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Review Article

Evolving Paradigm of Precision Medicine in Cardiovascular Disease

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ABSTRACT

In the year 1892, Sir William Osler, the legendary Canadian physician and one of the four founding professors of Johns Hopkins Hospital, said "If it were not for the great variability among individuals, medicine might as well be a science and not an art". It is this heterogeneity among patients with seemingly homogenous medical conditions, that form the basis of what we today refer to as precision medicine. The fundamental of precision medicine is based on the tenets of 'The right drug for the right patient at the right time'. Personalized or precision medicine found immense popularity in oncology. With the completion of Human Genome Project and the advent of genomics, big data and artificial intelligence, 21st century saw rapid progress of precision medicine in predicting, diagnosing and treating cancer. However, the same has not happened to cardiovascular diseases, the biggest killer of humanity. In this review article, we aim to address the concepts, components, outcomes and applications of precision medicine in general, and to review the evolving paradigm of how precision medicine is shaping the management of cardiovascular diseases. We delve deep into the aspects of risk prediction, preventative measures, and targeted therapeutic approaches for cardiovascular diseases. We also look at the recent trends and current applications of precision medicine in this area, the problems they solve and the challenges they possess, and what is in store for the future. Finally, we review the application of artificial intelligence specific to cardiovascular diseases, and the role of precision medicine in interventional cardiology.

KEYWORDS

Precision, Medicine, Personalized, Cardiovascular, Big data, Artificial intelligence, Machine learning, Genomics, Multiomics, Interventional cardiology.

Introduction

The Paradigm of Precision Medicine

In the last couple of decades, precision medicine has captured the imagination of researchers, doctors, patients and common man alike. There are reasons for this. From the days of practicing medicine based on clinical signs and symptoms of a disease, we have come a long way in digging deeper into individual attributes of a patient. This has resulted in a paradigm shift from treating the disease to

treating the patient. Precision medicine does 'precisely' that. It is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. This approach overcomes the limitations of reductionism in medicine, which presumes that all patients with the same signs of disease share a common pathophenotype and, therefore, should be treated similarly. Basically, precision medicine allows doctors and researchers to predict the most accurate treatment and prevention strategies for a specific group of people suffering from or vulnerable to a particular disease. It is in contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for the average person, with less focus on the differences between individuals. Evidence-based medicine is the foundation of contemporary clinical practice. Precision medicine makes this happen at an individual patient level and results in better clinical outcomes [1-7].

Definitions

There are multiple ways of articulating what precision medicine exactly is, and therefore it is no wonder that there are multiple definitions available.

- Tailoring the practice of medicine better to use known heterogeneity among individuals has been facilitated by advances such as gene sequencing, computational approaches for large datasets, and linkage of genomic data with longitudinal data.
- Use of molecular or other biomarkers (or related algorithms) that characterize differential disease risk, severity or ability to apply targeted treatment approaches to a defined subpopulation of patients.
- Medical care designed to optimize efficiency or therapeutic benefit for particular groups of patients, especially by using genetic or molecular profiling.
- A form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease.

Although definitions of precision medicine vary, it is broadly understood to be the treatments targeted to the needs of an individual patient on the basis of genetic, biomarker, phenotypic or psychosocial characteristics that distinguish a given patient from another patient with similar clinical presentation [8-13].

Overlapping Nomenclatures

The terms precision, personalized, stratified, and individualized medicine are related terms, with evolving use across multiple disciplinary domains. Similarly, there are terms like 'targeted therapy' or 'deep phenotyping' which are also used in the same context. The lack of specificity and interdisciplinary consensus around the meaning of these terms has resulted in different stakeholders using these terms interchangeably.

According to the National Research Council, "personalized medicine" is an older term with a meaning closely resembling "precision medicine". However, concerns were raised regarding the word "personalized". Experts opined that it could be misinterpreted to imply that treatments and preventions are being developed uniquely for each individual. However, in precision medicine, the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors [14-18].

Components of Precision Medicine

Precision medicine reconciles evidence-based medicine with the growing armamentarium of medical options and technologies. In today's world of big data and advanced data crunching capabilities, multiple, interdisciplinary technologies work in tandem and complement each other to culminate in precision medicine. Advancement in gene sequencing, computational approach for large datasets and linkage of genomic data with longitudinal data is ushering in newer possibilities. The spectrum of these individual components are ever expanding. Here are some of them.

- Multi-omics

o Genomics
o Proteomics
o Metabolomics
o Transcriptomics
o Epigenomics
o Microbiomics

- Biomarkers

o Disease biomarkers
o Prognostic biomarkers

- Environment
- Lifestyle
- Genetics
- Ethnicity
- Systems biology

o Big data
o Artificial intelligence
o Machine and deep learning algorithms

Precision medicine incorporates standard clinical and health record data with all of the above for deep phenotyping. These phenotypic data can then be analysed within the framework of molecular interaction networks, often referred to as interactome, to uncover previously unrecognized disease phenotypes, relationships between diseases, and select pharmaco-therapeutics or identify potential protein-drug or drug-drug interactions [19-21].

Outcomes of Precision Medicine

In terms of the objectives of precision medicine and what it ought to deliver, there are two broad categories:

A) Personalized treatment strategies; treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations.

B) Precision medicine as a model that integrates clinical and other data to stratify patients into novel subgroups; it is hoped that these have a common basis of disease susceptibility and manifestation and thus potentially allow for more precise and novel therapeutic solutions.

Thus, the focus of precision medicine is on the stratification of patients. This is sometimes referred to as a novel taxonomy, and is derived using large-scale data that go beyond the classical signs and symptoms approach. The end result of precision medicine is identifying treatable traits, i.e. disease subgroups that can be treated in a better way because of more precise and validated phenotypic recognition or due to a better understanding of the critical causal pathways.

However, it must be taken into consideration that precision medicine is not equal to a simple convergence of new technologies. For instance, information relevant to genomics knowledge needs effective integration with genetics, metabolomics and clinical phenotypes (including symptoms, signs, biochemistry, image and pathological features) to create a complete individualized biological database, which can contribute to diagnosis and treatment based on individualized patient's condition [22-25].

Application of Precision Medicine

One of the earliest and most obvious applications have been targeted therapies in cancer. Determination of the human epidermal growth factor receptor 2 (HER-2) in breast cancer patients is often cited as an example. Initially HER-2 was discovered to be a prognostic factor with positive patients having a higher probability of a more aggressive course of disease. Subsequent trials showed the efficacy of the monoclonal antibody Trastuzumab, directed against and epitope on HER-2 protein. Currently, Trastuzumab is given only to the sub-group of HER-2 positive females. Another example is the cell growth signaling protein BRAF, which is present in an altered form (known as BRAF V600E) in many melanomas. Vemurafenib targets this mutant form of the BRAF protein and is approved to treat patients with inoperable or metastatic melanoma that contains this altered BRAF protein.

In 2018, The US Food and Drug Administration (FDA) granted breakthrough approval to larotrectinib, an oral tyrosine kinase (TRK) inhibitor indicated for the treatment of advanced solid tumours in adult and paediatric patients with neurotrophic receptor tyrosine kinase (NTRK) gene fusion. It became the first cancer drug for a specific genetic mutation, and not a traditional cancer type. In the same year, osimertinib was approved for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.

Targeted therapies are currently the focus of anticancer drug development. They are a cornerstone of precision medicine that uses information about a person's genes and proteins to prevent, diagnose, and treat disease.

The spectrum is rapidly growing. Today, newborn screening, prenatal screening and diagnosis, neurodegenerative diseases, asthma, infection and a lot of other diseases are being managed with the help of precision medicine [26-29].

Precision Medicine in Cardiovascular Diseases (CVD)

CVD are the number one cause of death globally. More people die annually from CVDs than from any other cause. An estimated 17.9 million people died from CVDs in 2016, representing 31% of all global deaths. Of these deaths, 85% are due to heart attack and stroke. Out of the 17 million premature deaths (under the age of 70) due to non-communicable diseases in 2015, 37% are caused by CVDs. Prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 in 2019, and the number of CVD deaths steadily increased from 12.1 million in 1990, reaching 18.6 million in 2019. This number is estimated to rise to > 23.6 million by 2030 [30,31].

Therapeutic Area	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib
	Lung cancer	EML4-ALK	Crizotinib
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs
Infectious disease	HIV/AIDS	CD4+T cells, HIV viral load	Highly active antiretroviral therapy
Cardiovascular disease	Coronary artery disease	CYP2C19	Clopidogrel
Pulmonary disease	Cystic fibrosis	G551D	Ivacaftor
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs
Hematology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents
Endocrine disease	Multiple endocrine neoplasia type 2	RET	Prophylactic thyroidectomy
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy
Psychiatry	Alcohol-use disorder	GRIK1	Topiramate
Pharmacogenomics	Smoking cessation	CYP2A6	Varenicline
Ophthalmology	Leber's congenital amaurosis	RPE65	Gene therapy

Table 1 gives a snapshot.

In spite of these telling statistics, CVD have long been neglected in precision medicine initiatives. The fact that CVD often develop slowly, and over course of many years, it is perceived wrongly to be more benign than other diseases like cancer. But at the same time, the relatively slow disease progression provides an opportunity to identify those at risk, offer preventive strategies and start therapy earlier.

Over the past fifty years, attempts to medically manage CVD has been achieved through the adoption of lifestyle modifications, including dietary, tobacco, and exercise interventions, as well as evidence-based therapies that aimed to modify a clinically recognizable and commonly shared cardiovascular or at-risk phenotype. Despite the relative success of this approach, the related issues of disease prevention and cure have been elusive, primarily because of imprecise deep phenotyping of individuals needed to characterize sub-groups of disease.

Although this paradigm of care can ameliorate symptoms and affect disease progression, outcomes are not always certain. Particularly when targeting a chronic complex illness like atherothrombotic CVD that does not have a single root cause. To address this issue, it is necessary to understand the totality of CVD at a granular and integrative molecular level.

This conventional approach to management of CVD is basically an overly simplistic view of the multiple contributors to and complexity of an individual's CVD phenotype. It is now appreciated that other factors, such as exposure to the natural, personal, and social environments, contribute to an individual's highly personalized CVD phenotype. Integration of this large body of data points lends itself towards a more stringent pathophenotype, one that is amenable to precision medicine.

Thankfully, the situation is improving. In cardiovascular medicine, the potential of precision medicine applies to all stages of the disease development. This includes risk prediction, preventative measures, and targeted therapeutic approaches. Precision medicine, as mentioned earlier, depends on the inputs from multiple sources, and not just genomics. In fact, it heavily depends on established biomarkers, functional tests, and imaging. In real world clinical practice, cardiovascular medicine generally relies on noninvasive diagnostic procedures and symptom-based disease management. While disease like oncology and immunology have migrated to molecular diagnostics that lend themselves to precision medicine approaches, there are immense opportunities in the CVD space to implement precision medicine approaches by focusing on common diseases such as hypertension, conditions with diagnostic and prognostic uncertainty such as angina, and conditions that are associated with high mortality and economic burden.

The concept of precisely understanding the problem in and individual patient, and taking best possible medical steps in nothing new in CVD. Doctors do take help of biomarker-based diagnostic criteria, specific and quantifiable criteria driven therapeutic decisions, and monitoring of therapeutic strategies using imaging and other techniques. Following are some of the examples:

- Definitions of acute coronary syndromes based on cardiac troponins
- Hypertension based on blood pressure or thresholds
- Diabetes based on measures of glycemic control
- Heart failure not only based on symptoms but also on ejection fraction

In all of the examples mentioned above, appropriate therapeutic approach can be chosen depending on the precise characterization of disease.

However, the era of big data is ushering in new possibilities. With rapid advances in molecular medicine in general and the widespread availability of genetic and genomic data in particular, like the ability to sequence the whole genome of individual patients at reasonable cost, cardiovascular medicine is witnessing promising opportunities. Increasingly detailed molecular characterization of CVD has the potential to translate into equally precise therapies.

It's easier said than done. The spectrum of CVD is significantly broad and encompasses diseases related to blood vessels, the myocardium, heart valves, the conduction system, and developmental abnormalities. In spite of these fundamental challenges, there has been a recent surge in our molecular understating of CVD syndrome. Following are some of the examples:

- Mutation in the low-density lipoprotein receptor (LDLR) gene that causes familial hypercholesterolemia
- Mutation in beta-myosin heavy chain and other sarcomeric proteins that are causal for hypertrophic cardiomyopathy
- Mutation in the fibrillin (FBN1) gene that causes Marfan syndrome
- Mutations in the alpha subunit of the type V voltage-gated sodium channel (SCN5A) was initially described as a single causal gene for inherited long QT syndrome. Since then, other phenotypes have been associated with the mutation, including Brugada syndrome and dilated cardiomyopathy
- Loss-of-function mutation in PCSK9 and mutations in zinc transporter 8 that protect obese individuals from diabetes mellitus

In essence, the complexities of the CVD phenotype with significant biologic diversity, owing to its numerous genetic, metabolic, and environmental mediators, means that there is no single therapy that will cure the disease. Drugs made to target a single factor in a multifactorial disease like CVD is unlikely to succeed. That has been the Achilles heel. This is where modern precision medicine approaches have stepped in CVD. Protein interaction network-targeted therapy that uses a combination therapy strategy targeting multiple steps in a signalling pathway or network identified by deep phenotyping, is such an example [32-37].

There are several recent examples of precision medicine approaches with the use of advanced molecular methodologies to discover unique individual traits within a clinical syndrome that has underlying heterogeneity. Here are some of the examples:

- The P2Y12 inhibitor clopidogrel has a range of inter-individual variability, with some individuals being non-responders.

o This is a phenotype that has been associated with genetic determinants and an increase in ischemic events.

o Loss-of-function alleles in CYP2C19 (CYP2C19*2 and CYP2C19*3) have been associated with poor drug responsiveness, while the gain-of-function allele CYP2C19*17 is associated with increased bleeding risk.

o This information has been used to tailor therapy in patients with drug-eluting stents [38].

- Soluble carrier organic anion transporter 1B1 (SLCO1B1), which regulates statin influx and metabolism in the liver, has been associated consistently with myopathy.

o Patients who are either homozygous or heterozygous for the rs4263657 polymorphism have an increased risk for rhabdomyolysis with statin use; therefore, it is now suggested that individuals with this specific single nucleotide polymorphism (SNP) avoid statin drug [39,40].

- Anticoagulant Warfarin, has a narrow therapeutic index but wide inter-individual variation.

o Warfarin is metabolized in the liver by oxidation by cytochrome P450 2C9 (CYP2C9), and inhibits the protein vitamin K epoxide reductase complex subunit 1 (VKORC1).

o There are 10%–50% variability in dose requirements to genotypes, particularly SNPs in CYP2C9 (CYP2C9*2, CYP2C9*3) and VKORC1 (rs9923231).

o FDA has taken a cognisance of these genetic variants and updated the drug packaging to include information on dosing based on CYP2C9 and VKORC1 genotypes [41,42].

- Genetic variants have been identified that modify the response to other relevant cardiovascular drugs, including beta-blockers (ADRB1, ADRB2, GRK5, GRK4); angiotensin converting enzyme inhibitors (ACE, AGTR1); diuretics (ADD1, NPPA, NEDD4L); and calcium channel blockers (CACNB2, CACNA1C).

o In the near future, genetic testing may be routinely deployed as a companion diagnostic to guide selection of these drugs [43].

- Inherited connective tissue disease due to variants in ACTA2, MYH11, or TGFBR2 may potentially prompt consideration of surgical intervention at a smaller aortic aneurysm diameter [44].
- Targeted therapies, including antibody-based therapeutics, gene editing, and silencing technologies, are either available or under development for several genetic diseases like long QT syndrome (LQTS), Duchenne muscular dystrophy (DMD), TTR cardiac amyloidosis and Fabry disease [45].
- Approximately 70% of LQTS cases have variants in sodium and potassium channels (KCNQ1, KCNH2, and SCN5A). These genotypes designate subtypes LQT1, LQT2, and LQT3, respectively.

o These designations suggest the most appropriate and effective medical interventions.

o Mexiletine, a voltage-gated sodium channel blocker, has been shown to reduce arrhythmic events in LQT3, whereas β-blockers may be pro-arrhythmic.

o Whereas, β-blockers can reduce the risk of cardiac events in both LQT1 and LQT2, and genotype can help suggest the most effective β-blockers for each [46,47].

- In order to identify genetic risks for CVD which may lead to personalized treatment and better outcomes, Baylor College of Medicine cardiologists and the Human Genome Sequencing Center Clinical Laboratory developed HeartCare™, a custom test targeting genes that influence risk for CVD and related conditions. The HeartCare™ panel analyzes 158 genes associated with a risk for CVD and related conditions, including aortic aneurysms, cardiomyopathies, arrhythmias and hypercholesterolemia. The test also examines an individual's genetic risk for sensitivity to certain prescribed medications including clopidogrel, warfarin and statins [48,49].

The Role of Artificial Intelligence (AI) in Precision Medicine for CVD

In the 21st century, the paradigm is shifting from traditional statistical tools to the use of AI in cardiovascular medicine to enable precision medicine in CVD. In today's era of big data, huge amounts of multi-disciplinary data can be processed by AI to automatically generate new hypotheses, instead of physicians having to do the same. AI driven computational modelling assists precision medicine by integrating individual patient data (the phenotype) to stratify risk and identify more precise therapeutic solutions and simulate the effects of a therapy in the individual person of interest. AI, therefore, will potentially assist physicians in making better clinical decisions.

Although the application of AI in CVD is still in its nascent stage, big data analytics using AI will eventually be the most important contributor to CVD management. Here are some of the recent advances:

- AI has the ability to classify new genotypes or phenotypes of heart failure (HF) with preserved ejection fraction (HFpEF), and novel diagnostic echocardiographic parameters could potentially lead to novel targeted therapy.
- AI may also improve the accuracy, reproducibility and precision of 2-dimensional speckle-tracking echocardiography (2D-STE) quantitation and other cardiac imaging methods.
- Facilitate identification of novel genotypes or phenotypes of heterogeneous syndromes, such as HFpEF, Takotsubo cardiomyopathy, hypertrophic cardiomyopathy, primary pulmonary hypertension (PH), hypertension (HTN), and coronary artery disease (CAD), leading to personalized, targeted therapy.
- Big data analytics using AI can also play a critical role in taking important clinical decisions, such as selection of antiplatelet agents in individuals who are post–percutaneous coronary intervention (PCI), anticoagulant agents in individuals with non-valvular atrial fibrillation (AF), and pharmacogenomics in individuals.
- Big data analytics has the potential to identify unknown risk factors for acute coronary syndrome (ACS), spontaneous coronary artery dissection (SCAD), or Brugada syndrome, and use of statins in the older population.

In summary, big data (genetics, social media, environmental, and lifestyle-related factors, or "omics" data) can be stored through electronic health records (EHR) or precision medicine platforms, and can be shared for data analysis with other physicians or researchers through secure cloud systems. Big data analytics using AI (machine learning, deep learning, or cognitive computing) will enable precision CVD medicine. In the near future, cognitive computers, such as IBM Watson, as well as technology initiatives from companies like Apple and Google, will be the standard in health care facilities and assist physicians with their decision making and prediction of patient outcomes, facilitating precision medicine in CVD [50-53].

Precision Medicine in Interventional Cardiology

AI driven technologies are invaluable for patient-tailored device selection and treatment in interventional cardiology space [54].

In 2010, for the first time, the 'Heart Team' concept was integrated into the European Society of Cardiology revascularization guidelines, inspired by expert opinion and by the SYNTAX coronary revascularization trial. The concept has been ensconced class I recommendation in both the European and ACC/AHA guidelines and has gained increasing traction in context of complex and multi-modality procedures. This is a classical instance of the application of precision medicine in interventional cardiology. The multidisciplinary heart team makes systematic use of intravascular imaging for left main stem stenting and plaque modification technology. The heart team is a tool to integrate multiple perspectives from different disciplines that are involved in the management of a patient. The consensus of the heart team is personalized and therefore specific to the individual patient [55,56].

Intravascular imaging with intravascular ultrasound (IVUS) or optical coherence tomography optimizes clinical outcomes. IVUS assesses plaque composition and distribution before PCI and can identify multiple abnormalities such as under-expansion, malposition or edge dissections after PCI. These quantitative and qualitative characteristics may be used to guide targeted, patient-tailored device selection and result in optimal lesion preparation and stent deployment with proper expansion and apposition [57].

Virtual Physiological Human (VPH) project is an example of AI based patient-specific modelling to support medical decision and simulate therapeutic strategies that relate uniquely to one particular patient. VPH models can incorporate numerous patient-specific variables, such as lifestyle, medical history, physical examination, diagnostic tests and genetics to make reliable predictions in CVD [58,59].

HeartFlow FFRCT generates a patient-specific 3D model of the coronary arteries from static coronary CT images and simulates pressure, velocity and blood flow to predict the fractional flow reserve. It facilitates assessing coronary physiology and subsequently the functional importance of a particular stenosis in the coronary arterial tree. Computational modelling is used to compare a unique CT scan of a patient with a database of CT scans to determine the clinical importance of stenosis. Non-invasively, it shows whether PCI would be effective. It may also predict the effect of coronary stenting, including residual coronary flow after PCI. This technique will potentially allow patients with vulnerable plaques to be identified, in whom PCI might have prophylactic benefit [60,61].

The FEops HEARTguide integrates CT imaging with tissue and device characteristics to simulate device-host interactions and predict calcium displacement, device deformity, residual periprosthetic leak and occurrence of conduction abnormalities secondary to focal pressure phenomena in patients who undergo transcatheter aortic valve implantation (TAVI) for severe aortic stenosis. Computational modelling helps to identify and select the best device for a specific anatomy, whether it is in the coronary or structural heart space [62,63].

The optimal duration of dual antiplatelet therapy (DAPT) is contentious. Among patients who complete one year of dual antiplatelet therapy after PCI without an ischemic or bleeding event, continuing therapy decreases stent thrombosis and MI, but increases bleeding. Use of Intravascular technology in complex lesion and plaque modification tools in calcified lesions, augmented by AI driven prediction rule assessing ischemic and bleeding risks helps to determine DAPT strategy [64].

Conclusion

Precision medicine holds promise for improving many aspects of healthcare. Technological advances in sequencing and interpreting the genome, as well as our ability to convert this information into effective treatments, are rapidly evolving. Today we are better equipped to find and target disease-causing variants. We are now building capabilities to change these variants at the genome level, editing them out before they have the opportunity to manifest disease. These advances in genomics, together with technological innovations both in the laboratory and in computational biology is propelling us forward into a new era of cardiovascular care. Our goal of giving each individual the right treatment at the right time no longer seems to be utopian.

Although randomized trials remain the pinnacle of evidence-based medicine and backbone of contemporary clinical practice, physicians need to figure out how to implement the best clinical option for each individual patient. Further refinement by advanced computational modelling in concert with artificial intelligence and computer learning will be a prelude to the medicine of the future. Augmented ability in precision medicine will allow us to predict which treatments will work best for specific patients, better understanding of the underlying pathophysiological mechanisms of various diseases and improved strategies to prevent, diagnose, and treat a wide range of diseases.

In cardiovascular medicine the potential of precision medicine applies to all stages of the disease development and includes

risk prediction, preventative measures, and targeted therapeutic approaches. Precision medicine is set to evolve based on the new developments in 'multi-omics' and at the same time heavily depend on established biomarkers, functional tests, and imaging. As clinical genome sequencing becomes more common and basic science techniques like CRISPR and induced pluripotent stem cells become more relevant and widespread in clinical applicability, the paradigm of cardiovascular medicine will migrate towards more precise and accurate with our diagnoses and treatment.

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