Ethical, Legal and Social Aspects of Precision Medicine

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What Will You Learn in This Chapter?

In this chapter, the importance of the ethical, legal, and social aspects (ELSA) under the view of PM research and implementation is illustrated, which is focused on understanding ELSA basic concepts related to the opportunity of sharing genomic and health-related data, ensuring continued progress in our knowledge of human health and well-being. Overall, the citizens' data and risk to privacy, informed consent, and data regulation are being discussed.

Rationale and Importance

The purpose of this chapter is to provide a framework for the ethical, social, and legal aspects and to focus on specific issues that are key to the development and interventions of PM. At present, the healthcare system faces significant challenges in adopting a safe and effective, personalized medicine approach on prevention, diagnostic, and therapeutic. Health data must be collected, processed, stored, and distributed under the legal requirements in place within that country or region. In this line, Ethics on Health is the set of principles or values to guide every conduct in the health field, specifically oriented to the use of health data and health technologies. The PM ethical aspects illustrated in this chapter reflect the application of new technologies with the allocation of needed resources.

The most important regulations briefly described in this chapter are included in Box 11.1.

Box 11.1 The Selected Ethical Lines Followed in This Chapter

Universal Declaration of Human Rights[1] – 1948. Selected articles dealing with the key topics illustrated in this chapter

Article 27 guarantees the rights of every individual «to share in scientific advancements and its benefits» (including to freely engage in responsible scientific inquiry as well as «to the protection of the moral and material interests resulting from any scientific production of which [a person] is an author»

Article 4: Human genome no give rise to financial gains

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[1]This section on https://www.ohchr.org/Documents/Publications/ABCannexesen.pdf

M. Hasanzad (ed.), *Precision Medicine in Clinical Practice*,
https://doi.org/10.1007/978-981-19-5082-7_11

Article 5e: Outlines the idea of consent
Article 7: Outlines the idea of confidentiality
Article 12: States benefit from advances in genetics and medicine available at all about dignity and human rights

International Declaration on Human Genetics. Data – UNESCO (2003)[2] Human genetic data have a special status because:

1. They can be predictive of genetic predispositions concerning individuals
2. They may have a significant impact on the family, including offspring, extending over generations, and in some instances, on the whole, group to which the person concerned belongs
3. They may contain information on the significance of which is not necessarily known at the time of the collection of the biological samples
4. They may have cultural significance for persons or groups

Declaration of Helsinki (1° v: 1964; last: 2013)[3] The Declaration of Helsinki lays down ethical principles for medical research involving human subjects, including the importance of protecting the dignity, autonomy, privacy, and confidentiality of research subjects, and obtaining informed consent for using identifiable human biological material and data. Convention on Human Rights and Biomedicine (Oviedo Convention)[4] is the only international legally binding instrument exclusively concerned with human rights in biomedicine, and its Additional Protocol concerning Genetic Testing for Health Purposes. Oviedo Convention contains specific provisions relating to genetics (Articles 11 to 14), particularly predictive genetic tests and interventions on the human genome

11.1 Ethical, Social, and Legal Aspects of PM: Research and Healthcare Context

This chapter starts with this sentence of Archbishop Desmond Tutu, the Nobel Peace Prize laureate who helped end apartheid in South Africa, who has died this year (quoted by Jance)[5]:

> …….. My dream is that by including all peoples in understanding and reading the genetic code we will realize that all of use belong in one global family – that we are all brothers and sisters..…

Nowadays, the concept of bioethics is moving fast and combines the values of science, medicine, law, and philosophy under healthcare.

Usually, ethical and legal aspects are followed in parallel not only because they are related but also because they answer diverse complementary issues. Legal is linked to law or policy, including professional codes of practice. Not always an ethically right situation concurs with what is legally permissible, and this opens the floor for a discussion to revise the law under the ethics of the issue.

There are universal and unintentional biases such as the herd mentality that tend to reinforce the "values" of the society we live in. These are not necessarily the ones that are the most defensible or even the ones that are in line with what we think our ethical principles are, and they are very often difficult to identify and correct. These aspects are not discussed in this chapter. The fundamental concepts and principles that typically influence bioethical reasoning such as respect for autonomy, prevention of evil, equity, etc. are briefly illustrated.

[2]This section on https://en.unesco.org/about-us/legal-affairs/international-declaration-human-genetic-data

[3]This section on https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[4]This section on https://rm.coe.int/168007cf98

[5]https://www.quotemaster.org/author/Desmond+Tutu

The respect for autonomy allows human beings to be able to make decisions for themselves, and it is one of the pillars of ethical and legal requirements to accept medical treatment or diagnostic tests. Citizens have to understand all the relevant information about the risks and benefits, not being pressured to have to accept this test or procedure and with sufficiently autonomous choices.

However, persons need to reflect on how far their individual decision should be respected when weighed against other individual considerations. It is the harm principle, so long as individuals' choices do not pose a threat of serious harm to others, they should be respected [1].

11.2 Data Sharing: Clinical Care and Research

The World Economic Forum during a Global Precision Medicine Council[6] in 2019 elaborates a synthesis of the key policy and governance gaps for the PM implementation and their possible solutions to overcome them:

1. Data sharing and interoperability
2. Ethical use of technology
3. Societal trust and engagement
4. Access and fair pricing
5. Responsive regulatory systems

One of the main obstacles described in the application of genomics is data-sharing complexity. It can be also applied to all new technologies on PM [2]. With the PM advances, data sharing is crucial and several guidances are being developed. However, there is still a fragmentation in the policy landscape across specific organizations and data types. The difficulty in sharing the data are grouped on:

- Lack of policy harmonization
- Lack of structural support
- Legal and ethical hurdles
- Cultural barriers

However, the bias in the selection of data is really crucial as it can make results not generalizable, facilitate the dissemination of existing prejudices, and also exacerbate disparities in healthcare. All these consequences reduce the reliability of the related technologies.

The most adequate way to move the PM toward a greater competent data-sharing ecosystem is to involve policymakers. Central policy themes had to incorporate, as priorities, the privacy, consent, and data quality and the crucial interoperability, attribution, and public engagement. From the side of public engagement, a simplification of informed consent procedures, privacy-preserving data processing, and encouraging data quality are needed. From the scientific side, reevaluating interoperability, attribution, and facilitating participatory governance are also requested [3].

Considering privacy and confidentiality, clear rules are needed as data sharing has important implications for the population (individual and group). To encourage transparency and public trust in the use of data, citizens should have a role as accountable for their data and have the possibility to decide on some aspects of management as the control over data access and distribution practices. This citizen participation should be a rule, above all, for genetically isolated populations, disease groups, ethnic groups, minority groups, or specific communities. Examples are hereditary cancers or genetic diseases, where the information to the family is crucial as there is the risk of developing the related disease.

Data sharing, in the context of new diagnostic and therapies, requires clear rules from protecting patient data and other legal risks to technical difficulties and institutions' unwillingness to collaborate. Indeed, data infrastructures for biomedical research are working to combine multiple data formats for a complete exchange of data without losing information under a harmonized ethical and legal framework [4].

Lastly, by increasing the data protection rules and surveillance, the risk of data leakage due to secondary use of data without consent will be

[6] WEF_Global_Precision_Medicine_Council_Vision_Statement_2020.pdf

avoided and with this, the risk of data misuse that induces stigmatization and discrimination.

Bioethical research is being further applied following the innovation tools on PM research.

11.3 Patient Recruitment

Subject enrollment starts with the individual selection within the pool of eligible subjects, followed by the engagement and the retention. Recruitment must follow the fair distribution of burdens and benefits, ensure the social value of research, enhance scientific validity, minimize risk to subjects, protect the vulnerable, and enhance benefits to participants.

11.4 Informed Consent (IC)

The requirements of informed consent in the context of PM will be revised under the ethical view in this section and under the legal framework under the GPDR section.

The IC follows the ethical requirements deriving from the Declaration of Helsinki[7]: "Right to human dignity and right to the integrity of individuals." Briefly, the three most important objectives of the informed consent under the Clinical Trials Regulation are first, to provide full details about the study for the appropriate participant's information; second, the future use of data and the disclosure of the research results to patients; and lastly, the possibility of unexpected new information and considerations regarding genetics. Based on this information, patients decide whether they want to participate in the study or not.

Details of the study include the length of their participation, the number of participants, participants' duties and rights (number of visits, filling of forms, treatment compliance, etc.), procedures that encompass their participation and risks of such procedures, and the possibility to be randomly assigned to any of two groups: control and experimental.

Participants in research projects must give their own informed consent under clear and precise information, without technicalities, and ideally in a limited but complete way, with a space for asking questions and enough time for a meditated decision to participate.

They need to understand that if they can conclude, at any moment, their participation in the study without impact on the quality of healthcare provided to them, there will be no loss of benefits; thus, they are otherwise entitled.

The information must include [5]:

- Alternative treatments related to their medical condition.
- Any foreseeable risks to the participating subject or to others, such as the fetus in case a woman gets pregnant (if there are any because of the gender unbalance).
- Adverse events that can occur and what to do in case of occurrence, whom to contact, where to go, and who will cover medical costs. They have to receive specific information on what costs will not be covered and which are covered as participants because if there is a liability policy for lesions due to the trial, that information should also be provided to participants.
- What will happen after the end of the trial (control visit, valuation of new symptoms).

Another important aspect of this "consent process" is the exact information on the individual and public benefits of sharing their data. Whether there are not individual benefits, this must be stated clearly too.

Essential for a right informed consent is an ideal ethical framework[8]: providing information about how the data privacy is being implemented and on how data sharing promotes public health and addressing the supervision of risk of patients.

Dynamic informed consent: It is a tool that is based on a personalized communication platform that aims to facilitate the consent process. This

[7] https://www.who.int/bulletin/archives/79(4)373.pdf

[8] Framework for Responsible Sharing of Genomic and Health-Related Data http://genomicsandhealth.org

tool facilitates participants to make autonomous and informed choices on whether or not to participate in research projects. It is very useful to support continuous two-way communication between researchers and participants.

However, improving consent models and their application will require a mix of traditional and innovative educational approaches to engaging the public more generally.

11.5 Pediatric Informed Consent

Children and teenagers face up to different levels of participation [6]:

1. Unable to contribute own views after unappropriated information process
2. Can form views and express opinions, but cannot make independent decisions after an appropriate information process
3. Has intellectual capacity and maturity to make own decisions, but is still considered minor in her/his domestic legal systems after an appropriate information process

The role of parents in making decisions on their behalf must consider the child's best interest, without forgetting their individuality. Parents should consider children's both current and long-term welfare being conscious of their evolving developmental capacities.

Although clinical studies are needed to find personalized diagnostic and treatment, there are some core recommendations to include children or younger adults in research:

1. Only if pertinent and safe.
2. Use of information that is easy to understand for participants.
3. Encourage participation through the assent process.
4. Research ethics committees (REC) should include experts in childhood (psychology, health, etc.) when reviewing projects that involve children and promote their participation through young persons' advisory groups.

An example of an essential adequately conceived and conducted clinical research in children is the field of rare diseases. Genomic testing is able to improve the diagnosis and classification of a personalized treatment for children. Thereby, clinicians and researchers should evaluate the benefits and risks of new applied technologies. Last but not least, the inclusion of the children and young patients is important on the making process and the design of projects and new medical devices.

To sum up:

- Information provided to children and adolescents should be given in a language appropriate to their age.
- Level and assent should be obtained from minors who are in the range of age that allows them to assent.
- Accept the voluntariness of their participation: it will not occur if they do not want to, even if their parents have authorized their participation in the study.

11.6 Unsolicited or "Incidental" Findings

Clinicians and researchers have to face up with unexpected findings. The situation is more and more frequent with the new technologies such as genetic information. Questioning about how to deal with incidental findings is of huge importance not only for diagnostic testing [7].

These can be related to the different levels of adult-onset disorders and can have family implications, even reproductive implications on carrier status for recessive disorders.

The whole exome sequencing (WES) and the most recent PCR-free whole genome sequencing (WGS) [8] bring also to deal with other legal aspects such as the identification of nonpaternity or adoption or the identification of areas of the excessive absence of heterozygosity (SNP array), as an indicator of consanguinity and raise suspicions of abuse/incest.

Following the recommendation of the European Society of Human Genetics[9], the following options

for reporting these data can be extracted: to give the opportunity to opt-out; to prefer targeted/hypothesis-based approaches (sequencing and/or analysis) in the clinical setting; and, the most transparent, to develop protocols for the return guide of unsolicited results.

These reports should be made by health professionals, especially if the data suggests serious or preventable health problems. With the advancement of new technologies and genetic treatments, the development of specific guidelines on what, how, and to whom (patient, family, social services) unsolicited information must be disclosed is essential. Information that should be given without interference in the autonomy of the rights of the family and the needs of health interests.

FAIR Data Principles are a set of guiding principles in order to make data findable, accessible, interoperable, and reusable [9]. Scientific data management and stewardship follow these principles as guidance in all the sectors of the digital ecosystem. They are rules that describe how research outputs should be organized so they can be more easily accessed, understood, exchanged, and reused. Major funding bodies, including the European Commission, promote FAIR data to maximize the integrity and impact of their research investment.[10]

11.7 Genetic Service and Biobanks

Subsequent to the needs of researchers to go back to participants whenever their data or specimens are used, the biobanks have been structured.

The ISO 20387 published to help organizations get the most out of the standard requires biobanks to implement quality management [10]. These requirements deal with improving the quality of biological material and data collections that are stored and shared, enhancing the outcomes of collaboration, strengthening trust between partners, and advancing research and development. Briefly, the biobanks describe challenges to follow it is:

- To obtain consent for the storage and use in unspecified future research
- Preservation of donors' confidentiality
- Interpretation and management of incidental findings
- Ownership and control of tissues
- Acknowledgment and management of cultural sensitivities
- Reporting of results
- Community participation
- Benefit-sharing
- Return of materials to communities and disposal of unused material

The OECD Guidelines on Human Biobanks and Genetic Research Databases, 2009, provide "guidance for the establishment, governance, management, operation, access, use and discontinuation of human biobanks and genetic research databases ('HBGRD'), which are structured resources that can be used for the purpose of genetic research and which include: (1) human biological materials and/or information generated from the analysis of the same; and (2) extensive associated information" [11].

HBGRD foster that data and materials be rapidly and widely available to researchers with respect to human rights and freedoms, and the protection of participants' privacy and the confidentiality of data.

In addition, HBGD also minimize risks to participants, their families, and potentially identifiable populations, develop and maintain clearly documented operating procedures for all the processes (procurement, collection, labeling, registration, processing, storage, tracking, retrieval, transfer, use and destruction, data and/or information), and finally, ensure that the results of research conducted using its resources, regardless of the outcome, are made publicly available.

[9] https://www.eshg.org/index.php?id=home

[10] https://ec.europa.eu/info/sites/default/files/turning_fair_into_reality_1.pdf

11.8 Institutional Review Boards (IRB)

The IRB has the aim to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB " has the authority to approve, require modifications in (to secure approval), or disapprove research. This board is responsible for the protection of the rights and welfare of human research subjects."

Independent review by an IRB or equivalent is an important part of a system of protections aiming to ensure that ethical principles are followed and has an important role in protecting research participants from possible harm and exploitation.

11.9 The General Data Protection Regulation (GDPR) and Related Definitions

GDPR is the acronym commonly used for General Data Protection Regulation (2018)[11], which unites all data protection legislation across the member states of the European Union. It also includes Switzerland, Norway, Liechtenstein, and Ireland.

It considers the basic definition of personal data "is any information relating to an identified or identifiable natural person (data subject). In other words, any information that obviously relates to a particular person and can be used to identify them."

Biological materials, alone or with the associated data, can allow the identification of persons (directly or through a code controlled by a third party, e.g., clinical care).

11.10 Reidentification and Pseudonymization

Pseudonymization is "when data is masked by replacing any identified or identifiable information with artificial identifiers." Even if patient's names are reidentified and/or replaced with an identification code, they can be identified and are not anonymous. Reidentification of single participants in genome-wide association studies is possible [12].

11.11 Blockchain

Blockchain is a decentralized list of digital archives linked by cryptography. Each record or block contains a cryptographic hash of the previous block ad example mathematical algorithm, timestamp, and data of that transaction. Blockchain technology offers a secure open ledger to record digital transactions, managed by a peer-to-peer network [13].

Blockchain databases are designed to be only-ever-created, and not edited or deleted. For this reason, it is used in healthcare to increase the security of various transactional activities in the healthcare space. It can decrease bureaucracy and manual inefficiencies, improve the quality of care and privacy of patient data, and ensure up-to-date fields with a high level of security and privacy of data, and data is encrypted in blockchains and can only be decrypted with the patient's private key [14]. Their use in the healthcare sector needs a comprehensive guide through a functional and technical understanding.

It has been described that blockchains permit healthcare stakeholders to collaborate without the control of central management and support immutable audit trails useful to record critical information. It can use and identify the different sources of data ensuring the robustness and availability of data.

11.12 Personal Data

According to the GDPR regulation, if personal data is also sensitive data, it requires "special protection." It distinguishes between the concept of "personal data" and "sensitive data."

Sensitive data is a set of special categories that should be handled with extra security (Article 6 of the GDPR), including some exceptions described (Table 11.1).

[11] https://www.gdpreu.org/the-regulation/key-concepts/personal-data/

Table 11.1 GDPR identifiers' considered personal data

Personal data	No personal data
Name and surname	Information deceased person
Email address	Properly anonymized data
Phone number	Information about public authorities and companies
Home address	
Date of birth	
Racial or ethnic origin (S)	
Gender	
Political, religious, or philosophical opinions (S)	
Credit card numbers	
Data held by a hospital/ doctor and health data (S)	
Photograph identifiable	
Identification card number	
A cookie ID	
Internet Protocol (IP) address	
Location data	
Advertising identifier of phone	
Code assigned and any set of information related to the code	
Genetic data (S)	
Biometric data (S)	
Sexual life or sexual orientation data (S)	

Sensitive data are indicated with (S)

Health data are personal data on the physical or mental health of a natural person, including the provision of healthcare services, which reveal information about his or her health status (Art. 4 GDPR).

Genetic data are the acquired genetic characteristics of a natural person which give unique information about the physiology or the health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question (e.g., DNA, RNA analysis, and other data that may be inferred from samples' analysis).

Health and genetic data need to be processed with additional conditions and security measures.

Some countries established additional security measures [15], such as storing of the database, protecting data by enforcing a double authentication factor (e.g., token, double password), allowing to send these data via email just as an attachment, restricting access to facilities, and if possible implementing biometric control access system.

The company/sponsor or site that collects personal data from data subjects is called a "data controller." It is the natural or legal person who determines the processing of personal data (decides what data to collect, how long to store the data, how to analyze the data, etc.) and ensures compliance with principles of GDPR (security measures, data subjects rights, etc.).

The company (CRO, laboratories, service providers, principal investigator, or monitors) that is employed to process that data is called a "data processor," natural or legal person who processes personal data and is responsible in case of infringement of the instructions or infringement of the specific obligations under GDPR (bound by a contract, Article 28).

GDPR Regulation applies in the context of the activities of an establishment of a controller or a processor in the Union, regardless of whether the processing takes place in the Union or not. GDPR Regulation applies always to EU individuals.

11.13 International Transfers of Personal Data: Regulation (EU) 2018/1725

EU data protection rules apply to the European Economic Area (EEA: EU Member States and Iceland, Liechtenstein, and Norway). As the controller for the processing of personal data, EU institutions (EUIs), bodies, offices, and agencies are accountable for the transfers within and outside the European Economic Area.

EU works to facilitate the use of the range of alternative transfer tools to protect data protection rights when data are transferred to countries whose domestic law does not ensure an adequate level of data protection.

A brief description of the main related articles of this Regulation (EU) 2018/1725 has been illustrated in the following text [16].

…" Art. 45: Adequacy decision European: Commission has decided that the third country in question ensures an adequate level of protection. Such a transfer shall not require any specific authorization. The EUI or its processor can provide appropriate safeguards, by using transfer tools according to Article 48, such as standard contractual clauses for transfers, or for transfers from a processor of an EUI to sub-processors by also using transfer tools within the meaning of Article 46 of the GDPR (Binding corporate Rules; Code of conducts; Certifications; Standard Contractual clauses). Article 49 describes certain specific situations or derogations.

Concerning the transparency of dates, Article 13 illustrates the information that has to be included: briefly, the identity and contact details of the controller and the data protection officer (Article 37), the purposes of the processing and the legal basis, the recipients of the personal data, the fact that the controller intends to transfer personal data to a third country and reference to the appropriate or suitable safeguards, and time of storing and rights of the data subject, including the right to withdraw consent at any time and right to complain. The right not to be subject to a decision based solely on automated processing is also regulated by Article 22.

Article 7 Rec.33/34 illustrated consent as a legal basis for data processing. Shortly, it must be a freely given, specific, intelligible, and easily accessible form, clearly distinguishable from the other written declarations, and very explicit regarding special categories of data and about how data will be processed. It is important to underline that this consent can be withdrawn at any time, and data subjects should be allowed to give their consent not only to the full project but also to certain areas of scientific research, or to parts of research projects.

It is also described as a "secondary use" of data in accordance with Article 89 "further processing for […] scientific research purposes […] shall, not be considered to be incompatible with the initial purposes." It refers solely to situations where the sponsor may want to process the data of the clinical trial subject "outside the scope of the protocol," but "exclusively" for scientific purposes. However, patients must be informed of this possibility. Article 28 of clinical trial regulation indicates at the time of the request for informed consent for participation in the clinical trial. The GDPR writes that "it would require another specific legal ground than the one used for the primary purpose."

Concerning the data collected, "it must be limited to what is necessary in relation to the purpose and stored in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the personal data are processed" (Article 5).

Lastly, regarding the personal data breach, GDPR indicates the notification to data protection authorities and affected individuals following their discovery. It is considered as a "breach of security, leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed."

As PM becomes further incorporated into clinical practice, the regulation of these important ethical, social, and legal aspects should be harmonized among different countries and adapted to the continually evolving science and technology.

11.14 Equal Access to Personalized Care

Lack of diversity in research contributes to health disparities in PM. It can be affected by a bias in the collection of data during the involvement of minority groups weakly represented in the healthcare system. It has been recognized that including minorities and avoiding structural racism is needed on the integration of biased data, and on the analysis of the results.

Some investigators theorize that the differences in health outcomes' race-associated are really due to the effects of "structural racism" and recommend that research studies need be available not only for patients living in countries where targeted therapies are subsidized. In some

countries, it is the only possibility to access the clinical services through which these therapies might be offered.

It is evident the influence that racism still has overall in healthcare, as described in a complex disease hospital algorithm applied [17], where black people were selected with less frequency to improve care than white people. In this line, three levels of structural racism on health have been defined [18] with the aim of understanding the mechanism and fight against it: institutionalized, personally mediated, and internalized.

Institutionalized racism refers to material conditions and access to power, personally mediated to prejudice and discrimination and internalized to stigmatized races on own abilities and intrinsic worth.

Scientific racism, conscious or unconscious, is a fact to be avoided. Otherwise, it gives the risk of the perpetuation of inaccurate notions of human populations such as the real implication of phenotypes, the already well-documented fact that 99.9% of humans are identical, the difference among gene frequency and gene expression, and the biological roots of behavior and physiology.

The implementation of PM initiatives requires ethnic data diversity and appropriate ethnic racial representation in their cohorts. In this way, a trusting relationship with these minority groups has to be consolidated to succeed in their research objectives, such as the collection and integration of health data [19]. Inequalities can be eradicated if the research efforts will be addressed to avoid this inaccurate idea.

11.15 National Strategy or National Plan on Personalized Medicine

PM as a global concern in research and implementation on healthcare is linked to the healthcare systems. These are heterogeneous worldwide and depend on the region and country. However, healthcare needs to be comparable, and the best solutions are often found on a transnational level with the development of common strategies, standards, and frameworks with cross-border collaborations and interactions.

The WHO defines a national health strategy[12] as "a document or set of documents that lay out the context, vision, priorities, objectives and key interventions of the health sector, multisectoral or disease programmed, as well as providing guidance to inform more detailed planning documents." A strategy provides the "big picture" and the road map for how goals and objectives are to be achieved. A national health plan is a document or set of documents that provide details on how objectives are to be achieved, the time frame for work, who is responsible, and how much it will cost. This may come in the form of a multi-year plan, supported by annual operational plans that allow for adjustment as a program.

In this direction, national genomic or PM strategy and national plan should be developed, mainly to allow detailed knowledge of the genetic background and the distribution of rare and common variants varies across populations and for admixed populations (underrepresented).

11.16 Examples of International Networks Working on Sharing Data

The Global Alliance for Genomics and Health (GA4GH) is a policy-framing and technical standards-setting organization, seeking to enable responsible genomic data sharing within a human rights framework. Their strategic plan (GA4GH Connect) aims to drive the uptake of standards and frameworks for genomic data sharing within the research and healthcare communities in order to enable responsible sharing of clinical-grade genomic data by 2022. [20].

The plan follows four lines of work: from the development of standards, tools, and frameworks to overcome technical and regulatory hurdles, the identification of world genomic data initiatives sourced that provide guidance on standards development, providing mechanisms and recommendations to create internal consistency and technical

[12] https://www.who.int/ehealth/publications/overview.pdf

alignment across GA4GH Work Streams and product deliverables, and finally, facilitating two-way dialogue with the international community, including national initiatives, major healthcare centers, and patient advocacy groups.

Medical information commons (MIC) are networked environments to shared resources in diverse health, medical, and genomic data on large populations [21].

The American College of Medical Genetics and Genomics[13] is an interdisciplinary professional membership organization of the entire medical genetics team including clinical geneticists, clinical laboratory geneticists, and genetic counselors. They elaborate on guidelines, technical standard, and position statements on laboratory and clinical genomic data sharing to improve genetic healthcare. Recently, they have published recommendations for reporting incidental findings in clinical exome and genome sequencing.

The National Institute of Allergy and Infectious Diseases (NIAID)[14] supports and complies with the data-sharing policies, including the NIH Genomic Data Sharing (GDS) Policy. Genomic summary results (GSR) generated with NIH funding should be made freely available on the Internet with no access restriction.

The current development of European Countries' recommendations for dealing against in-equalities in health care (EU, study policies, 2018)[15] reflects the growing interest in national and European authorities in personalized medicine and other personalized approaches to health. It is also evidenced by the development of national plans by some countries, as well by the foundation in 2016 of the International Consortium for PM (ICPerMed)[16] and the umbrella Coordination and Research supporting initiatives. All of them are supported by the European Commission funds.

11.17 Intellectual Property of PM

Following the WIPO[17] definition of intellectual property (IP), it refers to creations of the mind, such as inventions, literary and artistic works, designs, symbols, names, and images used in commerce. WIPO is the global forum for intellectual property (IP) services, policy, information, and cooperation.

Gene sequences and their expression patterns due to the capacity to better identify and personalize detriment of tumor types become of considerable economic value to them discovered through protection as intellectual property rights.

Not all the inventions can be patented, for example, diagnostic tests based on purely natural principles or phenomena cannot be patented, as in the case of Myriad Genetics [22]. This company has discovered and commercialized several genetic tests for the risk of developing the disease, assessed the risk of disease progression, and guided treatment decisions across medical specialties After several legal procedures, the Myriad patents have been revoked (USPTO) or strongly limited in their scope (EPO). The Supreme Court of the United States concluded that genomic DNA is not admissible for patents, while synthetic DNA remains patentable.

The loss of intellectual property protection and the consequent loss of economic returns can make access to the market difficult. In terms of PM, the proven clinical utility seems to facilitate better protection of intellectual property [23].

The European Commission Directorate General Research and Innovation, the European Innovation Council and SMEs Executive Agency (EISMEA), and the European Union Intellectual Property Office (EUIPO)[18] are working together on developing intellectual property (IP) management. Among diverse activities, they are elabo-

[13] https://www.acmg.net/ACMG/Education-and-Events/

[14] https://www.niaid.nih.gov/research/genomic-data-sharing

[15] https://www.europarl.europa.eu/RegData/etudes/IDAN/2020/646182/EPRS_IDA(2020)646182_EN.pdf

[16] International Consortium for Personalised Medicine (ICPerMed). Available: http://www.ICPerMed.EU [Accessed 06 Sep 2020]

[17] https://www.wipo.int/about-wipo/en/

[18] https://ec.europa.eu/info/news/commission-and-european-union-intellectual-property-office-commit-closer-collaboration-intellectual-property-support-market-uptake-research-results-2021-nov-10_en

rating the Code of Practice for smart use of IP (expected by the end of 2022). The code of practice for the smart use of IP (ERA policy action 7) is a bottom-up initiative with the aim of providing support to R&I stakeholders via recommendations and practical examples on how to handle challenges related to intellectual assets in the current R&I context such as " increasing awareness, harmonizing rules and procedures, fostering cooperation of industry with research organizations/universities, and providing support and guidance on intellectual assets management".

11.18 Health Technology Assessment (HTA)

HTA is a multidisciplinary process that uses stated clearly and in detail methods to determine the value of health technology at different points in its life cycle. HTA drives the decision-making to promote an equitable, efficient, and high-quality health system [24].

From the ethical view, the objective of this assessment is to decrease or eliminate the risk of factors that can contribute to health disparities in PM. Factors usually relate to the high cost of new technologies and applied treatment that limit access to these new services. Although the benefit of PM technologies has been demonstrated, not all healthcare systems are able to support this high reimbursement. This economic limitation causes a disparity in the provision of care to those who can afford it. In addition to the cost of the new technologies, the health system also needs to invest in literacy and continuous medical training in these technologies. To solve this risk, new protocols and national guidelines on HTA are being developed and trying to support it. The major points of this assessment of health technology are:

- follow the specific rules and regulations of the health care system in which decisions are made.
- be accountable to the health care system within which they operate.
- the Coverage/reimbursement of a product within a determined health care system follows the basis of effectiveness, costs, and system affordability (value for money, priorities, and values within the system)
- demonstrate the evidence on safety, relative effectiveness, economics, and budgetary impact; social, ethical, legal, and organizational impact.

HTA requires the participation of all appropriate interest groups and must follow the condition to be equitable and efficient.

The ethics of HTA is represented by transparency, timeliness, and accountability. Moreover, a good assessment process seeks to benefit more patients and society regardless of the outcome of the assessment. The outcomes (such as recommendations) extend the ethics of professional practice and consider ethical principles of justice, benefit, and harm.

Potential ethical issues during the HTA process [25] can be related to the next considerations:

the scope of the HTA and the choice of research methods; the existence of driving forces behind the plan to perform the assessment (relevant reasons for performing/not performing an HTA on the topic, interests of the technology producers); the chance of related technologies to be morally contentious; the interests of the content expert group should be discussed openly in order for the work to be conducted in an objective and independent way; the choice of endpoints in the assessment; and morally relevant issues related to the selection of meta-analyses and studies has to be carefully considered [26].

11.19 Patient Empowerment/ Involvement

As explained previously in this book, public engagement is needed to evaluate the points of view of citizens toward novel technologies and programs and to ascertain their acceptability, potential ethical issues, and challenges in imple-

mentation and scalability, helping the health system in the decision-making process.

The population's characteristics and credence limited their engagement. It has been demonstrated in several studies, such as the results obtained from the survey used for the assessment of public attitudes toward donating and sharing own genomic information and data (project "Your DNA, Your Say," part of the Regulatory and Ethics Work Stream of the Global Alliance for Genomics and Health). The final report showed that the profile of people unwilling to donate their genomic information that more likely to be older, of lower education background, childless, and identifying themselves as part of an ethnic minority [27].

Citizens should also participate in the research process; therefore, their educational training and socioeconomic hurdles should be properly addressed. Nowadays, literacy and engagement of citizens is an emerging policy priority in the national governmental strategies and plans [28]. Citizens' experience should directly be included in the implementation of PM in the health system. Indeed, they should be already involved in the initial step of identifying policy priorities, as well as in the policy planning and implementation phases.

11.20 Incentives: Consideration

Incentives can be the payments or gifts offered to subjects as reimbursement for their participation. There is clear evidence that people are more likely to contribute in research projects when they receive an economic incentive.

Incentivizing patients has been a practice in the United States for almost 200 years. In the last century, compensation became more frequent and the ethics of payment and the potential effects on research is already opened. The financial incentive is described as the primary factor encouraging healthy participants to enroll in phase I trials and becomes less so in phase II and phase III trials, principally in developing countries. All the socioeconomic-related aspects create a potential bias on research [5].

The participants should be aware of the conditions under which they will receive partial or no payment. Usually, incentives should not be high enough to exert a coercive or undue influence in their decision to participate in the study and include transportation costs, food, general checkup, and compensation for work hours lost during visits.

11.21 Direct-to-Consumer Genetic Testing

Nowadays, with the era of the direct-to-test easily acquired on the web, direct-to-consumer genetic testing is also increasing. These tests, as products of PM, collect both risks and benefits.

The practical benefits are evident. However, also the psychological effects of the home tests result, without the right interpretation and right oversight. It is needed a link with clinically right advised care. Other risks are, not with minor importance, the incorrectly reported data and the misinterpretation of positive and negative results.

One example described is an app to predict sexuality based on findings of a massive study on the genetics of same-sex sexual behavior, without the right interpretation of the results of this study [29].

11.22 Work and Genetic Discrimination

Article 9 of GDPR, regarding the process of sensitive data on the work, indicated that processing is prohibited unless one exception applies. One of these exceptions is the "Purposes of preventive or occupational medicine, for the assessment of the working capacity of the employee, medical diagnosis, the provision of health or social care or treatment or the management of health or social care systems and services on the basis of Union or Member State law or pursuant to contract with a health professional and subject to the professional secret."

Following the concept of genetic information as sensible data, the US Equal Employment

Opportunity Commission (EEOC)[19] defines "genetic information" as all information about the following:

- Individual's genetic tests.
- Genetic tests of an individual's family members' information about the manifestation of a disease or disorder in an individual's family members.
- Family medical history is included in the definition of genetic information because it is often used to determine whether someone has an increased risk of getting a disease, disorder, or condition in the future.
- Individual's request for, or receipt of, genetic services.
- Participation in clinical research that includes genetic services by the individual or a family member.
- The genetic information of a fetus carried by a pregnant woman or by a woman family member.
- The genetic information of any embryo legally held by the individual or family member using an assisted reproductive technology.

Title II of the Genetic Information Nondiscrimination Act of 2008 (GINA)[20], which prohibits genetic information discrimination in employment, took effect on November 21, 2009.

In regard to genetic testing, the potential for using this to deny a job due to a person's predisposition to a present or future medical problem has led many countries to adopt legal measures. Several EU Member States have introduced legislation prohibiting genetic discrimination such as France, Sweden, Finland, and Denmark. Others have prohibited or restricted the collection of genetic data from employees without their explicit consent as seen in Austria, the Netherlands, Luxembourg, Greece, and Italy.

11.23 Notes About Equity

Since the adoption of the Oviedo Convention,[21] developments in biomedicine and society have participated in increasing disparities in access to healthcare. Indeed, new innovative treatments and diagnostic may not be accessible to everyone due to their high price. The Council of Europe is addressing these developments through its Committee on Bioethics concerning the Oviedo Convention and has published a Strategic Agenda[22] to guide the answers to new ethical challenges in human rights and shared European values.

Nowadays, several grades of unequal society with historically marginalized minorities and communities are observed worldwide. Thereby, speaking about higher quality, safe, and equitable healthcare means speaking about removing involved obstacles like poverty, discrimination, lack of access to goods, fair pay, education, and safe environments.

Implementation of PM tools in the health system attempts to explore health equity as a fair and just opportunity to be as healthy as possible. Considering equality means each citizen or community receives the same resources or opportunities. However, equity recognizes that each citizen has different requirements and, in this way, needs to receive the essential resources and opportunities to reach an equal outcome.

This process includes preventative care and also personal care treatments. And the health system needs to monitor how to design systems or public health activities. In this way, it would be feasible to provide what each population needs to maximize quality care and outcomes for populations. In this direction, the health system has to increase actions supported by resources and infrastructure, focusing on system redesign.

PM studies will be completed following all applicable laws and regulations including the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice

[19] https://www.eeoc.gov/genetic-information-discrimination

[20] https://www.oregon.gov/gov/policies/diversity/Documents/docs/Genetic%20Information%20Nondiscrimination%20Act%20of%202008.pdf

[21] This section on https://rm.coe.int/168007cf98

[22] https://rm.coe.int/strategic-action-plan-final-e/1680a2c5d2

(GCP) the ethical principles that have their origins in the Declaration of Helsinki,[23] the updated version of the General Data Protection Regulation (EU) 2016/679 (GDPR), and other applicable privacy laws.

11.24 ELSA Research Versus ELSA on PM Research

Ethical Legal and Social Aspects (ELSA) research must not be confused with the compliance of research projects with the aforementioned ethical and legal requirements such as international treaties, GDPR, and ethics guidelines. Instead, ELSA research is an inter- and transdisciplinary research area in which researchers from the social sciences and humanities, law, and theology address and critically reflect broad questions about the ethical, legal, and social aspects of science, technology, and innovation, often in the area of biomedicine.[24] Box 11.2 provides some exemplary questions raised by ELSA research. Being in an interdisciplinary research area, ELSA researchers often cooperate with researchers from other disciplines, either from the social science and humanities or the natural sciences, and – being transdisciplinary – also with a broad set of stakeholders in research and innovation including patients and citizens.

Box 11.2 Examples for ELSA Questions

ELSA research raises issues such as the following:

- What is the impact of certain research and innovation on fair and equal access?
- Are there groups particularly affected or excluded by new technology (e.g., because of economic and educational status, gender, being part of a minority or from a disadvantaged geographical area, etc.)?
- To what extent does healthcare innovation implicitly or explicitly continue or even strengthen existing inequalities? What can be done to avoid this?
- To what extent does a particular area of research and innovation impact sensitive areas, e.g., human dignity, equality, autonomy, privacy, and animal rights?
- How do different stakeholders such as health professionals, policymakers, patients, and the public perceive and evaluate such innovations and their potential impact?
- How can they be discussed and deliberated?
- How does a certain innovation affect certain professions and cooperation between different stakeholders (researchers from different disciplines and areas, different healthcare practitioners, industry, policymakers, patient organizations, communities)?
- Does a new technology necessitate new regulation? In what way?

ELSA research answers the critique from inside and outside the research system as well as from society of the dominant mode of doing research and innovation which might not sufficiently address the abovementioned questions. It originates from a critical bottom-up movement from various disciplines such as philosophy, bioethics, technology assessment, and science and technology studies (STS). However, ELSA research also has important roots in science policymaking and research funding. In the US American context, research on Ethical Legal and Social Implication (ELSI) of biomedicine has its

[23] current official version: Fortaleza, 2013; https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-researchinvolving-human-subjects/

[24] This section on ELSA research builds heavily on work of Hub Zwart, Laurens Ladeweerd and Arian von Roij who describe the origins of ELSA research (Zwaart et al. 2014).

origins in the Human Genome Project. As such, ELSA has always been related to new types of data and hopes for more personalized medicine. It has political roots in the movement for more public involvement in research and innovation policy. It has been adopted and adapted in EU Framework Programmes since 1994 as looking into the ethical, legal, and social aspects of emerging technologies [30]. The concept of ELSA is still widely used in the medical field but has been replaced in EU research and innovation policy by cognate concepts like Responsible Research and Innovation [31] or Open Science. These frequent changes demarcate slight but important semantic shifts in emphasis of the thematic areas targeted by research funding programs and also impact on the research topics which are funded and subsequently addressed.

Being an inter- and transdisciplinary endeavor, ELSA research has challenges for both researchers from natural science and medicine on the one side and social science and humanities, law, and theology on the other side. These challenges are not uncommon for inter- and transdisciplinary research and, apart from the difficulty of getting to know one another, to understand what ELSA is about,[25] and finding a shared language also includes the right degree of proximity and autonomy in the relationship between natural scientists and ELSA researchers.

ELSA research is also highly relevant for personalized medicine. While individual characteristics of patients have always been considered in medicine, new developments in genomics and data sciences have fuelled the emergence of practices subsumed under the term precision medicine, with high hopes for more individualized treatment of patients. From an ELSA perspective, this trend raises several questions on issues such as anonymization, genetic discrimination, and data governance [32]. Thus, several authors emphasize the importance to consider patient and citizen's perspectives in (precision) medicine [33, 34].

Precision medicine is in many ways interrelated with trends toward digitalization and big data. Scholars [35] comment critically on this and claim the rise of data-driven rather than a knowledge-driven science. Other authors [36] raise awareness of new forms of biases that may appear with the widespread use of health data. Thus, with the rising importance and quantities of data in medicine, new ethical [37], legal, and policy debates [38] emerge. Machine learning- and artificial intelligence (AI)-based support systems add another layer to these debates on bias and challenges to privacy [39].

Precision medicine and related infrastructures like biobanks are repeatedly framed as public goods in scientific discourse, which is to sway some socio-ethical concerns [40]. Proponents of such communitarian ethics emphasize societal benefits and community management over individual concerns, which also translates in respective practices for open forms of informed consent, which allow wide applications with collected health data [41]. Critics claim that these models undermine established notions of informed consent and thus individual control over data [42]. In line with this development and the broader trend for self-quantification through digital technologies, such as apps, health management becomes, to some degree, an individual endeavor. Some authors argue that personalized medicine does not necessarily fuel the ongoing trend toward individualization of responsibilities in health, but that solidarity-driven approaches to health do not contradict this trend [34].

We conclude that ELSA provides a critical reflection on developments in medicine and research and innovation more broadly. While other policy documents gained more prominence in the EU policy landscape in the last decade, ELSA is still a timely and useful concept, especially in medicine. With its origins in the Human Genome Project in the United States and the public engagement discourse in Europe, it has always been tied to precision medicine to some extent. The recent advances in data-driven medicine and AI intensify the need for reflection as paradigmatic foundations of medical research and innovation begin to change.

[25] The Societal Readiness Thinking Tool is a practical guide for researchers to identify ELSA questions in their research (Bernstein et al. 2022). It can be downloaded from the Internet at https://newhorrizon.eu/thinking-tool

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