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RESEARCH ARTICLE

Genetic Research: The Role of Citizens, Public Health and International Stakeholders

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Abstract:

Background:

Genetic research has become an indispensable instrument for medical research, and the subjects involved have both divergent and convergent interests.

Objective:

The possibility of having more detailed genetic information undoubtedly offers benefits for the health of the subject, but could also pose risks and make the subject vulnerable to discrimination.

Methods:

The scientific community has viewed very favorably the public health utility of family history, in which data from a family whose members suffer from chronic pathologies is collected and filed, in order to develop a sort of "stratification of family risk."

Even though in the last decade the scientific and juridical literature has contributed greatly to the topic of biobanks, the perplexities that continue to surround this theme give the idea that current ethical protocols on research are inadequate.

Results:

Researchers, citizens, International stakeholders, mass media, Public Health and Governments play a key role in genetic research. It is obvious that the methods used for genetic research do not present intrinsic risks; they are much less dangerous than other activities of diagnosis and research. Before authorizing a research project, it is important to reflect on the responsibility and transparency of the studies to be conducted, and on the impact they may have on the interests of public health.

Conclusion:

We believe that the highest priority need is to develop a common language on the theme, as is the case in the sphere of clinical experimentation where rules of good clinical practice, albeit at times conflicting, have led to uniform convergences in the scientific world on the points to be actuated.

Keywords: Biobanks, Genetics research, Role of citizens, International stakeholders, Public health, Chronic pathologies.

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1. INTRODUCTION

DNA is "the deepest and most essential patrimony of the human person" [1], because it is shared with other people from the same geographical area. It may predict future events or the

possibility that may occur. It is easy to obtain, and can be of interest to third parties [2] such as family members, insurance companies and employers.

Therefore, there is great interest in this information, especially since genetic predisposition has been clearly demonstrated for various diseases such as cardiovascular pathologies [3, 4] diabetes [5], late onset Alzheimer [6], schizophrenia [7]

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bipolar disorder [8], autism [9], cancer [10 - 12] and rare diseases [13].

The collections of tissues derived from human bodies and used for the extraction of genetic material have become known under various names such as biobanks, biolibraries, tissue repositories, genetic databases, or DNA banks.

The OECD defined human biobanks and genetic research databases as 'structured resources that can be used for the purpose of genetic research, which includes human biological materials and/or information generated from the analysis of the same; and extensive associated information [14]

Samples used for genetic diagnoses or purposes closely related to genetic data are collected in a genetic biobank [15]. These collections have the particular characteristic that the identity of the donor can be connected to his/her personal, genealogical and clinical data.

The purpose of genetic biobanks [15] is to support research to identify the mutations that cause genetic diseases, since they permit researchers to collect material from families affected by the same pathology, with an enormous saving of energy and funds.

There has been an acceleration in the study of "complex diseases" [16] whose etiopathogenesis involves both genetic and environmental factors, as the existence of biobanks has enabled greater comprehension of pathogenetic mechanisms, development of new diagnostic instruments and the design of treatment strategies [17]. The enormous number of samples available has made it possible to identify a distinction between "susceptibility" and "genetic causality."

Another particularly fertile field for genetic research is that of chronic pathologies. The *Evaluation of Genomic Applications in Practice and Prevention* (EGAPP) [18], created in 2004 by the *CDC National Office of Public Health Genomics* in the United States, has studied the genetic aspects of many tumoral pathologies by referring to samples in biobanks, with good applicative outcomes.

At the same time, when biobanks facilitate the study of various factors of genetic risk related to an illness, they potentially influence the societal conceptions of responsibility, group identity and future options [19].

In fact, new quandaries emerge when genetic research identifies groups of subjects who carry genes that place them at higher risk for a disease. These "individuals at risk" fall into a disease category that is ambiguous because of the slippage between the risk factor and the disease itself [20]: they are not ill, but may become so. How should they be treated? As sick people? As healthy people at risk? Should they be counselled not to have children? Should they be subjected to higher health insurance premiums? Epistemic change influences cultural change, and in this case can lead to the creation of a cultural current that views genetic research with suspicion.

In the scientific literature, genetic exceptionalism [21, 22] is the line of thought according to which all the information derived from DNA, because of the intrinsic characteristics of the genetic patrimony, must be considered a separate category from the common information that can be deduced from in-

depth family anamnesis, and should be afforded particular protection.

The need for genetic privacy [23] is fueled by the fear of discrimination, social stigmatization, family problems, loss of control of one's identity, as well as the psychological implications, because genetic information can be "potentially embarrassing and uniquely personal" [24].

This issue entails not only political but even more importantly ethical and social choices, because the fundamental rights of the person are involved, as well as individual and collective interests.

2. METHODS

In this work, we will discuss the role that researchers, physicians, ethics committees, citizens, public health officials and international stakeholders can play in the promotion and control of genetic research that draws upon biobanks. We will examine the current situation in Italy and compare it with that of other Western countries.

3. RESULTS AND DISCUSSION

3.1. Physicians/Investigators (And Research Ethics Committee)

To date, the lack of a common legislative framework in Europe and the world has allowed local researchers considerable independence, but has limited the ability to create transnational biobanks [25], a significant exception being the EuroBioBank, "a network of biobanks that stores and distributes quality DNA, cell and tissue samples for scientists conducting research on rare diseases genetic material and rare diseases" [26].

However, recent years have seen a growing awareness that transnational collaboration is essential researchers have access to a greater quantity of biological samples. It is no coincidence that in the recent years there has been an increase in the number of transnational associations and entities involved with genetics, which permit the circulation of ideas in various affiliated nations. An example is the P3G Consortium [27], an international not-for-profit organization that catalogues experiences in the field of population genetics, in order to build common research strategies to facilitate harmonization and open the door to future collaborations. Another valid example of openness in this sense is the pan-European Biobanking and Biomolecular Resources Research Infrastructure - European Research Infrastructure Consortium (BBMRI-ERIC [28]), whose funding includes a grant from the European Unions' Horizon 2020 research and innovation program.

In this context, it is noteworthy that in multicentric studies, data are often collected and then transmitted to third parties.

That operate in different nations, which in turn have different sets of legislation on the subject, but this by no means exempts those who receive this data from responsibility for the correct handling of the information. It is extremely important that the personal data remain the exclusive prerogative of the research, and not be exploited for purposes other than the research itself.

The scientific community has viewed very favorably the public health utility of family history [29], in which data from a family whose members suffer from chronic pathologies is collected and filed, in order to develop a sort of “stratification of family risk.”

These few examples help us understand how essential it is to expand the borders of genetic research to improve public health.

It is obvious that the methods used for genetic research do not present intrinsic risks; they are much less dangerous than other activities of diagnosis and research. However, there is an “information risk” for the patient [30], who may suffer psychological harm from receiving the genetic test results themselves or from the way the results are conveyed, or for the patient’s relatives, since the results may have repercussions for them as well.

In order to deal with these ethical and legal implications, North American organisations, followed by European Union ones, have published guidelines or ethical codes that serve genetic professionals on an international scale. Another issue to be faced is the problem of incidental findings discovered in the course of the research. The committees of the Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) Network [31] asserted that researchers must limit themselves to informing participants about the research results; they have no moral obligation to undertake clinical tests on the basis of these results, according to the principle that clinical research is distinct from medical care in both its aims and its guiding moral principles. However, physicians are required to provide complete information expressed in terms that the subject can understand. In addition, once the information has been obtained from the genetic tests, physicians will tend to give more or less importance to certain data on the basis of their scientific and cultural formation.

Obviously, the problem is complicated in the case of anonymous samples: on the one hand, donors cannot be informed if a genotype at risk is revealed, but on the other hand, they do not run the risk that their genetic data may be misused.

Anonymization of data in the constitution of biobanks is of particular importance because it entails the irreversible loss of the connection between personal data and genetic information. The connection constitutes the added value of biobanks. When biobanks are established, the decision whether to anonymize data or not is of crucial importance. When the connection between personal data and genetic information is irreversibly eliminated, donors are protected from misuse of their information. However, it is also true that the ability to know the identity of the donor of a sample is an added value, as donors can be informed of findings that may prove crucial to their health and well-being.

The first to grasp the importance of this aspect were the Scandinavian nations. For example, a 1999 document of the “Swedish Medical Research Council [32]” defined biobanks as collections of human tissue samples, the origin of which must always be traceable. Italy lacks a national law on the subject, but the 2016 Authorisation for the use of genetic data prepared by the Guarantor for the Treatment of Personal Data states that

the treatment of genetic data is allowed only for purposes of prevention, diagnosis or treatment of the subject, or of scientific research, or for purposes of proof in civil or penal cases, according to the dictates of law.

Thus Italy allows scientific research on genetic material, as long as it respects the rules set forth in the Authorisation for the use of genetic data. Instead, there is no specific legislation on the establishment and use of biobanks.

Of central importance in this legislative vacuum are the ethics committees [33], which evaluate the ethics of studies on genetic data, and also express opinions on research programs that involve the study of data or samples when for particular reasons it is not possible to inform the donors [34 - 36].

Serious vigilance on the part of the Research Ethics Committee and self-control on the part of researchers are the basis for credible genetic research that respects human dignity.

3.2. The Role Of Citizens

The possibility of having more detailed genetic information undoubtedly offers potential benefits for the health of the subject, but could also pose risks and make the subject vulnerable to discrimination in cases in which the genotype is used to draw conclusions about the phenotype.

Early knowledge about one’s own genetic characteristics and the probability of contracting a pathology provides the basis for taking preventive measures. In the case of a multifactorial disease, that is, one in which there is an association between environment and genotypic characteristics, steps can be taken to prevent the pathology by adopting changes in lifestyle, diet, work and the environment itself.

But knowledge of genetic information can change an individual’s self-perception and deeply influence the character of his or her social organization, in cases in which the genetic patrimony could be an obstacle to a certain type of work. There could also be significant implications for family planning. *For example*, if a couple is aware that one of them has a predisposition to a genetic disease, they may choose not to have children [37]. Or when Non-Invasive Prenatal Testing (NIPT) are performed, information about the fetus could induce a disproportionate and unjust recourse to abortion in nations that permit it, becoming a form of biological eugenics [38, 39] or of “positive eugenics [40]”, the goal of which is to avoid unfavorable medical conditions [41], rather than impose a genetic structure on future generations [42].

According to the Denver Post [43], 80 to 90 percent of women who receive a positive result from an amniocentesis test for Down Syndrome choose to terminate the pregnancy. Their decision is not made on the basis of a moral evaluation [44], but is grounded in concern about how having a Down Syndrome child will affect their life as a couple.

Clearly, knowledge about the fetus’ state of disability can give the couple greater awareness of their situation as parents, whether they choose to terminate the pregnancy or prefer to continue with the birth of a disabled child.

It is fundamental that citizens be well informed, so that they will not make extreme choices that lack grounding in valid science, or worse, refuse to consider genetic testing to under-

stand their health problems.

The scientific community has been reflecting for many years on the need to inform citizens adequately about the issue of genetic research. In this regard, numerous international studies have explored people's awareness about the risks of genetic engineering, their rights to receive or give information (including the responsibility to family and society), and their involvement in public debate on genetics. One example is the "European COB [45]" - Challenger of Biomedicine, Meetings and Minds.

The committees of the Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) Network [46] assert that participants in research, if they have given informed consent, must be informed of the results of a study and participate in an appropriate clinical follow up.

It is evident that directly involved citizens, such as those suffering from neurodegenerative pathologies or cancer [47], are more likely to donate their tissues and support the establishment of biobanks designed to study their pathology, while the average citizen for whom this issue has no relevance, or members of ethnic or religious minorities, tend to be reluctant to participate in genetic studies.

While it is commonly accepted that a patient who participates in a genetic study must be thoroughly informed, it is not so obvious that average citizens involved in population studies' must be educated about the new technologies and their use, or the risks and benefits to the community they may pose

This issue came to international attention in 1996, when Icelandic citizens gave explicit consent for an initial collection of DNA and implicit consent for a second one for the deCODE Genetics [48] study, which also gathered sensitive health-related data archived in the nation's Health Sector Database. There was international debate on the importance of transparent provision of information so that citizens are fully aware of the ramifications of their involvement.

Since 2005, numerous conferences on the subject have been organized with the participation of the community of scientists and bioethics specialists, and representatives of organizations of patients. The conclusions drawn at these gatherings have stressed the need for developments in legislation and monitoring systems. They have also emphasized the importance of avoiding pressure from economic interests and providing equal access to treatment. They have stated that freedom of choice is paramount, and have discussed the decision-making powers of ethics committees.

They have pointed out that the lack of public participation in the debate regarding new genomic technologies [49 - 51] highlights a deficit in Western democracies, while, conversely, active involvement promotes social justice, confirming Kant's view that all people and their points of view on the issue are important [52].

If the national healthcare system were able to identify families or entire populations that have a predisposition to certain genetic diseases, it could establish prevention and early treatment programs for these categories. If, instead, citizens do

not wish to participate in genetic screening programs, the healthcare authorities will not have the data they need for identifying these predispositions, and consequently the subjects at risk will not benefit from actions the authorities might have been able to undertake to identify and treat these categories of at-risk citizens. By now it is clear that patients need to take on a key role in genetic research [53], not only because doing so directly provides material for studies, but also because they can influence their governments' choices about the research programs to be undertaken to improve the general health of the nation.

Certainly, it is not possible to foresee exactly how discoveries related to genetics will affect a society. *e.g.*, the pharmaceutical industry could bring very effective drugs to the market but charge exorbitant prices, affordable only to a few citizens. On the other hand, the total opposite could happen. Therefore, while today it is impossible to answer questions about distributive justice, it is nonetheless important that civil society be aware of these issues and observe future developments in biobank-based research with an eye to this important aspect.

Citizens who make available their own body or health data when they participate in epidemiological studies or research on a disease can benefit from the opportunity to know the biological characteristics of their own state of health. Just as important, their choice demonstrates the importance of social solidarity, because their entire community benefits from the knowledge acquired from the study. In fact, citizenship in a community is a source of rights, but also of responsibilities toward that community.

The duty of social solidarity was emphasized by the Universal Declaration on the Human Genome and Human Rights, adopted unanimously by UNESCO in 1997 [52, 54], which is the first document of universal importance in the field of bioethics. It was written to provide ethical and legal principles for the promotion of freedom of research, human dignity, solidarity and international cooperation.

Subjects who voluntarily participate in genetic research or who are invited to participate, because of clinical reasons or for purposes of statistics, must be informed about the consequences of having a genetic test done or not having it done.

Social solidarity may strongly influence the decision of citizens to participate in genetic research in the interests of benefit-sharing. As stated in the Declaration on the Human Genome [55] (1997), "Benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual. Freedom of research, which is necessary for the progress of knowledge, is part of freedom of thought. The applications of research, including applications in biology, genetics and medicine, concerning the human genome, shall seek to offer relief from suffering and improve the health of individuals and humankind as a whole (art. 12)".

The HUGO Ethics Committee [56] (2000) approved a declaration on the sharing of benefits from genetic studies, which should not only have positive effects for the health of subjects involved in the research, but also should provide broader and more immediate gain for these communities in terms of investments in welfare by private firms that benefit

financially from the samples donated.

The HUGO [57] Statement on human genomics databases (2002) also indicates that these biobanks should be “global public goods” and that there should be “fair and equitable” distribution of the benefits of research. It also called for recognition of the rights of researchers, institutions and business entities to a “fair return” for their intellectual and financial contribution (recommendation 6).

On the basis of social solidarity and the duty of subsidiarity of citizens who participate in genetic research, some authors [58 - 60] have proposed using biological samples for future research even without specific informed consent, or when there is a generalized consent that allows any kind of future research without specifying the details. In this way, citizens would not benefit personally from the research but could contribute to the common good in terms of public health.

Others go much farther, perhaps in doing so undermining social solidarity. Some authors have proposed dynamic consent, obtained through the use of new computer technologies to reach patients [61]. This method of acquisition of consent, through a digital communication interface, facilitates two-way communication to stimulate a more engaged, informed and scientifically literate participant population where individuals can tailor and manage their own consent preferences.

Regardless of the method used to obtain informed consent, it is evident that studies on genetic material have significant ethical-legal and social reverberations, and thus great caution is required in governing access to the data, as well as in controlling how it may be made public.

Just think of how insurance companies could use genetic data of members of the genetic underclass [62] (the subclass of people who do not have access to healthcare coverage for “genetic” reasons) or how pharmaceutical firms [63] might discriminate against less widespread genotypes, for whom bulk drugs are ineffective: these minorities of individuals with particular genotypes would end up not receiving drugs specifically for them.

3.3. Mass Media

In this context, according to the Council of Europe [64], the mass media play an important role in the spread of information about genetics, and are key to promoting the citizen participation in the discussion on the human genome.

In the case of the UK Biobank and that of the Icelandic deCODE Genetics project, the mass media encouraged the legitimacy of the existing research infrastructures.

3.4. Public Health And Governments

Since the early 1990s, the establishment of biobanks has been considered an attractive economic activity [65] because the results of scientific research based on biobank samples could serve in drug development, could inform disease prevention policies, and could be useful to insurance corporations in designing and adapting policies. The problem is that this economic aspect can undermine the social solidarity that motivates the donation of these tissues from which genetic data can be obtained. Economic interests could come to outweigh

the needs of medical science, and thus the benefits of the results obtained would not be shared with the very populations who were the object of the studies.

The potential alliance of public healthcare policies and genetic research depends on choices currently being made.

The task at hand is certainly difficult because entire chapters of the education and perception of scientific knowledge must be re-written, with the unavoidable emergence of new responsibilities (who should manage a national biobank, and how should it be run?)

A new approach is needed for the classic themes of ethics such as informed consent and data security, as well as autonomy and privacy (either in an existential sense or as a practical problem of confidentiality [66])

In our opinion, a government-run national biobank would best protect the interests of the people who donated tissues.

The literature on the theme provides no uniform interpretations of the role of genetics in public health: many countries tend toward total interference of research in the life of citizens (*e.g.*, Denmark [67, 68], Belgium [69], Iceland, and Australia [70]) while others have taken a more prudent approach, that is, they have not created national infrastructures, but, as in the case of Italy, have many small collections at public or private institutes.

The difference between the two approaches is substantial. When a national government acquires and uses genetic data from its citizens, storing this information in a national databank, an individual’s genetic information can serve health of the entire national community. Instead, when genetic data is stored and used by a number of many small public or private institutes, an individual’s genetic information can serve his or her family and a few involved individuals, such as spouses.

Clearly, in both choices, it is important to identify new responsibilities and opportunities, not only those gained but also those lost [71].

We do not believe that the best choice is “total interference” by the government, as in the example of Iceland, in which a national government gathers genetic data on all its citizens and uses this information to define nationalized healthcare initiatives to meet needs that may arise. Instead, we think it important to promote the culture of the establishment of a biobank to obtain useful results for families and all of society.

The greater the number of samples collected in a national biobank, the more feasible it is for genomic analysis to move from scientific, clinical, governmental and commercial settings to that of personalized genomic medicine for the nation’s citizens. However, what will happen if “stratified medicine” [71] becomes “stratified markets”? When the potential sales to certain subgroups or entire nations are too insignificant to merit investment by pharmaceutical firms, these people could end up lacking the “personalized genomic medicine” that could cure their health problems. Would this social injustice be addressed by their governments, which, after all, promoted a national biobank of its citizens’ biological samples?

Before authorizing a research project, it is important to reflect on the responsibility and transparency of the studies to

be conducted, and on the impact, they may have on the interests of public health.

3.5. International Stakeholders

The theme of the human genome has been addressed in terms of respect for human dignity and the fundamental rights of the person by numerous international documents, such as the Recommendation of the Committee of Europe regarding genetic data and tests [72], the 1977 Convention on Human Rights and Biomedicine, the 1997 UNESCO Universal Declaration on the Genome and Human Rights, the EU's 2000 Charter of Fundamental Rights, the November 1996 Code of Conduct of the International Labour Organization on the protection of the personal data of workers, the Helsinki Declaration of the World Medical Association (June 1964 and successive modifications), and the European Commission Working Document on Genetic Data adopted March 17, 2004 by the Working Party for the Protection of Individuals with regard to the processing of personal data.

The Treaty on the Functioning of the European Union (TFUE), in requiring institutions and organisms of the EU, as well as the member states, to respect the free circulation of personal data in the exercise of activities that have to do with the application of the law of the Union (art. 16) also established that "independent authorities" (instituted by law CE/2001/45 e and reasserted by the new Regulation (UE) 2018/1725) should supervise this.

Even though in the last decade the scientific and juridical literature has contributed greatly to the topic of biobanks, the perplexities that continue to surround this theme give the idea that current ethical protocols on research are inadequate [73].

Now, as never before, international organizations have a crucial role in delineating the route for correct integration of genetics in public health.

Stakeholders can influence the government and its changing public healthcare policy, but coordination between them at various levels is fundamental.

It would be interesting to produce an internationally recognized ethical-legal code of good practice concerning the use of biological samples, one that would enable all researchers wherever they work to gain access to biobanks in the same way, and that would establish the same technical regulations for the organization of the biobanks. Another idea could be a "free zone for research," where the same technical regulations would attain, and where the maximum protection of human dignity would be ensured. Furthermore, it would be interesting to establish a European observatory on genetic studies, or even a world-level one, similar to the observatory on clinical experimentation of drugs managed by the EMA, which would make known the dimension of international level genetic studies, to stimulate transnational debate to make data sharing successful and sustainable.

CONCLUSION

Genetic research has become an indispensable instrument for medical research, and the subjects involved have both divergent and convergent interests.

On the one hand, the public wants research to advance so that gains can be made for the health of everyone and benefits can be shared, but at the same time, people are frightened by the risk of possible discriminatory uses of the information acquired. On the other hand, researchers and research institutes call for greater incentives for their work, appealing to the principle of solidarity, and at the same time demand the rights to exploit the intellectual property associated with their discoveries.

There are also the international stakeholders whose excessive protection of information risks are slowing or even paralyzing scientific progress.

Finally, there are the governments of the individual nations who, digging in and waiting for greater clarification on the theme, have failed to legislate appropriately or have abdicated their role to technical organisms (*e.g.*, the Guarantor in Italy), without resolving the problem, except in a sectorial way.

In this Babel of overlapping and at times conflicting interests, one risks losing sight of the objective: personalized medicine that can truly help patients.

Genetic data must be used not to exploit, but to serve the person. Freedom and responsibility must be the twin guiding lights for establishing parameters for the use of biological samples. An evaluation of how this technology impacts the various aspects of the future of society is urgently needed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/ humans were used for the studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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