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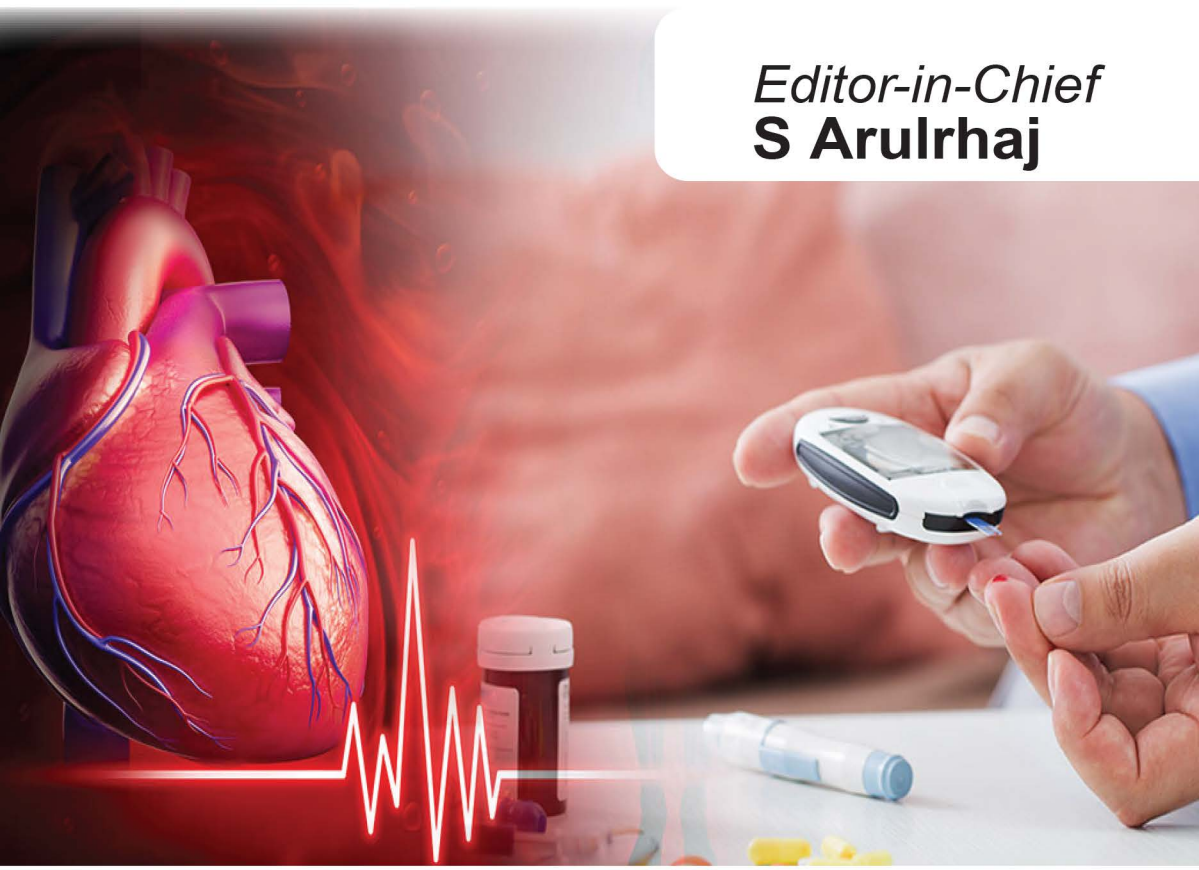
Clinical Update
CARDIO-DIABETES MEDICINE

Cardiology Obesity Lipids Diabetes



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2nd Edition

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CHAPTER

3

Precision Diabetes in India Where We are Today

G Vijayakumar

INTRODUCTION

The concept of precision medicine is becoming increasingly popular. The use of big data, genomics, and other "omics" like metabolomics, proteomics, and transcriptomics could make the dream of personalized medicine become a reality in the near future. The joint American Diabetes Association/European Association for the Study of Diabetes position statement for the management of hyperglycemia in type 2 diabetes mellitus (T2DM) encourages clinicians to consider a patient-centered approach.[1] Precision medicine is an emerging and promising approach that combines individual data on genes, biomarkers, and physiological and behavioral data to predict risks and responses to disease in a highly precise manner.[1]

SIX COMPONENTS OF PRECISION MEDICINE[1]

1. *Precision diagnosis*: It involves refining the characterization of the diabetes diagnosis for therapeutic optimization or to improve prognostic clarity using information about a person's unique biology, environment, and/or context. Precision diagnostics may involve subclassifying the diagnosis into subtypes, such as is the case in maturity-onset diabetes of the young (MODY), or utilizing probabilistic algorithms that help refine a diagnosis without categorization. Careful diagnosis is often necessary for successful precision therapy, whether for prevention or treatment. This is true where subgroup(s) of the population must be defined, within which targeted interventions will be applied, and also where one seeks to determine whether progression toward disease has been abated. Precision diagnosis can be conceptualized as a pathway that moves through stages, rather than as a single step.

   The diagnostic stages include: (1) an evaluation of prevalence based on epidemiology, including age, or age at diagnosis of diabetes, sex, and ancestry;

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(2) probability based on clinical features; and (3) diagnostic tests that are interpreted in the light of (1) and (2). A diagnosis in precision medicine is a probability-based decision, typically made at a specific point in the natural history of a disease, and neither an absolute truth nor a permanent state.

2. *Precision therapeutics*: It involves tailoring medical approaches using information about a person's unique biology, environment, and/or context for the purposes of preventing or treating disease (see "precision prevention" and "precision treatment", below).
3. *Precision prevention*: It includes using information about a person's unique biology, environment, and/or context to determine their likely responses to health interventions and risk factors and/or to monitor progression toward disease. Precision prevention should optimize the prescription of health-enhancing interventions and/or minimize exposure to specific risk factors for that individual. Precision prevention may also involve monitoring of health markers or behaviors in people at high risk of disease, to facilitate targeted prophylactic interventions.
4. *Precision treatment*: It involves using information about a person's unique biology, environment, and/or context to guide the choice of an efficacious therapy to achieve the desired therapeutic goal or outcome while reducing unnecessary side effects. Today, the objective of precision therapy is to maximize the probability that the best treatment of all those available is selected for a given patient. It is possible that in the future, precision diabetes medicines will be designed according to the biological features of specific patient subgroups, rather than for the patient population as a whole.
5. *Precision prognostics*: It focuses on improving the precision and accuracy with which a patient's disease-related outcomes are predicted using information about their unique biology, environment, and/or context. The focus of precision prognostics includes predicting the risk and severity of diabetes complications, patient-centered outcomes, and/or early mortality.
6. *Precision monitoring*: It may include the detailed assessment of biological markers (e.g., continuous glucose monitoring), behaviors (e.g., physical activity), diet, sleep, and psychophysiological stress. Precision monitoring can be achieved using digital apps, cutaneous or subcutaneous sensors, ingestible sensors, blood assays, etc. The intelligent processing, integration, and interpretation of the data obtained through precision monitoring are the key determinants of success. Precision monitoring may be valuable for precision prevention [e.g., in type 1 diabetes mellitus (T1DM)], precision diagnostics (e.g., where diagnoses are based on time-varying characteristics), and precision prognostics (e.g., where disease trajectories are informative of the development of key outcomes).

DIFFERENCE BETWEEN PRECISION MEDICINE AND PERSONALIZED MEDICINE

The precision medicine model includes patient engagement, digital health, genomics, molecular technologies, data sharing, and data science. In process,

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precision medicine magnifies evidence-based medicine for healthcare delivery. Clinical guidelines for precision medicine derived from population-level studies are precisely modified depending on patient-specific attributes to optimally treat them and to gather knowledge of new significant biological determinants.[2] Personalized medicine is an approach that rests on genetic, epigenomic, and clinical information to tailor patient-specific treatments and to comprehend the vulnerability of the patient to specific disease types.[3] Additionally, it also considers patient preferences, beliefs, attitudes, knowledge, and social context.

PRECISION MEDICINE IN DIABETES

The foundation of precision medicine in T2DM, like all other complex diseases, is population genetics **(Fig. 1)**. Mutation in the hepatocyte nuclear factor homeobox A (*HNF1A*) gene causes rare monogenic diabetes that can be successfully treated with sulfonylureas. Neonatal diabetes, diagnosed during infancy, is shown to have mutation in the genes encoding the adenosine triphosphate (ATP)-sensitive potassium channel [potassium voltage-gated channel subfamily J member 11 (KCNJ11) and ATP-binding cassette transporter sub-family C member 8 (ABCC8)]. On the other hand, variation in ataxia telangiectasia mutated (ATM) and solute carrier family 2 member 2 *(SLC2A2)* genes has been associated with metformin resistance or intolerance.[4]

The drive to develop precision medicine for diabetes is based on major technological advances such as high resolution "omics" assays, wearable devices that track the behaviors and exposures, and digital imaging. Intelligent integration of the data received from these technologies can provide detailed digital impressions of a person's physical condition, his past exposure and ongoing susceptibility to certain risk factors, and how he/she might respond to specific antidiabetic therapies. Eventually, all of this has the potential to substantially improve the prediction, prevention, and treatment of T2DM.[4]

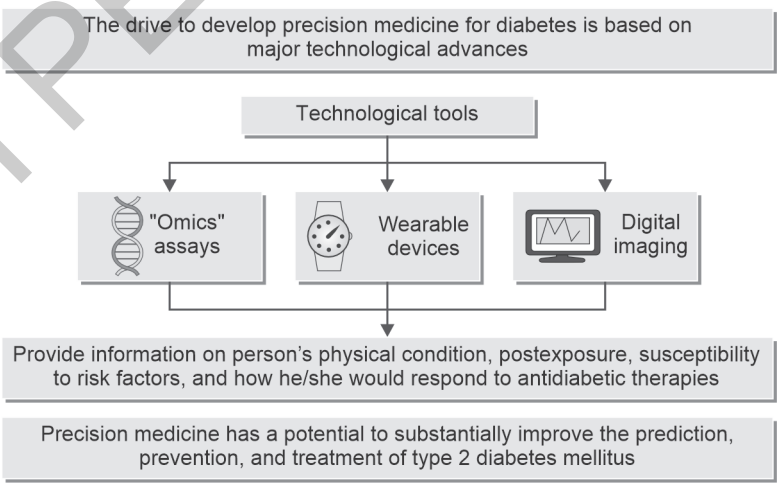

FIG. 1: The role of precision medicine in diabetes.

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Role of Pharmacogenetic Studies

Pharmacogenetic studies can be helpful in achieving one or several major objectives including patient stratification, target identification, and functional characterization. Patient stratification can help in identifying and defining subgroups of individuals who are more or less likely to experience clinical responses or side effects due to the drug. Target identification can ensure the discovery of novel drugs that can illustrate the mechanism of action and open new therapeutic avenues; pharmacogenetic experiments play a role in functional characterization as well. This may provide insights with respect to the mode of action of the gene product or the cell type in which it is expressed. This will eventually help target the right medication to the right person at the right time.[5]

Path to Precision Medicine in Type 2 Diabetes Mellitus

Although the objective is clear, the path to optimize prevention and treatment of diabetes and other diseases using precision medicine is still unclear. In this regard, a few precision medicine initiatives propose a clear plan for clinical translation as displayed on the slide. Some of the factors that should be considered in order to achieve this objective may include understanding of the disease, identifying disease-specific biomarkers, vertical integration of biomarkers and algorithms, regulatory engagement, patient engagement, testing of biomarker/s in clinical trials, clinician engagement, regulatory approval, implications on the health economics, clinical translation, and patient feedback.[4]

PRECISION MEDICINE FOR DIFFERENT STAGES OF DIABETES

Genetic testing can be considered effective in precision diagnosis and treatment selection of MODY and neonatal diabetes. Furthermore, genomic markers can predict genomic variants to predict the risk of T1DM and T2DM **(Fig. 2)**. As burden of diabetes lies in its multisystem complications, genetic

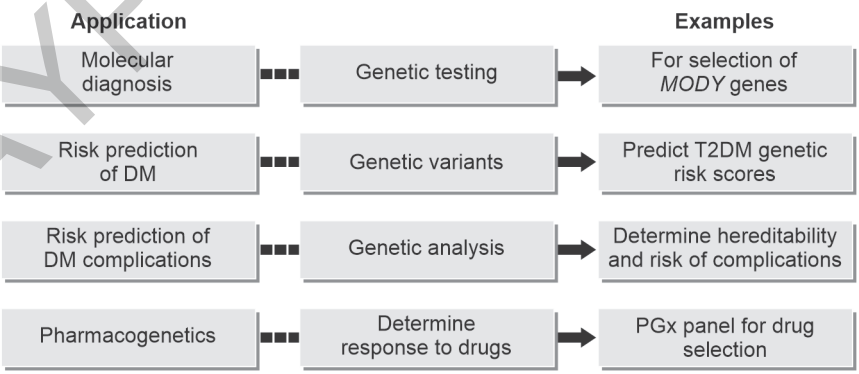

FIG. 2: Precision medicine in different stages of diabetes.

(DM: diabetes mellitus; MODY: maturity-onset diabetes of the young; PGx: pharmacogenomics; T2DM: type 2 diabetes mellitus)

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analysis of diabetic patients may provide vital information on the heritability of some of the complications associated with diabetes. However, it is important to note various confounding factors such as large number of confounders (e.g., age, sex, disease duration, smoking, obesity, control of blood lipids, blood glucose, and blood pressure), multiple drugs, and other nondiabetes-related factors (e.g., glomerulonephritis, renal stones, and drug toxicity), which can confound the genetic analysis of diabetic complications. Pharmacogenomics, on the other hand, might help practitioners to select a treatment with maximal efficacy and minimal side effects.[6]

Usefulness of Precision Diabetes in Monogenic Diabetes[7]

- *Neonatal diabetes mellitus*:
  - Helps to differentiate transient neonatal diabetes from permanent neonatal diabetes.
  - Helps to stop insulin administration and switch to high-dose sulfonylurea if the children have KCNJ11 or ABCC8 mutations.
  - Diabetes caused by *SLC19A2* gene mutations can be successfully treated with thiamine.
  - Early detection and treatment of Wolcott–Rallison syndrome ensures earlier detection and management of liver abnormalities.
  - Developmental disorders of the exocrine pancreas require replacement of pancreatic enzyme in addition to insulin.
  - Helps detect various genetic syndromes associated with neonatal diabetes mellitus.
- *Maturity-onset diabetes of the young*:
  - Patients with *HNF1A* and 4A MODY can be taken off insulin and treated with low-dose sulfonylurea.
  - Glucokinase (GCK)–MODY patients require only a diet regimen and all pharmacological treatment can be stopped, except if they become pregnant.

Practice Precision Medicine: Patient-centric Approach

Patients and consumers need to be a part of precision medicine to achieve its potential to the fullest. However, understanding important patient rights is necessary before patient engagement. Some important patient rights include the following:[8]

- Understanding the informed consent. Patients should know what exactly constitutes truly informed consent.
- Patients should know about the owner of their genetic information and who would make decision about what results and how they will be used.
- Securing genomic systems to ensure that data privacy is assured.
- Understanding which of the outcomes matter the most to them.
- Freedom to voice their preferences on sharing genomic and other information.

It is important that patients express their preferences and requirements, while they are assured that their data is secure.

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Patient Responsibilities in Precision Medicine

The concept of patient preference depends on the idea that patients should play a decisive role in their own healthcare by actively controlling their health status, providing consent approval for genetic data use in healthcare research, and also participating in the decision-making process regarding their treatments. Additionally, it is important that patients are vocal about their treatment preferences and their choice of healthcare professionals.[8]

Physician's Rights in Precision Medicine

In order to successfully transition precision medicine into medical practice, the following categories need reform, so that it will support the current and future physicians through this change. These three categories include medical curriculum reform, specialist training, and ongoing physician training.

1. *Medical curriculum reform*: Medical students need to undergo additional courses on genetics or genomics. Making genetics a core competency, introducing biomedical and bioinformatics, offering a dedicated track in medical school, integrating emerging research into graduate medical education, etc., can help.
2. *Specialist training*: It is necessary to increase the number of subject matter experts. The role of the specialists becomes complementary to that of the physicians and will also be critical to ensuring a successful implementation of the precision medicine model.[9]
3. *On-going physician training*: Current medical professionals rely on continuing medical education courses or certification courses in order to match the changes implemented in medical curriculum reform. Additionally, proper staffing (a certain percentage of qualified staff) is necessary. Additionally, competitive salaries for medical geneticists and specialists are necessary to attract more professionals to this field.[9]

Physicians' Responsibilities in Precision Medicine

In the era of precision medicine, it is essential that the patient–physician relationship is strong. Contemplating the patient as a person is considered to be a more holistic approach to precision medicine and offers greater promises to provide personalized care based on genomics, pharmacogenomics, proteomics, and metabolomics, among others. The physicians must be aware of the patient's psychological, social, cultural, behavioral, and economic situations in the management of the illness. The physicians should direct questions to understand the patient's values and goals of life, belief related to health factors, and personal preferences.[9]

The correct interpretation of direct-to-consumer genetic testing by the physician will be considered standard care in precision medicine initiatives in the future. Knowledge of the estimated increased or decreased risk of developing a particular disease based on the assessment of the odds ratio and the effect

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size may prove helpful while discussing with the patients.[10] In short, physicians should explore each individual's psychological, social, cultural, behavioral, and economic situations and their impact on a person's experience of health and illness.

CONCLUSION

A multitude of approaches is being made in the field of precision diabetes. It is too early to say that we have reached a stage where every patient with diabetes can be given a personalized form of treatment; we are beginning to understand that one size does not fit all. In the case of T2DM, clustering of the disorder has now been identified as the first step in precision diabetes. In the years to come, precision diabetes can be expected to play a big role in improving the quality of life of people with all forms of diabetes and help them achieve better control of their diabetes and thereby prevent complications.

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Salient Features

- Cardio-diabetes medicine is an emerging subspecialty of medicine
- *Clinical Update: Cardio-Diabetes Medicine* is the first book, which will give overall knowledge to practicing physicians on cardiodiabetology, covering both diabetes and cardiology aspects
- Type 2 diabetes mellitus is a coronary equivalent, which justifies the development of cardiodiabetology
- Diabetes and cardiovascular disease are two sides of the same coin
- Linkages and pathophysiology of cardiovascular diabetes in diabetes medicine are well analyzed and explained
- Clinical diagnosis, evaluation, and management of cardiovascular disease in diabetes are aptly highlighted
- Diabetes, cardiovascular disease, and chronic kidney disease—the Deadly Triplet—are correlated
- Digital interventions in cardio-diabetes medicine are well depicted
- Preventive aspects are very well highlighted.

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