Different perspectives on translational genomics in personalized medicine

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Abstract

Personalized medicine is a relatively new and interesting concept in the medical and healthcare industries. New approaches in current research have supported the search for biomarkers, based on the genomic, epigenomic and proteomic profile of individuals, using new technological tools. This perspective involves the potential to determine optimal medical interventions and provide the optimal benefit-risk balance for treatment, whilst it also takes a patient's personal situation into consideration. Translational genomics, a subfield of personalized medicine, is changing medical practice, by facilitating clinical or non-clinical screening tests, informing diagnoses and therapeutics, and routinely offering personalized health-risk assessments and personalized treatments. Further research into translational genomics will play a critical role in creating a new approach to cancer, pharmacogenomics, and women's health. Our current knowledge may be used to develop new solutions that can be used to minimize, improve, manage, and delay the symptoms of diseases in real-time and maintain a healthy lifestyle. In this review, we define and discuss the current status of translational genomics in some special areas including integration into research and health care. (J Turk Ger Gynecol Assoc 2022; 23: 314-21)

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Introduction

Multiomics-integrated techniques, particularly genomic data acquired from new sequencing technologies, have made a significant contribution to expanding and deepening understanding of the molecular mechanisms of diseases. Translational genomics plays a crucial role in creating an informational bridge between diseases and health conditions (1-4). The goal of translational genomics is to improve human health by taking discoveries in genetic research and applying them to the clinic. The evolution of translational genomics for the management and treatment of various disorders is offering new perspectives for clinicians in managing medical conditions (3,5-6).

The terminology of the genomic sequence, which was released by the Human Genome Project in 2001, does not fully reflect the genome of individuals. This term is accepted as a reference DNA sequence, consisting of all human DNA landmarks without being based on any individual-specific information (7). As a result, the requirement for personalized genomic data to explain particular risk factors for genetic disorders stimulated researchers to develop new DNA sequencing technologies. Due to the developments in advanced technologies, both the cost and time of personal genome sequencing have decreased significantly (4,8). Genomic sequencing is now widely accepted as an essential tool for evaluating gene-linked diseases and is used in a variety of routine tests. As a result,

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personal genomic sequencing data, combined with medical records, provide medical professionals with important insights into the factors linked with genetic disorders and aids in the detection, diagnosis, and treatment of a wide range of complex diseases. It also enables medical professionals to administer targeted therapy (4,8,9).

In this review, we discuss different perspectives of translational genomics in human health. First, its general relation with personalized medicine with descriptions and explanations of terms and studies. We also discuss the impact of translational genomics on cancer research and women's diseases. In relation to this, the connection between translational genomics and pharmaceutical industries is considered.

Translational genomics in personalized healthcare

Personalized medicine (also known as personalized genomics, or genomic medicine) describes the approach for preventing and treating diseases that consider the genome, lifestyle, and environment on an individual basis. In contrast to the "one-size-fits-all" concept, this patient-specific approach also supports the assessment of individual risks, and the personalization of disease prevention and disease-management strategies in healthcare (1).

Next-generation sequencing (NGS) techniques have recently made significant progress in the detection of genetic diseases and pioneered personalized treatments by enabling the analysis of patient-specific genomic variations (10). New sequencing techniques enable massively parallel sequencing of millions of DNA/RNA molecules at a relatively small cost. In recent years, there has been an increasing interest in different NGS technologies because of their capacity to sequence rapidly and efficiently. Different sequencing options, such as exome sequencing (11,12), RNA-seq (13,14), ChIP-seq (15,16) and whole-genome sequencing (WGS) (17,18), are available depending on the type of sample being sequenced and the region of interest in the genome. The term "genome sequencing" refers to both genome and exome sequencing options. However, it should be pointed out that there are regions of the genome that are not mapped in "whole genome" or "whole exome" technologies. The genetic basis of a disease may be related to either small- or large-scale modifications of DNA sequences, such as single nucleotide variants, insertions and deletions (indels), copy number variations, and structural variants (19).

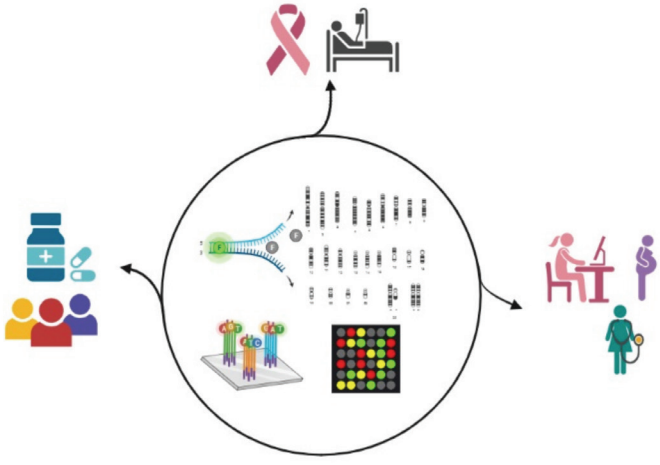

Figure 1. Graphical abstract

Clinical genome sequencing is not only a technology. Due to the clinical considerations, it requires extra components in addition to the technology. Since the Human Genome Project was completed, studies to integrate genetic information into clinical practice in health services have accelerated (8,9,19). However, this integration brings many challenges, including social, ethical, legal, educational, economic, and technical problems. The integration process also requires answering questions about how to produce, analyze, store, and use this information together with other medical data. Since the interpretation of genomic data needs the abilities of a specialist besides the general medical expertise of many clinicians, the integration process should be supported by a variety of experts, including genomic laboratory specialists, geneticists, and genetic consultants (8,20). Extensive research has been carried out into integration of genomic data into clinical practice (20,21).

The analytical process for a novel genetic variant includes several processes. Besides in silico analysis of the variant, biological characterization of the variant which includes the type, the location, and the frequency is also performed (22). Additionally, variant-related case studies, case controls and also functional studies should be considered. Clinical characteristics include the relation of the variant with disease or phenotype, as well as functional analyses of the mutation's effect in vitro or in vivo. The location of the variant is also be considered. The location mostly indicates the regions of genes (specific exons) or certain types of mutations (for example, activating) that are known to be related to a specific disease (19). Similarly, if known disease-causing mutations are all gain-of-function, other mutation types (e.g., stop or silent mutation) is less likely to be regarded as pathogenic (19). Additionally, specifics of the mode of inheritance, the prevalence of disease, and onset age are all essential variables with regard to the disease. Lastly, the clinical features and pedigree must be evaluated when reporting results—is this a diagnostic assessment or screening? How many other tests have been completed? It should also be considered whether there are other phenotypic data that may be useful in the interpretation of the results and how phenotypic

data should be interpreted. Is there any other phenotypic data that might be useful in interpreting the results and how should they be interpreted? Thus, this interpretation needs practical and clinical genetic knowledge (19,23).

Many clinical conditions can benefit from the use of translational genomics. However, interaction and collaboration between physicians and patients will occur in the light of a quality laboratory procedure, analytical validation, ongoing proficiency testing, bioinformatics analysis, and appropriate interpretation and reporting of data. This field is a fast-growing area, and it will surely lead to the emergence of new bioinformatics and genetic analysis professions (3,10,24).

Impact of translational genomic on cancer

Over the last few decades, genomic data has been used in many different fields, such as cardiovascular diseases, infectious illnesses, endocrinology, metabolic medicine, and hematology, to personalize health care. Oncology is another area that has seen a huge increase in the use of genomic data for diagnostic, prognostic and therapeutic assessment (25). Since cancer is partly a genetic-based disease, understanding the genetic structure of cancer improved our diagnostic, prognostic and therapeutic strategies (26). The rapid developments of high-throughput sequencing and bioinformatics tools have led to considerable success with the current massive effort (27). In the last decades, the identification of mutations in patient tumors has expanded our knowledge of many cancers due to remarkable advances in NGS technology (28). However, numerous questions about the clinical application of NGS for therapeutic decision-making remain unanswered. Questions range from how extensively the cancer genome should be characterized to how to explain altered genes that may result in a drug's response, to more social concerns like medical education and data sharing (3,29).

Currently, most cancer treatments have systemic effects on patients. While its efficiency is high in reducing cancer lesions, it is not as effective as targeted therapies. As a result of this systemic approach, some patients having more aggressive cancer types which may be undertreated, and conversely, patients with less aggressive types can be overtreated. Therefore, it is important to determine and treat the tumor of each patient on an individual basis. To reach this stage of cancer treatment, there has been a huge amount of research into many of the types of cancer, especially the more prevalent cancers. As a result of genetic approaches to cancer types, many candidate biomarkers for detection and prognosis have been discovered, but only a few have been validated in clinical practice. Some important challenges, such as tumor heterogeneity, cancer progression, the origin of cancer, and biomarker performance, have hindered biomarker identification. The development of cancer biomarkers will be driven by technological breakthroughs. As ultra-high-throughput sequencing technologies, such as WGS, improve and become more cost-effective, they can be used to identify rare, highly penetrant, high-risk alleles for many cancers and to determine cancer screening protocols for individuals at high risk. The challenges of carcinogenesis, cancer heterogeneity, and the tumor microenvironment mean that a unidirectional diagnostic approach is unlikely to be useful. Rather, the diagnosis will be a multi-step procedure that begins with the identification of at-risk patients, then followed by a sampling step, ideally involving a minimally invasive biosample such as blood or urine, and finally by molecular imaging to identify the lesions (24,25).

For risk assessment, screening, diagnosis, prognosis, and treatment of cancer, several cancer-specific genetic tests are performed. *MLH1, MSH2* (including *EPCAM*), *MSH6, PMS2* genes are screened for Lynch syndrome (hereditary nonpolyposis colorectal cancer), whereas *BRCA1* or *BRCA2* genes are screened for assessing risk-reducing surgery for breast and ovarian malignancies (24,30-32). Cervical cancer screening includes human papillomavirus (HPV) genotyping (24,33). *BCR-ABL, E2A-PBX1, TEL-AML1,* and *MLL* fusions and rearrangements are used to personalized leukemia treatment (24,34). Breast, colon, and prostate malignancies, and lymphoma-specific gene expression patterns can also be utilized to diagnose and for prognosis of the disease (25).

Targeted therapy strategies have been well characterized and are one of the treatment approaches applied by oncology. Cancer biomarkers and targeted therapeutics are key elements for the pharmaceutical industry. Those currently available pharmaceutical products are derived from the combination of molecular and clinical research, known as translational research (35). Many genes with mutations in a small number of hotspots are currently targetable by specific therapeutics. While Herceptin (trastuzumab) was developed to treat HER2-positive breast cancer, gefitinib and erlotinib were developed to target therapy for EGFR mutations in lung cancer and glioblastoma. Additionally, RAF inhibitors are also used in the treatment of melanoma. Many types of research are now being conducted that can be used to improve the success of personalized medicine via targeted therapy (3,25,32).

Numerous studies into cancer have led to many novel discoveries potentially translatable to the clinic for diagnostic and therapeutic applications. These have identified new treatment options that can be applied to other tumor types and expanded our knowledge of cancer pathways (36-38). Thus, a deeper understanding of cancer mechanisms will be realized

to target it with much greater therapeutic precision.

Personalized medicine in women's healthcare

Determining risk susceptibility considering women's age, health status and ability to respond to treatments, provides optimal care for women. Personalized medicine provides significant health and economic benefits for women, health services, and society, in order of enhanced medical decision-making, administration of suitable therapies, optimized disease preventive approaches, and reduced exposure to or avoidance of drugs with a lower efficacy. Additionally, it includes reduced exposure to potentially harmful pharmaceuticals, lower healthcare costs, improved approval of the treatment process, and lastly improved therapeutic tolerance and compliance in a variety of conditions (3,5,39). Multidisciplinary management with different specialists, including gynecologists and obstetricians, oncologists, pathologists, molecular biologists, and geneticists, has had an indisputable positive role like the traditional diagnosis and treatment process (40).

Women differ from men because of hormonal changes which are associated with several diseases and health status changes throughout their life. Sex and gender have been considered when planning the strategies for the management of diseases in precision medicine because biological gender has a range of genetic, epigenetic, and hormonal implications regarding disease mechanisms, development, and course (41).

Although personalized medicine is most widely used in the field of oncology, problems during the pregestational and gestational periods can be evaluated and overcome using precision medicine. With cell-free fetal DNA (cffDNA) obtained from maternal circulation as a minimally-invasive approach, it is possible to obtain genomic and molecular information from a fetus. Although it is a screening test, the list of disorders that can be detected by cffDNA is gradually growing. Increased usage of this test has provided more specific and accurate decisions with improved outcomes. Prenatal testing is preferred by many couples since it allows them to be aware of disease risk and implementation strategies to optimize newborn health. (42).

Preterm birth, described as delivery before 37 completed weeks of gestation, occurs in approximately 10% of all pregnancies and is the primary reason for neonatal morbidity, mortality, and lifelong health issues. Preterm birth can be caused by a variety of factors, including genetics, infection, inflammation, intrauterine bleeding, maternal stress, uterine overdistention, and nutrition, despite the fact that the pathophysiology is unknown. On the other hand, some molecular processes, such as changes in chemokines and cytokines resulting in reduced progesterone receptor function, play a role in the development of preterm delivery (43). Thus, understanding the predisposition of a woman for preterm delivery and personalized management provides optimal care for both the mother and fetus (44).

Preeclampsia is the most prevalent hypertensive disorder in pregnancy, affecting 2% to 8% of all pregnancies. It is a syndrome characterized by new-onset hypertension and proteinuria that appears after 20 weeks of pregnancy (45). Poor placentation is the main theory explaining the development of preeclampsia. However, multifactorial mechanisms, including oxidative stress, inflammation, immune maladaptation and angiogenic imbalance, have contributed to preeclampsia development (46). The determination of an individual's risk and the management of disease based on a personalized approach may prevent some preeclampsia-associated poor outcomes (47). Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is a potentially lethal pregnancy condition and is a subtype of preeclampsia (48). Both disorders are most common in the third trimester of pregnancy or shortly after childbirth. Personalized medicine is promising in HELLP syndrome, as in preeclampsia (49). Drugs should be prescribed by a personalized approach to pregnant women considering this change because during pregnancy, the woman's body also undergoes many changes which can affect drug pharmacokinetics (50).

Recurrent pregnancy loss is characterized by the loss of two or more pregnancies at any gestational age. Recurrent implantation failure refers to the failure of in-vitro fertilization attempts with good quality embryos three times. Both unfavourable conditions may be associated with several risk factors and causes (51). Management approaches should be determined based on an individual's set of characteristics. There are many treatment options depending on the underlying etiologic reason of the conditions (52). These two conditions are stressful, both for couples and their clinicians who seek to find an effective treatment option. Therefore, personalized medicine is a promising approach in this disease group too (53). In future, human genetics-inspired fertility regulators promise both understanding the underlying etiopathogenetic mechanisms of the disease and determining treatment approaches (54).

Throughout the last decade, large-scale genomic research using NGS technology has led to a better understanding of molecular pathways in relation to the genetic features of gynecological malignancies. As a result, cancer classification strategies, new diagnostic tools, and treatment methods have been developed. Early diagnosis and targeted treatment options for these gynecological malignancies have become possible, based on the identification of several mutations using tumor molecular profiling. Subsequently, personalized medicine is becoming more common with increasing patient demand (55). These new generation therapeutic options differ from chemotherapeutic agents in terms of their mechanism

of action. While chemotherapeutics target inhibition of DNA replication and mitosis, these recent agents act through signalling pathways, stroma, immune microenvironment, and vasculature in tumor tissues (56).

Endometrial cancer is the most prevalent type of cancer of the female reproductive tract. New insights into the pathophysiology and genetic risks of endometrial cancer have been gained due to advances in molecular methods and genome-wide analysis (57).

Cervical cancer is the fourth most common malignancy among women worldwide. When the molecular mechanisms underlying HPV persistence and related cervical cancer is clarified, the prognosis of women with HPV infections can be predicted at an earlier stage. Thus, clinicians can apply a personalized approach to these women greatly reducing the psychological and economic burdens of cervical cancer screening and HPV vaccination programs (58).

Ovarian cancer is the gynecological cancer with the highest mortality rate and there is currently no effective ovarian cancer screening method. Ovarian cancer is currently treated with extensive cytoreductive surgeries and systemic chemotherapy strategies. Despite these treatment approaches being generally efficient in treating ovarian cancer, chemoresistance and the recurrence of the disease are frequently seen after treatment. Due to its high heterogeneity, ovarian cancer has a high rate of recurrence. These days, to reduce the rate, precision medicine strategies are considered as life-saving approaches for ovarian cancer. With the widespread use of personalized medicine, ovarian tumors can be detected at an earlier stage with the greatest chance for optimum care (59). Hereditary breast and ovarian cancer, Peutz-Jeghers and Lynch syndromes are types of hereditary gynecologic cancers (60). A person's risk of these diseases increases if the person has a family history of these diseases. Genetic testing and counselling through personalized medicine has provided a chance for women with these family histories for the detection and management of the disease (61). As with other cancer types, ovarian cancer-related biomarkers will elevate the survival ratio in the future and will be used routinely in the clinic (36,62). Genomic-based therapy, such as PARP inhibitors in ovarian cancer, like other gynecologic malignancies, will provide modern standard-of-care strategies in the future (63).

Another area of personalized medicine in women's life is menopausal hormone treatment. The age, length, duration of menopause, and genetic variants in sex steroid metabolism can shape hormone therapy individually (64). Personalized medicine will provide a more natural approach to overcome undesirable symptoms, such as urogenital tract atrophy, menstruation abnormalities, vasomotor symptoms, sleep problems, and mood disturbances during the menopausal transition, as opposed to hormone treatments (65).

Pharmacogenetics and translational genomics

In determining drug doses in the classical pharmacological approach, individual factors such as age, body weight or body mass index, or markers indicating organ functions, such as creatinine and bilirubin levels, are considered (66). However, it is well known that there are significant differences in treatment response and side effect profile when standard doses are used in healthy adults, even of the same age and body structure. Adverse drug reactions or insufficient therapeutic responses are some of the most important concerns for modern medicine because it causes serious morbidity and mortality as well as increased health costs. In the last 50 years, it has become understood that personal genetic characteristics are the most important factors determining the pharmacokinetics, maximal effectiveness, and adverse event profiles of the drugs (67).

Pharmacogenetics is a combination of pharmacology and genetics. It examines the genetic variations underlying different clinical and laboratory responses to pharmacological agents. In the last decades, pharmacogenetics has expanded rapidly and has gained wider acceptance in parallel with the development of genetic science. It now includes genomics, transcriptomics, proteomics and metabolomics, and has evolved into "pharmacogenomics" (67,68).

How do genetic variations affect drug metabolism and outcomes? The genetic variations may alter the expression and function of certain drug-metabolizing enzymes, drug-binding or processing proteins, which in turn cause variations of drug plasma levels and therapeutic effects. In addition, genetic variations may change the structure of the target molecules for any given drug. The best-known drug-metabolizing enzymes are the cytochrome P-450 family members, sulfotransferases, methyltransferases, and uridine diphosphate-glucuronic transferases (67,68).

Pharmacogenetic-based drug selection is very important in some clinical situations. For example, clopidogrel is an irreversible platelet ADP receptor antagonist which inhibits platelet activation and aggregation and is used for the prevention or the treatment of arterial thrombosis (69). Aspirin and clopidogrel combination are standard dual antiplatelet therapy in acute myocardial infarction patients and in coronary stent implementation (70). Clopidogrel is a prodrug that must be converted to an active metabolite by the enzyme CYP2C19. Patients with *CYP2C19* loss-of-function polymorphisms are unable to metabolize clopidogrel, the drug remains ineffective, and the risk of thrombosis and death increases (71). If a patient has a *CYP2C19* loss-of-function polymorphism, it is recommended to use other anti-platelet drugs, or the clopidogrel dose should be increased with appropriate drug monitoring (72). In 2010, the FDA attached a black box warning

to the clopidogrel label to inform physicians and patients regarding this issue. Although clinical practice guidelines in cardiology are still not clear about the recommendations on genetic testing for clopidogrel users, recent studies showed that the selection of antiplatelet drugs with genotyping improves the clinical outcomes of percutaneous coronary implementation procedures in high-risk patients (72,73).

There was limited information regarding the complex genetic basis of drug metabolism and effectiveness until the "Human Genome Project". Initially, the high cost of genetic testing and lack of studies showing the clinical utility of genetic information in real life has created a challenge. In the last two decades, however, the data obtained by NGS and Genome-wide Association Study revealed an enormous diversity of genetic variants that potentially affect the metabolism of drugs. The next step, the functional studies showing how these variants affect the level of a given drug, is proceeding rapidly. Now in many centers in Europe, Canada, and the United States, the aim is to combine this information with the electronic health record systems for the realization of highly individualized treatment (74).

The serious side effects and limited success of conventional cytotoxic cancer treatment have been the driving force for the development of more effective therapies. In the last decades, the distinct molecular mechanisms involving the development of certain cancers have been elucidated. This data opened the era of the targeted therapy approach. Cancer cell-specific monoclonal antibodies, small molecules, enzymes, hormones, microRNAs, and genetically modified host T-cells are important in modern cancer treatment. In any cancer center in developed countries, the treatment plan is now determined according to the specific genetic characteristics of the cancer of an individual patient. If a patient has *BCR/ABL*-positive chronic myeloid leukemia, first-generation tyrosine kinase inhibitors are started as initial therapy. The efficacy of the treatment is monitored by regular *BCR-ABL* analysis by quantitative PCR test. If this analysis shows inadequate response, an NGS analysis is performed for evaluating additional mutations in the *BCR/ABL* molecule from the patient's CML cells. NGS data will specify which type of tyrosine kinase is more effective for this patient. With this approach, it is possible to achieve complete remission in more than 95% of CML patients. The same steps are now true for many cancers (74,75).

NGS studies have provided data on both individual cancer-related and drug-metabolizing enzymes-related variables very quickly and cost-effectively. This makes it possible to select more potent and less toxic targeted therapies which are especially important in elderly and frail patients (76).

Discussion

There has been a dramatic growth in the availability and application of genomic tests and this development is expected to continue. The application of WGS as a standard measure for each patient is foreseeable, given the expanding knowledge of genotype-phenotype relationships and reducing the sequencing costs. The majority of genomic research focuses on finding new genes and determining the clinical validity and utility of new tests. However, translating genomic technology and NGS into personalized preventive and medical care continues to be a significant challenge. Especially, new technological advancements allow for extensive testing, sometimes conducted outside of traditional laboratories, with the goal of improving health outcomes. Personalized medicine approaches in current research have provided search for biomarkers based on the "-omic" profile of individuals with new technological tools.

Conclusion

To sum up, the advent of personalized medicine provides more precise, predictable, and powerful healthcare. The final goal of personalized medicine and also translational genomics is to increase health quality. Further research across translational genomics will be important in improving the effective, efficient, and equitable translation of genomic data into more effective management of cancer, pharmacogenomics, and women's health. A basic understanding of translational genomics' characteristics, limits, and risks are thus important for clinician and scientist.

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