Original Article: Personalized Medicine: Tailoring Treatment Plans Based on Genetic Profile

Ouldouz Navaei
Master of Industrial biotechnology, university of Milano bicocca, Milan, Italia (Orcid ID: 0009-0008-2694-7952)

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ABSTRACT

Genetic technologies in personalized medicine have revolutionized the management of anticoagulant therapy. Despite their vital role in preventing blood clots, these drugs pose numerous challenges in dose adjustment and side effect management due to the varying responses of patients. Genetic analysis has enabled the provision of personalized, safer, and more effective therapy by identifying genetic differences in related genes such as CYP2C9 and VKORC1. By precisely adjusting the dose, reducing side effects, accelerating the treatment process, and reducing costs, this technology not only improves the quality of life of patients but also paves the way for new standards in healthcare. However, challenges such as high costs, limited access, and privacy issues require attention and resolution. In this approach, the genome of the individual in question is compared with reference genomes, and based on the information obtained, the individual can be treated in an appropriate and specific way. In fact, the genetic nature of the individual determines the treatment strategy. One aspect of personalized medicine is the use of pharmacogenomics. In this method, a more appropriate and informed drug is provided by using and knowing the sequence of an individual's genome. In conventional medicine, drugs are often prescribed with the idea that the effect of the drug is the same for everyone, but in fact this is not the case and each person responds differently to the drug depending on the nature of their genome sequence. Therefore, various factors must be taken into account. For example, depending on these sequences, side effects, the required amount of drug, the likelihood of successful treatment, and the prognosis of the disease will all be unique to each individual.

Introduction

Medical genetics is one of the new sciences that has expanded rapidly in recent years [1], so that we are witnessing new scientific findings in this field every day, and considering the many unknowns in this regard, its boundaries seem unattainable [2]. Medical genetics has become much broader than other medical fields and requires a lot of knowledge and its own tools. So far, more than thousands of genetic diseases and syndromes have been discovered and described, and their number is increasing every day [3].

Hence, there is a need for a comprehensive, rapid, reliable and up-to-date system for

Corresponding Author:* ***Ouldouz Navaei* *(ouldouz.navaei@unimib.it)*

diagnosing and treating this type of genetic disease [4], which has been designed and produced by taking into account all the needs of the medical genetics community and patients in this group. This system has been designed and developed as a set of application software for genetic management, diagnosis, and counseling. Since classical systems in medical sciences have many limitations and are not able to process a large number of diseases, there is a need to design and build a new system that can analyze such a large number of genetic diseases and meet the needs of genetic specialists [5-7].

Computer systems have unique capabilities, including extensive and rapid processing of information, updating, and a very high reliability coefficient, which makes them suitable for the development of this type of software. Many efforts have been made around the world to develop such software systems. First-world countries use these software systems extensively in their healthcare systems, but such a comprehensive software system has not yet been developed in our beloved country of Iran [8].

Given the defective structure and unprofessional staff working in the country's genetic centers, developing a similar foreign software system is vital [9].

On the other hand, correct diagnosis of the disease is vital in the treatment and monitoring of patients, which is a difficult and, in most cases, time-consuming task due to the large number of genetic diseases and their complex symptoms, and can prevent the effectiveness of timely treatments due to the long time it takes to diagnose the disease [10].

Among the problems in Iran today are incomplete and incorrect diagnoses in the field of genetic diseases. Due to the wide spread of this group of diseases, some patients are not correctly diagnosed and many, unnecessary and expensive genetic tests are imposed on patients, which unfortunately puts a lot of pressure on patients and the country's healthcare system. Also, the opportunity for timely treatment and a more comfortable life is lost in children and infants [11].

Genetic evaluation for precise dose adjustment in blood thinning treatments

Adjusting the precise dose of blood thinning drugs such as warfarin is one of the most sensitive challenges in the treatment of patients who are at risk of blood clots [12]. These drugs, with their narrow therapeutic window and different reactions among patients, require continuous monitoring and precise dose adjustments. One of the main factors in these differences is the genetic characteristics of patients, which can affect how the drug is metabolized and the body's response to it. Genetic evaluation allows doctors to adjust the drug dose in a scientific and precise manner by identifying genetic variations in related genes such as CYP2C9 and VKORC1 [13].

1- CYP2C9 gene: Responsible for the metabolism of warfarin in the liver. Mutations in this gene can reduce the rate of drug breakdown and increase the risk of excessive drug accumulation in the body, which may lead to severe bleeding [14].

2- VKORC1 gene: Affects a patient's sensitivity to warfarin. Changes in this gene may result in the body needing less or more of this drug [15].

Benefits of genetic evaluation in dose adjustment

1- Reduced side effects: including severe bleeding or ineffective treatment due to inappropriate dosage [16].

2- Reduced dose adjustment time: Reduces the need for repeated tests and the trial and error process.

3- Increased treatment safety: Improved adherence to treatment protocols and reduced risks associated with treatment [17].

4- Cost savings: Reduced additional tests and hospitalizations related to drug side effects.

Challenges of genetic evaluation in dose adjustment

1- Cost of genetic tests: May not be available to all patients.

2- Complexity of interpreting results: Requires high expertise and advanced equipment [18].

3- Ethical and privacy issues: The collection and storage of genetic data may raise concerns. Genetic assessment is a new and effective approach in personalized medicine that allows for precise dose adjustment in blood thinning treatments. This method, by reducing side effects, increasing treatment effectiveness, and improving patients' quality of life, paints a bright future in the management of diseases related to blood clots. With technological advances and reduced costs, the wider use of this approach could become a new standard in anticoagulant therapy [19].

Personalized medicine: The impact of genetics on the effectiveness and safety of anticoagulant drugs

Personalized medicine, as one of the emerging branches of modern medicine, studies the impact of genetic characteristics on patient treatment. In the field of anticoagulant drugs such as warfarin, the personalized medicine approach plays a key role in increasing the effectiveness of treatment and reducing side effects [20-22]. These drugs, which are used to prevent blood clots, require careful dosage adjustment. Because the slightest error can lead to serious complications such as bleeding or ineffective treatment. A person's genetic characteristics play an important role in determining the response to anticoagulant drugs. Genetic variations in genes such as CYP2C9 and VKORC1 can affect the metabolism and sensitivity to these drugs:

1- CYP2C9 gene: This gene is responsible for breaking down and excreting warfarin in the body. Mutations in this gene may lead to a decrease in the rate of drug metabolism, which increases the risk of drug accumulation and complications such as severe bleeding [23].

2- VKORC1 gene: This gene determines the body's sensitivity to warfarin. Genetic variation in this gene can lead to a change in the patient's need for a lower or higher dose (Figure 1).

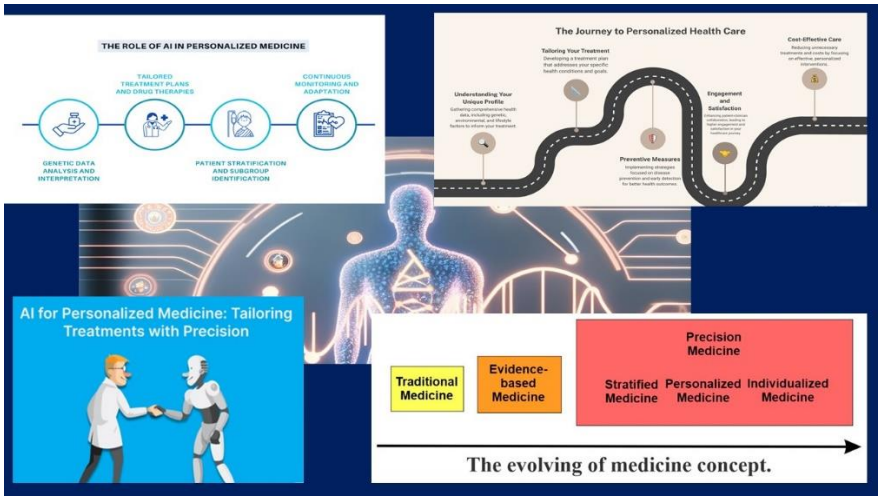

Figure 1. Personalized Medicine: Tailoring Treatment Plans Based on Genetic Profile

Effects of personalized medicine in anticoagulant therapy

1- Increasing the effectiveness of treatment: Determining the dose according to the patient's genetics significantly increases the likelihood of treatment success [24].

2- Reducing the risk of side effects: Accurate dose adjustment minimizes the risk of bleeding or inadequate clotting [25].

3- Accelerating dose adjustment: Using genetic information reduces the time required to reach the optimal dose.

Future challenges and needs

1- Access to genetic testing: This technology is not yet available to all patients.

2- Educating doctors and patients: There is a need to increase awareness about the benefits and applications of personalized medicine.

3- Privacy laws: Protecting patients' genetic information is a major challenge that requires comprehensive legislation [26].

Personalized medicine has brought about a fundamental change in anticoagulant treatment using genetic analysis. This approach not only helps to increase the safety and effectiveness of treatment, but also opens up new horizons in medicine by reducing costs and improving the quality of life of patients. With further technological advancement and cost reduction, this approach can become an integral part of everyday treatments [27].

Genetic technologies in reducing side effects and improving the effectiveness of anticoagulants

Anticoagulant drugs, including warfarin, are important tools in the prevention and management of diseases related to blood clots, but one of the main challenges in the use of these drugs is the narrow therapeutic window and the possibility of serious side effects. Genetic differences between patients play an important role in the response to these drugs and can lead to problems such as severe bleeding or ineffective treatment. Genetic technologies, as an advanced approach, have made it possible to identify these differences and fine-tune the treatment. Genetic analysis offers a way to reduce side effects and improve the effectiveness of anticoagulants by identifying the diversity of genes related to metabolism and drug sensitivity [28].

Key genes in anticoagulant therapy

1- CYP2C9: This gene is responsible for breaking down and excreting warfarin in the body. Certain mutations in this gene can slow down the metabolism of the drug and increase the risk of drug accumulation and its side effects.

2- VKORC1: This gene determines the body's sensitivity to warfarin. Changes in this gene may determine whether a patient needs a lower or higher dose [29].

3- F5 and F2: These genes are associated with predicting the risk of blood clots in patients and can influence decisions about the use of anticoagulants.

Application of genetic technologies

1- Fine-tuning the dose: Using genetic data to determine the appropriate initial dose reduces the risk of side effects such as severe bleeding or ineffective treatment.

2- Prevention of side effects: Identifying people with high sensitivity or slow metabolism can help prevent complications.

3- Reduce the time to reach the optimal dose: By using genetic analysis, the trial-and-error dose adjustment process is eliminated and treatment begins faster [30].

4- Increase the effectiveness of treatment: Adapting treatment to individual genetic characteristics significantly increases the effectiveness of the drug.

Benefits and challenges

1- Benefits: Reduce complications, improve the quality of life of patients, reduce treatment and hospitalization costs, and accelerate the treatment process [31].

2- Challenges: High costs of genetic testing, limited access in some regions, and issues related to the privacy of genetic information.

By providing accurate analyses, genetic technologies have created a unique opportunity to optimize anticoagulant therapy. This approach is a big step towards personalized medicine by reducing risks and increasing effectiveness. With the further development of these technologies and increasing their availability, it can be expected that therapeutic management in the field of anticoagulant drugs will become a safer and more efficient standard[32].

Creating personalized medicines based on each person's genetic makeup

Imagine you have visited your doctor for a simple or complex illness. The doctor takes a sample of your blood or hair and, by analyzing your genetic makeup, prescribes you a completely personalized medicine. Although this is currently not practically possible for the treatment of most diseases, the future of medicine and treatment is moving towards creating personalized medicines for each person based on their genetic information [33]. Pharmaceutical and therapeutic studies and the interaction effects of drugs on people's metabolism have led researchers to conclude that the best treatment method is to create and prescribe personalized medicines based on the genetic characteristics of individuals. This can increase the effectiveness of the drug and reduce its side effects [34].

In this regard, pharmacogenomics studies come to the aid of scientists. In pharmacogenomics, inherited genetic differences in drug metabolism pathways are investigated and the role of genetic differences in drug response is investigated through the systematic study of genes, gene products, and individual variations in gene expression and function.

If this is implemented, people whose diseases are directly related to their genetics will benefit greatly. In this way, the chances of treating mental illnesses such as depression, types of cancer, brain diseases such as brain degeneration and neurodegenerative diseases such as Alzheimer's and Parkinson's, which are directly related to individuals' genetics, will increase significantly [35].

The history of pharmacogenomics dates back to 510 BC. When Pythagoras realized that consuming fava beans would cause death in some people, but would have no effect on others. However, new studies in this field began in the second half of the 20th century, following the increase in human knowledge about genetics. Pharmacogenetics and pharmacogenomics have become controversial topics in the fields of bioethics and medicine. The widespread use of these sciences, which will include the treatment of common and rare diseases, will have a great impact on society. Due to the nascent nature of these sciences, many questions have been raised regarding ethical issues and possible solutions to human problems [36].

For example, to what extent can access to individuals' genetic information be important in their private lives and jeopardize their privacy? In addition, issues such as drug safety, access to it, and establishing justice in patient treatment are also issues that need to be considered. Personalized medicine is a new approach to medicine in which medical interventions are based on the individual characteristics of patients, which include their genetic and phenotypic information. With the emergence of sciences such as genomics, proteomics, lipomics, etc., which identify

individual differences between individuals, it will become possible to produce drugs and diagnostic biomarkers and screen for diseases, so that doctors can determine the type and amount of medication for each patient individually, based on the genetic and genomic characteristics of each individual [37].

Using molecular analyses, various genetic variants can be identified, which makes it possible to screen individuals at risk of developing a specific disease, design and prescribe medications that are appropriate for the patient's genetic background, and thus provide the most appropriate diagnosis and treatment method for the patient. In fact, personalized medicine will be the bridge between current medicine and future medicine [38].

The increasing advances in medical science have made the diagnosis and treatment of diseases more efficient. One of these advances is the Human Genome Project, which, with its completion, opened a new window to the world of medicine from the perspective of genetics. The completion of this project marked the beginning of a new era called post-genomics, which led to the introduction of new scientific concepts such as genomics, proteomics, and pharmacogenomics into the world of medicine. The sequencing of the human genome, along with the progress and development of open technologies, which are mainly referred to as Omics, has improved human knowledge about disease and health and provided the basis for personalized medicine [39].

The integration of information from disciplines that end in Omics, which allows general structural patterns to be developed towards specialization, is a promising approach. This approach is the definition of personalized medicine, which means using the genetic or molecular characteristics of individuals to determine their type of treatment. However, one of the most important problems in the field of personalized medicine is the transformation of scientific research and discoveries into the direction of return and obtaining the best treatment results, which, with the help of bioinformatics, can bridge the gap between systems biology research and clinical trials [38].

It has been a long time since the discussion of designing unique drugs for each patient has been raised, but it seems that this issue has gained serious momentum in the pharmaceutical field, and if planning to deal with this innovative area is not included in the policies of the Ministry of Health and the Food and Drug Administration [39], sooner or later we will face problems in managing the market of drugs that enter the pharmaceutical market based on this feature. Creating the necessary infrastructure and laboratory capacity for genetic evaluation of patients and guiding them towards taking or not taking a drug will be a prerequisite for dominating this market.

Drug Discovery and Drug Development

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Pharmacogenomics and bioinformatics refer to the effects of genetic polymorphisms and genomic variants on drug response. Its knowledge can help in selecting the optimal drug, dosage and treatment process and avoid adverse drug reactions. Disease-related genetic and bioinformatics knowledge guides pharmaceutical companies to design

pharmacogenomics and individualized doses and dosages [41].

This is done by observing the genetic patterns and polymorphisms of these genetic elements that show interaction with the drug or its by-products and are somehow related to the pharmacogenomics of the drug. Adverse drug reactions are reported to be a leading cause of death among hospitalized patients and account for the majority of $17–29 billion in annual medical error costs. Adverse drug reactions have also been reported to contribute to loss of trust in the healthcare system and decreased satisfaction among both patients and healthcare professionals [42].

Medicine and Personalized Medicine

The pharmacogenomics approach enables pharmaceutical companies to design drugs that meet the requirements of specific genetic subgroups of the general population. The main goal of pharmacogenomics and bioinformatics is to identify patients for whom drug efficacy can be predicted and to use them to reduce the risk of adverse drug effects [43].

The promise of prescribing drugs based on patients' genetic profiles is known as personalized medicine. This reduces the guesswork of prescribing medications, thereby increasing trust in both physicians and patients, and modifies the prevailing approaches to drug discovery and development, diagnosis, treatment, and disease prevention strategies. It is also beneficial for society, as it avoids the use of expensive drugs in patients whose disorders are not treated by these drugs. Bioinformatics also provides information resources related to pharmacogenomics, which contain information on different types of polymorphisms and examines the variable drug-dependent response [44].

It has been reported that various drugs exhibit adverse drug reactions, often leading to hospitalization and in some cases, death. Investigations into such drug reactions have led to the withdrawal of drugs from the market [45]. This is immediately followed by a series of lawsuits for drug abuse. The pharmacogenomics approach to drug development strategy offers an opportunity to reverse this trend.

It is promised that it may lead to the development of precise drug substances. Precision drugs refer to drugs that are tailored to the genetic makeup of individuals. These drugs can be evaluated in short and simple clinical trials and will show adverse effects on them. Pre-prescription genetic testing and bioinformatics analysis greatly reduce the chance of misprescribing [46].

Use of useless drugs

In the process of drug discovery and drug development, pharmaceutical companies tend to focus more on the original drugs that are prescribed to more than 20 million people, known as blockbuster drugs.

The result is a lack of drugs that could be developed to treat diseases that affect only a small number of people. These drugs or potential drugs are known as abandoned or orphan drugs [47].

A pharmacology strategy for drug development may revive these abandoned drugs if it can be proven that there are potential beneficiaries for these drugs. From a commercial point of view, if a pharmaceutical company can benefit from something like the status of abandoned drugs in its product, this will help encourage the classification of populations based on pharmacokinetics with bioinformatics. Because the reduction in the size of a population can be compensated for by drug prioritization.

This is the only way that pharmaceutical companies can be encouraged to abandon this blockbuster bias. In recent years, various

authorities have recognized the potential of pharmacogenomics in drug design and development and have encouraged such approaches to drug discovery and delivery. As pharmacogenomics technologies continue to emerge and grow, international regulatory bodies are developing pharmacogenomics guidelines and regulations [48].

However, despite the increasing attention and documented potential and commitment of pharmacogenomics-based drug development strategies, there has been ongoing resistance to this approach on the part of pharmaceutical companies. The reason for this resistance is the perception that a pharmacogenomics strategy and bioinformatics analysis lead to a significant loss of market share for drug analysis. Moreover, such a perception is not seen from the outside and is considered a myth by some consumers. They reported that the pharmacogenomics strategy has the potential to increase the size of the drug market [49].

Barriers to Progress in Drug Development and Design Pharmacogenomics is based on genomic variations, specifically in coding or near coding regions. It is very difficult to predict gene variations with bioinformatics tools that affect drug response. Single nucleotide polymorphisms play a major role in variable drug response. SNPs occur every 100–300 bases along the three billion base human genome.

Therefore, millions of these must be identified and analyzed by bioinformatics software to determine their involvement in drug response. Limited awareness and knowledge of the relationship between gene variants and variable drug response also acts as a limiting factor for drug design and drug delivery processes [50]. Because many genes are likely to influence responses, obtaining a big picture of the effect of gene variations is extremely time-consuming and complex, and for this we need a genetic profile of each individual, which is not possible in the near future and is very time-consuming even with current bioinformatics software.

Physicians will also need to perform an additional diagnostic step to determine which drug is appropriate for each patient. To accurately interpret the diagnosis and recommend the best course of treatment for each patient, all prescribing physicians, regardless of specialty, will need a better understanding of genetics. Some ethical considerations must also be addressed before routine clinical implementation of pharmacogenomics. At the same time, the economics of pharmacogenomics testing will play a major role in determining its future use from the perspectives of patients, physicians, insurance companies, governments, and pharmaceutical companies [51].

Early Examples of Personalized Medicine

Personalized medicine has over the years included many treatments that are selected based on an individual's genetic profile. This type of medicine is used not only to treat diseases, but also for early diagnosis and prevention of disease. Here are some classic examples of personalized therapies in the past.

1- Warfarin: Warfarin is a blood thinner that, if used incorrectly, can cause dangerous drug reactions. The drug targets its target, the VKORC1 gene, and is partially metabolized by the CYP2C9 gene. Natural genetic differences in these two genes cause differences in how different people respond to warfarin. For this reason, the US Food and Drug Administration (FDA) has recommended that the dose of warfarin be adjusted according to the individual's genotype to avoid side effects [52].

2- Primaquine (PQ): Primaquine is used to manage malaria. However, some soldiers who used this drug in the past developed severe anemia and jaundice. It was later found that these people had certain genetic variants in the

G6PD gene that led to these complications. Therefore, currently, before prescribing primaquine, the patient needs to be genetically tested to determine whether they have these variants or not [53].

3- Imatinib: Imatinib is a drug used to treat chronic myelogenous leukemia (CML). This drug inhibits an enzyme called tyrosine kinase that is increased by the combination of two genomic regions, one containing the abl gene and the other containing the bcr gene. This genetic combination, known as the Philadelphia chromosome, leads to the development of CML in many tumors. However, not all patients with CML have this genetic mutation, and therefore imatinib is only prescribed to those who do.

These examples illustrate how personalized medicine based on individuals' genetic differences can lead to better treatment and prevention of side effects [54].

Contemporary examples of personalized medicine

Drugs such as warfarin, PQ, and imatinib, which appear to be effective, or to work without side effects, only when a patient has a specific genetic profile, have generated great interest in identifying factors such as genetic variants that influence a patient's response to various drugs and interventions. This interest in developing personalized medicines to treat diseases has also extended to personalized disease monitoring and personalized prevention strategies. Here we briefly describe a few very recent examples of this activity [55].

Mutation-specific therapies

Instead of developing a drug and then identifying factors that influence its effectiveness or side effects through observational studies of people taking the drug, efforts are now underway to identify the specific genetic profiles that patients have and then design treatments that uniquely target those profiles. For example, the drug Ivabra, mentioned earlier, is designed to treat people with cystic fibrosis (CF) who have specific pathogenic mutations in the CFTR gene [56].

The CFTR gene has many functions, but one set of functions is determined by the structure of a gate in the protein encoded by the CFTR gene. This structure can open and close to control the movement of salts in and out of cells. If the CFTR gene is dysfunctional, the gate closes, causing mucus and other substances to build up in the lungs. Different mutations in the CFTR gene cause different types of disorders. For example, some mutations cause the CFTR gene to produce nothing, whether the gate is open or closed [57].

Other mutations cause the gate to malfunction. Ivaca is designed to keep the gate open for longer periods of time in the presence of certain mutations that normally cause the gate to close. So Ivaca is only useful for a small subset of CF patients whose CFTR mutations cause this particular gating problem. The links between genetic variants and the effectiveness and side effects of drugs are growing.

A second example involves a class of cancer treatments known as immunotherapies. Although there are many different types of immunotherapies, they all seek to stimulate, or activate, a people own immune system to attack the cancer. One type of immunotherapy takes advantage of a unique set of potential genetic changes in a cancer patient's tumor cells, called neoantigens.

These neoantigens are often capable of eliciting an immune response if they are properly recognized by the host's immune cells. Essentially, this type of immunotherapy works by taking cells from a patient that mediate their immune responses, such as T cells, and then modifying those cells to specifically recognize and target the neoantigens on the patient's tumor.

These modified cells are then returned to the patient's body, where they can attack the tumor cells that are emitting the neoantigen signals. Cytotoxic T-cell therapies like these, plus immunotherapies, have generally had considerable success, but they can be very patient-specific for two reasons [58].

First, a patient's neoantigen profile may be so unique that cytotoxic T cells engineered to recognize and attack a specific set of neoantigens will not be effective in someone whose tumor does not have those neoantigens. Second, if autologous constructs are used, the patient's own T cells are altered and therefore unlikely to function well in another patient. Although efforts are being made to develop allogeneic constructs in which T cells from one individual are altered and introduced into another patient's body, these are being vigorously pursued [59].

Personalizing early detection strategies

If an individual is susceptible to a disease, or is prone to relapse, they should be monitored. It is now believed that this monitoring should be done using individual rather than population criteria to make claims about evidence or signs of disease or a pathogenic process.

Population criteria are derived from epidemiological data and population surveys and include examples such as cholesterol levels above 200 as an indicator of heart disease risk, or systolic blood pressure above 140 as an indicator of high blood pressure, stroke risk, or heart disease. Personal criteria are determined from historical values of a measurement collected over time for an individual and are used to measure how much future values of that measurement might deviate for that individual [60].

Significant deviations from historical values or historical averages are considered an indicator of changing health status, regardless of whether those values exceed a population threshold. For example, Drescher et al. examined the application of personal thresholds to CA125 levels collected from a sample of women, some of whom developed ovarian cancer. The authors found that in all but one case, the use of personal criteria identified ovarian cancer at the same time or, more importantly, earlier than the use of population-based thresholds. Furthermore, the authors showed that the use of personal criteria could identify ovarian cancer on average almost a year earlier than the use of population-based criteria. As the cost and availability of tests and surveillance technologies improve, the use of personal criteria is likely to become a standard in health surveillance protocols [61].

Personalized disease prevention

The use of genetic information to develop personalized disease prevention strategies is now well established in the scientific community, but it has not yet been widely used in clinical practice. There are many good examples of how the use of genetic information can lead to a reduction in disease risk as well as a reduction in complications from standard treatment and screening strategies. One prominent example concerns colon cancer, which, despite being a highly preventable disease, remains the third leading cause of cancer death [62].

In 2012, Lea and colleagues reported that colon cancer patients who took aspirin after surgery and had somatic mutations in the PIK3CA gene had improved overall survival and a reduced risk of cancer-related death compared with patients whose cancer had wild-type PIK3CA.

In 2015, Nan et al. reported different effects of aspirin use on colorectal cancer risk depending on a person’s genotype, with individuals with different genotypes having either a reduced, increased, or unchanged risk of colorectal cancer with aspirin use.

Given that aspirin use can cause serious side effects such as intestinal and intracranial bleeding, it would be ideal to limit its use to individuals who are predicted to have side effects based on their genotype [63].

As another example, in 2018, Jun et al. reported the use of risk prediction models developed to determine when to start colorectal cancer screening. Currently, the guidelines only use age and family history as covariates. Jun et al. showed that using information about an individual's environmental exposures and genetic profile, particularly the presence of genetic variants associated with colorectal cancer, the recommendations for when to start screening can be changed by as much as 12 years for men and 14 years for women [64].

Personalized and person-centered drug testing

Although we have argued that personalized medicine has its roots in a large number of historical insights and precedents, mainly related to genetics and rare diseases, its recognition as a standard approach that should be widely accepted by the biomedical and clinical research communities is relatively recent.

This suggests that not enough time has passed since this recognition for researchers to demonstrate that personalized medicine is truly effective in a variety of settings, and this could motivate its widespread adoption. In this regard, questions arise about how society can evaluate or test the usefulness of personalized medicine. Below, we describe three emerging strategies for evaluating personalized medicine [65].

These include N-of-1 clinical trials, treatment-matching trials, and comparative clinical trials, and argue that while these strategies are modeled on elements of traditional randomized clinical trials, they differ significantly from them [66].

N-of-1 Clinical Trials

If there is no reason to believe that one set of treatments better matches an individual's profile than the others, then there is a trade-off between those treatments. In this case, it is an empirical question of which treatment is likely to be optimal for the individual [67].

Trials that focus on an individual's response to different treatments to determine an optimal treatment are known as N-of-1 trials or single-subject trials. N-of-1 trials often use a simple crossover design or even repeated crossover designs such as "ABABAB" designs, where "A" and "B" refer to different treatments, and the "ABABAB" sequence refers to the order in which the treatments are given to the patient. Alternating these treatments and collecting data on an individual's response to those treatments allows comparisons of these treatments. Randomization, blinding, washout periods, multiple endpoints, and many other design elements can be used in N-of-1 trials. N-of-1 trials, which involve giving different treatments sequentially to an individual and assessing outcomes for each, need to account for serial correlations between observations as well as possible carryover effects from one treatment to another, but these issues can largely be resolved with appropriate analytical methods and study design [68].

Crossover-based N-of-1 trials are impractical and even unethical in situations where a person is suffering from an acute or life-threatening condition, because switching from one treatment to another may exacerbate the condition. However, sequential N-of-1 designs, in which measurements are continuously monitored in real time to determine whether a treatment is causing harm or benefit, have been proposed for these situations. Given that the focus of an N-of-1 trial is on identifying an optimal treatment for an individual, rather than on the average response to a treatment in the entire population, which is usually the focus

of traditional randomized trials, these trials may be the most appropriate option to conduct in real clinical practice when the clinician is faced with a trade-off, as reviewed by Hogan and Sim [69].

Trials of treatment matching

If evidence is found that specific features in patients' profiles can be used to identify a treatment modality that might be effective for each of them, then the question arises of how one can test the hypothesis that giving these individuals a treatment modality based on these matches will lead to better outcomes than giving them treatment based on another design or strategy. It is possible to test each individual match, but this may require many small clinical trials that can be logistically complex and difficult to find funding and infrastructure to implement. Alternatively, one could test a whole matching strategy against an alternative way of delivering interventions. This is the motivation behind the "basket" and "umbrella" trials that are currently used mainly in oncology [70].

In oncology, basket and umbrella trials enroll multiple patients in a trial, knowing that each may have unique characteristics in their profile that indicate which treatment is appropriate. Basket trials enroll patients regardless of the specific tissue affected by the cancer. Umbrella trials, on the other hand, only consider a specific tissue. Each patient's tumor is typically profiled through DNA sequencing [71].

The tumor genome is analyzed to see if there are any actionable "driver" changes in the tumor, such as mutations that affect specific genes that are likely to contribute to tumor growth. If the mechanisms of action of a treatment agent are understood well enough, it may be possible to tailor the drugs to the changes in the tumor. For example, if the EGFR gene in the tumor is mutated and overexpressed, it would make sense to use a drug such as cetuximab, which inhibits the EGFR gene [72].

Each patient is therefore directed to a specific treatment basket. If the trial fails, it could be argued that the matching design was flawed, not necessarily the treatments considered in the trial. It would also be wrong to assume that the concept of personalized medicine is flawed because a basket or umbrella trial fails. Some basket trials have only one basket and no comparison group, but rely on determining which patient profiles are associated with better outcomes for the treatment being tested. Treatment matching designs are likely to become a standard in medicine [3].

Comparative clinical trials

Comparative and sequential clinical trials have been used for decades, but their attention and use in the context of personalized medicine is relatively new. Indeed, comparative trials have made one of their main goals to minimize the amount of time a patient is on a treatment that is likely to be less effective. In the context of personalized medicine, if there is a trade-off between available treatments or between an untested treatment and a conventional treatment for an individual patient, it may be impractical or even harmful to evaluate the effects of each treatment on the individual to determine the best option for that individual [73]. This is because some treatments may not be beneficial at all for that individual. Given this, it makes sense to implement studies in which biomarkers indicating response or side effects are collected from each trial participant and these markers are monitored to determine if there are signs that a treatment is not working. If there are signs, for example, that a treatment is not working, the individual can be switched to a new treatment [74].

Although adaptive designs can be difficult to design because of their real-time evaluation and updating components and may generate

data that are more complex to analyze than data from fixed, non-adaptive trials, they are often seen as a more ethical option. In addition, it is possible to add adaptive components to N-of-1 and pooled trials, as well as to treatment-adaptation trials. Although the number of articles describing adaptive trials is increasing, Murphy and colleagues have attracted considerable attention because they focus on reducing the time a patient is on treatment with an inappropriate treatment [75].

New Strategies and the Next Generation of Person-Centered and Personalized Medicine

Recent research and clinical activities have outlined new areas for personalized medicine. We will discuss four of these activities below and provide a brief overview of each. These activities include the use of patient-derived cellular and organoid "avatars" to determine the best treatments for that patient, the use of intensive diagnostic and individual monitoring protocols to identify signs of disease, the development of personalized digital therapies, and the use of person-centered and personalized medicine approaches in the treatment of patients with fertility problems [76].

Patient-Derived Cellular Avatars

It is now possible to take cells from individuals and use induced pluripotent stem cells, or "iPSCs," to produce cell types relevant to a patient's condition, without the need for direct biopsy of the affected tissue [77]. This allows researchers to essentially create a "disease in a dish" cellular model of the patient's condition. These cellular avatars can be studied in vitro to identify key molecular pathologies that can inform how best to choose the best treatment for a given patient (Figure 2).

The use of iPSC technologies in this way could be expanded using several new technologies that have recently been developed to create better models of an individual's condition. For example, if a patient has a known mutation that causes their condition, it would be possible to use CRISPR-based tests and related constructs to create isogenic cells, some of which have the mutation of interest and some do not. Comparing these cells provides direct insight into the effects of mutations, while controlling for the effects of the genetic background associated with the patient's genome [78].

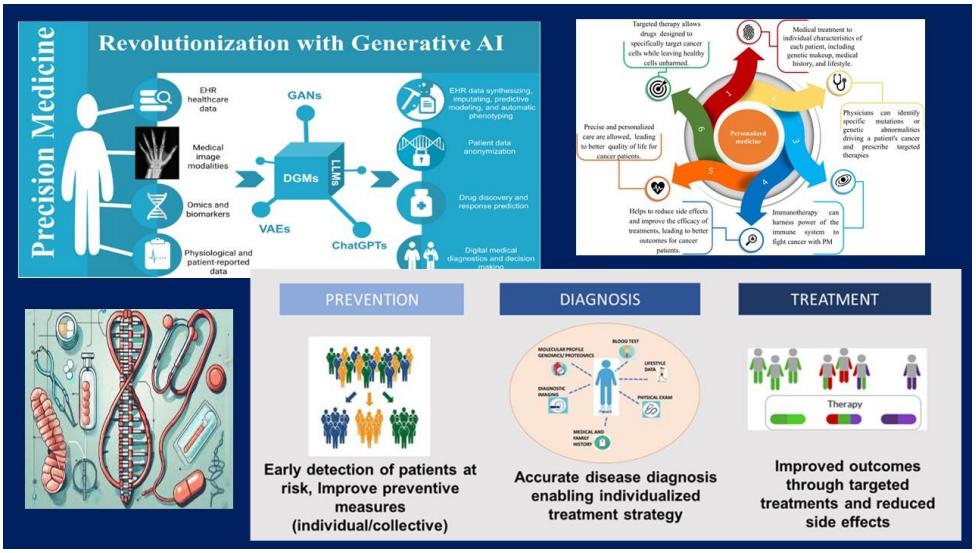

Figure 2. Revolutionizing personalized medicine with generative AI

In addition, it is possible to create partial organs or "organoids" from cells obtained from an individual. Organoids can provide further insight into the molecular pathologies relevant to an individual patient's condition, because they can model cellular interactions and more general tissue function. To achieve truly personalized medical care, the use of patient avatars derived from their own cells could be integrated with other patient-related information and protocols for acting on that information [9].

Shor and Nazor describe the motivation and integration of various aspects of patient diagnosis, treatment selection, and monitoring, including patient avatars. One important aspect of using patient-based cellular avatars in personalized medicine is that they can facilitate personalized drug monitoring. Virtually thousands of drugs and compounds have been tested against patient cells or organoids that may have been modified with CRISPR technologies to identify drugs or compounds that uniquely correct the patient's molecular defects. If the drug or compound is indeed approved for use, it may be possible to test it under a protocol that retargets the drug to the patient of interest [79].

The use of patient-derived cells in personalized drug monitoring initiatives in cancer has shown some success, as tumor biopsies can provide a suitable material for drug monitoring. The biggest concern with this approach is whether laboratory models adequately capture relevant pathological and drug response information that may influence the patient's response to the selected drug.

A more direct strategy for selecting a laboratory treatment for cancer could involve implanting a device into a patient's tumor and then administering different drugs through that device to see which ones have an effect [80].

Personalized and person-centered health monitoring

The availability of low-cost genotyping and sequencing technologies allows individuals and their healthcare providers to assess their risk of disease due to genetic factors or to make a genetic diagnosis if a disease is present. Furthermore, with the availability of health monitoring devices, blood-based clinical tests ordered online, low-cost imaging devices, and so on, various aspects of an individual's health can be monitored continuously or near continuously.

With this in mind, it makes sense to combine genetic risk assessment or diagnosis with health monitoring. A number of individuals with specific diseases and conditions have benefited from a genetic diagnosis. Because this diagnosis may uncover genetic pathological mechanisms or identify potential targets for drug therapies. In addition, a number of individuals have been intensively monitoring their health to detect signs of changing health status, some of which may be related to genetic susceptibility.

These new approaches to personalized medicine combine genetic technologies and intensive health monitoring to provide a better understanding of individual health conditions. This trend could lead to earlier detection of diseases and increased effectiveness of treatments, while allowing individuals to make more informed health decisions by better understanding their genetic risks. As technology advances and the availability of these tools increases, personalized and person-centered medicine is expected to become a standard practice in healthcare.

Monitoring individual health status and establishing personal criteria

Monitoring changes in individual health status is not a simple task, especially if the measures

collected have not been assessed in a population. In this case, there is no standard of comparison to determine whether these measures are abnormal or not. However, society is quickly realizing the value of establishing personal criteria rather than population criteria. Population criteria are usually derived from epidemiological data and population surveys and include characteristics commonly used to determine disease status, such as a cholesterol level above 200 for heart disease or a systolic blood pressure above 140 mm Hg for high blood pressure. Personal characteristics are derived from longitudinal or historical values of a measure collected from an individual and may be unique. The use of these characteristics in some contexts suggests that they may perform better than population criteria [81].

Digital therapies and personalized app content

The emergence of smartphones has attracted the attention of many researchers in the health field, as a tool for collecting health data through various apps, as well as providing advice, feedback, education, imagery, music, text messages, or communication with other resources that can help an individual with a specific condition or disease.

This has led to the emergence of the concept of "digital therapy." A smartphone app that is designed to treat and relieve an individual affected by a medical or psychological condition. The content provided by a digital therapy app can vary depending on the information collected about the individual and their response to the content provided in the app. In this way, the app can be personalized. Many digital therapies have been evaluated to assess their ability to engage users and their usefulness [82].

The U.S. Food and Drug Administration (FDA) has developed guidelines for registering digital therapies as health technologies that are eligible for insurance coverage, and has evaluated and approved many of them. The first approved digital therapy, an app for substance abuse, was approved in 2017. How digital therapies can be integrated into the healthcare process is still an open question [83].

Personalized and person-centered interventions in fertility and infertility

Personalized medicine strategies and approaches can also be applied to fertility treatments. For example, it has been suggested that real-world data collected routinely from patients attending fertility clinics and fertility treatments could be used to analyze patterns, patient subgroups, and individual patient profiles that could help explain variations in fertility rates and treatment responses.

The results of these analyses could help guide future care for patients with fertility problems. In the context of the use of digital medicine, suggestions have been made for the development of smartphone applications that could provide personalized content for education on improving pregnancy chances. Genetic variants that affect fertility have also been identified and could be used to support diagnosis or personalized intervention programs. Finally, adaptive experimental designs have been proposed that could be used to evaluate the efficacy of personalized approaches in increasing awareness of the timing of pregnancy and fertility [84].

In addition to these more traditional approaches to personalizing fertility interventions, there are many emerging strategies for enhancing fertility in women that go beyond traditional methods of ovarian stimulation. For example, it is now possible to harvest egg cells and ovarian tissue samples from a woman and then transplant them into her at a time when she may be most likely to

become pregnant. This method is particularly personalized because it works with a person's own cells and takes into account their wishes for pregnancy. However, it is only effective if the stored tissues are viable and undamaged. Although in theory, the relevant cells in these tissues could be corrected using gene editing techniques. A more controversial and personalized fertility approach involves the concept that cell reprogramming technologies can be used to generate sperm and egg cells from other cells obtained from an individual, which can be edited to create new gametes for fertilization. This concept is known as "in vitro gametogenesis. [85]"

Conclusion

Drug design is a very complex, costly and time-consuming process. Both bioinformatics and pharmacogenomics provide great support to overcome the cost and time constraints. Bioinformatics describes a wide range of drug-related databases and software that can be used for various purposes related to drug design and development process. Pharmacogenomics also provides genome-wide information on variable drug response which is very important for pharmaceutical companies to design new drugs. Although bioinformatics and pharmacogenomics are still in their early stages and currently face obstacles that show enough potential to help the drug development process in the near future. Person-centered and personalized medicine at various levels that can help understand their response to a treatment and then provide tailored treatment is essential. Because clinically significant variability between individuals has been identified and will continue to exist. The availability of modern biomedical technologies, such as DNA sequencing, proteomics, and wireless monitoring devices, has enabled us to identify this diversity and indeed has highlighted the need for personalized treatments at some level. Future challenges related to this reality will be not only to improve the efficiency of how individuals are characterized, but also to improve the methods for producing and evaluating personalized and person-centered medicines to demonstrate their efficacy. This does not mean ignoring treatments that are universally effective.

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