Revista portuguesa de saúde pública

www.elsevier.pt/rpsp

Original article

Ethical and legal challenges of personalized medicine: Paradigmatic examples of research, prevention, diagnosis and treatment☆

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ARTICLE INFO

Article history:
Received 28 July 2014
Accepted 9 October 2014
Available online 18 November 2014

Keywords:
Personalized medicine
Biobanks
Genetics
Genomics
Genetic tests
Gene therapy
Public health law and ethics

ABSTRACT

This article overviews the important ethical and legal challenges of different steps of the personalized medicine journey such as research, prevention, diagnosis and treatment by discussing paradigmatic examples including biobanks, genetic tests and gene therapy. Scientific progress in the area of genetics, the completion of the Human Genome Project and the ability to sequence genomes for competitive prices have offered the promise of revolutionizing healthcare and raised important challenges to classical paradigms in the biomedical law and ethics fields. Issues such as informed consent, privacy and confidentiality, and discrimination require particular analysis in this context. In the last years the concept of personalized medicine has been a source of considerable hype and hope. Law and ethics should be important allies to limit the former and potentiate the later.

Desafios éticos e legais da medicina personalizada: exemplos paradigmáticos de investigação, prevenção, diagnóstico e tratamento

Palavras-chave:
Medicina personalizada
Biobancos
Genética
Genómica
Testes genéticos
Terapia génica
Direito e ética em saúde pública

RESUMO

Este artigo sumariza alguns dos desafios ético-legais mais importantes das diferentes etapas da medicina personalizada, partindo da investigação, passando pela prevenção e pelo diagnóstico, e terminando no tratamento. Esta análise é realizada através da discussão de exemplos paradigmáticos de cada etapa, como os biobancos, os testes genéticos e a terapia génica. O progresso científico na área da genómica, a finalização do Projeto do Genoma Humano e a capacidade de sequenciar genomas inteiros a preços cada vez mais competitivos originaram a promessa de revolucionar a área da saúde e colocaram desafios importantes a alguns conceitos tradicionais nas áreas da ética e do direito biomédico. Consequentemente, temas como o consentimento informado, a privacidade e

☆ Sections 2 and 3 of this article are based on and continue the work started in Faria, PL and Cordeiro, JV "Public Heath: ethical and legal challenges in a nutshell". In: Yann Joly & Bartha Maria Knoppers, eds., *Routledge Handbook of Medical Law and Ethics*, Routledge, 2014.

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http://dx.doi.org/10.1016/j.rpsp.2014.10.002
0870-9025/

a confidencialidade e a discriminação exigem uma análise atenta e particular neste contexto. Nos últimos anos, o conceito de medicina personalizada tem sido, simultaneamente, uma fonte de expetativas exageradas e de grande esperança. O direito e a ética devem ser aliados fundamentais para limitar as primeiras e potenciar a última.

Introduction

Personalized medicine is a term that refers to medicine that is specifically designed to a given individual based on its genomic information.[1] In the last years, particularly since sequencing genomes left the realm of science fiction and became a fact of life, the concept of individualized healthcare has become a source of great hope. In parallel, the capacity to use genetic data to develop specific tailor-made therapies in the immediate future has been greatly exaggerated by some, generating unfounded hype. In order to separate hype from hope in this context we must strive to fully understand and not underestimate both the potential and the limitations of current knowledge about the genetic basis of disease. With that in mind, there is little doubt that the advances in genetics and genomics in recent decades have been outstanding. Of these, the Human Genome Project (HGP), due to its massive dimension and the unprecedented attention it received from outside the scientific community has polarized most discussions.[2,3] However, irrespective of how enthusiastic or skeptical we are about the progress that the HGP has already forged, we must not isolate this project from other work – past, present and future.[4]

A global analysis of the advances in the area of genetics and genomics highlights one trend that is common to most scientific and technological progress – exponential progression. This trend can be illustrated by a popular anecdote about the origin of the board game of chess. The story goes that sometime during the 6th century a vizier made an extraordinary offer to an Indian ruler: a beautiful chessboard. The king was so impressed by it that he gave the vizier the possibility to choose any present of his liking. Used to be met with extravagant requests, the king was surprised when the vizier asked for a grain of wheat for the first square of the chessboard, two grains for the second, four for the third, and so on, doubling the amount of wheat for each new square. Unaware of the consequences, the king ordered his men to calculate the amount of wheat necessary to satisfy the vizier's request and give it to him as promised. As the calculation was completed, the king realized it was not possible to find enough wheat in the entire world to satisfy the request.[5]

Like the king in this story, most of us do not easily grasp the full implications of the exponential function at first. It is more intuitive to think in linear terms. Therefore, as advances in science are sometimes wrongly placed in a linear scale instead of in an exponential one, future context is not properly evaluated and estimations of future ramifications miss the point. Almost eight millennia went by between the agricultural and the industrial revolutions. Yet, only one hundred and twenty years passed between the industrial revolution and the creation of the light bulb.[6] Human communication in today's world is largely web-based but the internet was only launched worldwide less than 25 years ago.[7]

The same principle applies to progress in the area of genetics and genomics. Following on centuries of questioning that led to Mendel's laws of genetics in the second half of the nineteenth century, vital breakthroughs emerged in the last fifty to sixty years. These include the discovery of the structure of DNA, which was reported in 1953 and the genetic code in 1966, which led to the establishment of the so-called "central dogma" of molecular biology (DNA makes RNA makes Protein).[4,8,9] A decade or so later, Sanger and others developed DNA sequencing methods.[10] In 1991 the HGP was launched and in 2003 it was finished.[2,11] In the last decade, the genomes of different species have been sequenced – including the first human personal genome in 2008 – and the first synthetic genome was produced and used to start up a bacterial cell.[4,12] Also, different projects have sprouted from these advances, such as the sequencing of disease genomes, including cancer, the development of biobanks or the offering of genetic tests directly to consumers.[4] Hence, in science in general and in genetics and genomics in particular, progress is happening fast and its ramifications are multiple and difficult to estimate and predict.

This article aims to analyze and discuss relevant challenges posed to law and ethics by some of the advances in genetics and genomics and the possibility of achieving meaningful personalized medicine in the future. Much has been written about the advent of genomics and, particularly, about its ethical and legal implications.[3] The conclusions intertwine with developments in other scientific areas and with broader socioeconomic transformations, which involve complex issues such as privacy, liberty, discrimination and market economics. Therefore, this article can only aim to offer a general analysis on this topic. It aims to discuss different steps of the personalized medicine journey through a law and ethics lens, including research, prevention and diagnosis, and, finally, treatment. The examples that will be discussed for each step are biobanks, genetic tests and gene therapy, respectively.

Research: biobanks

Biobanks, which in general terms can be described as organized collections of biological material and/or associated information, can vary significantly in terms of nature, size, aim, duration, ownership or governance model.[13] This variation contributes to the difficulty in selecting clear and precise legal definitions, which are important for establishing

adequate regulatory regimens. In the last years, biomedical research biobanks have gained impressive momentum, particularly because: (i) they facilitate the testing of basic science observations in samples with clinical relevance; (ii) expand access to a large number of samples confering greater significance to research studies; (iii) guarantee uniformization of sample preparation and improve reproducibility of research results; (iv) potentiate research collaborations between scientists, clinicians, ethicists and other professionals.[14,15]

In terms of ethical and legal challenges, the debate has intensified since the historic case of the national DNA database in Iceland, which received legal support by the 1998 *Act on Health Sector Database* (HSD) of the national Parliament. Such Act allowed the constitution of a nation-wide biobank[a] and its licensing to a private company, deCODE Genetics. These facts raised significant concerns, namely related to privacy of individuals included in the databank, the selected informed consent processes and the possible collision between public interest and profit-oriented company interests.[16,17,b] Since the Icelandic HSD case great discussion surrounding the ethical, legal and social issues and implications of research biobanks has ensued. In summary, these issues are varied and can usefully be divided in main clusters as Solbakk and others have suggested[18]: (i) issues concerning how biological materials are entered into the bank; (ii) issues concerning research biobanks as institutions; (iii) issues concerning under what conditions researchers can access materials in the bank; problems concerning ownership of biological materials and of intellectual property arising from such materials; (iv) issues related to the information collected and stored, e.g. access-rights, disclosure, confidentiality, data security, and data protection.

As these authors point out there is considerable overlap between clusters and certainly all are very relevant. This article will focus on the challenges to informed consent and to privacy and confidentiality.

Informed consent is the cornerstone of biomedical ethics[19] and, in most countries, participation in a biobank for research purposes requires informed consent procedures, as does participation in most research projects that require the use of biological material.[20,21] This requirement constitutes one of the most fundamental norms of research regulation, which is condensed in the first sentence of the Nuremberg Code: "*The voluntary consent of the human subject is absolutely essential*".[22] Accordingly, the main international law and ethics normative instruments related to research on genetic data either directly or indirectly refer to the primacy of the human being and consequently to the primordial importance of informed consent.[23,c] Such principles are also inscribed in the national legal frameworks of different countries,[24,d] both at a Constitutional and infra-Constitutional level. Hence, most regulations require that biological material and associated information are only used for research purposes with the knowledge and consent of the person from which these were derived. These rules apply also to large-scale research projects such as biobanks. On the contrary, there is considerable debate about whether the traditional informed consent paradigm is appropriate for these projects. Even assuming the terminology "informed consent" is appropriate, which is not straightforward, the adequate type of that informed consent is debatable.[25,26] Different authors present different arguments to sustain that the classical models of informed consent are not adequate to genetic biobanks and should be adapted or substituted by different paradigms.[21,27–31] These arguments are varied and include: (i) the scope of the original consent regarding secondary uses of samples and the impracticality of the constant need for re-consent; (ii) the complex issue of authorization or request for sample destruction; (iii) the nature of the information to provide to donors; (iv) the difficulties in fully guaranteeing genetic sample anonymity; and (v) the lack of clear and uniform rules to delimit the extent of property rights over samples and research results.[32–34] Moreover, as biobanks are often inserted in large national and international networks, informed consent models (or alternative agreements) must either be universal or easily adaptable to permit information and sample sharing while still accommodating ethical, legal, social and cultural differences.[35–38] Taken all this together and factoring in public perceptions, other authors propose that informed consent models – of any type – should be averted. Alternatively, it should be assumed that participants are willing to delegate decisions on proxies, which most of the times are research ethics committees, that are better placed to evaluate and manage the situation.[39,40] On the other hand, others suggest adopting undetermined models such as broad or open consent,[25,28,41] or alternatives such as conditional authorizations for sample donation and gift agreements.[25,30]

In conclusion, clear rules are both lacking and essential in this field. Efforts to select the most adequate agreements for biobank participation must be mindful that individual and fundamental values such as liberty and autonomy must be balanced and made compatible with the common good and the human right to enjoy the benefits of science and its applications.[33,e]

[a] It was in fact a tripartite biobank – one biobank containing DNA samples from a significant proportion of the Icelandic population, and two separate databases consisting of genealogical information and health records.

[b] More recently, some of these issues have re-emerged, following two significant financial moves involving the company, one in 2009 (deCODE sold the database to avoid bankruptcy) and a more recent one in 2012 (deCODE was bought by another company).

[c] See as examples the *Convention on Human Rights and Biomedicine* (Council of Europe 1997, article 2); the *Declaration of Helsinki* (WMA 2013, articles 24–29); the *Universal Declaration on the Human Genome and Human Rights* (UNESCO 1997, article 5(b), article 5(e)); and the *International Declaration on Human Genetic Data* (UNESCO 2003, article 2(iii), article 6(d), article 8, article 9).

[d] Including Iceland. Icelandś original Act on Health Sector Database from 1998 did not specify the requirement for informed consent but set up an opt-out scheme instead (article 8). Subsequently, the Iceland Supreme Court declared the Act on Health Sector Database unconstitutional, which prompted the inclusion of an informed consent requirement in the Act.

[e] See: *Universal Declaration of Human Rights* (United Nations 1948, articles 27 and 29/2); *International Covenant on Economic, Social and Cultural Rights* (United Nations, 1966, article 15).

One additional yet related and fundamental issue that deserves ethical and legal analysis in the context of biobanks is that of privacy and confidentiality.[25,42–46,f] This issue is particularly important because genetic information has the inherent potential to link biological material to the individual from which it originated and, moreover, because the information included in biobanks for research purposes is usually linked to other health data.[47] Furthermore, respect for private life, in the case of genetic information deserves careful analysis as this information relates not only to the individual but also to his/her family.[48,g] In the case of privacy rights and genetic information included in biobanks, we can once again turn to Iceland's *Act on Health Sector Database* for historical context. In a very interesting case from the last decade, the Iceland Supreme Court held that in the case of genetic information, privacy rights are broadened beyond an individual sphere to encompass close family members (in this particular case a daughter).[49,50] Hence, in the context of genetics, individual rights can blend into family rights. Therefore, this should be explained in the clearest terms to biobank donors, which is a very difficult task. Furthermore, confidentiality rights (and their possible limitations), which lie downstream of privacy rights, should also be explained, understood and respected. Weighting and balancing of the values at stake are still important despite the fact that most patients choose to share information of genetic risk with family members.[51] Therefore, it is essential to implement safeguards to protect confidentiality agreements in the context of biobanks and to prevent or minimize confidentiality breaches that could considerably damage public trust. Such trust is essential to potentiate these fundamental research infrastructures which offer great hope for future diagnosis and treatment of disease.

Prevention and diagnosis: genetic tests

Since the beginning of the HGP, particularly from the second half of the last decade onwards, the costs of genetic sequencing have decreased dramatically.[52,h] In parallel, genetic testing is now widely available and can assume multiple forms, which complicates the adoption of uniform definitions for regulatory purposes.[53,54] For example, genetic tests can be performed at different stages – preconception, preimplantation (on human embryos), prenatal (on a fetus), on newborns, during childhood and adulthood; use different techniques – chromosome analysis, flurescence in situ hybridization (FISH), DNA microarrays, whole exome sequencing (WES) or whole genome sequencing (WGS), and serve different purposes – diagnostic, predictive of disease or response to drugs, forensic or research. Furthermore, as testing human genes and genomes can now constitute a profitable marketable activity, gene tests are currently offered not only by public laboratories but also by private companies.[55] The expansion of genetic testing is such that under the promise of individualized solutions, public laboratories and private companies now offer to diagnose genetic disease or test our predisposition to develop different conditions in the future, all this at competitive prices. There are currently genetic tests that cover diseases such as certain types of cancer, diabetes, cardiovascular and mental diseases, conditions such as obesity, and attributes such as muscle performance, and baldness, among others. More, our individual responses to particular drugs and chemicals, our ancestry details and even genetic matchmaking are all testable or promised as such so long as we agree to provide a sample of our DNA for analysis, which in most cases is as simple and risk-free as providing a blood or saliva sample. In this complex context, it is essentil to separate hype from hope. Indisputably, this genetics-for-all reality (maybe not really for all as discussed in the final section) yields great potential but is also accompanied by significant challenges, some of which are ethical and legal.[56]

Many of these challenges are posed by the expanding reality of direct-to-consumer (DTC) genetic tests, which as the name indicates are offered by companies and laboratories directly to consumers via the internet, television or other media, without the involvement of an healthcare provider or practitioner. In some cases, these tests are offered using intricate marketing and results communication practices involving parties from different jurisdictions, which complicates an ethical and legal analysis.[56] Nonetheless, some challenges can be clearly identified. Firstly, without the intermediation of a healthcare practioner or the direct access to a genetic counselor consumers are unprotected from the pernicious effects that may arise from misleading or unhelpful information. In this context, it is important to pay attention to the genetic test's analytical validity, clinical validity and, clinical utility.[55,56] The analytical validity, a measure of a test's detection accuracy, must be well established and certified. This necessity has prompted efforts on different countries to license laboratories that perform genetic testing by requiring specific professional training, clear record keeping standards and periodical assessment of methodologies.[56] Furthermore, regulatory lacunae should be filled by careful adaptation of quality control norms already in place for other clinical laboratory tests or pregnancy tests, for example. Secondly, translating a positive result into clinical significance, which determines the clinical validity of the test, is not straightforward and involves mastering accurate scientific notions of probability, risk, and variance. These concepts are difficult to estimate, to explain and to be fully understood. Nonetheless, the test's results and limitations should be explained (and understood) as clearly as possible. Thirdly, we need to consider the tests' clinical utility, or the usefulness of the test's results in terms of prevention, diagnosis or treatment. Undoubtedly, the utility of a positive or negative result is difficult to estimate, particularly when no therapy or prophylactic measures are availlable. Hence, the decision to take a genetic test should be preceeded by a comprehensive informed consent process that includes discussion about what the test can and cannot

[f] This subject is also central to debates in public health. See, for example, the *Draft NIH Genomic Data Sharing Policy Request for Public Comments* of late 2013, available here: http://www.gpo.gov/fdsys/pkg/FR-2013-09-20/pdf/2013-22941.pdf.

[g] See also: *International Declaration on Human Genetic Data* (UNESCO 2003, article 4 a(ii)).

[h] See also DNA Sequencing Costs, Data from the NHGRI Genome Sequencing Program (GSP) available here: http://www.genome.gov/sequencingcosts/.

predict and the existence or inexistence of targeted therapeutical or preventive strategies.[57] Misleading information potentially resulting in delayed visits to the doctor, raised anxiety and stress or batteries of unnecessary additional tests, must be avoided or mitigated. In parallel, the privacy of genetic information should also be protected[42] and it is essential to guarantee that the tests' results are confidential and not accessible to third parties without consent.

Overall, clear boundaries for DTC genetic testing should be established, including conditional involvement of healthcare providers and professional couseling; standards for premarket reviews; limits to advertising and marketing; specific oversight of results reports; delimitation of provisions from public budgets and health insurance coverages.[58] To enforce these rules, public powers may need to intervene. In a recent example from the USA, concern surrounding some of these issues, particularly the lack of analytical and clinical test validation, test advertisement without premarket approval, and the use of information from consumers, led the FDA to issue a warning to the DTC genetic tests company 23andMe, asking it to stop returning results to consumers until completion of a review process.[i] In response, the company suspended its health-related genetic tests to comply with the directive and latter presented the appropriate corrective measures.[59,j] This process, although perceived by some as an unjustified ingerence in a matter of personal liberty and individual autonomy,[60] demonstrates that public health authorities play a key role in demanding the necessary safety and quality standards for genetic tests in order to protect consumers.[59]

On a different note, as laboratories expand analysis and look beyond single genes, the issue of incidental findings gains importance. Should patients be informed about findings in genome regions that differ from the focus of the original search? And what if that search is conducted without seeking the patient's consent? These questions have generated a fair amout of discussion in Europe and the USA recently[61,62,k] and some of the answers, which are currently straightforward for standard medical tests, might require additional pondering in the case of genetic tests.[63–65] Nonetheless, according to relevant legal norms, the informed consent paradigm and the principle of patient autonomy, patients have a right to decide what to be and not to be tested for. Furthermore, they also have a right to know and a right not to know.[62,66] Being mindfull of these patient's rights without neglecting specific challenges posed by genetics is the best (and perhaps only) way to extract the full potential of genetic tests for medicine.

Importantly, particular and added attention must be dedicated to prevent unrestricted testing of the most vulnerable. Most international ethical and legal norms are clear in establishing that informed consent to procedures involving those who are incapable of consenting is fundamental.[l] Such consent should be given by legal representatives only after being provided with sufficient information "*regarding the purpose and the nature of the test, as well as the implications of its results*".[m] Furthermore, whenever possible, the will of the person being tested should be considered in proportion to his/her degree of maturity and capacity to understand,[n] which underlines the importance (and difficulty) of transmiting and understanding notions such as probability and risk.

In terms of testing the most vulnerable, the subject of genetic testing in children[67] and specifically of Newborn Genetic Screening Programs [NGSP] is particularly important.[68,69] Firstly, in terms of informed consent, the role of parents and legal representatives is not always clear.[70] One one hand, parental consent seems necessary, as parents are in a privileged position to defend the children's own interest, most tested diseases are rare and a possible false positive result will cause unnecessary stress. On the other hand, the overall benefits of testing far out-weigh individual harms and bureaucratic procedures place considerable burdens on health systems. This dillema is ongoing and for example for different NGSP, voluntary, opt-in, opt-out, conditional, implied and mandatory consent models have been proposed and selected.[68,70] Ultimately, decisions on a regulatory level should respect human rights, consider practical aspects and all availlable options, take into account the values of each society and be reviewed periodically in order to be adjusted if necessary.

In conclusion, different genetic tests pose different regulatory challenges and require dedicated attention.[71] The difficulties in establishing general risk–benefit analyses in this context justifies the need for functional, nuanced and adaptable legal and ethical responses that simultaneously protect individual rights and permit the advancement of medicine and science.

Treatment: gene therapy

Discovering the genetic basis of disease, making risk predictions based on genetic information and improving diagnostics are the first steps toward a cure. Advances in research, prevention and diagnostics should be accompanied by the development of valid therapies. There are, particularly in the field of pharmacogenomics, important and already very significant examples of how genetic data can improve treatment options.[72–75] Concurrently, when we think about personalized medicine most of us think of administering the right drug for

[i] FDA Warning Letter available here: http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm.

[j] FDA Close Out Letter available here: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm391016.htm.

[k] See also the following update from the American College of Medical Genetics and Genomics: https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf.

[l] See, for example, the *Declaration of Helsinki* (WMA 2013, articles 19–20 and 29); the *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes* (Council of Europe 2008, articles 9–12); the *Convention on Human Rights and Biomedicine* (Council of Europe 1997, articles 5–6); and the *Universal Declaration on the Human Genome and Human Rights* (UNESCO 1997, article 5).

[m] *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes* (Council of Europe 2008, article 11).

[n] *Convention on Human Rights and Biomedicine* (Council of Europe 1997, article 6).

the right patient at the right time. In parallel to the advances in pharmacogenomics, other genetics-based treatments have been developed, including gene therapy. Different gene therapy definitions exist and two of them are particularly relevant from an ethical and legal perspective because they originate from the competent regulatory agencies in both the USA and Europe. According to the European Medicines Agency (EMA), gene therapy medicinal products must have two characteristics:

(a) "*contain an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;*
(b) *its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence*".[76]

As for the FDA, gene therapy products are defined as "*products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient*".[77]

As the complexity of both definitions illustrates, gene therapy can be performed in very different ways and originate different types of genetic alterations. An essential first distinction in terms of gene therapy regulation is between germ line and somatic genetic changes. The former involves genetic alterations that can then be passed on to the offspring and the latter consists in genetic changes that are restricted to the individual and not passed on to future generations.[78] Germ line gene therapy (or the broader term "inheritable genetic modification"[79,80]) is prohibited for safety and ethical reasons in most countries and, directly or indirectly, deserves the attention of international biolaw and bioethics documents.[81–84,o] On the contrary, the limits of somatic gene therapy have been the subject of intense debate in the last decades and are far more controversial, particular for safety reasons.[78,85,86] Ever since the first FDA-approved gene therapy trial in September 1990 in the USA, which aimed at treating the monogenetic disease adenosine deaminase deficiency (ADA-SCID), several other trials were approved in the USA and elsewhere, including Europe.[78] Nonetheless, the issue of patient safety became a serious concern following the death of 18-year old Jesse Gelsinger during a gene therapy trial at the University in Pennsylvania, in 1999.[87,88] This tragic event prompted the scientific and legal communities to pause and reassess the methodologies applied to gene therapy in both fields. Gelsinger's death was directly related to the adenovirus vector used to deliver the gene (in his case the ornithine transcarbamylase gene), which elicited a fatal immune reaction. In other circumstances, another vector type used in gene therapy – retrovirus – has caused oncogene activation and cancer. The most prominent cases were those of the French children who developed leukemia as a result of their participation in gene therapy trials for X-linked severe combined immunodeficiency (SCID-X1), during the first half of the last decade.[89–92] In terms of patient safety, the challenge lies on how to reasonably estimate risks and benefits, be it for trial participants in experimental therapies or for patients in the case of approved therapies.[86] Therefore, a rigorous informed consent process is particularly important in order to guarantee that the risks and potential benefits are properly explained (and not exaggerated) and understood. Autonomous informed decisions are only made when the subject is competent, aware of potential risks, has access to a reasonable estimation of benefits and is free from coercion.[19] Hence, like in other therapies, special attention must be paid to the most vulnerable, such as the terminally ill, in order to guarantee that the differences between clinical care and clinical research are properly clarified and understood.[93–95] Furthermore, informed decisions are only possible once relevant conflicts of interest affecting investigators and/or clinicians are fully disclosed and appropriate measures are in place to guarantee that those conflicts do not damage the integrity of the process.[86]

Since Jesse Gelsinger, gene therapy has come a long way in dealing with ethical issues, technical obstacles and safety concerns. Concurrently, the number of approved and conducted trials worldwide has grown significantly in the last years.[96] Therefore, it is expected that an expanding number of gene therapy products will be approved for clinical use in the near future. The first ever approval occurred a decade ago in China, but again not without ethical controversy. In 2003 and 2005, the Chinese State Food and Drug Administration (SFDA), approved the products Gendicine and Oncorine for clinical use (recombinant adenoviruses containing the tumor suppressor-gene P53 for treatment of head-and-neck squamous cell carcinoma and nasopharyngeal carcinoma, respectively). Notably, this approval was given without prior conduction of phase III clinical trials.[97–99] Conduction of phase III clinical trials for gene therapy is sometimes exceptionally challenging, especially in the case of monogenic disorders, which have low prevalence within a population making patient recruitment particularly difficult. However, that was not the case in the swift approval of Gendicine and Oncorine in China, which seem to have resulted more from an overall permissive regulatory framework than from the impossibility to meet practical contingencies. Importantly, discrepant regulatory landscapes of innovative therapies in different parts of the world can have significant ramifications that deserve ethical and legal attention such as the expanding reality of medical tourism that has been extensively debated in the context of stem cell-based therapies but to which gene therapy is no exception.[100–102]

The reduced recruitment pool for large clinical trials and the lack of interest from investors in developing therapies for a small market have long been identified as obstacles in the case of most orphan diseases and therefore apply also to different gene therapies. These obstacles have been tackled by dedicated legislation in some countries, including the USA, Japan,

[o] See also: *Convention on Human Rights and Biomedicine* (Council of Europe 1997), *Universal Declaration on Bioethics and Human Rights* (UNESCO 2005), *Universal Declaration on the Human Genome and Human Rights*. (UNESCO 1997), *Declaration of Helsinki* (WMA 1964).

Australia and also in the European Union.[p] More recently, as gene therapy clinical trial sponsors became more aware of regulatory constraints, increasing numbers of gene therapies are being developed as orphan drugs in order to make the most of the flexibility that these legal regimes allow.[103] Remarkably, in July 2012, gene therapy for an ultra-orphan disease, lipoprotein lipase deficiency, was historically approved by the EMA.[104,q] Hence, the first – and so far only – gene therapy product approved for clinical use outside China (alipogene tiparvovec, also known as Glybera, an adeno-associated viral vector carrying the LPL gene) benefited from regulation that took into account the difficulty in obtaining data in rare diseases and considered evidence derived from a very small number of patients.[105] In spite of this, the approval process of Glybera was not straightforward and exposed the difficulties of product evaluation and authorization that companies developing gene therapy products face today.[103,106] Some of these difficulties, prominently time and financial pressures and the lack of predictability and precise criteria for future approval can jeopardize ongoing research and development efforts[96] and therefore require dedicated attention from regulatory bodies.[105]

As gene therapy becomes clinically available an additional issue that begs further ethical analysis is that of its acceptable aims. In which medical contexts is it acceptable to consider genetic alterations – in all conditions or only in severe ones? And if we choose the latter what should be considered as "severe" and how often should such assessment be revised? In fact, deciding on whether or not a given medical condition is worthy of genetic intervention is a complex decision that invites careful consideration. In order to do so, specific disease mechanisms, individual circumstances of patients, potential benefits and expected harms must be taken into account. Furthermore, gene therapy is expensive therapy. Therefore, the questions of access, equality and, from a provider's perspective, resource allocation, are critical issues to be dealt with also by ethics and the law. The human right to enjoy the benefits of science and its applications should be balanced by appropriate public and private funding schemes that combat the potential for deepening inequality and the onset of new sources of discrimination.

Genetics and genomics: diversity and discrimination

In order to take full advantage of the potential of personalized medicine we must distinguish hype from hope. Sequencing our genomes has become increasingly cheaper and we are now able to access an amount of data that was unimaginable a few years ago. However, our capacity to manage and interpret such big data is still insufficient to fully understand, prevent, diagnose and treat disease. Furthermore, as we trust scientific progress to help us achieve a better health, we must also confront ourselves with the downsides of the personalized medicine endeavor, in order to properly address them.

One of the most important risks that should be mentioned is that of genetic discrimination. In this respect, I select one sentence from South Africa's anti-apartheid activist and Nobel Peace Prize laureate Archbishop Desmond Tutu that properly illustrates the basis for this discussion. Writing for the journal *Science* about the commemoration of the 10th anniversary of the HGP, he said:

> "My dream is that by including all peoples in understanding and reading the genetic code we will realize that all of us belong in one global family – that we are all brothers and sisters. Wow!"[107]

In 2010, Tutu had donated his own cells for the study of genetic diversity. Results from that study showed that he shared ancestry with a Kalahari Bushman from Namibia.[108] These and other findings deserved the following comments from Webb Miller, a professor of biology at Penn State University and co-author of the study:

> "On average there are more genetic differences between any two bushmen in our study than between a European and an Asian", and:
>
> "To know how genes affect health, we need to see the full range of human genetic variation, (. . .)".[r]

Fundamentally, the beauty of genetic diversity should be studied and understood in parallel with the universality of our human heritage. Simultaneously, we should all be protected from interpretations that may lead to genetic discrimination. Hence, biobanks that selectively target a subset of the population based on social notions of race or the actions of employers, insurers or governments that use genetic information resulting from genetic tests to favor a given genetic trait, are all forms of genetic discrimination that may constitute a violation of human rights. Furthermore, genetic interventions in the context of gene therapy could also involve a risk of discrimination that should not be underestimated. Firstly, strictly speaking of somatic interventions, these therapies are extremely expensive and are expected to remain so in the near future. This fact should highlight the importance of fairness and equality in access to health – which are elements of the human right to health[s] – and remember the human right to enjoy the benefits of science and its applications. Secondly, one must bear in mind the unknown challenges of germline alterations and the potential for discrimination that justify the

[p] See, amongst others: USA – Orphan Drug Act (1983), Japan – Orphan Drug Regulation (1993), Australia – Orphan Drug Policy (1998), EU – Regulation (CE) N°141/2000 (2000). More info at: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=PT&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_COMPARISON.

[q] More information here: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/07/news_detail_001574.jsp&mid=WC0b01ac058004d5c1, here: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002145/human_med_001480.jsp&mid=WC0b01ac058001d124 and here: http://ec.europa.eu/health/documents/community-register/html/o194.htm.

[r] See The Guardian news article here: http://www.theguardian.com/science/2010/feb/17/desmond-tutu-genome-genetic-diversity.

[s] See WHO Fact sheet n°323 available here: http://www.who.int/mediacentre/factsheets/fs323/en/.

general prohibition that is in place today and that is likely to be maintained and perhaps even strengthened in international law in the future.[50,109,110] Importantly, this issue is linked with the broader issue of human enhancement that has been the subject of intense debate since the HGP and will certainly continue to be for years to come.

In parallel, the potential for genetic discrimination in the context of the personalized medicine endeavor is never complete without addressing the issue of data privacy. This matter is very complex and cannot be looked at in isolation from broader social phenomena that point toward an erosion of privacy in our daily lives. Furthermore, the issue of privacy is recurrent whether we discuss research, diagnosis or therapy.[111] A good example is that of companies offering DTC genetic tests, which aim to or do already run biobanks for research purposes. The possibility that individual information, including genetic information, present in biobank databases is coupled with private health data and held by profit-oriented entities raises important ethical and legal questions in terms of transparency and data protection regulation. Additionally, raw genetic information, held by institutions should not only be protected from access by third parties without consent but also be accessible by the individuals from which that information was derived.[66,112,113] This discussion is fundamental whether one defends the particular nature of genetic information or whether one sees genetic data as similar to any other health data.[21,45,114,115] Therefore, the issue of genetic privacy is central to the personalized medicine debate and its particular challenges should be addressed in order to gather public trust and approximate the advancement of science and technology to societal concerns, principles and values. Finally, these fundamental premises, the nature of DNA and genetic information and the approximation of science and society, are also central to a debate that cannot be developed here but which is of ethical and legal relevance as well – the issue of patenting of human genes. This debate has significant ramifications and recent developments on the subject deserve a dedicated analysis, which can be found elsewhere.[116,117]

Conclusion

Scientific progress is exponential and so are its highest promises and subversive potential when it is used abusively. We must bear in mind that the same progress that has led to enormous gains in terms of both quantity and quality of life throughout the years, has also permitted that a great deal of destructive behavior hindered science's most altruistic efforts. Estimating the potential for progress and disruption involves not only analyzing current developments by different social, cultural and historical perspectives but also embarking on prognosis exercises to envisage future tendencies. Both these exercises are very complex and prone to error and bias and therefore must be approached with caution. However, complexity should not serve as an excuse for inaction. History is full of examples where abusive uses technology and science or the misrepresentation of its aims led to great problems and in some cases suffering. Also in the case of genetics and personalized medicine we must make sure that we have collectively learned from those episodes. We can start by distinguishing hope from hype and finding in law and ethics essential allies to limit the later and potentiate the former.

Final note

In Portugal, some of the most relevant ethical and legal challenges discussed above have been subject to dedicated legislation and the opinion of important national ethics bodies. The general solutions of the Portuguese ethical and legal framework in this context, some of which are very unique,[118] together with the corresponding main normative instruments for each example discussed in this article, are presented in Table 1.

Conflicts of interest

The authors have no conflicts of interest to declare.

Table 1 – Summary of the Portuguese ethical and legal framework on some of the most relevant ethical and legal challenges of personalized medicine. Examples of research (biobanks), prevention and diagnosis (genetic tests), and treatment (gene therapy) are presented, as well as other relevant general norms. The corresponding main normative instruments for each example are also indicated.

	Relevant national normative instruments	Informed consent	Privacy and confidentiality	Other
General	*Legal and regulatory documents* - Constitution of the Portuguese Republic (CRP); - Portuguese Penal Code; - Portuguese Civil Code; - Health Basis Law (Law 48/90 of 24 August); - Law 12/2005 of 26 January on personal genetic information and health information; - Law 67/98 of 26 October on the protection of personal data; - Law 21/2014 of 16 April on clinical research - Norm 015/2013 of the Directorate-General of Health on informed consent for treatment, diagnosis and participation in research studies - Norm 16/DSMIA (2001) of the Directorate-General of Health on informed consent in pre-natal diagnosis *Opinions of the National Council of Ethics for the Life Sciences* - 43/CNECV/2004 on personal genetic information and health information;	- General principle – the moral and physical integrity of every individual is inviolable. The law protects individuals against any illicit offense or threat to their physical and moral personality. (**CRP, art. 25/1; Civil Code, art. 70**); - Informed consent excludes the unlawfulness of the act when it refers to freely disposable legal interests and the act does not offend social mores. Presumed consent equals express consent when it can be reasonably assumed that the agent would have consented under those specific circumstances. Minimum age for valid consent is 16 years old. (**Penal Code, arts. 38, 39**; **Civil Code, art. 340**); - Every patient has the right to consent or refuse health care and to be informed about his/her situation, alternative treatment and prognosis (**Health Basis Law -Law 48/90, Base XIV/1/a, b**): - Informed consent rules in the case of medical-surgical treatments and the duty to inform and clarify (**Penal Code, arts. 149, 150, 156, 157**).	- Everyone shall possess the right to protect the privacy of their personal and family life **(CRP, art. 26/1)**; - General principle - the processing of health and genetic data is prohibited. *Exceptions:* other legal provisions; express consent from the data subject; vital interests of the data subject in the case of incapacity; National Data Protection Authority (CNPD) authorization on the grounds of public health interest provided that non-discrimination and security measures are implemented; necessity for the purposes of preventive medicine, medical diagnosis, treatment or the management of health-care services provided that information is processed by an individual bound by professional secrecy and CNPD is notified (**Law 67/98, arts. 7, 15, 27**); - Processing of health and genetic information must respect all adequate measures to protect confidentiality (includes security of the premises, equipment and information) and to enforce the professional duty of confidentiality (**Law12/2005, art. 4/1**); - Health information can only be used with written authorization from the person to whom it pertains (or legal representative) (**Law12/2005, art. 4/3**); - Genetic information must be subject to legislative and administrative measures of reinforced protection in terms of access, security and confidentiality (**Law12/2005, art.6/6**);	- Fundamental principle – dignity of the human person (**CRP, art. 1**); - Everyone shall possess the right to legal protection against any form of discrimination (**CRP, art. 26/1**); - The law shall guarantee the personal dignity and genetic identity of the human person, particularly in the creation, development and use of technologies and in scientific experimentation (**CRP, 26/3**); - Health information, including genetic data is property of the person to whom it pertains and it cannot be used for any other purposes than health care and health related research, or other purposes defined by law (**Law 12/2005, art. 3/1**); - Stored biological material remains property of the person from whom it was collected and, in case of death or incapacity, of his/her relatives (**Law 12/2005, arts. 18/2, 19/13**); - In special circumstances, when information is important for the treatment or the prevention of a genetic disease in the family, information can be used in the context of genetic counseling – even if it is no longer possible to obtain the informed consent from the person to whom it belongs (**Law 12/2005, art. 18/6**); - Relatives in direct line of ascent or descent, as well as second degree relatives, can access a stored sample of genetic material, in case it is necessary to obtain a better knowledge of their own genetic status, but not to know the genetic status of the person to whom the sample pertains or of other family members (**Law 12/2005, art. 18/7**);

Table 1 (*Continued*)

	Relevant national normative instruments	Informed consent	Privacy and confidentiality	Other
	- 56/CNECV/2008 on the direct sale of genetic tests to the public - 68/CNECV/2012 on genetic information, genetic databases and genetic tests; - 57/CNECV/09 on the rights of patients to information and informed consent.		- Health and genetic information must be separated from the remaining personal information, namely through different levels of access (**Law 67/98, art. 15/3**, **Law12/2005, art. 4/5**); - The access to health and genetic data by the person to whom it pertains, or by a third party with consent, is made through an authorized physician chosen by the owner of the information (**Law 67/98, art. 11/5**, **Law 12/2005, art. 3/3**).	- The commercial use, the patent registration or any type of financial gains derived from biological samples, as such, is strictly forbidden (**Law 12/2005, art. 18/8**); - Human genetic heritage is not patentable (**Law 12/2005, art. 20**); - Principle of non-discrimination – no one can be discriminated due to the presence of a genetic disease or due to his/her genetic heritage (**Law 12/2005, art. 11/1**); - Promotion of research, protection of personal genetic identity, clinical and analytical validation of genetic tests, the response to drugs, as well as genetic screening tests, will be object of future specific regulation (**Law 12/2005, art. 22/2**) - *these regulations are still lacking but are expected to be published during 2014.*
Research: Biobanks	*Legal documents* - Law 12/2005 of 26 January on personal genetic information and health information; - Law 67/98 of 26 October on the protection of personal data; - Law 21/2014 of 16 April on clinical research. *Opinions of the National Council of Ethics for the Life Sciences* - 43/CNECV/04 on personal genetic information and health information; - 68/CNECV/2012 on genetic information, genetic databases and genetic tests.	- Written and express consent (given by a competent person or the legal representative of an incompetent one) is mandatory for inclusion in research biobanks and involves the necessary explanation about the nature and aims of the research, person responsible, procedures and potential risks and benefits. The use of samples for other aims requires re-consent or irreversible anonymization (**Law 12/2005, arts. 16/4, 18/4, art. 18/5, 19/5**); - Collection of biological products is subject to separate informed consents for health care purposes and for biomedical research purposes; the consent must include the	- Only anonymized health information can be accessed for research purposes (**Law 12/2005, art. 4/4**); - Regulation of the creation, maintenance, management and security of genetic databases for health research must follow the protection of personal data law (**Law 12/2005, art. 7/2**) ; - Privacy and confidentiality of samples and data must always be ensured; particularly by avoiding storage of identified material, controlling access to the collections and guaranteeing safety in terms of losses, changes and destruction (**Law 12/2005, art. 19/8**); - Only anonym or irreversibly anonymized samples can be used. The use of identified or identifiable samples should be limited to studies that cannot	Definition of biobanks (**Law 12/2005, art. 19/1**); - No one can collect or use human biological samples or its by-products with the purpose of creating a biobank without authorization from an entity accredited by the health authorities and by the CNPD if the biobank is associated to personal information (**Law 12/2005, art. 19/2**); - Biobanks should only be created for providing health care services (including diagnosis and prevention) or basic or health related research (Law 12/2005, art. 19/3); - Biobanks should only accept samples in response to requests from physicians and not directly from subjects or their relatives (**Law 12/2005, art. 19/4**); - The conservation of samples of dried blood on paper obtained in neonatal screenings or others, must be considered in the light of the potential benefits and risks it poses to individuals and

Table 1 (*Continued*)

Relevant national normative instruments	Informed consent	Privacy and confidentiality	Other
	purpose of the collection, the duration of storage of the samples and its by-products and mention the possible disclosure of the results (**Law 12/2005, arts.18/1, 19/5**); - Informed consent can be withdrawn at any time. In case of death or incapacity relatives can withdraw consent. In both cases all samples and its by-products must be permanently destroyed (**Law 12/2005, art.18/3**); - In the case of retrospective use of samples, or in special situations in which it is not possible to obtain consent from the persons involved (due to the amount of data or of subjects, to their age or similar reasons) the material and the data can only be processed for the purposes of scientific research or for collecting epidemiological or statistical data (**Law 12/2005, art. 19/6**).	be conducted in any other way (**Law 12/2005, art. 19/9**); - Commercial entities are not allowed to use samples that have not been anonymized (**Law 12/2005, art. 19/10**); - If there is an absolute need to use identified or identifiable samples, these should be coded and the identifying codes must be kept separately, but always in a public institution (**Law 12/2005, art. 19/11**); - If the biobank has identified or identifiable samples and if the communication of studies results can be foreseen, a medical geneticist should be involved in the process (**Law 12/2005, art. 19/12**). - Genetic databases and records that allow the identification of family members must be managed and supervised by a medical geneticist or another physician if the former is not available (**Law 12/2005, art. 7/3**).	society; those collections can be used for family studies in the context of genetic counseling or for genetic research, if they are previously and irreversibly anonymized (**Law 12/2005, art. 19/4**); - Stored biological material is considered to be property of the person from whom it was collected and, in case of his/her death or incapacity, of his/her family members; the material should be stored for as long as it proves useful for present and future relatives (**Law 12/2005, art. 19/13**); - Researchers responsible for the studies on samples stored in biobanks should verify that the rights and interests of the persons to whom the biological material pertains are protected; this includes the protection of privacy and confidentiality, but also the preservation of the samples that may be necessary to diagnose family diseases in the future (**Law 12/2005, art. 19/14**); - Researchers responsible for biobanks have the duty to watch over their conservation and integrity and to inform the person from whom consent was obtained of any loss, change or destruction, as well as of the decision to abandon the research or to close the biobank (**Law 12/2005, art. 19/15**); - The law must define rules for licensing and quality assurance of biobanks (Law 12/2005, art. 19/16) – *these regulations are still lacking but are expected to be published during 2014*; - The transfer of a large number of samples or collections to other national or foreign entities must respect the original purposes of the biobank and for which consent was obtained, and must also be approved by the responsible ethics commissions (**Law 12/2005, art. 19/17**);

Table 1 (*Continued*)

	Relevant national normative instruments	Informed consent	Privacy and confidentiality	Other
				- The creation of databanks that describe a particular population and possible data transfers must be approved by the National Council of Ethics for Life Sciences; if the databanks are representative of the national population the approval of the National Parliament is required (**Law 12/2005, art. 19/18**); - The scientific community must have free access to the data resulting from research on the human genome (**Law 12/2005, art. 16/2**); - Research on the human genome is subject to the approval by ethic commissions from hospitals, universities or research institutions (**Law 12/2005, art. 16/3**).
Prevention and diagnosis: genetic tests	*Legal documents* - Law 12/2005 of 26 January on personal genetic information and health information; - Law 67/98 of 26 October on the protection of personal data. *Opinions of the National Council of Ethics for the Life Sciences* - 43/CNECV/04 on personal genetic information and health information; - 56/CNECV/2008 on the direct sale of genetic tests to the public - 68/CNECV/2012 on genetic information, genetic databases and genetic tests.	- Written express informed consent (given by a competent person or the legal representative of an incompetent one) is mandatory to perform genetic tests (**Law 12/2005, arts. 9/1, 9/2**); - Genetic testing of minors can only be requested for their benefit, with written consent from their parents or legal tutors and always seeking first the minors own consent (**Law 12/2005, art. 17/4**); - Collection of DNA samples for genetic testing is subject to separate informed consents for health care purposes and for biomedical research purposes; the consent must include the purpose of the collection and the duration of storage of the samples and its by-products. The future use of samples for other purposes requires	- Only genetic information that has immediate bearings the patient's current status of health can be registered in the medical records, except in the case of genetic services that keep private separate files (**Law12/2005, art.6/4**); - Medical records from genetic services containing genetic information regarding healthy persons, cannot be accessed, shown or consulted by physicians, other health care professionals or staff (**Law12/2005, art.6/5**); - The existence of a link between a health care professional and any other sector of activity – including insurance companies, professional entities or suppliers of goods and services of any kind – does not exclude compliance with confidentiality duties (**Law12/2005, art.6/8**); - Every citizen has the right to know if a medical or research record contains genetic information about himself/herself and his/her family, the uses of that information and the storage time before	- Genetic diagnostic or pharmacogenetic testing must follow the general principles that regulate all other health care interventions or services (**Law12/2005, art.9/1**); - The detection of the heterozygosity status for the diagnosis of recessive diseases, the presymptomatic diagnosis of monogenic diseases and the tests of genetic susceptibility in healthy persons can only be carried out by request of a medical geneticist, following a genetic counseling consultation (**Law12/2005, art. 9/2**); - The results of genetic testing should only be communicated to the person concerned or, in case of diagnostic testing, to the legal representative or to the person designated by the person concerned and during a proper medical consultation (**Law12/2005, art. 9/3**); - In situations of risk of severe, late-onset diseases with no cure or proven effective treatment, any presymptomatic or predictive testing must be preceded by a previous psychological and social evaluation and by the

Table 1 (*Continued*)

Relevant national normative instruments	Informed consent	Privacy and confidentiality	Other
	re-consent or irreversible anonymization (**Law 12/2005, arts.18/1, 18/4, 18/5**); - Physicians have a duty to inform about the transmission mechanisms of genetic diseases, and the risks for the subject and relatives, as well as to provide guidance for future counseling (**Law 12/2005, art. 17/7**); - Presymptomatic, predictive and preimplantation tests should not be performed in persons suffering from mental disablement and who cannot fully appreciate the implications of this type of tests or give their informed consent to its execution (**Law12/2005, art. 9/6**); - Everyone has the right to refuse submitting to a genetic test (**Law12/2005, art. 17/2**).	destruction (**Law 12/2005, art.6/9**); - In the case of heterozygosity, presymptomatic and predictive testing, the results should only be communicated to the person concerned and can never be communicated to third parties without his/her written express consent – this also refers to other physicians or other health care professionals who are not involved in the process of testing of the person in question or of his/her family (**Law 12/2005, art. 9/4**); - In case of prenatal and preimplantation testing, the results should only be communicated to the mother, to the parents or to their legal representatives (**Law12/2005, art. 9/5**).	follow-up of the patient after the tests results (**Law12/2005, art. 9/7**); - The frequency of the genetic counseling and the form of the psychological and social follow-up should be determined based on the severity of the disease, on the usual age of onset and on the existence, or inexistence, of a proven treatment (**Law12/2005, art. 9/8**); - No one can be discriminated due to the results of a genetic test, including those performed with the purpose of obtaining or maintaining a job, subscribing health and life insurances, having access to education, as well as for purposes of adoption, whether regarding the adopter or the adoptee (**Law12/2005, art. 11/2, 12-14**); - Everyone has the right to receive genetic counseling and, if appropriate, psychological and social support, before and after submitting to genetic tests (**Law12/2005, art. 17/3**); - The right to obtain medical, psychological and social follow-up as well as genetic counseling cannot be affected because of a refusal to take a genetic test (**Law12/2005, art. 11/3**); - A fair and equitable access to genetic counseling and genetic testing is guaranteed to all and the needs of the populations that are more strongly affected by specific genetic diseases should be safeguarded (**Law12/2005, art. 11/4**); - It is illicit to create any list of diseases or genetic characteristics that may support the request of genetic tests or of any king of genetic screening (**Law12/2005, art. 17/1**); - No predictive tests regarding late-onset diseases and that have no cure or proven effective preventive treatment can be requested

Table 1 (*Continued*)

	Relevant national normative instruments	Informed consent	Privacy and confidentiality	Other
				for minors. Prenatal diagnosis of diseases that usually begin in adulthood and that have no cure cannot be done just for parental information (**Law12/2005, arts. 17/5, 17/6**); - In case of genetic screening, populations and individuals have the right to be protected against stigmatization (**Law 2/2005, art. 17/8**); - Persons with special needs, including patients with genetic pathologies and their families, are entitled to protection in regards to healthcare information (**Law 12/2005, art. 17/9**); - The government must regulate genetic tests of heterozygosity status, presymptomatic, predictive or prenatal and preimplantation tests, in order to avoid that national or foreign laboratories without the support of a multidisciplinary medical team offer them without oversight (Law 12/2005, art. 15/1) – *these regulations are still lacking but are expected to be published during 2014*; - The Government is responsible for determining the rules for accreditation, certification and licensing of public and private laboratories that perform genetic tests (Law 12/2005, art. 15/2) – *these regulations are still lacking but are expected to be published during 2014*.
Treatment: gene therapy	*Legal documents* - Law 12/2005 of 26 January on personal genetic information and health information; - Law 67/98 of 26 October on the protection of personal data; - Law 21/2014 of 16 April on clinical research. *Opinions of the National Council of Ethics for the Life Sciences* - 43/CNECV/04 on personal genetic information and health information.	- Written express informed consent (given by a competent person or the legal representative of an incompetent one) is mandatory to participate in clinical research trials and involves the necessary explanation about the nature and aims of the research, procedures and potential risks and benefits (**Law12/2005, art. 16/4, Law 21/2014, art. 2/j, 6/1d**) - Gene therapy medical treatments follow the general informed consent rules.	- Only anonymized health information can be accessed for research purposes (**Law 12/2005, art. 4/4**). - All information in the context of a clinical trial is confidential. Those involved in clinical studies have a duty of secrecy regarding all personal data they have access to. This duty remains even after their involvement in the study is over (**Law 21/2014, art. 51**). - It is the investigator's role to assure that confidentiality measures are in place during preparation, conduction and conclusion of clinical trials, namely regarding personal information of trial participants (**Law 21/2014, art. 10/g**).	- Alterations to the human genome can only be made for prevention or therapy (**Law 12/2005, art. 8**); - Clinical trials involving gene therapy require special authorization by the National Medicines Agency (INFARMED) (**Law 21/2014, art. 27/2a**); - Alterations of "normal characteristics" and of germ line are forbidden (**Law 12/2005, art. 8, Law 21/2014, art. 27/6**); - The scientific community must have free access to the data resulting from research on the human genome (**Law 12/2005, art. 16/2**); - Research on the human genome is subject to the approval by ethic commissions from hospitals, universities or research institutions (**Law 12/2005, art. 16/3**).

After the submission of this article an important piece of legislation was approved in Portugal that is directly related to its subject. Decreto-Lei n.° 131/2014 de 29 de agosto (DL 131/2014), provides the specific regulation required by Law 12/2005 of 16 of January in terms of protection of the confidentiality of genetic information, genetic databases for healthcare and health research, conditions for offering and conducting genetic tests and the terms of genetic counseling. In accordance with this update, please refer to DL 131/2014 whenever in this table it is indicated that a specific regulation is still lacking but expected to be published in 2014.

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