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REVIEW

Predictive genomic tools in disease stratification and targeted prevention: a recent update in personalized therapy advancements

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Abstract

In the current era of medical revolution, genomic testing has guided the healthcare fraternity to develop predictive, preventive, and personalized medicine. Predictive screening involves sequencing a whole genome to comprehensively deliver patient care via enhanced diagnostic sensitivity and specific therapeutic targeting. The best example is the application of whole-exome sequencing when identifying aberrant fetuses with healthy karyotypes and chromosomal microarray analysis in complicated pregnancies. To fit into today's clinical practice needs, experimental system biology like genomic technologies, and system biology viz., the use of artificial intelligence and machine learning is required to be attuned to the development of preventive and personalized medicine. As diagnostic techniques are advancing, the selection of medical intervention can gradually be influenced by a person's genetic composition or the cellular profiling of the affected tissue. Clinical genetic practitioners can learn a lot about several conditions from their distinct facial traits. Current research indicates that in terms of diagnosing syndromes, facial analysis techniques are on par with those of qualified therapists. Employing deep learning and computer vision techniques, the face image assessment software DeepGestalt measures resemblances to numerous of disorders. Biomarkers are essential for diagnostic, prognostic, and selection systems for developing personalized medicine viz. DNA from chromosome 21 is counted in prenatal blood as part of the Down's syndrome biomarker screening. This review is based on a detailed analysis of the scientific literature via a vigilant approach to highlight the applicability of predictive diagnostics for the development of preventive, targeted, personalized medicine for clinical application in the framework of predictive, preventive, and personalized medicine (PPPM/3 PM). Additionally, targeted prevention has also been elaborated in terms of gene-environment interactions and next-generation DNA sequencing. The application of 3 PM has been highlighted by an in-depth analysis of cancer and cardiovascular diseases. The real-time challenges of genome sequencing and personalized medicine have also been discussed.

Keywords Predictive biomarkers · Pharmacogenomics · Precision medicine · Vaccines · Personalized medicine

Introduction

The emergence of personalized medicine in the healthcare industry begins with the failure of the less efficient 'trial and error' approach of dosing, resulting in drug toxicities, serious side effects, adverse reactions, drug interactions, and possible disease pathogenesis. Consequently, the healthcare cost has skyrocketed with increased discomfort to the patient. Current therapies have been generally based on scientific research by relating to evidence obtained through clinical research [1]. However, there has been no significant progress in the field of targeted medicine. To surmount the progression of the above-stated problems, the concept of personalized medicine evolved which aimed at treatment and facilitating prevention. Personalized medicine (PM)

Highlights
- Technical advancements in the fields of genomics in predictive, preventive, and personalized medicine have been on the rise.
- Predictive information on modifications in genetic makeup or any gene mutation can prevent disease manifestation.
- Personalized medicine (PM) is a medical approach for patient classification based on illness subtypes, risks, diagnoses, or therapy responses using specialized diagnostic tests.
- Personalized medicine based on genome analysis aims to enhance therapeutic outcomes and decrease adverse effects important to physicians and patients.

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is comprehended as a medical methodology wherein the patients are segregated on their subtype of the disease, hazards, diagnosis, or therapy response utilizing specific diagnostic tests. As personalized medicine involves population stratification based on their susceptibility to a particular disease or response to therapy, thus it is also termed stratified medicine [2, 3]. That specific population will be targeted to get benefits therapeutically with the help of clinical biomarkers like HercepTest. It is a partial quantitative immunohistochemical assay to estimate HER2 protein overexpressed in breast cancer tissues. It mainly determines the overexpression of HER2 protein. This test is indicated in those patients for whom trastuzumab (Herceptin®) treatment is considered [4]. The vision of personalized medicine (PM) relies on the right drug, dose, time, and patient condition. The roots for the development of PM depend upon multidisciplinary healthcare teams, viz., genomic, proteomic, clinical, and assimilated techniques that aid in understanding the molecular behavior of disease and its earlier detection via utilization of existing biomarkers. Additionally, it decreases financial expenditure and time by enhancing the quality of patient's lives, thus indirectly improving patient compliance [5]. The patient populations who do not react to drugs as anticipated and conventional healthcare that were not successful are targeted via PM. PM possibly is an approach to treat disease with significant precision. Furthermore, precision medicine is a model for healthcare delivery based on the diagnosis made with accuracy and precision, i.e., the actual disease state and the pathological mechanisms associated with it [6]. The concept of personalized medicine and precision medicine are distinguished from one another; still, they both harmonize with each other in view of their application [7].

The concept of chemical individuality: contribution of Garrod

Archibald Edward Garrod, an English physician (1857–1936), was the person to coin the concept of chemical individuality regarding health and disease. One can address him as an intellectual father of precision medicine. In 1902, he published the incidence of alkaptonuria—a study of chemical individuality [8]. Later, in 1909, he mentioned four diseases in his book "*Inborn Error of Metabolism*" viz., alkaptonuria, albinism, cystinuria, and pentosuria, which are innate Mendelian autosomal recessive traits. Furthermore, in 1931, he published another book, "*Inborn Factors in Diseases*," where he claimed that alkaptonuria is due to the alternative pathway of metabolism. He portrayed that the four diseases mentioned above are extreme examples of variations in chemical functioning. Although, these variations exist in the minority in every individual [9]. This raised the concept of the "*Chemical Individual*," which can also be linked to diathesis, i.e., an individual tendency to suffer from a disease or group of diseases. Garrod was more interested in "*inborn factors*." According to him, no two individuals of a species are similar physically or in the chemical process. He also conceded the importance of environmental conditions in demonstrating the inborn error of metabolism. Genetic and environmental factors are the contributing risk factors that may be attributed to disease phenotype [10].

Role of system biology (SB) as a predictive approach

System biology is the computational and mathematical analysis and modeling of complex biological systems. It is based on the concept of "*holism*" or "*wholism*" for biological research. It is considered that several systems of the human body are considered as a "whole" and not as a collection of various parts. It is strictly contradictory to "*reductionism*" or "*atomism*," which considers that the human body consists of different biological parts with individualized functioning [11]. Although indirectly, system biology depends upon reductionism research as the knowledge of the function and composition of smaller entities gives a broad overview of the whole system. The rationale behind the study of system biology of the human body is hugely complex, i.e., it consists of genomes that differ by six million bases [12]. Additionally, differences in lifestyle, diet, and environmental exposure of an individual permit the possibility of a massive range of disease patterns. System biology is studied with two basic concepts, experimental system biology and computational system biology [13]. Experimental system biology is best explained with the help of several—omics approaches. It involves the diagnosis, prognosis, and therapy, which relies on a personalized approach, i.e., the study of biomarker profiles. On the other hand, computational system biology is based on two further concepts, i.e., one is predictive diagnostics, i.e., artificial intelligence and machine learning, and the other is dynamic modeling approaches [14]. Artificial intelligence (AI) is the intelligence imparted to the machine so that machines can become equally capable as humans for functioning. In contrast, machine learning is applying an AI mechanical machine's ability to learn automatically (without being programmed) and improve itself from experience [15]. This concept identifies the statistical patterns in larger populations. Patterns are what a machine is programmed to identify in each data. Using this, it attempts to recognize an identical pattern in another data set. Thus, it lacks the mechanical approach, i.e., caveats in connections between input programs and outcomes [16]. To overcome these limitations, dynamic modeling approaches came into the picture. This approach considers fixed points in high dimensional space, i.e., health and disease, as stable attractors, as the voyage from health to disease or vice versa may

be gradual (signs of aging) or sometimes sudden (general organ failure) [17].

Predictive diagnostics

The latest advances in molecular genetics have enabled us to grasp the genetic elements that underlie interindividual variations in all aspects of medication response, including sensitivity towards drugs, toxicity, and dose. The use of forecasting approaches by predictive diagnostics and analytics aids practitioners in envisioning upcoming events based on the evidence [18]. Healthcare professionals may employ this data to diagnose diseases early, make important choices, and give patients at-risk preventive therapy. The recent core techniques linked to predictive diagnostics include data modeling, artificial intelligence (AI), data mining, and machine learning [19].

Data modeling involves statistical analysis of collected historical data to evaluate the possibility of potential outcomes. In healthcare, data modeling is used to create a thorough model of how particular data changes with time. It enables physicians to forecast how patients will respond to medications [19]. It can be better illustrated with the investigation conducted on youngsters. It can be difficult to identify psoriasis in youngsters. The clinical presentation of children is different from that of adults, which presents challenges. The objective of the study is to determine which consensus diagnostic criteria are most accurate at predicting childhood psoriasis and to provide a shortlist of those criteria. With the help of experienced investigators, case–control diagnostic accuracy research examined 18 clinical criteria in 12 dermatology units in the UK during the time period of 2017–2019. A total of 330 subjects (children under 18 years of age) were recruited for the study, out of which 170 were diagnosed with psoriasis and 160 were diagnosed with scaly and inflammatory rashes. Backward logistic regression was used to determine the most appropriate predictive factors, and bootstrapping statistical procedure was used for internal validation. The best-predictive model has shown 76.8% sensitivity and 72.7% of specificity. This research presents examination- and history-based evidence on the clinical characteristics of childhood psoriasis and suggests seven risk factors viz. family history, scale, and erythema in the scalp, inside external auditory meatus, on elbows and knees, persistent, well-defined erythematous rash on the body, umbilicus, and in napkin area that has strong discriminative power in patients receiving secondary care [20].

In addition to data modeling, the management of patient data by AI can reduce the risk of human error and free up time for healthcare professionals [21]. Currently, artificial intelligence (AI) will be used to support the detection and management of spinal disorders. The potential applications of AI in the area of diagnostic testing include diagnostic support for conditions requiring extremely specific knowledge, such as pediatric trauma, scoliosis, and spinal cord malignancies. Adolescents have been screened for scoliosis using moiré topography, which characterizes the 3-D surface of the trunk with band patterns; however, the meaning of the band patterns is not always evident. Researchers, therefore, developed a scoliosis screening technique that determines vertebral rotations, the Cobb angle, and spinal alignment using moiré images. As per this screening system, the Cobb angle is estimated by a convolutional neural network (CNN) which calculates the locations of the 17 spinous processes, 12 thoracic and 5 lumbar vertebrae, and the angle of rotation of each vertebra. The reliability of scoliosis screening is anticipated to increase using the suggested method of predicting the Cobb angle and AVR from moiré images using a CNN [22].

Furthermore, from the perspective of personalized, predictive, and preventative medicine (PPPM), AI strategies present a significant potential for customized and early disease detection. It is crucial that AI-based models are thoroughly evaluated in order to implement PPPM in clinical settings. One of the steps in the validation process is evaluating the model using patient-level data from a separate clinical randomized trial. Recruitment criteria, though, can influence the statistical analysis of cohort research findings and obstruct the use of a model. In this work, the datasets were gathered from two important dementia cohorts—the Alzheimer's disease neuroimaging initiative (ADNI) and AddNeuroMed. Both datasets were thoroughly compared to determine the extent to which data from separate clinical cohorts differ from one another. Significant variations between the two cohorts were found in the comparison at the level of individual characteristics. Results that were derived from a single cohort dataset may not be as generalizable as a result of such systematic discrepancies. Regardless of the differences found, the validation of an earlier model created by the ADNI for the forecasting of individual dementia risk scores 244 on AddNeuroMed individuals was promising. High prediction performance of above 80% resulted from external validation up to 6 years before dementia diagnosis was achieved. In summation, the research identifies obstacles in performing external validation of AI-based models on cohort research findings. It is one of the few instances in the domain of neuroscience where such external validation was carried out. The proposed model serves as clear evidence for the viability of trustworthy models for tailored predictive diagnostics [23].

In data mining, physicians are able to determine the best medication for a variety of diseases by comparing symptoms and therapy options [24]. Hepatitis is an infectious disease that impacts illness, death, overall health, life span, and other socioeconomic effects. Hepatitis must be diagnosed as soon

as possible in order to be effectively treated. In order to diagnose hepatitis, the researchers used, compared, and analyzed a number of data mining classification algorithms, such as the C4.5 algorithm, Naive Bayes, and *k*-nearest neighbor. The C4.5 technique is the best method with the highest accuracy, followed by the *k*-nearest neighbor method and the naive Bayes method. These models were evaluated by cross-validation, confusion matrix, and ROC curve techniques.

In addition, nowadays, gestational hypertension or pregnancy-induced hypertension (GE/PIH) is a very common problem in females during their pregnancy times. In normally conceived pregnancies, it is linked to activin A, which encourages human trophoblast invasion during the first trimester. The evidence is inadequate concerning the predictive utility of activin A for GE/PIH in females undergoing in vitro fertilization (IVF) therapy, and it is unclear if integrin β1 promotes activin A–increased trophoblast invasion. Researchers investigated the function and fundamental molecular pathways of integrin β1 in activin A–promoted invasion in immortalized (HTR8/SVneo) and primary human extravillous trophoblast (EVT) cells. To examine the predictive/diagnostic significance of activin A in IVF pregnancies, a case–control study was conducted. The results demonstrated that activin A administration boosted integrin β1 expression, and integrin β1 knockdown significantly reduced both basal and activin A–induced HTR8/SVneo cell invasion. The TGF-β type I receptor inhibitor, i.e., SB431542 stopped activin A from increasing integrin β1 expression and SMAD2/SMAD3 phosphorylation. Integrin β1 expression that was elevated by activin A was reduced as a result of the elimination of ALK4 or SMAD4 from both cells. According to these findings, integrin β1 regulates activin A–promoted invasion of trophoblast via SMAD2/3-SMAD4 mechanism, and the predictive/diagnostic value of activin A in maternal serum during the first trimester for GE/PIH may differ in the IVF cohort [25].

Targeted prevention: study of gene-environment interactions and development of vaccines

Structure of a gene

The linear sequence of nucleotides forms a gene. Phosphodiester bonds join these nucleotides in a sequence between 50 and 30 carbons of nucleotide's deoxyribose moiety. A long-stranded DNA of a gene possesses a promoter that manages the gene activity and its coding and non-coding sequences. Coding sequence ascertains which protein gene creates, while non-coding regulates the condition of gene expression. The functional unit of the gene is known as an allele which has differences in DNA bases sequence that contributes to an individual's unique physical features. The coding and non-coding sequences are copied by transcription, producing an mRNA copy of the gene's information which further synthesizes protein with the help of genetic code [26].

The phrase "targeted prevention" describes measures intended to stop people from developing adjustment issues by lowering the risk or by putting into practice advantageous or protective characteristics discovered through studies of human development [27]. Genetic testing is now widely used to reveal modifications in genetic makeup or any gene mutation that may lead to disease. This genetic information is used to identify rare diseases or cancer. The most common example is the investigation of genetic markers to identify the disease risk at or before birth. Therefore, genetic factors were used by clinicians to know the prior risk of disease before the manifestation of clinical symptoms, and this could help to prevent disease by targeted prevention.

To understand the concept of targeted prevention, one must analyze the effect of gene-environment interactions in the establishment of disease. Several genes and environmental factors, as well as complicated interactions among them, play important roles in the development of many prevalent ailments. Since the specific risk factors can only be determined after thorough examinations of the interactions between several components, specifically between various genes and environmental factors, such epidemiological approaches prevent making an accurate prediction [28].

Throughout an individual's lifespan, the genetic data from germ cell lines is constant. Therefore, it is impossible to develop preventive therapy for these genetic variables. However, gene editing has been an exuberant development in recent years. It helps scientists to understand the contribution of a gene to disease conditions. The mechanism may involve the introduction of the repair genome sequence for mutation at the targeted site. Still, this field needs more exploration.

On the other hand, environmental influences, particularly those related to dietary and exercise habits, can be altered via individual efforts. Therefore, preventive therapies focused on enhancing these characteristics are feasible. Even in the era of genomic medicine, the primary prevention of getting a disease in the first place by enhancing personal lifestyle behaviors will continue to be the emphasis of preventive medicine [29].

Finding out about gene-environment interactions has several benefits, one of which is identifying target lifestyles for whom interventions should be targeted. Only the link between genetic changes and the development of diseases can be determined by large-scale genomic investigations like genome-wide association studies (GWASs). Such research, however, cannot give information on the proper preventive treatments. Therefore, in those with the high-risk genetic

polymorphisms discovered by GWASs, only broad dietary and exercise treatments, such as the adoption of low-calorie diets and high-intensity exercise regimens, would be carried out [30]. Recently, some methods have been developed by researchers to understand gene-environment interaction. The case–control design has been used in GWASs recently. In these investigations, the frequency of chromosomal alterations in the case and control groups was compared. However, investigations of the interactions between genes and the environment carry a significant risk of major bias. DNA samples can be taken for case–control research even after the disease has manifested because germ cell line DNA information is stable during an individual's lifetime. To understand the disease's cause, however, environmental data must be gathered prior to the commencement of the illness. It is necessary to gather a lot of data on lifestyle choices for gene-environmental interaction investigations.

The performance of gene-environmental interaction analyses is facilitated by additional research with a prospective cohort design. Such studies have the disadvantage of having lengthy follow-up times and significant expenditures, though. Numerous massive prospective genomic cohort experiments have been conducted or are now being planned for across the globe, including Tohoku Medical Megabank (TMM) project [31], UK ALSPAC [32], and the Kyushu and Okinawa Population Study (KOPS) [33]. Furthermore, Mendelian randomization, a technique based on Mendel's second law, the law of random assortment, is a significant way of examining gene-environmental interactions. Besides relying solely on environmental factors, researchers are now turning to genetic markers, such as SNP variations, for which data may be gathered through GWASs [34]. Since germ cell line–derived genetic information cannot be altered while a person is alive, the potential of reverse causation may be ruled out. Additionally, this strategy can be an effective tool when significant bias and/or covariates may alter the study outcomes because of the law of random assortment. In observational studies, drinking coffee has been associated with a lower risk of cardiovascular disease, but it is unknown if the associations are causal. To determine if coffee drinking may play a causative role in cardiovascular disease, researchers used a Mendelian randomization study. The results of this Mendelian randomization study provided absolutely no evidence that coffee drinking influences the risk of cardiovascular disease, raising the possibility that earlier observational studies were biased [35]. In a different study, researchers examine if serum levels of testosterone differ among depressed and healthy females and whether there is a meaningful association using meta-analytical and Mendelian randomization techniques. Absolute serum levels of testosterone are significantly correlated with female depression, according to a meta-analysis. This correlation is still present in the premenopausal group whereas borderline significance is reached in the postmenopausal group. The Mendelian randomization analysis's findings were unable to establish a link between low testosterone and depression. Thus, it can be concluded that in healthy and depressed women, testosterone levels differ, which is most likely a symptom of the illness [36].

In addition to the analysis of gene-environment interaction, the development of vaccines has also played a major role in targeted prevention. Most of contagious diseases have previously been controlled and prevented by the use of vaccines, which has significantly improved public health and prolonged life expectancy [37]. Immunotherapeutic and vaccination techniques have subsequently been used to treat diseases that are not contagious. These potential antigens have specifically been targeted for vaccination and immunotherapeutic treatments in a number of malignancies of non-infectious origin, that most often create modified proteins during malignant transformation [38]. Many potential therapeutic strategies rely on creating self-proteins that have undergone mutations or other changes in order to overcome immunological tolerance and frequently serve as antigens [39]. Recently, mass preventive therapy techniques that target all *Mycobacterium tuberculosis* (MTB)-infected persons are unrealistic in high-burden tuberculosis (TB) countries because present screening tools for MTB infection have low predictive sensitivity for accurately identifying who will acquire TB disease. Here, investigators go over interesting observations for a risk-targeted test-and-treat strategy that focuses on an extremely specific transcriptome biomarker that can detect people with TB infection who have not yet sought medical attention as well as people who are most likely to proceed to active TB disease. These risk-targeted approaches could provide a quick, moral, and affordable way to reduce the burden of the disease and stop transmission. They would also be essential to attaining TB eradication in nations that are close to accomplishing that goal. Researchers also discuss CORTIS (Correlate of Risk Targeted Intervention Study), which could serve as concrete evidence for the approach. According to biomarker status, one such trial is now recruiting 1500 high-risk and 1700 low-risk people in South Africa and assigning high-risk participants at random to TB preventive therapy or standard of care treatment. By assessing the COR as a prognostic test for the emergency, assessing the effectiveness of preventive therapy in COR + participants, and offering a preliminary evaluation of a test-and-treat strategy, the CORTIS design addresses essential needs for the execution of risk-targeted test-and-treat strategies [40]. Another notable malignancy where HER2 is a common growth factor is breast cancer. The AE36 hybrid peptide (aa776-790), which is formed from the intracellular region of the HER2 protein and the core region of the MHC class II invariant chain, is the foundation of the innovative, HER2-directed vaccination AE37 (the

Ii-key peptide). As the AE37 vaccine, this hybrid peptide is administered along with a GM-CSF immunoadjuvant [41]. The investigators concluded that with the development of the Ii-key peptide and the HER2-specific AE37 vaccine, peptide vaccines are still an effective and desirable technique in the treatment of cancer. Further study is required to expand the use of the Ii-Key peptide technology beyond the AE37 vaccination.

Recent updates on personalized medicine development using predictive diagnostics

The addition of genomic data in a knowledge-based healthcare system is an approach to utilize the full potential of that information to optimize patient care. Genomic testing involves high-throughput DNA sequencing, pharmacogenomics, and circulating cell-free nucleic acids [42]. High-throughput DNA sequencing or next-generation sequencing (NGS) technique is employed to ascertain the sequencing of the whole genome or a part of the genome in a single biochemical reaction. NGS involves multiple techniques of genome sequencing, i.e., whole-genome sequencing, clinical exome sequencing, whole transcriptome sequencing, and single-cell sequencing as shown in Fig. 1 [43]. It is done by a non-Sanger-based sequencing technique in which parallel sequencing of multiple DNA fragments is done. Later, fragments are pieced and mapped together to a reference genome via bioinformatics analysis. A brief compilation of genomic techniques is highlighted in Table 1. Biomarkers are the pointers or indicators of processes and responses to therapeutic intervention, viz. normal biologic, pathogenic, or pharmacologic, which can be measured objectively. They can be of mainly three types: diagnostic, predictive, and prognostic [44]. The diagnostic biomarker is associated with the diagnosis or severity of the disease. It can detect the problem before the appearance of their symptoms.

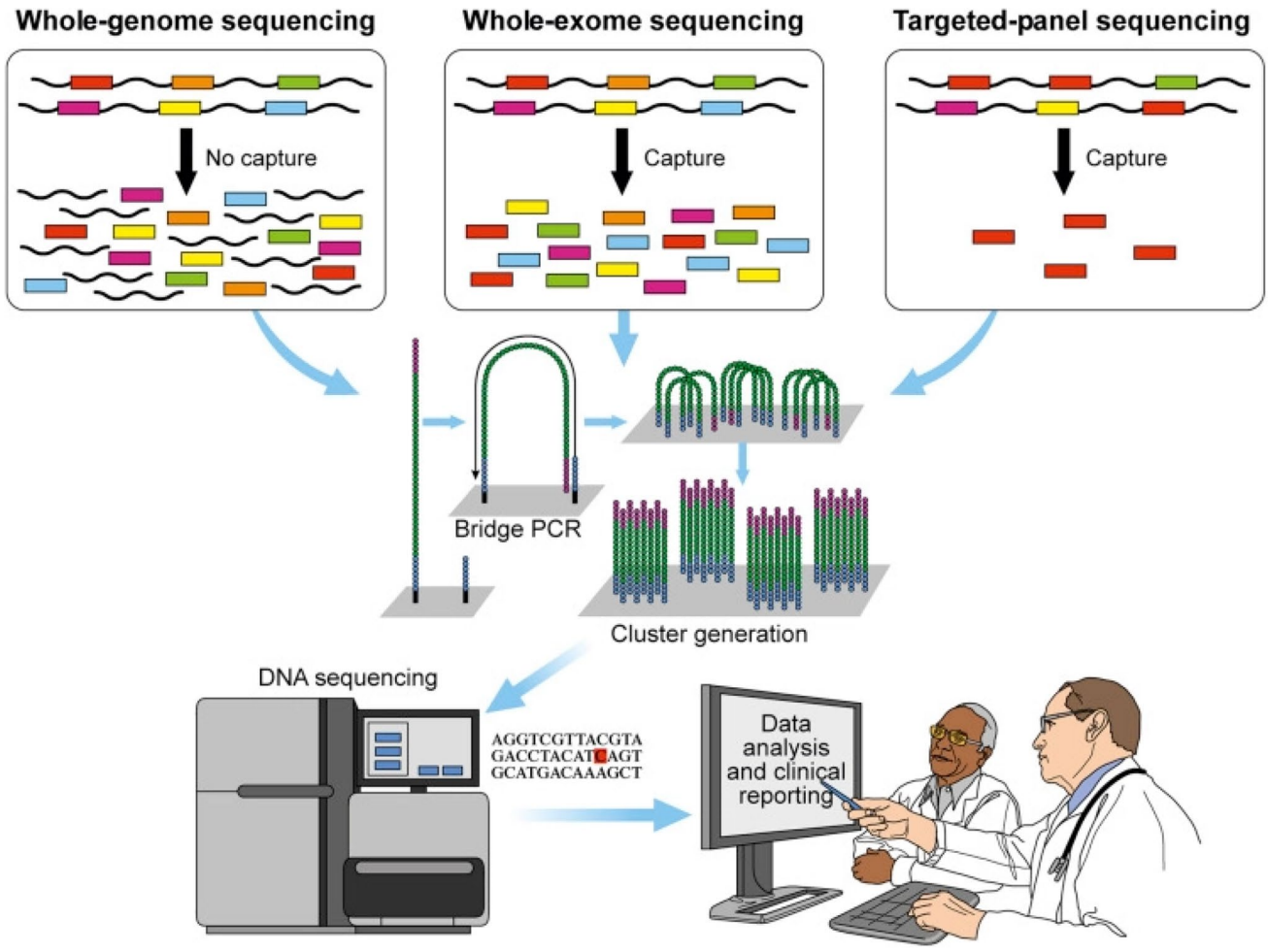

Fig. 1 Diagrammatic illustration of application of distinct next-generation sequencing technologies adopted with permission from Klein et al. [91]

Table 1 Genomic technologies utilized in the development of personalized medicine [93, 94]

Technique	Description	General Steps
Whole Genome Sequencing (WGS)	It is an analytical technique to assay human genetic variation at the base sequence level.	**NEXT-GENERATION DNA SEQUENCING** Whole Genome Sequencing (WGS) Whole Transcriptome Sequencing Clinical Exome Sequencing (CES) ⬇ **BIOINFORMATICS ANALYSIS** Identification of variant (excluding mutations and polymorphisms); variants preference via presumed inherited disease pattern; prediction of variant effects via computer simulation; formerly reported mutations identification; prioritize novel mutations via existing knowledge of gene function ⬇ **FUNCTIONAL VALIDATION** Expression of proteins, functions of proteins in cells, Disease animal models
Clinical Exome Sequencing (CES)	It is a genomic technique for determining sequence of protein-coding region of genes in a genome. It includes two steps: one is the selection of subset of DNA which encodes proteins and other is to sequence the selected DNA via DNA sequencing technology. It is usually applied in rare diseases.	
Whole Transcriptome Sequencing	It comprises the measurement of complete complement of transcripts in a sample at a given time. It is used to determine the functional parts of genome and the changes in expression of genes with time.	
Single Cell Sequencing	It evaluates the sequence information from individual cells with next generation sequence technique. It gives a higher resolution of cellular differences. It helps to understand the individual cell functioning in its microenvironment.	

A diagnostic biomarker is a screening biomarker utilized to differentiate between healthy individuals and individuals with acute disease [45]. Hicks and Coquoz 2009 stated that an individual's DNA remains stable for his lifetime, and this stability represented by the biomarkers are termed DNA biomarkers. Any changes in DNA sequence level of DNA biomarkers viz. Single-nucleotide polymorphisms (SNPs), short tandem repeats (STRs), deletions, and insertions will reveal the genetic alterations of any disease [46]. Another example is the evaluation of serum prostate-specific antigen (PSA) in the early detection of prostate cancer [47]. Diagnostic biomarkers can be obtained via liquid biopsies (discussed later in this section). With the concept of personalized medicine, it is necessary to understand the difference between prognostic and predictive biomarkers. Predictive biomarker differentiates individual into two categories, i.e., one who has the possibility to develop the disease and one who has not, while prognostic signifies the disease progress in a set of the population under standard therapy [48]. Prognostic biomarkers trace the disease path, i.e., indicate the probability of disease progression, reduction, and potential clinical episodes. For the study of cancer, conventional biomarkers are the size of the tumor and the quantity of tumor-positive lymph nodes, which aids in estimating cancer stages and diagnosis. In clinical trials, prognostic biomarkers enrich populations that are more likely to progress. This increases statistical power and thus, reduces the cost of drug development and guides decisions regarding the aggressiveness of the treatment [49]. Examples of biomarkers currently utilized in diagnosing diseases are tabulated in Table 2. *Pharmacogenomics* is holding an essential position in the development of personalized medicine. Pharmacogenomics combines pharmacology and genomics for a better understanding of genetic variations that affect the biological effects of the active molecules, therapeutic effects, and side effects. It is the science for developing effective and safe medications that will alter a person's genetic makeup (such as drug-gene interaction, which leads to enzymatic inhibition and induction, which may alter the drug's metabolism). It gives information about

Table 2 Examples of biomarkers in current use [95, 96]

S. no	Name	Application	Indication	Description and outcome
1	BluePrint®	Predictive	Breast cancer	A molecular subtyping test that analyzes 80 genes activity for stratification of tumor in the three following subtypes: luminal-type, HER2-type and basal-type
2	Epidermal growth factor receptor (EGFR)	Predictive	Advanced non-small-cell lung cancer	The epidermal growth factor family of receptor tyrosine kinases (ErbBs) participate in controlling cell proliferation, survival, differentiation and migration. This mismanages in regulation leads to cancer. Therapy to this problem involves EGFR TKI (tyrosine kinase inhibitors) or chemotherapy
3	IL28B	Predictive	Hepatitis C virus 1 (HCV-1)	Protein in humans is encoded by the IL28B gene. Individuals with chronic Hepatits C show polymorphism near this gene and show a good response to treatment with pegylated interferon (PegIFN) combined with ribavirin (RBV)
4	MammaPrint®	Prognostic	Breast cancer	Genomic test which examines the activity of certain genes in early stage of breast cancer Observes the activity of 70 genes and compute a recurrence score (either low risk or high risk)
5	OncoTypDX	Predictive/prognostic	ER-positive, HER2-negative breast cancer, colon cancer	Genomic test that analyzes the activity of a group of genes. Work in two ways: one is to estimate a woman's risk of early stage, estrogen-receptor-positive breast cancer coming back (recurrence) and chemotherapy can be recommended or not. Other is to determine the risk of DCIS (ductal carcinoma in situ) and its recurrence in woman and the radiation therapy can be recommended or not
6	SLCO1B (solute carrier organic anion transporter family member 1B1)	Predictive	Myocardial infarction	This gene forms the protein which helps in clearing drugs from the blood by transporting them in the liver. Alterations in transporting activity affects statins, ACE inhibitors and methotrxate and may result in myalgia and rhabdomylosis

which treatment will work best and avoids the drugs which may cause adverse effects through a personalized dosage regimen as per individual genetic makeup [50] [51].

Furthermore, biological sample estimation for circulating cell-free nucleic acids provides a concrete idea for personalized therapy of a specific disease. Circulating cell-free nucleic acids comprise small DNA fragments, i.e., cfDNA, mRNA, and microRNA, which circulate free in the blood due to normal body physiology or several clinical conditions. The sampling and estimation of circulating cell-free nucleic acids are also termed liquid biopsy [52, 53]. T tumor cells (CTC): molecular specimen for cancer cells that are shed from a primary tumor or a metastatic site due to the formation and growth of tumor cells and entering the bloodstream. The half-life of CTC is 1 to 2.4 h. Their physicochemical properties are different from normal blood cells, which helps in their diagnosis. CTCs have already been investigated for different cancers, viz. lung, breast, and pancreatic [54].

Circulating tumor DNA (ctDNA): these molecules are approximately 150 bp in length and are double-stranded and that are highly fragmented. The source of ctDNA is a primary tumor, CTC, and micrometastasis. The half-life of ctDNA is from 15 min to several hours. The unique physiochemical individualities viz., presence of tumor-specific mutations aberrant methylation, opy number variants, and chromosomal rearrangements. PNA clamping PCR, BEAMing Safe-SeqS, digital PCR, and WGS are the techniques for detecting ctDNA (Fig. 2). The ctDNA diagnosis has been established for gastroesophageal cancer, pancreatic cancer, and lung cancer patients [55].

CTCs and ctDNA investigations have smoothened the roads for novel analytic and predictive opportunities and are recommended for the foundation of liquid biopsy. Considerably, they may contribute to the development of personalized medicine.

It is deemed a liquid biopsy revealing metastasis in action by harnessing information about the patient's disease status. It is non-invasive and can be used repeatedly. United States Food and Drug Administration has cleared the cell search system for counting CTC in whole blood. Mitochondrial DNA (mtDNA): mitochondria has a minute amount of DNA known as mitochondrial DNA. Mutations in mtDNA may lead to severe illnesses, including cancers.

Applications of personalized medicine: a recent update

Cancer

The model and practice of personalized medicine is a meticulous and logical approach intended to conquer diseases like cancer. Cancer is a prime center for personalized medicine advancements in specific and successful therapy which could further assist chronic conditions. Personalized medicine of cancer concentrates on harmonizing highly precise and effective therapy for every cancer patient depending on the genetic profile of the individual [56]. Cancer is an extremely heterogeneous disease showing inter-patient and intra-patient variability. Different types of cancers with a variety of genetic contributors are summarized in Table 3**.** The gene expression patterns in cancer are varied in different cancer types although the DNA may be the same in different cancers [57]. The gene expression microarray technique permits us to investigate the gene expression profile of several genes at a single time and differentiate gene expression profiling of both cancerous genes and normal genes. The personalized medicine approach is based on target-based therapies, molecular target identification, and the design of clinical trials [56].

Initiating the clinical application of target-based therapies in the treatment of chronic myeloid leukemia (CML). The

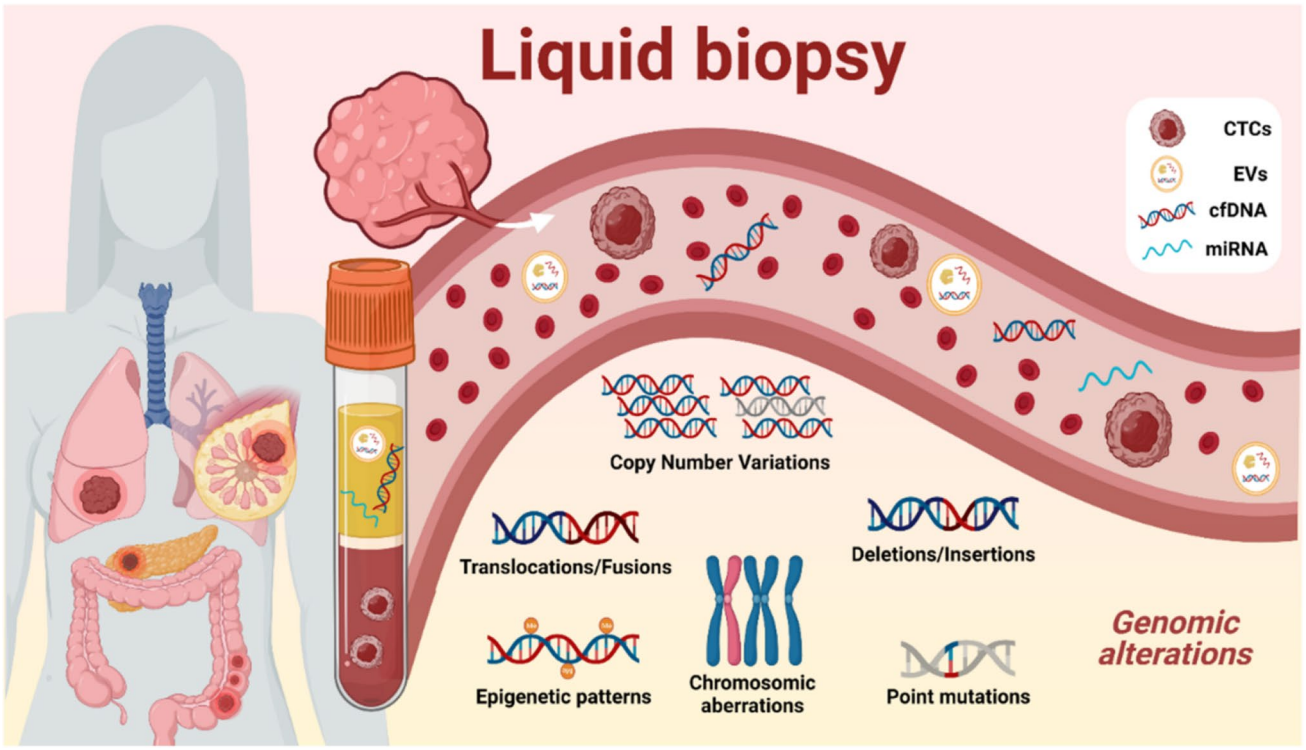

Fig. 2 Comparison of tissue and liquid biopsy in diagnosis adopted with permission from Palacín-Aliana et al. [92]

Table 3 Research work highlighting genetic contributors to different kinds of cancer [97–101]

Type of cancer	Description	Genetic contributors	Reference
Breast cancer	Factors contributing to breast cancer: • Genetic • Environmental • Behavioral (diet, exercise, and lifestyle) Preventive approaches: mammogram screening	BRCA1 and BRCA2 mutations	[97]
Colon cancer	Common treatments available are: • Chemotherapy • Radiation • Surgery Colonoscopy screening When colon cancer is treated at an early stage, many patients survive at least 5 years after their diagnosis If colon cancer does not recur within 5 years, the disease is considered to be cured. Stage I, II, and III cancers are considered potentially curable	• Oligopolyposis: POLE, POLD1, NTHL1 • Juvenile polyposis syndrome: BMPR1A, SMAD4 • Cowden syndrome: PTEN • Peutz-Jeghers syndrome: STK11	[98]
Lung cancer	Two main types: • Non-small cell lung cancer (NSCLC) • Small cell lung cancer (SCLC) • Cancer made up of both types is called mixed small cell/large cell cancer Regular treatment techniques: surgical and chemotherapy	• Li-Fraumeni syndrome: TP53 tumor-suppressor gene • EGFR susceptibility syndrome: EGFR variants, T790M in particular • SFTPA1 and SFTPA2 variant carriers	[99]
Prostate cancer	Screening procedures: digital rectal exam and prostate-specific antigen (PSA) test Three common treatments: • Chemotherapy and hormonal therapy • Surgery • Radiation Comprehensive geriatric assessment was developed to know about the patients who respond to therapy	Pathogenic variants in genes, such as BRCA1, BRCA2, the mismatch repair genes, and HOXB13	[100]
Lymphoma and leukemia	Approaches for the stratification of lymphoma subtypes: • Refining clinical prognostic models for better risk stratification • Use of high-throughput technology to identify biologic subtypes within pathologically similar diseases, "response-adapted" changes in therapy via imaging with [(18)F]-fluoro2-deoxy-d-glucose positron emission tomography (FDG-PET), and anti-idiotype vaccines	B-ALL with intrachromosomal amplification of chromosome 21 (iAMP21), B-ALL with translocations involving tyrosine kinases or cytokine receptors (BCR-ABL1-like ALL) CRLF2 and PAX5 alterations, TP53, CREBBP, and ERG mutations, characteristic genetic aberrations in BCR-ABL1-like B-ALL	[101]

Philadelphia (Ph) chromosome is the genomic marker for CML, a rare malign progressive condition of the hematological system of the body. The Ph chromosome gives rise to an abnormal gene mutation with aberrant kinase activity, which causes an accumulation of reactive oxygen species and genetic instability that is important for the course of illness [58]. Some genes are associated with the control of the proliferation and death of cells viz. the epidermal growth factor receptor (EGFR), tumor protein p53 (TP53), or Schmidt-Ruppin A-2 proto-oncogene (SRC). Cell adhesion is controlled by catenin beta 1 (CTNNB1), or genes associated with TGF-β, such as SKI-like proto-oncogene (SKIL), transforming growth factor- beta 1 or beta 2 (TGFB1 or TGFB2), and TNF-α pathways, such as tumor necrosis factor (TNFA) or nuclear factor kappa B subunit 1 (NFKB1). Some important miRNAs, such as miRNA-451 and miRNA-21, are dysregulated in CML, and this has been linked to the molecular control of pathogenesis, the evolution of disease states, and the effectiveness of therapies [59]. In a recent study for the development of personalized medicine, an intense gradient boosting decision tree approach was used to create the LEukemia Artificial Intelligence Program (LEAP) to prescribe tyrosine kinase inhibitors (TKIs) for patients with CML in the chronic phase (CML-CP). Randomly, 126 test groups and 504 training/validation groups were created from a group of CML-CP patients. The training/validation cohort

was used for threefold cross-validation to develop the LEAP CML-CP model using 101 variables at diagnosis. The LEAP CML-CP model was then used to analyze the test group, and an ideal TKI therapy was prescribed for each patient. Backward multivariate analysis was used to identify the diagnosis age, the extent of comorbidities, and prescribed TKI therapy while bootstrapping was used to internally validate the LEAP CML-CP prescription. In this model, choosing a course of treatment in accordance with the LEAP CML-CP–tailored prescriptions is linked to a higher likelihood of survival than choosing a course of treatment with a LEAP CML-CP non-recommended medication [60].

One more example of key mutation identification is human epidermal growth factor receptor 2 (HER2) positive breast cancer. Twenty percent of all breast cancers fall under the subtypes known as human epidermal growth factor receptor 2 (HER2)-enriched (HER2-positive), which is distinguished by the overexpression of the HER2 receptor and the absence of the estrogen and progesterone receptors. Anti-HER2 and cytotoxic drug treatments can't stop the aggressive nature and high mortality of the HER2 subtype [61]. With adjunction of trastuzumab to chemotherapy (alone), the disease progression was found to slow down with an increased response rate and prolonged survival time. Adding lapatinib to chemotherapy helps to attain more delay in disease progression. The survival time was increased with the combination of pertuzumab, trastuzumab, and chemotherapy (i.e., docetaxel) compared with the chemotherapy and trastuzumab only. Improvement in the length of progression-free survival with lesser adverse effects was observed with ado-trastuzumab emtansine therapy (a conjugate of a HER2 monoclonal antibody) [62]. The above two examples establish the fact that the identification of key mutations can assist a significant number of specific cancer patients. Succeeding several approaches are accessible at present to spot the significant molecular targets for therapeutic interference. Its clinical efficacy is still constrained by the development of drug resistance, so it is necessary to look into novel agents and create a risk score system to enhance therapies and assess patient prognosis.

To elucidate this, A TCGA cohort was examined for differentially elevated mRNAs linked to Her2-positive breast cancer. The prognostic risk scoring system was developed using univariate and Lasso Cox regression model analysis. The clinical factors viz. age, size of the tumor, location of tumor near lymph node, and metastasis were also incorporated for univariate and multivariate analyses to confirm the sensitivity and specificity of the risk scoring system. Furthermore, the research value of the mRNAs as essential genes was investigated based on correlation and copy number variation mutation studies. Consequently, four upregulated mRNAs (RDH16, SPC25, SPC24, and SCUBE3) and two downregulated mRNAs (DGAT2 and CCDC69) were among the six mRNAs that were screened and found in this study to create a predictive risk score system. To assess patient prognosis, the risk score system can classify Her2-positive breast cancer specimens into high- and low-risk groups. The risk scoring method developed during this research is useful for implementing early diagnosis and individualized treatment as well as for improving the screening of high-risk individuals with Her2-positive breast cancer [63].

A non-randomized open-label interventional with a new phase II trial concept had been initiated where the researchers will use massive parallel sequencing (MPS) to combine predictive markers (hormonal receptors, HER2, TP53, CHEK2, and RB1) with the insights currently available from prior trials. The study is known as the PETREMAC trial (PETREMAC)—PErsonalized TREatment of High-risk MAmmary Cancer. A total of eight arms had been utilized for the therapy of breast cancer. The primary outcome measures the value of predictive and prognostic markers for mutations in 300 cancer-related genes in the time duration of 10 years. Mutations were evaluated in breast cancer samples by next-generation sequencing before giving preoperative treatment. The secondary outcome measures therapy-induced genetic/epigenetic alterations in the tumor tissue, and the objective-response rate of personalized medication [64].

Gastrointestinal cancers account for more than a quarter of all cancer diagnoses and more than a third of all cancer-associated deaths globally. These are frequently discovered at a late stage when treatment choices are restricted. Liquid biopsy is one of the best options to screen the biomarkers at an early stage. In one of the recent investigations, researchers studied the differences in the proteomes of pancreatic benign and premalignant cysts on twenty patients with 12 males and 8 females having a mean age of 62 with the help of thermal liquid biopsy (TLB). Numerous common proteins were identified, and the researchers also developed a new TLB serum score based on certain characteristics that reveal cyst differences. The existence of a specialized TLB as a diagnostic tool for clinical samples from patients with unknown pancreatic cysts could be a significant benefit in the detection of premalignant pancreatic cancer lesions [65]. Another investigation is based on an inhibitory immune molecule, i.e., LAG-3 which suppresses the activation of T cells and secretion of inflammatory cytokines. T cell concentration in the colon cancer microenvironment is critical for the host's innate and adaptive immunity. In patients with stage II colon cancer, the expression of LAG-III on tumor-infiltrating lymphocytes (TILs) can predict the outcome. One hundred and forty-two stage II colon cancer patients were involved in the study. Their colon tissues were collected and immunohistochemical staining for LAG-3 was carried out on tissue microarrays (TMAs). TILs from both the tumor front and the

tumor center were tested for LAG-3 expression, which was graded as either positively or negatively. The disease-free survival (DFS) was the key terminal point of the experiment. The expression of LAG-3 on TILs was substantially related to an improved 5-year DFS in patients with stage II colon cancer. LAG-3-positive TILs on the tumor front were primarily responsible for the effect on DFS. LAG-3 testing could aid in predicting outcomes in patients with stage II colon cancer and possibly identifying those who would benefit from adjuvant treatment. As a result, LAG-3 could be used as a predictive biomarker in patients with stage II colon cancer [66].

One more investigation to show how metabolic evaluation can be utilized to improve diagnosis of the disease and patient prediction in urological malignancies, as an example of personalized medicine. With the recent introduction of immunotherapies and tyrosine kinase inhibitors (TKI)-targeted medicines, the therapeutic picture for metastatic renal cell carcinoma (mRCC) has substantially improved in recent years. In patients with clear cell renal cell carcinoma, deletions in 9 and 14 chromosomes can signal poor sensitivity to anti-PD-1/PD-L1 monotherapy [67]. The measurement of body composition, including characteristics like skeletal muscle density (SM), and visceral fat, is a new way of predicting health outcomes in mRCC patients treated with immune checkpoint inhibitors. Regarding the research in personalized medicine, Martini et al. suggest that the identification of risk factors based on body composition indicators such as total fat index could be predictive and prognostic of treatment outcomes in mRCC [68].

One of the main reasons for cancer-related mortality is lung cancer. It is difficult to make a timely detection of lung cancer using computerized feature selection from a vast number of features. Generally, physical characteristics are used in later stages of cancer diagnosis, while negative effects have already been developed because of aberrant somatic mutations. In a study, researchers have examined lung cancer-related altered genes that provide valuable insights into protein amino acid sequences to derive unique patterns that can be used to effectively predict cancer at its earliest stages.

Cardiovascular diseases

The leading cause of death globally is cardiovascular disease (CVD) [69]. If necessary, action is not implemented, the number of fatalities from CVD may exceed 23 million by 2030, which represents 30.5% of the global burden of disease [70].

The best type of research to assess the importance of particular genes is "Mendelian Randomization." Three main assumptions underlie Mendelian randomization: firstly, risk factors should be linked to genetic variation; secondly, genetic variation must not be linked with confounding variables; and lastly, only genetic variations should affect the result via risk factors [71]. The most prevalent genetic alterations are loss-of-function (LoF) mutations. Table 4 highlights the genes responsible for the major CVDs. The time is now right for the cardiovascular landscape to take a more individualize approach to therapy owing to newly discovered clinical conditions and new treatment alternatives. Researchers are stratifying the patients on the basis of genetic differences and then targeting the diseases with the help of personalized medicine [72, 73]. Fig. 3 highlights the biomarkers associated with heart failure.

Warfarin (VKORC1 encoded gene) and clopidogrel (encoded gene is CYP2C19), are two well-known examples of cardiovascular medications for which individual response is influenced by genetic polymorphism and are used to stop the clotting of blood [74]. Drugs that alter lipid levels and consequently lessen atherosclerosis and the incidence of myocardial infarction are affected differently by genetic variation. A severe side effect of statins is the mutation of the gene which affects the transporter SLCO1B1, a threat to myopathy patients [75]. Another instance is the inhibition of cholesteryl ester transfer protein by dalcetrapib, which is indicated to boost the production of high-density lipoproteins. A clinical trial is currently being conducted to even more thoroughly evaluate the possibility that patients with a particular polymorphism in the encoding gene adenylate cyclase 9 may be benefited from dalcetrapib [76]. The impact of the gut microbiota on the CVS is another developing field of study with the opportunity to culminate in personalized treatment. For instance, certain gut bacteria produce substances that can cause atherosclerosis or thrombosis by using specific food components. If gut bacteria-specific therapies can be created, profiling a person's microbiome might help determine the best course of therapy [77]. The development of a drug is very challenging, still, clinical trials give new hope for cost-effective personalized therapies.

According to the conventional medical paradigm, CVDs have become an economic and societal burden globally. A prospective, observational cohort study has been initiated in China on March 10, 2021, entitled "Precision Medicine Study on Cardiovascular Disease (PRECISE)" which is estimated to be completed by October 30, 2035. It involves the 20,000 participants of both sexes with monogenic CVDs enrolled in this trial after receiving their informed consent. At recruitment, the researcher will gather the participants' baseline clinical data, which may include a thorough physical exam, laboratory analysis of urine and blood, electrocardiography, a 24-h Holter, echocardiography, MRI, and other tests as needed. All patient's blood, saliva, urine, and feces are among the samples kept collected, as are the myocardium samples from patients who had cardiomyectomy surgery. To investigate the unique gene mutations, genetic risk

Table 4 Compilation of genes responsible for the different types of cardiovascular diseases

Cardiovascular diseases	Characteristics of the disease	Genes associated
Cardiomyopathies (enlargement, thickness, or rigidity of the heart muscle)		
Hypertrophic cardiomyopathy (HCM)	The heart muscle becomes thick	*Autosomal dominant genes* • MYH7 gene encodes the myosin heavy chain [102] • TNNsT2 encodes cardiac troponin T [103] • MYBPC3 encodes myosin-binding protein C [104] • TNNI3 encodes cardiac troponin I [105] *Syndromic genes without isolated left ventricular hypertrophy (LVH) including*, • Autosomal recessive GAA gene as in Pompe disease, X linked GLA which presents as Anderson-Fabry disease, FHOD3, encodes "Formin homology 2 domains containing 3" [106] *Genes with definitive role:* MYBPC3, MYH7, TNNT2, TNNI3, TPM1, ACTC1, MYL2, and MYL3 were categorized [107]
Dilated cardiomyopathy (DCM)	The heart muscle begins to dilate, stretching and becoming thinner	• Most common DCM-associated gene is TTN-truncation • TTN encodes Titin, which is the largest known structural protein of the heart, it attaches to the *Z*-disc from one side and expands to the *M*-line region of the sarcomere from the other side [108] • Approximately 5% of DCM's causes are due to LMNA missense and truncating mutations [109]
Restrictive cardiomyopathy (RCM)	The chambers of the heart become stiff over time	• TTR gene variants and APOA1 are the main genetic perturbations in amyloidosis [110] • There is a lack of adequate data about non-infiltrative RCM genes, nevertheless, TNNI3, TNNT2, TNNC1, TPM1, TTN, MYH7, MYL2, MYBPC3, MPN, DES, FLNC, LMNA, and BAG3 was labeled as associated genes in RCM [111]
Arrhythmias (mutation of potassium, sodium, and calcium ion channels and their interacting proteins)		
Long QT syndrome (LQTS)	fast, chaotic heartbeats (arrhythmias)	• LQT1: loss-of-function mutation in the KCNQ1 gene which encodes the α subunit of the slow rectifier current (IKS) [112] • LQT2: loss-of-function mutations in KCNH2, which encodes α subunit of the rapid rectifier current (IKr) [113] • LQT3: gain of function in SCN5A, which results in amplified late sodium current (INa) [114]
Brugada syndrome (BrS)	Heightened risk for ventricular tachyarrhythmias and sudden cardiac death	• Genetic alteration in the SCN5A gene [115] • CACNA1C, GPD1L, HEY2, PKP2, RANGRF, SCN10A, SCN1B, SCN2B, SCN3B, SLMAP, and TRPM4 are some other rare genes associated with Brugada syndrome [116] • Mutations in SCN10A, which encodes α subunit Nav1.8 sodium channel [117]

Table 4 (continued)

Cardiovascular diseases	Characteristics of the disease	Genes associated
Short QT syndrome (SQTS)	Movement of ions through channels within the cell membrane is affected marked shortened QT intervals and sudden cardiac death	• Potassium and calcium channelopathies are the main pathophysiologies in SQTS[118] • SQT1: KCNH2 • SQT2: KCNQ1 • SQT3: KCNJ2 • SQT4: CACNA1C • SQT5: CACNB2 • SQT6: CACNA2D1 [119]
Idiopathic ventricular fibrillation (IVF)	An exclusion diagnosis is made in a cardiac arrest survivor when there is no underlying etiology found	• DPP6 was reported in Dutch families [120] • CALM1 was reported in a Moroccan family [121] • RYR2 causes a leaky channel at diastolic levels of Calcium under non-stress conditions [122]
Coronary artery diseases (variants in two loci (LTA and LGALS2)) [123]		
LDL cholesterol metabolism	Increased blood pressure and blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels	LDLR, PCSK9, APOB, HNF1A [124]
Vascular remodeling/plague formation	Patchy intimal plaques (atheromas) that encroach on the lumen of medium-sized and large arteries	ADAMTS7, HDAC9, COL4A1, COL4A2 [125]

factors, and prospective targeted therapies, genomic testing will be carried out. The primary outcome of this investigation will measure the number of subjects with cardiovascular mortality and all-cause death with an average of 5 years. The secondary outcome will be investigated as the number of patients with cardiac failure, stroke, and malignant arrhythmia [78]. Another prospective randomized pharmacogenomic-based, four-treatment parallel cohort active comparator study had been conducted on 300 critical patients with hypertension who have never been treated before. All sexes 25–60 years of age are eligible for the trial. Every participant had their genetic analysis genotyped for SNPs (single-nucleotide polymorphisms) in initial genetic screenings with a custom SNP array and will then be medicated with 4 mg Peri (perindopril) or 12.5 mg HCTZ (hydrochlorothiazide) in accordance with their genetic makeup. As a control group, patients without any genetic information will be randomly assigned to either HCTZ or Peri therapy. There will be an 8-week treatment period and a 10–12-week study. It is the possibility of four cases: patient showing HCTZ profile and undergoing HCTZ treatment; patient receiving Peri therapy with a Peri profile; patient without a Peri or HCTZ profile, and therapy for the subject with both profiles are based on the profile with the greater proportion of positive contributors. The primary outcome measured systolic blood pressure and diastolic blood pressure within the time frame of 4–8 weeks. The secondary outcome ensures the implementation and updating of the genetic profile for both drugs by employing 128 distinct SNP variations [79].

Challenges

Despite all of PM's great potential and present advantages, certain constraints represent a threat to the emerging success story. To begin with, not all therapies can be customized. Personalization of therapy for common diseases is a common difficulty PM encounters in this sector. As much emphasis is placed on complex illnesses like cancer and metabolic disorders, common diseases contain a large range of genetic variants that are rarely researched [80].

An additional problem with personalizing common diseases is that rare gene discovery will result in millions of rare genes due to the vast population size, and personalized therapy will entail generating thousands of medicines for the same condition. This will certainly limit PM's application to common ailments like the common cold, malaria, and diarrhea [81].

Another disadvantage of PM is that drug response is influenced by extrinsic variables other than genes. Genomics and gene-based therapies have been in practice for several decades. Nevertheless, personalized gene therapy has witnessed only limited success. It has been well-reported that

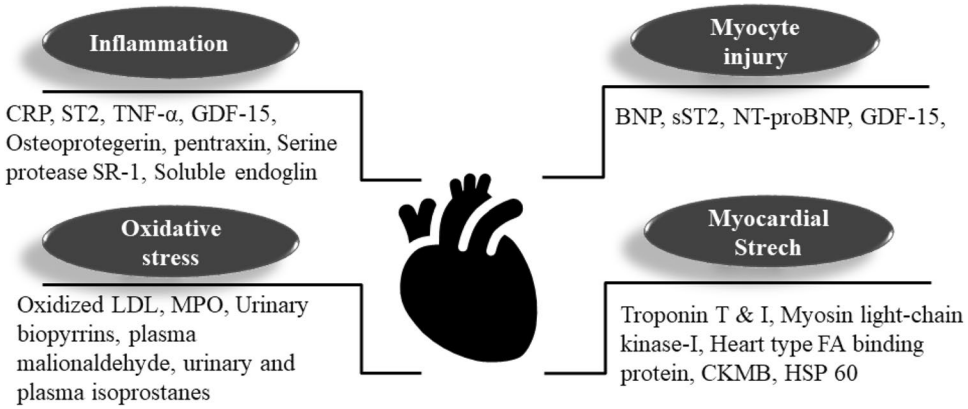

Fig. 3 List of biomarkers associated with the heart failure

introducing new genes into a biological system is extremely vulnerable to failure. New genes need to be integrated effectively for the desired response. Generally, the body's defense systems signal a potential turn-off towards unusually working genes. In addition, the genes that are delivered to an organ also need to be activated so that they could manufacture the necessary proteins. This has been seen as a challenge in itself, as newly introduced genes respond in varied ways. Correcting a wrong protein or a trait is the utmost requirement with any genomic personalized therapy. However, the challenges enroute to achieve this are enormous. The genetic response to medications is influenced by nutrition, lifestyle, and outbreaks. The latter means that someone may have a particular gene trait, but that trait is meaningless until they are subjected to an external disease [82].

Another stumbling block is the government's and other healthcare organization's insufficient assistance. Considering genetic variants manifest in a large ethnic area, PM should ideally be promoted over the world. PM has been recognized and included in health programs in industrialized countries such as the USA and Europe to promote its development. Countries that are already behind in traditional care will undoubtedly have fewer resources to devote to PM [83]. PM also must deal with moral, regulatory, and societal factors. There have been concerns that categorizing patients into cultural minorities will lead to societal segregation, something authorities are attempting to avoid. Moreover, the rejection of treatment to patients caused by genetic categorization may be misunderstood by the public at large and misinterpreted as treatment refusal [84].

In addition to the above-mentioned challenges, maintaining the quality of life-saving medical procedures and therapies has been a great challenge globally irrespective of developed, developing, or underdeveloped countries. The European Association for Predictive, Preventive, and Personalized Medicine (EPMA) has recommended an integrated strategy combining various faculties and disciplines to overcome this challenge. Although there have been several promising initiatives that have been introduced to implement the measures suggested by various authorities, there is still a need for consolidation and improvisation in policies and frameworks that are crucial for the success of predictive, preventive, and personalized medicine. Over the last century, scientific advancements have opened the path for improved treatment outcomes for a variety of ailments. Patient mortality is influenced by pharmacogenomic predispositions, the emergence of multidrug resistance, prescription, and formulation mistakes. The conception of "personalized" or "precision" treatments offers a way to solve these challenges and, as a result, lower mortality rates.

The underlying principles of genomic and personalized medicine will necessitate the construction, standardization, and unification among effective genomic tools into healthcare systems and clinical procedures as medical science embraces genomic techniques that allow more precise disease prognostication and therapies, such as "whole-genome" investigation of sequence variation, gene regulation, polypeptides, and metabolic products. These tools, when combined with genomic data, will enable a profound transformation toward a complete strategy that will detect individual risks and guide clinical treatment and strategic planning, laying the groundwork for a more educated and effective patient care approach. As a result, technical breakthroughs in genetics can be credited with guiding the healthcare sector toward individualized care, which has the potential to improve people's lives.

Conclusion and expert recommendations

A paradigm change in medical practice is currently taking place with the goal of addressing a disease by finding the unique fingerprint that the disease imprints on a person. As far as a customized data-driven approach, as made possible by the unification of multi-omics methods, may feature each patient individually. The moral, social, and legal implications of this task are numerous as discussed above in the challenges section [85]. Since the complexity

of a vast range of extragenomic parameters weakens the reliability of PM models based primarily on genomic data, numerous theoretical and methodological pillars upon which PPPM is founded need to be re-examined. Numerous genetic risk variations with negligible effects have been identified for most common diseases, making it challenging to draw a clear picture of who is truly at "risk" and for what.

The advancements and influence of preventive and personalized medicine in clinical practice will determine whether it becomes a fundamental part of diagnosing, treating, and preventing illness. Furthermore, ongoing genomic research, the integration of translational medicine and PM, the advancements in individual genetic analysis, and the documented evolution of traditional medicine to PM have already shown much progress. Numerous continuing genetic studies are aimed at laying a solid platform for preventive and personal medicine. Tremendous progress has been achieved in the genetic detection of breast cancer through molecules like hormone receptors and ribonucleic acid [86]. Nevertheless, such molecular-testing methods are rarely used to investigate the genetic foundation of disease onset and progression.

The Personal Genome Effort, started by Harvard University's George M. Church in 2005 with the hope of creating personal genomes accessible to the public and fostering quick interaction with interested parties at a reasonable cost, is yet another continuing genomic project. Personalizing illness risk factors, biological traits, and personal ethnic backgrounds is the goal of the obtained genetic data. Furthermore, another area of progress that points to PM is in the realm of Translational Science (TS). The transition of preclinical innovations to clinical use is the focus of TS [87]. The applications of TS comprise biomarkers to anticipate potency and evaluate toxicity, constructing animal models that imitate human patterns of disease, bioinformatics, and developing a comparable image analysis software both for experimental and clinical trials to decrease failure rates at subsequent stages of drug development [88]. In the future, instead of looking for imaginary "pathogenic targets" and "miracle cures," interventions should focus on figuring out how to "attenuate" the metabolomic pattern of a disease in an "accurate" and effective way. Innovative methods showed that it was possible to identify patient subsets with the same disease who had unique active mechanisms and distinct pathophenotypes that could be successfully addressed with quite different treatments [89, 90]. Such screening is carried out using a systems biology technique and does not depend on specific targets as it concentrates on the whole system behavior under investigation.

Expert recommendations:

- Establishment of an integrated approach for successful and effective implementation of the policies confined to PPPM as recommended by the EPMA.
- Consolidation and constant improvisation in policies and frameworks relevant to genomic sequencing that are crucial for the success of predictive, preventive, and personalized medicine should be formalized.
- The influence of genome sequencing in preventive and personalized medicine will determine whether it becomes a fundamental part of diagnosing, treating, and preventing illness. Therefore, strategies must be put in place to make PPPM influential.
- Further large-scale in-depth clinical studies are crucial to overcome the challenges associated with genome-based personalized therapy.

In conclusion, it could be observed that the overall relevance of PPPM strategies may vastly depend on action plans that are laid for efficient implementation of the policies and careful planning by the government agencies dealing with this. Research on the sustainability of the measures adopted, patient-focused outcomes, and disease management goals may be crucial for the success of a PPPM plan.

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Declarations

Competing interests The authors declare no competing interests.

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