Examining the Role and Efficiency of Personalized Medicine in the Diagnosis, Prevention, and Treatment of Diseases

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ABSTRACT

Personalized medicine refers to a set of diagnostic, treatment, and prevention activities and approaches based on which patients are classified according to their personal characteristics and medical procedures are performed for them. The purpose of this article is to investigate the importance of personalized medicine, the factors that cause people to differ in their response to treatment, the methods and techniques used to achieve the goals of personalized medicine, and finally to use this method to investigate the possible differences of people in the answer is treatment. Based on this method, either drugs that have been made before are personalized for each person, or recombinant protein drugs are used. Based on the type of factor that has made a person different in response to treatment and medicine, the right type of medicine and the necessary and sufficient dose are prescribed for the person. According to the available reports, regarding the COVID-19 disease, the differences mentioned in different people can be effective in the growing course of the disease, and the use of a personal medical approach leads to the introduction of a safe, effective, and accurate treatment method for different people. But we can say that the most important goal in personal medicine is prevention. Such a way that before contracting the disease, enduring the pain, and finally enduring the side effects of different drugs for treatment, the probability of the occurrence of the disease with the continuous monitoring of the biological indicators of various diseases, which are also identified through personal medicine, in people be checked for health.

Key words: Personal medicine, Treatment of diseases, Diagnosis of diseases, Prevention of diseases

INTRODUCTION

The structure of DNA was first discovered in 1953 by Watson and Crick. This discovery created a tremendous transformation in medical science and since then, scientists have been able to bring great achievements by studying this material day by day [1, 2]. The result of several years of investigations in the field of genetics was the completion of the human genome project [1, 3]. This project is an example of an international effort that officially started in October 1990 and lasted for thirteen years. The goals of the project were to determine the complete sequence of 3 billion DNA subunits, determine all human genes, and make genetic information available for further biological investigations. All these developments led to the use of the term "personalized medicine" in 1999. The process of the aforementioned evolution is shown in Figure 1 [4-7].
Today, the emergence of new technologies has made personalized medicine a more tangible reality, which enables researchers to establish a meaningful relationship between the changes in the profile of molecules in biological fluids or different body tissues and the individual's clinical behavior [7] and from information to use this relationship obtained in the direction of diagnosis, prevention and targeted treatment. The purpose of this article is to investigate the importance of personalized medicine, the factors that cause people to differ in their response to treatment, the methods and techniques used to achieve the goals of personalized medicine, and finally to use this method to investigate the possible differences of people in the answer is treatment.

**Reasons for the need for personalized medicine**

The entire DNA content of an organism, which includes its genes, is called the genome. Genes carry the necessary information to make all the essential proteins of the body. These proteins determine how the organism looks and how the body's metabolism or defense against infection and even its behavior is. Since the human genome map is unique, each person's response to each specific treatment or medication is different, which shows the necessity of using personalized medicine in addition to the influence of environmental factors on the body's metabolism [4].

For example, although the interaction of 24 types of Angiotensin-converting enzyme 2 (ACE2) proteins with a wide range of proteins in different body tissues has been announced by a group of scientists [8], the intensity and weakness of this interaction are different in different people which not only leads to the appearance of disease with different degrees but also affects the performance of prescribed drugs. Statistics show that the response to the acute respiratory syndrome 2 coronavirus, as well as the severity of the disease, is different between men and women of different age groups, races, and geographies. These differences and changes can be explained by the genetic differences of the hosts [9]. Even subtle genetic differences between individuals may affect the viral life cycle and the host's innate and adaptive immune response. Regarding the disease of COVID-19, the reports of the World Health Organization show that the death rate of this disease is 2.8% in men and 1.7% in women. Also, the reports recorded in the Hong Kong hospital that men (32%) need more special care when faced with this disease compared to women (15%), confirm this issue. Possible factors affecting the difference in gender for this disease can be the difference in the immune system between women and men, which has caused women to suffer from viral infections less than men [10].

Experiments have shown that the presence of two enzymes, Angiotensin-converting enzyme 2 (ACE2) and Transmembrane protease, serine 2 (TMPRSS2), are very important for the entry of acute respiratory syndrome coronavirus 2 into host cells [9]. When the coronavirus infects a human cell, the virus uses the serine 2 protease enzyme to prepare and cleave the S protein into S1 and S2 subunits. S1 has a receptor binding domain (RBD) through which acute respiratory syndrome coronavirus 2 can directly bind to the angiotensin-converting enzyme receptor 2 on the host cell (Figure 2).
Figure 2. Schematic representation of novel coronavirus showing target proteins and its mechanism of host entry.

Then S2 plays a role in cell membrane fusion [11, 12]. This connection causes the receptors of angiotensin-converting enzyme 2 to not be able to perform one of their vital functions, which is to prevent the formation of fluid in the lungs during infection [10].

It has been observed that the estrogen hormone in women plays a protective role not only by activating the SARS immune response but also by directly suppressing the replication of the acute respiratory syndrome coronavirus 2. It also inhibits the activity or expression of various components of the Renin-angiotensin system and is specifically able to re-regulate the expression of angiotensin-converting enzyme 2 [13]. In addition to the lungs, the angiotensin-converting enzyme receptor 2 is also expressed in the liver, kidneys, and prostate [14], which can be a reason for the greater sensitivity and susceptibility of men to the occurrence of severe symptoms of COVID-19. On the other hand, it has been stated that men may have a higher expression of serine 2 protease in the lung, which will increase the ability of acute respiratory syndrome coronavirus 2 to enter cells [14]. Among other factors that cause different responses in different people, single nucleotide polymorphisms of protein-drug binding and different drug interactions can be mentioned, which are discussed below.

**Single-nucleotide polymorphism**

Variations in the DNA sequence cause unique differences between individuals. For example, these changes can be parts that are added or deleted in the DNA sequence. One of these changes is single-nucleotide polymorphism, which occurs as a result of the replacement of one nucleotide with another nucleotide and usually occurs in the genome of members of the community of a biological species or even between a pair of chromosomes in an individual. There are more than 3 million single-nucleotide polymorphisms in the human genome, which are considered important genetic markers for evaluating the course of the disease and predicting the response to drugs in different patients [15]. Therefore, many efforts have been made to develop efficient, fast, and cost-effective technologies to achieve progress in disease diagnosis and appropriate treatment of each person based on their genome with single-nucleotide polymorphism analysis.

One of the important effects of polymorphism of single-nucleotides is influencing the drug effect or its metabolic pathway [16]. For example, in recent studies, the effect of genotype on the activity of warfarin as an anticoagulant drug has been studied. Warfarin prevents the formation of vitamin K-dependent blood clotting factors. Oxidation of vitamin K, which leads to the production of epoxy vitamin K, is the main factor in the carboxylation of blood coagulation factors and their binding to the phospholipid surfaces of the endothelium of blood vessels. This epoxy form of vitamin K is converted to its previous state by the enzyme Vitamin K epoxide reductase (VKOR). Warfarin prevents the work of this enzyme, especially Vitamin K epoxide reductase complex, subunit 1 (VKORC1), and in this way reduces the sources of vitamin K in the body. This event leads to a decrease in the production of blood clotting factors. As a result, the body's pre-produced reserves are reduced in a few days and the anticoagulant effects of the blood become visible [17].

Studies have shown that mutations in the Vitamin K epoxide reductase complex, subunit 1 (VKORC1) gene cause different drug sensitivities. In one of the conducted studies, Yang et al. studied one of the single-nucleotide polymorphisms on the Vitamin K epoxide reductase complex, subunit 1 (VKORC1) gene to improve the efficacy
and safety of warfarin. Also, by using optimized conditions for polymerase chain reaction and using surface-enhanced laser desorption and ionization time-of-flight mass spectrometry method, they were able to identify all single-nucleotide polymorphisms occurring on this gene that affect the activity of warfarin drug put, to identify completely in less than five hours.

In the polymorphism of the discussed technonucleotides, most of the shifts between adenine (A) and guanine (G) nucleotides were seen. The usual sequence of these two nucleotides in the Vitamin K epoxide reductase complex, subunit 1 (VKORC1) gene is the AG genotype, which is prescribed for this group of people with the usual dose of warfarin. Patients with the AA genotype that have a lower amount of the normal Vitamin K epoxide reductase complex, subunit 1 gene (VKORC1) will require a lower dose of warfarin. On the other hand, those with GG genotype are resistant to warfarin and it is better to prescribe a higher dose of the drug to achieve the desired therapeutic effect. In another part of this study, the effect of different genotypes on the process of drug metabolism and its removal from the body was also investigated. Normally, warfarin is eliminated by transforming into a hydroxylated metabolite by liver microsomal enzymes (cytochrome P450). This gene controls the activity of the warfarin drug. If a person has single-nucleotide polymorphisms, the side effects of warfarin will be more for this person and finally, a lower dose of warfarin should be prescribed for the patient [16]. Similar studies on Aspirin [18], Paclitaxel [19], and Trastuzumab [20] have also been reported, which all confirm the influence of single nucleotide polymorphisms of genes involved in drug activity and metabolism.

In the reports, the effect of some polymorphisms on the gene of angiotensin-converting enzyme 2 and the occurrence of arterial hypertension, diabetes, stroke, coronary artery disease, and the thickness of the heart vessel wall have been mentioned [21-23]. Therefore, it is important to investigate the possible effect of single-nucleotide polymorphism of angiotensin-converting enzyme 2 in the interaction of this enzyme with glycoprotein S of acute respiratory syndrome coronavirus 2 [24].

Drug-protein binding
One of the other reasons for the different activity of drugs among different people is the difference in the free concentration of the drug in biological environments. Considering that, in most cases, only free drug molecules in the blood can diffuse through the membrane in the body, respond to treatment, and finally be excreted, the difference in their free concentration causes a difference in the level of drug activity and response to treatment.

Studies have shown that the most important reason for this phenomenon is the binding of the drug to the protein. This connection can affect the activity and final fate of drugs after entering the bloodstream and play an important role in the absorption, distribution, and excretion or metabolism of many drugs in the bloodstream. By holding the drug due to protein binding and limiting its release, the pharmacokinetic half-life of the drug increases and leads to the limitation of the level of access to the target tissue [25]. The drug usually binds to serum proteins such as Human albumin serum (HAS), Alpha-1-acid glycoprotein (AGP), or other lipoproteins [26]. Human serum albumin is one of the main proteins in blood serum with a concentration between 30 and 50 grams per liter. This compound has three homologous regions, each of these three regions consists of two sub-regions named A and B, and the whole structure maintains its stability by 17 disulfide bonds.

**Figure 3** shows the general structure of human serum albumin. This protein has different functions in the blood, including helping to regulate osmotic pressure and pH control in the bloodstream.

![Figure 3. The general structure of human serum albumin and two main drug binding sites.](image-url)
Since there are two active sites in the structure of human serum albumin, one of its main roles in the blood is to carry a large number of small substances such as hormones, fatty acids, and drugs [25, 27]. In the studies, it has been found that large heterocyclic compounds such as coumarins, sulfonamides, and salicylates are bound through site I and aromatic carboxylic acids and profanes are bound through site II [28]. The amount and manner of binding of a drug to human serum albumin can lead to changes in the duration of effect, metabolism, and free concentration of the drug in plasma. There are various factors in which the disease can affect the drug-protein binding interactions in the blood. These factors cause the amount of this connection to increase or decrease. If a factor increases this connection, the free concentration of the drug in the blood will decrease and the pharmacological effect of the drug will decrease, and a higher dose should be prescribed for this person to have an effective result, or vice versa. One of the factors that may cause changes in these connections is protein concentration. Another factor that can change the binding of the drug to protein is that the structure of a protein changes as a result of the disease process [25, 26].

For example, studies have shown that diabetes leads to increased non-enzymatic glycation of serum proteins such as human serum albumin. Glycation, which is a non-enzymatic reaction of sugars with proteins, in which glucose combines with free amine groups on a protein (Figure 4), changes the shape of proteins and removes the protein from its functional form [26].

**Figure 4.** Schematic work for the study of binding interactions of the albumin-gliclazide-drug system.

**Drug interactions**

Another important issue that leads to the difference in the activity of drugs in different people is drug interaction. The simultaneous use of two or more drugs that have a high degree of protein binding may cause competition between drugs to occupy binding sites on proteins, and as a result, one of the two drugs binds to a lesser extent, which leads to an increase in the free concentration of the drug will be different. Of course, it should be noted that this problem happens in practice when one of the two drugs consumed even in the therapeutic concentration range saturates the binding sites relatively. For example, the simultaneous use of phenylbutazone and warfarin will cause a slight increase in the free concentration of warfarin. Since this drug is in the therapeutic concentration range, about 99% will be bound and 1% will be free, so increasing the free part of warfarin will intensify its pharmacological effects, which will cause bleeding during the first hours after taking the drug [29].

**Principles of personalized medicine**

In conventional medicine, a specific drug is prescribed to all patients with a dose related to certain characteristics of the patient such as weight and sex. In this method, any drug-based prevention or treatment suffers from two limitations, the first limitation is that drugs will not be active for 100% of people [30], the percentage of activity of some drugs is shown in Figure 5.
According to Figure 5, antidepressants are inactive for 38% and asthma drugs for 40% of people [31]. The second limitation is the safety features of each drug. An active drug that has a high effect on patients is likely to cause side effects, the severity of which varies from person to person. Every year, many cases of side effects of drugs are reported by the pharmaceutical industry [30], while personalized medicine is one of the important approaches to personalizing drugs. In this method, patients with a specific disease are divided into different categories based on the genome map or the presence of specific biomarkers in the tests performed. For patients belonging to each category, taking into account their genetic diversity and lifestyle, a special drug appropriate to this subgroup is prescribed (Figure 6).

This method provides more precise treatment along with better clinical management. In 2008, only 5 personalized medicines were reported on the website Personalized Medicine Coalition (PMC). Meanwhile, in 2016, this
number reached 132 cases [31]. Also, the probability of contracting various diseases for each person is extracted from his genetic map. This causes early diagnosis of the disease, which leads to timely prevention [32].

New approaches to personalized medicine

Recombinant proteins

Today, the use of recombinant proteins (especially with a personalization approach) has become increasingly popular for the treatment and management of some of the most complex medical conditions. Proteins used in the treatment of human diseases can be produced by recombinant DNA technology [33]. Another important achievement is the development of recombinant proteins that can enter cells. These drugs create new opportunities for treatment by targeting intracellular mechanisms or replacing active intracellular enzymes [34]. Currently, by using living organisms and using recombinant DNA technology, a cost-effective tool for the production of recombinant proteins on a large scale has been provided [35]. More than half (55%) of recombinant proteins are produced by microbes (40% by bacteria and 15% by yeast). E.coli is the first and most widely used host for the production of heterologous proteins [35, 36].

The recombinant insulin produced by E.coli is the first recombinant drug that was approved by the Food and Drug Administration in 1980 [35]. The production processes of therapeutic recombinant proteins usually include a series of complex steps, each of which has a significant impact on the quality of the produced protein and ultimately the safety and efficacy of the final product. Designing effective and efficient processes requires a deep understanding of how the formation and various factors affect product quality and activity. It is expected that therapies based on protein drugs will require advanced analytical methods to confirm the protein structure and activity of the product during the manufacturing process. Different mass spectrometry techniques coupled with different separation methods such as gas or liquid chromatography are known as essential analytical tools to identify recombinant proteins [37]. Zhang et al. [38] using the Reversed-phase high-performance technique of liquid chromatography-mass spectrometry (RP-HPLC-MS) investigated the quality of monoclonal antibodies produced by Chinese rat ovarian cells. This antibody is used to treat a large number of diseases (e.g., oncology, inflammation, and autoimmune diseases). This monoclonal antibody molecule contains two identical light chains and two identical heavy chains, as shown in Figure 7.

![Figure 7. Schematic structure of IgG1 monoclonal antibody.](image)

In total, the monoclonal antibody has sixteen disulfide bonds, two of which are located in the hinge part of the antibody structure, which are responsible for maintaining the three-dimensional structure of the monoclonal antibody. To verify the structure of the produced antibody, first, the mentioned proteins are digested using protease enzyme, and the peptides forming the antibody are produced. Then, the peptides are identified by Reverse-phase high-performance liquid chromatography-mass spectrometry (RP-HPLC-MS) technique. The Nanoelectrospray quadrupole time-of-flight mass spectrometry (nanoESI-QTOF MS) technique can also be used to sequence peptides containing disulfide bonds, and the N-terminal Edman sequencing technique can be used to confirm
connections (formation of disulfide bonds). If one of the peptides is not detected, it indicates that the disulfide bond has not been formed, so the prepared antibody will not have its main function [38].

In a study by Bai et al. by experimenting on mice, they succeeded in preparing a vaccine by expressing the S or N proteins of the coronavirus in the recombinant baculovirus system. Baculovirus systems are widely used for the production of recombinant proteins in insect cells due to their high level of expression and appropriate post-translational modification. The results showed that the recombinant Clovirus can be directly injected into mammalian cells and cause the production of virus antibodies. This strategy is considered safe because baculoviruses do not replicate in mammalian cells and do not induce a cytopathic effect [39].

**Early diagnoses for prevention**

With codified information in personalized medicine, it is possible to introduce biomarkers that indicate the risk or presence of disease before clinical signs and symptoms appear. This information provides an opportunity to focus on prevention and early intervention rather than reacting at advanced stages of the disease. Genetic diagnostics examining the genome and finding genetic mutations helps prevent disease before it occurs. As a result of these preventions, the costs of treatment and medicine are reduced and the person is freed from performing invasive diagnoses [40].

In a study, Frank et al. investigated pulmonary arterial hypertension and found biomarkers of this disease. In this study, volatile organic compounds in the breath of patients with pulmonary artery hypertension were investigated using the selective ion flow mass spectrometry technique to find suitable biomarkers for this disease. By comparing the profile of volatile organic compounds in the breath of patients with pulmonary artery hypertension and healthy controls, they were able to identify the biomarkers of this disease. The increase in these biomarkers indicates that the person is suffering from this disease and should take measures for prevention [40].

**CONCLUSION**

The goals that the personalized medical treatment system pursues include choosing the right and effective medicine for different people, reducing the cost of medicine and treatment, reducing the side effects of medicines, and finally reducing the duration of treatment and quick recovery of the patient. It is also possible to use this method to consider the possible differences of people in the response to the acute respiratory syndrome 2 coronavirus in the course of treating the disease of COVID-19. So far, some cancer, cardiovascular, infectious infertility, and nerve diseases have been treated with personalized medicine. According to this method, medicines that have been made before are personalized for each person, or recombinant protein medicines are used. Based on the type of factor that has made a person different in response to treatment and medicine, the right type of medicine and the necessary and sufficient dose are prescribed for the person. It can be said with certainty that the most important goal is prevention, which is proposed in personal medicine, so that before contracting the disease and enduring the pain and finally the side effects of various drugs for the treatment of the patient, the probability of the occurrence of the disease with continuous monitoring of markers Biology causes various diseases.

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**REFERENCES**


