# Genomic Drivers in Cardiac Surgical Decision Making: From Molecular Mechanisms to Precision Operative Interventions

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**Abstract**

The integration of genomic medicine into cardiac surgery represents a paradigm shift from traditional, size-based population metrics to patient-specific, gene-driven therapeutic strategies. Pathogenic variations in structural, contractile, and metabolic genes fundamentally dictate the natural history of cardiovascular diseases, altering vascular wall integrity, myocardial stress tolerances, and perioperative pharmac-dynamics. This article reviews the transition from basic monogenic associations to advanced multi-omic risk stratification in cardiac surgery. We detail the molecular mechanics of heritable thoracic aortopathies (e.g., FBN1, TGFBR1/2, ACTA2), genetic cardiomyopathies (MYH7, MYBPC3, LMNA), and congenital structural anomalies (e.g., 22q11.2 deletion). Furthermore, we examine the critical role of perioperative pharmacogenomics (CYP2C19, VKORC1) in mitigating graft failure and thromboembolic events. Finally, we explore future innovations, including machine learning-integrated "digital twins," in vivo CRISPR-Cas9 therapeutic genome editing, and transcriptomic profiling for post-operative management, establishing a comprehensive architecture for contemporary precision cardiac surgery.

**Keywords:** Precision Cardiovascular Medicine; Heritable Thoracic Aortic Disease; Pharmacogenomics; Next-Generation Sequencing; Surgical Thresholds; Genetic Cardiomyopathies.

## 1. Introduction

For decades, structural cardiac surgery relied heavily on macroscopic anatomic metrics to guide clinical interventions. Decisions regarding prophylactic aortic replacements, septal myectomies, or structural congenital repairs were primarily directed by maximum diametric thresholds, hemodynamic gradients, or functional symptom classifications. However, substantial clinical heterogeneity within identical phenotypical cohorts demonstrated that macroscopic data alone fails to accurately predict catastrophic events, such as acute aortic dissections, sudden cardiac death, or accelerated graft failure. The advent of high-throughput next-generation sequencing (NGS), encompassing targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS), has illuminated the profound impact of the patient's genetic architecture on surgical outcomes. Genetic variations influence tissue biomechanics, cellular signalling, inflammatory responses, and drug metabolism. Consequently, contemporary cardiac surgery is transitioning into an era of precision medicine, where genetic profiles directly guide pre-operative timing, intra-operative technique selection, and personalized post-operative management protocols.

Key Structural Concepts: Monogenic vs. Polygenic Risk
Understanding genetic risk in cardiac surgery requires distinguishing between monogenic disorders and polygenic risk profiles.

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                    CARDIOVASCULAR GENETIC RISK                   │
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     MONOGENIC VARIATION        │               │     POLYGENIC VARIATION
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› Single nucleotide variant     │               │ • Cumulative impact of multiple
  with large effect size.       │               │   common variants (SNPs).
› High clinical penetrance.     │               │ • Low individual effect size.
› Examples: FBN1, TGFBR1,       │               │ • Quantified via Polygenic Risk
  MYH7, LMNA mutations.         │               │   Scores (PRS).
› Direct surgical trigger.      │               │ • Modulates long-term outcomes.
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## 2. Discussion

Genomic medicine is transforming cardiac surgery by shifting from empirical metrics to personalized, mutation-specific management for heritable diseases [1, 2, 3]. Genetic analysis and multi-omic staging now enable optimized surgical timing, targeted therapeutics, and improved risk stratification for conditions like aortic disease and cardiomyopathy [4, 5, 6, 8, 9, 11]. Furthermore, integrating genotype-guided strategies is essential for modern mechanical support and transplantation, utilizing tools like cell-free DNA for rejection monitoring [13, 14]. Detailed information is available in the academic literature regarding genomic medicine in cardiac surgery

1. Molecular Phenomapping Over Standard LVEF
   Traditional management relies heavily on Left Ventricular Ejection Fraction (LVEF). Multi-omics overrides this by clustering patients into molecular phenogroups based on their unique DNA, RNA, and protein signatures. This allows clinicians to distinguish between patients who have identical echocardiographic presentations but completely different underlying cellular disease pathways. (1,2)

2. Genotype-Directed Mechanical Circulatory Support (MCS) Timing
   Certain genetic variants carry an exceptionally high risk of sudden cardiac death (SCD) and rapid, malignant remodelling before significant changes in LVEF occur:

- LMNA (Lamin A/C) & FLNC (Filamin C): These mutations cause highly arrhythmogenic phenotypes. Multi-omic monitoring identifies the exact molecular window of decompensation, prompting early, prophylactic Left Ventricular Assist Device (LVAD) implantation or urgent transplant listing.
- TTN (Titin Truncating Variants): Patients with TTN truncations show high rates of reverse remodelling. Multi-omic profiling helps identify which of these patients can be medically optimized versus those requiring mechanical support. (1,2)

3. Pre-operative Prediction of Right Ventricular (RV) Failure (1)
Acute RV failure after an LVAD implantation is a catastrophic complication. By integrating pre-operative plasma proteomics (e.g., measuring concentrations of specific inflammatory and metabolic proteins) with myocardial transcriptomics, surgeons can predict which patients lack the right ventricular reserve to handle the sudden fluid shifts of an LVAD. This directly informs the decision to plan a primary Biventricular Assist Device (BiVAD) or move directly to transplantation. (1)

4. Liquid Biopsies and Non-Invasive Post-Transplant Surveillance
Multi-omics eliminates the need for frequent, invasive, and painful endomyocardial biopsies to check for organ rejection:

- Donor-Derived Cell-Free DNA (dd-cfDNA): When a transplanted heart faces cellular injury or rejection, it releases fragments of its DNA into the recipient's bloodstream. Quantifying the percentage of dd-cfDNA via high-throughput sequencing acts as a real-time, highly sensitive "liquid biopsy." (1,2)
- Peripheral Blood Mononuclear Cell (PBMC) Gene Expression Profiling: Tracking RNA expression patterns in the recipient's immune cells allows clinicians to detect early signs of acute cellular rejection days or weeks before structural tissue damage occurs.

5. Metabolic Re-programming Dynamics
Advanced HF causes the myocardium to shift its primary fuel source from fatty acid oxidation to less efficient glycolysis. Liquid chromatography-mass spectrometry (LC-MS) metabolomics tracks these circulating metabolic shifts, allowing clinicians to tailor perioperative metabolic support and optimize mechanical device parameters based on real-time cellular energy demands. (1,2)

1. Heritable Thoracic Aortic Diseases (HTAD) and Surgical Thresholds
The most profound clinical application of genomics in adult cardiac surgery lies in heritable thoracic aortic diseases (HTAD). Pathogenic variants disrupt the extracellular matrix, vascular smooth muscle cell (VSMC) contractile apparatus, or the transforming growth factor-beta (TGF-beta)) signalling pathway, predisposing patients to dissection or rupture at smaller diameters than degenerative aneurysms.

TGF-beta Pathway Receptor and Ligand Mutations

Pathogenic variants in TGFBR1 and TGFBR2 cause Loeys-Dietz Syndrome (LDS) Types 1 and 2, while SMAD3 mutations cause LDS Type 3 (Aneurysms-Osteoarthritis Syndrome). These present

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a highly aggressive vascular phenotype. Paradoxically, loss-of-function mutations in these components trigger a compensatory, paradoxical upregulation of systemic TGF-beta signalling, accelerating matrix metalloproteinase synthesis and destroying the medial layer of the aorta. Due to this high tissue fragility, current guidelines recommend prophylactic aortic root replacement at an absolute diameter of 4.5 cm, or as low as 4.0 cm in patients with severe extra-aortic features or a family history of early dissection.

Extracellular Matrix Defects

Marfan Syndrome, driven by mutations in FBN1, impairs the synthesis of fibrillin-1, a structural glycoprotein essential for microfibril assembly and TGF-beta sequestration. The standard surgical threshold for prophylactic root replacement in FBN1-positive patients is 5.0 cm. However, this threshold lowers to 4.5 cm in the presence of rapid expansion 0.3 cm/year, a family history of dissection at small diameters, or a desire for pregnancy.

VSMC Contractile Apparatus Alterations

Mutations in ACTA2 (encoding smooth muscle alpha -actin and PRKG1 (encoding cGMP-dependent protein kinase 1) impair the contractile tone and mechanotransduction capability of vascular smooth muscle cells. Patients harbouring ACTA2 or PRKG1 mutations frequently present with acute Type A aortic dissection at normal or minimally dilated aortic diameters 5.0 cm, mandating early prophylactic intervention when the aorta reaches 4.5 to 5.0 cm.

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                AORTIC DIAMETER INTERVENTION THRESHOLDS

Sporadic / Degenerative   ├──► 5.5 cm

Bicuspid Aortic Valve     ├──► 5.5 cm (Decreases to 5.0 cm with risk factors)

FBN1 (Marfan Syndrome)    ├──► 5.0 cm (Decreases to 4.5 cm with risk factors)

ACTA2 / PRKG1 Variants    ├──► 4.5 – 5.0 cm

TGFBR1 / 2 (LDS 1 & 2)    ├──► 4.0 – 4.5 cm
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2. Intra-operative Surgical Technique Selection

Genotype identification changes the physical architecture of the operation:

- Valve-Sparing Aortic Root Replacement (VSRR / David Procedure): Genetically triggered aortopathies in young patients are primary indications for VSRR, provided the aortic valve leaflets are structurally normal and not severely stretched. Replanting the native valve into a synthetic conduit prevents the long-term morbidity of mechanical prostheses and lifelong anticoagulation.
- Total Aortic Root Replacement (Bentall Procedure): In patients with highly virulent mutations (e.g., TGFBR1 or PRKG1) combined with structurally deformed leaflets or significant fenestrations, complete composite graft replacement is preferred over VSRR to mitigate the high risk of secondary valve failure.

- Contraindication of Endovascular Interventions: Thoracic Endovascular Aortic Repair (TEVAR) is strictly avoided as an elective treatment for syndromic HTAD. The radial force of endovascular stent-grafts against fragile, genetically compromised tissue causes structural complications, including retrograde Type A dissections, stent-graft induced new entry tears (SINET), and severe endoleaks.

3. Genotype-Guided Decisions in Cardiomyopathies

In patients undergoing surgical correction for structural heart disease, simultaneous genomic data alters the scope of the procedure.

Hypertrophic Cardiomyopathy (HCM)
Surgical septal myectomy (Morrow procedure) remains the gold standard for symptomatic left ventricular outflow tract (LVOT) obstruction. Genetic testing reveals pathogenic variants in sarcomeric genes—primarily MYH7 beta-myosin heavy chain and MYBPC3 (myosin-binding protein C)—in approximately 50-60% of cases. Identification of these sarcomeric mutations, particularly when combined with a history of non-sustained ventricular tachycardia (NSVT) or extensive late gadolinium enhancement (LGE) on cardiac MRI, alters intra-operative strategy. Surgeons will concurrently implant an Implantable Cardioverter-Defibrillator (ICD) during the myectomy procedure to prevent sudden cardiac death (SCD).

Lamin A/C (LMNA) Cardiomyopathies
Mutations in the LMNA gene, which encodes nuclear envelope structural proteins, cause a highly arrhythmogenic form of dilated cardiomyopathy. LMNA mutations carry an exceptionally high risk of malignant ventricular arrhythmias and rapid heart failure progression, independent of the left ventricular ejection fraction (LVEF). When a patient with an LMNA mutation undergoes surgery, standard clinical thresholds are bypassed to favour early prophylactic ICD placement or advanced mechanical circulatory support evaluation.

4. Congenital Heart Disease (CHD) and Multi-System Considerations
Genomics provides vital insights into tissue healing and systemic vulnerabilities during congenital heart surgery:

- 22q11.2 Deletion Syndrome (DiGeorge Syndrome): This microdeletion is present in up to 30% of patients with conotruncal anomalies, such as Tetralogy of Fallot (TOF) and Interrupted Aortic Arch. Its presence alerts the surgical and ICU teams to serious extracardiac anomalies, including thymic hypoplasia (requiring irradiated blood products to avoid graft-versus-host disease), severe hypocalcemia secondary to parathyroid hypoplasia, and a higher risk of postoperative airway complications.
- Trisomy 21 (Down Syndrome): Strongly linked with Complete Atrioventricular Septal Defects (AVSD). Patients with Trisomy 21 have a genetic predisposition to accelerated pulmonary vascular remodelling’s, leading to early-onset, irreversible pulmonary arterial hypertension (Eisenmenger syndrome). Consequently, the surgical timeline is moved forward, requiring definitive repair within the first 4 months of life.

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5. Pharmacogenomics in Post-Operative Care

The impact of genomics extends past the operating room, influencing the patency of surgical constructs and long-term survival metrics:

- CYP2C19 and Antiplatelet Therapy: Following Coronary Artery Bypass Grafting (CABG), dual antiplatelet therapy (DAPT) is essential to maintain vein graft patency. Patients with CYP2C19 loss-of-function alleles (*2, *3) cannot efficiently metabolize clopidogrel into its active thiol metabolite. This leads to inadequate platelet inhibition and a higher risk of acute graft thrombosis. Genotype-directed post-CABG care uses alternative antiplatelet agents, such as ticagrelor or prasugrel, in clopidogrel non-responders.
- CYP2C9/VKORC1 and Anticoagulation: Following mechanical valve replacements, safe dosing of the vitamin K antagonist warfarin depends heavily on polymorphisms within the CYP2C9 (drug metabolism) and VKORC1 (pharmacological target) genes. Utilizing pharmacogenomic dosing algorithms during the early post-operative phase reduces initial dosing fluctuations, lowering the risk of catastrophic bleeding or acute valve thrombosis.

Summary and Future Innovations

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                     FUTURE INNOVATIONS IN PRECISION SURGERY
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[Digital Twins] ──► Combining multi-omics with real-time hemodynamic models to
                    predict the exact day of aortic failure or graft occlusion.

[CRISPR In Vivo] ──► Base/prime editing during cardiopulmonary bypass to silence
                     hypertrophic genes or correct monogenic defects.

[Spatial Omics]  ──► Real-time tissue transcriptomics inside the OR to assess
                     microvascular viability and optimize surgical margins.

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The future of cardiac surgery is deeply intertwined with advancements in functional genomics, molecular therapies, and computational medicine:

1. Patient-Specific "Digital Twins": Integrating patient-specific genomics, transcriptomics, and multi-omic data with high-resolution computational fluid dynamics (CFD) enables the creation of virtual cardiovascular "digital twins". These models predict the precise timeline of aortic wall failure or graft occlusion, transitioning care from generalized guidelines to individualized surgical timing.

2. Therapeutic Genome Editing: The translation of in vivo CRISPR-Cas9 base and prime editing platforms holds the potential to treat inherited cardiac diseases before advanced structural damage occurs. Future protocols may feature intra-operative delivery of gene-editing vectors directly into the

myocardium or aortic wall during cardiopulmonary bypass to correct pathogenic variants (such as MYH7 or FBN1), preventing disease progression.

3. Intra-operative Spatial Transcriptomics: Real-time transcriptomic profiling of myocardial and vascular tissue in the operating theatre will allow surgeons to evaluate tissue viability, microvascular inflammation, and metabolic stress at a molecular level. This data will refine surgical margins during remodelling procedures and predict post-operative recovery trajectories with high accuracy.

   Integrating advanced genomics into cardiac transplantation and mechanical circulatory support (MCS) is a clinical necessity, enabling precise patient selection, the prediction of right ventricular failure, and the identification of genetic drivers like LMNA or FLNC that dictate aggressive management (14, 15). Furthermore, molecular surveillance via donor-derived DNA offers a non-invasive alternative to endomyocardial biopsies for post-transplant rejection monitoring, while genetic screening optimizes anticoagulation strategies for device-induced thrombosis (15,19). 1. Molecular Phenomapping Over Standard LVEF

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## Genetic and Molecular Markers in Cardiac Transplantation

| Marker Name | Phase | Biological Source / Sample Type | Clinical Utility & Surgical Decision Impact |
|---|---|---|---|
| **LMNA** *(Lamin A/C)* | **Pre-Transplant** | Genomic DNA (Blood/Saliva) | **Aggressive MCS/Transplant Listing:** Highly arrhythmogenic variant causing rapid heart failure progression. Prompts early mechanical support or listing bypassing conventional ejection fraction cutoffs. |
| **FLNC** *(Filamin C)* | **Pre-Transplant** | Genomic DNA (Blood/Saliva) | **Malignant Arrhythmia Risk:** Predicts high burden of ventricular arrhythmias and sudden cardiac death. Drives early prophylactic ICD placement or urgent transplant evaluation. |
| **TTN** *(Titin Truncating)* | **Pre-Transplant** | Genomic DNA (Blood/Saliva) | **Myocardial Recovery Potential:** Associated with higher rates of reverse remodeling. Helps identify candidates who may be medically optimized vs. those requiring definitive mechanical support or transplantation. |

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|---|---|---|---|
| **Proteomic Profile** *(e.g., GDF-15, IL-6, TNF-α)* | **Pre-Transplant** | Blood Plasma | **RV Failure Prediction:** Pre-operative signature maps systemic inflammation and right ventricular strain. Dictates whether a patient receives an isolated LVAD vs. primary BiVAD or urgent transplant listing. |
| **dd-cfDNA** *(Donor-Derived Cell-Free DNA)* | **Post-Transplant** | Recipient Blood Plasma | **Non-Invasive Allograft Rejection Screening:** Quantitative tracking of donor DNA fragments in recipient circulation. Serves as a highly sensitive "liquid biopsy" to detect subclinical acute cellular or antibody-mediated rejection without invasive tissue sampling. |
| **GEP** *(Gene Expression Profiling / 20-Gene Panel)* | **Post-Transplant** | Peripheral Blood Mononuclear Cells (PBMCs) | **Immune Quiescence Surveillance:** Measures RNA expression profiles of recipient mononuclear cells. A low risk score rules out active acute cellular rejection, significantly reducing the necessity for routine endomyocardial biopsies. |
| **CYP3A5 (*3, *6, *7)** | **Post-Transplant** | Genomic DNA (Blood/Saliva) | **Immunosuppressant (Tacrolimus) Dosing:** Determines "expresser" vs. "non-expresser" status. Tacrolimus clearance varies up to 3-fold based on genotype; guided dosing achieves therapeutic trough targets faster, preventing early graft rejection or calcineurin inhibitor toxicity. |
| **TPMT / NUDT15** | **Post-Transplant** | Genomic DNA (Blood/Saliva) | **Immunosuppressant (Azathioprine) Safety:** Identifies poor metabolizers prone to life-threatening bone marrow suppression. Directs critical pre-treatment dose reductions or selection of alternative therapies (e.g., mycophenolate mofetil). |

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