# 4 Precision Medicine in Cardiovascular Disease Practice

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**What Will You Learn in This Chapter?**

In this chapter, we will get familiar with personalized medicine in the field of cardiology, the genetic basis of most common cardiovascular diseases, and the role of genetics in pharmacotherapy. We will also discuss the ethical issues in personalized medicine and the perspective of this field in cardiology.

**Rationale and Importance**

Personalized medicine is important in early diagnosis; choosing the best treatment options, including the most suitable pharmacotherapy in familial arrhythmias; and preventing adverse drug reactions in the field of cardiology. Recognizing the best treatment and preventive strategy is individualized. It is crucial for healthcare providers to apply the most appropriate approach to patients.

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## 4.1 Introduction

Personalized medicine (PM) is a concept that modifies therapeutic strategies according to each individual's genomic, epigenomic, and proteomic profiles [1]. The major concept of PM is the treatment and care of patients with a particular condition while considering individual alterations in genetics, exposures, and lifestyle [2]. Cardiovascular diseases (CVD), the most common cause of death all over the world [3], have genetic risk factors, and the pharmacokinetics of cardiology drugs have a broad spectrum of different genotypes [4]. Moreover, genome-wide associated (GWA) studies have revealed several genetic variants that are associated with cardiology conditions such as cardiomyopathies, arrhythmias, and coronary artery diseases. Thus, determining genetic information and applying PM strategies are useful in the effective preven-



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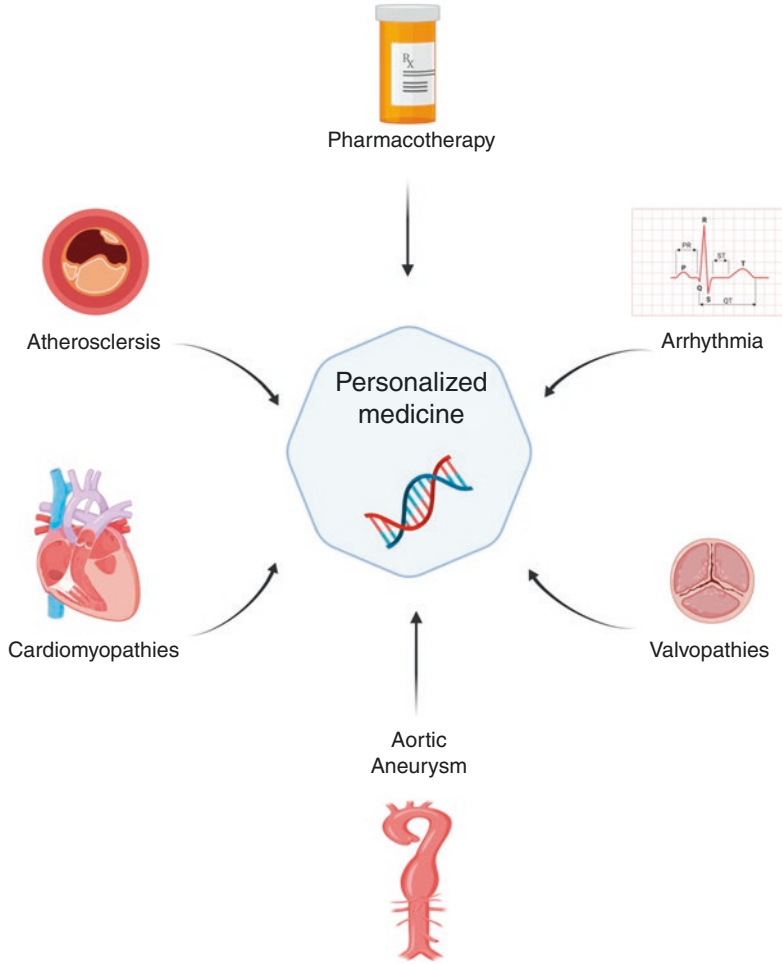


**Fig. 4.1** Personalized medicine in cardiovascular disease. This figure was created with Biorender.com. All rights and ownership of BioRender content are reserved by BioRender

tion and treatment of several cardiologic conditions (Fig. 4.1).

## 4.2 Drugs

### 4.2.1 Warfarin

Warfarin is an anticoagulant that is often prescribed for the treatment and prevention of thromboembolic events in people with prosthetic heart valves, atrial fibrillation, venous thrombosis, and a history of stroke. Warfarin dose requirements, drug response, and risk of bleeding are influenced by environmental factors (such as vitamin K consumption, age, gender, and concurrent medications) and by genetic variations [5]. *VKORC1*, *CYP2C9*, and *CYP4F2* are considered the main genes that may influence warfarin metabolism and cause genetic variations.

#### 4.2.2 *VKORC1*

The *VKORC1* gene encodes the target enzyme of the warfarin drug, the vitamin K epoxide reductase enzyme, which is responsible for reducing vitamin K epoxide to the active form [6]. A common non-coding variant of *VKORC1* that occurs in the promoter region of the gene, c.-1639G>A (rs9923231) polymorphism, affects protein expression and is associated with warfarin sensitivity and lower dose requirements. Patients who are carrying one or two "A" alleles at -1639

require lower warfarin doses than -1639G/G homozygotes [1, 7, 8]. The c.-1639G>A allele frequency shows a discrepancy among different ethnic groups and is more common among Asians, Caucasians, and African Americans [2, 9, 10]. Besides, other less common coding *VKORC1* polymorphisms (such as Asp36Tyr) are associated with warfarin resistance and higher dose requirements [4, 11].

### 4.2.3 *CYP2C9*

*CYP2C9* is a member of the cytochrome P450 superfamily (CYP450) that metabolizes the more potent warfarin S-enantiomer. *CYP2C9*1* is the wild-type allele in the "normal metabolizer" phenotype (those with normal enzyme activity and metabolism). Individuals carrying two well-characterized variant alleles, *CYP2C9*2* and *CYP2C9*3*, are known to be more sensitive to warfarin, require lower doses to achieve the therapeutic range, are at a higher risk of bleeding, and take longer to achieve a stable INR compared to normal metabolizers [12, 13]. The maintenance dose requirements of warfarin in patients with *1*1, *2*2, and *3*3 genotypes are reported as 5.28 mg/day, 3.04 mg/day, and 0.5 mg/day, respectively [14]. Other *CYP2C9* variants (*CYP2C9*5*, **6*, *8**, and **11*), which are more common among African Americans, are also associated with decreased enzyme activity and dose variability [15].

### 4.2.4 *CYP4F2*

*CYP4F2* is the vitamin K oxidase enzyme and acts as an important counterpart to *VKORC1* (vitamin K reductase enzyme), limiting vitamin K accumulation in the liver [16]. A known variant of *CYP4F2*3* (c.1297C>T, rs2108622) has been shown to affect enzyme activity and dose requirements of warfarin [17]. Caucasian individuals who carry two "T" alleles require a higher dosage of warfarin (1 mg/day) compared to those with two "C" alleles, which is explained by the reduced function of the enzyme in those with "T" alleles [18]. Thus, including this *CYP4F2* variant in warfarin dosing models is helpful in dose prediction in Asians and Europeans, but not in African Americans [19–21].

### 4.2.5 P2Y12 Inhibitors

Clopidogrel is a prodrug, and genetic variants influence the catalytic activity of the CYP P450 isoforms (such as *CYP2C19*, *CYP1A2, CYP2B6, CYP2C9*, and *CYP3A*) and affect the efficiency of active metabolite generation [22]. The most common *CYP2C19* loss-of-function alleles are *CYP2C19*2* (G681A) and *CYP2C19*3* (G636A), and the most common allele that results in increased enzyme activity is CYP2C19*17 [23]. Therefore, based on the *CYP2C19* genotypes, patients are categorized as ultrarapid metabolizers (*1/*17, *17/*17), extensive metabolizers (*1/*1), intermediate metabolizers (*1/*2, *1/*3, *2/*17), and poor metabolizers (*2/*2, *2/*3, *3/*3) [24]. The ABCB1 gene polymorphisms are also known to be associated with clinical outcomes in clopidogrel-treated patients [25]; however, the association has been inconsistent across studies, with several studies finding no relationship between *ABCB1* variants and the antiplatelet effect of clopidogrel [26]. Prasugrel and ticagrelor are both stronger P2Y12 inhibitors than clopidogrel and lower platelet reactivity more effectively, irrespective of the *CYP2C19* genotype [27, 28]. Moreover, polymorphisms of the other isoforms of the CYP450 system appear to not influence prasugrel pharmacokinetics or pharmacodynamics [28].

### 4.2.6 Statin

Statins, HMG-CoA reductase inhibitors, act by inhibiting cholesterol biosynthesis and increasing low-density lipoprotein cholesterol (LDL-C) uptake by hepatocytes. *SLCO1B1* and *ABCB1* are proteins that play a role in the transportation of statins. The *SLCO1B1* 521C (rs4149056) variant is associated with a reduction of the lipid-lowering effect of simvastatin, atorvastatin, lovastatin, and pravastatin. Three ABCB1 gene polymorphisms

(1236T, 2677T, and 3435T) have been linked to statin pharmacokinetics and toxicity. HMG-CoA reductase is an important enzyme in cholesterol synthesis and is inhibited by statins within hepatocytes. The H7 haplotype of HMG-CoA reductase is associated with decreased lipid-lowering response to statins [29]. Polymorphisms in the *CYP3A* gene, such as *CYP3A4*22* (rs35599367) and *CYP3A5*3* (rs776746), have been shown to reduce CYP3A4 enzyme levels and activity, as well as to affect the pharmacokinetics of simvastatin, atorvastatin, and lovastatin [30, 31].

## 4.3 Cardiomyopathies

### 4.3.1 Hypertrophic Cardiomyopathy (HCM)

HCM is one of the common hereditary cardiac diseases, which is associated with two main pathogeneses; the first one is defects in myocardial filaments, associated with sarcomeric genes, and the second one is metabolic and infiltrative disorders [32]. The gene variants that are associated with HCM are the *MYH7* gene, which encodes the myosin heavy chain [33], *TNNsT2* which encodes cardiac troponin T [34], *MYBPC3* which encodes myosin-binding protein C [35], *TNNI3* which encodes Cardiac troponin I [36], and *FHOD3* which encodes "Formin homology 2 domains containing 3" [37]. Moreover, there are some syndromic genes without isolated left ventricular hypertrophy, including the autosomal recessive *GAA* gene as Pompe disease [38], and X-linked *GLA*, which presents as Anderson-Fabry disease [39]. Genotype-positive patients have been shown to present with illness approximately 10 years earlier, to have a greater maximum left-ventricular wall thickness, and to have a higher proportion of family history of HCM and sudden cardiac death than others [40].

### 4.3.2 Dilated Cardiomyopathy (DCM)

A strong familial component has been reassuringly confirmed in DCM [41]. About 111 genes are associated with DCM. The most associated gene is *TTN*, which encodes Titin, the largest structural protein of the heart [42]. Another gene variant that is associated with approximately 5% of the causes of DCM is *LMNA* missense and truncating mutations [43]. *LMNA* mutations are the main genetic cause of arrhythmogenic DCM.

### 4.3.3 Restrictive Cardiomyopathy (RCM)

RCM, one of the rarest and poor-prognosis cardiac disorders, is characterized by a normal-sized left ventricle with a hypertrophic atrium. Amyloidosis, as an infiltrative disorder, is the most common cause of RCM. *TTR* gene variants and *APOA1* are the main genetic perturbations in amyloidosis [44]. There is a lack of adequate data about non-infiltrative RCM genes; however, *TNNI3*, *TNNT2*, *TNNC1*, *TPM1*, *TTN*, *MYH7*, *MYL2*, *MYBPC3*, *MPN*, *DES*, *FLNC*, *LMNA*, and *BAG3* were labeled as associated genes in RCM [45, 46]. Most of these genes encode sarcomeric proteins. Moreover, *CRYAB*, which encodes heat-shock proteins (such as crystallin B and *BAG3*), is also reported in some studies [45, 47].

## 4.4 Thoracic Aortic Aneurysm/ Aortic Dissection (TAAD)

Several causal genes have been identified in syndromic and non-syndromic TAAD. Variants in the smooth muscle contractile (SMC) genes, including *ACTA2, MYH11, MYLK,* and *PRKG1*, have been associated with non-syndromic TAAD [48]. Syndromic TAAD is associated with several connective tissue disorders and their corresponding genes, including Marfan syndrome (*FBN1*), Loeys-Dietz syndrome (*TGFBR1, TGFBR2, SMAD3*, and *TGFB2*), Ehlers-Danlos syndrome (*COL1A1, COL1A2, COL3A1, COL5A1,* and *COL5A2*), arterial tortuosity syndrome (*SLC2A10*), and Shprintzen-Goldberg syndrome (*SKI*) [49]. Marfan syndrome patients with *FBN1* mutations have a low risk for acute aortic dissections at diameters less than 5.5 cm and for aneurysms of other arteries [50].

Common genetic variants at 15q21.1, in the *FBN1* gene, are associated with an increased risk of TAAD in the general population and are common pathogeneses of aortic disease in Marfan syndrome and sporadic TAAD [51]. Loeys-Dietz syndrome patients with *TGFBR1* and *TGFBR2* mutations are at higher risk of aortic dissections at aortic diameters less than 5.0 cm, and these patients have aneurysms and dissections of other arteries. Furthermore, studies have shown that *TGFBR1* mutation carriers may have a lower risk of aortic dissection with minimal enlargement than *TGFBR2* mutation carriers [52]. *MYLK* encodes the Ca2+/calmodulin-dependent myosin light-chain kinase, which phosphorylates the regulatory light chain in smooth muscle cells to initiate contraction [53]. *MYLK* missense variants were shown to be associated with earlier-onset aortic events compared to haploinsufficient variants [54].

## 4.5 Valvopathies

Aortic stenosis (AS) is the narrowing of the aortic valves that leads to obstruction of blood flow from the left ventricle (LV) to the aorta. The incidence of AS is increasing with the aging population. Today, AS is not considered a passive degenerative disease anymore. It is associated with a dynamic, complex, and highly regulated pathobiological process that leads to a multitude of events [55]. The characterization of the whole protein complements of the genome, which is termed "proteome," is the major goal of proteomics that could improve the patient's management. Analysis of the cell or tissue is a suitable platform as they are eventually the targets for novel medications and should provide important evidence for treatment discovery.

As a result, lipoproteins and oxidized phospholipids play a significant role in AS that generates inflammation, apoptosis, and calcification of the aortic valve [56]. *LPA* genetic variants linked to Lp(a) levels are significantly linked to aortic valve calcification and incident AS [57]. Accordingly, to manage the progression of AS, aiming lipoprotein(a) is a potential therapeutic target. The other potential mechanisms are:

1. Calcium deposition: which includes calcium, phosphate, vitamin D, fibroblast growth factor 23 (FGF-23), and PTH; the vitamin D/PTH axis biomarkers are the most verified factors [58]. The N-terminal propeptide of human procollagen type I (PINP), beta carboxy-terminal cross-linking telopeptide of type I collagen (β-CTx), osteocalcin, osteopontin, osteoprotegerin, and fetuin-A are the other suggested factors [59–62].
2. Inflammation: limited factors are associated with inflammation, which leads to AS. Remarkably, in contrast with CAD, C-reactive protein (CRP) is not associated with the progression of calcified aortic valve disease [63].
3. Cardiac remodeling, B-type natriuretic peptide (BNP), and cardiac troponin are potentially informative about the myocardial consequences of AS. Higher NT proBNP was associated with a higher grade of AS severity and NYHA class [64]. Cardiac troponin was identified as a separate variable associated with mid-wall fibrosis of the myocardium as part of a clinical risk score that predicts cardiovascular events in asymptomatic AS [65]. Biomarkers of extracellular matrix remodeling such as Fibulin-1 are significantly and inversely correlated with AVA index [66].

Personalized medicine contains a multimodal approach that might be especially useful for decision-making in patients with asymptomatic AS rather than patients with AS. Defining which patients could benefit from each therapeutic strategy would be possible with PM, for example, utilizing a transcatheter instead of the surgical aortic valve.

### 4.5.1 Mitral Valve Replacement

In patients with significant mitral regurgitation (MR) due to floppy mitral valve (FMV)/mitral valve prolapse (MVP), mitral valve replacement is crucial. Due to the significant variability in the size of the mitral annulus, one ring size can't fit all. The mitral "personalized ring" is a novel device constructed intraoperatively [67]. These "personalized rings" provide excellent support of

the mitral annulus, which avoids annular dilatation and paravalvular leak.

## 4.6 Arrhythmia

### 4.6.1 Long QT Syndrome (LQTS)

LQTS is defined as QTc ≥480 ms in an asymptomatic patient or a QTc ≥460 ms in the presence of unexplained syncope [68]. Patients with LQTS are at high risk of arrhythmogenic syncope, polymorphous ventricular tachycardia (torsade de pointes), and sudden arrhythmic death [69]. LQT type 1 is caused by loss of function mutation in the *KCNQ1* gene which encodes the α-subunit of the slow rectifier current ($I_{KS}$) [70]. LQT type 2 arises from loss-of-function mutations in *KCNH2*, which encodes the α-subunit of the rapid rectifier current ($I_{Kr}$) [71]. In contrast, a gain of function in *SCN5A* will cause LQT type 3, which amplified late sodium current ($I_{Na}$) [72]. Based on LQTS genotyping studies, the best therapeutic option in LQT types 1, 2, and 3 has shown to be β-blockers [73, 74].

### 4.6.2 Brugada Syndrome (BrS)

Inward sodium current impairment compared with the transient outward potassium current ($I_{to}$) in the right ventricular outflow tract is the key pathogenesis of BrS [75]. The most common genetic mutation in BrS, which could be detected in 21% of the patients, is the loss of function in the *SCN5A* gene. Loss-of-function mutations in *SCN5A* reduce the overall available sodium current (INa) through either (1) impaired intracellular trafficking of the ion channel to the plasma membrane or (2) through altered gating properties of the channel [76]. *CACNA1C*, *GPD1L*, *HEY2*, *PKP2*, *RANGRF*, *SCN10A*, *SCN1B*, *SCN2B*, *SCN3B*, *SLMAP*, and *TRPM4* are some other rare genes associated with BrS [77]. *SCN10A*, which encodes α-subunit Nav1.8 sodium channel, is one of the most novel mutations and is responsible for 5 to 16 percent of BrS [78, 79].

### 4.6.3 Short QT Syndrome (SQTS)

SQTS is defined as QTc ≤330 ms, or QTc interval <360 ms, and at least one of the following conditions: history of cardiac arrest or syncope, family history of sudden cardiac death (SCD) at age 40 or younger, or family history of SQTS [80]. Potassium and calcium channelopathies are the main pathophysiology in SQTS [26, 27]. Gain of function mutations in *KCNH2*, *KCNQ1*, and *KCNJ2* genes (associated with potassium channels) are responsible for SQT type 1, 2, and 3, respectively [81, 82]. Loss of function in *CACNA1C*, *CACNB2*, and *CACNA2D1* (associated with calcium channels) leads to SQT 4, 5, and 6, respectively [83, 84].

### 4.6.4 Idiopathic Ventricular Fibrillation (IVF)

IVF is defined as resuscitated ventricular fibrillation (VF), which had no other causes for VF, that is, metabolic, toxicological, cardiac (including other channelopathies and structural heart disease), respiratory, and infectious causes [68]. IVF is responsible for 6.8% of sudden cardiac death causes [85]. IVF pathophysiology is mainly due to an abnormality affecting the microstructural myocardial or Purkinje system [86]. Several genes have been found in association with IVF, *DPP6* was reported in Dutch families [87], *CALM1* was reported in a Moroccan family [88], and *RYR2* causes a leaky channel at diastolic levels of calcium under non-stress conditions [89].

### 4.6.5 Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

The main clinical manifestation of CPVT is episodic syncope occurring during exercise or acute emotion in individuals without structural cardiac abnormalities [90]. CPVT1 is caused by a mutation in the *RYR2* gene, which encodes the cardiac ryanodine receptor and accounts for 65% of the CVPT cases [91]. *RYR2* gene affects intracellular

calcium hemostasis and excitation-contraction coupling of the heart [92]. Mutation in the *CASQ2* gene, which encodes cardiac calsequestrin (a calcium-buffering protein within the sarcoplasmic reticulum), accounts for 2–5% of the CPVT cases [93]. Some other genes associated with CPVT are *TECLR* [94], *TRDN* [95], *CALM* [96], and *CALM2* [97]. *ANK2* and *KCNJ2* may phenocopy CPVT; hence they are associated with LQT4 and LQT7, respectively [98, 99]. However, no specific gene could be found for almost one-third of CPVT cases [100].

### 4.6.6 Progressive Cardiac Conduction System Disease (PCCD)

PCCD is defined as impulse conduction progressive delay through the His-Purkinje system with right or left bundle branch block (RBBB or LBBB) [101]. The first reported gene associated with PCCD was *SCN5A*, which encodes the cardiac sodium channel $Na_V$ 1.5 [102]. *SCN5A* mutations could also be found in BrS type 1; thus, there is a significant overlap between BrS and PCCD. Individuals carrying this mutation may manifest isolated forms of each BrS and PCCD or coexisted forms [103]. Mutations in *TRPM4* gene, which encodes a $Ca^{2+}$-activated but $Ca^{2+}$-impermeable cation channel [104], are associated with PCCD as well as familial AV block and RBBB [105]. PCCD may be associated with HCM in the presence of mutations in *PRKAG2*, *LAMP2*, and *GLA*; also it may be accompanied by DCM in the occurrence of *LMNA*, *DES*, and *TNNI3K* alterations [106].

## 4.7 Coronary Artery Disease (CAD)

### 4.7.1 Genes and Mechanism

In addition to several traditional risk factors (such as smoking, hypertension, diabetes, dyslipidemia, and obesity), a strong genetic basis had been also identified for CAD. According to early GWA studies [107, 108], variants in two loci (*LTA* and *LGALS2*) are associated with pathogenesis and increased risk of myocardial infarction (MI). However, later studies failed to show such association between polymorphisms in *LTA* and *LGALS2* and myocardial infarction [109]. In 2007, GWA studies identified SNPs at the 9p21.3 locus, which is located near the *CDKN2A* and *CDKN2B* genes and is associated with a 30–40% increased risk of CAD [110, 111].

GWA studies for plasma lipoprotein traits have identified several common single nucleotide polymorphism (SNP) variants that are strongly associated with plasma LDL. Common variants in genes associated with LDL-C levels (*PCSK9, LDL-R, APOB, APOE, SORT1, ABCG5-ABCG8, ABO, LPA*, and *NPC1L1*), genes associated with triglyceride levels (*LPL, APOA5, ASGR1, ANGPTL4, APOC3,* and *TRIB1*), and the gene encoding cholesteryl ester transfer protein (CETP), which is associated with HDL-C levels, have been linked to CAD [112, 113]. SNPs on chromosome 1P13 have a strong association with LDL and have also been independently linked to CAD and MI [110, 114]. Not all mutations are associated with an increased risk of CAD, in some cases; inactivating mutations may decrease CAD risk in conclusion. *PCSK9*, *NPC1L1*, and *ASGR1* mutations result in CAD risk reduction by lowering LDL cholesterol levels [11, 12, 115]. Lipoprotein lipase (*LPL*) hydrolyses lipoprotein-bound triglycerides and reduces triglyceride levels consequently. *LPL* loss of function is associated with an increased risk of CAD [116]. Apolipoprotein A5 (*APOA5*) increases LPL activity [116]. In contrast, apolipoprotein C-III (*APOC3*) and angiopoietin-like 4 (*ANGPTL4*) reduce LPL activity, and they are associated with CAD [117, 118]. *APOA5* mutations increase plasma triglyceride levels [116]; nonetheless, *APOC3* loss-of-function has opposite effects, which causes a reduction in plasma triglycerides levels [117].

### 4.7.2 Premature CAD

GWA studies have identified a considerable number of genetic variants that are associated with

premature CAD. Genetic variants in genes such as *PCSK9, LDL-R*, and *NPC1L1* contribute to premature CAD either directly or via traditional cardiovascular risk factors. Variants in locus 9p21.3, which is located on chromosome 9, are also associated with the risk of developing premature CAD [119]. It has been shown that a mutation in LDL receptor (LDLR) may lead to LDL metabolism dysfunction and thus increase the risk of premature CAD [120]. *LDLR* plays an important role in CAD pathogenesis by increasing LDL cholesterol and triglyceride-rich lipoproteins levels [121].

### 4.7.3 Vascular Inflammation and Remodeling

The encoding genes of cytokines (*CXCL12*) [112] and interleukin 6 (*IL6*) [122] are associated with CAD by vascular inflammation. *SH2B3* is one of the novel mutations associated with an increased risk of CAD [122]. *SH2B3* mutations trigger an elevation in numerous inflammatory mediators in left ventricle tissues including NRLP12, CCR2, and IFNγ [123]. There are two types of vascular remodeling, constrictive remodeling and expansive remodeling. Constrictive remodeling produces more stable plaque and narrow lumen, in contrast, expansive remodeling causes less stable plaque with no narrowing effect on the lumen [124]. *ADAMTS7* is one of the novel genes associated with CAD and plaque formation, but not plaque rupture [125]. *MIA3* is another gene associated with CAD, which regulates the levels of large proteins such as collagen VII [126].

## 4.8 Hypertension

Hypertension is one of the major risk factors for CAD. Based on CHARGE Consortium, *ATP2B1*, *CYP17A1*, *PLEKHA7*, and *SH2B3* were associated with systolic blood pressure (SBP); *ATP2B1*, *CACNB2*, *CSK-ULK3*, *SH2B3*, *TBX3-TBX5*, and *ULK4DBP* were associated with diastolic blood pressure (DBP); and *ATP2B1* was labeled for hypertension [127]. According to another large-scale study, *CYP17A1*, *CYP1A2*, *FGF5*, *SH2B3*, *MTHFR*, *c10orf107*, *ZNF652*, and *PLCD3* genes caused hypertension [128].

## 4.9 Recognizing Ethical Issues and How to Deal with Them

Many patients are aware of the benefits of PM although their knowledge of its potential appears to be limited [129]. Patients in oncology request information about PM more frequently than patients with other diseases [130]. Even if patients are aware of the phrase "personalized medicine," some of them don't understand the concept of PM [131], which may affect the participation of patients in medical decision-making.

Professionals also describe a lack of knowledge about PM. According to the conducted studies, cardiologists have the lowest information about PM among family physicians, cardiologists, and oncologists [130].

One of the major ethical concerns in this field is data confidentiality not being guaranteed properly [132]. Besides sharing data with the legal system, patients are concerned about data sharing with families in cases where information about a genetic disposition needs to be shared with all at-risk family members.

Test results or the testing process itself can also cause harm for patients. This harm can be caused by professionals' misinterpretation of the results or making the wrong therapeutic decisions [133]. Besides mentioned issues, the psychological burden from knowing or expecting the assessment results is considerably high. Accordingly, harm to benefits must be evaluated in every patient.

In contrast with clinical practice, in which test results are only beneficial when they provide reliable and actionable evidence that can be used for clinical decisions, there is a lack of evidence in PM results and practice guidelines in

this field. The cost-benefit ratio of PM is also questionable whether other treatment interventions would not have a superior benefit. PM costs are supposed as being massive and caused by a much minor proportion of the total patient population [134].

## 4.10 Digital Twin "Prospective of Precision Medicine in Cardiology"

The idea of digital twins was initially discussed in David Gelernter's book in the early 1990s [135]. A digital twin is a digital imitation or representation of a physical object, process, or service, but also beyond that. In other words, it is a virtual prototype (data plus algorithms) that will dynamically connect the physical and digital worlds and that will utilize modern technologies, such as smart sensors, data analytics, and artificial intelligence (AI), to monitor system performance, detect and prevent failures, and explore new advancements. A digital twin is intended to make a virtual representation of a physical object, test it, and optimize it in the virtual space, until the virtual representation meets the desired performance, at which point it can be built or enhanced (if already built) in the real world [136]. Collecting real-time data streams from linked clinical, health, and other sensors and combining these mass data with advanced data analytics, cloud computing, and artificial intelligence (including machine learning) will generate highly potent networked computational resources, which could be used in real-world decision-making. Precision cardiology could be established by the utilization of cardiac digital twins (CDT) [137]. This cardiovascular model will maximize the interaction between anatomical and physiologic understanding of the cardiovascular system. Treatment and prevention of cardiovascular disease will be based on precise predictions of both the underlying causes of disease and the pathways; hence, these predictions will be promising with CDT utilization.

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