The State of the Art and the Future of Precision Medicine: A Comprehensive Literature Review

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Abstract

Precision medicine is a new discipline of medicine that attempts to deliver individualized therapy and prevention based on each individual's clinical, genetic, genomic, and environmental data. Precision medicine treats each patient as an individual rather than as a general case of a disease. By offering the appropriate medication to the right patient at the right time, precision medicine has the potential to enhance health outcomes and quality of life. However, there are certain problems and limits to precision medicine, such as high prices, privacy concerns, ethical concerns, and impediments to integration into clinical practice. The text examines precision medicine's history, applications, technology, and future possibilities. It recounts the history of precision medicine from ancient times to the present, emphasizing some of the field's milestones and successes. It examines genetics, molecular diagnostics, environmental exposures, lifestyle habits, societal influences, and microbiome composition, among other elements and areas of precision medicine. It also investigates the role of precision medicine in the COVID-19 pandemic, as well as the obstacles and prospects for continued precision medicine research and application in health systems. It finishes by identifying potential future research and innovation paths in the realm of precision medicine.

Introduction

Personalized medicine or precision medicine (PM) is an advancing healthcare field that is based on each person's specific clinical, genetic, genomic, and environmental information (1). Precision medicine takes the patient into account rather than the illness. A disease can affect a number of patients but they might react differently to the same therapy because every patient is distinctive. To address individual demands, bio-clinical discoveries must be applied particularly to the subject at hand (2) [figure 1].

On the other hand, PM comes at a cost, including expenses for data collection, processing, and storage as well as for training the

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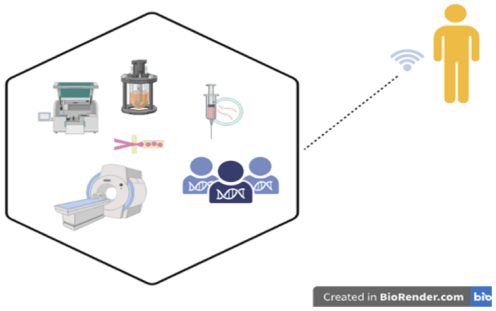

Figure 1: Role of bioclinical discoveries in addressing individual demands

medical staff that handle bio-data. In addition, there may be some privacy issues as a result of the necessity for extensive data collection, which may be exploited for unethical purposes (3). However, personalized medicine has the potential to increase the quality and longevity of human lives by providing "the right treatment to the right patient at the right time" thus reducing health costs (2). The success of PM depends on the development of precise diagnostic tools that can recognize patients who will respond favorably to targeted therapy (4). Precision medicine has achieved some important milestones over time. The PM concept first appeared in the treatment of malaria in around 2700 BC by addressing the need for improved diagnostic tools and treatment plans depending on the genetic makeup of the patient. (5) [figure 2].

Figure 2: Personalized Medicine Timeline

The classical period from Herodotus, when the practice of medicine was split into categories and every doctor was a specialist for one disease, one body part, further clarified the adaptation of that ancient "Egyptian Medicine "to an individual's health situation (6). This is the first evidence of personalized medicine, since the doctors understood that grouping diseases into categories based on the sections of the body might help them better understand the disease and as a result, produce more effective treatment. Greeks were enthralled by this method of treatment, which is why they frequently praised Egyptian medicine in their treatises (6). To provide good treatment at that ancient time, doctors had to consider the patient's wants and beliefs (7). According to Hippocrates, "Diseases might be treated from their origin". As a result, they focused more on the personalized approach to the disease (8). Early in 1950s, researchers began to gradually understand the need of evidence based medicine. The approach of today's "Personalized Medicine" was founded on the prediction of drug response (9). Despite that PM has received a lot of attention recently, there are still a number of barriers preventing its use in clinical practice. The COVID-19 epidemic has recently brought these limits to light (5). However, the genetic makeup of each patient in the COVID-19 pandemic is widely acknowledged to be one of the key determinants of medication effectiveness and toxicity (10). Based on the latest genome-wide association summary statistics for severe COVID-19, a recent study indicated an increased risk of severe COVID-19 for individuals who had genetically raised levels of circulating ACE2 protein (11). The early applications of personalized medicine were in oncology and genetics, particularly in genomics, a subfield of genetics that investigates how different people respond to different therapies (12). Personalized medicine's various applications aim to use broad, precise and unbiased data for providing special critical care (13). For instance, one of its primary uses is genomics, which aids in therapeutic efficacy and safety determination based on individual genetic differences (14). Molecular diagnostics is another significant aspect of personalized medicine for patients with cancer, in

which treatment and diagnosis are integrated, and plays an essential role in the progression of personalized medicine by early detection and diagnosis, predicting disease prognosis, guiding treatment selection, identifying drug resistance as well as enabling clinical trials and drug development. (15). Nowadays PM includes the incorporation of new technologies such as DNA sequencing, proteomics, imaging protocols, and wireless health monitoring devices (16). Facilitated by analytics, these technologies have been delivering a comprehensive picture of molecular and cellular alterations underlying various diseases which play a vital role in providing tailored patient management to each person (17). Several technologies must be established, standardized, and integrated in order to efficiently apply personalized medicine in health systems. For predictive information, these methods include family history, health risk assessment, and clinical decision support. Using these methods in conjunction with genetic data is critical for detecting individual risk and influencing treatment decisions [figure 3].

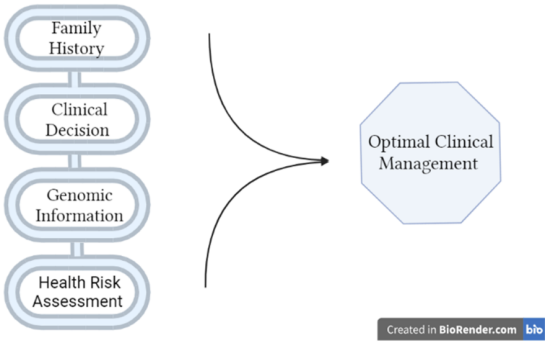

Figure 3: Fundamentals of Personalized Medicine

Additionally, a standard Health Risk Assessment is one of the most important fundamental bases of personalized medicine that can assess each person's chance of developing the most common chronic diseases. All of this lays the foundation for a more informed and practical approach to patient care (1). Nonetheless, there are some future challenges facing the integration of PM in the healthcare system. These include looking for new modes of characterizing patients, therapy personalization, developing individual medications and disease prevention methods. An example is using human cell cultures for applying more relevant models which will improve the personalized selection of medicines based on disease's nature and patient's comorbidities (16). However, overcoming several barriers in education, accessibility, regulation, and reimbursement is crucial for further integration of personalized medicine into the clinical (18).

Utilization of Personalized Medicine in Low- and Middle-Income Countries

There is a considerable divergence across the third world and developed countries between people distribution and global health expenditures (19). In 2010, a study conducted a systematic analysis to all data sources available for spending by the government on health in developing countries. It stated that public financing of health from local sources has increased globally by 100 % from 1995 to 2006 (20). However, a majority of low and middle-income countries experienced a reduction of funding during the same time. Personalized medicine will increase these disparities and many low and middle-income countries may not benefit from the applications of personalized medicine due to the high costs, limited access to healthcare facilities, ethical and legal concerns and the lack of infrastructure and technology. (21). Nevertheless, in the last few years some promising large genomic programs have emerged from the Middle East region and played a vital role in the understanding of the unique genetic construct, in addition, they served as the basis for personalized medicine in the region (22).

Applications of precision medicine

Pulmonology

The use of proteomics is one of the promising applications of precision medicine that has been widely used in respiratory diseases [Figure 4].

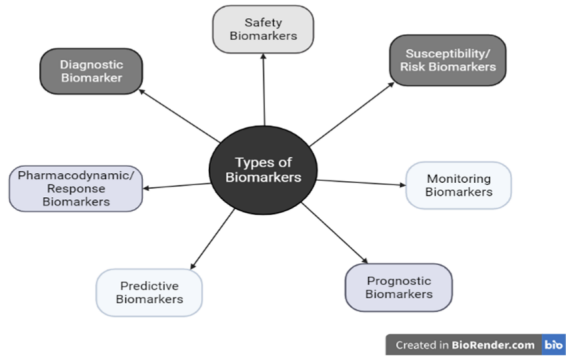

Figure 4: The seven types of biomarkers according to "Atlas Antibodies"

Proteomics recognizes proteins related to a particular disease in order to identify novel biomarkers that can be used to guide therapeutic interventions. This is done by obtaining samples from different sources such as serum, Broncho alveolar lavage (BAL), and tissues. Another potential application is single-cell transcriptomic analysis, which is a form of single-cell RNA sequencing that uses the RNA concentrations in individual cells to count the level of gene expression (23). These technologies have been employed in several pulmonary conditions such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis as illustrated in Supplementary Table 1. Asthma: Several studies applied proteomics in the personalized diagnosis of asthma (Supplementary Table 1). A study conducted by Wu and colleagues on four asthmatic patients and healthy controls using BAL fluid analysis after segmental allergic challenge (24). SDS-PAGE separation and Nano liquid chromatography-mass spectrometry (LC-MS/MS) analysis were used to identify potential biomarkers expressed differently in asthmatic (24). This study identified more than 1500 proteins, 160 of which were selected to be differently expressed in challenged asthmatic patients (24). Examples include serum proteins, metabolic enzymes, calcium-binding proteins, and matrix metalloproteinase such as MMP-9 (a potential biomarker) and its inhibitor TIMP-1(2). Cederfur and colleagues applied affinity chromatography of BAL fluid to analyse galectin-3 and galectin-8 in order to identify the profile of galectin binding proteins in the airways (25). Authors took sampled from four mild asthmatics and four healthy controls and then compared galectin-binding glycoforms using shot-gun proteomics(25). LC-MS/MS analysis of BAL fluid identified 175 proteins of high certainty to asthmatic samples, of which a glycoform haptoglobin was identified as a gelactin-8 binding protein exclusively expressed in asthmatics (25). O'Neil et.al. analysed bronchial biopsies from healthy controls and asthmatic subjects treated with budesonide, and identified seven proteins differently expressed in asthmatics compared to controls (26). These included proteins involved in cellular movements and immune cell trafficking with roles in collagen fibrillin formation, protein elongation, and chemotaxis (26). Moreover, Ingenuity Pathways Analysis (IPA) of these proteins showed associations with multiple biological functions including respiratory disease, cell to cell signalling, haematological system development and function, and tissue development (26). Decreased expression levels of alpha-2-macroglobulin and vimentin suggested possible suppression of inflammation in response to budesonide (26). The authors proposed that these proteins reflect the proteomic changes caused by glucocorticoids, whereas the significantly changed proteins in the placebo-treated patients reflect a natural progression of the diseases (26). Single cell transcriptomics was also applied in asthma (Supplementary Table 1). Wang et. al applied single-cell RNA deep sequencing to elucidate the immune cells landscape of lung

tissue in steroid-resistant asthma exacerbation (27). To achieve this goal, they used a mouse model of lipopolysaccharide (LPS)-induced steroid-resistant asthma exacerbation, which was induced by house dust mite (HDM) (27). By analysing CD45+ immune cells in lung tissue of mice treated by either saline, HDM/LPS +vehicle (VEH), or HDM/LPS +dexamethasone (DEX), single-cell RNA sequencing identified 102 distinct cell clusters with specific molecular markers (27). Among these, 20 major clusters of cells were identified as known immune cell types, including four subpopulations of monocytes, innate lymphoid C2 (ILC2), T regulatory cells (Tregs), and basophils (27). It's worth mentioning that Specific cell clusters of basophils, (ILC2, and CD8+ memory T cells were the predominant sources of interleukin-4 (IL-4) and interleukin-13 (IL-13) transcripts whose expressions resulted in dexamethasone resistance (27). COPD Ohlmeier et al. analysed lung tissue and sputum of severe, stage IV COPD patients and normal subjects using bi-dimensional gel electrophoresis (2-DIGE). Surfactant protein A (SP-A) was highly expressed in COPD samples compared to normal or fibrotic tissue taken from Idiopathic Pulmonary Fibrosis (IPF) patients , a result that was confirmed using western blotting and immunohistochemistry (28). In addition, SP-A was detected in alveolar type II cells and macrophages both in the control and in the COPD lungs (Stages II-IV) indicating no differences in SP-A localization between the patient groups (28). Moreover, morphometric quantification of SP-A overexpressing areas showed a 3.7-fold elevation in Stage II-III COPD, 3.4-fold in Stage IV COPD, and 7.5-fold in samples of alpha antitrypsin deficiency in comparison to the control, significantly suggesting SP-A as a potential COPD biomarker (28). In another study using 2-DIGE, MS, and western blotting, Ohlmeier and colleagues analysed lung tissues from IPF and COPD patients to investigate the difference in the receptor for advanced glycation end products (RAGE) isoforms including full-length RAGE (FL-RAGE), C-terminal processed full-length RAGE (c-RAGE), and endogenous secretory RAGE (esRAGE) in both diseases (29). The study showed that the expression of FL-RAGE and c-RAGE but not esRAGE were decreased in COPD samples (29). RAGE was 2.1 and 3.4 folds lower in mild COPD and severe COPD, respectively as compared to normal individuals, hence c-RAGE expression correlates with COPD progression (29). In regard to IPF, the three RAGE variants declined. Therefore, c-RAGE can be used as a biomarker to monitor the progression of COPD (29). Pastor et al. extracted proteins from BAL samples taken from patients with either COPD only, lung cancer (LCA) only, or both (COPD/LCA) (30). Then, extracted proteins were separated into spots by 2-DIGE and examined by matrix-assisted laser desorption/ionization-time of flight (MALTI-TOF) mass spectrometry (30). Results showed that 6 proteins were up-regulated in LCA group, while 1 protein was down-regulated in comparison to the control group (30). On the other hand, ALDH3A1, AKR1C3, PKM2, PYGM and PPIA were found to be significantly up-regulated in both LCA and COPD/LCA groups in comparison to the healthy control group (30). In addition, CAT, PRDX1, PRDX2, and PRDX5 were up-regulated in COPD and COPD/LCA groups when compared with LCA-only group (30). When validated by western blotting, the results showed that Heat shock protein 70 (HSP70) expression is increased in all 3 pathological study groups (COPD, LCA, LCA/COPD) as compared to the control group (30). The PKM2 protein expression was increased only in patients with LCA, with or without COPD, but not in the COPD or control groups (30). On the other hand, PDX1 was incrementally expressed in COPD/LCA and COPD only groups, as compared to the LCA and control groups (30). Finally, ARK1B10 shows greater expression only in the LCA group (30). These findings demonstrate that these proteins can be employed as biomarkers for diagnosis and prognosis of

both diseases early during the course of illness. Cystic Fibrosis Cystic fibrosis (CF) is an autosomal recessive disorder caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene. CFTR is a protein chloride channel that belongs to the family of adenosine triphosphate-binding cassette (ABC) transporters (31). Proteomics have been implemented in understanding proteins involved in CF. Pollard et al. compared protein expression in CF cells with wild-type CFTR-repaired matched controls, which resulted in identifying 20 differently expressed proteins (32). Srivastava et.al. analysed 507 proteins in CF sera using an antibody capture microarray, which revealed that 46 proteins were elevated in CF patients compared to controls, which were validated by reverse capture protein microarray (33). Proteomics was also used to compare respiratory exosomes between CF, primary ciliary dyskinesia, and asthma. Virginie et.al. extracted respiratory exosomes from 12 patients using BALF then utilized immuno-electron microscopy and western blotting to characterize these exosomes (34). Mass spectrometry was used to analyse these proteins, and allowed the identification of 665 proteins that can be reliably quantified. Of these, 14 proteins were differently expressed among study samples (34). After classifying these proteins into different clusters according to their protein abundance profiles, 4 proteins were found to be increased specifically in CF samples compared to PCD and asthma, which are Neutrophil gelatinase-associated lipocalin (LCN2), Superoxide dismutase (SOD2), Glutathione peroxidase 3 (GPX3), and S100A12 Synaptosomal-associated protein 23 (SNAP23) (34).

Endocrinology

Diabetes Mellitus Precision medicine can be used for proper classification of monogenic diabetes mellitus types. The most studied type of monogenic diabetes is maturity-onset diabetes of the young (MODY) which have several subclasses (35), as well as in other applications [Figure 5].

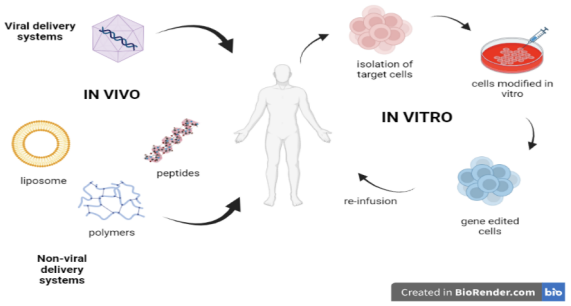

Figure 5: Approaches to gene therapy

For example, MODY 3 (which is the most common form) is caused by mutation in HNF1A gene which encodes the transcription factor hepatic nuclear factor 1- (HNF1-) which is structurally similar to hepatic nuclear factor 4- (HNF4-), the mutated gene in MODY1 (35). Diagnosis of MODY1 or MODY3 is important for proper clinical therapy because those patients have been found to be hypersensitive to sulfonylureas (36) . Hypersensitivity in these patients is due to decreased expression of these two genes in the liver, resulting in a higher circulating levels of sulfonylureas which means that MODY1 and MODY3 patients need approximately one-tenth of the sulfonylureas dose (37). On the other hand, mutations in the gene GCK encoding the enzyme glucokinase is another cause for MODY, specifically resulting in MODY 2 (38). Interestingly, MODY 2 patients don't progress to the microvascular and macrovascular complications associated with diabetes mellitus at a rate greater than non-diabetic populations (38). Thus, they don't need pharmacological therapy, although they may present with mild hypoglycemia which may lead to insulin-resistance (38). Therefore, proper diagnosis of patients with these types by determining the correct genetic defect will greatly affect the therapeutic plan of each patient. In addition, precision medicine has been implicated in discovering biomarkers for both diabetes and prediabetes. For example, non-coding RNAs (NCRNAs) are functional types

of RNA that are not involved in protein synthesis, though are involved in the development of many diseases (39). Certain types of NCRNAs were recognized as expressed biomarkers in many tissues in diabetes, namely microRNAs (miRNAs) and long non-coding RNAs (LncRNAs) (39). Many studies found that miRNA-376, miRNA-432, miRNA-200, and miRNA-16 were expressed in pancreatic beta cells (40),(41),(42). Other studies demonstrated the expression of LncRNA H19, LncRNA MEG3 , and LncRNA MALAT1 in pancreatic beta cells as biomarkers (43),(44),(45). On the other hand, biomarkers were identified for prediabetes and their disease progression. Alfaqih et al. analysed serum samples of 130 subjects with prediabetes and 130 controls and genotyped them for three single nucleotide polymorphisms (SNPs) in the ADIPOQ gene; namely rs266729, rs1501299 and rs2241766 (46). They found that adiponectin lowers the risk of prediabetes. In contrast, the GT genotype of rs1501299 increased the risk of prediabetes, in addition to TT genotype (46). Leptin was also linked with increasing risk of prediabetes. Aljunabi et al. analysed serum leptin of 122 prediabetics and 122 controls and investigated the association of three genotypes of the LEP gene with prediabetes using PCR-restriction fragment length polymorphism (47). They found that leptin levels were significantly increased in the prediabetic group, with GA genotype and A allele of rs2167270 being significantly associated with an increased risk of prediabetes morphism (47). Single-cell RNA sequencing was implicated in revealing the cell landscape in may tissues in diabetes. Using single-cell transcriptomics, Theocharidis et al. profile cells from the foot, arm, and peripheral blood mononuclear cells, which revealed enrichment of a unique population of fibroblasts overexpressing MMP1, MMP3, MMP11, HIF1A, CHI3L1, and TNFAIP6 and increased M1 macrophage polarization in the diabetic foot ulcer patients with healing wounds (48) . Lu et al. analysed data of three human diabetic kidneys and their controls to study potential landscape of the immune cells reactions and identify potential gene expression in these cells, which revealed that differentially expressed marker genes of immune cells were EIF4B, RICTOR, and PRKCB (49). These genes were significantly enriched in the mTOR pathway, which were confirmed to be up-regulated in diabetic nephropathy (49). Supplementary Table 2 summarizes the potential applications of precision medicine as shown in these studies. Thyroid diseases Proteomic profiling and other techniques such as single-cell sequencing and organoid culture were used to study potential biomarkers in many thyroid diseases, as well as to further understand the pathogenesis of these diseases (Supplementary Table 3 & Figure 6).

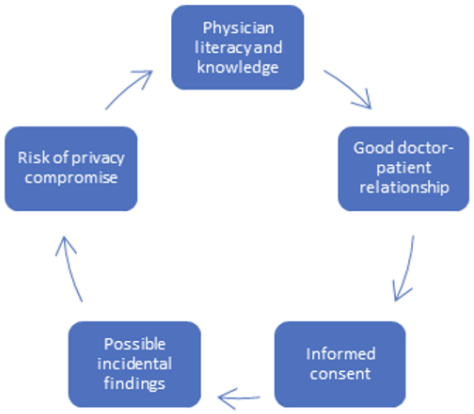

Figure 6: The interconnected cycle of PM ethical issues.

Ben abdel-kamel and colleagues investigated the urinary proteome of patients with hyperthyroidism by analysing urinary samples of nine patients who were age-matched with healthy subjects, before and after antithyroid treatment carbimazole (50). They used 2-DIGE and MALTI-TOF mass spectrometry to determine the difference in urinary protein abundance between hyperthyroidism patients and euthyroid controls, which revealed significant differences in abundance of 35 pro-

teins, with 25 proteins being up-regulated and seven down-regulated proteins in samples of hyperthyroid subjects (50). Up-regulated proteins included serotransferrin, transthyretin, serum albumin, ceruloplasmin, and alpha-1B-glycoprotein (50). On the other hand, the notably down-regulated urinary proteins were plasma kallikrein, protein glutamine gamma-glutamyl transferase, and serpin B3 (SERPINB3) (50). In addition, Xio et al. studied samples taken from 24 patients of Hashimoto thyroiditis (HT) and healthy subjects showed that 125 proteins were differently expressed in HT group, in contrast to the control group (51). After further screening, 44 proteins remained, of which 26 proteins were highly expressed in HT, with 18 proteins being relatively low (51). Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis on the up-regulated and down-regulated protein indicated that up-regulated proteins are related to cell adhesion, gene expression, and lipid transport. While GO analysis on down-regulated proteins revealed that enzyme inhibitor activity, redox reactions, and ubiquitination-related protein degradation pathways were significantly enriched in HT patients (51). A large proportion of proteins up-regulated in the HT group was related to immune response, such as annexin A6 (ANXA6), calreticulin (CALR), and cyclase associated actin cytoskeleton regulatory protein 1 (CAP1) (51). The study also examined the gene expression levels of four chemokines associated with HT after organoids culture, among which CCL2 and CCL3 chemokines where significantly up-regulated (51). This may suggest that HT organoids from HT patients represents the characteristics of HT tissue in a good way. Proteomic profiling was also applied in papillary thyroid cancer (PTC). Luo et.al. studied serum exosomes characterize the biological functions of serum-purified exosomes (SPEs) in PTC patients with and without lymph node metastasis (LNM) in addition to healthy subjects (52). Using a combination of LC-tandem mass spectroscopy analyses and TMT labelling, 1569 proteins with two or more unique peptides was identified, of which 697 differently expressed proteins were found in PTC samples of patients with LNM (52). Notably, biological pathway analyses showed that integrin signalling was activated in SPEs of PTC patients with LNM compared to those without LNM (52). Wei et al. performed proteomic profiling for the global and acetylated proteins of PTC (53). Specimens of cancer tissue and adjacent normal tissue were taken from ten female patients with Tumor-Node-Metastasis (TNM) stage III PTC (53). After separately applying TMT labelling and LC-MS/MS methods to the assays of global proteomics and acetylated proteomics, 147 among 1923 proteins in tumour tissue were considered differently expressed proteins in global proteomics, with 78 up-regulated proteins and 69 being down-regulated (53). On the other hand, 57 out of 311 proteins identified as acetylated proteins in tumour tissue were identified as differently expressed acetylated proteins, including 32 up-regulated and 25 down-regulated proteins (53). In addition, single-cell RNA sequencing is used to depict the local cell landscape in thyroid-related diseases. Li et al. used single-cell RNA sequencing to characterize the changes at the transcriptional level of the cellular components involved in orbital connective tissue in thyroid-associated ophthalmopathy (TAO) (54). The study showed that lipofibroblasts with RASD1 expression were significantly detected in inflammation and adipogenesis associated with TAO (54). The study also showed a notable role of ACKR1+ endothelial cells in TAO pathogenesis (54). CD8+ T cells showed the terminal differentiation phenotype (B3GAT1+KLRG1+) in orbital connective tissue (54). In addition, CD8+/CD57+ cytotoxic T lymphocytes where found to be two sources of IFN-, which plays an important role in TAO with its ability to induce production of multiple chemo-attractants and glycosaminoglycan by orbital fibroblasts (55). The study showed that C4+ T cells highly expressed CCR7 and PDCD1 which is a T cell exhaustion marker

(56),(56). On the other hand, CD8+ T cells showed the terminal differentiation phenotype (B3GAT1+KLRG1+) in orbital connective tissue (Z. Li et al. 2022).

Rheumatology

Ankylosing spondylitis Ankylosing spondylitis (AS) is a chronic, rheumatologic diseases characterized by multiple joints inflammation (57). Fischer et al. used Nano LC-MS/MS to analyse serum proteins from 18 AS patients and nine age and gender-matched healthy subjects (57). The study identified 316 proteins, 22 of which were either up or down-regulated in AS patients compared to healthy controls (57). C-reactive protein (CRP), complement proteins, amyloid P-component serum protein (APCS) and Serpin3A were among the up-regulated proteins, whereas TF Serotransferrin, SERPINA6 Corticosteroid-binding globulin, and TTR Transthyretin were among the down-regulated proteins. In addition, APCS and inter-alpha-trypsin inhibitor 2 (ITIH2) revealed high diagnostic value for AS using "Receiver Operating Characteristic Analysis" of combined serum levels of these two proteins (57). Blood components were analysed in many studies to identify potential biomarkers that can aid the clinical diagnosis of the diseases. Liu and colleagues analysed serum proteins from fifteen AS patients and sixty health subjects using TMT-based quantitative proteomic study (59). The results identified 762 proteins from the sera of these patients, of which 46 proteins were up-regulated and 56 were down-regulated in AS patients compared to healthy subjects (59). Among them, C-reactive protein (CRP), complement factor H-related protein 3 (CFHR3), -1-acid glycoprotein 2 (ORM2), serum amyloid A1 (SAA1), fibrinogen (FG-), and fibrinogen (FG-) were the most significantly up-regulated proteins associated with inflammation (59). On the other hand, S100A8, fatty acid binding protein 5 (FABP5), and thrombospondin 1 (THBS1) were the most notably down-regulated proteins (59). Yu et al. performed systemic proteomic and phosphorylation analyses of peripheral blood mononuclear cells (PBMCs) to identify potential pathways involved in the pathogenesis of AS (60). LC-MS/MS revealed 782 differentially expressed proteins (DEPs) and 122 differentially phosphorylated proteins (DPPs) in AS patients compared to healthy subjects (60). The authors verified the DEPs using parallel reaction monitoring (PRM) analysis. It showed that multiple proteins involved in antigen processing and presentation pathway such as HSP90AA1 and HSPA8, platelets activation including ITPR1, MYLK and STIM1, and leucocytes trans-endothelial migration such as MYL12A, MYL9 and ROCK2 pathways were highly expressed in PBMCs of AS patients (60). Supplementary Table 4 summarizes the features of several applications of precision medicine in ankylosing spondylitis.

Haematology

Hemoglobin diseases With regards to hemoglobin diseases, two technologies have made progress lately, which are gene therapy and genome-editing technology (61). Gene therapy means the insertion of a functioning copy of the hemoglobin (Hb) gene into the patient's blood stem cells using a lentivirus vector (61). This technology was investigated in many studies, for example, a study conducted by The San Raffaele Telthon Institute which evaluated safety and efficacy of autologous hematopoietic stem cells genetically modified with GLOBE lentivirus (62). On the other hand, genome-editing technology implies deleting, repairing, replacing or switching off defective genes with a healthy copy (61). This approach is believed to be more effective in diseases affected by a single gene. One example of using this technology is the application of fetal hemoglobin in the treatment of sickle cell disease or thalassemia, given the fact that fetal hemoglobin can relieve some complications of these diseases (63). Genetic association studies revealed that sequence variants in the

gene BCL11A can be a candidate negative regulator of gamma-globin expression which affects fetal hemoglobin levels, making it a promising therapeutic target (64). Thrombotic thrombocytopenic purpura Precision medicine was also applied in many thrombotic diseases, such as thrombotic thrombocytopenic purpura (TTP). TTP is a systemic disorder characterized by platelets clumping in the microvasculature resulting in the damage of many organs such as the heart, kidneys, and brain. It arises from autoantibodies directed toward the enzyme ADAMTS13, resulting in its congenital deficiency or inhibition (61). Sequencing analysis of ADAMTS13 gene has been performed in patients with congenital TTP demonstrating more than 150 mutations (65). Other candidate genes in acquired TTP were discovered to be targets for drug discovery, such as HLAs DRB1-11 and DQB1-03 which were found to be susceptibility alleles, and DRB1-04 which had a protective effect against the development of TTP (66).

Dermatology

Precision medicine is applied to many dermatological conditions, especially inflammatory diseases such as atopic dermatitis and psoriasis, using a modern technique called single-cell RNA sequencing. The main aim is to identify reliable biomarkers and promising targeted therapies applied to each disease specifically (Supplementary Table 5). Regarding atopic dermatitis (AD), He et al. studied lesional and non-lesional samples taken from patients with AD and healthy controls (67). COL6A5+ COL18A1 + fibroblasts were found to be novel cell sub-populations unique to AD skin lesions (67). In addition, CCR7-expressing dendritic cell population was found to be specific to AD lesions (67). Also, Salimi et.al. showed that the number of innate lymphoid cells 2 (ILC2) which are implicated in the pathogenesis of AD, was significantly higher in lesional skin biopsies from patients with AD as compared to healthy individuals (68). In case of psoriasis, it's well documented that CD8+ T-cells increase in psoriatic lesions although these cells are phenotypically heterogeneous and have different properties regarding their functions (69). Liu et. al found that two pathogenic cytotoxic type 17 T-cell subsets of CD8+ were recognized in psoriatic skin biopsies from 11 patients and 5 healthy individuals via single-cell transcriptomics (70). Penkava and colleagues applied single-cell sequencing on samples of synovial fluids taken from patients with psoriatic arthritis (71). They found that CD8+ T cells expressing CXCR3 were abundant in samples of psoriatic arthritis, in addition to elevated expression levels of ligands CXCL9 AND CXCL10, which give a clearer picture of the immune cells landscape involved in psoriatic arthritis (71).

Transplantation surgery

Precision medicine was employed in many aspects of solid organ transplantation, as it gives the ability to discover new biomarkers to predict or monitor the rejection or tolerance state of the graft. In addition, to further elucidate the immune cells subtypes that are involved in these reactions and reveal their characteristics. Moreover, compare the unique features of the signalling pathways between different cellular sub-groups (Supplementary Table 6). Proteomic studies were used for many types of transplantation to elucidate the immune cells landscape of many rejection reactions and determining potential biomarkers to monitor the success of transplantation procedures. Cheng and colleagues identified 18 differentially expressed proteins in a rat model of acute rejection hepatic allograft compared to matched-tolerance allograft (72). Among these, 4 proteins were found to be up-regulated, such as serotransferrin precursor and Hemopexin precursor, which belong to cell proliferation and transport (72). In a study conducted by Massoud et al., serum samples from patients with acute cellular rejection (ACR) and a control group of liver transplantation patients were analysed. The results revealed 41 dif-

ferentially expressed proteins in the experimental group, of which 28 were up-regulated while 13 were down-regulated in the ACR group as compared to the non-ACR group (73). The most significantly up-regulated proteins were Ubiquitin-conjugating enzyme E2, HSP60, and NFAT1 (74). On the other hand, the most significantly down-regulated proteins were Human apolipoprotein CI, Nuclear protein, and Zinc alpha-2-glycoprotein (73). Proteomic studies were also applied to elucidate biomarkers for delayed graft function (DGF) in kidney transplantation. Hu et al. analysed the serum of 27 recipients who had undergone kidney transplantation, of which 11 recipients were complicated with DGF (74). The results showed that plasma Corin level was significantly decreased in recipients with DGF as compared to recipients without DGF. Plasma Corin was also found to be down-regulated in mouse model with induced renal ischemia/reperfusion injury, which suggest that Corin can be a potential biomarker for DGF after kidney transplantation (74). Smith et al. analysed serum samples from ten kidney transplant patients before and two days after transplantation, 5 of which were diagnosed with DGF (75). The results showed that 34 candidate proteins were significantly different in DGF and non-DGF groups (75). Among these, aminoacylase-1(ACY-1) was undetectable preoperatively but increased markedly postoperatively, particularly in the DGF group, and was prioritized for further investigations. Overall, the study revealed a potential prognostic utility of serum ACY-1 levels for long-term outcomes in patients with delayed graft function following renal transplantation (75). Single-cell sequencing is also applied in solid organ transplantation to define the transcriptomic landscape involved in the immunologic reactions associated with these conditions. Li et al. analysed PBMCs and liver tissue samples from 4 transplantation patients and 3 healthy subjects to understand the immune cells heterogeneity in liver transplantation (76). The study found that the proportion of CCR6+/ CD4+ T cells increased within liver transplant tissue in addition to exhausted CTLA4+/CD8+ T cells and proliferating MKI6+/CD8+ T cells which were also significantly increased (76). Furthermore, the study identified LDLR as a novel marker of activated Myeloid-derived suppressor cells (MDSC) to prevent liver transplant rejection (76). To further define the transcriptomic landscape in Chronic Antibody-Mediated Rejection (cABMR) after renal transplantation, Kong and colleagues analysed PBMCs from cABMR patients and control subjects (77). The study showed that genes associated with pro-inflammatory response and immune regulation such as MTND6, CXCL8, NFKBIA, NFKBIZ were up-regulated in T- and B-cells (77). Moreover, the authors found that differentially expressed genes (DEGs) in gamma-sigma T cells, CD8 effector T cells, and CD8_MAI T-cells were up-regulated in the cABMR group (77). These genes include MT-ND6, CXCL8, S100A9, and NFKBIA. It's worth mentioning that the u-regulated expression of MT-ND6 may be associated with mitochondrial oxidative stress, whereas CXCL8 and S100A9 are involved in the activation of neutrophils (77). The findings of these studies can provide a large pool of potential biomarkers and targets for individualized therapy (Supplementary Table 5). Pharmacogenomics and personalized medicine Pharmacogenomics (PGx) is concerned with investigating how a person's reaction to drug therapy, including drug sensitivity, resistance, and toxicity, is influenced by genetic variations. (1). Each person's genomic variation heavily influences the efficacy and toxicity of drug treatment. (2) The goal of pharmacogenomics is to develop personalized and targeted therapy based on a person's genomic variations to optimize drug treatment efficacy and reduce toxicity. (3). This requires identifying the association between a genotype and a drug-induced phenotype by analysing the pharmacodynamics and pharmacokinetic effects of the drug. (4). Advanced sequencing technologies, including whole genome sequencing and whole exome sequencing, offer a broader scope for

analysis and a higher precision for studying the effects of genetic variants on drug therapy response compared to microarray technologies (4). Although pharmacogenomics research is not limited to a specific disease, it has a significant impact on cancer therapeutics where researchers had to adopt a multiple-gene perspective (5,6). Germline genomic variations are of great importance in pharmacogenomics research since they influence the pharmacokinetics and pharmacodynamics of drug therapy independent of cancer development (2,5). The main objective of PM is to match each therapeutic intervention with the patient's molecular profile. In recent years, the study of human genetics has been advanced by state-of-the-art sequencing technologies, leading to a better understanding of the connection between genetic variation and human health (7). PM has widely utilized genetic research, and one of its emerging applications is pharmacogenomics-informed pharmacotherapy, which involves tailoring drug selection and dosing to a patient's genetic features. Pharmacogenomics variation has been established to play a significant role in drug efficacy and safety, and international scientific consortia such as Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) [have created treatment guidelines for several drug-gene interactions. (8). However, the integration of pharmacogenomics into routine clinical care is still limited due to various barriers, ranging from basic pharmacogenomics research to implementation. To improve pharmacogenomics knowledge, it is necessary to study rare genetic variants that have been previously neglected and validate their functional and clinical impact through pre-clinical models and in-silico tools (9). To facilitate the widespread adoption of pharmacogenomics, ongoing international coordinated efforts are being made to overcome existing barriers and provide new tools and insights into its clinical application (10). In South Africa, only a couple of universities; University of Cape Town and Stellenbosch, are actively participating in the field of pharmacogenomics, along with the South African Genome Program. The South African PM program has demonstrated that Pharmacogenomics PGx testing is a promising treatment approach (11). Currently, the PM Program is primarily focused on cancer, but there is potential for other areas, such as large genome sequencing analysis, to include the diverse African genome (11). The Australian National Genomic Healthcare Initiative is reviewing a proposal regarding National Medicare Funding for genome testing (11). Australia's National Health and Medical Research Council is creating a research strategy based on omics, which considers clinical guidelines and data repositories to address various ethical, legal, and social issues (ELSI) barriers (11) Regarding Asian countries, Japan has directed its attention towards cancer research, the establishment of significant biobanks, and conducting extensive genome-wide association studies through RIKEN. Japan is also constructing a large DNA database to facilitate pharmacogenomics analysis (11). Pharmacogenomic testing is now available for an increasing number of drugs, allowing pre-screening of patients and personalized selection of the appropriate drug and dosage. (12,13). Currently, over 10% of FDA-approved medications provide pharmacogenomic information in their labelling, and this proportion is gradually increasing as more PGx biomarkers are identified and verified. (14) Oncology In oncology, precision medicine often involves detecting mutations in cancer genomes to anticipate whether a patient will respond or become resistant to a particular therapy. This is a crucial matter not only in clinical settings but also in research because many drugs that could be beneficial in a subset of patients are discarded during development due to their lack of effectiveness in a large portion of patients. Therefore, identifying predictive biomarkers may allow for the selection of appropriate patient groups for more logical clinical trials (5). The discovery of molecular alterations in cancer that can be targeted by drugs has ushered in a new era in oncology (15). Significant progress has

been made in identifying druggable biomarkers in breast, lung, and melanoma cancers (16,17). In breast cancer, hormonal receptors and other pinpointed biomarkers such as PIK3CA or ERBB2 mutations have completely changed the therapeutic approach for luminal breast cancer patients (17,18). The detection of HER2 amplification has also led to the identification of another important subgroup of patients who benefit from anti-HER2 inhibition in all clinical settings (19,20). Similarly, the identification of EGFR mutations and EML4-ALK translocation in non-small cell lung cancer has improved outcomes for advanced diseases (21,22). The identification of the BRAF-V600E mutation and the use of BRAF and MEK inhibitors have significantly improved clinical outcomes in patients with advanced melanoma. (23). These are just a few examples of how precision medicine is applied in daily clinical practice. The genomic revolution has also impacted most solid tumours, including "orphan diseases" such as extra-hepatic cholangiocarcinoma (24). In recent decades, significant breakthroughs in cancer biology research have revealed the inner workings of how tumours form, proliferate, and spread to other parts of the body (25). These mechanisms are characterized by various distinguishing features, including genetic mutations, (26) chromosomal abnormalities, epigenetic changes, (27), and dynamic interactions between tumours and their hosts (28). Although these features contribute to cancer development, they also create vulnerabilities or targets that researchers can exploit to develop drugs. One such drug is Imatinib (29), which has become a hallmark of the potential for developing personalized cancer therapies (29). Imatinib is used to treat chronic myelogenous leukemia (CML) by specifically targeting and deactivating a mutant tyrosine kinase caused by the fusion of two genes (BCR-ABL). The mutation is created in cells following an abnormal chromosomal translocation resulting in cancerous transformation and uncontrolled growth (30).

Gynaecologic oncology

Gynaecological cancers pose a significant threat to women's health (31). Ovarian, cervical, and endometrial cancers are the most common demonstrating high incidence, mortality, limited late efficacy, easy recurrence, and drug resistance (32). Histological classification is the gold standard for patient stratification, and it is an important predictor of survival and a determinant factor of surgery and adjuvant therapy. However, molecular information, including genomic, transcriptomic, and proteomic characterization, can provide more precise diagnosis and treatment for gynaecological cancers. (32) Precision medicine has become a pioneer in the treatment of gynaecological cancer, and genetic screening and targeted medicine have become routine for oncology clinicians. However, the application of precision medicine in gynaecological oncology is limited, and effective targeted drugs are still lacking due to the incomplete understanding of the pathogenesis of gynaecological tumours (32). Preservation of fertility is another concern in the treatment of gynaecological tumours, and fertility-sparing surgery has been applied to early-stage malignant tumours (32). More specific neoplasm staging is needed, and genetic information should be considered to optimize neoplasm staging and avoid unnecessary overtreatment. Overall, more research is needed to elaborate on the molecular characteristics of individual tumours and their relationship to disease outcomes, and biomarkers for seeking precise treatment should be explored. (33) The implementation of personalized medicine in gynaecologic oncology is still a work in progress. Key genetic mutations, known as "driver mutations," have been discovered in ovarian, endometrial, and cervical cancers. These mutations include BRCA mutations, NOTCH, P13K, BRAS/MEK, FOX 1, p53 in ovarian cancer; TP53, PTEN, P1K3CA, and KRAS in endometrial cancer; and P1K3CA, TP53, RB1 in cervical cancer (34). Scientists are developing therapies that specifically target these mu-

tations, which can disrupt tumour cell growth through various mechanisms such as interrupting tumour cell stroma, vasculature, and aberrant signalling mechanisms (35).

Non-Small Cell Lung Carcinoma (NSCLC)

In 2013, the Food and Drug Administration (FDA) approved erlotinib and afatinib as the first-line treatment for advanced-stage NSCLC with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations. As personalized medicine gained popularity, the indications for EGFR TKI (tyrosine kinase inhibitors) use in patients without a known EGFR mutation were removed from the National Comprehensive Cancer Network (NCCN) guidelines in 2015 and restricted to those with EGFR exon 19 deletions or L858R mutations in October 2016. (36). However, subsequent oncogene-targeted therapies were developed for molecularly defined subgroups during the clinical drug development process based on preclinical data. This led to the rapid approval of novel biomarker-based drugs for NSCLC patients, including those with anaplastic lymphoma kinase (ALK+), ROS1-rearranged, or BRAFV600E-mutant disease (37,38,39). Osimertinib, a third-generation EGFR TKI, was initially licensed based on its activity against EGFR with an original activating mutation and/or the T790M mutation, which is selected for EGFR-mutant NSCLC by first-generation and second-generation EGFR TKIs (40). The NCCN recommends testing for multiple desirable molecular changes in NSCLC specimens, including mesenchymal-epithelial transition factor receptor (MET), rearranged during transfection (RET), neurotrophic tropomyosin receptor kinase (NTRK), and human epidermal growth factor receptor 2 (HER2). This is based on preliminary evidence of clinical efficacy of different targeted agents in molecularly defined patient subgroups, most of which occur in lung adenocarcinomas (36).

Oncologic Pharmacogenetics

FDA-approved medications used to treat different types of cancer, such as lung, breast, and gastrointestinal tumours, can be paired with biomarkers to personalize treatment (41). Although germline variations can also predict the therapeutic and adverse effects of anticancer drugs, (2,42) most pharmacogenetic options in oncology involve somatic mutations that predict the pharmacodynamic effects of oncologic drugs (43,44,45). One widely studied pharmacogenomic approach is using protein kinase-inhibiting drugs to treat tumours with specific mutations, like those in the EGFR gene. Retrospective studies have shown that NSCLC patients with EGFR overexpression and sensitivity to gefitinib and erlotinib have a 75% response rate, compared to 10% in patients without these features (46). Mutations in other types of EGFR also predict better pharmacotherapeutic responses (46), and the identification of mutations in potential drug targets has enabled the development of novel drugs to treat previously untreatable types of cancer. For example, vemurafenib, a BRAF kinase inhibitor, is used to treat metastatic melanoma when positive for a BRAF V600E mutation (47).

Breast cancer

Breast cancer (BC) has become more prevalent and deadly in recent times, making it a significant global concern. Unfortunately, it is currently the primary cause of cancer-related deaths among women worldwide (48). The traditional method of treating patients with a single standard dosage has not been effective and has led to drug toxicity and treatment failures. This inefficacy has been observed in numerous patients with different diseases, with failure rates ranging from 38-75%, with some patients showing no response to the drug at all (48). Recent molecular investigations revealed that BC is not a single disease, but rather a combination of various diseases with different biological behaviors. Therefore, pre-

cision medicine is the most suitable approach in such cases. This new approach to oncology is being implemented at various levels of breast cancer management, including predicting treatment efficacy, prognosis, and developing new treatments through clinical trials (48).

Neurology

PM has emerged as a significant concept in medicine and is increasingly becoming a crucial objective in treating multiple sclerosis (MS) (49). The central unresolved issue in MS is how to manage and acquire a better understanding of the progressive form of the disease. Addressing this will necessitate novel techniques to target compartmentalized processes in the central nervous system (50). The current diagnostic criteria for multiple sclerosis (MS) require evidence of neurodegeneration detected through neuroimaging before a diagnosis can be made (51) However, the goal of personalized medicine should be to identify individuals who are more prone to developing MS, even before any neurological damage occurs. One approach is to screen first-degree relatives of MS patients, allowing those at increased risk to make lifestyle changes that can minimize the chances of developing the disease. Additionally, regular check-ups with a neurologist can help detect any early signs of neurological damage. In the future, personalized gene therapies could be considered for these individuals. Unfortunately, there is a lack of well-established predictive biomarkers for MS. (52) However, antibodies to Epstein-Barr virus nuclear antigens in serum have shown promise as predictive biomarkers, as studies have found increased antibody levels prior to the onset of MS. (53) Genetic variations, such as single nucleotide polymorphisms (SNPs) and expression-level signatures in susceptibility genes, including microRNAs (miRNAs), may also serve as important parameters for predictive biomarkers. Genome-wide association studies (GWASs) have identified over 100 genes or gene loci associated with MS development, including genes related to myelin proteins and the immune system. (54) Epilepsy In the context of genetic epilepsy, genetic diagnoses can identify treatment-relevant subgroups of patients, particularly those with single pathogenic variants that can be targeted for specific gain or loss of function. Copy number variants and polygenic risk may also help to prognosticate in the future (55,56). There is a spectrum of increasing precision and personalization in treating epilepsy, from correcting a well-defined genetic mechanism in the context of individualized factors to using existing anti-seizure drugs or newly repurposed drugs with superior efficacy in genetically defined groups of patients (57,58). Pyridox(am)ine 5'-Phosphate Oxidase (PNPO) deficiency is an uncommon neurometabolic disorder characterized by severe epilepsy in newborns. The seizures can be controlled by pyridoxal phosphate (PLP), but not by pyridoxine. (59) In 2005, it was discovered that mutations in the gene responsible for encoding pyridox(am)ine 5'-phosphate oxidase (PNPO) are the cause of pyridoxal phosphate-dependent epilepsy (60). Unlike pyridoxine-dependent epilepsy caused by mutations in ALDH7A1, the genetic alteration in PNPO deficiency directly affects the metabolism of vitamin B6. PNPO plays a crucial role in the synthesis of pyridoxal 5'-phosphate, which is the active form of vitamin B6. The phenotypic spectrum of PNPO deficiency has expanded, with over 50% of affected individuals showing a later onset of symptoms or an unexpected response to pyridoxine instead of PLP. (60) This variability in symptoms poses challenges for accurate diagnosis and targeted treatment. As genetic testing becomes more comprehensive, atypical presentations of PNPO deficiency are likely to be identified through gene panel or exome sequencing rather than traditional biochemical or single gene tests. (61) Therefore, it is important to recognize that treatable neurometabolic epilepsies can manifest as nonspecific early-onset epileptic encephalopathies, and rapid genetic testing should be incorporated into the diagnos-

tic process for these conditions. (62) Parkinson's disease Precision medicine has been applied to Parkinson's disease (PD) by studying the genetic mutations associated with the disease. For example, the glucocerebrocidase gene (GBA) responsible for Gaucher's disease has been found to increase the frequency of PD in heterozygote carriers. GBA mutations are the most relevant genetic risk factor for PD, affecting 5-10% of patients (63). Enhancing the activity of glucocerebrocidase (GCase) has been shown to regulate or attenuate alpha-synuclein activity, which is implicated in the formation of misfolded oligomeric alpha-synuclein (63). Similarly, mutations in Leucine-rich repeat kinase 2 (LRRK2) have been linked to PD and inhibiting the function of heat shock protein 90 (Hsp90) can lead to a breakdown of the complex formation between Hsp90 and LRRK2 (64). Small-molecule chaperones, such as ambroxol and isofagomine, have been shown to increase mutant GCase activity (65,66,67), and histone deacetylase inhibitors can reduce the recognition of misfolded GCase by Hsp90 and increase residual enzyme levels. (68). Patients with GBA gene mutation variants are associated with a specific cognitive subtype in PD with rapid cognitive decline progressing to dementia (69), and LRRK2 inhibitors could be targeted at carriers of the LRRK2 gene. (70). Furthermore, specific genetic forms of PD may have susceptibility to specific patterns of non-motor symptoms, and personalized medicine should include tailored screening for these symptoms and tailoring drug treatment to avoid aggravating the risk of hallucinations (71). Pramipexole (PPX) is an effective treatment for depressive symptoms in patients with Parkinson's disease (PD), either as a monotherapy or as an add-on to levodopa in patients with mild to moderate depression. However, severely depressed PD patients have been excluded from these studies for ethical and safety reasons, so these findings cannot be generalized to them. Adverse events reported in these trials, such as gastrointestinal and sleep disturbances, as well as dyskinesia, were consistent with the known safety profile of the drug.46 Parkinson's disease patients with depression and anxiety may benefit from PPX's motor and antidepressant effects if a slow dose titration is carried out (72) and careful monitoring for impulse control disorders (ICD) and somnolence is performed using scales such as Epworth Sleepiness Scale (ESS) or Parkinson's Disease Sleep Scale (PDSS) (73). PPX may be a better alternative to commonly used selective serotonin reuptake inhibitors (SSRIs), which may worsen PD tremors and parkinsonism (74,75), while PPX can be more effective on motor function. Pramipexole has been rated as "efficacious" for the treatment of depression 3 by the Movement Disorder Society (MDS) Evidence-based Medicine Committee (73). Although PPX is not currently recommended for the management of sleep disturbances in PD, various studies suggest a potentially beneficial role of PPX in improving idiopathic sleep behaviour disorder (iRBD). (76) However, the pathophysiology of this action is unknown, and further controlled trials are needed to confirm the data. As robust guidelines for sleep behaviour disorder (RBD) management in PD is currently unavailable, (77) a trial with PPX at a low dosage on RBD should be considered as a personalized medicine approach. (78) Alzheimer's disease Alzheimer's disease (AD) is an interesting field for precision medicine due to its complexity and lack of effective treatments (79). Treating all AD patients as a single group is misguided since there are differences in genetic predisposition and symptom presentation (79). In fact, individual differences in drug metabolism can render a particular drug ineffective in 70% of Alzheimer's patients (80), and differences in the rate of clinical progression must be considered when selecting appropriate therapy (81). Personalized medicine can be successfully applied to AD, with risk assessment, early diagnosis, and tailored clinical treatment being the main tenets. A comprehensive risk assessment, considering genetic and environmental factors, is crucial to establish a monitoring protocol and initiate treat-

ment in the early stages of the disease. AD development occurs in three stages: latency, prodromal, and dementia (82,83,84). Detecting genetic risks and identifying the disease during the latency stage are important challenges in AD treatment (79). Genome-wide association studies have identified a list of candidate genes for further investigation (85,86). The PM [Ma9] approach involves a preliminary family history and genetic analysis of the patient, especially for early-onset AD, and can inform patients about modifiable environmental risk factors such as obesity, hypercholesterolemia, sedentary lifestyle, and smoking (83). ApoE 4 allele has been identified as a Late-Onset Alzheimer's Disease LOAD susceptibility gene, and patients presenting this isoform should avoid activities that may provoke brain injury (83,86,87). Genetic markers can also be useful in designing clinical trials, as demonstrated in two risk-assessment trials on asymptomatic individuals (85).

Psychiatry

Various medications can be utilized to alleviate the severity of symptoms or treat different psychiatric conditions. However, a patient's response to these medications can be highly variable (13) due to numerous personal health risk factors, such as gender, age, liver and renal function, blood pressure, body fat, alcohol and drug consumption, and drug interactions. Additionally, genetic factors, including an individual's unique genetic makeup, can influence drug response, affecting both pharmacokinetic parameters that determine drug absorption, distribution, metabolism, and excretion, and pharmacodynamics parameters that impact the mechanisms of action of the drug. (88,89) Pharmacogenomics (PGx) is the examination of how genetic variations in individuals may affect their response to drug therapy. (14) Schizophrenia Schizophrenia is a persistent mental illness with a varied genetic and neurobiological basis that impacts the early development of the brain. The disorder is characterized by a mixture of psychotic symptoms like hallucinations, delusions, and disorganization, along with difficulties in motivation and cognition (90). By concentrating on the various symptom domains of schizophrenia, it may be possible to discover endophenotypic markers, such as those for negative symptoms and cognitive impairments, in addition to positive symptoms. These markers could aid in the creation of new therapeutics that target cellular and molecular targets, rather than just the dopamine 2 receptor. In the future, further progress may be made by targeting other processes, such as glutamatergic, cholinergic, and cannabinoid receptor targets. Personalized medicine techniques, including pharmacogenetic variants and biomarkers, could also be used to ensure a tailored and safer use of antipsychotics (91).

Cardiovascular System

Precision medicine initiatives have historically overlooked cardiovascular diseases, possibly due to the misconception that these conditions develop slowly over many years and are less severe than other diseases like cancers and rheumatologic disorders. Nevertheless, given the significant number of people at risk for cardiovascular diseases, they present an excellent opportunity for precision medicine strategies (92). The gradual progression of many cardiovascular conditions allows for early identification of those at risk, implementation of preventive measures, and the initiation of therapies during the early stages of the disease (93). The cardiovascular continuum offers various options to address risk factors, detect disease at its early stages, make treatment decisions based on diagnostic tests, and prevent further disease advancement (93). Precision medicine targets cardiovascular diseases including hypertension (94), angina, coronary artery disease (95), dilated cardiomyopathy, and cardiac resynchronization therapy (96). These approaches encompass not only novel molecular and genetic diagnostic methods but also improved risk assessment scores based on existing data (97,98). Cardio-oncology

Precision cardio-oncology is a crucial concept that takes into account both cardiovascular and cancer treatment risks for each patient. (99) This approach is well-suited to predict and manage cardiotoxicities with precision care and can be achieved through the integration of large amounts of data using precision medicine. By analysing an individual's cardiovascular biology through genetics, pharmacogenomics, proteomics, and radiomics (100), as well as personal traits identified through machine learning, clinicians can guide precise treatment for heart failure (101). Furthermore, genetic discoveries from candidate gene studies and genome-wide association studies are aiding in the individualized approach to cancer patients, by identifying genetic variants that make them susceptible to Cancer Therapy-Related Cardiac Dysfunction Cardiology (CTRCD). (102)

Recent Advances in Precision "Personalized" Medicine

Significant advances have been made in the field of personalized medicine in recent years. These advances have contributed to better patient care by revolutionizing disease prevention, diagnosis, and treatment. The term "personalized medicine" was recently replaced with "precision medicine" to avoid the misconception that the approach is unique to each individual patient. (1) Instead, the focus is on identifying the most effective treatments and preventions based on genetic, environmental, and lifestyle factors. (1) However, the two terms are still used interchangeably by some people. To identify such interpersonal differences, genetic testing must be done, and a good patient history must be taken. I. Molecular profiling A. Next Generation Sequencing When it comes to genome sequencing for the identification of genomic mutations, New Generation Sequencing (NGS) is being increasingly used in clinical research, cancer biology, and pharmaceutical development (2,3) seeing as it has become more rapid, accurate and affordable than before. In contrast to whole-genome sequencing (WGS) and whole-exome sequencing (WES) which sequence large portions of DNA (entire genomes and exomes respectively), targeted sequencing (TS) focuses on targeted regions for specific diseases or gene panels related to drug response prediction (3). This means that the overall cost and data burden can be reduced, not to mention the increased sensitivity and sequencing depth. The capacity of TS to identify subclonal mutations, sequence circulating tumour DNA (ctDNA), and monitor minimal residual disease also makes it a valuable genetic tool for tracking disease evolution and studying drug resistance. (3) Yi-Zhou Jiang et al. conducted a study to evaluate the efficacy of subtyping-based targeted therapy for refractory metastatic triple-negative breast cancer (4). NGS panel of targeted sequencing was conducted on the metastatic tumour samples, and the patients were classified into 7 subtypes based on the results. Patients in each subgroup were given the most appropriate treatment. The objective response rate of the 69 enrolled patients was 29.0%, and the percentage of patients that experienced complete recovery, partial recovery or stable disease was 42.0%. Two subgroups specifically accrued more patients and displayed favorable outcomes. Another study by Amy Burd et al. used genetic and cytogenetic analysis to assign suitable treatment to Acute Myeloid Leukemia patients based on the dominant clone. (5) This trial proved that this new approach to AML therapy is safe for the large majority of individuals and that treatment assignment based on a dominant clone can be applied to almost all older patients with AML. B. Omics technology With the advancement of genomic medicine, scientists realized the growing need to integrate other omic techniques to provide an even more precise and tailored approach for patient care. According to Dai et al. "omics" is the probing and analysing of vast amounts of data representing the structure and function of an entire makeup of a certain biological system at a particular level. By integrat-

ing techniques such as epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics with the standard genomic sequencing, we get an approach often referred to as "multi-omics" (6,7,8). Together, these techniques create a comprehensive molecular profile unique to each individual, encompassing not only the sequence of nucleotides itself, but also complex cellular processes such as genetic regulation, epigenetic DNA or DNA-associated protein modification, and metabolite regulation. These technologies enable the identification of disease-associated biomarkers, characterization of disease subtypes, and prediction of treatment response. David G. Coffey et al. integrated multi-omics with high-throughput screening to investigate the relationship between in-vitro drug sensitivity and gene expression and mutation profiles in patients with multiple myeloma (9). They found a correlation between the expression of 105 genes and mutations in 12 genes, and in vitro cytotoxicity. The techniques they used were whole-exome sequencing (WES), RNA sequencing of bone marrow plasma cells, and ultradeep targeted sequencing of circulating tumour DNA (ctDNA). Zutao Yu et al. published a study earlier this year (10) presenting a new DNA sequencing technique called Chem-map. Chem-map allows researchers to perform in-situ mapping of the interactions between small molecules, and DNA or chromatin-associated proteins with exceptional precision. Since many life-saving drugs (such as chemotherapeutics) interact with DNA to treat diseases, understanding where and how they bind to the genome will massively aid in improving and developing new therapeutic interventions. Chem-map, in conjunction with other genomics techniques will facilitate mechanistic studies and further development of genome- and epigenome-targeting drugs II. Therapeutic Innovations A. Gene Therapy The development of such brilliant profiling techniques served as a foundation for the building and developing of precision-based therapies and drugs. Gene therapy, a concept that was first introduced back in 1972 (11) as a promising potential treatment for genetic diseases has only recently begun to demonstrate substantial clinical benefit. The treatment involves introducing genetic material into cells to replace, complement, or repair faulty genes (12). This genetic material can be introduced by viral or bacterial vectors (modified to remove their ability to cause infectious disease) (13), whole genes engineered into plasmids, or other forms of treatment like oligonucleotides and mRNA. Unlike viral vectors that can only mediate gene addition, new genome editing technologies resemble a precise tool for gene addition, ablation, and correction. This approach can be applied to cells outside the body (ex vivo), or the editing components can be directly delivered in vivo for genome editing within the body (14). The highlight of genomic editing technologies in recent years was the discovery of CRISPR-Cas9 in 2012 (15). The CRISPR-Cas9 nucleases can be effectively engineered to precisely cut DNA at desired locations. This is accomplished by designing a specific short guide RNA (gRNA) that is complementary to the target site of interest. In comparison to viral gene addition therapies, the clinical use of genome editing technologies is still in its early phases, although it is projected that many genome editing clinical trials are anticipated to start in the upcoming years. One notable example of gene therapy is the application of precision medicine in the treatment of ALS (Amyotrophic Lateral Sclerosis), a progressive neurodegenerative disorder. Through personalized approaches, researchers have identified specific genetic mutations associated with ALS and developed targeted therapies to address these mutations. ALS-directed gene therapy includes antisense oligonucleotides, RNA interference, CRISPR, adeno-associated virus (AAV)-mediated trophic support, and antibody-based methods (16). CAR-T cell are T-cells engineered to express chimeric antigen receptors (CARs) that are specific for tumour antigens. CAR-T cell therapy has shown remarkable success in treating certain hematological malignancies, such as certain types of

leukemia and lymphoma. (17) Since 2017, six CAR-T cell therapies have been approved for hematological cancers by the Food and Drug Administration (FDA). Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) were the first to be approved in 2017 for the treatment of patients up to 25 years of age with refractory/relapsed B-cell precursor acute lymphoblastic leukemia (ALL) and adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapies. In 2020, Tecartus (brexucabtagene autological) was approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) and ALL. Two more drugs were approved in 2021, Breyanzi (lisocabtagene maraleucel) and Abecma (idecabtagene vicleucel). Finally, in 2022, Carvykti (ciltacabtagene autoleucel) was approved for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy. Kymriah, Yescarta, Tecartus, and Breyanzi are anti-Cluster of Differentiation (CD)19 CARs, and Abecma and Carvykti target B-cell maturation antigen (BCMA). (18) Gene therapies for Severe combined immunodeficiency due to adenosine deaminase (ADA) deficiency (ADA-SCID) include the retroviral vector gene therapy Strimvelis which was recently proven to be unsafe after one patient developed a lymphoproliferative disorder several years after receiving the treatment (19), and Lentiviral vector gene therapy where no such events have been reported and had a 100% survival rate at 24 and 36 months with only two treatment failures in 50 patients from the US and the UK (20) Onasemnogene abeparvovec or Zolgensma is a gene therapy approved by the FDA in 2019 for the treatment of spinal muscle atrophy (SMA) (21). It is a recombinant adeno-associated viral vector that contains normal human survival motor neuron protein (SMN1). (22) B. Bioprinting Organ shortage and donor scarcity have become concerning problems that need to be addressed. 3D bioprinting might be a replacement for allograft tissues, lowering the risk of organ rejection since the tissues are made from the patient's own cells (23). By precisely positioning biologics, such as living cells and extracellular matrix (ECM) components, in the required 3D hierarchical architecture, three-dimensional (3D) bioprinting is a potential and ground-breaking biofabrication technique (24). III. Artificial Intelligence and Machine Learning Artificial intelligence (AI) and machine learning algorithms have revolutionized various aspects of personalized medicine. These technologies can analyse vast amounts of patient data, including genomic information, medical records, and imaging data, to identify patterns, make predictions, and assist in treatment decision-making. AI-driven algorithms can help in the interpretation of complex genetic variations, prediction of drug response, and identification of potential therapeutic targets, thereby improving personalized treatment strategies. (25) Prevention Screening is a crucial step in preventative medicine and can be made more efficient and accurate with the use of artificial intelligence especially in preventable diseases like colorectal cancer (CRC). AI assistance could be integrated into colonoscopies, computed tomographic colonography (CTC), and capsule endoscopies (CE) to increase detection rate, for a higher adenoma detection rate (ADR) than adenoma miss rate (AMR). (26) Wang et al. compared adenoma detection rates (ADR) between standard colonoscopy and real-time automatic polyp detection system assisted colonoscopy in 1058 patients and found a significantly increased ADR in the AI group (27). Hart et al. used personal health data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) to train seven machine learning algorithms to identify individuals at high risk for endometrial cancer. When compared with 15 physicians, the algorithms were better at identifying above average risk women (28). Ethical implications of personalized medicine Every new emerging field faces several questions that raise some alarm either to the scientific community or the public. Even though personalized

medicine/precision medicine has been studied for almost a decade now, but certain ethical considerations are still under investigation and review of its applicability in highly variable communities with different backgrounds, religions, and standards of health care. This field isn't yet widely introduced in the Middle East. Different issues facing PM regarding research and its ability to 'do no harm' such as ethical consideration; informed consent, confidentiality, accessibility by underprivileged communities and ethnic minorities, and incidental findings are highlighted. Informed consent Informed consent is as much based on the physician's understanding and knowledge as the patients'. The physician should have enough information and knowledge as well as the ability to convey that to the patient as well as establishing an excellent doctor-patient relationship. Making individualized therapeutic decisions needs a greater level of literacy and is influenced by the patient's preferences and values (1). Our traditional practice of obtaining consent from our patients should be restructured to better fit the wide range of genetic information. The American College of Physicians published a position paper shedding some light on this matter; Position 3: "Patients will need assistance from their physicians to understand the risks, benefits, and uncertainty of direct-to-consumer genetic medical testing" (2). The best interest of the patient should be the researcher's main aim, but because genetic testing can provide a wide range of genetic information for not only the patient, but also their families and sometimes communities, this may subject certain families to exploitation and stigmatization, which also indicates the importance of literacy of the physician so they can better convey the implications of genetic testing to the patient while also being considerate for their social and religious norms. Confidentiality The principle of confidentiality is a bit tricky regarding genetic information as it is of importance to the whole family and the next generations. The whole dilemma revolves around the idea that the patients who seek genomic testing should be informed of the implications of the results on different family members and thus, make informed decisions about their desires or lack thereof to disclose certain parts of their results. The American Medical Association Code of Ethics also identifies the professional duty to protect the confidentiality of patient's genetic information and to identify the circumstances under which patients are expected to inform biological family members of the availability of information related to risk for disease (3). Some physicians deny that data privacy and safety can be guaranteed as new technological advancements and information hacking trends emerge every day. Physicians fear delay in treatment in cases of infectious diseases -especially STDs- and other socially sensitive medical conditions may result from the fear of confidentiality breaches and social embarrassment, "At the first glance confidentiality is absolute, but when the immediate and serious risk to the health of the third party emerges, confidentiality may breach." (4). Accessibility by Underprivileged Communities and Ethnic Minorities Fear of disparity in public health creates a serious ethical dilemma, as physicians believe that PM isn't available to different communities and ethnic groups equally. It mostly relies on whether the general health system in a certain area follows out-of-pocket payments or other methods and insurance companies' willingness to provide coverage for this field. Out of 104 physicians taking a survey in the US, only 38.5% believed that PM is available to all ethnic groups. (5) PM practices are generally expensive and thus limiting its access, this raises a warning flag in the area of health justice to different communities giving that information collected from these wealthy communities cannot be generalized worldwide due to differences in genetic makeup and environments. Incidental Findings The wider the familial involvement in genetic testing, the higher the chance to come across additional findings beyond the aim of the original test like non-paternity and genomic variants with serious health implications. The American College

of Medical Genetics and Genomics (ACMG) recommended disclosure of incidental findings originating from the whole-genome analysis which took the four bioethical principles of autonomy, justice, beneficence, and non-maleficence under debate in personalized medicine (6). The question remains if autonomy should take precedence over beneficence or not, as ACMG gives priority to beneficence. These findings should be anticipated before performing any tests and should be thoroughly discussed with the patients.

Conflict of Interest

The authors declare that they have no competing interests.

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