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THE ROLE OF PRECISION MEDICINE AND GENOMICS IN CARDIAC SURGERY

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ABSTRACT

Background: Precision medicine, driven by advances in genomics, is reshaping the approach to diagnosis, risk assessment, and treatment planning in cardiac surgery. By analyzing genetic variation and molecular pathways, clinicians can move beyond standardized protocols toward individualized surgical care.
Methods: This review synthesizes recent literature on the integration of genomic technologies - such as whole genome sequencing, gene expression profiling, and pharmacogenomics - into the preoperative, intraoperative, and postoperative phases of cardiac surgery. Sources include peer-reviewed articles, clinical trial data, and translational research reports published over the past 20 years.
Results: Genomic profiling enables improved risk stratification, early detection of hereditary cardiovascular diseases, and identification of genetic biomarkers predictive of surgical outcomes. Pharmacogenomic insights allow optimization of perioperative drug therapy, reducing complications and enhancing recovery. Emerging applications include bioinformatics-driven surgical planning and integration of multi-omic data for real-time decision support. However, challenges remain regarding data interpretation, ethical considerations, and integration into clinical workflows.
Conclusion: Precision medicine and genomics hold significant promise for improving patient-specific outcomes in cardiac surgery. Their successful implementation will require robust clinical evidence, interdisciplinary collaboration, and infrastructure to manage and interpret complex genomic data. Ongoing research is likely to expand their role from risk prediction to fully individualized surgical strategies.

KEYWORDS

Precision Medicine, Genomics, Cardiac Surgery, Personalized Medicine, Genomic Profiling, Genetic Testing

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1. Introduction & Background:

Over the past decades, cardiac surgery has undergone remarkable progress, driven by advances in operative techniques, perioperative management, and medical technology. These innovations have contributed to higher survival rates and better quality of life for individuals with complex cardiovascular disease. Nevertheless, surgical planning and postoperative care have traditionally been guided by population-based recommendations, which may overlook significant differences in patient biology, coexisting conditions, and responses to treatment. As a result, a uniform “one-size-fits-all” treatment approach can lead to suboptimal outcomes in certain cases, highlighting the importance of developing more individualized therapeutic strategies. Precision medicine: According to The US National Human Genome Research Institute precision medicine integrates an individual’s genomic profile, environmental exposures, and lifestyle and uses that information for personalized diagnostic, and preventive strategies (Delpierre & Lefevre, 2023). Collected data also help with the modification of therapeutic strategies driven by detailed clinical evaluation of the patient’s phenotype(Sethi et al., 2023). Precision medicine reaches beyond population - based protocols seeking optimalization of therapeutic efficacy while minimizing adverse effects. Heterogeneity of diseases manifestations, their prevalence and treatment options make precision medicine particularly useful in cardiology. Genomics: Genome-wide association studies (GWAS) analyze genetic variants of multiple genomes to identify those with a significant statistical correlation to a given trait or disease (Uffelmann et al., 2021). By using GWAS data, it is possible to identify specific gene variants associated with e.g., perioperative myocardial infarction (MI) (Kertai, Li, Li, et al., 2015) or new-onset atrial fibrillation (AF) (Kertai, Li, Ji, et al., 2015) after coronary artery bypass surgery. In addition to GWAS, polygenic risk scores (PRS) estimate genetic predisposition to a particular disease and was used to predict e.g., adverse outcomes - AF, MI, stroke or bleeding complication after coronary revascularization (Aittokallio et al., 2022). Rapid advances - such as next-generation (NGS) and whole-genome sequencing (WGS) - are enhancing the diagnostic yield in conditions like congenital

heart disease (CHD), with growing evidence that genome sequencing can inform personalized risk stratification following cardiac surgery. The integration of precision medicine and genomics into cardiac surgery offers numerous opportunities. Preoperatively, it can help with the selection of surgical techniques and perioperative protocols by identifying patients at higher risk for complications such as arrhythmia, thrombosis, or impaired wound healing. Intraoperatively, awareness of genetic influences on myocardial protection, inflammatory responses, and anaesthesia metabolism can force personalized management strategies. Postoperatively, it can contribute to optimizing pharmacotherapy, and improving long-term outcomes. This publication aims to describe the role of precision medicine and genomics in cardiac surgery. It will summarize not only practical applications and new technologies, but also their limitations and challenges.

2. Key Principles and Technologies:

2.1 Multi-Omics Integration

The paradigm of precision medicine as applied to cardiac surgery has advanced to incorporate a comprehensive spectrum of "omics" data, which includes not merely genomics but also transcriptomics, epigenomics, proteomics, metabolomics, and microbiomics (Gu et al., 2022; Zhan et al., 2023). The methodical integration of these disparate and dynamic datasets facilitates a process designated as "deep phenotyping," a practice that affords a more granular and exhaustive comprehension of an individual's biological state and specific disease characteristics than could be achieved through genomics alone (Chahal et al., 2025). Such a multi-omics methodology is conceptualized to surmount the inherent limitations of single-omics analyses, which are capable of providing only a static representation of a biological system. Through the superimposition of multiple strata of biological information, it becomes possible for clinicians to construct a more complete elucidation of the molecular alterations and pathway perturbations that underlie cardiovascular pathologies, thereby culminating in more precise diagnostic and therapeutic modalities (Zhan et al., 2023). This integrated approach provides a more holistic view of disease, capturing the complex interplay between an individual's genetic predispositions and environmental or lifestyle factors that collectively influence cardiovascular health (Palaparthi et al., 2025).

2.2 Genetic Testing

Genetic testing represents an indispensable component in the corroboration of clinical diagnoses across a range of heritable cardiovascular conditions, among which are cardiomyopathies, channelopathies, and aortopathies (Biernacka et al., 2024). Its principal function is the clarification of clinical or phenotypic diagnoses, a matter of particular consequence in clinical scenarios characterized by overlapping features or atypical presentations wherein a definitive diagnosis proves challenging (Balakrishnan et al., 2024). By way of example, genetic analysis possesses invaluable utility in the differentiation of idiopathic hypertrophic cardiomyopathy (HCM) from its phenocopies, such as Fabry disease or transthyretin cardiac amyloidosis, conditions that are associated with entirely distinct prognoses and management pathways (Nomura & Ono, 2023).

Following the identification of a pathogenic or likely pathogenic variant in an index patient, the implementation of cascade genetic testing is unequivocally recommended for all at-risk biological relatives (Biernacka et al., 2024; Musunuru et al., 2020). This proactive screening protocol is of critical importance for identifying asymptomatic familial individuals who may harbour the same etiologic variant. Such identification permits the institution of regular clinical surveillance and preventative interventions for those who test positive, whereas relatives who test negative can frequently be exonerated from intensive, lifelong clinical observation, a resolution that provides considerable psychological relief and concurrently conserves healthcare resources (Biernacka et al., 2024).

The outcomes of genetic assessments exert a direct and substantial impact on clinical management and therapeutic decision-making (Musunuru et al., 2020). For instance, individuals who carry certain genetic variants associated with Loeys-Dietz syndrome or specific pathogenic *ACTA2* variants are understood to be at an elevated risk for aortic dissection at smaller aortic diameters; consequently, clinical guidelines recommend the consideration of earlier prophylactic aortic surgery for these persons in comparison to the standard thresholds applied in cases of Marfan syndrome (Biernacka et al., 2024). In a similar fashion, the identification of particular genotypes in cardiomyopathies, such as those affecting the *DSP* or *LMNA* genes, may reveal a heightened risk for malignant arrhythmias, thereby lowering the threshold for the implantation of a primary prevention implantable cardioverter-defibrillator (Balakrishnan et al., 2024; Nomura & Ono, 2023).

Advancements in genetics have significantly enhanced the comprehension of the underlying pathomechanisms of cardiovascular diseases, thereby preparing the way for the development of highly targeted,

gene-specific therapeutic interventions (Biernacka et al., 2024). To illustrate, research that utilizes gene-editing technologies such as CRISPR has demonstrated the potential for correcting disease-causing variants in induced pluripotent stem cell-derived cardiomyocytes. This development presents future therapeutic possibilities, including the fabrication of personalized, genetically corrected grafts for the treatment of conditions like hypoplastic left heart syndrome, with the fundamental objective of rectifying the root etiology of the disease rather than merely managing its symptomatic manifestations (Geddes et al., 2020).

2.3 Pharmacogenomics (PGx)

Pharmacogenomics, the discipline concerned with investigating the influence of an individual's genetic constitution on pharmacological responses, affects both therapeutic efficacy and the risk of adverse reactions (Bhoyar & Nirmal Chandu, 2025; McDonough, 2021). The central objective of this field is the identification of specific genomic markers, such as single nucleotide polymorphisms, that exhibit a correlation with interindividual variability in drug response, knowledge which facilitates the formulation of safer and more efficacious medication strategies tailored to a patient's genetic profile (Bhoyar & Nirmal Chandu, 2025; McDonough, 2021). This area is of particular import to cardiovascular medicine, wherein genetic variability in loci encoding drug-metabolizing enzymes (for instance, the cytochrome P450 family), transporters, and therapeutic targets can substantially alter the efficacy and toxicity of widely prescribed medicaments. Archetypal examples include the anticoagulant warfarin, for which variants in *CYP2C9* and *VKORC1* influence dosing requirements, and the antiplatelet agent clopidogrel, the bioactivation of which is contingent upon the function of the *CYP2C19* enzyme (McDonough, 2021). Polymorphisms in genes such as *ADRB1* (beta-1 adrenergic receptor) and *CYP2D6* have also been shown to significantly affect patient responsiveness to beta-blocker therapy in heart failure (Palaparthi et al., 2025). Moreover, PGx testing can inform the administration of lipid-lowering therapies; variants in the *SLCO1B1* gene, for example, are associated with an augmented risk of myopathy in patients prescribed simvastatin, and such genetic information can guide safer prescribing practices (McDonough, 2021).

2.4 Artificial Intelligence (AI) and Machine Learning (ML)

The processing and interpretation of the voluminous and complex data generated by genomic and multi-omics inquiries necessitate the application of computational technologies of fundamental importance, namely Artificial Intelligence (AI) and Machine Learning (ML) (Olawade et al., 2024). AI and ML algorithms are capable of identifying recondite patterns within large datasets, predicting disease risks, facilitating the discovery of novel biomarkers, and optimizing therapeutic strategies (Palaparthi et al., 2025). Within the context of cardiac surgery, ML models have demonstrated superior predictive capabilities for outcomes such as mortality and postoperative complications when compared to traditional scoring systems like EuroSCORE II (Gadhachanda et al., 2025; Leivaditis et al., 2025). These advanced analytical systems can integrate extensive patient data - including genetic profiles, imaging results, and clinical histories - to produce individualized risk assessments that inform clinical decision-making with greater precision. For example, ML models can analyse complex medical images with a level of detail that may surpass human capacity, improving diagnostic accuracy for conditions identifiable through echocardiography, MRI, and CT scans (Olawade et al., 2024).

2.5 Single-Cell Genomics

By permitting the deconvolution of complex tissues into their constituent cell types and states, the analysis of gene expression at the single-cell level, primarily through single-cell RNA sequencing (scRNA-seq), affords an unprecedented insight into the cellular heterogeneity that characterizes cardiac tissues and the molecular mechanisms of disease (Chaudhry et al., 2019; Yu et al., 2023). This technology reveals unique transcriptional signatures associated with both normal physiology and pathological conditions such as myocardial infarction and heart failure, which are often obscured in bulk tissue analyses (Chaudhry et al., 2019). The resultant detailed cellular maps are instrumental in identifying novel and rare cell subpopulations, such as distinct fibroblast and macrophage subtypes involved in cardiac fibrosis and atherosclerosis. This allows for a deeper understanding of their functional roles and the elucidation of the intercellular communication networks that drive cardiac development and disease progression (Yu et al., 2023).

2.6 CRISPR and Gene Editing

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), particularly the CRISPR-Cas9 system, represents an emergent gene-editing technology with the potential to correct the specific genetic defects that underlie many inherited cardiac conditions. This technology enables the precise modification of DNA sequences, offering a therapeutic avenue for directly targeting and repairing disease-causing mutations through mechanisms such as homology-directed repair (HDR). Although preclinical studies have demonstrated its utility in correcting mutations associated with conditions such as hypertrophic cardiomyopathy and Duchenne muscular dystrophy in cellular and animal models, its clinical translation is contingent upon overcoming substantial challenges pertaining to in vivo delivery to cardiac tissue, the potential for off-target effects, and significant ethical considerations surrounding germline modifications. Nevertheless, CRISPR-based technologies signify a promising frontier for developing curative, rather than merely palliative, treatments for genetic cardiovascular disorders (Bonowicz et al., 2025).

3. Applications in Cardiac Surgery and Cardiovascular Disease Management

3.1. Enhanced Diagnostic Assessment and Familial screening

The application of polygenic risk scores (PRS), which aggregate the effects of numerous genetic variants across the genome, facilitates the identification of individuals with a heightened inherited susceptibility to cardiac conditions that may necessitate surgical intervention, such as coronary artery disease and inherited aortopathies. This approach can identify individuals whose genetic risk is equivalent to that conferred by a single monogenic mutation, often before traditional clinical risk factors become apparent (Viigimaa et al., 2022). The integration of PRS with conventional clinical risk factors has been shown to enhance the accuracy of risk prediction, thereby enabling more targeted preventative strategies, such as earlier initiation of statin therapy, and informing the timing and nature of surgical consultations (Jain, 2017; Viigimaa et al., 2022).

Genetic testing plays a pivotal role in clarifying diagnoses for diseases that present with similar clinical manifestations. For instance, it can accurately differentiate various underlying causes of cardiac hypertrophy, such as TTR amyloidosis, Fabry disease, or sarcomeric hypertrophic cardiomyopathy (HCM) (Harper et al., 2017). According to the American Heart Association genetic testing is recommended for conditions such as HCM, DCM, Long QT Syndrome, Brugada Syndrome, thoracic aortic aneurysms, Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and familial hypercholesterolemia (FH) to support familial screening (Musunuru et al., 2020). In rare and familial forms of cardiovascular disease (CVD), the identification of single-gene mutations has become increasingly accurate, enabling the development of clinically valuable diagnostic tests for inherited cardiomyopathies, arrhythmias, and aortic disorders (Marian et al., 2016). The proactive identification of genetic causes is critical not only for the patient but also for protecting other family members from the consequences of a missed diagnosis, informing crucial decisions about family screening and planning (Dainis & Ashley, 2018).

Whole-exome sequencing has emerged as a useful tool in the study of CHD, successfully identifying a spectrum of detrimental genetic variations, including single nucleotide variants and copy number changes, that contribute to disease pathogenesis. This approach systematically interrogates the protein-coding regions of the genome, allowing for the detection of both rare and novel mutations associated with CHD. Complementary to these genomic discoveries, single-cell transcriptomics has revolutionized our understanding of CHD at a cellular level. By providing a high-resolution view of gene expression within individual cells, this technology has enabled the precise characterization of cell-type-specific transcriptional profiles in cardiac tissues. It can pinpoint which specific cell types are most affected by a genetic mutation. For example, it might show that a mutation alters the gene expression only in the cardiac progenitor cells that are responsible for forming the heart's valves, thus explaining why a patient has a specific valvular defect (Nappi, 2024).

3.2. Risk Stratification and Prognosis

Genomic information facilitates a more refined pre-operative risk assessment through the incorporation of an individual's genetic predispositions to specific complications, such as acute kidney injury following cardiac surgery, or to adverse reactions to anaesthetic or supportive medications (Leivaditis et al., 2025). Machine learning models that integrate both clinical and genetic data have demonstrated an ability to predict a range of postoperative outcomes - including mortality, length of stay, and delirium - with greater accuracy than traditional risk models (Gadhachanda et al., 2025; Leivaditis et al., 2025). This provides a more personalized basis for surgical planning, resource allocation, and patient counselling regarding procedural risks and expected recovery trajectories (Gadhachanda et al., 2025).

Genomics offers insights into specific disease-causing pathways, which support biomarker-based precision diagnostics and allow for more accurate prognosis stratification. In inherited cardiac conditions (ICCs) like Long QT Syndrome (LQTS), identifying the underlying genetic mutation can significantly influence clinical management and help evaluate the risk of sudden cardiac death (Giudicessi & Ackerman, 2013). LQT1, caused by pathogenic variants in the KCNQ1 gene, results in dysfunction of the IKs potassium channel and carries the highest risk of sudden cardiac death (SCD) during conditions of heightened sympathetic activity, particularly vigorous physical exertion such as swimming. Although overall mortality is lower in LQT1 than in LQT3, the risk of arrhythmic events increases markedly with activities that elevate catecholamine levels, especially in males under 15 years, adult females, and individuals with a history of syncope or markedly prolonged QTc (>500 ms) (Choi et al., 2004; Schwartz et al., 2012). LQT2, linked to mutations in the KCNH2 gene and impairment of the IKr potassium channel, is most often associated with SCD precipitated by sudden auditory or emotional stimuli, typically occurring at rest or during sleep. Risk is greatest in females, particularly during adulthood and the postpartum period, with triggers including abrupt loud noises (e.g., alarm clocks, telephones) and emotional distress (Schwartz et al., 2012). LQT3, resulting from gain-of-function mutations in the SCN5A gene and augmentation of the late sodium current, presents with fewer events than LQT1 or LQT2 but a substantially higher case fatality rate. Arrhythmias in LQT3 are frequently bradycardia-dependent, occurring most often during sleep or rest, with carriers of specific high-risk variants, such as the ΔKPQ mutation, demonstrating particularly high lethality regardless of QTc duration (Nagatomo et al., 2002; Perez-Riera et al., 2018; Wilde et al., 2016). Particular genotypes (such as LQT1, LQT2, and LQT3) can guide the selection of the most suitable medications; for example, mexiletine can be used in LQT3, and nadolol is the most effective β-blocker in LQT2 (Abu-Zeitone et al., 2014; Mazzanti et al., 2016).

Genomic risk scores (GRS), also known as polygenic risk scores, represent a key innovation in this field. These scores integrate information from a large number of common genetic variants to quantify an individual's cumulative genetic predisposition to complex, multifactorial diseases such as coronary artery disease (CAD). GRS can identify individuals at high genetic risk for CAD, even in the absence of traditional risk factors like dyslipidemia or hypertension. This is particularly valuable for identifying "silent" high-risk individuals who would be missed by conventional risk calculators. A high GRS can serve as a powerful catalyst for both patient and clinician action. For patients, understanding their elevated genetic risk can significantly enhance their motivation to adopt lifestyle modifications (e.g., diet, exercise, smoking cessation) (Hasbani et al., 2022; Naderian et al., 2025). For clinicians, a high GRS can justify the earlier initiation of preventative therapies, such as statin treatment, in individuals who might otherwise not meet the criteria for such interventions based on age or lipid levels alone (Kullo et al., 2016).

Familial hypercholesterolemia is characterized by elevated plasma low-density lipoprotein cholesterol (LDL-C) and early coronary heart disease onset. FH has a monogenic autosomal dominant transmission, and molecular diagnosis implies a higher cardiovascular risk for index cases and relatives. It is caused by pathogenic variants in three main genes: LDLR, APOB, and PCSK9 which are linked to the autosomal dominant form of the disorder. Individuals with FH need prompt, intensive, and long-term lipid-lowering treatment to decrease the incidence of atherosclerotic cardiovascular disease (Bouhairie & Goldberg, 2015). A study conducted by Jones et al. revealed that after genomic information on FH was disclosed, changes were observed in clinician practices, patient behaviours, and intermediate outcomes. Clinicians enhanced lipid-lowering treatments, while patients pursued genetic counselling, underwent lipid testing, and showed improved adherence to their lipid-lowering medications. Consequently, lipid levels decreased, and more patients achieved their target cholesterol goals (Jones et al., 2022). On the other hand, according to Mizuta & Santos, screening the general population for FH is not currently cost-effective based on existing willingness-to-pay thresholds. Nevertheless, lowering the cost of testing, screening individuals at younger ages, or incorporating FH testing into wider multiplex screening panels could enhance both its clinical benefits and economic value (Mizuta & Santos, 2025).

3.3. Personalized Treatment Strategies and Surgical Planning

Genomic information plays a crucial role in helping clinicians select appropriate therapies and determine the optimal timing for surgical procedures. In certain inherited connective tissue disorders involving pathogenic variants in genes such as *ACTA2*, *MYH11*, or *TGFBR2*, genetic results may justify recommending surgical repair of an aortic aneurysm at a smaller diameter than standard guidelines would typically advise (Kostiuk et al., 2018).

Inherited connective tissue diseases, such as Marfan syndrome and Loeys-Dietz syndrome, predispose individuals to thoracic aortic aneurysms and dissections. Genetic variants play a pivotal role in determining the optimal timing for aortic repair surgeries (Chou & Lindsay, 2020). Marfan syndrome is primarily associated with mutations in the FBN1 gene, leading to abnormal fibrillin-1 protein. Studies have shown that individuals with certain FBN1 mutation (HI-*FBN1*) experience more rapid aortic dilation, necessitating earlier surgical intervention (Franken et al., 2017). Loeys-Dietz syndrome is caused by mutations in the TGFBR1, TGFBR2, SMAD2, or SMAD3 genes. These mutations lead to dysregulated TGF-β signaling, resulting in vascular fragility. The timing of aortic repair in Loeys-Dietz syndrome is influenced by the specific genetic variant present, with certain mutations (TGFBR1 and TGFBR2) associated with more aggressive disease progression (Chou & Lindsay, 2020).

In pediatric cardiac surgery, genomic sequencing is rapidly emerging as a pivotal tool for forecasting post-operative outcomes, supplementing traditional risk stratification approaches that have historically relied on clinical variables such as the type and complexity of CHD and the patient's overall health status. Growing evidence indicates that damaging variants in chromatin-modifying genes-responsible for regulating DNA packaging and expression and cilia-related genes which are critical for cellular structures involved in development are strongly associated with increased rates of mortality, cardiac arrest, and prolonged mechanical ventilation following congenital cardiac surgery (Garrod et al., 2014; Watkins et al., 2025). These genetic vulnerabilities, which may impair organ development and compromise resilience to surgical stress, exert their greatest influence in patients with complex CHD phenotypes, those undergoing technically demanding operations, and individuals with extra-cardiac anomalies, where they act synergistically with surgical and physiological stress to amplify risk. Conversely, the absence of such high-risk genotypes can indicate a substantially reduced likelihood of adverse events, offering prognostic reassurance. By integrating genomic data with established clinical assessments, surgical teams can achieve more precise risk stratification, optimize operative planning, and individualize perioperative management - advancing the principles of precision medicine in the care of children with CHD (Landstrom et al., 2021; Watkins et al., 2025).

Krane et al. reported that in severe conditions such as Hypoplastic Left Heart Syndrome (HLHS), precision genetics may enable prediction of which fetuses with early-stage HLHS are most likely to benefit from high-risk prenatal procedures such as balloon aortic valvuloplasty by identifying their specific underlying genetic abnormalities (Krane et al., 2021).

Genetic information was primarily used to retrospectively understand disease mechanisms or to confirm diagnoses. However, contemporary practice shows a clear shift toward a more proactive and forward-looking role, particularly in surgery. Genetic testing now plays a crucial role in guiding targeted therapies and determining the optimal timing for surgical interventions. Notably, genome sequencing - especially when integrated with artificial intelligence - has the capability to predict clinical outcomes following congenital cardiac surgery. This marks a significant advancement, transforming genomics from a tool for diagnosis or explanation into one that actively predicts and guides treatment, thereby improving surgical decision-making, patient selection, preoperative risk evaluation, and intraoperative management to enhance both precision and safety (Dainis & Ashley, 2018).

3.4. Novel Therapeutic Development

Although this discussion centers on cardiac surgery, the evidence consistently emphasizes the emergence of targeted and mechanism-based medical therapies that may eliminate the necessity for some invasive procedures. These medical advancements could potentially reduce the need for surgery, alter its timing, or even change the extent of surgical intervention required (Gelb, 2022). For example, preventing calcific aortic valve disease through medical means could significantly delay or entirely avoid the need for valve replacement surgery.

Targeted therapies - including antibody-based therapies, advanced gene editing and gene silencing techniques are either already in use or being actively developed for various genetic cardiovascular disorders such as LQTS (Wilde et al., 2022), Duchenne muscular dystrophy (DMD) (de Boer et al., 2022), transthyretin (TTR) cardiac amyloidosis (Benson et al., 2017), Fabry disease (El Dib et al., 2017) and Pompe disease (van Capelle et al., 2018).

Andelfinger et al. reported the treatment of two critically ill infants with Noonan syndrome caused by gain-of-function mutations in the RIT1 gene, who presented with severe hypertrophic cardiomyopathy, using the MEK inhibitor trametinib. This treatment also normalized dysplastic pulmonary valve leaflets, demonstrating genotype-specific precision medicine (Andelfinger et al., 2019). Another promising area

involves restoring NOTCH signalling in patients with bicuspid aortic valve (BAV) linked to NOTCH1 mutations, aiming to prevent or slow valve calcification - an approach that might serve as an effective treatment for many affected individuals (Garg et al., 2005; Nigam & Srivastava, 2009). Table 1 summarizes the utilization of genomics in several genetic diseases related to the heart.

Table 1. Specific Genetic Conditions and Their Surgical/Therapeutic Implications

Genetic Condition	Genomic Understanding/Implication	Impact on Surgery/Treatment	Sources
Inherited Connective Tissue Disease (*ACTA2, MYH11, TGFBR2* variants)	Genetic variants prompt consideration of surgical intervention at smaller aortic aneurysm diameters.	Directly influences surgical timing and approach.	(Kostiuk et al., 2018)
Congenital Heart Defects (CHD) (e.g., Tetralogy of Fallot, Transposition of Great Arteries, chromatin-modifying/cilia-related genes)	Damaging genotypes predict adverse post-operative outcomes (mortality, cardiac arrest, prolonged ventilation); genetic insights guide family screening and planning.	Predicts post-operative risk, informs family screening and planning.	(Watkins et al., 2025)
Hypoplastic Left Heart Syndrome (HLHS)	Genetic studies suggest prediction of benefit from *in utero* balloon aortic valvuloplasty.	Impacts pre-natal intervention decisions.	(Krane et al., 2021)
Noonan Syndrome (*RIT1* gain-of-function)	*RIT1* gain-of-function alleles lead to successful treatment of severe HCM and pulmonary valve issues with MEK inhibitor.	Offers non-surgical alternatives (genotype-specific precision medicine).	(Andelfinger et al., 2019; Ilic et al., 2024)
Bicuspid Aortic Valve (BAV) (*NOTCH1* variants)	*NOTCH1* variants suggest potential for restoring NOTCH signaling to prevent or slow valve calcification.	Potential to obviate or delay surgery.	(Garg et al., 2005; Nigam & Srivastava, 2009)
Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), Arrhythmias (LQTS, Brugada, CPVT)	Genetic testing clarifies diagnosis, facilitates familial cascade screening.	Clarifies diagnosis, enables precise risk stratification, guides selection of targeted medical therapies.	(Moore et al., 2025; Verdonschot et al., 2019; Wilde et al., 2022)

4. Challenges and Future Directions:

The transition from a population-centric to a personalized, genomics-driven approach in cardiac surgery is not without significant challenges. Realizing the full potential of precision medicine requires concerted efforts to overcome technical, logistical, and ethical hurdles. A fundamental challenge lies in the effective integration and analysis of the massive and diverse datasets generated from various "omics" platforms, including genomics, transcriptomics, and proteomics. These platforms produce high-dimensional data that must be synthesized to create a coherent and clinically actionable patient profile. Rigorous validation studies and the development of clear clinical guidelines are essential to ensure the safe and effective application of these discoveries in practice (Dainis & Ashley, 2018). As genomic data becomes more central to clinical care,

so too do the ethical and sociopolitical challenges surrounding its use. Key issues include maintaining patient data privacy and confidentiality, preventing genetic discrimination by employers or insurers, and ensuring equitable access to precision medicine technologies for all patients, regardless of their background (Mudd-Martin et al., 2021). The efficacy and cost-effectiveness of personalized medicine approaches in cardiac surgery cannot be assumed. The field requires a new generation of large-scale, well-designed clinical trials that are appropriately powered to demonstrate the clinical utility of genomic-guided therapies. These trials must be designed to account for genetic heterogeneity and patient-specific risk profiles, providing the robust evidence needed for widespread clinical adoption (Dainis & Ashley, 2018). Looking forward, the continued leveraging of AI and machine learning will be crucial for overcoming many of these challenges. AI can assist in identifying new genetic biomarkers, predicting disease progression with greater accuracy, and personalizing treatment plans by sifting through complex data that is unmanageable by human analysis alone. This technology has the potential to streamline data interpretation and accelerate the translational journey from discovery to clinical application (Krittanawong et al., 2017; Leivaditis et al., 2025).

5. Conclusions

Precision medicine and genomics are fundamentally reshaping the landscape of cardiac surgery and broader cardiovascular care. This transformation is driven by a profound shift from generalized to individualized patient management, enabled by advanced sequencing technologies, sophisticated AI-driven data analysis, and innovative biological tools like iPSCs and CRISPR. These advancements collectively lead to significantly enhanced diagnostic accuracy, the implementation of highly personalized treatment strategies, and ultimately, improved patient outcomes.

Significant progress has been made, particularly in understanding and managing inherited and congenital heart conditions, where genomic understandings have direct implications for surgical planning, precise risk stratification, and the development of targeted therapies.

The trajectory of precision medicine in cardiac surgery points towards continued technological innovation, deeper and more comprehensive integration of multi-omics data, and the development of increasingly sophisticated predictive models and novel mechanistic therapies. Addressing the remaining technical, ethical, and systemic barriers will be paramount to fully realize the immense promise of precision medicine, ensuring its benefits are broadly accessible and effectively integrated into the future of cardiovascular care for all patients.

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