Quality of Life (2024) 15(3-4):145-154

DOI: 10.7251/QOL2403145K **UDC:** 616-006.04:677.51/.52

Review

Personalized Medicine in Oncology: Ethical Considerations and Current Practice

Jasmina Krehic[1], Maja Banjin[2]

[1]*Department for Clinical Pharmacology, General hospital "Prim. dr. Abdulah Nakaš" Sarajevo, FBiH, BiH, jasminakrehic@yahoo.com*

[2]*Department of Gastroenterology and Oncology, General hospital "Prim. dr. Abdulah Nakaš" Sarajevo, FBiH, BiH, banjinmaja@yahoo.com*

ABSTRACT: Personalized Medicine aims to provide targeted therapy specifically designed according to inherited and/or acquired risk factors present in different subgroups of patients. One of the milestones in tumor research was the realization that tumors are much more complicated and dynamic than it was believed 20 years ago. From year to year, thanks to the extreme advances in molecular oncology, genomics and proteomics, our knowledge of tumors keeps growing, which has led to the emergence of new drugs that target the weaknesses od tumors. Molecular pathways, based on knowledge of genetic characteristics, have identified possible therapeutic targets for certain groups of patients within a seemingly unique clinical phenotype or disease. Stratifying complex and heterogeneous groups of patients in this way led to a better definition of disease subgroups, with a more precise risk-benefit ratio. Selecting patients who will respond to a given drug and avoiding exposure to potential side effects of patients who will not respond to therapy increases the effectiveness of the drug, reduces the risk of unnecessary side effects or drug interactions that could cause serious complications and significantly increase treatment costs. In parallel with the advancement of personalized medicine, with all its advantages, new ethical considerations are being raised, especially issues of patient privacy, confidentiality, data protection, and patients' rights to fairness. The training on how to handle moral and ethical dilemmas while taking into account social, religious, and local societal values and practices can be very beneficial for the healthcare professionals and treating oncologists.

Keywords: carcinogenesis, personalized medicine, ethical considerations

INTRODUCTION

Cancer is not a single disease. There are more than 200 types of cancer. The process of tumor formation (carcinogenesis) occurs in several stages (Nowell, 1976; Amin et al., 2017) as a result of the actions of a number of endogenous and exogenous factors that lead to the damage at the gene level. It can be triggered by chemical, physical and biological agents called carcinogens. The process of carcinogenesis occurs in four stages:

- initiation - exposure of the cell to the appropriate dose of carcinogens that leads to the formation of mutations as irreversible changes in the DNA. Initiation alone cannot lead to the formation of tumors;
- promotion - stimulation of the proliferation of altered cells;
- progression - the stage in which, due to the accumulation of genetic mutations, autonomic growth of the tumor occurs and the initiator and promoter are no longer needed;
- malignant neoplasm (cancer) - malignantly transformed cells have the ability to invade and metastasize.

Tumors in humans are thought to be of monoclonal origin, meaning they were formed from a single transformed cell that continues to divide while avoiding normal control mechanisms. Cell proliferation often depends on an external signal that reaches receptors on the cell membrane, from there it is transmitted through the membrane to the cytoplasm and finally reaches the nucleus where DNA synthesis

begins. Normal cell genes play an important role in every segment of this signaling pathway, and most of them encode proteins by which external signals encourage cells to divide, differentiate, or die. Based on their enzymatic activity, proteins are divided into growth factors, membrane and cytoplasm kinase protein, guanosine triphosphatase (GTF), nucleus proteins and other proteins in the cell. The cell growth signal is transmitted from the membrane receptor to the cytoplasm by phosphorylation of these proteins. Malignantly transformed cells have a specifically altered behavior compared to normal cells and their most important phenotypic characteristics are autonomy, clonality, anaplasia and the ability to metastasize. During growth, a number of new cells are formed from the primarily transformed cell, many of which acquire some new traits by creating new clones, so we can say that the tumor is actually a population of very heterogeneous cells. This diversity may refer to morphology, proliferation, antigenity, biochemical products, invasiveness, metastasis, and susceptibility to therapy. This heterogeneity can change over time, some clones disappear, others prevail, so the characteristics of tumors can also change completely. The transition of normal to a transformed cell carries with it the acquisition of innate genetic instability and more frequent mutations compared to normal cells and the continuous creation of numerous variants. Many tumors during growth show an increasing degree of malignancy (Hanahan & Weinberg, 2000). The consequence of sequential selection over time leads to the appearance of abnormal subtypes genetically and biologically prone to greater invasiveness and metastasis. At the molecular level, carcinogenesis is a multistage process that occurs with the progressive accumulation of genetic damage, whereby the accumulation of somatic mutations, and not the order of their occurrence, is considered to be responsible for the development of malignant disease. Mutations in at least five or more tumor-related genes are thought to be crucial in carcinogenesis. Genes that by their mutation directly lead to tumor formation are called protooncogenic or oncogenic genes and their products are needed for the formation and maintenance of a malignant condition. They can alter the interrelationship of cells, their growth, division and differentiation. They are divided into cellular oncogenes that represent DNA sequences that are capable of causing malignant cell transformation and cellular proto-oncogenes that are formed by changing the structure and expression of normal cellular genes, which are necessary in the regulation of vital biological processes of the cell. Malignant transformation requires not only the activation of oncogenes, but also the inactivation of a completely different group of genes – antioncogenes or tumor suppressor genes, whose protein products inhibit tumor growth and activate apoptosis (programmed cell death). The p-53 gene protein is the most important tumor suppressor gene, which loses its function through mutation and is believed to be the most commonly mutated gene in human malignancies. A major unresolved problem in the therapy of malignant disease stems from primary resistance to therapy. In every tumor there are those cells that are "dormant" for a long period of time and which, along with preserved internal metabolic activity and mitochondrial metabolism, are insensitive to chemotherapy, because they are in a state of autophagy. In immunotherapy, primary resistance is due to the chemical barriers that the tumor establishes by producing growth factors and cytokines that T cells cannot overcome and reach the tumor. There are other causes of tumor cell resistance, e.g. when the T lymphocyte population is unable to act ("bad T lymphocytes") or when the number of active T lymphocytes is minor, which hinders interaction and causes a heterogeneous therapeutic response. One of the milestones in tumor research was the realization that tumors are much more complicated and dynamic than it was believed 20 years ago. From year to year, thanks to the extreme advances in molecular oncology, genomics and proteomics, our knowledge of tumors keeps growing, which has led to the emergence of new drugs that target the weaknesses od tumors. About 650 oncogenes associated with the tumor have been found, it is known that the growth and development of tumors often rests on blocking tumor suppressor genes, so today's research is largely focused on testing substances that establish the activity of the suppressor gene or, in turn, inhibit

oncogenes. In fact, oncology therapy is being developed today in the direction of targeted treatment or immunological control of tumors. According to today's indicators, if all the knowledge of primary prevention were applied, a third of malignant tumors in humans could be prevented; if early detection knowledge were applied a third would be curable; and if today's knowledge of immunology and signaling pathways in carcinogenesis were applied, a third of malignant diseases could be controlled for years while preserving the quality of life (Belikov, 2017; Amin et al., 2017).

Epidemiological data

Cancer is a devastating disease, and epidemiological data are worrying: 12 million people are diagnosed with cancer every year (32,000 every day) (Thun, DeLancey, Center, Jemal, & Ward, 2010).; nearly 8 million people die from cancer every year (20,000 deaths a day, 14 people every minute). The number of people who are diagnosed with cancer is predicted to increase by 69% from 2008 to 2030. *European Alliance for Personalized Medicine Report from Irish Presidency Conference* 2013, and World Cancer Report 2014, (McGuire, 2015) encourage urgent action, given the following factors:

- The global cancer burden has doubled over the last 25 years and is set to double again before 2030 (Executive Summary)
- As well as incidence and mortality increasing, prevalence is rising even more quickly, as more patients are alive within five years of diagnosis
- The worldwide cost of cancer due to premature death and disability is $895 billion (not including direct medical costs) (p. 299)
- Additionally, the proportion of the population in low- and medium-income countries aged over 65 is expected to increase by 5-10% (p. 450)
- In view of the strong association between cancer rates and age, these will combine to increase the cancer burden by 2030, with low- and medium-income countries most affected (p. 450)

Personalized Medicine

Personalized Medicine aims to provide targeted therapy specifically designed according to inherited and/or acquired risk factors present in different subgroups of patients. The foundations for this approach lie in the results of research that determine the origin of the disease at the molecular level, and thus provide insight into the complexity of the factors that lead to the occurrence of the disease.

A definition by European Alliance for Personalized Medicine (EAPM, 2013) states that personalized medicine most frequently refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and stratified prevention. It may also involve imaging and other technologies.

From the very beginning of medicine, throughout its history, the most important goal has been to understand the basic mechanism that leads to disease and, based on these findings, to create appropriate therapeutic approaches. Due to the lack of pathophysiological knowledge, advances in medicine were based on an empirical approach and, consequently, pharmacology was guided by the idea of creating one or more medical products that treat a large population of patients "infected" with a single disease. This one-size-fits-all approach was beneficial for certain medical conditions, such as pain or headaches, but over time it became clear that diseases such as different types of malignancies were difficult to fit into this classic doctrinal approach (Spear, Heath-Chiozzi, & Huff 2001). In the final two decades of the last century, the therapeutic approach focused on the abnormality of the malignant cell itself, on signal transduction processes and protein traffic routes that regulate cell functions. A number of tyrosine and serine threonine

kinase inhibitors and monoclonal antibodies targeting signal receptors were researched. Some of them showed antitumor activity and through clinical research achieved inclusion in standard therapeutic protocols, but most of the tested substances that showed antitumor activity in basic studies did not confirm this in clinical studies, i.e. did not achieve a better therapeutic effect than classical chemotherapy. However, even this small "amount of success" has produced a strong optimism in the world of oncologists about the future of the treatment of malignant diseases. According to this optimistic concept, it is predicted that future patients will undergo only needle biopsy of the tumor for the diagnosis to be established and, based on the genetic characteristics of the tumor, an active successful therapeutic protocol will be applied. We already have genetic tests for certain tumors and for certain genetic changes that direct us to the choice of therapy and the favorable outcome of treatment.

Personalized medicine-a change in the treatment paradigm

Molecular targeted (biological) therapy is a completely new form of treatment that requires comprehensive information about the origin of the disease at the molecular level and complete insight into the complexity of the factors that lead to the onset of the disease. The modern, generally accepted term for this new direction in oncological treatment is "personalized medicine", which in literature goes by various synonyms - stratified, precise, molecular, genomic or tailored medicine (Roden & Tyndale, 2013; Biweber, 2013; Shen, & Hwang, 2010; Ross et al., 2003; Eng, 2013; Smart, Martin & Parker, 2004). In a narrow sense, personalized medicine is the systematic use of information about the individual patient with the aim of choosing the optimal prevention and treatment. The importance of this approach in medicine stems from the fact that each person has their own specific genomic-proteomic, i.e. molecular profile, which is responsible for the specificity and severity of their disease, as well as the reaction of that person to drugs. The ultimate goal of personalized medicine early diagnosis, before the onset of clinical symptoms, which would ensure timely introduction of optimal preventive measures. When the disease becomes clinically visible and with symptoms, personalized medicine aims to identify the characteristic and individual biomarker profile, endophenotype, and accordingly adapt and specify the ideal curative therapy (Eng, 2013; Smart, Martin & Parker, 2004). In this way, the prognosis for malignant tumors and other diseases with a fatal outcome could change drastically.

Personalized therapy and nanomedicine

In order for personalized or precise medicine to be developed, advances in analytical methods called high-flow methods are necessary. Their introduction into medicine enables the creation of real personalized medicine, because it directly or indirectly ensures the application of genomic and proteomic research with the aim of enabling prevention and treatment tailored to each person.

At the beginning of the 21st century, the knowledge we gained on the human genome brought an accelerated advancement of bioanalytical technologies also known as "omics" (Ocana, & Pandiella, 2010). The "omics" methods (transcriptomics, proteomics, metabolomics, lipidomics, glycomics, structural genomics, etc.) are based on nanotechnologies engaged in the research, development and application of structures, devices and systems up to 100 nanometers in size (1 nm = 10^{-9} m), i.e. atoms, molecules and macromolecules. The application of nanotechnology in the treatment, diagnosis, monitoring and control of biological systems is defined under the name nanomedicine. It studies nanoparticles that act as biological mimetics (e.g., functionalized carbon nanotubes), nanomachines (e.g., those made of DNA), nanofibers, and polymer nanostructures that serve as biomaterials (e.g., nanoporous membranes), as well as various devices that operate at the nanoscale (e.g., microchip drug delivery devices), capable of targeted delivery

of drugs, genetic materials and diagnostic agents to specific cells and extracellular spaces in the body. One of the main goals of nanomedicine is the research of rational and targeted delivery of therapeutic and diagnostic agents with precise identification of targets (cells and receptors), as well as the selection of appropriate nano-carriers that should ensure the achievement of the desired goal with as few side effects as possible. For optical detection, quantum dots (nanoparticles) are used that can be adjusted to emit light of a certain color, so they have already been used in some research to monitor the metastasis of tumor cells. The application of nano-tools could contribute to the understanding of complex regulatory and signaling networks that control the behavior of cells in physiological and pathological conditions. The application of the mentioned technologies in biomedicine enables the knowledge of the factors involved in the development of the disease on an individual level, i.e. for each individual patient. High-flow methods and nanomedicine represent the technological base of "omics", and "omics" are comprehensive methods that obtain information in one step or analysis, i.e. characterization of all or most members of a certain family of molecules. Transcriptomics is a systematic analysis of all genes in an organism, and proteomics is a systematic analysis of protein expression that includes the separation, identification and characterization of proteins in an organism. The term proteome, which has been used since 1994, as the linguistic equivalent of the term genome (protein complement to a genome), denotes all the proteins that the genome expresses during life (Chen, & Snyder, 2013). Proteins are integral parts of molecular complexes, signaling networks and organelles that are functional parts and important regulators of cellular processes, which includes "circulation" of proteins (recycling and degradation), post-translational modifications, subcellular localization, and the so-called protein-protein interactions. Protein-protein interaction leads to the formation of complexes that are involved in the transmission of signals through the cell. Based on our knowledge on genomics and proteomics, we got to know the molecular nature of the disease better and developed a "cellular map", which resulted in our better understanding of malignant diseases through the expression, interaction and function of proteins. These findings further helped us in the process of diagnosis, classification, prognosis and assessment of the therapeutic result, which leads us to real personalized medicine based on the patient's proteomic profile. Progress in understanding the genetic and epigenetic complexities of clinical phenotypes has brought numerous information with possible predictive, diagnostic and prognostic value, and at the same time helped our understanding of the genetic background of many monogenetic and genetically complex diseases (Bieber, & Broich, 2013; Dorfman, Khayat, Sieminowski, Golden, & Lyons 2013; van den Broek, Visser, Allaart, & Huizinga, 2013). Molecular pathways, based on knowledge of genetic characteristics, have identified possible therapeutic targets for certain groups of patients within a seemingly unique clinical phenotype or disease (Trusheim, Berndt, & Douglas, 2007). Stratifying complex and heterogeneous groups of patients in this way led to a better definition of disease subgroups, with a more precise risk-benefit ratio (Olson et al., 2014; Suh et al., 2013). Selecting patients who will respond to a given drug and avoiding exposure to potential side effects of patients who will not respond to therapy increases the effectiveness of the drug, reduces the risk of unnecessary side effects or drug interactions that could cause serious complications and significantly increase treatment costs (Fernald, Capriotti, Daneshjou, Karczewski, & Altman, 2011). EAPM (The European Alliance for Personalized Medicine) was launched in March 2012, with the aim of improving patient care by accelerating the development, delivery and uptake of personalized medicine and earlier diagnostics, through consensus. EAPM states that in practice, rather than having a unique treatment for each individual person, patients are sub-divided into groups based on their "molecular make up", i.e. using biomarkers (Grice et al., 2009). This definition does not mention any of genetic or genomic profiling, primarily referring to a pharmacogenetic and pharmacogenomic technologies (Lazarou, Pomeranz, & Corey, 1998). Genetics is the study of heredity and genomics is defined as the study of genes and their

functions, and related techniques. Thus, pharmacogenetics refers to genetic differences/genetic variations in metabolic pathways that can affect individual responses to drugs, while pharmacogenomics is more complex and it analyzes entire genome – the complete set of DNA within a single cell of an organism. And, if we take into account that adverse drug reactions (ADRs) rank as fourth leading cause of death in United States and that ADRs are significant cause of morbidity, with the fact that many diseases have a genetic component with tests already available, the role of pharmacogenetic, pharmacogenomics and other genetic and genomic research is priceless.

The Future of Personalized Medicine

Global analyses of genomes and proteomes are being intensively developed and technologically and methodologically improved, and their application is entering clinical medicine. The most important means on which personalized medicine will be based in the future are biomarkers (World Health Organization, 2006; Olson et al., 2014; Suh et al., 2013; Fernald, Capriotti, Daneshjou, Karczewski, Altman, 2011). Tremendous progress in various "omics" fields has triggered numerous studies aimed at the improved understanding of the genetic, epigenetic and other pathophysiological mechanisms that lead to the complexity of diseases with wide clinical and heterogeneous phenotypes. These technologies will provide a step-by-step discovery of new biomarkers, allowing endophenotype-based stratification of patients according to elaborated criteria. Beyond that aspect of research, much effort will go into evaluating biomarkers until they are accepted for clinical use (Roden, & Tyndale, 2013). Identification of relevant biomarkers and their validation will be available only when biological samples from biobanks are thoroughly processed and confirmed with clinical phenotype information (Suh et al., 2013). The enormous amount of data that must be available in this context is highly dependent on sophisticated bioinformatics-based algorithms (Trusheim, Berndt, & Douglas, 2007; Olson et al., 2014;Suh et al., 2013). Therefore, establishing and combining high-quality biobanks with collected representative biological samples, high-quality phenotype information, and innovations in the biotechnological system are crucial in biomarker research and validation. Biomarkers are tumor- or host-related factors linked to the biological behavior of tumors and the prognosis for the patient. Biomarker detection aims to: aid in establishing a diagnosis with a more precise determination of the stage of the disease, aid in the selection of patient treatment, and predict or monitor the response to therapy. In clinical trials, with the help of biomarkers, the pharmacological or biological mechanism of action of drugs can be confirmed, biomarkers can influence the development of test protocols, can help in the selection of patients and the appropriate dose of the drug, and can influence the reduction of the risk of unwanted events.

Endophenotype-Based Stratification of Heterogeneous Clinical Phenotype and Implications for Personalized Medicine

Each disease is determined by a more or less wide range of individual symptoms that complement the clinical phenotype, while having the same diagnosis. Clinical heterogeneity is often a mirror of complex pathophysiological mechanisms that may have different genetic and epigenetic origins. Similarly, the heterogeneity of clinical response to classical therapy includes the risk of giving drugs with serious side effects to patients whose body will not respond to those drugs (Grice et al., 2009). This is a special and important aspect for which medicine is trying to find an answer. Advances in our knowledge of the genetic and epigenetic background and diversity of pathophysiological mechanisms will lead us to separate complex phenotypes into much clearer and homogenized defined subgroups that will be characterized by biomarker and endophenotype profiles. Therefore, it is realistic to expect that most diseases will be redefined in subgroups according to molecular taxonomy based on biomarkers (Momper, & Wagner, 2014; Bieber, 2012). In ad-

dition to genetic and epigenetic information, as well as knowledge about biochemical and immunological pathways, numerous other facts will be integrated, such as type of diet, lifestyle, exposure to environmental factors and many others (Morgan, & Huttenhower, 2012). Only then will the individual profile of each patient be better understood, and we can hope that in the future we will make a turn from the current approach of disease treatment to a preventive approach. The current approach to personalized medicine requires the interaction of numerous participants in the process, which brings with it numerous challenges. Success is strongly dependent on progress in identifying relevant biomarkers, which allow us to stratify complex phenotypes and identify those patients who will have the best response to a given drug with the lowest possible side effects. Finally, it should be mentioned that personalized medicine includes significant ethical and socioeconomic issues that are important at all levels (Kesselheim, & Shiu, 2014; Schleidgen, & Marckmann, 2013; Phillips et al., 2014). The development of personalized medicine requires large population studies that will collect data on groups of people with the same or similar characteristics, from the environment in which they live and where they were born, lifestyle, as well as data obtained by collecting biological samples from biobanks. The combination of these data will be the basis for creating a more detailed classification of disease subtypes and will help us better understand the responsibility of the biological basis and environmental factors for each individual.

The relationship between financial investment and ethics in personalized oncology

Cancer is expensive. Worldwide, the financial cost to an individual has been shown to be significant. The European Commission (EC) has allocated around *€ 900 million* to *personalized medicine*, enabling research over the latest 5-year period via the Health Theme of the Seventh EU Framework Programme for Research and Technological Development (FP7). Or, if we look at how drug prices are rising: in 2000, the average cost of one year of a new systemic cancer therapy (SACT) was less than $10,000, while 20 years later, a new drug for a similar indication costs more than $100,000 for the same duration treatment. French National Cancer Institute spent *€ 1,7 million* on testing for EGFR biomarkers in 16.724 lung cancer patients – the tests showed that only 1724 patients (10% of the tested individuals) would respond to the available treatment (gefetinib or erlotinib). The savings for not treating 15.000 nonresponders amounted to € 69 million based on the median *treatment period of 8 weeks.* Therefore, the cost of personalized medicine in oncology is increasing. On the other hand, the conflicting priorities of the pharmaceutical industry, local and national governments, the international medical community, and patients need to be reviewed and balanced. So in order to optimize the care of cancer patients, ethical considerations from the physician's point of view must be taken into account.

PERSONALIZED MEDICINE IN ONCOLOGY: ETHICAL CONSIDERATIONS

In parallel with the advancement of personalized medicine, with all its advantages, new ethical considerations are being raised, especially issues of patient privacy, confidentiality, data protection, and patients' rights to fairness. Personalized medicine benefits all stakeholders in healthcare.

The beginning of ethical considerations takes us back to 1951, when 30-year-old Henrietta Lacks, the descendant of freed slaves, was diagnosed with cervical cancer, a strangely aggressive type, unlike any her doctor had ever seen. He took a small tissue sample without her knowledge or consent. A scientist put that sample into a test tube, and, though Henrietta died eight months later, her cells - known worldwide as HeLa - are still alive today. They became the first immortal human cell line ever grown in culture and one of the most important tools in medicine: Research on HeLa was vital to the development of the polio vac-

cine, as well as drugs for treating herpes, leukemia, influenza, hemophilia and Parkinson's disease; it helped uncover the secrets of cancer and the effects of the atom bomb and led to important advances like cloning, "in vitro" fertilization, and gene mapping.

Since 2001, five Nobel Prizes have been awarded for research involving HeLa cells. There's no way of knowing exactly how many of Henrietta's cells are alive today. One scientist estimates that if you could pile all the HeLa cells ever grown onto a scale, they would weigh more than 50 million metric tons—the equivalent of at least 100 Empire State Buildings.

Today, nearly 60 years after Henrietta's death, her body lies in an unmarked grave in Clover, Virginia. But her cells are still among the most widely used in laboratories worldwide, bought and sold by the billions. Those cells have done wonders for science, and Henrietta's legacy involves the birth of bioethics.

The medical and ethical case of Henrietta Lacks has been described in the bestseller "The Immortal Life of Henrietta Lacks" by Rebecca Skloot. This is a bestseller that takes readers on an extraordinary journey, from the "colored" ward of Johns Hopkins Hospital in the 1950s to stark white laboratories with freezers filled with HeLa cells, from Henrietta's small, dying hometown of Clover, Virginia, to East Baltimore today, where her children and grandchildren live and struggle with the legacy of her cells.

The complete genome of the HeLa cells was sequenced and published on 11 March 2013 without the Lacks family's knowledge (Koelsch, Przewrocka, & Keeling, 2013; Landry et al., 2013). After concerns were raised by the family, the authors voluntarily withheld access to the sequence data (Callaway, 2013[a]).

It is clear that the main dedication of physicians has always been to provide the best possible care for their patients. The ethical argument supporting techniques used for personalized medicine at the beginning was the need to reduce the incidence of mortality and morbidity caused by ADRs with later improvement of efficacy and, finally, with diagnosis of different diseases and tumor subtypes.

And finally, in order to further reflect on this topic, we remind you of important declarations:

- A Declaration of Geneva (May 2006) states: "The health of my patient will be my first consideration; I will respect the secrets that are confided in me, even after the patient has died."
- Modern version of Hippocratic Oath written by Louis Lasagna (1964) states: I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know.

CONCLUSION

In order to fully understand the real impacts of personalized medicine in oncology both on the recipients and on the health system, a broad ethical analysis is also necessary, which will take into account the specificities of cancer care and critically evaluate the scientific progress of personalized medicine in oncology.

A fundamental issue that underlies the struggle within the oncology community is that there is no consensus about what defines value in cancer care. One definition of value is that the benefits in expected life extension and improved quality of life are obtained at a reasonable cost. The professional norm is that the first and foremost responsibility of oncologists is to do what is best for their patients. This norm is eroding in the face of the ever-increasing growth of health care costs, but it still influences the practice of many oncologists.

Additionally, in recent years, emphasis has been focused on professionalism, justice, dignity, empathy, truthfulness and honesty, which are crucial in cancer and are an essential aspect of medical care. The treating doctor have the responsibility of safeguarding the patient's privacy and confidentiality and this forms the basis of any doctor-patient relationship. Breach of confidentiality is a grave violation of an individual's human rights (Callaway, 2013[b]; Storm et al., 2005; Coleman, Evans, & Barrett, 2003). While "

the beneficence" and "non-maleficence" prioritise the rights and welfare of the patient, "autonomy" refers to the individual's right to choose and pursue whatever they like. In that situations adhering to the four fundamental bioethical principles—respect for "autonomy, non-maleficence, beneficence, and justice"—proposed by Beauchamp and Childress (1994)—help decision-makers reach morally sound conclusions in the face of tremendous difficulty (Soumita, Vivek, & Bhattacharya, 2019). And another way of looking at it brings us to concerns about the privacy and security of big data, including genetic data, especially in the context of commercial genetic testing services.

Conflict of interest
There are no conflicts of interest.

Financial support and sponsorship: None

REFERENCES:

Amin, M.B., Greene, F.L., Edge, S.B., Compton, C.C., Gershenwald, J.E., Brookland, R.K., Meyer, L., Gress, D.M., Byrd, D.R., & Winchester, D.P. (2017). The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 67(2):93-99. doi: 10.3322/caac.21388. Epub 2017 Jan 17. PMID: 28094848.

Beauchamp, C., Beauchamp, T.L., & Childress, J.F. (1994). Principles of biomedical ethics. (4th ed.). Oxford University Press, New York, Oxford

Belikov, A.V. (2017). The number of key carcinogenic events can be predicted from cancer incidence. Sci Rep. 7(1):12170. doi: 10.1038/s41598-017-12448-7. PMID: 28939880; PMCID: PMC5610194.

Bieber, T. (2012) Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratifi ed medicine.Allergy. 67(12):1475–82.

Bieber, T., & Broich, K. (2013[b]). Personalised medicine. Aims and challenges. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 56(11):1468–72.

Callaway, E. (27 March 2013[a]). "HeLa publication brews bioethical storm". Nature. doi:10.1038/nature.2013.12689.

Callaway, E.(15 March 2013[b]). "Most popular human cell in science gets sequenced". Nature. doi:10.1038/nature.2013.12609

Chen, R., & Snyder, M. (2013). Promise of personalized omics to precision medicine. Wiley Interdiscip Rev Syst Biol Med. 5(1):73–82.

Coleman, M.P., Evans, B.G., & Barrett, G. (2003). Confidentiality and the public interest in medical research—will we ever get it right? Clin Med 3:219

Dorfman, R., Khayat, Z., Sieminowski, T., Golden, B., & Lyons R. (2013). Application of personalized medicine to chronic disease: a feasibility assessment. Clin Transl Med. 2(1):16.

Eng, C. (2013). Molecular genetics to genomic medicine practice: at the heart of value-based delivery of healthcare. Mol Genet Genomic Med. 1(1):4–6.

European Alliance for Personalized Medicine Report from Irish Presidency Conference March 20th/21st 2013.

Fernald, G.H., Capriotti, E., Daneshjou, R., Karczewski, K.J., Altman, R.B. (2011). Bioinformatics challenges for personalized medicine. Bioinformatics. 27(13):1741–8.

Hanahan, D., & Weinberg RA. (2000). The hallmarks of cancer. Cell. 100(1):57-70. doi: 10.1016/s0092-8674(00)81683-9. PMID: 10647931.

Kesselheim, A.S., & Shiu, N. (2014). The evolving role of biomarker patents in personalized medicine. ClinPharmacol Ther. 95(2):127–9.

Koelsch, C., Przewrocka, J., & Keeling, P. (2013). Towards a balanced value business model for personalized medicine: an outlook. Pharmacogenomics. 14(1):89–102.

Landry, J.J., Pyl, P.T., Rausch, T., Zichner, T., Tekkedil, M.M., Stütz, A.M., Jauch, A., Aiyar, R.S., Pau, G., Delhomme, N., Gagneur, J., Korbel, J.O., Huber, W., & Steinmetz, L.M. (2013). "The genomic and transcriptomic landscape of a HeLa cell line". G3 (Bethesda) 3 (8): 1213–24.

Lazarou, J., Pomeranz, B. H. & Corey, P. N. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279, 1200-1205.

McGuire, S. (2015). World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv Nutr. 2016 Mar 15;7(2):418-9. doi: 10.3945/an.116.012211. PMID: 26980827; PMCID: PMC4785485.

Momper, J.D., & Wagner, J.A. (2014). Therapeutic drug monitoring as a component of personalized medicine: applications in pediatric drug development. Clin Pharmacol Ther. 95(2):138–40.

Morgan, X.C., & Huttenhower, C. (2012). Chapter 12: Human microbiome analysis. PLoS Comput Biol. 8(12):e1002808.

Nowell, P.C. (1976). "The Clonal Evolution of Tumor Cell Populations: Acquired genetic lability permits stepwise selection of variant sublines and underlies tumor progression". *Science*. **194** (4260):23–28. doi:10.1126/science.959840.

Ocana, A., & Pandiella, A. (2010). Personalized therapies in the cancer "omics" era. Mol Cancer. 9:202.

Olson, J.E., Bielinski, S.J., Ryu, E., Winkler, E.M., Takahashi, P.Y., Pathak, J., et al. (2014). Biobanks and personalized medicine. Clin Genet. 86:50–5.

Phillips, K.A., Ann, Sakowski, J., Trosman, J., Douglas, M.P., Liang, S.Y., & Neumann, P. (2014). The economic value of personalized medicine tests: what we know and what we need to know. Genet Med. 16(3):251–7.

Roden, D.M., & Tyndale, R.F. (2013). Genomic medicine, precision medicine, personalized medicine: what's in a name? Clin Pharmacol Ther. 94(2):169–72.

Ross, J.S., Linette, G.P., Stec, J., Clark, E., Ayers, M., Leschly, N., et al. (2003). Breast cancer biomarkers and molecular medicine. Expert Rev Mol Diagn. 3(5):573–85.

Schleidgen, S., & Marckmann, G. (2013). Re-focusing the ethical discourse on personalized medicine: a qualitative interview study with stakeholders in the German healthcare system. BMC Med Ethics. 14:20.

Shen, B., & Hwang, J. (2010). The clinical utility of precision medicine: properly assessing the value of emerging diagnostic tests. Clin Pharmacol Ther. 88(6):754–6.

Smart, A., Martin, P., & Parker, M. (2004). Tailored medicine: whom will it fi t? The ethics of patient and disease stratifi cation. Bioethics. 18(4):322–42.

Soumita, G., Vivek, R., & Bhattacharya, S. (2019). Ethics of cancer care: beyond biology and medicine. Ecancermedicalscience 13:911

Spear, B.B., Heath-Chiozzi, M., & Huff J. (2001). Clinical application of pharmacogenetics. Trends Mol Med. 7(5):201–4.

Storm, H., Brewster, D.H., Coleman, M.P., Deapen, D., Oshima, A., Threlfall, T. et al (2005). Guidelines for confidentiality and cancer registration. Br J Cancer 92:2095–2096

Suh, K.S., Sarojini, S., Youssif, M., Nalley, K., Milinovikj, N., Elloumi, F., et al. (2013). Tissue banking, bioinformatics, and electronic medical records: the front-end requirements for personalized medicine. J Oncol. 368751.

Thun, M.J., DeLancey, J.O., Center, M.M., Jemal, A., & Ward, E.M. (2010). The global burden of cancer: priorities for prevention. Carcinogenesis. 31(1):100-10. doi: 10.1093/carcin/bgp263. Epub 2009 Nov 24. PMID: 19934210; PMCID: PMC2802672.

Trusheim, M.R., Berndt, E.R., & Douglas, F.L. (2007). Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov. (4):287–93.

van den Broek, M., Visser, K., Allaart, C.F., & Huizinga, T.W. (2013). Personalized medicine: predicting responses totherapy in patients with RA. Curr Opin Pharmacol.13(3):463–9.

World Health Organization (2006): The Safety of Medicines in Public Health Programmes_ Pharmacovigilance an essential tool. © World Health Organization, 1-61.

Recived: December 29, 2023
Accepted: January 31, 2024