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Personalized Medicine: A Solution for Today and Tomorrow

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ABSTRACT

Personalized medicine is a multidisciplinary area that contains several techniques to provide patients with more efficient, cheaper, and fewer side effects treatment strategies. In customized medicine, each patient is viewed individually in order to provide more specific and efficient treatment. Using liquid biopsy, pharmacogenetics, point-of-care-testing, multi-omic-based technologies, wearable technologies, organoids, and 3D printers are some of the strategies covered in this review. Omics technology is promising for data collection, and management is vital for health records to combine complete information in one single platform. 3D printer technologies give opportunities to produce multi-drug tablets with controlled and targeted drug release. Additionally, organoids are the other biomaterial approaches to mimic the tumoroid microenvironment to develop new treatment strategies. Increasing demand for personalized medicine affects the improvement scope of this technology; personalized medicine is a vital and urgent area to improve.

Keywords: Personalized medicine, Liquid biopsy, Point-of-care-testing, Pharmacogenetic, Wearable devices, biomaterials, organoids/spheroids

INTRODUCTION

The starting point of personalized medicine is to eliminate the understanding of "one-size-fits-all" (1). Personalized medicine or P4 (predictive, preventive, personalized, and participatory) contains prevention, diagnostic, and treatment conditions depending on an individual's characteristics, such as transcriptomics, metabolomic markers, epigenetics, and genetic profiles (2,3). As a result, personalized medicine provides patients with fewer side effects, more efficacy, and lower cost of health (4). Nowadays, personalized medicine is a vital approach in the healthcare industry because personalized medicine is a form of medical intervention that enables the development of patient-specific treatment methods and drugs based on an individual's genomic, epigenomic, and proteomic information (5).

Therefore, developing treatment or disease prevention strategies according to the patient's genetic background, environmental factors, and geographical conditions will be a more effective treatment method. In addition to treating disease, personalized medicine is also of great importance in preventing disease (6) as personalized medicine aims to administer the correct prediction, diagnosis, therapeutics, and drug to the right patient at the right time (7). The development of personalized medicine allows for the development of targeted therapeutic drugs as well as combination therapies and optimized use of already existing drugs (8). In this way, optimal drug administration is realized, and a practical result is obtained for the patient. The presence of diagnostic methods and diagnostic kits required for these procedures is an excellent criterion for personalized medicine (9). Although personalized medicine is considered a groundbreaking innovation, it is also known to have some limitations caused by a misunderstanding of the molecular mechanisms of some diseases. These difficulties may arise from insufficient genetic markers due to an inadequate understanding of the molecular mechanisms of some diseases.

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The global market size of personalized medicine was 14.4 billion dollars in 2021 in Europe, and it is estimated that this number will increase up to 27.3 billion dollars (10), as it is promising to reduce general public health expenses. For example, adequate treatment balances the health system's cost and reduces hospital stays. Furthermore, in drug development, clinical trials seem to increase efficiency by optimizing phase trials through a personalized medicine approach, and we can reduce the number of thousands of people used in phase 3 trials and reduce the cost of these trials (11). The following parts of this review will describe the diagnostic techniques, advantages, and disadvantages to explain today's needs and tomorrow's expectations.

The Advantages of Personalized Medicine

The advantages of personalized medicine could be collected briefly under three subtopics: 1) better treatment methods for patients, 2) better outcomes for every individual and health system, and 3) development of more efficient medicines. Advances in patient health demonstrate the benefits of personalized medicine. As it could be understood from the name of personalized medicine, individuality is the main point of this field, and these three advantages are the main scope of personalized medicine. Furthermore, providing advanced treatment to patients, enhanced drug efficacy, and changing health systems increase treatment efficiency with improved therapeutic strategies. Considering with advantages of the personalized medicine, this review will cover sections represented in Figure 1.

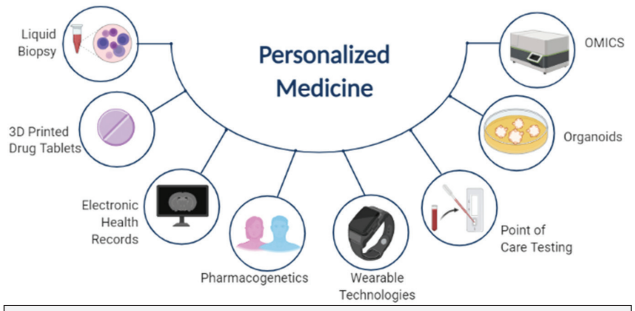

Figure 1. Summary of personalized medicine mentioned in this article (Created with BioRender.com).

Liquid Biopsy

Comparative research is generally carried out parallel with solid biopsy in the current liquid biopsy studies. Although liquid biopsies are not currently available for clinical use, they can be applied to monitor the progress of certain types of diseases. It might be used to diagnose and track the progress of diseases in future research. It is highly preferred because of its accessibility and low-cost method for patients and clinicians compared to solid biopsy. However, before reaching this level, extensive research should be done on the biomarkers of diseases. The liquid biopsy includes different soluble factors, such as hormones, circulating tumor cells, proteins, tumor markers, miRNA, and circulating cell-free nucleic acids (Figure 2) (12). Therefore, it provides detailed biological information about a patient who has genetic differences. The liquid biopsy may soon have clinical uses for diagnosing and following certain disease types. Therefore, a liquid biopsy will be a helpful technology that holds promise for the future.

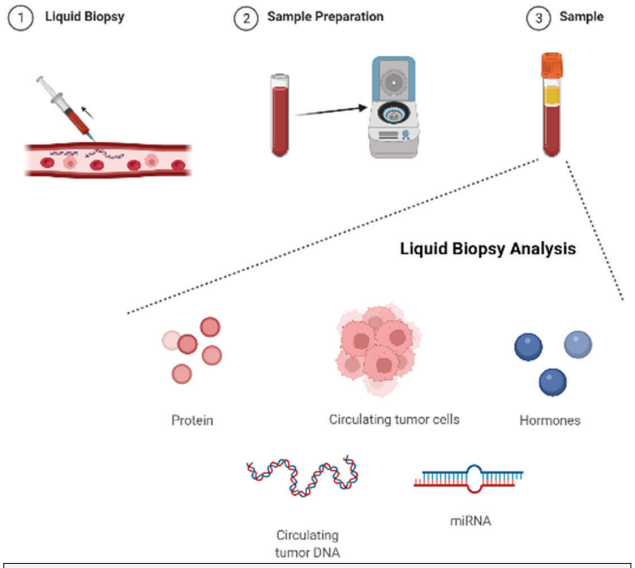

Figure 2. Schematic summary of liquid biopsy sample preparation and usage areas (Created with BioRender.com).

Liquid biopsy has plenty of advantages as much as disadvantages; in many patients, early-stage cancer and advanced disease may not be detected. Small amounts of ctDNA (circulating tumor DNA) and CTC (circulating tumor cell) and insufficient biomarkers may cause problems in diagnosis (13). The main difficulty in CTCs is the identification and characterization of cells. It is challenging to identify early-stage diseases because it is low in concentration and rare. Therefore, compassionate methods must be developed to collect and analyze CTC (14). In addition, the same gene variations can be present in several tumor types, so testing must be done in conjunction with other diagnostic tools to diagnose and prognosis accurately. In order to prevent these problems, it is necessary to develop biomarkers for the diseases to be investigated and fully clarify the different localizations at different stages of the disease.

Moreover, it is required to develop biomarkers for different mutations that cause diseases. In addition to these, there are FDA-approved liquid biopsy usage examples. For instance, CellSearch is the only FDA-approved EpCAM-based test, and it is also considered the "gold standard" for CTC detection. As mentioned, the primary purpose of this technique is to count epithelial CTC biomarkers such as CD45-, EpCAM+, CK 8+, and 19+ in whole blood. This kit defines CTC in cancer patients (15). In many studies on breast cancer and prostate cancer, positive results have been obtained by looking at the presence of CTC (16).

Another example is, in 2016, the FDA approved the cobas® epithelial growth factor receptor (EGFR) Mutation Test v2 to determine the eligibility of non-small cell lung cancer patients to receive specific EGFR tyrosine kinase inhibitors (17). In addition to

blood samples, there are diagnostic methods in different body fluid samples, one of which is urine used in bladder cancer. Various biomarkers are also present in urine samples (18,19).

Most physicians do not consider patients as individuals during prescriptions in clinical practice, but the applied treatment could be effective for some patients while not affecting others. Thus, it is essential to evaluate patients as individuals, and it is necessary to accept every individual as unique to increase the effectiveness of the treatment efficiency. Biomarkers are critical for predicting the disease pathway and selecting the appropriate treatment with the highest response (20,21). Not all but common diseases could be detected using a newly developed technique using the patient's blood called serum proteome, with the advantages of using the patient's blood rapidly and cheap compared with other omic-based methods (20). Depending on the serum protein detection techniques, the drug screening and treatment strategies could be arranged by serum proteome technique (20).

Pharmacogenetics

Pharmacogenomics deals with how patients respond to drugs based on their genetic background and treats drug therapy following the patient's genotype. Differences in drug response are due to inter-patient variability because all patients do not respond to the same drug in the same way (22).

The disease that has seen the most successful results in pharmacogenomics is cancer. For example, researchers have discovered many single nucleotide polymorphisms, variations in a single base pair in a DNA sequence that lead to breast cancer, and can prescribe the best treatment (23). Apart from giving the best results in the treatment of patients, pharmacogenomics has other benefits, such as saving time and costs. To protect patients from the side effects of drugs, pharmacogenomics does not work by using a single medicine; instead patients try many drugs until they find which medication works best for them (23). Moreover, there are various limitations in applying pharmacogenetic tests: validated markers, validated tests, dosing algorithms, and laboratories with good laboratory practice (24). Therefore, to increase the usage of pharmacogenetics, it is of great importance to find new pharmacogenetic markers, increase the number of approved tests, and control and follow up the tests distributed for their clinical applications. Moreover, there are many biomarkers approved by the FDA, such as HLA-B, ESR, EGFR and HER2 (24–26). In addition, drugs and many possible gene interactions might be applied to enhance the usage of pharmacogenetics (27).

Point-of-Care Testing

Laboratory analyses play a significant role in diagnosing diseases and monitoring drug therapy. Following the importance of laboratory analysis, point-of-care testing (POCT), inpatient beds and operating rooms are developing rapidly. POCT aims to provide low-cost care close to patients' homes, reducing the time between sampling and analysis (28). Point-of-care testing is a laboratory-medical discipline that is rapidly emerging in clinical practice. POCT is characterized by outcome-based therapeutic actions with the aid of pre-prepared reagents.

Biosensors are generally used in POCT devices, and various POCT analyzers are available to protect against the adverse effects caused by physiological factors, storage environment, and sampling techniques. Additionally, the contents of the drugs used by the patient may have an effect on the test results (29,30). These devices are grouped according to practical uses by measurement mode, sensor characteristics, and complexity criteria (31). Commonly used POCT tests are reviewed in Table 1. In addition, POCT

Table 1. Commonly used point-of-care testing (POCT) applications.

Common Point-of-Care Tests			
Test	**Clinical Setting**	**Markers**	**References**
Blood gases	ICU settings, emergency rooms, operating rooms	tetralogy of Fallot (TOF), acute exacerbation COPD (AECOPD)	(32,33)
Cardiac markers	Emergency rooms	Troponin, CKMB, NTproBNP, D-Dimer	(34)
Creatinine	Radiology suites before contrast administration	KIM-1, MCP-1	(35)
Diabetes (glucose, HbA1c)	Home monitoring for patients with diabetes, inpatient monitoring for glycemic control	Hemoglobin A1c, FA, GA, OGTT, Adiponectin	(36)
hCG (pregnancy)	Emergency rooms, ICU settings	hCG	(37,38)
Infectious diseases	Outpatient and emergency settings for treatment decisions and cohorting or isolation	CRP, RSV, IL-1, IL-6	(39,40)
PT/INR	Coagulation clinics, cardiology practices, home monitoring	PT/INR	(41)
Urinalysis	Physician offices	interleukin-18 (IL-18), plasma neutrophil gelatinase-correlated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP)	(42)

HbA1c: hemoglobin A1c, hCG: human chorionic gonadotropin, HIV: human immunodeficiency virus, ICU: intensive care unit, INR: international normalized ratio, PT: prothrombin time, RSV: respiratory syncytial virus.

devices have some required features such as easy to use, safe to use, easy to store, long-lasting, and consistent results with laboratories (28).

Biological Databases (Omic data) and Electronic Health Records

Big data, which is mainly the visualization of data (43,44), has changed the biomedical research pathway since it was first introduced in 1997. Collecting data is much faster than analyzing the data; therefore, molecular integration is essential when considering electronic health records (43,45). Data collection and analysis are crucial for identifying electronic health records and for drug and biomarker improvements of neurodegenerative diseases, cancers, cardiovascular diseases, and other critical or noncritical diseases (44). The first human genome sequence got the door to customizing the medicine in 2008 (46,47). Genomic data gives information about predicting and preventing disease with more targeted therapy options. More than 5,000 single-gene disorders could be recently treated (46). On the other hand, genetic test centers are increasing in demand, with over 55,000 centers. Moreover, the other important part of these genetic test centers is to help with diagnosis and detection of cancer, neurodegenerative diseases, and cardiovascular and other diseases (46). Additionally, personalized medicine promises the correct dosing of drugs. Knowing the patient's characteristics prevents adverse effects from the drugs and increases their efficacy.

Metabolomics is metabolites profiling of biological organisms, and biomarker of diseases in personalized medicine is the crucial concept of metabolomics. With other omics (transcriptomics, proteomics, and genomics), a disease's mechanism and pathophysiology could be analyzed in more detail, and with this advantage, the treatment strategies could be applied to the patient more efficiently (48). Determination of a target in biological organisms like small molecule quantification or identification is the critical point of omic-based technologies with computational techniques.

The relevance of genomic testing affects the individualizing of healthcare, and electronic health records have become an integral approach to collecting all data (diagnosis, medications, allergies, results, reports, etc.) from a patient in a single platform (46).

The central concept of personalized medicine is to customize health care, and for that reason collecting and analyzing data are two essential components of personalized medicine (49). Although data collection resources could be variable, like wearable devices, clinical trials, video streams found in elders' houses to detect falls, imaging tools, and genomic services, there could be some security risks with noise, missing data, or artifacts (50). In the field, there are some genome projects such as Baseline Study, Genome Atlas, 100,000 Genome Project, Encyclopedia of DNA Elements, 1,000 Genome Project, the UK Biobank Exome Sequencing Consortium, and SHGP (Saudi Human Genome Project) (50,51). The variety of countries with different genome projects provides a variety of detection of rare diseases with high impact; thus, artificial intelligence becomes a step forward to analyze and determine rare diseases with genome sequencing by analyzing genome databases (51).

When we talk about databases, the data collection capacity is enormous; for example, only neuroimaging produces 10 petabytes every year (43). In addition, data collection favors genomics complementary to liquid biopsy results (43). Finally, using artificial intelligence with collected data gives another opportunity for personalized medicine to interpret the results from data (4).

Radiomics are the medical imaging part of omic-based technologies, and it is vital to diagnosis and clinical decisions (52). Furthermore, radiomics are like a bridge between imaging and personalized medicine; giving more attention to radiomics could provide a more proper response in terms of treatment technology (52).

Wearable Technologies

Wearable devices have revolutionized the field of continuous patient follow-up outside the clinic. It is provided regularly to the patient through mobile applications or digital health. Real-time monitoring can take patient care and follow-up out of hospital rooms so that it follows patients wherever they go. Many wearable devices are used in medical research that can be classified into three main categories: mechanical, physiological, and biochemical (53).

The developing wearable technology provides people with a healthier lifestyle, metabolic status, diagnosis, and treatment opportunities. These wearable devices include smartwatches, wristbands, hearing aids, tattoos, subcutaneous sensors, and electronic textiles (54).

Distinguishing health-related and actionable data from the data density of wearables is a significant challenge. Algorithms are being developed to overcome this difficulty in analyzing various data. Based on the data from wearable devices, digital biomarkers of the disease have emerged (55). Another positive aspect of patient follow-up in wearable devices is that they can be used in drug development. The physiological data collection can be used in drug development, dosage determination, and dosing frequency adjustment. However, some problems arise in the use of this technology. These issues include scientific, regulatory, ethical, legal, data management, infrastructure analysis, and security issues (56).

Organoids

Personalized medicine is an urgent area for modern oncological treatments because biomarkers for diagnostic approaches become essential instead of tumor site detection. In addition, determining the molecular feature of the tumor and treating that feature could be easier than treating the whole tumor by mimicking tumor structure in vitro with organoids (57).

The other crucial personalized medicine strategy for cancer or tumoroid tissue treatment is to create spheroids or organoids

from the patient's tumor cells to examine drug efficacy, determine disease progression, and develop a treatment (3). Understanding the tumoroid microenvironment is possible in vitro 3D platforms like spheroids and organoids for drug testing and new treatment strategies. The best perspective is to recapitulate the tumor tissue in a 3D environment from the patient's tumor cells, most probably cancer stem cells. 3D tumor spheroids or organoids give information on the intercellular interactions and morphology of the tumor, and this knowledge improves the best treatment strategies with appropriate screening techniques (3,58).

Besides the treatment strategies, it is possible to use organoids/spheroids for drug testing to observe the efficacy of the drugs on the patients *in vitro.* Halfter and colleagues used spheroids obtained from the tissue and the cell line to compare the effectiveness of the therapeutics (59). This study is the only one strategy to understand the spheroid's chemotherapeutic efficacy, which could be improved with organoid banks not only for drug testing, but also for developing treatment strategies to understand disease progression.

3D Printed Drug Tablets

The other important concept for personalized medicine is materials and techniques to produce drug tablets for different types of diseases with high drug release controllability. The shape and the size of the drug can be arranged using the software of 3D printers (49,60). The biomaterial used to create a drug ought to be biocompatible with FDA approval. Moreover, the production techniques should be FDA-approved as well. The drugs to treat patients could be a part of the population, but not for everybody; therefore, customized drug tablets become a step forward for specific patient groups who are tested and decided after physician examination. Customized drug tablets are potentially simple, inexpensive, much more effective, and could be multiple drugs in a tablet. Depending on the fabrication technique, the dosage, carriers, release period, and several drugs could be arranged in a tablet utilizing 3D printing technology (49).

The challenges of 3D printed drugs are caused mainly by 3D printer technology, dosage formulations, safety, regulations, and quality controls (60).

Future Aspects

Personalized medicine's market size is estimated at $87 billion in 2023 (1), and the prediction of the genetic testing market for 2024 will be over $22B, and the genomics will be in patients' hands (46).

The increasing need and demand for personalized medicine show that the disease pathophysiology and biomarkers are related to each other. Therefore, collecting data and analyzing the data could possibly be reached as an effective treatment with fewer side effects and more efficacy (61).

The multi-omic approach will be vital to improving personalized medicine; the concept of multi-omic is basically combining DNA and RNA alterations, metabolomics, and proteomics. Data analysis combined with artificial intelligence will make personalized medicine more precious in the future (4). Moreover, using *in vitro* studies with organoids is the other necessity for personalized medicine approaches due to the high capability of recognition and targeted drug release abilities (1), (57). From this perspective, we reviewed recent technologies such as wearable technologies, organoids, and 3D-printed drug tablets. These technologies possess a critical market share in the current medical monitoring, diagnosis, and treatment modalities by providing personalized solutions for everyone. Especially wearable technologies promise to promote point-of-care technologies with accurate and sustainable data providing capacity.

CONCLUSION

The use of personalized medicine in clinical practice is expected to increase. It is thought that the interest in this field will grow as health technology progresses. All of the various methods used for personalized medicine mentioned above can potentially create significant changes in the field of health by using them for drug development, diagnostic kit development, and data collection. The main goal of personalized medicine should be better to define disease development, have more effective treatment responses, and reduce health costs. For this purpose, it is necessary to inform pharmaceutical companies, insurance companies, researchers, and society. In this way, interest and knowledge in this crucial field in health technology should be increased, and this area should benefit from both work areas and treatment methods.

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Peer Review: Externally peer-reviewed.

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