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SPECIAL ARTICLE

Ethical and legal aspects of oncogenomics

K. Stankov[1], D. Draskovic[1], M. Mikov[2]

[1]Clinical Center of Vojvodina, Medical Faculty of Novi Sad, University of Novi Sad, Novi Sad; [2]Department of Pharmacology, Medical Faculty of Novi Sad, Novi Sad, Serbia

Summary

The discovery of the genes and cellular pathways that play fundamental roles in several diseases, and the understanding of many diseases at a molecular level due to the advances in the field of genomics, have revolutionized the diagnosis, therapy and prevention of human diseases. Application of genetic testing in numerous medical fields, including pharmacogenomics and oncogenomics, raised numerous ethical questions and introduced legal instruments that are aimed at ensuring the appropriate protection of human research participants. For the effective development of human genomics and translation of novel, validated biomarkers into potentially useful clinical applications in personalized medicine, there is a need for clear ethical standards and principles in all phases of clinical research.

Key words: bioethics, oncogenomics, personalized medicine, translational research

Oncogenomics in the era of personalized medicine

The recent rapid pace of discovery in genomics and biotechnological progress are impressive and hold great promise for use in drug discovery, translational and personalized medicine [1,2]. Advances in throughput, quality and efficiency of sequencing methods, such as the next generation sequencing techniques, will assist genome-wide association studies (GWAS) and generate vast quantities of rich data on many thousands of individuals. As sequencing technologies move from the lab bench to the clinic, they have important impact and usefulness for solving complex biological problems and for predicting phenotypes from genotypes, but they also raise important ethical issues [3,4]. This article reviews the current scope of oncogenomics, and the ethical implications that should be considered carefully both in genomics research and in the clinic.

Molecular and cell biology have revolutionized not only diagnosis, therapy and prevention of human diseases, but have also greatly contributed to the understanding of their pathogenesis. Genomics has provided the first systematic approaches to discover the genes and cellular pathways that play fundamental roles in disease. GWAS strategy consists in screening the genome, using high coverage genotyping arrays, from 100,000 to 2.3 million single nucleotide polymorphisms (SNPs) per array [5]. These data increasingly allow to define the individual risk for a given disease and to predict the individual prognosis of a disease as well as the efficacy of therapeutic strategies for personalized medicine [6].

The field of human genome research is in a rapid discovery phase. Completion of the Human Genome Project in 2003, the Phase 1 HapMap project in 2005, and the first phase of the Encyclopaedia of DNA Elements (ENCODE) project in 2007, have provided scientists with a wide array of research tools to apply to important medical issues, while simultaneously deepening the understanding of the architecture and function of the genome. The recent initiation of the second phase of the ENCODE project, the "1000 Genomes" project and The Cancer Genome Atlas (TCGA), promise to accelerate the acquisition of new knowledge [7,8]. The rapid developments of next-generation sequencing technology and bioinformatics are directed towards the goal of a "1,000 dollar genome sequence", as an important tool to realize personalized medicine: perfectly tai-

Correspondence to: Karmen Stankov, MD, PhD. Clinical Center of Vojvodina, Medical Faculty of Novi Sad, University of Novi Sad, Hajduk Veljkova 1, 21000 Novi Sad, Serbia. Tel: +381 64 209 3376, Fax: +381 21 420 348, E-mail: stankov_karmen@uns.ac.rs

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loring diagnostics and treatments to a patient's genetic make-up [9].

Over the past decade, human genome catalogues enabled the discovery of the specific genes for Mendelian (monogenic) diseases and resulted in establishing genetic associations between genomic loci and complex (multigenetic) traits, many of them diseases [10]. Therefore, the comprehensive genomic approaches have resulted in the identification of ~2,850 genes underlying rare Mendelian diseases, ~1,100 loci affecting common polygenic disorders and ~150 new recurrent targets of somatic mutation in cancer [8]. As of May 2011, over 800 GWASs have been published on 150 human diseases and traits, reporting over 2,400 SNPs with statistically significant associations and odds ratios [11]. These discoveries are propelling research throughout academia and industry. Genome-wide association studies highlighted numerous genes, coding and non-coding variants, implicated in disease pathogenesis [12].

Oncology offers multiple examples of how genomic medicine has changed disease understanding. A major near-term medical impact of the genome technology revolution will be the elucidation of mechanisms of the cancer pathogenesis, leading to improvements in the diagnosis of cancer and the selection of the proper cancer treatment, including the advances in gene therapy, epigenetic-based therapies and gene silencing [13-15].

TCGA, a 10-year multi-institutional effort aims to characterize the cancer genome. Thanks to second-generation sequencing technologies, several cancer genomes have been recently sequenced, including acute myeloid leukemia, breast cancer, non-small-cell lung cancer, and small-cell lung cancer [16]. Tumor-gene-expression signature models, combined with clinically relevant data such as survival outcomes, provide one of the clearest examples of the use of genomic information clinically as prognostic tools. MammaPrint® and Oncotype DX® are two such prognostic tests that are now clinically available for use in breast cancer, significantly predicting the risk of metastatic recurrence and improving the clinical decision-making [11].

Complex disorders, including cancer, have a multifactorial etiology, caused by several genes and environmental causes. Researchers nowadays study the myriad of genetic polymorphisms and variants, which may represent risk factors for common diseases [12,17-20]. A full understanding of the genetic and molecular basis of diseases will require capturing much of the genetic variation across human populations. Accomplishing this will involve collaborations with relevant communities, taking into account how genomics is understood and perceived by different racial, ethnic and cultural groups, to form effective partnerships that will ensure that such research is sound and ethically conducted [21]. The use of GWAS in medical research and the increased ability to share data give a new approach to the serious ethical questions of consent, feedback of results, privacy, and the governance of research. GWAS create particular challenges because they produce fine, detailed genotype information at high resolution, and the results of more focused studies can potentially be used to determine genetic variation for a wide range of conditions and traits [22].

Ethical issues in genomics research and genomic medicine

The era of personalized medicine, as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease" (National Cancer Institute), brings in focus the ethical implications of research and genetic testing, such as informed consent, that are also relevant to translation of genetic/genomic data into clinic. Personalized clinical medicine raises several important ethical issues such as cost and equity of access, confidentiality and disclosure, and the most important fact that the unit of concern is the risk to the family and not only to the tested individual [23].

Ethical regulation should be applied in each phase of genomic research in medical genomics, during the current period of transition from the investigational to the practical personalized medicine. Consumers should be protected from harms of premature translation of research findings, while encouraging the innovative and cost-effective application of novel data into personalized medical care [6]. Taking into consideration that the distinctions between genetic and genomic medicine are considered more quantitative than qualitative [6], but also that the similarities between genetic and nongenetic predictive testing appear much greater than the differences [24], both genetic and genomic research share very important ethical and legal implications.

As recently stated by the Director of Human Genome Project Francis Collins [25], the consequences of genome research have thus far been modest, with the exception of significant advances in cancer, macular degeneration and prediction of drug responses. GWAS in cancer already identified over 150 regions associated with two dozen specific cancers [18]. This rapid pace of development in genomics is followed by the increasing concern in the field of "genethics", defined as the "study of the ethical issues that arise out of the science of genetics and the uses of genetic technologies" [26].

Genomic research advances and creates large a-

mounts of data, and therefore very important recommendations for genomic research have been proposed and published by McGuire et al. [27]. Three major ethical concerns are considered and used to guide research practice and stimulate policy development: a) reporting back research results; b) obligations of researchers to third-party relatives; and c) future uses of samples and data. Three recommendations are issued regarding returning of research results: 1) the obligatory formal research protocol for whole genome sequencing and evaluation by the ethics board; 2) provision of training for physicians to enable the communication of research results, follow-up and clinical care; 3) only validated data of known clinical significance should be integrated into the health record. Obligations for third-party relatives are also guided by three recommendations: 1) implications for family members should be discussed during the initial informed consent process; 2) investigators ought to strongly encourage the research participant to discuss the research data and make a family decision about data release; 3) as long as the GWAS data are validated, the permissibility of unauthorized disclosure will depend on the clinical relevance of the information and the potential to avert or alleviate known health risk. Future use of samples and data sharing must be consistent with the original informed consent, or in some circumstances in which the participant has agreed to re-contact, re-consent might be warranted [27].

Ethical issues in genomics research and genomic medicine include ensuring appropriate protection of human research participants, since they are often including vulnerable populations (for example, children and the disabled) and deceased individuals [21,28]. For special ethical considerations about genetic and genomic testing for cancer-predisposing genes in children, numerous recommendations and guidelines are developed. Testing for cancer-predisposition genes in children is indicated if a malignant disease can develop in childhood and if evidence-based-risk-reduction strategies exist and should be implemented in childhood. Examples include retinoblastoma-gene testing, RET-gene testing for MEN2 and APC-gene testing for familial adenomatous polyposis (FAP) [23]. The current American Medical Association guidelines for genetic testing in children suggest that when no treatment is available for children at risk for an early-onset disease, the option to test the children should be placed at the parents' discretion [24]. On the other hand, carrier testing in children for an early-onset disease with available treatment options is recommended and sometimes required, including the parents' informed consent [24].

Preimplantation genetic diagnosis (PGD) is an alternative for prenatal diagnosis, giving couples with a high genetic risk the opportunity to have unaffected children without having to consider termination of pregnancy [29]. PGD should be included in each reproductive health care program. It is recognized as an important alternative to pre-natal diagnosis. However, diagnosis from a single cell remains a technically challenging procedure, and the risk of misdiagnosis cannot be eliminated [30]. On the other hand, PGD for genetic defects with incomplete penetrance, such as cancer, is a very controversial issue from the ethical point of view. Doubts about the moral acceptability of PGD increase if there are preventive/therapeutic options for the carrier [31]. The discussion mainly focuses on hereditary tumors, more particularly hereditary breast and ovarian cancers caused by mutations in BRCA 1 and 2. While the proposed applications of PGD caused significant commotion in many countries, there now seem to gain an increasing support. This should be no surprise, as the life-time risk of breast cancer for a female carrier may be as high as 85% in seriously affected families, her risk of ovarian cancer as high as 60%, periodic medical examinations aimed at early detection are not (entirely) reliable, while preventive surgery is rather invasive and has adverse effects on the quality of life [31].

Appropriate genomic medicine counseling includes communicating with patients about the uncertainty and the evolving nature of predictions based on genomic information; interpreting information from direct-to-consumer genetic tests (DTC); ensuring fair access to genomic medicine; assessing the effectiveness of genomically informed diagnostics and therapeutics; using genomic information to improve behavior change interventions; addressing issues associated with preimplantation, prenatal and postnatal genetic diagnoses; and determining how constructs of race and ethnicity relate to the biology of disease and the potential to advance genomic medicine [21].

Oncogenomic testing and ethical issues

With the emergence of newer and cheaper technology to scan an individual's genome, the likelihood increases that clinically relevant research results will be revealed [32]. Genetic testing has indeed been introduced for predispositions to adult-onset breast, ovarian and colon cancer, but for a wide range of other common conditions genetic susceptibility testing has still to come [33].

Oncogenomic testing is a comprehensive approach that became part of the core practice in cancer prevention and management. Novel translational oncogenomics research is rapidly expanding with a view

to the application of new technologies, findings and computational models in both pharmaceutical and clinical areas [34]. Genetic and genomic testing in oncology is the unique domain of personalized medicine, since it "is now *de rigueur* used in medical oncology, where it has shifted traditional paradigms", as stated by Offit [6].

The identification of DNA mutations predisposing to cancer susceptibility is now expanding to include whole-genome profiling for personalized approaches to cancer patients and DTC genetic testing. Knowledge about the ethical and legal implications of genetic testing is becoming essential for oncologists, who are being asked with increasing frequency to counsel their patients with respect to the medical, psychological and social repercussions of genetic information, even when obtained outside the context of an established patient-doctor relationship [35].

There is hope that the time will come soon when oncologists will be able to characterize the molecular fingerprint of a tumor, which represents the genetic profile of malignancy. Molecular genetic testing can detect both highly penetrant gene mutations and polymorphisms [36]. Genetic information refers to genetic testing for patients and/or for family members up to fourth-degree relatives. When a cancer-predisposing mutation has been identified in the family, predictive genetic testing offers an opportunity to practise preventive oncology, since the goal in this specialty is to limit the effect of cancer by means of prophylactic surgical measures or early detection [23]. However, there may also be negative implications of returning results to participants, such as emotional distress, the dissemination of premature conclusions, and additional resources and costs associated with conveying results [37]. At present, there is no standard mechanism for disclosing research results. There is an urgent need to educate medical care providers to become specially trained to interpret and communicate data and provide sufficient counseling to proband and his or her relatives [27].

The era of genomics presents the promise of personalized prevention and drug treatment, which has been met with enthusiasm by many people, but called into question by others. In the light of these new developments in research, there is a pressing need to assess the possibilities for, and implications of genetic testing and screening in common diseases from both a clinical and a societal perspective. As with genetic testing in rare Mendelian disorders, these assessments should comprise analytic validity, clinical validity, clinical utility, and ethical, legal and social issues, as well as health economic aspects. Should a genetic test for a common disease have sufficiently high clinical utility in a specific setting, and should implementation in health care be potentially worthwhile, then the framework for its implementation has to be determined: clinical genetics, medical specialist care, primary care as a genetic screening program or as a commercial offer [12].

An excellent example of hereditary common disease is breast cancer. Only 10% of all breast cancers are hereditary, and <1% of the general population is estimated to carry a mutation in BRCA1 or BRCA2. Women who carry a BRCA mutation are given options of early and intensive surveillance, chemoprevention and prophylactic surgery. The role of oncologists and geneticists is to help women understand their risk status and undertake preventive and risk-reducing strategies in order to reduce the morbidity and mortality associated with hereditary or familial cancers. Since the initial application of BRCA testing in oncology practices, special concern has been raised regarding the limited predictive power of genetic testing, due to the low gene penetrance, the possibility of new mutations and the role of environmental factors in carcinogenesis and tumor progression. Furthermore, preventive and interventional measures are still being developed with the risk that the genetic testing may have negative psychological repercussions for individual professional and family life [35].

The predictive testing of apparently healthy children may be justified if the results of such testing achieve a positive balance between the medical benefit of testing and the potential harm. In some of the familial cancer disorders such as FAP, screening for tumors in early or mid-childhood may be warranted for those children known to carry disease-associated gene mutations [38]. After identification of the pathogenic mutation, the predictive testing of the family members has high accuracy, practically 100%. Mutation-positive subjects can accordingly be advised to appropriate surveillance or prophylactic treatment, while the follow up of the mutation-negative subjects can be discontinued [38]. Recognition of a hereditary cancer syndrome in a family provokes anxiety in the family members. The possibility of genetic testing for the diagnosis of the mutation status of the relatives may cause ambivalent feelings. A mutation-negative result naturally is reassuring but the finding of a pathogenic mutation may increase anxiety, even though it enables appropriate surveillance and treatment. The finding of a mutation-positive result in FAP or hereditary nonpolyposis colon cancer (HNPCC) causes worry about the organization of permanent surveillance and proper prophylactic treatment throughout the rest of the life, including screening and testing of all family members [38].

Further integration of personalized medicine into the clinical workflow requires overcoming several barriers in education, accessibility, regulation and re-

imbursement The integration of genomic research into the clinic needs to be standardized and streamlined [11]. Ethical thinking will inevitably continue to evolve as the science does, and quality, privacy and justice in genomics will continually be invoked [39,40]. The benefits and harms of genetic and non-genetic testing in oncology are similar, with the main differences emphasizing the ethical implications of genomic information for family members. Clinical validity and clinical utility are guiding the clinical management of certain tumors and improve health outcomes by reducing morbidity and mortality. The magnitude of the medical benefit depends on many technological and analytical factors, but above all on principal bioethical postulates of avoiding any medical or psycho-social harm and on the patient informed consent being a *sine qua non*. Application of strictly ethical and non-discrimination policies such as the European Council protocol on genetic testing for health purposes and GINA in USA [41,42], will significantly improve the willingness of patients to work with physicians and genetic counselors and to undergo any genetic test that contributes to better management of their health care and health choices.

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