Principles of Precision Medicine

1

Bagher Larijani, Hamid Reza Aghaei Meybodi, Negar Sarhangi, and Mandana Hasanzad

What Will You Learn in This Chapter?

Healthcare is quickly moving toward precision medicine, which appears to offer a better understanding of human physiology through genetic knowledge and insight and technological advancements. Precision medicine is necessary to alleviate unnecessary adverse reactions to medical care which can result from the current one-size-fits-all approach, technologies that encourage the healthcare ecosystem to develop and deliver genetic-based care and manage customizations. Accordingly, this chapter has a special focus on the introducing of precision (personalized) medicine. At the beginning of this chapter, the general definition of synonymous terms of personalized medicine will be discussed. At the end of this chapter, precision medicine and evidence-based medicine will be addressed to provide the future of the medical practice.

Rationale and Importance

Precision medicine is an emerging medical practice that utilizes an individual's genetic profile to direct decisions taken in the field of disease prevention, prediction, and personalized treatment.

Precision medicine, because it is concentrated on the unique genetic makeup of each patient, is beginning to overcome the limitations of conventional medicine. It is increasingly enabling healthcare providers to shift the emphasis on medicine from response to the prevention and also the prediction of the disease susceptibility, especially in common diseases.

Precision medicine improves the health impact of existing treatments by enhancing the matching process between patients and treatments and by improving patient understanding of the risk of serious side effects.

The rationality behind precision medicine is understanding the different genetic backgrounds which have impacts on the response of individuals to therapeutic interventions.

The concept of "one medicine for all patients with the same disease" does not hold, and a more individualized approach is needed because of significant individual variation; some individuals show no response, while others show a strong response.

B. Larijani · N. Sarhangi
Personalized Medicine Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

H. R. Aghaei Meybodi
Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

M. Hasanzad (✉)
Personalized Medicine Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Medical Genomics Research Center, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

M. Hasanzad (ed.), *Precision Medicine in Clinical Practice*,
https://doi.org/10.1007/978-981-19-5082-7_1

1.1 An Introduction to Precision Medicine in Clinical Practice

By the mid-twentieth century, health professionals had developed a certain kind of individualized approach to the treatment of patients. The rise of genetics came in the twentieth century. The huge amount of scientific discoveries made in the field of genomics has been supposed to allow the personalized/precision medicine approach to move from a previously hopeful dream to an effective truth. Precision medicine became more meaningful at the beginning of the twenty-first century with the integration of the Human Genome Project, which leads to the transformation of personalized medicine from an idea to a reality. The project adopted a new approach linking the genetic makeup of individuals and their health [1–4].

Genomics many claims revolutionize the medical practice and healthcare by enabling early diagnosis and disease management to be more precisely targeted at each patient.

In the evidence-based medicine approach, many existing drugs are authorized and developed based on their efficiency in a large population of individuals, but future medicines are developed as personalized solutions to the needs of a particular patient.

Each individual has a highly specific genomic, transcriptomic, proteomic, and metabolic profile which can contribute to specific pathological symptoms of disease, response to treatment, and disease severity.

Clinical practice encounters major challenges, including emerging rapidly spreading new infectious diseases, fast-growing common diseases such as type 2 diabetes (T2D) and cancers, changes in the clinical manifestations of some diseases in the treatment process (e.g., drug-resistant or adverse drug reactions), and population shifts (i.e., aging).

In the context of common disorders, the conventional "one-drug-fits-all" approach involves trial and error before effective treatment is established. And clinical trial data for a new drug shows only the average response of the study group.

The theory and statement for personalized medicine have attracted the greatest attention among many exciting fields. The individualized approach appears to be a critical feature of healthcare in the coming decades. Personalized/precision medicine aims to improve treatment outcomes through new molecular taxonomy for disease and reduce adverse drug reactions (ADRs) that affect both the clinicians and the patients.

The potential of precision medicine applies to all clinical disciplines including oncology, cardiology, and all stages of the disease development that many benefits for patient care have been mentioned. Some evidence-based examples are briefly explained in each chapter of this book.

1.2 Definition of Precision Medicine

The personalized medicine idea is not new and is traced back at least to the time of Hippocrates. He believes in the individuality concept of disease. He said, "It is even more essential to remember what kind of individual the disease has than what kind of disease the individual has" [5].

An early example of personalized medicine was the first known blood compatibility test for transfusion using blood typing methods, the genetic basis in favism, and cytochrome P450 2D6 function determination [6, 7].

The term personalized medicine appeared in a publication that discussed the change in the role of family physicians in the modern world of medicine and technology. The personalized medicine approach is considered as an art of the medicine [8].

The role of pharmacogenetics (as a part of personalized medicine) in clinical practice has been published by Gupeta et al. [5]. No officially recognized consensus on the definition of personalized medicine exists. The term "personalized medicine" appeared in the literature in MEDLINE in 1999 by an article entitled "New Era of Personalized Medicine: Targeting Drugs for Each Unique Genetic Profile" [9].

Various terms, including personalized medicine, precision medicine, p4 medicine, individualized medicine, and stratified medicine, have

been used interchangeably, to describe the concept of personalized medicine.

In particular, the concept of targeted therapy has had a significant impact in one area of discipline, called oncology. The National Cancer Institute (NCI) provides personalized medicine definition as follows: "A form of medicine that uses information about a person's genes or proteins to prevent, diagnose, or treat disease." In cancer, personalized medicine uses specific information about a individual's tumor to help make a diagnosis, plan treatment, find out how well the treatment is working, or make a prognosis.

Examples of personalized medicine include using targeted therapies to treat specific types of cancer cells, such as HER2-positive breast cancer cells, or using tumor marker testing to help diagnose cancer, also called precision medicine [10].

The Personalized Medicine Coalition has defined personalized medicine as "the application of genomic and molecular data to better target the delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition" [11].

In several reports, personalized medicine is defined by emphasizing the signature of genetics for getting more effective therapies as well as disease predisposing and early interventions that might prevent disease or delay disease progression [12].

In a brief definition, personalized medicine is the selection of the right drug at the right dose for the right patient at the right time [13].

Several stages were described for personalized medicine in different studies: patient's risk analysis to allow early detection and/or prevention; increased diagnostic accuracy by better definition of diseases and phenotype description, targeted treatment pharmacogenomics advancement, integration of genomics data and its derivatives, including transcriptomics, proteomics, metabolomics with clinical health records, evaluation of clinical outcomes, and the infectious environment and its various properties [14–17].

Individualized medicine described individual drug metabolism in the context of pharmacogenomics some contexts, including gene therapy, stem cell therapies, and cancer vaccines are considered in the individualized medicine definition [18–22].

Precision medicine is defined for the first time by having three main characteristics: the ability to recognize the presence of these causal elements of disease, a knowledge of what causes a disease, and the ability to treat the origin or causes efficiently [23].

In 2011, the National Research Council of the US National Academies in their report "Toward Precision Medicine" was provided a particular definition for precision medicine as precise disease taxonomy based on molecular data. The potential of genomics as an emerging technology was introduced for the investigation of the molecular features of the disease [24].

Precision medicine is defined as a state-of-the-art molecular profiling, which helps establish accurate diagnostic, prognostic, and therapeutic approaches tailored to a patient's needs [25].

Trusheim and colleagues defined stratified medicine as "where therapies are matched with specific patient population characteristics using clinical biomarkers" [26].

The clinical biomarker which could be used in diagnosis and targeted therapy as an example of stratified medicine was seen in BCR-ABL-positive tyrosine kinase genotype in chronic myeloid leukemia patients who are likely to respond to imatinib (Gleevec®), an inhibitor of this kinase [26].

P4 medicine was introduced by the development of the systems biology approach. The term p4 medicine as an alternate term of personalized medicine stands for its personalized, predictive, preventive, and participatory features by applying the "omics" approach, i.e. genomics, transcriptomics, and proteomics [27].

Pharmacogenomics (PGx) is one of the most important components of personalized medicine which focuses on the association between genetic variations and drug response [28].

The role of genetic variants in the modulation of variability in drug actions was proposed by the physician-scientist Sir Archibald Garrod around the year 1900. He presented the term "chemical individuality" [28].

1.3 Pharmacogenomics

The history of the genetic basis for drug response phenotypes dates back to the early 1950s. The word "pharmacogenetics" was first coined by Friedrich Vogel in Heidelberg, Germany, in 1959 [28]. The antimalarial drug primaquine causes acute hemolytic crises in individuals with the glucose 6-phosphate dehydrogenase (G6PD) deficiency [28]. Another adverse drug reaction was reported for succinylcholine that is administered as anesthesia. A genetic variant in gene encoding pseudocholinesterase causes adverse drug reactions like apnea [28].

The term pharmacogenomics is now used to explain how multiple genetic variants across the genome (DNA and RNA) can affect drug response, while pharmacogenetics is the study of DNA variations related to drug response [29]. The drug response pathway is performed through pharmacokinetics (PK) which is drug absorption, distribution, metabolizing, and elimination, or pharmacodynamics (PD), which is modifying drug target or by disrupting the biological pathways that shape a patient's pharmacologically sensitive [30].

Pharmacogenomics information can help physicians decide medication selection, dose adjustment, and treatment period and prevent adverse drug reactions. Furthermore, pharmacogenetics can contribute to the development of new therapeutic agents [30–33]. Only 30–60% of prescriptions are clinically successful, and 7% of all hospital admissions are partly related to adverse drug reactions every year.

Every gene contains single nucleotide polymorphisms (SNPs) that occur throughout the human genome in every 1000–3000 base pairs [34]. It is shown that certain genetic polymorphisms are associated with anticancer drugs response.

Variability of drug response is a major concern which is indicated in the era of personalized medicine. Over the last decade, significant progress has been made in our knowledge of the contribution of genetic differences in pharmacokinetics and pharmacodynamics to interindividual variability in drug response.

The human genome consists of nearly 20,000 protein-coding genes. Maybe the most common variations are SNPs, described as single-base differences that exist between individuals. More than 22 million SNPs have been observed in the human genome [35].

SNPs which result in the substitution of amino acids are referred to as non-synonymous. Non-synonymous SNPs that exist in coding regions of the gene (e.g., exons) may have an impact on protein's activity and show a considerable impact on drug responses which can affect protein metabolism and transport.

Synonymous polymorphisms do not result in the substitution of amino acids; however, those happening in the gene regulatory region (e.g., promoter region, intron) may change the gene expression pattern and the amount of protein. Other types of variations that may impact gene expression or protein conformation include insertion-deletion of polymorphisms (indels), copy of number variants (CNVs), and short tandem repeats (STR) [36].

1.4 Precision Medicine in Clinical Practice

The precision medicine have emerged that would bring approximately dramatic changes in healthcare systems.

The concept of precision medicine is relatively new but appears to hold promising results. Some of the potential benefits of precision medicine are discussed below [4, 37–39].

1.4.1 The Effectiveness of Care

Currently, physicians do not fully understand how certain treatments will affect a particular patient. With precision medicine, medical providers can apply personalized treatment methods for each of their patients, thus increasing the likelihood of recovery.

1.4.2 Preventive Medicine

Early diagnosis of genetically caused disease is possible through genetic screening methods, and prevention of such disease is possible by an understanding of individual risk.

1.4.3 Cost-Effectiveness

Precision treatment by pharmacogenetics approach can reduce the cost of care, and increasing the chance of more effective treatments and decreasing adverse drug reactions.

1.4.4 New Taxonomy

Precision medicine proposes a new classification for diseases and categorizes them by genetic variations rather than symptoms.

1.4.5 Population Healthcare

The study of genetic patterns in the population as a whole can help identify and develop the causes of particular diseases and develop specific treatments. Consequently, precision medicine can reduce trial and errors in the clinical practice and take into account preventive measures for common diseases.

Eventually, precision medicine is aimed to be used in prevention and personalized treatment approaches for all health problems. At present, its daily application in many disease states is relatively growing. Precision medicine is already routinely used in certain areas of medicine, such as cancer care.

Precision medicine components in use today usually involve the following:

Genomic testing (sometimes referred to as molecular or genetic testing) aims to identify alterations in disease-related chromosomes, genes, or proteins. Genomic and technological methods have enabled the potential to rapidly test biological specimens for mutations of interest at a significantly reduced cost to the patient. Although the first human genome has taken more than 10 years to complete, commercial companies are now offering testing of target genes with turnaround times of days to weeks. These tests are commonly provided as a panel of targeted genes with gene coverage generally ranging from assessment of hotspot regions (well-characterized mutational sites within the gene) to full gene sequencing. Analysis of protein expression by immunohistochemistry or panels could also be used to evaluate molecular aberration. Despite technological developments, genomic testing still has a considerable economic burden on the patient [40, 41]. Targeted therapies affect specific disease-driven molecules, such as cancer molecules that promote angiogenesis or affect cell growth and tumor progression [42, 43].

Targeted treatments are drugs that interfere with specific genes (molecular targets) involved in a given disease. Numerous targeted therapies are being established and authorized for cancer treatment management. The majority of drugs currently available fall into two different types of drugs [44, 45]:

- Commercial antibodies aimed to track particular protein targets in cancer cells or other related cells are named monoclonal antibodies.
- Chemicals targeting specific molecules or pathways are called small-molecule drugs.

Genetic markers are genetic characteristics that provide information about an individual (such as the risk for disease or likelihood to respond to a particular treatment).

Genomic information has been used in the delivery of healthcare, and now genetic markers for prevention, treatment, and survival have been identified [46]:

- Risk markers help screen patients efficiently.
- Prognosis markers help us understand who is at risk of rapid progression, recurrence, and

outcomes based on their genetic makeup, not on the treatment chosen.
- Predictive markers help guide medical decisions, such as adverse drug reactions (e.g., pharmacogenomics).
- Response markers determine the patient's response to a specific treatment.
- Recurrence and toxicity markers affect the long-term quality of life of a patient once cancer treatment has been completed.

Accordingly, patients will live longer with fewer complications from their treatment.

1.5 Precision Medicine and Evidence-Based Medicine

The main difference between evidence-based medicine (EBM) and traditional medicine is that EBM requires better evidence than has traditionally been the case. Evidence-based medicine refers to the integration of clinical experience, patient preferences, and best available evidence in the decision-making process related to patient healthcare [47].

Guidelines are provided for evidence-based medicine from the highest level of evidence derived from multiple randomized controlled clinical trials to solve specific clinical problems [48].

EBM and precision medicine has been developed based on medical evidences and genomics profile, respectively. Precision medicine differs greatly from EBM. EBM seeks to determine the best practice approach for a patient who is showing general knowledge of the population but precision medicine is the individualization of care by focuses on the unique characteristics of a particular patient [47, 49].

Medical professionals encounter several problems for prescriptions in the context of evidence-based medicine: a significant percentage of lack of efficacy in some medicines, EBM promoting the standardized use of therapy that does not address response variations in each patient, high incidence of adverse drug reactions, and clinical trials focusing on taking statistical information on the general populations and applying them to the patient. EBM ignores the outliers, but PM focuses on the outliers [50, 51].

Predictions based on mechanical knowledge of the genetic or environmental effects of drug reactions may be incorporated into the design of randomized clinical trials (RCTs). EBM guidelines may be more PM-friendly by incorporating a more patient-centered approach. EBM and PM are both complementary in their approaches, such that there is a need for collaboration between experts in both fields in the advancement of science in clinical practice and its applications in the treatment of each patient [51].

1.6 Genomics Precision Medicine

Recent technological advancements in genomics and many other OMIC sciences (transcriptomics, proteomics,...) have revolutionized the conventional and future practice of clinical medicine.

Diagnosis of most challenging rare diseases is now feasible with a high degree of accuracy with the new technologies. It is now possible to diagnose "gene-specific" and "genome-driven" genetic disorders.

Genomic precision medicine is a revolution that will empower patients to take control of their healthcare. There is a growing awareness of pharmacogenomics (PGx) as a key part of personalized medicine. Since June 2018, over 250 FDA-approved drugs are labeled for prescribing based on the patient's genomic profile, a number that has tripled since 2014 [52, 53].

Genomic medicine is a promising medical discipline that applies genomic information about an individual as part of their clinical

care in prediction, prevention, and tailored treatment in precision medicine approach; this definition is presented by the National Human Genome Research Institute (NHGRI) [54]. Genomic medicine is capable of revolutionizing the healthcare of patients with rare or common diseases to implement precise diagnosis, improved disease risk assessment, prevention through screening programs, and personalized treatment. By understanding the genetic architecture of many diseases, the gap between basic and clinical research has been quickly filled. Therefore, we are entering a new era in clinical medicine.

With the new concept of genomic medicine, primary care achieves its goal in maximizing health benefits and minimizing unnecessary harms to patients [55]. The applications of precision medicine are numerous, but it truly requires genomic medicine potential. The adoption of genomic medicine in patient care got more attention for achieving high-quality evidences for supporting the clinical decisions in common diseases [56]. A key milestone in genomic medicine was the human genome project in 2003, but this success is the only one of many milestones in the journey of genomic medicine from Mendel to next-generation sequencing (NGS) [57].

The achievement arising from the Human Genome Project was the beginning of the post-genomic era, rather than the end of one [58]. Today, genetic testing using high-throughput approaches is pursued by a growing number of physicians. Rapid development in high-throughput technologies such as "next-generation" DNA sequencing and genome-wide association study (GWAS) has facilitated the use of genomic medicine to perform better management in several diseases from Mendelian to complex disease. Moreover, whole exome sequencing (WES) has been used in the workup of patients with undiagnosed conditions [59, 60]. Hence, genomic medicine achievements lead to a major clinical advance in the management of common diseases including different types of cancer and cardiovascular disease in the context of precision medicine. Additionally, remarkable advancement has been obtained in pharmacogenetics and pharmacogenomics through analyzing genetic variants [61].

1.7 "Omics" and Precision Medicine

The suffix "omics" in science and technology such as genomics, transcriptomics, and proteomics refers to such technologies which have been applied in the development of personalized (precision) medicine. Some of the important "omics" with impact in clinical practice of medical disciplines are described in various chapters of this book.

During the last decade, omics science has revolutionized translational medicine [62] Omics (X-omics) describes high-throughput experimental technologies, providing the tools for widely monitoring disease processes at a molecular level that focuses on big data. The publication of the full human genome sequence was a breakthrough in the history of omics research [63, 64].

The suffix "ome" derives from "chromosome" and includes a complete set of biological fields such as genomics, transcriptomics, proteomics, metabolomics, and other omics. The "omics" approach implies a comprehensive, or global, evaluation of a set of molecules.

Traditional molecular methods are time-consuming and not adequately efficient, while omics sciences which are based on high-throughput analytical methods have proven to be accurate and more efficient, enabling scientists to better understand the molecular architecture of common diseases [65, 66]. Multi-omics (X-omics) is a neologism that provides a tremendous opportunity for improvement for precision medicine (Fig. 1.1).

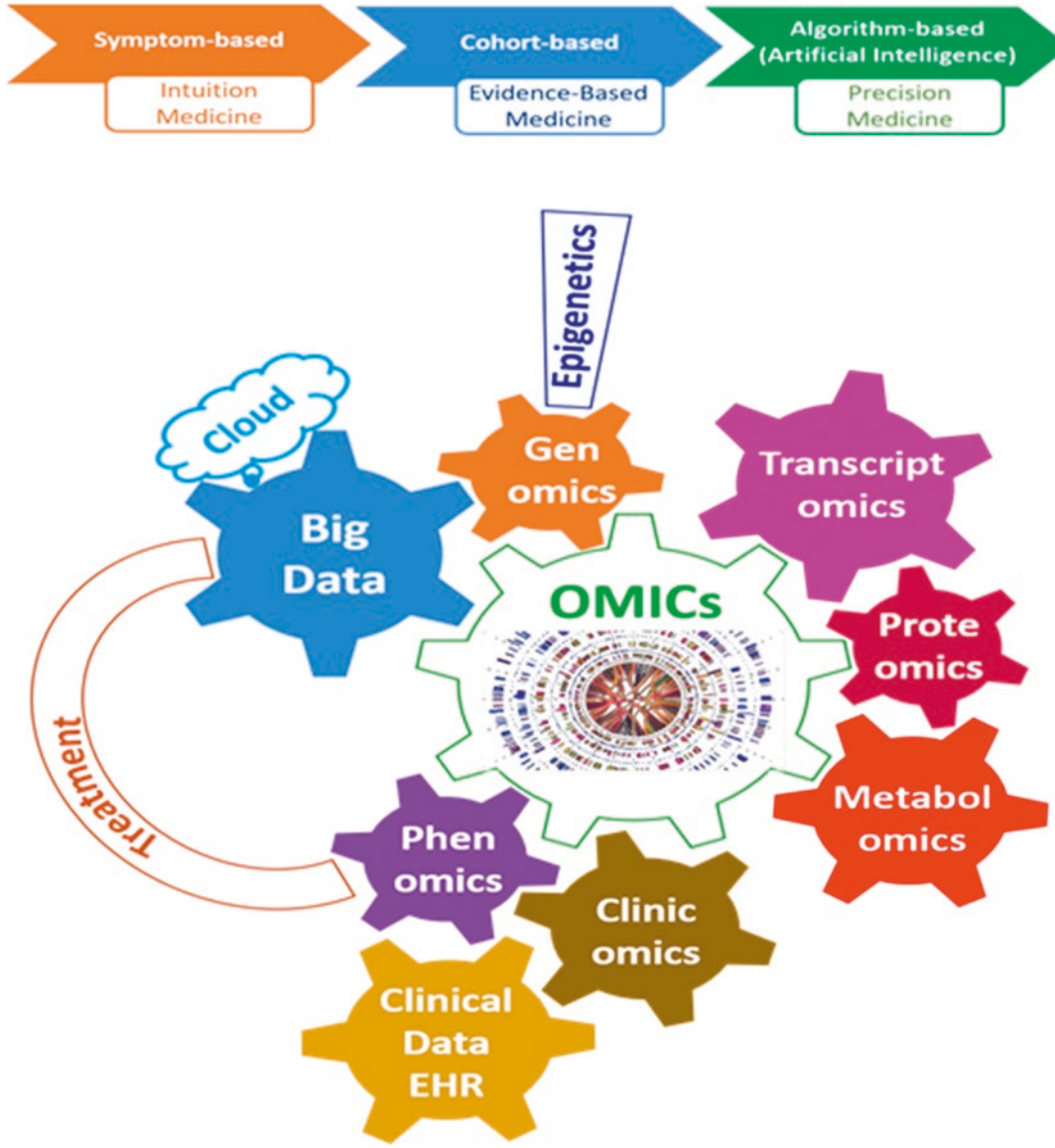

Fig. 1.1 Precision medicine approach is a journey which has been passed through intuition medicine and evidenced-based medicine. This new approach should apply "omics" technologies. Multi-omics technologies including genomics, transcriptomics, proteomics, metobolomics, etc. by producing a large amounts of data and in combination with patient phenotypes integrate a great scientific revolution in the practice of medicine

Precision medicine offers a way to change the clinical approaches which provide precise prevention, diagnosis, and treatment options. With the development of next-generation sequencing (NGS) and RNA sequencing (RNA-Seq) technologies, precision medicine is becoming attractive and practical that holds great promise for future success.

1.8 Personalized Medicine, Artificial Intelligence, and Digital Twin

Noncommunicable diseases (NCDs) mainly type 2 diabetes mellitus (T2DM), cancers, cardiovascular diseases (CVDs), and chronic respiratory diseases (CRDs) are the leading cause of death worldwide [67]. The complexity of common diseases is related to the involvement of thousands of genes that have different patterns among patients with a similar diagnosis. It shows poor diagnostics which only relies on a small number of biomarkers with limited specificity or sensitivity.

Digital and genomic medicine may be able to overcome this problem by processing and integrating massive data from digital devices, imaging, electronic health records, and omics [68].

Digital equipment and services play an essential role in supporting both physicians and patients in today's medical and healthcare practices. Digital twins are an engineering idea that has been applied to complicated systems. The developing digital twin technology is being acclaimed as an intriguing and promising method for advancing medical research and improving clinical and public health outcomes. Digital twins can help care systems to be more personalized and proactive. A virtual model of a physical object having dynamic, bi-directional links between the physical thing and its corresponding twin in the digital domain is known as a digital twin [69, 70].

The digital twin parts include the physical component in the physical space, the digital representation of the physical component in virtual space, and the links between the two, that is, information moving between the physical and digital components [71].

Another significant modern aspect of a digital twin is its capacity to predict how the process will perform. Prediction accuracy gradually is increasing through novel technologies such as artificial intelligence (AI). Medicine and public health will be revolutionized by intelligent AI, which combine data, knowledge by different algorithms.

Personalized medicine needs the collection and analysis of massive amounts of data (big data from a mix and health records), and new approaches like digital twins and AI accelerates this process. Digital twins are high-resolution models of patients that computationally medicate with hundreds of drugs to determine the best drug for the patient [71]. Digital twins will be important in offering highly personalized treatments and interventions, and their main features, such as digital thread tracing and monitoring, will allow them to do so. The banks of human digital twins may one day be crucial for very successful clinical trial matching, among other applications.

References

1. Gameiro GR, Sinkunas V, Liguori GR, Auler-Júnior JOC. Precision Medicine: changing the way we think about healthcare. Clinics. 2018;73:e723.
2. Seyhan AA, Carini C. Are innovation and new technologies in precision medicine paving a new era in patients centric care? J Transl Med. 2019;17(1):114.
3. FS C, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793–5.
4. Horne R, Bell JI, Montgomery JR, Ravn MO, Tooke JE. A new social contract for medical innovation. Lancet. 2015;385(9974):1153–4.
5. Gupta R, Kim J, Spiegel J, Ferguson SM. Developing products for personalized medicine: NIH research tools policy applications. Per Med. 2004;1(1):115–24.
6. Carson PE, Flanagan CL, Ickes C, Alving AS. Enzymatic deficiency in primaquine-sensitive erythrocytes. Science. 1956;124(3220):484–5.
7. Mahgoub A, Dring L, Idle J, Lancaster R, Smith R. Polymorphic hydroxylation of debrisoquine in man. Lancet. 1977;310(8038):584–6.
8. Gibson WM. Can personalized medicine survive? Can Fam Physician. 1971;17(8):29.
9. Langreth BR, Waldholz M. New era of personalized medicine: targeting drugs for each unique genetic profile. Oncologist. 1999;4(5):426.
10. National Cancer Institute. NCI dictionary of cancer terms–personalized medicine. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/personalized-medicine
11. Abrahams E, Ginsburg GS, Silver M. The personalized medicine coalition. Am J Pharmacogenomics. 2005;5(6):345–55.
12. Moon H, Ahn H, Kodell RL, Baek S, Lin C-J, Chen JJ. Ensemble methods for classification of patients for personalized medicine with high-dimensional data. Artif Intell Med. 2007;41(3):197–207.

13. Meaney E, Sierra-Vargas P, Meaney A, Guzmán-Grenfell M, Ramírez-Sánchez I, Hicks JJ, et al. Erratum to "Does Metformin Increase Paraoxonase Activity in Patients with the Metabolic Syndrome? Additional Data from the MEFISTO Study". Clin Transl Sci. 2015;8(6):873.
14. Hong K-W, Oh B. Overview of personalized medicine in the disease genomic era. BMB Rep. 2010;43(10):643–8.
15. Brand A. Public health genomics and personalized healthcare: a pipeline from cell to society. Drug Metabol Drug Interact. 2012;27(3):121–3.
16. Møldrup C. Beyond personalized medicine. Pers Med. 2009;6(3):231–3.
17. Fierz W. Challenge of personalized health care: to what extent is medicine already individualized and what are the future trends? Med Sci Monit. 2004;10(5):RA111–RA23.
18. Srivastava P. Drug metabolism and individualized medicine. Curr Drug Metab. 2003;4(1):33–44.
19. Gravitz L. The story "A Fight for Life that United a Field". Nature. 2011;478:163–4.
20. Baker M. Reprogramming Rx. London: Nature Publishing Group; 2011.
21. Hall JG. Individualized medicine. What the genetic revolution will bring to health care in the 21st century. Can Fam Physician. 2003;49:12.
22. Graham-Rowe D. Overview: multiple lines of attack. Nature. 2011;480(7377):S34–S5.
23. Boguski MS, Arnaout R, Hill C. Customized care 2020: how medical sequencing and network biology will enable personalized medicine. F1000 Biol Rep. 2009;1:73.
24. Cancer Diagnosis Progran (CDP). Director's Challenge: Toward a Molecular Classification of Cancer. https://cdpcancergov/scientific_programs/specs/1/challenge/directors_challenge_initiativehtm#:~:text=Classification%20of%20Cancer-,Overview,molecular%20alterations%20in%20human%20tumors (1999).
25. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. N Engl J Med. 2012;366(6):489–91.
26. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov. 2007;6(4):287–93.
27. Hood L. A personal journey of discovery: developing technology and changing biology. Annu Rev Anal Chem. 2008;1:1–43.
28. Meyer UA. Pharmacogenetics–five decades of therapeutic lessons from genetic diversity. Nat Rev Genet. 2004;5(9):669–76.
29. Food and Drug Administration, HHS. International Conference on Harmonisation; Guidance on E15 Pharmacogenomics Definitions and Sample Coding; Availability. Notice. Fed Reg. 2008;73(68):19074.
30. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526(7573):343–50.
31. Relling MV, Dervieux T. Pharmacogenetics and cancer therapy. Nat Rev Cancer. 2001;1(2):99–108.
32. Weinshilboum R, Wang L. Pharmacogenomics: bench to bedside. Discov Med. 2009;5(25):30–6.
33. Wheeler HE, Maitland ML, Dolan ME, Cox NJ, Ratain MJ. Cancer pharmacogenomics: strategies and challenges. Nat Rev Genet. 2013;14(1):23–34.
34. Sachidanandam R, Weissman D, Schmidt SC, Kakol JM, Stein LD, Marth G, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. Nature. 2001;409(6822):928–34.
35. National Center for Biotechnology Information, National Library of Medicine. Database of single nucleotide polymorphisms (dbSNP). National Center for Biotechnology Information, National Library of Medicine… 2015.
36. Robert F, Pelletier J. Exploring the impact of single-nucleotide polymorphisms on translation. Front Genet. 2018;9:507.
37. Kasztura M, Richard A, Bempong N-E, Loncar D, Flahault A. Cost-effectiveness of precision medicine: a scoping review. Int J Public Health. 2019;64(9):1261–71.
38. Ginsburg GS, Phillips KA. Precision medicine: from science to value. Health Aff (Millwood). 2018;37(5):694–701.
39. Mathur S, Sutton J. Personalized medicine could transform healthcare. Biomed Rep. 2017;7(1):3–5.
40. Shendure J, Findlay GM, Snyder MW. Genomic medicine–progress, pitfalls, and promise. Cell. 2019;177(1):45–57.
41. Horton RH, Lucassen AM. Recent developments in genetic/genomic medicine. Clin Sci (Lond). 2019;133(5):697–708.
42. Ke X, Shen L. Molecular targeted therapy of cancer: the progress and future prospect. Front Lab Med. 2017;1(2):69–75.
43. Seebacher N, Stacy A, Porter G, Merlot A. Clinical development of targeted and immune based anti-cancer therapies. J Exp Clin Cancer Res. 2019;38(1):156.
44. National Cancer Institute. Targeted Cancer Therapies. https://www.cancergov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet.
45. Slastnikova TA, Ulasov AV, Rosenkranz AA, Sobolev AS. Targeted intracellular delivery of antibodies: the state of the art. Front Pharmacol. 2018;9:1208.
46. Krzyszczyk P, Acevedo A, Davidoff EJ, Timmins LM, Marrero-Berrios I, Patel M, et al. The growing role of precision and personalized medicine for cancer treatment. Technology. 2018;6(03n04):79–100.
47. Masic I, Miokovic M, Muhamedagic B. Evidence based medicine–new approaches and challenges. Acta Inform Med. 2008;16(4):219.
48. Goldberger JJ, Buxton AE. Personalized medicine vs guideline-based medicine. JAMA. 2013;309(24):2559–60.

49. Tonelli MR, Shirts BH. Knowledge for precision medicine: mechanistic reasoning and methodological pluralism. JAMA. 2017;318(17):1649–50.
50. Kumar D. The personalised medicine: a paradigm of evidence-based medicine. Ann Ist Super Sanita. 2011;47:31–40.
51. de Leon J. Evidence-based medicine versus personalized medicine: are they enemies? J Clin Psychopharmacol. 2012;32(2):153–64.
52. Drozda K, Pacanowski MA, Grimstein C, Zineh I. Pharmacogenetic labeling of FDA-approved drugs: a regulatory retrospective. JACC Basic Transl Sci. 2018;3(4):545–9.
53. Food and Drug Administration (ADA). Table of pharmacogenomic biomarkers in drug labeling (2018). https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
54. National Human Genome Research Institute (NHGRI). Genomics and Medicine. https://www.genomegov/health/Genomics-and-Medicine
55. Davies K. The era of genomic medicine. Clin Med. 2013;13(6):594.
56. Rubanovich CK, Cheung C, Mandel J, Bloss CS. Physician preparedness for big genomic data: a review of genomic medicine education initiatives in the United States. Hum Mol Genet. 2018;27(R2):R250–R8.
57. Roden DM, Tyndale R. Genomic medicine, precision medicine, personalized medicine: what's in a name? Clin Pharmacol Ther. 2013;94(2):169–72.
58. Sykiotis GP, Kalliolias GD, Papavassiliou AG. Hippocrates and genomic medicine. Arch Med Res. 2006;37(1):181–3.
59. Raza S, Hall A. Genomic medicine and data sharing. Br Med Bull. 2017;123(1):1–11.
60. Manolio TA, Green ED. Leading the way to genomic medicine. Am J Med Genet C Semin Med Genet. 2014 Mar;166C(1):1–7.
61. Semiz S, Dujic T, Causevic A. Pharmacogenetics and personalized treatment of type 2 diabetes. Biochem Med (Zagreb). 2013;23(2):154–71.
62. Manzoni C, Kia DA, Vandrovcova J, Hardy J, Wood NW, Lewis PA, et al. Genome, transcriptome and proteome: the rise of omics data and their integration in biomedical sciences. Brief Bioinformatics. 2018;19(2):286–302.
63. Yan S-K, Liu R-H, Jin H-Z, Liu X-R, Ye J, Shan L, et al. 'Omics' in pharmaceutical research: overview, applications, challenges, and future perspectives. Chin J Nat Med. 2015;13(1):3–21.
64. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. Science (New York, NY). 2001;291(5507):1304–51.
65. Bluett J, Barton A. Precision medicine in rheumatoid arthritis. Rheum Dis Clin. 2017;43(3):377–87.
66. Au TH, Wang K, Stenehjem D, Garrido-Laguna I. Personalized and precision medicine: integrating genomics into treatment decisions in gastrointestinal malignancies. J Gastrointest Oncol. 2017;8(3):387.
67. Hunter DJ, Reddy KS. Noncommunicable diseases. N Engl J Med. 2013;369(14):1336–43.
68. Topol EJ. A decade of digital medicine innovation. Sci Transl Med. 2019;11(498):eaaw7610.
69. Kamel Boulos MN, Zhang P. Digital twins: from personalised medicine to precision public health. J Pers Med. 2021;11(8):745.
70. Björnsson B, Borrebaeck C, Elander N, Gasslander T, Gawel DR, Gustafsson M, et al. Digital twins to personalize medicine. Genome Med. 2020;12(1):1–4.
71. Grieves M. Digital twin: manufacturing excellence through virtual factory replication. White Paper. 2014;1:1–7.