

Precision Medicine: A New Paradigm in Therapeutics

Abstract

A key goal of clinical care is to treat patients as individuals and to approach therapeutics in such a way that it has optimal efficacy and minimal toxicity. With swift technological advances, such as genomic sequencing and molecular targeted drug exploitation, the concept of precision medicine has been robustly promoted in recent years. Precision medicine endeavors to demarcate diseases using multiple data sources from genomics to digital health metrics in order to facilitate an individualized yet “evidence-based” decision regarding diagnostic and therapeutic approaches. In this way, therapeutics can be centered toward patients based on their molecular presentation rather than grouping them into broad categories with a “one size fits all” approach. This review article is aimed to provide a broad overview of the advent and emergence of precision medicine in view of its current implications.

Keywords: Precision medicine, preventive medicine, therapeutics

Introduction

Health care is centered on working out generalized solutions that can treat the largest number of patients with similar symptoms. At the launch of President Obama’s Precision Medicine Initiative, precision medicine (PM) was described as “providing the right treatment at the right time to the right person and taking into account patients’ health history, genes, environments, and lifestyles.”^[1] The recent completion of the Human Genome Project, along with technological advances for characterizing patients using “omics” including proteomics, metabolomics, and genomics, provides a unique and exciting opportunity for PM to play an important role in clinical decision-making.^[2] The objective of this review is to focus on a realistic scenario for the evolution of PM, to explore the issues affecting its development and implementation and the role of regulatory agencies in its adaptation. This paper also highlights the roles and applications of PM. The studies in high impact journals were searched on PubMed using Boolean terms (AND/OR) to capture relevant articles for this review.

Evolution of Precision Medicine (PM)

In the past, making clinical decisions was solely done on the basis of clinical

experience and pathophysiological rationale.^[3,4] The current scenario acknowledged as “evidence-based medicine” is more experience-based and entails judicious use of current best evidence in making decisions about the care of individual patients. Evidence-based medicine (EBM) is grounded on three fundamental principles, the hierarchy of evidence based on study design: systematic reviews to avoid selection bias, and patients’ values and preferences.^[5] Many researchers have criticized EBM for focusing on groups of patients rather than on the individual.^[6,7] Specifically, when evidence is reported for treatment efficacy after trials, the results are often based on the average treatment effect and do not apply to all patients.

Personalized medicine is an older term that is often used interchangeably with PM. It seeks to utilize treatment or prevention strategies that are tailored to an individual’s disease process or symptoms.

In this era with cheap genome sequencing, advanced biotechnology, health sensors that patients use at home and collection of information about patients’ journeys in health care categorized under digital health, the health care becomes increasingly bespoke which is called “PM.”

PM is defined by the National Institutes of Health as, “an emerging approach for disease treatment and prevention that takes into account individual variability in genes,

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environment, and lifestyle for each person.” PM seeks to incorporate technology into medicine to create a data ecosystem that can better identify and treat an individual patient’s disease. This approach aims to seamlessly integrate clinical phenotypes and biological information from imaging to laboratory tests (including -omics data) and health records. To facilitate drug discovery from PM-driven studies, investigators have developed new trial designs—such as basket or umbrella trials—which have been used in numerous precision oncology cancer studies.^[8-10]

Foundation of PM

The implementation of PM on a wider basis requires better identification of “the right patient,” who should receive a particular treatment and “the right dose,” dose required to be given to each patient with the potential to respond. Hence, it is essential to understand the key reasons for variation in response to treatment,^[11] which can be considered under two main groups:

- I. Pharmacokinetic variability includes variability in:
 - A. Subject phenotype: weight, body surface area, organ status, age, ethnicity, gender, microbiome
 - B. Subject genotype: polymorphisms in metabolizing enzymes or transporters
 - C. Disease response or progression with time
 - D. Lifestyle and environmental factors such as concomitant medications, diet, smoking
 - E. Adherence to treatment, drug formulation, route of administration, and dosing regimen.
- II. Pharmacodynamic variability includes polymorphism in drug target or downstream pathway and driver mutations of disease heterogeneity.^[11]

Role of Disease Heterogeneity in PM

Specific molecular pathways have been identified which are abnormal in subgroups of patients and drugs have been developed that are active against those targets and pathways. For various diseases, several mechanisms produce similar sets of signs and symptoms,^[12-14] suggesting that disease heterogeneity is an important source of response variability in terms of selecting the right treatment. The significance of taking disease heterogeneity into account can be elucidated with the example of drug vemurafenib, which selectively targets mutated b-raf kinase in tumors with a *V600E* mutation in the b-raf gene and is an effective treatment for melanoma but is less effective in colorectal carcinoma with the same mutation.^[15] Presumably, additional factors account for greater heterogeneity in colorectal carcinoma and its response than in melanoma.

Role of Therapeutic Drug Monitoring in PM

Therapeutic drug monitoring (TDM) has a substantial role to play in the execution of PM as it allows doses to be adjusted in individual patients in order to achieve

a predetermined target exposure, thereby, reducing pharmacokinetic variability with a reduction in overall response variability.^[16] Drug doses may be adjusted based on markers such as glucose/glycosylated hemoglobin, cholesterol, prostate-specific antigen, blood pressure, etc. When suitable biomarkers are available, their use to guide dosing would be expected to reduce response variability, more so, than the dose adjustment based on plasma drug concentration. Recent studies suggesting the presence of exposure-effect relationships support the potential value of TDM for biologic agents in rheumatoid arthritis and some cancers; trials are underway to determine if adjusting dose to maintain a target exposure can improve efficacy.^[11]

Illustrations of Implementation of PM

There are various established examples of the application of PM in the literature which comprise its use directed to drug individualization, dose individualization, and treatment through target identification. To appreciate the effectiveness and translational value of PM, let us take the examples of its implementation in the following disorders.

Cancers

The field of oncology has been a clear pioneer of PM. The move toward personalized therapies was likely in part due to the general cytotoxicity and severe side effects of existing “one size fits all” cancer drugs along with the identification of associated tumor-specific vulnerabilities as potential drug targets.^[17] Therapies can now be designed to more precisely target cancer cells through two primary methods: selectively disrupting pathways necessary for cancer cell survival or growth (pathway-based targeted therapy), and artificially modulating patients’ immune systems to generate a response against cancer cells (immunotherapy).^[11] Targeted therapies spare healthy cells and promote the substratification of tumor types, allowing treatments to be tailored correspondingly.

- i. Imatinib, which targets *BCR-ABL* fusion gene in chronic myelogenous leukemia (CML) and gain-of-function mutations in the genes encoding mast/stem cell growth factor receptor KIT or platelet-derived growth factor receptor- α (PDGFR α) in gastrointestinal stromal tumors (GISTs), served as one of the first clinical success stories for targeted cancer treatment^[18]
- ii. Overexpression of tyrosine-protein kinase erbB-2 (HER2) is associated with an aggressive form of breast cancer with poor prognosis but responds significantly to trastuzumab, a monoclonal antibody that targets HER2, which has shown a significant survival benefit in these patients^[19]
- iii. The emergence of resistance to anti-cancer drugs has disputed the pathway-based approach in cancer treatment. Advances in understanding tumor resistance and the mutations responsible for it have led to the

development of the next generation of kinase inhibitors. Osimertinib, a third-generation EGFR tyrosine kinase inhibitor, was designed to target the T790M mutation that provides resistance to other EGFR inhibitors^[20,21]

- iv. Patients with tumors that express high levels of programmed death-ligand 1 (PD-L1) respond better to pembrolizumab, an Anti-programmed death-ligand 1 antibody than those with little or no expression^[20,21]
- v. Around 40% of patients with metastatic colon cancer do not respond to cetuximab and panitumumab because of the mutation of the *KRAS* gene. This discovery led to the recommendation that only patients without a mutation in the *KRAS* gene should be treated with the above drugs.^[22]

Asthma

Despite producing profound reductions in eosinophils, mepolizumab, an IL-5 antibody, was proved to be clinically ineffective in patients with moderate asthma.^[19] About a decade later, it was confirmed to be highly effective in the subset of patients with hypereosinophilic syndrome.^[20,21] It was, hence, presumed that the IL-5 eosinophil pathway is less important in most asthmatics, and there is no clinical benefit from blocking it. This is an example to signify the role of disease heterogeneity in choosing the right drug for the patients.

There is a piece of established evidence suggesting that the efficacy of omalizumab, an IgE antibody, depends on free IgE levels to be <50 µg/mL. Its dosing is adjusted for body weight and baseline IgE to achieve the necessary reduction in IgE levels.^[23]

Metabolic disorders

- i. Diabetes Mellitus (DM): Despite availability of several classes of drugs for DM, both oral and insulin preparations, treatment is often given on trial and error basis or on affordability of medications rather than the underlying pathophysiology, hence, most of the patients do not achieve proper blood glucose control^[24] mainly because all guidelines aim at the management of an average patient rather than personalized, PM^[25] Up to 3% of cases of diabetes diagnosed in children have monogenic diabetes, most common being mutation in transcription factor gene *HNF1A*, which present before the age of 25 years and are responsive to sulfonylureas (SUR). SUR is also a first-line treatment in neonatal diabetes with *KCNJ11* and *ABCC8* gene mutation.^[26-29] Neonatal Diabetes, diagnosed in infancy, affects 1:400,000 live births, roughly ½ develop permanent diabetes. Of later, around 70% are estimated to carry a mutation in genes encoding ATP-sensitive K⁺ channel (*KCNJ11* and *ABCC8*), this mutation blocks the closing of K⁺ATP channels, preventing beta-cell depolarization and insulin secretion.^[30] Treatment with SUR rectifies this defect in ~90% cases, allowing discontinuation of exogenous insulin.^[31]

New classes of glucose-lowering drugs 1 (GLP1) receptor agonists, DPP-4 inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors extend the ability to treat type 2 DM with reduced rates of hypoglycemia, less frequent self-monitoring of blood glucose, and without weight gain. These drugs were initially developed on the basis of metabolic physiology.^[30,32] The mechanisms of action and safety of SGLT2 inhibitors and GLP1 agonists were subsequently validated by the analysis of genetic variation at *SLC5A2* (gene encoding for SGLT2) and GLP1 receptor in individuals and large population studies.^[33]

- ii. Dyslipidemia: Development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is a transparent specimen that implicated genetic, phenotypic, and molecular findings to serve as the basis for pursuing PCSK9 as a drug target for the treatment of hypercholesterolemia. PCSK9 is demonstrated to be a hepatic secretory protein that enters circulation and binds to low-density lipoprotein (LDL) receptors (the primary source for clearance of circulating cholesterol), ultimately mediating LDL receptor endocytosis and subsequent degradation.^[34] PCSK9 inhibition results in a surplus of available LDL receptors, thereby, reducing plasma LDL-C levels. A significant reduction (36–60%) in LDL-C was demonstrated following the administration of alirocumab and evolocumab, leading to their US FDA approval.^[34] Loss of function mutation of the *ANGPTL4* gene is associated with good lipid profiles and lower risk of coronary artery disease.^[35] Animal models back these effects of monoclonal antibodies,^[35] further supporting *ANGPTL4* as a candidate drug target in coronary artery disease.

PM In Preventive Role

- a. PM plays a substantial role in the reduction in adverse drug reactions (ADRs) which may intensify adherence. Many ADRs result from variation in genes that code for drug-metabolizing enzymes like CYP450, which can result in the drug being metabolized at a faster or slower rate than normal^[36,37]
- b. Pharmacogenetics of an individual has a great deal to play in prediction of the risk of adverse events and it identifies as to who are the patients who should not receive a particular drug. In patients with HIV infection, with the *HLA-B*5701* gene, abacavir may lead to multi-organ system hypersensitivity. Hence, genetic testing is recommended for all patients to be prescribed abacavir^[38]
- c. Similarly, the presence of allele *HLA-B*1502* is associated with Stevens-Johnson syndrome in patients taking carbamazepine^[39] and *SLCO1B1* is associated with Simvastatin-induced myopathy, hence, making the screening of these biomarkers essential to determine the susceptibility of patients to these drugs.^[40] This implies

the impact of pharmacodynamic variability on drug selectivity

- d. Polymorphisms in enzyme vitamin K epoxide reductase convertase 1 alters sensitivity to the effects of warfarin, which is now being considered in dosing algorithms^[41-43]
- e. The value for PM approaches for the improvement of the population's health rests on the adaptability of these approaches to whole populations and preferably to the prevention of disease. For example, identification of genetic aberrations associated with familial cancer syndromes has led to therapeutic options to reduce the risk of cancer development. Among patients who test positive for multiple endocrine neoplasia 2, a total thyroidectomy is the only method to prevent medullary thyroid cancer^[45]
- f. In the case of patients with BRCA mutations, prophylactic bilateral mastectomy and salpingo-oophorectomy are options to reduce breast and ovarian cancer risk, respectively. Bilateral prophylactic mastectomy reduces the risk of breast cancer by at least 95% among women with a deleterious mutation in the *BRCA1* or *BRCA2* gene^[46,47]
- g. A noninvasive method of cancer prevention includes regular screening or tamoxifen as antiestrogen therapy. The latter has shown to be beneficial among women with BRCA2 mutations specifically and reduced breast cancer risk by 62%^[48]
- h. Some chemoprevention therapies in familial cancer syndromes include the use of 600 mg per day of aspirin to reduce the risk of colorectal cancer in Lynch syndrome carriers.^[16]

Regulatory Facets of PM

Companion diagnostics can identify a group of patients highly likely to respond to medication, predict adverse effects, and monitor response to a medication.^[49]

Though FDA has laid down some regulatory policies and guidance documents on clinical pharmacogenetics, it faces a major challenge to develop a clear, viable pathway for approval of new targeted diagnostics, therapeutics, and theragnostics.

Discussion

The proponents of PM suggest it has the potential to refocus medicine from reaction to prevention, direct the selection of optimal therapy, improve quality of life, reduce ADRs, increase treatment adherence, and reduce overall health care expenses.^[24,50]

Having discussed the recompenses of PM, it is equally important to throw some light on the other school of thought considering the potential bottlenecks in its implementation, which are summarized as under.

- a. "One dose for all" is convenient for prescribers and any recommendations that bring about treatment

individualization and dose flexibility will add complexity. Management is easy when dosing is done by a clinical endpoint or a biomarker which is simple, cheap, and easily measurable, but it is more challenging when more complex or expensive tests are required^[11]

- b. Genotype-guided prescribing is conceptually simple as it usually requires knowledge of a single genotype per drug, and yet is still a challenge to implement because there are many drugs, many genotypes and the tests along with their interpretation are unfamiliar^[11]
- c. PM could mean higher medication prices for specific subgroups of patients, though it is important to understand that it is a way to avoid the costs of unnecessary and inappropriate treatment measures for individuals not responsive to specific therapeutic approaches^[51]
- d. In addition to the problem of financial support for the development of new therapies, populations of developing countries remain without a sufficient amount of collected genomic data. For instance, India has 20% of the global population but represents only 1% of genetic data^[51]
- e. Establishment of frameworks for organizing, compiling, and expounding the influx of data that can keep pace with rapid scientific innovations will require the promotion of handling and proficiency in interpreting "omics" data, dealing with complexity and volume of new information^[52]
- f. The cost-effectiveness of this approach is highly argued upon. The global market for PM was valued at USD 43.6 billion in 2016 and is predicted to get tripled in the next decade.^[53] The economic dynamics of PM differ from conventional medicines, as the nature of approach in PM means it is likely to be approved for use only in a specific subpopulation, limiting the number of patients eligible for treatment with a given drug. Owing to the smaller market share, the competition to produce cheaper drugs between manufacturers may be less than conventional drugs. Collectively, these factors will impact the cost-effectiveness of PM
- g. There are legal, social, and ethical considerations associated with this concept. A major concern about genetic data is its linkage to databases that enables inferences about a person's social, cognitive, moral, cultural, health, sexual identity, to which participants had not consented^[54]
- h. While these approaches yield some degree of promise at the level of individual treatment and diagnosis, they are much more problematic when targeted at the population level, aiming to identify or improve the health of a large-scale high-risk population^[55]
- i. Improving the classification of disease is beneficial principally only if therapies are available. In the absence of treatment options, a better description of pathogenic processes may yield little benefit to the population even if it may benefit other patients in the future.^[56]

Table 1: Global precision medicine initiatives

Country (name of project, website)	Goals of programs
Australia (Australian Genomics Health Alliance) https://www.australiangenomics.org.au/	Develop a national framework for translating omics discoveries into clinical research and practice, including advice on the return of results from genomics research and clinical testing
Belgium (Belgian Medical Genomics Initiative, BeMGI) http://www.bemgi.be/	Predict clinical outcomes from genomic information and fulfill a pilot role toward concerted integration of genomic information in clinical care in Belgium.
Canada (Genome Canada) https://www.genomecanada.ca/	Large-scale research projects focused on the application of genomics in the area of precision health. Precision health can be seen as a more evidence-based approach to decision-making with regards to health care and public health.
Estonia (Estonian Program for Personal Medicine) https://en.wikipedia.org/wiki/Estonian_Genome_Project	Sequence 5K individuals, develop Estonian genotyping array, pilot of 50K Estonian Biobank members, offer to all 35-65 years (~500K) and link to EMR
France (Genomic Medicine 2025) https://aviesan.fr/fr/aviesan/accueil/toute-l-actualite/plan-francemedecine-genomique-2025	Deploy the instruments of the genomic care pathway and to allow access to genomic medicine for all concerned (patients and their families as indicated) in the territory
Israel (Bench To Beside Project) https://www.weizmann.ac.il/WeizmannCompass/sections/features/the-bench-to-beside-project	Weizmann Institute and Clalit project aiming to sequence 100,000 Israeli genomes from selected patients
Japan (Implementation of Genomic Medicine Project, IGMP) http://www.src.riken.jp/english/project/person/	Use genomics for optimized diagnosis, treatment, and prevention
Korea (Genome Technology to Business Translation Program) http://www.cdc.go.kr/NIH/eng/main.jsp	Use genomics to develop early diagnosis and treatment approaches for personalized and preventive medicine
Luxembourg (Centre for Systems Biomedicine) https://www.fr.uni.lu/recherche/priorites_de_recherche/luxembourg_centre_for_systems_biomedicine_lcsb	National Centre of Excellence in Early Diagnosis and Stratification of Parkinson's Disease
Singapore (POLARIS) https://www.a-star.edu.sg/polaris/	Pilot TGFBI testing for disease diagnosis and family risk assessment in stromal corneal dystrophies, then implement 90-gene panel for gastrointestinal cancers
Thailand (Pharmacogenomics and Personalized Medicine) http://www.thailandpg.org/	Implement pharmacogenomics card to identify risk for top ten drugs with risk for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), integrated with nationwide pharmacovigilance program
United Kingdom (Genomics England) http://www.genomicsengland.co.uk/	Sequence 100K whole genomes and link to National Health Service records to treat individual patients and better understand cancer, rare and infectious diseases
United States (All of Us) https://allofus.nih.gov/	Recruit one million participants representative of the population and share data from EMRs, digital health and genomics to enhance scientific discovery and clinical care

Source: Adapted from reference 91. EMR=Electronic medical records

Conclusions

The current era is of four Ps: preventive, predictive, precision, and participatory medicine. We are transitioning from an age of gold standards to one in which generalizations give way to patient-specific diagnostics and therapeutics. The term "Predictive" medicine has come into play as the technology is allowing us to better understand not only our genomics but also our epigenetic response to environmental changes, the resulting proteome in each of our cells and posttranslational modifications affecting our proteins. The National Research Council (NRC) expressed concern that "personalized medicine" may be misconstrued to mean that completely individualized treatments are available for every unique patient, which is not the case. PM has replaced the

term 'personalized medicine' as it merely refers to tailoring of medical treatment to the individual characteristics by classifying subpopulations using their common genetic patterns, lifestyles, drug responses, environmental, and cultural factors. "Participatory" medicine emphasizes that patients should play a decisive role in their own health care by actively controlling the health status and participating in the decision-making process regarding their treatment. It is necessary to bridge EBM and PM as outliers cannot be treated with EBM. The knowledge of PM could allow the transition from reactive to proactive medicine. Long-term goals of PM are better disease delineation and stratification, detection and monitoring of disease symptoms as early as possible, identification of presymptomatic individuals,

monitoring the evolution of the disease, and management of disease, making it less costly and with fewer adverse effects. Digital versions of data pertaining to the health status of patients constituting the electronic health record, such as medical and treatment histories, allows easy and secured electronic information retrieval. Various initiatives have been taken to implement PM globally, which have been summarized in Table 1 (adapted from reference 59). Obstacles in the way of PM are incomplete legal protection to prevent genetic discrimination, lack of comprehensive health care technology system, and a medical education system that has no skilled physicians who know how to incorporate PM diagnostics or pharmacogenomics into their practice. Efforts such as clinical path initiatives are paving way for collaborations with the pharmaceutical industry to address the challenges and accelerate progress in PM.

Some people from the medical community feel that the unstinting focus on PM is a diversion from the main aim of producing a healthier population and are not convinced that investing in biomedical research will result in unlimited rewards in finances. This could be a worthwhile investment with significant positive medical and socioeconomic outcomes for achieving “health for all.”

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