Presidenza del Consiglio dei Ministri

CNB
COMITATO NAZIONALE PER LA BIOETICA

CNBBSV
COMITATO NAZIONALE PER LA BIOSICUREZZA LE BIOTECNOLOGIE E LE SCIENZE DELLA VITA

Bioethical reflections on precision medicine and diagnostic-therapeutic developments

19 November 2020

CONTENTS

Presentation

The opinion was drawn up in the context of a mixed working group, between the Italian Committee for Bioethics (ICB) and the National Committee for Biosafety, Biotechnology and Life Sciences (ICBBSL).

The document initially describes the key aspects, from a technological and epistemological point of view, of the "genetic revolution" over the last two decades, which has allowed the development of precision medicine (PM): under the first profile, the reference is to next generation sequencing technologies (NGS) and to "gene editing" techniques, under the second profile, to the transformation of the paradigms of human genetics that marks the transition to a "post-genomic" and "holistic" concept of the human body.

After distinguishing precision medicine, centred on the stratification of patients based on the molecular profile, from "personalized medicine", tailored to the specific characteristics of the individual, the opinion illustrates, giving some examples, of the state of the art of PM (pharmacogenomics and diagnostic-therapeutic advances). In addition to the difficulties encountered in implementing this promising approach to post-genomic medicine, it then focuses on the bioethical and bio-legal issues it raises. The issues related to the different way of understanding the pathogenesis of diseases and, consequently, their traditional classification, are reported, as well as those of an organizational-formative nature and highlights the challenges related to the balance between the resources to invest in the most innovative research on which the hopes of many patients converge, and those necessary to continue research in more traditional sectors, from which an improvement in the health conditions of the population in general is expected. From a bioethical and bio-juridical point of view, specific questions arise regarding protection of the privacy of subjects receiving medical care, participating in clinical trials and/or donating their biological samples.

The opinion recommends that the introduction of PM should respect the bioethical principle of equity in health care, avoiding abuses in the prescription and performing of genetic tests, making more investments in innovative research (pharmacogenomics would already allow an economic return capable of balancing costs by avoiding wasteful spending on ineffective and/or harmful drugs) and that it should adopt legal instruments to protect the personal identity of patients, without prejudice to the sharing of data and collaboration, at national and international level, between research centres.

In addition, it calls for a reorganization of the health care system needed to support the expansion of PM and recommends implementation of planning aimed at innovation in the provision of services (increase in the number of centres equipped with the expertise required for PM, control of quality standards of laboratories, promotion of disciplinary interaction, adaptation of informed consent) and planning of public information and awareness-raising strategies on the importance of the new findings of human genetics, with reference to the "best practices" that already have produced remarkable results in this direction.

The document is accompanied by a glossary.

The coordinators of the group who drafted the text are: Profs. Monica Toraldo di Francia and Bruno Dallapiccola (for the ICB) and Giuseppe Novelli and Paola Grammatico (for the ICBBSL), with the contributions of Profs. Maurizio Benato, Carlo Casonato and Laura Palazzani (of the ICB) and Prof. Antonio Amoroso (ICBBSL).

The opinion made use of the auditions by Profs. Paola Grammatico, Giuseppe Novelli, Bruno Dallapiccola and Barbara Prainsack (Department of Political Sciences at the University of Vienna and Department of Social Sciences, Health and Medicine at King's College London; member of the European Group on Ethics in Science and New Technologies).
The document was voted unanimously by those present at the ICB on November 19, 2020, by Profs Salvatore Amato, Luisella Battaglia, Stefano Canestrari, Carlo Casonato, Bruno Dallapiccola, Antonio Da Re, Mario De Curtis, Riccardo Di Segni, Lorenzo d'Avack, Giampaolo Donzelli, Mariapia Garavaglia, Marianna Gensabella, Assunta Morresi, Laura Palazzani, Lucio Romano, Massimo Sargiacomo, Monica Toraldo di Francia.
Advisory members, delegated by the Presidents of their respective institutions, despite their not having the right to vote, assent was given by: Dr. Maurizio Benato, the delegate for the President of the National Federation of MDs and Dentists Colleges; and Prof. Carlo Petrini, the delegate for the President of the National Institute of Health.
Profs: Carlo Caltagirone, Silvio Garattini, Tamar Pitch, Luca Savarino, Lucetta Scaraffia, Grazia Zuffa, absent from the session, subsequently assented along with Prof. Paola Di Giulio, the delegate for the President of the Superior Health Council, and Dr. Carla Bernasconi, the delegate for the President of the National Federation of the Orders of Italian Veterinarians.
The opinion was approved on November 19, 2020 by the members of the ICBBSL, Profs: Andrea Lenzi (President), Antonio Amoroso, Antonio Bergamaschi, Carlo Caltagirone, Roberto Cingolani, Fabio Fava, Paolo Gasparini, Maurizio Genuardi, Marco Gobbetti, Paola Grammatico, Mauro Magnani, Piero Angelo Morandini, Luigi Naldini, Ferdinando Nicoletti, Giuseppe Novelli, Pierfranco Pignatti, Roberta Siliquini, Paolo Visca.

1. Premise: the "genetic revolution”

The "genetic revolution" of the past two decades has essentially been a technological and epistemological revolution.

1.1 Next-generation sequencing technologies

The rapid evolution of so-called second generation genome sequencing technologies (*Next Generation Sequencing*, NGS) has transformed and accelerated the research and diagnosis of many diseases. In fact, the versatility of these machines makes it possible to interrogate them at various levels of depth, from the analysis of single genes, to the exome (*Whole Exome Sequencing*, WES), that is the coding part of the genome (less than 2%), or to the whole genome (*Whole Genome Sequencing*, WGS, about 3.1 billion bases)[1]. All this can take place quickly and at extremely lower costs than was necessary in 2000, when the first sequence of the human genome was made public. Compared to the 100 million dollars and the many months required twenty years ago, today for a few hundred euro it is possible to obtain a "genomic analysis" in a few days.

Despite these impressive advances, we still do not know the precise number of human genes and we are not able to interpret all the variations identified by the NGS techniques, many of which remain at the moment of uncertain significance (so-called *Variables of Uncertain Significance* - VUS).

1.2 Gene editing

On a different side, genetic engineering has also seen the emergence of new highly innovative techniques, capable of modifying the DNA sequences of living organisms with high precision[2]. Among them, the so-called "gene editing", or genetic editing, which uses "molecular scissors" to cut the DNA in precise points, in order to eliminate some parts, correct and/or replace others. The best known technique is the one identified with the acronym CRISPR-Cas9[3]. As noted in a previous ICB document, the novelty does not consist so much in the idea of selectively modifying the genome of every living being, but rather "in the molecular assembly carried out to perform the editing operation, which opens up prospects for intervention unimaginable until a few years ago, with characteristics of precision, specificity, relative simplicity, easy accessibility, efficiency and low costs”. With this technique, with multiple cognitive and applicative potentials, it is possible to study the structural organization of the genome of each organism through the modification of the sequences, and therefore of the functions of the DNA genome, and monitor the results within the cell or organism. In theory, by intervening on the mutations affecting the coding part of the genome (about 20

[1]ICB, *Management of "incidental findings" in genomic investigations with new technology platforms*, 17 March 2016.

[2] ICB *Ethical Issues in gene-editing using Crispr/Cas9,* 23 february 2017

[3]*Ibid* CRISPR-Cas9 (*Clustered Regularly Interspaced Short Palindromic Repeats*) is "a technical acronym that indicates a short sequence of RNA (ribonucleic acid) built in the laboratory, programmed to identify a specific region of the genome and guide the Cas9 enzyme (which belongs to the group of restriction nucleases), a sort of 'biological scissor' capable of cutting DNA in the region chosen by the researcher. The part of the DNA removed, as 'defective', can be eliminated or replaced with a 'normal' sequence ".

thousand genes can be analyzed today), it could become possible to “fix a disease-gene or build disease models, even sequentially modify several genes that act additively to give rise to complex diseases"[4]. A highly promising procedure, however, there is still much to learn, for example regarding the potential effect of a specific correction on the function of other genes.

1.3 Epistemological change

It is easy to understand how even the reference paradigms of human genetics have undergone a profound transformation when it was recognized that "between the genotype and the phenotype there are numerous products, which share the suffix 'omic', currently used to indicate a large number of disciplines, or biomolecular derivatives (including the transcriptome, the proteome, the metabolome), which identify different functional expressions of genes". These products, whose characteristic is non-static, as "they change significantly during life, in different ways in various organs and systems", define as a whole "the integrome", or "the ideally most appropriate parameter to describe the individual genomic and post-genomic profile”[5].

With this paradigm shift there has been a marked detachment from the idea that a person can be defined solely on the basis of the genome sequence inherited at the time of conception.

The abandonment of the old conception of genetic determinism, in favour of a "post-genomic" and "holistic" conception of the human body, which considers the continuous changes mentioned above "to a large extent dependent on the individual exposome, that is, on lifestyles and from the environment in which we develop, grow and live”, has then led to the necessary convergence of systematic approaches to diseases which include new diagnostic tools, “omics ”investigations, new mathematical and computational tools.

Already in the 2016 ICB document it was anticipated that this new approach to genomic research would revolutionize the traditional paradigm of medicine based on signs and symptoms, addressing the patient as a "typical figure", setting itself instead an ambitious goal in the development of Precision, Preventive, Predictive and Participatory medicine (so-called "4P medicine").

2. Precision medicine and personalized medicine

There are still uncertainties regarding the definition of the contents and the aims of "*precision medicine*", as the term is often used as a synonym for "personalized medicine". In this document the ICB, in collaboration with the National Committee for Biosafety, Biotechnologies and Life Sciences (ICBBSL), aims to illustrate - in the context of the genetic revolution described above - both the procedures and purposes of "precision medicine" (PM), as well as the bioethical, bio-juridical, educational and organizational issues that its adoption raises, at the same time highlighting, from the beginning, why it is not appropriate at present to consider it as a form of medicine tailored to the specific characteristics of each individual ("*personalized medicine* "in the strict sense)[6],

[4] *Ibid*

[5] ICB, *Management of “incidental findings”*, cit.

[6] Also "*tailored medicine*". It should also be mentioned that for some years the notion of "Precision Public Health" has also appeared. On 6 and 7 June 2016, the University of California San Francisco, in partnership with the White House and the Bill & Melinda Gates Foundation, hosted

even if ideally it aspires precisely to move from the uniqueness of the individual patient to develop increasingly specific and targeted therapies.

2.1 The definition of the National Institute of Health (NIH)

The *National Institute of Health* (NIH) defines *precision medicine* as "an emerging approach for the treatment and prevention of disease that takes into account the individual variability of genes, environment and lifestyle in each person". To implement this innovative approach, the *All of us* project was launched in the USA under the Obama presidency, with the aim of collecting at least one million biological samples of American citizens of various ethnic origins, in addition to data relating to their styles of life, environment, diet, etc. This project was followed by similar ones in various parts of the world, while as regards Italy the "Plan for the innovation of the health system based on omics sciences", approved on 17 October 2017 by the State-Regions Conference, has, so far, remained on paper[7].

Precision medicine, in the broad meaning attributed to it by the NIH, aims to identify a molecular target (mutation(s)) responsible for a disease and the "drugs" (not necessarily just molecules, but also modified cells) that are most effective in blocking its clinical effects. To develop this approach it is necessary to:

a) make use of the collection and integration of a large amount of data (big data) and biological samples, containing information regarding individuals (including clinical information, lifestyles, environment, genomic profile), to then stratify the patients into molecular subgroups based on their predisposition to a particular pathological form and/or their response to a particular type of pharmacological treatment[8];

b) integrate omics techniques, including those that investigate the functional aspects of the genome (transcriptome, proteome, metabolome, methylome), and those that investigate the most significant "environmental" component of each person, the microbiome, or the complex of bacteria that lives with the host and has a modulating action on the genome;

---

the "Precision Public Health Summit" to discuss how the precision medicine approaches could be applied in the public health arena to improve the health of the population, also favouring equity. The topic is already the subject of a vast literature. An editorial in *The Lancet* makes it clear that, in its simplest form, precision public health is about "using the best data available to target interventions aimed at those who need it most effectively and efficiently. Nothing in this definition excludes traditional public health concerns "(R. HORTON Offline, *In Defense of Precision Public Health*, in "Lancet ", 2018 October 27; 392 (10157): 1504. But this is not the only definition proposed, e.g. in an article in “Jama”, precision public health is described in these terms: "Similarly to how precision medicine uses genomic and other personalized patient data to deliver the right treatment to the patient at the right time, precision public health is an emerging discipline that uses extensive population-specific data to deliver the right intervention to the right population at the right time. Precision public health uses data from traditional and emerging sources to target interventions for populations based on person, place and time, in part with a focus on reducing health disparities ”. (S. RASMUSSEN, M. KHOURY, C. DEL RIO, *Precision Public Health as a Key Tool in the COVID-19 Response*, in “Jama”, 2020 September 8, 324 (10), pp. 933-4.

[7] Objective of the "Plan for the innovation of the health system based on omics sciences": to outline "the ways in which genomic innovation should be grafted into the National Health Service in the areas of prevention, diagnosis and treatment, with a view to effectiveness (*evidence-based*) and sustainability (*cost-effectiveness*) of the NHS, for the purpose of improving the health of the individual and the population".

[8] In this regard, the expression "stratified medicine" is also used, because it is based on the identification of subgroups of patients with distinct pathological mechanisms or particular responses to treatments.

The ultimate goal of this systems medicine approach is to:

i. identify the cause and mechanism of the disease and the most appropriate drug for its treatment and/or prevention;

ii. develop new methods to test drug resistance, using pharmacogenetic analyzes, capable of identifying the genomic variants underlying the individual response to therapy, in terms of efficacy and prevention of adverse effects;

iii. design and launch new clinical trials to test new drugs;

iv. translate the results into the clinical part and monitor responses to therapy.

2.2 Technical difficulties

Despite the undeniable progress of recent years, the predictions made at the time of publication of the first draft of the human genome, which envisioned the immediate identification of all disease-genes, the development of predictive medicine and the development of individualized prevention protocols and therapy, after more than twenty years appear too optimistic.

Since 2010, the increasing availability of next generation sequencing technologies has allowed, however, to increase exponentially the discovery of new genes responsible for diseases, even if still a high number of patients affected by a disease, of a probable genetic nature, remain without certain diagnosis[9].

Several factors justify the current limitations:

1. About 85% of the 7-8,000 rare diseases known today concern conditions that occur with a frequency of lower than one case per million births.

2. The clinical pictures of many of these patients are relatively uncharacteristic and do not show clinical signs capable of evoking a specific disease.

3. There is significant inter-individual variability among people affected by the same condition, so even in the presence of a known disease, it may not be recognized due to its atypical presentation.

4. In 2-4% of rare disease patients the clinical picture results from the association of two diseases, which can give rise to clinical pictures different from those expected for the two individual diseases.

5. One could be faced with a new disease.

As regards complex diseases and phenotypes (more commonly affecting the adult population and the elderly, often with multiple pathologies rather than a single pathology), we currently know, with few exceptions, only a small part of their heritability. For this reason, the clinical implications of the many available studies remain limited, also due to the scarce predictive power of individual variations. Another limit is represented by the often very significant variability of the interethnic frequency of genetic polymorphisms, so the results of the associations between genetic variants and complex diseases, obtained on a given population, must be validated on the different populations before being transferred into clinical practice.

However, genomic analyzes have allowed us to decrypt part of our biological complexity, which makes each person unique: people differ by 4-5 million bases, 85% of these are rare, or private variants (with a frequency of less than 1%), with

[9] It has been estimated by the *National Institute of Health* that about 6% of all those who have a rare genetic condition remain undiagnosed, as well as at least 40% of children with mental disabilities.

functional effects in 95% of cases[10]. A significant part of the genetic variability consists of post-zygotic (somatic) mutations, estimated in millions[11]. Added to this are the functional effects on the genome induced by the environment, with consequences that are still largely unexplored and unknown.

Hundreds of studies, carried out in recent years, have analyzed huge samples of the population affected by complex diseases and samples of the non-affected population, in order to search for any differences between the two samples, in terms of frequency of genetic variations, potentially indicative of an association and therefore predictive of disease susceptibility. Considered globally, these studies have produced relatively limited results transferrable into clinical practice, since - as stated above - individual variations have a low predictive power and on average less than 15% of the heritability of phenotypes and complex diseases has been decrypted.

2.3 Why, at present, is it more appropriate to speak of "*precision medicine*" rather than "*personalized medicine*"?

One answer, of a more general nature, comes from the medical profession itself, as it argues that treatment can never be separated from the building of a "personalized" doctor/patient relationship, which also includes careful consideration of the characteristics specific to each patient, considered as a person, both in the diagnostic phase and in that of therapeutic decisions.

Going into detail, if it is true that the common starting point is that "these are patients, not diseases" - thereby deviating from traditional therapeutic approaches centred on statistical profiles and on a typical figure of the patient abstractly constructed and detached from a concrete context of life and relationships - to be able to speak in the proper sense of the "personalization" of care, it is necessary to know all the characteristics of a person, which in fact is not possible today for several reasons, already partially anticipated: health and disease do not depend only on our genome, but also on the environment (exposome) and on the effects of their interaction, which are currently little known; most of the genetic characteristics that make people different from each other are linked to rare variations, the effects of which are mostly unknown; only approximate knowledge of the non-coding part of the genome (98% of the DNA) is available; during development and throughout the course of life millions of somatic mutations are accumulated whose functional effects are largely unknown.

According to some scholars, "precision medicine" (PM), in its specific and limited meaning, could be described as a medicine which has intermediate connotations between conventional and personalized medicine[12], as it also relies on the stratification of patients based on specific characteristics and potential molecular targets.

[10] Rare or private variants differ from the polymorphisms that affect at least 1% of the population; due to their low frequency, their functional effects are in most cases unknown.

[11] A conservative estimate suggests that, in the brain alone, changes induced by the repositioning of transposable elements would give rise to at least 100 million different genomes.

[12] Cf. L. CHRIS, *Precision Medicine: What Barriers Remain*? in “Pharmaceutical Technology”, 2, March 2020, https://www.pharmaceutical-technology.com/features/precision-medicine-2020/.

3. Considerations on the state of the art of "precision medicine"

3.1 Pharmacogenomics

There are currently many cognitive limits on the impact of drug therapy, in particular as regards the efficacy and differential toxicity in the two sexes and at different ages of life, the optimal dosage of single molecules, the duration of treatment and pharmacokinetic interactions. and pharmacodynamics when using drug combinations. Even with these limitations, there is no doubt that many recent advances in PM have been driven by pharmacogenomics, the science that characterizes genetic variations and their interaction with the environment, in an attempt to explain why the same treatment is effective in some patients. and not in others and why in others still it produces often very serious adverse effects[13].

These researches have been guided in recent decades by observation of the limits of traditional pharmacology, often expensive and ineffective and/or harmful precisely because generalizing. The analysis of inter-individual genetic differences often allows us to understand and anticipate the different response to drugs. In fact, for the prescription of some innovative biological drugs, especially in the field of oncology, the characterization of the genetic profile of the patient is required in order to identify those who will benefit from it, compared to those for whom the drug is ineffective or could produce adverse reactions. In some cases, pharmacogenetics also allows to define the most appropriate dosage of the drug. An important part of the pioneering experience in this field has been made by oncology, which has made it possible to obtain very significant results, such as to recommend or make mandatory the characterization of the genetic profile of patients who are to undergo certain therapies, to identify those who can benefit most. This approach, which is integrated with pharmacokinetic and pharmacodynamic evaluations, has made it possible not to withdraw from the market products which, despite being harmful for a subgroup of patients with a specific genetic mutation, have instead proved to be of great benefit for other people affected by the same pathology. An emblematic example of this is Abacavir, a powerful antiviral used in the treatment of HIV, which in a small percentage of patients had created a severe hypersensitivity reaction, due to a particular genetic variation[14]. The discovery of the cause of this hypersensitivity made it possible not to withdraw the drug from the market.

Although the literature on the subject has expanded considerably[15], the costs of genetic tests have up to now constituted a limiting factor in the clinical translation of many of the genotype-phenotype correlations produced by pharmacogenetics. A critical aspect, however, remains the limited knowledge of the heterogeneity in the distribution of the drug in the various layers of the tumour.

3.2 Clinical practice and precision therapies

Advances in pharmacogenetics are matched by other advances in the therapeutic field, with the transition to *targeted therapy*, based on molecular

[13] From an interview with Prof. Giuseppe Novelli

[14] That is, the presence of a B5701 allele in the HLA system.

[15] See for example. “Pharmacogenomics Knowledge Base PharmGKB”, an interactive tool available to those who do research in pharmacogenomics http://www.pharmgkb.org.

targets, which allow patients to be stratified according to the different genetic mutations.

The molecular genetics technologies developed in recent decades have made it possible to obtain important results in the understanding of the genetic basis of tumours and rare diseases, but also of diseases with high frequency in the population, thus constituting a particularly important tool in the identification of molecules capable of acting directly on the molecular target that causes the disease.

The applications of precision medicine are exemplified by cardiovascular diseases, in the context of which cost-effectiveness studies have been reported that have shown how molecular investigations before administering the therapy, as well as guaranteeing the a priori identification of patients who will respond to the molecule, and in some cases even the most appropriate dose, make it possible to rationalize costs, reducing adverse reactions associated with taking the drug[16].

Oncology is certainly one of the areas in which precision medicine has developed the most. An example of how much these studies have helped to improve diagnosis in recent years is the liquid biopsy, a test that, through a blood sample, allows the extraction of circulating free DNA (cfDNA, *cell free DNA*) from the plasma. Using circulating tumour DNA (ctDNA, *circulating tumour DNA*), it is possible to search for genetic mutations that confer sensitivity or resistance to so-called "molecularly targeted" drug therapies. The first use of liquid biopsy for the purpose of predictive diagnosis for drug treatment was in patients with non-small cell lung cancer, in whom it may be difficult to perform tissue biopsy, a traditional tool for monitoring the genetic evolution of the tumour, but which is poorly tolerated due to its invasiveness, the contingent clinical conditions of the patient or location of the tumour. This approach also has the advantage of providing more information on tumour mutational burden and identifying emerging mutations in metastatic lesions during disease progression. It has been shown that this technique can also be used in the diagnosis of colorectal cancer[17], as well as in the post-operative evaluation of patients with other cancers of the digestive tract, for better prognostic evaluation[18]. Although the usefulness of liquid biopsy in

[16] C. L. DAVILA-FAJARDO et al., *Pharmacogenetics in the Treatment of Cardiovascular Diseases and Its Current Progress Regarding Implementation in the Clinical Routine*, in "Genes", 2019, 10, 261; doi: 10.3390 / genes 10040261. In this context, the study of variants of the CYP2C9 gene played a pioneering role, in which homozygotes for the CYP2C91 * 1 allele normally metabolize the drug S-Warfarin, while the CYP2C91 * 2 and CYP2C91 * 3 alleles reduce enzymatic activity, respectively by 30 and 80%. Warfarin is one of the most widely prescribed anticoagulants and acts by inhibiting the activation of coagulation factors dependent on vitamin K. Consequently, even a limited variation in its blood concentration it can lead to adverse reactions, including bleeding or loss of efficacy. Recently, the Association of Molecular Pathology and the College of American Pathologist produced recommendations (V.M. PRATT et al*, Recommendations for Clinical Warfarin Genotyping Allele Selection,* in "The J Mol. Diagn.", 22 July 2020) and reported the mutations in the genes involved in the metabolism of Warfarin (e.g. VKORK1, CYP4F2, CYP2C), providing useful data to create a minimum panel of variants to be analyzed, for a correct evaluation of the response to the drug by individual patients.

[17] A. DASARI et al., *CtDNA Applications and Integration in Colorectal Cancer: an NCI Colon and Rectal–Anal Task Forces Whitepaper*, in "Nature Reviews Clinical Oncology", volume 17, pages 757–770 (2020).

[18] K. SHODA et al., *Liquid Biopsy as a Perioperative Biomarker of Digestive Tract Cancers: Review of the Literature*, in "Surgery Today", 26 September 2020, DOI https://doi.org/10.1007/s00595-020-02148-7.

clinical practice has not yet been widely evaluated, numerous studies, including prospective ones, have confirmed its clinical and therapeutic importance.

Another example that can be cited is that of personalized treatment approaches that investigate the molecular heterogeneity of the H3K27M glioma on the basis of tumour biopsies; the safety and feasibility of these approaches has been demonstrated, although, in selected cases, the clinical efficacy deserves to be validated through larger clinical trials[19].

The characterization of risk alleles in a precision medicine context has recently been extended to the study of other complex and multi-factorial diseases, such as infectious ones. It has long been known that the response to infections varies between individuals, even when exposed to the same pathogen. In recent years it has been possible to identify subgroups of patients at risk, on the basis of which novel therapeutic solutions have been suggested. A recent and significant example concerns the COVID-19 pathology from SARS-CoV-2 infection. It has been shown that some specific genetic and immunological mutations are at the basis of 15% of severe forms of infection. These patients share a defect in the production of type I interferons (IFN), proteins that help regulate the activity of the immune system with antiviral functions. In 3.5% it was possible to identify specific alleles in 13 genes of the interferon family, already known to be involved in genetic susceptibility to influenza. Regardless of their age, people with these mutations are at greater risk of developing severe influenza or Covid-19[20], a fact that has immediate direct repercussions on their therapy. It suggests, in fact, their treatment with type 1 interferon, a drug known for more than 30 years that has no apparent side effects if taken for a short period of time. In the other patients, however, auto-antibodies have been identified (as in autoimmune diseases), which block the action of type I IFN (10-11% of severe forms). These auto-antibodies neutralize the antiviral effect of interferon and are present in over 10% of patients who develop severe SARS-CoV2 pneumonia, while they are not present in the general population. Their presence prevents type I IFN molecules from acting against the virus. The production of these antibodies directed against patients' immune systems probably reflects other genetic alterations currently under study. Patients with auto-antibodies may benefit from plasmapheresis (infusions of the liquid part of the blood of convalescent patients containing white blood cells and antibodies), or other treatments that can reduce the production of these antibodies by B lymphocytes[21]

[19] J. GOJO et al., *Personalized Treatment of H3K27M-Mutant Pediatric Diffuse Gliomas Provides Improved Therapeutic Opportunities*, in “Front Oncol.”, 2019; 9: 1436, published online 2020 Jan 10. doi: 10.3389/fonc.2019.01436, PMCID: PMC6965319, PMID: 31998633. The interest of molecular characterization in oncology is highlighted by a recent publication (The ICGC / TCGA *Pan-Cancer Analysis of Whole Genomes Consortium, Pan-Cancer Analysis of Whole Genomes*, in "Nature", 2020, 578, pp. (82–93), in which the results produced by an international consortium of thousands of researchers who, with an approach integrated analysis and sharing of data, analyzed 2,658 genomes of 38 tumour types. This study, in addition to representing an important advance in the understanding of cancer genetics, has laid the foundations for a second phase during which attempts will be made to use data to obtain new precision therapies.

[20] Q. ZHANG, *Inborn Errors of Type I IFN Immunity in Patients with Life-Threatening COVID-19*, in *“Science”,* 23 Oct 2020: Vol. 370, Issue 6515, eabd4570 DOI: 10.1126/science.abd4570.

[21] F. BASTARD et al., *Autoantibodies Against Type I IFNs in Patients with Life-Threatening COVID-19*, in “*Science”,* 23 Oct. 2020: Vol. 370, Issue 6515, eabd4585 DOI: 10.1126/science.abd4585.

3.3 Critical issues

Despite the availability of an increasing number of targeted treatments for the treatment of diseases, the possibility of treating numerous patient samples with precision therapies still faces a number of obstacles, starting with the prohibitive cost of many of these treatments (in some cases over a million euro per year). This leads to an unfair accentuation of inequalities in health, since for some patients there is a concrete possibility of aspiring to a cure, possibly even resorting to private financial resources, while many others have to give up hope of accessing the best therapies available. While the benefits of implementing precision medicine are obvious and the benefits in terms of improving health may over the long term be offset by an economic return, the costs of these treatments are currently putting a strain on the sustainability of the NHS and principle of universality which inspires it.

However, the cost of treatment is not the only obstacle to an equitable and non-discriminatory use of PM. Most of the genetic knowledge, for example, is based on the genomes of a limited group of individuals. Also, in the case of complex diseases, a high percentage of the genomes in genome-wide association studies (GWAS) are of European descent[22]. This profile indicates that most of the genetic information we have refers only to a part of the world population and therefore it can be considered accurate only for that part. The current logic of PM runs the risk of not addressing the variables that cause the majority of morbidity and mortality in the poorest countries. It is however necessary to clarify that this is an open question for complex diseases. In fact, many PM protocols apply to rare diseases, for which this problem does not exist.

From a clinical perspective:

1. It is not always possible to proceed with “targeted therapies”, as only few centres currently have the clinical, instrumentation and laboratory expertise required to provide PM.
2. With regard to onco-haematological diseases, the therapies can lead to specific toxicities for some patients, or even abnormal activation of the immune system which can cause serious side effects.
3. With regard to gene therapy, compared to the technique that makes use of the introduction by viruses or other vectors of functional copies of the gene to replace the mutated one, it must be considered that the level of efficiency must be sufficient for all target cells to be infected; moreover, the risk of immune reactions towards the virus is sometimes very high, so much so that some patients have to be treated in intensive care due to the immune response; finally, it is necessary to develop protocols capable of guaranteeing the effectiveness of the therapy over time.
4. The real limitation is that gene therapy is currently only available for very few of the thousands of Mendelian diseases, both because not all diseases present the conditions for developing such a therapy, and because protocols dedicated to all of those theoretically eligible have not yet been drawn up.

[22] Cf. A.C. NEED, D. B GOLDSTEIN, *Next Generation Disparities in Human Genomics: Concerns and Remedies*, in “Trends Genetics”, 25 (11), 2009, pp. (489-494).

From the organizational, financial and regulatory perspective:

1. There remain other barriers that limit access to genetic/genomic tests essential for referring patients to innovative treatments (for example, in Italy, Esima has not yet included these in the LEA); this is due to structural organization and clinical work that has to be "revolutionized" in order to meet the multidisciplinary coordination needs of PM.

2. Another obstacle to the development of research and its clinical translation is the limited propensity of large pharmaceutical companies to invest in therapies addressed to only few patients, given the high costs involved in the development of innovative therapies. Although the situation is still evolving, as several companies, large and small, are investing in "orphan" drug research whose world market is expected to reach 250 billion dollars in the next 5 years, it should not be forgotten that, at the moment, around 2000 "designated" drugs, whose conceptual validity or validity based on preliminary data recognized by the EMA, are still pending due to the lack of funding.

3. The paradigm shift in clinical trials and the regulatory uncertainties that have accompanied this step increase the tension between the need to ensure patient safety and that of speeding up the time for approval and marketing of new potentially decisive drugs for pathologies still lacking effective treatments[23]. Traditionally clinical trials are designed to test the safety and efficacy of drugs on increasingly large segments of the population, in the new perspective of PM they require calibration on small subgroups of patients, a condition that entails, in addition to greater costs, even greater difficulties in identifying and recruiting subjects with an appropriate molecular profile. Added to this is the further difficulty of providing, each time, sufficient evidence of safety and efficacy, as the design of trials aimed at small numbers presents statistical problems inherent in defining the risk/benefit profile of the product in question. The regulatory agencies, in turn, are still debating the question of the most appropriate criteria for evaluating the results of these new protocols and these uncertainties may have repercussions on the reluctance to invest in PM[24].

4. Open issues

PM poses a number of challenges to traditional medicine and raises various ethical issues.

4.1 Epistemological, scientific, and regulatory issues

Does the different way of understanding the concept of "disease" involve a different nosography and a different way of setting up clinical trials?

For those in favour of the new approach it would even be a question of "reinventing" disease[25], rethought in terms of chains of biological events that

[23] Cf. C. LO, Precision Medicine: What Barriers Remain?, cit.

[24] See L. KNOWLES, W. LUTH, T. BUBELA, *Paving the Road to Personalized Medicine: Recommendations on Regulatory, Intellectual Property and Reimbursement Challenges*, in "Journal of Law and the Biosciences", V. 4, Issue 3, December 2017, https://doi.org/10.1093/jlb/lsx030.

[25] See J. J. BERMAN, *Precision Medicine and the Reinvention of Human Disease*, Elsevier Academic Press, 2018. Already in 2011 the NIH had promoted an ad hoc committee to explore the possibility of a new taxonomy of human diseases based on molecular biology rather than on

ultimately result in a pathological event. If in the past we relied on signs and symptoms to identify the pathogenesis of a disease, with the risk of including biologically unrelated diseases under an imprecise diagnostic term, today a deeper understanding of their onset is considered necessary, so as to be able to assign each disease to classes that share the same pathogenesis. Even randomized controlled trials, which are still the gold standard of clinical trials, undergo a downsizing, because PM involves, as mentioned, a redefinition of the enrolment criteria, a new design for conducting the trial with small numbers of patients, new statistical and bioinformatics approaches, as is the case for rare disease research. This is a challenge that requires new regulatory flexibility[26], while bearing in mind that the statistical models developed according to the specific question that each study poses must always be validated and confirmed in order to be generalized[27].

Again in terms of rethinking the current regulatory framework, it is essential to deepen the reflection on the distance between research and therapy, a distance that PM tends to reduce. Also in this case, without falling into the temptations of *therapeutic misconception*, the key to a renewed regulatory approach could pass through a clear communication of the different dimensions that intersect in PM, with the consequent provision of an extension of the time dedicated, in the context of the therapeutic relationship, to information and obtaining the patient's informed consent.

4.2 Training and organization issues

How does the adoption of the PM perspective affect medical thinking and what does it involve in terms of organization of clinical pathways and the training of health professions?

The new paradigm of postgenomic medicine is revolutionizing, as mentioned in the introduction, the epistemological approach to the study of diseases, as the interpretative basis of every cellular and pathophysiological phenomenon is now delegated to molecular biology and "omics" sciences, while the organization of biological systems is represented as a network that changes continuously depending on the physiological state and in continuous interaction with the environment.

PM provides the clinician, through the evidence on dynamic pathological processes, the knowledge bases to implement precise diagnosis and therapeutic strategies.

If it is true that the improvement of the state of health of the population and of the single individual is intimately linked to healthcare organization and its performance, then, as highlighted in several national and supranational policy

---

signs and symptoms (https://www.nationalacademies.org/our-work/framework-for-developing-a-new-taxonomy-of-disease). See also X. ZHONGZHOU et al, *A Systems Approach to Refine Disease Taxonomy by Integrating Phenotypic and Molecular Networks*, in "EbioMedicine", (May 2018), https://www.sciencedirect.com/science/article/pii/S2352396418301233. According to this perspective, "The International Classification of Diseases", established a century ago and still sponsored by the WHO, would be largely lacking in the face of the results achieved by molecular biology in the era of big data.

[26] Both the European Commission and the NIH launched, in 2011, the International Consortium for Research on Rare Diseases (IRDiRC), including among its aims that of developing alternative methods for carrying out clinical trials with few patients.

[27] See I.R. KÖNIG et al., *What is Precision Medicine?* in “Eur Respir J”, 2017; 50: 1700391 https://doi.org/10.1183/13993003.00391-2017.

documents, to facilitate the desired development of PM, even the structure of healthcare organization should also be rethought according to a different design of the diagnostic-therapeutic-care pathway[28]. To this end it would be necessary to proceed to a greater unification of professional perspectives, favouring interdisciplinary work in a team in which the different disciplines feel involved and responsible for a shared process. Consequently, also professional and inter-professional training[29], strongly neglected in recent years, should be reoriented towards the acquisition of a solid medical and bioethical culture, continuously updated, with the expertise suitable to carry out work processes, with a high level of multidisciplinary integration, which is efficient, effective and equitable. It is therefore a question of inserting a new paradigm in university education and in the training of doctors and other professionals cooperating in the development of biomedical disciplines. Despite declared intentions, in Italy still little or nothing has been done in this direction.

4.3 Resource allocation and equity issues

Who risks staying on the sidelines or being excluded?

Among the challenges triggered by PM, particularly problematic, is the balance between the resources to invest in the most innovative research, on which the hopes of many patients converge, and which only in the long term could lead to a improved efficacy of treatment and in the efficiency of health expenditure, and the resources necessary to continue research in the more traditional sectors, from which an improvement in the health conditions of the population in general is expected.

If pharmacogenomics already today would allow an economic return capable of balancing the costs[30], avoiding wasteful spending on ineffective and/or harmful

[28] The "Plan for the innovation of the health system based on omics sciences", already mentioned, expressed the ambition to outline the modalities of implementation of biomedical innovations precisely through a "radical reorganization" of the service itself, with particular reference to indications contained in the document of the Council of The European Union, *Council conclusions on personalized medicine for patients,* published on December 17, 2015. The Conclusions invited member states to: "offer opportunities for education, training and continuous professional development to health professionals in order to equip them with the knowledge, skills and competences necessary to make the most of the benefits that personalized medicine brings to patients and health care systems; encourage cooperation in the collection, sharing, management and adequate standardization of the data necessary for effective research on personalized medicine and for the development and application of this medicine, in accordance with the rules on data protection; promote interdisciplinary interaction ".

[29] In recent years, inter-professionalism has become an important object of study both in the pedagogical and health fields. The need for a unified response to the health needs of patients requires the various professionals to synergistically integrate their skills and to work together constructively towards a common goal. Interprofessional training is recognized by WHO as an opportunity to prepare students of the health professions for collaborative practice (L. MONTAGNA, G. GAMBALE, M.G. DE MARINIS, *Esperienze di formazione interprofessionale in simulazione. Experiences of Interprofessional Education in Simulation,* in Quaderno *La simulazione: un'innovativa metodologia didattica nella formazione degli operatori sanitari*, "Medic", 2015; 23 (2), pp. 42-49.

[30] One of the main obstacles to the implementation of pharmacogenomics in the clinic has been the number of studies aimed at demonstrating the cost-effectiveness in terms of clinical outcomes. There are currently at least fifteen detailed studies showing a reduction in expenditure in the region of 30-40% and, in the long term, even greater, considering that the cost of genetic testing decreases rapidly (Review in K. KREBS, L. MILANI, *Translating Pharmacogenomics into Clinical Decisions: do not Let the Perfect Be the Enemy of the Good*, in "Human Genomics" (2019) 13,39).

drugs, it is a different case for the most effective precision therapeutics, which weigh heavily on the NHS budget[31]. The risk of increasing already existing inequalities between those who can be treated, now or in the near future, and those who cannot, is real and is not even adequately mitigated by the numerous *ad hoc* fundraising initiatives for research promoted with the involvement of many actors (banking foundations, public and private, national and supranational scientific foundations, patient communities, etc.).

In addition to the problem of the prohibitive costs of many innovative drugs and the "tragic choices" required by these costs, perhaps, another problem should be considered at the origins, that of the influences exerted on the orientation of research. The fruitful alliance that has developed in recent decades between patient organizations and those who are able to accelerate the development process of new therapies and precision treatments[32], including the study of complex diseases, is a very significant result that however, it is not free from possible unintentional effects.

Citizen-patient organizations and their families, sharing their experiences, suffering, needs, fears, have organized themselves via internet into communities that can be defined as "biosocial"[33], with the dual purpose of providing internal support to their own members as well as, at the same time, representing a cohesive entity able to assert its own voice within the public debate. Not only do they promote campaigns in favour of medical-scientific research and equal access to social and health services, but they also claim their right to participate in the definition of research objectives and in the governance of biobanks, establishing new forms of relationships with scientific authorities and with pharmaceutical companies. The expansion of the presence and incisiveness of these virtual communities, while presenting many positive aspects, not least the willingness to invest in biomedical research, to donate their biological samples and to participate in clinical trials, also brings us to reflect on some possible critical aspects, including the danger that some “orphan” diseases are not represented and consequently, are neglected by fundraising campaigns and research. Added to this is the risk that, by basing their self-learning at least in part on the websites managed by large pharmaceutical companies, citizen-patients will be misled, in their commitment to achieve specific objectives, by the pressure of the economic interests at stake into anticipating treatments at increasingly early dates and their appropriateness being unproven.

See also P. LANTING et al., *Practical Barriers and Facilitators Experienced by Patients, Pharmacists and Physicians to the Implementation of Pharmacogenomic Screening in Dutch Outpatient Hospital Care - an Explorative Pilot Study*, pre-print, in "medRxiv", November 13, 2020.

[31] It should also be borne in mind that art. 4 of the "Plan for the innovation of the health system based on omics sciences" establishes that "the activities envisaged by this agreement are provided within the limits of human, instrumental and financial resources available under current legislation".

[32] An example is represented by the "*Pharmacogenetics and Stratified Medicine Network*", an association between health professionals, academic researchers, industrial partners, regulatory bodies and patients, created with the aim of increasing "stratified medicine" in the United Kingdom and facilitating its clinical transfer.

[33] N. ROSE, *The Politics of Life Itself. Biomedicine, Power and Subjectivity in the Twenty-First Century*, Princeton University Press, Princeton 2007, trad. it. Milano, Einaudi 2008.

4.4 "Privacy" protection issues

From a bioethical and bio-juridical point of view, specific questions arise regarding the protection of *privacy* of the subjects undergoing treatment, participating in clinical trials and/or donating their biological samples. In the era of *big data* and Artificial Intelligence (AI), the procedure of the pseudonymisation of personal data no longer constitutes, in certain contexts, a guarantee of confidentiality, as it is always possible, if desired, to trace the identity of the subjects concerned through the 'cross-referencing of information, with possible discriminatory repercussions, for those same subjects and their family members, in terms of insurance, work, etc. As already stated in the document of the ICB/ICBBSL on Artificial intelligence and medicine: bioethical profiles[34], in which the sharing of data was considered an indispensable "social good" for biomedical progress, the problem of the possible misuse of collected information was raised and the planning of regulatory initiatives suitable for preventing violations of the confidentiality of sensitive data called for. Also on this front, the identification of strategies to overcome the limits of current methods of protecting *privacy* is proving to be a difficult undertaking.

In addition, more flexible tools could be thought of to protect the identity, rights and non-discrimination of the sick person, without prejudice to the practice of *data sharing*, which is proving to be increasingly useful for clinical research. One possibility, albeit not easy to implement, is the adaptation of the regulations that sanction data abuse, in particular in the insurance and employment sectors.

5. Recommendations

In light of these considerations, the ICB and ICBBSL formulate the following recommendations.

1. As regards sustainability, the obstacles that limit the possibility of treating large samples of patients with precision therapies, due to the high costs of these therapies, lead to an unfair accentuation of the existing inequalities in terms of the protection of health, in contrast with the bioethical and bio-juridical principles of universality and equality underlying the NHS and with the principle of equality and non-discrimination enshrined in our Constitution and in the international documents on human rights, first of all is the fundamental right to health. In particular, the Convention on Human Rights and Biomedicine is recalled, which emphasizes the need to adopt adequate measures to ensure "equitable access to health care of an appropriate quality".

Being aware of the extent to which the costs of diagnoses and innovative therapies can affect the sustainability of our health system, the two Committees believe that the possibility of resorting to additional resources in the current context of the pandemic could provide an opportunity to implement some of those measures and to outline, in a far-sighted perspective, the ways in which genomic innovations can truly become an integral part of the pathway of prevention, diagnosis and treatment of diseases. The Committees therefore recommend a concrete commitment to facilitate the clinical translation of pharmacogenetics,

[34] ICB-ICBBSL, *Artificial Intelligence and Medicine: some ethical aspects*, 29 May 2020.

with particular reference to the stratification of patients, which would allow an immediate and important economic return through the appropriateness of treatment, avoiding wasteful expenditure on ineffective or harmful drugs.

2. Believing, at the same time, that it is necessary to establish precise rules to gain access to genetic tests of a specific clinical significance, through the regulation of prescribers, and recommending that interventions be prepared to combat misleading advertising and the offer to patients of clinically useless tests and/or inappropriate or not validated tests, whose abuse directly impacts the ethical and economic aspects of the health system, both in the public and private sectors[35].

3. Hoping, as far as research is concerned, for allocation of adequate funding in order to allow investment in the most innovative clinical studies, on which the hopes of many sick people, without treatments proven to be effective and lasting, today converge, with particular reference to the definition of the biological basis of diseases, essential for the development of drugs directed against specific molecular targets, without divesting resources from research relating to more traditional sectors.

4. Hoping that legal instruments will be adopted to protect the personal identity of patients, without prejudice to the sharing of data and collaboration, at national and international level, between research centres[36]. As already stated in other documents of the two Committees, the sharing of data must be considered an indispensable "social good" for biomedical progress, which however must coexist with the principle of confidentiality of personal data, which must be protected with suitable regulations to prevent any misuse.

5. With regard to the reorganization of the health system needed to support the expansion of Precision Medicine, the recommendation is for implementation of innovation-driven planning in the provision of services. Recommending in particular:

i. increasing the Centres equipped with the clinical, instrumentation and laboratory expertise required to provide PM and which share the same protocols.

ii. adopting measures aimed at preventing the proliferation of non-accredited medical genetics laboratories and/or laboratories that do not meet specifically required quality standards[37].

iii. Promoting, as proposed by the Council of the European Community, interdisciplinary interaction, especially between experts in genetics, in the use of statistical methodologies, bioinformatics, health informatics and epidemiology, and health professionals, to ensure correct interpretation of data, more efficient integration and interpretation of information from multiple sources and appropriate decisions on treatment options.

iv. Allocating a wider space for information and obtaining the consent of patients and subjects participating in clinical trials in PM, in order to fully explain the potential, but also the limits and possible risks of applications resulting from new knowledge.

[35] http://www.salute.gov.it/portale/lea/homeLea.jsp.
[36] Council of the European Union, *Council conclusions on personalised medicine for patients*, cit.
[37] ICB, Management of *"incidental findings",* cit.

6. In this context of change in the epistemological approach to the pathogenesis of diseases and the transition towards targeted therapies, based on molecular targets and on the stratification of patients based on molecular profile, the two Committees hope that special attention will be given to the training of professionals involved in the field of health.

Recommending, therefore that, along with continuous refresher courses, the professional training and inter-professional training of health care workers should be reoriented to equip them, on a cognitive and practical level, with knowledge, including bioethics, and the multifaceted expertise required to face the challenges of biomedicine.

7. The two Committees reiterate the need to implement information and awareness-raising strategies for the population highlighting the importance of the new acquisitions of human genetics, referring to the "good practices" that have already given significant results in this direction, an element that is of particular importance in this pandemic emergency[38].

6. Glossary

Adverse event – An unexpected event arising from the health care process, which results in unintentional and untoward harm to the patient.

Allele - Alternative form of a gene, occupying the same locus on a pair of homologous chromosomes.

Association - Presence, in a group of patients, of a particular allele, with a higher frequency than randomly expected.

Autoimmune diseases - Pathologies characterized by an abnormal reaction of the immune system, which attacks and destroys the healthy tissues of the body, mistakenly recognizing them as foreign.

B lymphocytes - Blood cells that produce antibodies that bind to the specific antigen and contribute to its destruction.

Base - nitrogenous - In biochemistry, it means one of the five bases that make up the nucleotides of DNA and RNA; they are divided into purines and pyrimidines, respectively adenine and guanine, and cytosine, thymine and uracil. Both purines are present in DNA and, among the pyrimidines are cytosine and thymine.

CRISPR-Cas9 - (Clustered Regularly Interspaced Short Palindromic Repeats) - Acronym for a short sequence of RNA (ribonucleic acid) built in the laboratory, programmed to locate a precise region of the genome and guide the

[38] For the study of host genomics, in the COVID-19 pandemic, a dozen International Consortia have been set up in a few months, including the *Covid Human Genetic Effort* Consortium (https://www.covidhge.com/). This Consortium has networked about a hundred laboratories, from all over the world, which exchange data and genomic information on a weekly basis, rapidly reaching important results for this pathology. The biggest challenge ahead, however, is to create data consortia that enable the sharing and interoperability of data quickly and securely.

Cas9 enzyme (a restriction nuclease) into it, a sort of "biological scissor" capable of cutting the DNA in the region chosen by the researcher. The removed part of the DNA, as "defective", can be eliminated or replaced with a "normal" sequence.

Disease gene - Gene responsible for a hereditary disease.

DNA - Deoxyribonucleic acid: nucleic acid present in chromosomes, in which genetic information is encoded.

DTC, Direct to consumer Genetic Testing - Genetic tests aimed directly at consumers, usually bought from private laboratories.

EMA - European Medicines Agency.

Enzyme - Protein that acts as a catalyst in biological systems.

Exome - Part of the genome formed by exons, the coding portion of DNA. Although it comprises less than 2% of all genetic material, it is made up of over 30 megabases (30 million bases) of DNA and is responsible for building most of our bodies.

Exposome - Set of environmental factors to which the individual is exposed, including lifestyles.

Expression - Change in the degree of manifestation of a phenotype of a particular gene.

Gene - Part of the DNA molecule of a chromosome that directs the synthesis of a specific polypeptide chain.

Gene editing - A type of genetic engineering in which DNA is inserted, deleted or replaced in the genome of an organism using engineered nucleases or "molecular scissors".

Gene therapy - Treatment of hereditary diseases through the addition, insertion or replacement of a normal gene (or several genes) in the cells.

Genetic code - Triplets of DNA nucleotides that code for different amino acids.

Genetic counselling - Service through which information is provided on genetic diseases, in relation to their diagnosis, mechanisms of onset, risks of occurrence or recurrence and options for their control and prevention.

Genetic polymorphism - Common genetic variation, present in at least 1% of the population.

Genome - All the genes contained in a cell.

Genomic DNA - DNA contained in chromosomes.

Genotype - Genetic constitution of a person.

Gliomas - Malignant neoplasms that can develop in any area of the central nervous system: namely in the brain or spinal cord.

GWA, Genome Wide Analysis - Whole genome analysis

GWS- Whole genome sequencing.

Heritability - Hereditary component of a complex trait.

HIV (Human Immunodeficiency Virus) - Human immunodeficiency virus, responsible for AIDS.

HLA - Human Leucocyte Antigens (human leukocyte antigens).

Homozygous - A subject who has identical alleles in a particular locus, in a pair of homologous chromosomes.

IF, Incidental findings - In the case of genetic and genomic analyzes it applies to mutations or variations that may have clinical implications, but which have been discovered by chance in the course of an “investigation” initiated for a different medical indication. Not all IFs are currently interpretable and may have an uncertain significance.

IFN type I interferons - Cytokine which is part of the family of interferons, proteins that help regulate the activity of the immune system with antiviral functions.

Integrome - Set of all integrated “omes” (genome, transcriptome, proteome, metabolome, etc.).

LEA - Essential levels of assistance, benefits and services that the National Health Service (SSN) is required to provide to all citizens.

Liquid biopsy - Venous blood sampling on which molecular analyzes can be performed when tumour tissue is not available.

Messenger RNA (mRNA) - Single-helix molecule complementary to one of the strands of the DNA double helix, which is synthesized during transcription, transfers information from the nucleus to the ribosomes of the cytoplasm, and acts as a template for protein synthesis.

Metabolic disease - Hereditary disease affecting a biochemical pathway, e.g. an inborn error of metabolism.

Metabolome - Set of metabolites of a biological organism, that is, all substances that participate in the processes of an organism.

Microbiome - Complex of bacteria that coexist with the host, performing various functions, including a modulating action on the genome.

Mitochondrial DNA (mtDNA) - Genetic patrimony of the mitochondrion, which codes for enzymes involved in energy-providing reactions, its mutations cause disease.

Molecular biology - Branch of biology that studies and interprets biological phenomena at the molecular level, considering the structure, properties and reactions of the chemical molecules that make up living organisms.

Multifactorial or complex diseases - Common diseases considered secondary to the additive effect of genetic variations and the environment.

Mutation - Modification of the genetic heritage, either at the level of a gene, or of a non-coding portion of the genome or of the structure or number of chromosomes; the mutation that occurs in a gamete is hereditary, that of somatic cells is not hereditary.

New mutation - Mutation that originates as a new event.

NGS, Next Generation Sequencing - Second generation sequencing, new genome sequencing techniques.

Nucleotide - Elementary structure of nucleic acids; each nucleotide consists of a nitrogenous base, a sugar and a phosphoric group.

Omics - Suffix that applies to numerous biomolecular disciplines in life sciences (e.g. genomics, transcriptomics, proteomics, metabolomics).

Pharmacodynamics - Study of the biological, biochemical and biophysical effects of drugs on the body.

Pharmacogenomics - Science that studies genetic variations and their interaction with the environment, to try to explain the different response to drugs.

Pharmacokinetics - Study of the temporal evolution of the concentration of drugs in the body, it is ideally divided into four phases: absorption, distribution, metabolism, excretion.

Phase 3 study - Phase 3 represents the last check before the drug is placed on the market and must therefore meet a very large number of requirements.

Phenotype – Observable characteristics (physical, biochemical and physiological traits) of a person, due to the interaction between genotype and environment.

Plasmapheresis - Infusions of the liquid part of blood that contains white blood cells and antibodies.

Predictive Test - Measures a person's susceptibility or resistance to a disease (usually late onset), different from the average of the general population.

Presymptomatic diagnosis - Investigations aimed at verifying whether a person has inherited a disease gene, before it manifests itself clinically.

Presymptomatic test - Determines whether a person has inherited a disease gene before it becomes clinically evident (also includes "late onset" genetic disorders).

Prevalence - The percentage of people who at a given time, in a given population, have a particular characteristic.

Protein - A complex organic compound consisting of hundreds or thousands of amino acids.

Proteome - Set of proteins of an organism or a biological system, that is the proteins produced by the genome.

Rare diseases - Diseases which, according to the European definition, affect less than 1 in 2000 people. Over 6000 rare diseases are known. Although individually rare, overall they affect about 30 million citizens in the European Union. 80% of rare diseases have a genetic origin and are often chronic and life-threatening.

Rare, or private variation - Genetic mutation, which has a frequency of less than 1% of the population.

Sequence - Set of DNA nucleotides; in the case of congenital malformations, it describes the defects that develop as a cascade of secondary events to an initial primitive factor.

Somatic (cells) - Non-germ cells in the body.

Somatic mutation - Confined to non-germline cells.

Structural gene - Gene that codes for proteins.

Syndrome - A complex of signs and symptoms associated with a particular clinical condition.

Transcriptome - Set of all transcripts (messenger RNA or mRNA) of a given organism or cell type.

Transfer RNA (tRNA) - Transfers activated amino acids from the cytoplasm to mRNA.

VUS (Variables of Uncertain Significance) - Genetic variation whose certain (normal or pathological) significance is, currently, not known.

WES Whole Exome Sequencing - Sequencing of the exome, corresponding to less than 2% of the genome where the coding genes are located.

WGS Whole Genome Sequencing – the analysis of the entire genomic sequence.