors related to biological mechanisms that take place in specific diseases. The greater the participation of the population, the more accountable the findings of the aforementioned tests will be.

In cases of life-threatening findings, an ad-hoc procedure is followed, coordinated by the study administrator and the responsible doctor, according to which the patient is informed as quickly as possible of his or her health conditions. The emergency department of the Schlanders hospital is responsible for immediate interventions, that may arise over the period in which in study will be active[12].

6. Informed consent procedure

The CHRIS study has a "longitudinal" prospective, meaning that the collaboration with the population aims at being "extended and prolonged" over time. To comply with this aim a "broad consent"[13] model has been introduced: it provides for an informative report in addition to an individual dynamic consent form, which allows a multiple choice selection to the patient and the possibility of changing conditions over time. A dynamic consent is a web-based platform that allows research participants to have an interactive relationship with biobanks and research centers. This type of model enhances the possibility of re-contacting participants, with the aim of giving updated information on specific research projects and allowing a straightforward procedure for donors to provide or revoke consent. A development that was brought by dynamic consent models is that these provide «more specific consents with active opt-in requirements for each downstream research project»[14]. As a consequence, dynamic consent forms allow a directional relationship between research institutions and participants, which is constant and interactive. The model at stake requires a continuous request of consent in case a new project has been designed, even when marginal differences exists between the initial and the new project: therefore donors will have to consent on both primary and secondary uses of their data. A pivotal feature peculiar to dynamic consents is the possibility for researchers to be able to inform participants about research projects they are involved in, through ad-hoc websites, SMS or e-mail in order to fulfill the aim of delivering detailed and real-time information.[15] Nowadays scholars propose to introduce a more advanced and much more complex model

[12] C. PATTARO, *The cooperative Health Research in South Tyrol (CHRIS) study: rationale, objectives, and preliminary results,* 3.

[13] Centro di Biomedicina EURAC Research, *Protocollo etico per lo studio CHRIS*, 08.03.2011, https://it.chris.eurac.edu/wp-content/uploads/sites/11/2018/03/CHRIS-protocollo-etico-2011.pdf.

[14] K.S. STEINBEKK, B.K. MYSHYA, B. SOLBERG, *Broad consent versus dynamic consent in biobank research: Is passive participation an ethical problem?*, in *European Journal of Human Genetics,* 21, 2013, 897-902.

[15] Other categories of informed consent are briefly going to be introduced. One of the most criticized classes of informed consent models is the "blanket model", according to which individuals donate their samples without any restriction. The fundamental limit of this approach is the absence of congruence between the will of the donor and the scope for which samples are going to be

of informed consent, focused on a further personalization of informed consent procedure. Already in 1979, in the Belmont Report, the principle of autonomy of participants to research programs has been highlighted and has played since then a central role in informed concept procedures. A further step towards autonomy of participants entails the adoption of a new perspective, mainly the one of research participants. An example of this innovative approach is the I-CONSENT proposal. The I-CONSENT project's aim is «to develop guidelines to help researchers utilize bidirectional and continuous communication during the process of informed consent, without losing sight of vulnerable populations, multiculturalism and gender perspectives »[16], by acknowledging the central role of participants in the informed consent process. The procedure is patient-centered in order to create an environment of trust and empathy between researchers and patients, in order to facilitate communication. In this way the so called paternalism of knowledge and the imposition of a hierarchy in the relationship researcher/ patient can be overcome. However some remarks should be taken into account in order to create the aforementioned relationship of trust. For instance employing a common language is pivotal for the participant. Sharing overcomplicated or overspecialized terminology is counterproductive for the establishment of mutual trust. A second aspect entails that «trust and trustworthiness are related to the time available for dialogue and communication». Time constrains in medical research may lead to think that this suggestion is just an illusion, however it should play a central role especially in population-based studies[17].

As we mentioned before, an ad-hoc procedure is observed in cases of unexpected results or so called «incidental findings» meaning unexpected information which could emerge during laboratory analyses. In these specific cases, it is necessary that the patient expresses his or her will with regards to his or her right to be informed in the eventuality that unexpected result come to the attention of researchers. If she expresses herself in the affirmative, right to be informed, she furthermore has the right to choose through which informative channel she wants her result to be sent. If she expresses herself in the negative, right of not being informed**,** she will have to give further specific information concerning whether she doesn't want

employed. In the absence of restrictions given explicitly by the participant to the various research projects, samples might undergo studies that conflict with the individual's fundamental values. on the other hand, broad or generic consent consists in procedure by which participants donate their samples for a wide range of projects, subject to specified restrictions. Donor's samples may be employed in future studies to the extent that an independent person or an ethical committee responsible for participant's protection acknowledges, that the project is valuable, ethical, that it poses no relevant risks and that there is no reason to think that it will conflict with the participant's fundamental values. Donors are asked to re-consent when ethically relevant differences between the first study and the future project arise. In order to ensure a high level of communication, sample holder should deliver more information regarding the studies conducted and the allow a higher degree of self-determination with regard to biological material. Lastly a "no consent" model provides that there is no possibility for accommodation of participants preferences with regards to participation conditions. These consent models are promoted in states in which there is no need for further provision protecting participant's privacy a part form relevant state law.

[16] J. FONS-MARTINEZ, C. FERRER-ALBERO, E. RODGERS, L. GLENNIE, J. DIEZ-DOMINGO, *I-Consent: presentation of the project and the importance of the participants' perspective in the informed consent process,* in *BioLaw Journal – Rivista di BioDiritto*, 1 Special issue, 2019, 3-10.

[17] F. MACIOCE, *Informed consent procedure between autonomy and trust,* in *BioLaw Journal – Rivista di BioDiritto*, 1 Special issue, 2019, 23-25.

to be informed in any case, or whether she wants to be informed only when the results involve the sexual sphere or matters related to reproductive choices, or whether she wants to be informed in the case in which the results may be relevant for the health conditions of her relatives. Incidental findings pose numerous issues, such as when can an information be regarded as "unexpected result" or not. In other words, when can an information be directly communicated to the participant. There are no fixed criteria that allow the recognition of parameters that may be relevant. In addition, tests that are carried out within the context of a research project may not be fit for reaching results that are valuable from a clinical point of view. Furthermore researchers may not have the expertise to evaluate form a clinical perspective the information they reached during the research process. However, on the other hand, failure to communicate or erroneous communication of such information is today an issue that has not been dealt with yet. As a matter of fact there is no dedicated legislation or relevant case law dealing with such responsibility[18].

The concept of broad and dynamic consent allows participant to change at any time, conditions regarding their previous dispositions. They are given the right to change options involved in the consent form and the right to decide whether they still want to take part to the study or whether they want to withdraw their consent for the use of their genetic data[19].

This feature is particularly relevant for long term studies, which comprise for instance follow-ups and close studies on genetic material, as a flexible structure of expressing one's consent is pivotal in building a relation of trust and transparency with patients involved. The choice of adopting this type of consent is in line with the general line of thought with regards to consent. What is conceived as classical and crystallized consent is not suitable with the needs and rights that have to be guaranteed to a voluntary participant to a study, which comprises the investigation of extremely sensible information regarding, in the first place the person from which the material has been collected, but also having a potential consequence on the patient's family. Therefore there is the need to rethink and promote an advanced model of informed consent, that both guarantees a wide room for scientific research and the protection of patient's rights. In this specific case study, stakeholders have been trying to implement improved features of expression of consent to foster this type of development in the scientific and legal sphere. Thanks to the wide access to electronic devices that the population has nowadays, an online platform has been developed, where each participant can access using an username and password. A dedicated page will open up where the patient is able to change his participation terms, give consent to take part to further research studies, connected to CHRIS population-based study, or to withdraw consent for the study. On the online platform many informative sources are provided in order to allow a better communication with potential participant and

[18] M. TOMASI, *Genetica e Costituzione. Esercizi di eguaglianza, solidarietà e responsabilità,* 2019, 464.
[19] Centro di Biomedicina, , *Protocollo etico per lo studio CHRIS.*

patients. Short videos, that easily outline how the study is carried out or links to educative sources, are a few examples which allow the participant to actively acquire knowledge on the research program and to be truly aware of what she is given consent to[20]. The platform renders much more accessible communication and contact or re-contact of participants. The introduction of the dynamic consent tackles a problem, which is not often taken into account in the analysis of informed consent procedures, namely the one of minors. Owing to the right to amend participation terms to the study at any moment in time through dedicated pages, minors, at the coming of age, will be able to express their own will with regards to their biological samples and may revise previous instructions expressed by parents.

The dynamic consent presents undoubtable positive aspects as regards to aspects such as the autonomy of the participant, the effectiveness of information's communication, the involvement of the patient, the subsequent ability to control biological samples and the guarantee of receiving valuable information on one's health condition in order to reach a personalized diagnosis and treatment if needed[21].

7. Privacy and data management

Biological material collected from each participant is codified, or as the GDPR defines this process[22], pseudonomyzed using and identification number. During the whole process of analysis and study by researchers, secrecy and privacy is guaranteed as every sample and data of participants is labelled with the corresponding identification number. The key for the conversion from pseudonomyzed identification numbers to the actual identity of the participant, is in the hands of the coordinator of the project and few other persons responsible for the study and will only be used in rare cases upon prior authorization of the Ethical Committee. Data are stored in a dedicated network specifically set up for the population-based study, which is controlled by a central server regularly monitored and backed up[23].

Participants will give explicit consent to data management, but will have the right of rectifying it at any time giving disposition regarding the processing, analysis and sharing conditions. They can decide to ask for the destruction of their genetic and biological material or indicate the period that they want the material to be conserved and the purposes for which data can be processed. At the moment of withdrawal of consent from the study, the person should specify whether he doesn't want to be contacted anymore, however her data will be put to use for the purposes to which she gave consent in the first place or other research programs in an anonymous form, or whether she doesn't want her material to be used for any other

[20] Centro di Biomedicina, *op. cit.,* 2.4 Consenso interattivo per studi di lunga durata
[21] M. TOMASI, *op. cit.*
[22] GDPR, Art. 4(5), https://gdpr-info.eu/art-4-gdpr/.
[23] C. PATTARO, *The cooperative Health Research in South Tyrol (CHRIS) study: rationale, objectives, and preliminary results,* 5.

further study, but just to confirm already acquired results, or finally whether she wants her biological material to be destroyed.

The hospital of Merano and the dedicated biobank in Bolzano store the genetic material. The Institute of Biomedicine, EURAC research, has legal custody over biological material, however participant have full decision making power over their genetic material. EURAC aims at continuing this population-based study for at least 20 years. If the project fails to pursue its aims/last the biological material will be destroyed if the safety and privacy standards can no longer be secured. However the Institute of Biomedicine ideally intends to keep the material for the whole life of the participant. In the consent form, a special clause is dedicated to the management of the biological material in case of death. The participants decide whether she wants them to be destroyed, completely anonymized and eventually used for research purposes within the limits of the given consent[24].

The health care system can also ask to access biological material in order to conduct studies with similar aims as the ones of the principal study, but these have to be specified in the informed consent form.

With regards to data sharing, participants are informed of the fact that population-based study imply sharing certain data with other research institutes. There are different levels of protection according to the sensibility of the data in question. No particular issues arise with the practice of sharing results or aggregate data, as these types of information has already been processed and rendered impossible to link to an identifiable person. When talking about raw data, such as height, weight, glucose levels alcohol or drugs consumption or genotypes, which are granted an even higher level of privacy, the scenario changes completely. In order to share this knowledge, ad hoc Data Transfer Agreements (DTA) are required. For further uses of genotype information, the explicit consent of the participant is required. Lastly personal data are never exchanged, with the exception of specific instances provided by law. Partner research institutes and consortia have access to the aforementioned data within the limits provided by in the DTAs[25].

8. From Meran Hospital to Bolzano Biobank

Biological material collected at Schlander's hospital are shipped at a temperature of 4ºC to Meran hospital in a dedicated CHRIS laboratory. Temperature is monitored during transportation through a specifically designed software, which tracks temperature measurements by using electronic thermometers placed nearby samples. In Merano, clinical and diagnostic assessments on biological material is carried out. In addition, samples are store under cryopreservation. The collected material is then sent to the Bolzano biobank, where DNA extraction is performed. Monitoring of operation carried out inside the biobank, such as sample management or standard procedures on biological samples, is provided by a Biobank Information

[24]Centro di Biomedicina, *op. cit.*
[25] Centro di Biomedicina, *op. cit.*

Management System (BIMS)[26]. Access to biological sample is regulated according to an access regulation for both internal and external use. In addition, the biobank has joined the BBMRI, Biobanking and Biomolecular resources research Infrastructure, in order to provide protocols that guarantee high biological and medical research. An «Bioresource Impact Factor code», BRIF6107, was assigned to CHRIS biobank in Bolzano, which ensures transparency on the use of sample and data in addition to the tracking of bio-resources[27].

9. Legal issues

From a scientific standpoint, the contribution of such studies, of which we have numerous examples, are an extremely useful tool to discover the relation between genome-environment interaction, with the aim of eventually leading to a more accurate diagnosis and, as a consequence, to a specific and targeted therapy for patients. Population-based studies are a clear example of the way in which subjects intertwine and create complex scenarios, that expert and practitioners have to unravel. Genomic studies, such as the aforementioned one, raise convoluted issues regarding many aspects linked to legal definitions and regulation. As we saw with the CHRIS project, technological developments have led to a much faster and transparent communication with patients, have changed completely the way in which data samples are stored and the whole process of scientific research has been renewed. However, developments have to be shaped within a legal framework, indeed this is where the most challenging issues have been raised. Usual classifications of privacy, property or informed consent ended up being challenged in order to fit the needs of scientific development.

Infrastructures such as population biobanks have been developed since the past century to provide for an ad hoc instrument to store biological material and the significant amount of data, that is involved in population-based studies. However the storage conditions and management criteria depend on various elements. At first a classification of the different identifiable types of biobanks is going to be provided. Biobanks can vary substantially from one another depending on various factors: how long have samples been in existence, whether data collection is aimed at being retrospective or prospective, whether samples are collected for research aimed result or whether there is also a clinical dimension involved, the types of samples that are stored and analyzed (e.g. tissues or DNA), the diseases that are investigated (common or rare diseases), the ownership of samples, whether they are financed by a public body or for commercial reasons only to mention a fews[28]. Because of the multiple variables that have to be taken into

[26] C. PATTARO, *The cooperative Health Research in South Tyrol (CHRIS) study: rationale, objectives, and preliminary results,* 5-6.
[27] *Ibid.*
[28] D. SHICKLE, M. GRIFFIN, EL-ARIFI, University of Leeds, *Inter- and Intra-Biobank Networks: Classification of Biobanks*, in *Pathobiology*, 2010.

consideration, it is particularly cumbersome to categorize biobanks through the use of specific groups. However a characterization is possible if we take into account single factors that are relevant in our discussion. For the scope of this paper the elements that are going to be analyzed are: the group of participants/donors, type of specimen collected, purpose of sample's use and supporting institution/ownership. The first variable regards the type of subject involved in the study and substantial distinction is drawn between population-based biobanks, where specimen of a portion of an identified society is collected, and disease-oriented biobanks, collecting specifically donors affected by a peculiar disease. A further distinction might be made on the basis of the specimen collected; three main categories are identified: DNA banks, Cell banks and Tissue bank (for example brain banks). The aim for which specimen is stored is a supplementary biobank characterization criteria, according to which research biobanks, biobanks for transplantation purposes or biobanks for therapeutic purposes can be distinguished. Finally biobanks are characterized on the basis of the institution supporting the infrastructure such as hospitals, universities or non profit organization. The groups that we just described regard mainly human samples biobanks, however these infrastructures may be also employed for storage of animal biological material or plant samples[29]. It is important to determine the type of biobank and the use for which sample are stored. Furthermore the governance of the biobank changes if stored samples derive from patients or healthy individual. The aims and limits outlined in the informed consent procedure play a fundamental role in the management of the biobank. Last but not least, national and international binding and non-binding rules direct the storage conditions and governance. At international level one of the most relevant legal instruments is the Oviedo convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine of 1997 and it provides the basic safeguarding principles for human subjects regarding scientific development. The main issue is that the principles contained in it are mandatory only for states that have ratified it. A pivotal aspect with regards to the Oviedo convention is that in one of its Recommendation, precisely Recommendation on research on Biological Matters of Human Origin, there is a specific reference to biobanks. The specific provisions within the recommendation provides for the protection of persons' rights with regard to secondary uses of samples for instance, it requires that an independent oversight shall be present within these institutions, that communication regarding activities shall be regularly provided. When turning to the European framework no specific piece of legislation has been introduced regarding biobank-centered research. Directive 2001/20/EC on clinical trials does neither refer to biobank-based research nor to the use of biological samples in research areas, however the principles enshrined in the directive and in the data protection regulation, recently entered into force, provide the main standards for storage conditions and

[29] A. Arampatzis, I. Papagiouvanni, D. Anestakis, M. Tsolaki, *A classification and comparative study of European Biobanks: and Analysis of Biobanking Activity and its Contribution to Scientific Progress*, in *Archives of Medicine*, 2016.

governance within the European Union. Because of the lack of pertaining legislation on the subject matter, at European level the legal framework is quite diverse. There have been governments implementing specific acts on biobanking activities and two main approaches can be identified: implementation through the use of specific legislation, such as in Sweden, or through the incorporation of provision within wider administrative and legislative instruments. Despite some divergences in the procedural aspects of implementation, some convergence is present with regards to the content of regulatory instruments: supervision should be carried out by competent national authorities, such as the national data protection authority; suitable security measures should be introduced to protect biological samples and the identity of the donors, for example pseudonomyzation of biological material; research ethics committees should assess research projects that are relying on biological samples or the possibility for participants to withdraw consent and when requested or expressly regulated the destruction of samples. These similarities may be a starting point to reach a higher level of specific regulation at European level as well, in order to promote the sharing of samples to reach meaningful findings[30]. The first time the term "biobank" was mentioned in international literature was in the 1990's and since then it has been a major topic of interest and study for researchers and practitioners, because of the ethical, scientific and legal issues that it carries with itself[31]. Not to mention the spread of such infrastructures for the collection of biological samples, both in large centers and in hospital. Such initiatives have been also promoted by private bodies in order to offer banking services for the storage of biological materials. Consortia, such as GIANT or BioShare, have been set up, given the rise of such services in order to aid and promote the sharing of meaningful information, alignment in terms of procedures and ethical guidelines and coordination when dealing with privacy and informed consent[32].

Development in scientific and biological knowledge has shown that biological samples and data carried within, cannot be separated, because of the enormous informational capacity contained in tissues, blood, urines ecc. From a legal standpoint, there is the need to have a series of guidelines at the international level to regulate these developments in terms of managements of samples, privacy of the patients or participants, renewed consent procedures and finding ways to adapt current needs to traditional legal categories. As we can master, a number of complex legal arguments may be analyzed, however property rights assignments on biological material and informed consent procedures, in the realm of recent European legislation, are going to be dealt with in this paper.

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[30] European Commission, Directorate-General for Research and Innovation, *Biobanks for Europe A challenge for governance,* report of the Expert Group on Dealing with Ethical and Regulatory Challenges of International Biobank Research, Publications Office of the European Union, 2012.

[31] M. MACILOTTI, U. IZZO, G. PASCUZZI, M. BARBARESCHI, *Legal aspects of Biobanks, Pathologica,* 2008, 102-115.

[32] C. PICIOCCHI ET AL., *op. cit.*

10. Property rights and biological material

Before considering the various aspects of property rights and biological material, it is important to recall that one particularly cumbersome feature arises from the needs of medical researchers to utilize biological materials for experimentation, while at the same time maintaining the privacy of individuals. Biological material constitutes a primary source of genetic data. Such an informational dimension of biological sample, rather than a mere "material" dimension, renders the job of protecting privacy, self-determination and property more difficult for law practitioners[33].

The assignment of property rights is a particularly delicate issue when talking about scientific research. Who owns biological samples and tissues? Many solutions have been proposed, however this question remains a very delicate one and with no unequivocal answer. There is no doubt in stating that some tissues can be defined as property of the donor, such as hair or organs, however biological samples, relevant to conduct research, have unique features, such as their reproducibility. There are many theories trying to untangle the convoluted relationship between biological samples and property rights, that stems primarily form the inestimable value in terms of genetic information contained in them. When talking about genetic data, a pivotal aspect to recall is that this type of knowledge is valuable to trace back genealogical links and to carve out relevant genetic information regarding the donor's family, that may be a source of discrimination or be used in an economic setting.

Property rights are a legal category adopted when describing a relationship between an individual and an object, from which a series of rights arise, that the individual can exercise on the latter. The right to use and dispose, the right to sell, the right to exclude third parties form the use of the object in question are just a few examples of such rights. When considering biological samples as the "res" in question, we realize that the number of proprietary rights that the donor can exercise on his or her own biological material is limited. The object in question, from a legal point of view, is regarded as being "extra commercium". Legal economists argue therefore that it is controversial to assign proprietary rights on biological tissues outside the boundaries of a market system. In addition to that, it is questionable to claim that the donor benefits from having ownership on his or her biological material. The knowledge and expertise to carve out relevant information from his or her biological material is usually absent. The solution is considered to be inefficient form an economical point of view, as the potential relevant knowledge contained in biological samples, that can be relevant for healthcare improvements, cannot be accessed from an ordinary citizen. Lastly, the autonomous management, by the donor, of knowledge that is obtained from biological material poses issues related to the genealogical links that genetic material establishes. Information contained in biological samples is pertaining not only the subject from which the material is extracted, but is characterized instead by a collective dimension. When granting the possibility exclusively to the donor to manage the

[33] M. MACILOTTI ET. AL., *op. cit.*

informational dimension of biological material, discrimination and privacy issues may arise in relation to other people sharing the same characteristics[34].

On the other hand, assigning proprietary rights solely to researchers involved in the studies of such biological samples, is equivalently questionable. The limits of this solution are that the donor is completely excluded form the management of his or her biological material, not to mention privacy and discrimination issues that would arise in this case scenario. From the above analysis, we deduce that an alternative solution must be identified in order to overcome difficulties when combining regulation and research on human samples. There is the need to respect the will and privacy of donors, while ensuring that scientific progress in fundamental matters, such as medical research, is not hampered. What has been done in biobanks is deal with biological material as a carrier containing data useful for scientific research. In order to be able to utilize human samples without overstepping the limits of the donor's privacy, biological material has been anonymized and treated as a mere physical support.

The project in analysis in this paper, namely the CHRIS population-based study, specifies in the informed consent module that EURAC research is designated as having legal custody of biological material, however not exercising full proprietary right on samples, as selling genetic material is not allowed and the participant can ask in any moment to destroy his or her samples[35]. However the Institute for Biomedicine of EURAC Research will have intellectual property over eventual results, findings or discoveries arising form the research project[36].

11. Informed consent procedures: issues and developments contained in the GDPR

The relationship between participants to research projects and research institutions is based on informed consent procedures. With regards to population-based studies, consent given by participants pertains the conservation and use of biological samples that are donated on a voluntarily basis. The informed consent procedure informs participants that privacy, during the conservation in biobanks and during the handling of samples in research centers, is guaranteed. In the Italian scenario, the Authorization of the Privacy Guarantor on the basis of article 90 of legislative decree 196 of 2003 set out a series of guidelines in relation to the content of informed consent procedures. Information provided to participants must be extensively illustrating the purpose and aims of the research project, outline in detail the type of samples that are going to be stored and processed, possible results that are going to arise form the storage of genetic data and explain the right of opposing to the storage for legitimate motivations. In addition, it must be recalled to the attention of participants that their consent should be given freely and voluntarily and it

[34] M. MACILOTTI ET. AL., *op. cit.*
[35] Centro di Biomedicina, *op. cit.*, par. 6.
[36] Centro di biomedicina, *op. cit.*, par. 11.

can be revoked at any time without implying consequence in terms of discrimination of the individual[37]. This peace of legislation has been replaced in 2018 with legislative decree 101/2018 amending the Italian Privacy code in order to comply with European legislation recently introduced. Genetic, biometric or health-related data can be object of processing if in compliance of with the requirements outlined in the General Data Protection Regulation (consent, necessity of complying with obligations or exercising rights of the holder, necessity of safeguarding vital interests of the holder).

From a legal standpoint, on the 25th of May of 2018 we witnessed the entry into force of an important piece of legislation of the European Union. The General Data Protection Regulation n. 2016/679 is repealing the previous legislation pertaining data protection, Directive 95/46/EC. The regulation has a wide scope of application and among the fields that are interested by it, some articles lay down important principles when it comes to scientific research and the protection of natural person's data. Importantly the regulation touches upon the notions such as the ones of genetic data, consent procedures, management of data in scientific research environments and a number of rights granted to natural persons. With regards to procedures of informed consent and the consequent relationship established by it between patients and researchers, a number of guidelines are provided, that to some degree elucidate from the legal point of view the management of data in scientific research giving a harmonized definition in the European context. Overall the regulation takes into account the field of research, although it is touched upon from a wide and to some extent unclear perspective. The most relevant articles affecting population-based studies, bio-banking and informed consent procedures are going to be analyzed next.

In the introductory part, precisely in article 4, the GDPR provides definitions such as the one of pseudonomyzation (5), consent (11) and genetic data (13), that are particularly relevant for population-based studies such as the one in question. Pseudonomyzation «means the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person»[38]. This principle is particularly relevant in the management of data within biobanks and over research periods in order to protect the donor's privacy and exclude issues of discrimination. As we have previously seen, within the Biobank of Bolzano and over studies conducted by researchers of EURAC institute on biological measure, this measure has been adopted to ensure anonymous handling of biological samples.

Secondly, the regulation addresses in an extensive way the principle of consent, which is both defined in Article 4(11) and consequently dealt with in Article 7. Consent should be intended as being the «freely

[37] M. MACILOTTI ET. AL., *op. cit.*
[38] GDPR, Art. 4(5).

given, specific, informed and unambiguous indication of the data subject's wishes»[39] . Article 7 analyzes core issues related to it such as the right of withdraw, specifying the fact that «it shall be as easy to withdraw as to give consent»[40]. In research fields, it is pivotal that the requirement of withdrawal is ensured, as in addition to the respect of the will of the donors, the objects in question are meaningful health and genetic information. The GDPR, in Recital 33, deals with an issue that is very controversial and problematic in the area of informed consent procedures. The regulation recognizes that in most research projects specific procedures and further uses of the donor's data is unknown in the moment in which the consent procedure is carried out. It is therefore challenging to obtain consent that covers all possible uses to which data may undergo, therefore the Recital states that «data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognized ethical standards for scientific research»[41] allowing the drafting of more broad consent models. Under Directive 95/46/CE this was not allowed, in particular consent models had to be tailored around a specific purposes and data subjects had to consent to that each specific uses of samples. However, data subject are still granted the possibility of giving consent to data processing to parts or areas of research projects only. Article 9 of GDPR establishes that processing of data relating to natural persons capable of leading to discrimination issues, such as race, sex preferences, religion ecc., shall be prohibited. The matter is elucidated in paragraph (2)(j), which constitutes an exception to the previous paragraph allowing processing of such data «for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes»[42], specifying further in Article 89(1) that ad hoc safeguard should be set up such as «technical and organizational measures»[43].

Recital 50 addresses the issue of «further processing of personal data» which is closely linked to research study environment, as in the aforementioned case of the MICROS population-based study in relation to the CHRIS project. It is importantly stated that further use of personal data initially collected for a different purpose should be allowed when «compatible with the purposes for which the personal data were initially collected». Moreover it is affirmed quite vaguely that «further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes should be considered to be compatible lawful processing operations»[44].

Last but not least, the regulation sets for a number of rights of the data subjects that must be present in informed consent procedures in order to inform in a clear and transparent way aims and rights in the hand

[39] GDPR, Art. 4(11).
[40] GDPR, Art. 7(3).
[41] GDPR, Recital 33.
[42] GDPR, Art. 9(2)(j).
[43] GDPR, Art. 81.
[44] GDPR, Recital 50.

of participants to population-based studies. Article 13 lists a number of requirements that need to be provided to data subjects from which the data is collected: relevant paragraphs with regards to informed consent procedures are: (1)(c), specifying the purposes for which the data will be processed and clarify the legal basis of the processing; (2)(a) establishes a period of time for which data is going to be conserved; (2)(b) provides for the «existence of the right to request from the controller access to and rectification or erasure of personal data or restriction of processing concerning the data subject or to object to processing as well as the right to data portability»[45] and finally and perhaps most importantly (2)(c) settles the right of withdrawal of consent. Overall the CHRIS project grants a wide range of rights to participants in order enhance the possibility of self-determining their biological material. EURAC institution, as we have previously seen, provides for an ad hoc webpage for each participant, in order to be able to exercise these rights in an easily and quickly accessible manner. Information is provided to donors through multiple channels from the recruiting phase and during the project itself. Local media, public meeting and informational online platforms educate the population of Val Venosta on the specific uses and aims for which their data are going to be analyzed and stored. More specifically, the exercise of the rights outlined in art. 13(2)(b) is rendered possible through dedicated web-pages, where donors may change the possibility of accessing and processing their data according to their fundamental values and beliefs. The CHRIS project is in compliance with art. 13, as it recognizes the right of participants to withdraw their consent to the project and consequently, it leaves a range of possibilities with regards to the future use or non-use of biological samples. A relationship of transparency and communication with the local population has been understood as one of the means to reach successful and meaningful results, therefore particular effort has been put in place in order to develop the aforementioned platforms granting a wide range of rights to participants.

12. Conclusion

In this paper we analyzed how a population-based study is carried out by taking into consideration a specific case study, the CHRIS Project in South Tyrol. We have focused on two specific legal issues, property rights and informed consent procedures, and eventually evaluated the position adopted by the governance of CHRIS in relation to these two legal issues. With regards to informed consent procedures, we tried to carve out the relevant guidelines provided by the General Data Protection Regulation 2016/679.

The case study that has been displayed shows how issues related to data management, privacy concerns, trust relations between research institutions and participants, can be brought to a higher standard through the use of ad hoc IT systems and particular tools rendering contact with the participatory population much more easier and transparent. Over the whole duration of the study, participants are enabled to freely

[45] GDPR, Art. 13(1)(c), Art. 13(2)(a).

change their mind on the consent conditions, that they previously accepted, granting a high degree of freedom of choice to donors and tackling some of the core issues arising from the changing nature of research. Both with regard to the consent procedure and the management of samples over the research period, CHRIS governance has provided for many essential requirements arising from the General Data Protection Regulation, such as the pseudonomyzation of sensible data over storage and research stages, allowing fast tracks for withdrawal of consent to the project or providing for a broad and dynamic consent model.

The case study has elucidated the fact that a flexible approach to management and regulation has to be adopted, when dealing with these realms of scientific research. In order to adequately cope with ethical, scientific and legal implications, a strict and uniform path would be of no help. The need of closer communication between private actors, such as research centers, and public institutions is crucial to overcome legal and ethical obstacles to a more transparent and tailored-around- projects research. Legal tools have to be provided, however, in order to carry out research in the most virtuous manner, a relation of trust has to be unceasingly built between researchers, law practitioners, but, most importantly, with ordinary citizens, that are willing to donate the of inestimable value data contained in their cells. Therefore, citizens need to have the possibility of accessing the maximum standard levels of intelligible scientific knowledge, in order to be able to choose the faith of their genetic heritage. This will be the driving force behind a more developed relationship between all actors involved in scientific research.