Review

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Personalized Medicine

Ethics and equity in rare disease research and healthcare

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Rapid advances in next-generation sequencing technology, particularly whole exome sequencing and whole genome sequencing, have greatly affected our understanding of genetic variation underlying rare genetic diseases. Herein, we describe ethical principles of guiding consent and sharing of genomics research data. We also discuss ethical dilemmas in rare diseases research and patient recruitment policies and address bioethical and societal aspects influencing the ethical framework for genetic testing. Moreover, we focus on addressing ethical issues surrounding research in low- and middle-income countries. Overall, this perspective aims to address key aspects and issues for building proper ethical frameworks, when conducting research involving genomics data with a particular emphasis on rare diseases and genetics testing.

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Considering the crucial role of genetic variation in the etiology of rare diseases, the development of next-generation sequencing technologies, and more precisely of whole exome sequencing (WES) and whole genome sequencing (WGS) both in research as well as in clinical settings, has had a crucial impact not only in the diagnosis, but also in the discovery and understanding of rare diseases. More precisely, the wide use and implementation of WES and WGS has enabled the capturing of rare variants and thus their association with rare disease phenotypes, compared with Genome Wide Association Studies, which are mainly used for the identification of common variants associated with common disorders. According to the CDC, a rare disease is defined as "a condition affecting fewer than 200,000 people in the United States or no more than 1 of every 2,000 people in Europe."

This perspective touches upon a couple of ethics and equity issues regarding rare disorders and patient enrollment in these disorders; genomics research; genetics testing; and ethical aspects and diversity in low or middle-income countries (LMICs). We begin by describing the ethical principles guiding regulatory processes regarding the consent and sharing of genomics data for research purposes. We also discuss the ethical and societal issues that raise from genomics studies (mainly in rare diseases) by emphasizing aspects pertinent in LMICs. Furthermore, we address important bioethics and societal aspects toward advancing the ethical framework for genetic testing. We conclude our perspective by providing examples for a variety of genetics tests – including those which are relevant for rare

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diseases – that can be accessed using the direct-to-consumer model, such as the internet or through pharmacy stores, while highlighting issues to carefully consider prior to buying these tests.

General ethical issues in public health

According to the CDC, public health ethics aims to define principles and values in order to guide public health actions and to provide a detailed framework for health decision-making [1]. Public health ethics covers issues related, but not limited to, the organization manner of healthcare in a certain country or region where there are public or private healthcare services; the main aim of providing such services; the quality and capabilities of health professionals and; the respective government attitudes to these issues and the values accepted in a specific society. To this end, there is a variety of philosophical perspectives (i.e., utilitarianism, liberalism and communitarianism) in order to shape answers to the question of how society and public health should be organized [2]. Each of these approaches though raises questions, such as providing a precise definition of 'health state' as well as defining the optimal organization and management manner of public health structures.

As stated above, public health ethics can be defined as the application of relevant principles and values to public health decision making. However, prior to applying an ethics framework, the following actions should be performed: identification and clarification of the specific ethical dilemma; analysis of any alternative courses of action and their consequences and selecting the optimal and most balanced course of action in order to resolve the dilemma [1]. In this perspective, we also aim to address concerns specific to LMICs and to this end, public health frameworks are closely related to the application of genomics medicine in these countries. Given the technological advances in the field of personalized medicine over the last years, a framework that examines the implications of genomics medicine in LMICs should be critically considered [3,4].

Discussions have been also made toward the delineation of ethical issues associated with a rare disease and orphan drug research. Although there is an increased number of US FDA and EMA approved orphan drugs, it is still essential to promote initiatives for orphan drug development in order to address efficiently the needs of patients with rare diseases. To this end, pharmaceutical companies' incentives should be lined up with any societal budgetary constraints, in order to provide secure, effective and timely treatments for the rare disease community [5].

Since public health ethics frameworks frequently refer to the concept of 'justice' as a principle operating as a limitation toward enhancing good health outcomes, 'justice' is often viewed as the moral foundation of public health. Consequently, the majority of public health ethics frameworks focus on four distinctive characteristics of public health, which are described as follows: health prioritization of populations rather than individuals; commitment to disease and injury prevention, rather than disease diagnosis and treatment; essential orientation toward outcomes and reliance on government action for public health ethics promotion [6].

Ethical & social aspects for performing research in rare diseases

In this perspective, we also discuss bioethical aspects of establishing guidelines and frameworks for research for individuals diagnosed with rare diseases. Importantly, researchers and clinicians should always keep in mind that there are additional ethical considerations of research on children, who represent 50% of the subjects with rare diseases [7]. As described above, well-established ethical rules should be applied for all clinical trials by both sponsors and researchers, and patients should be aware of their rights. For clinical trials involving pediatric patients or vulnerable patients unable to provide informed consent, additional rules should be applied. According to Article 8 of the General Data Protection Rules (GDPR), participant/legal guardian consent is necessary, when it comes to the ascertainment and use of data from children under 16 years old. However, other Member States may provide consent for a lower age, usually not below 13 years [8]. (Bio)samples obtained from the patients could be used for a variety of clinical research purposes, such as genome or proteome investigation, while data privacy shall be ensured for all primary and secondary uses of data.

An act aiming to empower and protect individuals, who may not be able to make decisions for themselves, lies in the Mental Capacity Act 2005 which was established in England and Wales in 2007. More precisely, this act enables individuals to plan ahead in case they are unable to make important decisions for themselves in the future.

Additional ethical issues in rare disease research, which should be carefully considered and addressed, include the rarity of these conditions and hence the emphasis or prioritization that should be applied for such diseases, as well as the genetic nature of the disease. An important societal aspect, which can also influence the ethical frameworks in rare disease research, can be concluded by the term 'solidarity'. According to Prainsack and colleagues [9], a

solidarity-based perspective incorporates a relational approach and helps to formulate new solutions to complex ethical and regulatory questions surrounding genomics research and genetic testing.

Whereas utilitarianism is primarily based on economic values, a solidarity-based perspective usually derives from noneconomic values. Therefore, a solidarity-based approach could perhaps better justify rare disease research by tackling issues such as caring for people toward the end of their lives, or by improving current policies for organ donation and for health data governance. Moreover, the most efficient way of addressing rare diseases is through highlighting the importance of universal care [9,10].

Data sharing in rare disease research

As highlighted in the RD-connect project [11], an efficient and robust framework shall be designed in order to deal with ethical issues surrounding the sharing of sensitive personal data (such as genomics and proteomics). As already mentioned, WGS and WES methods often lead to a big volume of output data, which should be carefully stored and encrypted. Data-protection and ethics-approval mechanisms are critically important and must balance protection of participants and the timely and efficient research. This balancing act is particularly a factor in rare diseases, given the inherent need for international initiatives which necessarily traverse multiple national approval processes that cover multiple different data types (genomics datasets, stored biosamples, proteomics data or information from databases, medical registries, patient records and questionnaires) [11].

A characteristic example includes clinical trials for schizophrenia, which is considered as a rare disease, since according to the National Institute of Mental Health, its prevalence in USA lies between 0.24 and 0.65%. Performing a clinical trial for individuals diagnosed with schizophrenia in Greece, requires a plethora of ethical regulations including formal approvals from the Ministry of Health, the Greek National Organization of Pharmaceuticals, the National and Local Ethics Committees. All these steps and procedures comply with the European and National Legislation. It is also of paramount importance to ensure the anonymization of trial datasets when it comes to data sharing among different countries in international initiatives. To this end, efforts to simplify, standardize and make interoperable aspects of consent, review and data sharing processes have been developed [12] and further measures are required.

Recruitment policies for patients with rare diseases

One of the main ethical and societal aspects surrounding rare diseases involves the selection of the optimal participant recruitment policy. In this section, we discuss various approaches by incorporating critical factors such as patient preference, transparency and patient engagement. Patient engagement in all stages of study design from conceptualization to protocol design, implementation and dissemination is central to patient-centered research.

A characteristic example lies in the case of a clinical trial toward the delineation of the genomics background of schizophrenia as performed by the National Institute of Mental Health (ClinicalTrials.gov Identifier: NCT00001486). In this study, fulfillment of the inclusion criteria indicated that probands and siblings, who could not provide their consent and were under guardianship, could participate in the study if the guardian signed the informed consent and the research subject also provided their written assent.

One approach to facilitate patient engagement in research involves obtaining permission from the patients for future contact about research. Specific examples describing this approach include institution-wide 'opt-in' or 'opt-out' approaches for future contact as well as permission-based platforms [13,14]. Patient action in order to ensure eligibility for the specific research purpose is described as the 'opt-in' approach, while the 'opt-out' approach assumes patient inclusion unless the patient actively refuses. Both approaches are 'patient centric', since the patient should be contacted prior to performing research, while broader outreach to potential participants (who may be interested) should be simultaneously allowed [15]. 'Opt-in' and 'opt-out' are equally patient-centric.

Overall, the research protocols must be accompanied and should contain the forms of informed consent/consent of the patient, while the option 'opt-out' is always highlighted and must be respected throughout the time of the research or clinical study. It is important to emphasize on the need of building up the collaboration of researchers with the physicians, who engage with the patients, in order to determine the patients that want to opt-in or opt-out from a clinical trial. In another alternative approach, rather 'ethically triggering', electronic health records (EHRs) could be used in order to de-identify data from patients and use these for further recruitment purposes.

Moreover, the aforementioned patient recruitment policies are applied in case of either common or rare diseases. However, the challenges stemming from the rarity of certain diseases may potentially influence the choice toward opt-out and more automated recruitment measures that are appropriately safeguarded and ethically defensible.

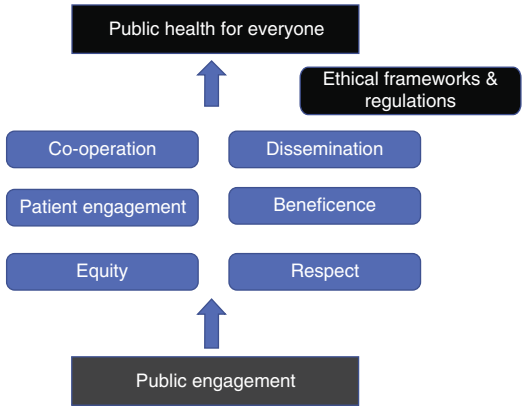

Figure 1. Illustrating a variety of different ethical principles for genomics studies. From top to bottom: 'Co-operation' refers to the collaboration between researchers, physicians and patients involved in the respective study; 'Dissemination' mainly refers to planning the engagement process throughout the project, and enabling the transfer of the study outcomes; 'Patient engagement' refers to the involvement and spirit of collaboration from the patients' side; 'Beneficence' indicates that the main priority or goal of any clinical trial or other research study is the welfare of the research participant; 'Equity' as a term supports operationalization of the right to the highest attainable standard of health as indicated by the health status of the most socially advantaged group and; 'Respect' refers to respect of the human life and dignity.

Similarly, dynamic consent models that provide timelier, flexible and personalized consenting processes can also be applicable in some situations. In dynamic consent models, participants are asked to consent to different activities over time via an IT interface. More precisely, such models have been mainly developed for biobanking purposes and include components encrypting securely personal sensitive data, while also allowing participant consent preferences to go with their data and samples when shared with third parties [16]. As stated in the previous sections, all patient data should be anonymized or encrypted or pseudonymized, in order to be compliant with the current legislation [17] as well as with the optimal recruitment policies.

In addition to this, both clinical and basic researchers should consider and address diversity in the recruitment policies of patients. Diversity aspects often include ethnicity, socioeconomic status, gender and age. To this end, researchers should also consider the differences between designing a study related to a particular rare disease occurring in a worldwide level compared with a rare disease, which is predominantly observed within specific populations (i.e., within geographic and sociocultural domains). In the former case, the application of a global informed consent with single multisite approval, would be expeditious. For the latter case, further and bespoke tailoring of the more individualized design and review processes are required.

Recruitment policies regarding genomics studies in LMICs

It goes without a doubt that opportunities should be created for indigenous communities, from which they could benefit and get informed about their genetic heritage. Moreover, relationships among the participants, the indigenous communities and their biospecimens/data should be preserved by the involved researcher community over time. Ethical aspects, surrounding the use of indigenous genomics data and supporting the diversity and inclusion of indigenous communities in genomics research, can be summarized as follows: building trust, where indigenous communities determine the level of data and metadata access; enhancing accountability, where the origin and provenance of samples should be recognized and maintained with the data, but disclosed in publications; improving equity, which can be achieved by the appropriate attribution of Indigenous communities in the relevant publications and by formalizing benefit-sharing agreements as appropriate [18].

Notably, in settings where researchers and patients do not have resources such as EHRs, or access to basic healthcare or adequate genetic knowledge that could inform their participation, the communication/outreaching strategy should be adjusted to comply with the respective level of genetics/genomics knowledge. This could be achieved not only by developing culturally appropriate means of engaging with research participants and communities during the research process, but also by building the capacity to support the appropriate identification and resolution of ethical, legal, and social issues (ELSI) issues, as raised by communities lacking the electronic infrastructure.

Security, privacy & access to genomics data

Among the common ethics issues regarding genomics studies and genetics testing are privacy and data security, access to data, equitability to service and public trust, as depicted in Figure 1 and which have been also described in the European Data Protection Supervisor (EDPS) [17]. Figure 1 illustrates a diagram linking these different ethical principles applied in genomics studies. More precisely, public engagement (i.e., raising awareness of research) combined with a set of important principles, namely co-operation, science dissemination, patient engagement

(i.e., actively involving people in research), beneficence, equity and respect, can lead to adoption of proper ethical frameworks and regulations, which will make public health available for everyone (Figure 1).

Historically, genomics data have been considered as a certain type of information, which requires both stringent privacy protection as well as explicit and well-defined consent processes [17,19,20]. Genomics data can be collected and stored under the auspices of public or private organizations and therefore concerns may be raised that accidental data release, hacking or data theft could lead to serious violations of privacy [20]. However, the perceived magnitude of these concerns needs also to be balanced against the current state whereby the identification of an individual through knowledge of their genetic variant(s) is difficult and unlikely to occur. Identification of a certain individual currently requires an extensive knowledge of its genotype and phenotype, alongside with information allowing to trace back that genotype/phenotype to a specific person [21]. To eliminate though this possibility, a variety of methods toward reducing the identifiability of data have been proposed, such as the following: limiting the proportion of released genomics datasets, while also ensuring identifiers via key coding (i.e., reversibly de-identifying) [21,22]. Regardless of the proposed methods for data security and privacy, researchers and individuals involved in such studies should always be careful, since these methods ameliorate but not eliminate, the risk.

Regarding stringent and explicit consent processes, the European Union member states require informed consent from the participants in a research project processing health data. 'Broad consent' is usually applicable in biobanking purposes, while 'tiered consent', where participants are invited to select from a set of options, is primarily applied in genomic testing. Moreover, there is the case of 'dynamic consent' models, which has already been described and it is also applicable in biobank studies. In cases, where a person is unconscious and his/her relatives are not contactable, consent for research cannot be obtained, thus raising ethical dilemmas about the appropriateness of deferred consent or consent from an independent physician [17].

The access and use of the genomic data are included among the ELSI regarding genomics studies and genetic testing. Concerns may be raised owing to the risk of the inappropriate use of genomics data, which could result in legal or financial complications, stigmatization as well as employment discrimination. To this end, terms of agreement regarding access to data and results from genetics testing are required and many countries have aimed toward this effort, including the United Kingdom [23]. It is also important to investigate whether the public is willing to share their genomics data, both within the healthcare service and for research purposes, especially when the aim is the improvement of public health and toward genomics discoveries. Interestingly, the public's concern about data access and use is usually raised when genomics data are to be shared with companies for profit making purposes [23]. Nowadays though, an increasing number of large-scale genomics studies include the involvement of private companies and industry, therefore it is essential to establish the appropriate guidelines and frameworks about data access and security prior to any genomics study. Similar principles regarding data access, security and privacy apply not only for genomics data, but also for other types of omics data, such as data stored in the form of EHRs, as well as samples obtained and stored in large biobanks (i.e., Estonian Biobank or Genomics England biobank).

Finally, McKeown and collaborators have emphasized on ethical issues surrounding the reuse of data from health data platforms. More specifically, the authors present a consent approach toward the challenges stemming from the exploitation of data platform models [24]. Their proposed consent approach, which is characterized as legitimate, is based on the reasonable expectations toward the reuse of (health) data, the concept 'integrity' according to Waldron, who states that a just outcome can be achieved if the process is carried out with integrity, and, the social aspect of public engagement, which is an important element toward embedding new research norms associated the technological changes [24].

Equitability & principles for ethical frameworks regarding genomics studies

Issues concerning the equitable access to the genomics medicine services, such as genetics testing, have also been raised during the last few years. This critical issue is seen mainly within remote and indigenous populations in developed countries and in LMICs. To this end, it is important to highlight that the concerns among LMIC and high-income countries are in principle no different (according to the authors' perspective); what differs though is usually the prevalence of the assessed genetic disorder. Interestingly, recent research findings indicate that disparities can be observed both in the access and the efficacy of clinical genetic services. A characteristic example applies to the case of African American women, who have been shown to have poorer access to *BRCA1* genetic testing compared with Caucasian women [25,26]. Moreover, it has been observed that patients of African and Asian ancestry tend to receive rather ambiguous results from genetic testing after exome sequencing, compared with patients of

Box 1. Solutions/recommendations for constructing ethical frameworks of genomics studies

- Ensure the security of the genomics datasets by preventing the de-identification of the included data.
- Support strict data protection policies and legislation.
- Balance the data security risk against the patients' benefits.
- Address efficiently any potential inequalities toward genomics services' access.
- Ensure the public trust toward practices associated with data collection, storage and appropriate data use.
- Promote and enhance the dissemination of the research findings.

European ancestry [26], this in large part is due to the lack of population specific genomic reference data [27] and the availability of culturally appropriate pre- and post-test counseling services.

Similar consent concepts could be adjusted and incorporated in the legislation of LMICs, always addressing though LMICs' needs and standards. To this end, the concept of 'broad' consent is equivalent to consent to governance, so a governance framework for genomics studies in LMICs should aim in promoting global health and research equity. Such a framework should be characterized by respect and trust, proper community engagement, ensuring privacy and confidentiality, feedback of the outcome and capacity strengthening [28]. Moreover, local context driven ethical and legal frameworks will be essential in order to establish functional genomic medicine programs. LMICs should also invest in biotechnology and in the appropriate training of healthcare professional and scientists, while also engaging, government agencies, the private sector and philanthropy toward this process [29].

Alongside with the appropriate capacity building for genomics research implementation, conducive platforms and legislation for medical/genomic scientists and clinicians in LMICs shall be created in order to able to use of genomics interventions. Moreover, specific genomic medicine policies and oversight framework like testing protocols, procurement processes, facility accreditation and adaptation of current health acts to this emerging field are all issues that require governmental support in order to be efficiently tackled [30]. It should be made clear though that law application and cultural attitudes may differ across the globe and GDPR policies do not cover research policies when using anonymized research data, which is also an important part of genomic and healthcare research.

To this end, community engagement and education coupled with adequate representation of under-represented groups, have been proposed as efficient ways of addressing the inequalities issue [31,32]. Moreover, public trust in genomics studies, genetics testing and genomics medicine services can be further improved via the codesign and implementation of up-to-date ethical and governance frameworks addressing the abovementioned issues (Box 1). Public trust in genomics studies lies within the certification that all procedures are compliant with the current legislation and GDPR [17].

According to EDPS, GDPR are described by the following principles for data protection: 'lawfulness, fairness and transparency', 'purpose limitation', 'data minimization', 'accuracy', 'storage limitation' and 'integrity and confidentiality' (EDPS, 2020). 'Accountability' is an additional principle referring to the ability to demonstrate compliance with the six aforementioned principles.

Overall, ethical principles and frameworks toward guiding genomics research should focus on developing technical standards and harmonized approaches, in order to allow an interoperable manner of sharing data from different sources, which will be sensitive to the ethical, legal, and social requirements of the data sources and the consumers. Moreover, establishing a global evidence base for knowledge sharing in personalized medicine, as well as drawing relevant issues to the attention of Ministries of Health, Science and Technology and Education, while also establishing Centers for Fast-Second Innovation via crowdfunding or via another innovative manners can be proven useful when drafting public health frameworks toward promoting personalized medicine globally [33,34].

Ethical issues regarding the different types of genetic testing

As also highlighted in the previous section, the rapid advances in next-generation sequencing technologies have led to rapid growth in the field of genetic testing industry. Nowadays, there is an ever-increasing number of private diagnostic testing laboratories providing a plethora of genetics testing services, which often employ a direct-to-consumer business model [35]. Characteristic examples are provided as follows: genetic tests used for the detection of single-gene (Mendelian) disorders; pharmacogenomics tests for the individualization of drug treatment toward genome-guided treatment modalities; 'predictive genomic testing' for complex disorders and phenotypic traits (i.e., cardiovascular diseases, osteoporosis, diabetes, athletic performance); nutrigenomics tests for the individualization of diet choices and assistance toward weight loss and; identity DNA testing [35].

To this end, it is very important to clarify two different genomics and genetics related terms. 'Genetics testing' refers to screening of specific genetic mutations scientifically proven to be associated with genetic disorders. 'Genomics research' usually refers to scanning of a person's or a cohort's genomes to identify potential biomarkers.

The aforementioned genetic test examples can be categorized in three main categories associated with the scientific validity as well as with current ethical frameworks [35]. The first category includes genetic tests for the diagnosis of inherited disorders and conditions that can be directly assigned to specific genomics variants, such as single-gene disorders and drug-treatment efficacy or toxicity. There is strong scientific evidence supporting the genotype-phenotype correlations for many, but certainly not all, or all aspects, of these tests and many of these are also used in the daily clinical practice (i.e., *CYP2D6* genetic testing) [35].

The second category includes genetic tests for the diagnosis of complex health states and/or disease conditions, which are often characterized either by a mediocre or incomplete knowledge of the genotype-phenotype associations (e.g., cardiovascular disorders, diabetes, osteoporosis) or they have a strong gene–environment interaction (e.g., nutrient uptake, athletic performance). Consequently, such tests are characterized by a poor scientific validity, usually deriving from the incomplete scientific evidence to support such associations. Therefore, by not allowing an accurate estimation of the disease risk, such tests could lead to false positive or false negative genomics findings [35].

Finally, the third category includes genetic tests that are not directly health-related, regardless of their scientific validity and accuracy. This category of tests is better showcased by the characteristic examples of well-publicized paternity cases, where no informed consent was given by the person, whose DNA has been isolated and tested (i.e., the 'infidelity DNA testing'). In these cases, legal consequences for the parties involved may differ between countries [36]. Undoubtedly, there has been an increased number of private molecular genetic testing services, namely via saliva and buccal swab collection kits (for DNA isolation), which are offered for sale directly by pharmacy stores. It should be made very clear though that these tests differ from the well-known and standard pregnancy or blood sugar test kits sold over the counter in pharmacies, since the latter does not involve the procedures of DNA isolation or genetics analysis. To this end, appropriate genetics education of the involved healthcare professionals, such as pharmacists and physicians, as well as those who might engage in such tests (the community), is essential [35].

Interestingly, concerns about the variable and often debatable accuracy of the different types of genetics tests may be heightened, where there are low levels of genetic knowledge and access to basic healthcare, such as in LMICs. Therefore, it is crucial to raise awareness about the variable accuracy of genetics tests not only in high-income countries, but in LMICs especially given the general lack of awareness in the field of personalized medicine. This lack of awareness could be potentially explained either by the fact that LMIC populations are often under-represented in large genome wide association and sequencing studies or by the fact that implementation of cost-effective approaches in personalized medicine field within LMIC settings is yet to be successfully performed.

However, and as highlighted in the works by Baynam and collaborators [37], emphasis should be placed on the need of raising awareness as well as on improving access to care for rare diseases specifically for African populations. Among the manners of achieving these goals are the inclusion of rare diseases in routine healthcare delivery in existing systems, the early and timely diagnosis for all (i.e., newborn screening programs), the emphasis on the unique needs of people with rare diseases and providing patient-centered care. Moreover, national government should create novel channels for information dissemination and ensure the sustainability of such channels, while multi-disciplinary and multi-national initiatives shall also be created in order to establish research collaborations and promote good clinical and genetic practices. To this end, the Human Heredity and Health in Africa (H3Africa) initiative, focuses not only on the development of the appropriate resources (i.e., toward clinical phenotyping, sample collection and biobanking, genomic analysis, bioinformatics, statistical and functional analysis), as well as on addressing critical in genomics research in Africa via the implementation of an appropriate ELSI infrastructure [38].

Conclusion & future perspective

With an ever-increasing number of technologies and 'omics' datasets (including genomics) becoming publicly available, it is essential to establish and adapt bioethical guidelines and frameworks for their proper and secure storage and use. Moreover, given the growing research interest in individualized therapy, it is important to continue to advance addressing ELSI in rare diseases populations as an exemplar of personalized health.

From this perspective, we discuss ELSI regarding the storage, privacy and access to mainly genomics data, while also highlighting approaches to the challenges inherent in these issues. Moreover, we raise the importance of equitable access to genomic medicine services, and aspects of patient recruitment in rare diseases research studies. Careful consideration should lie in constructing an ethics framework for the regulation and consent to the use

of genomics data in research and healthcare. Ethical frameworks should aim toward enhancing societal benefit (i.e., outcome from genomics research approaches, which the society generally benefits from), while addressing issues of consent and regulation in a way which weighs both the finite resources for publicly funded medical services and research, and privacy protection. When it comes to rare diseases, such ethical frameworks and processes include a rare disease data-sharing charter and standardized templates for informed consent procedures.

Another important issue highlighted herein concerns the selling of genetic tests in private pharmacy stores. We propose that both pre- and post-test genetic counseling must accompany the overall genetic testing process [39]. To this end, genetic counseling should guide the patient through the entire genetic testing process, in order to define the type of information that the patient wishes to acquire from the genetic test and what should be done with that information in terms of any post-test health modification.

Ethical dilemmas when creating public health frameworks include the need or not of testing all immediate or possibly at-risk family members of an assessed patient, the responsibility of following up on the tested patients, as well as, what happens when the tested patient does not want his family to be followed up. It is also crucial to define if obtaining consent for testing is equal with treatment consent and which are the potential consequences when the patient takes the test but refuses to follow a certain treatment plan. Last but not least, there is an urgent need for further improving ethical frameworks on how one should deal with coincidental findings such as nonpaternity.

In conclusion, the interpretation of the tsunami of 'omics' data (i.e., genomics, proteomics, transcriptomics), as produced from high-throughput technologies, is rapidly evolving, but still at an early stage, especially in terms of clear delineation of areas of proven, or unproven, clinical utility. This reinforces the need for further improving and revising current ethical and legal frameworks, so that these can adapt to all stages of knowledge generation from consent, ascertainment, storage, sharing, analysis, implementation and dissemination of outcomes.

Executive summary

- In this review, we are providing insight on key ethical issues in genomics research for rare diseases. Some key points stemming from this perspective are as follows:
  - Recent interest in the field of personalized medicine and genomics research further highlights the need for creating clear and precise ethical frameworks (general ethical issues in public health).
  - The field of rare disease research is often under-represented in the ethical, societal, and legal issues. More challenges though occur upon this field, often including confidentiality, lack of appropriate treatment methods and compounds, limited patient enrollment and public engagement (ethical and social aspects for performing research in rare diseases and equitability and principles for ethical frameworks regarding genomics studies).
  - Such ethical, legal, and social issues issues may be even more showcased in the case of LMIC countries (recruitment policies regarding genomics studies in LMICs and security, privacy, and access to genomics data).
  - International research (and nonresearch) collaborations could assist toward a better delineation of the different ethical principles for genomics studies (data sharing in rare disease research).
  - Integration of genetic counseling during the genetic testing process is highly recommended, so that the patients are informed about the benefits of the genetic testing, while also issues, such as misinterpretation of the genetic testing results, are avoided (ethical issues regarding the different types of genetic testing).

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•• **In this work, the authors address many important aspects and raise questions when constructing ethical frameworks in public health.**

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