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Rare Congenital and Inherited Cardiovascular Disorders: Advances in Diagnostic Pathways, Prognosis, and Multidisciplinary Care

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Abstract: The rare congenital and inherited cardiovascular disorders (RICVDs) encompass heterogeneous conditions that include structural, electrical, and cardiovascular disorders with often mild early findings yet carrying significant risks of arrhythmias, heart failure, and sudden cardiac death. Over the past decade, rapid advances in diagnostic imaging, next-generation sequencing, and computational analytics have transformed the capability for detecting disease at earlier, subclinical stages, coupled with individualized refinement in risk assessment. Novel echocardiographic strain parameters, high-resolution cardiac magnetic resonance tissue mapping, and CT-based coronary and aortic characterization now permit more detailed phenotyping. The expansion of gene panels and whole-genome approaches has also improved the diagnostic yield for cardiomyopathies, channelopathies, and syndromic disorders. Integration of molecular data with multi-modal imaging, increasingly facilitated by artificial intelligence and machine-learning tools, has enabled precision stratification and timely intervention in high-risk individuals. Parallel advances in perioperative management, catheter-based interventions, and targeted pharmacotherapy have improved survival and quality of life across childhood and adulthood. Contemporary care models stress the multidisciplinary coordination among cardiology, electrophysiology, congenital heart disease specialists, imaging experts, genetic counselors, and surgeons to provide continuity throughout the lifespan and address psychosocial, reproductive, and lifestyle needs. Nevertheless, diagnostic delays, unequal access to genetic testing, and limited specialized expertise continue to challenge the delivery of care worldwide, above all in resource-constrained settings. Therefore, innovations in computational modeling, gene editing, and tissue-engineering platforms have the potential to fundamentally reshape therapeutic approaches, while improvements in international registries and collaborative networks enhance evidence development for these rare conditions. Taken together, such advances herald a new era of proactive, biology-driven, and patient-centric management of RICVDs, providing a pathway toward better outcomes and more equitable care worldwide. This review synthesizes recent epidemiology, diagnostic innovations, prognostic determinants, therapeutic progress, and multidisciplinary care strategies in RICVDs, offering an integrated framework to guide current practice and future directions.

Keywords: Inherited cardiomyopathies; Congenital heart disease; Multimodal cardiac imaging; Next-generation sequencing; Precision cardiology; Sudden cardiac death; Multidisciplinary care; Rare cardiovascular disorders.

INTRODUCTION

Rare congenital and inherited cardiovascular disorders (RICVDs) represent a diverse group of various structural, electrophysiological, metabolic,

and genetic abnormalities originating either in early cardiac development or arising from pathogenic germline variants. Even though they are rare on their own, their combined influence is significant. Globally, it is estimated that 300-400 million individuals are affected by rare diseases, with a genetic basis underlying 70-80% of them [1], [2]. Among these, cardiovascular involvement represents one of the largest contributors to disability-adjusted life years due to its association with heart failure, arrhythmias, lifelong morbidity, and premature mortality.

Congenital heart disease remains the most common form of congenital anomaly around the world, occurring in about 1% of all live births and resulting in almost 40,000 cases per year in the United States alone [3], [4]. Although perinatal care and surgical intervention have greatly improved survival rates, complications such as pulmonary hypertension, ventricular dysfunction, rhythm disturbances, and aortic dilation are still very common and continue to require lifelong surveillance [5].

Inherited arrhythmia syndromes and cardiomyopathies are another major category of RICVDs and are now recognized as leading causes of SCD in individuals under 40 years. Studies estimate that 20-30% of SCD cases in the young are attributed to disorders such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia [6], [7]. The complex interaction of incomplete penetrance, age-dependent expression, and modifier genetic or environmental factors often results in a typically delayed diagnosis 5-10 years from first clinical manifestation [7].

Recent advances in diagnostic imaging have significantly improved the recognition and characterization of rare congenital and inherited cardiovascular disorders. For instance, tissue characterization by cardiovascular magnetic resonance (CMR) has become the non-invasive gold standard for detecting myocardial fibrosis and subtle morphological abnormalities, offering superior sensitivity compared with conventional echocardiography [8], [9]. Similarly, coronary computed tomography angiography allows for high-resolution depiction of congenital coronary anomalies, important in exertion-related cardiac events in young individuals and athletes. Studies also suggest that CCTA provides excellent diagnostic accuracy in delineating anomalous origin and course of coronary arteries [10], [11]. Echocardiographic innovations, including three-dimensional reconstruction and strain imaging, now allow for the detection of early myocardial dysfunction before overt structural remodeling, thus allowing for earlier referral and intervention.

The maturation of genomic medicine has markedly transformed the diagnostic landscape of inherited cardiovascular disorders. In particular, next-generation sequencing and comprehensive gene-panel testing now yield a molecular diagnosis in approximately 30-60% of patients with hypertrophic cardiomyopathy (HCM) and ~20-40% of those with dilated cardiomyopathy (DCM), though the exact yield can vary widely with cohort selection and testing depth [7]. Cascade genetic screening of first-degree relatives of genotype-positive probands enables the identification of at-risk carriers who may otherwise remain asymptomatic; some series report that family screening identifies affected relatives in roughly 30-40% of families [12]. The recently promulgated European Society of Cardiology (ESC) 2023 Guidelines on cardiomyopathies strongly recommend integrated cascade screening with both genetics and phenotypic assessment in relatives of affected individuals [13]. However, despite technological advances, overall diagnostic yields have plateaued or even declined in some clinical populations due to broader testing of individuals with less-specific phenotypes and the adoption of more stringent variant-classification criteria [12], [14].

The complexity and heterogeneity of RICVDs underscore the need for structured multidisciplinary models of care. Dedicated inherited cardiovascular clinics that integrate cardiologists, imaging specialists, geneticists, electrophysiologists, and genetic counselors have been shown to reduce diagnostic delays by 30-40%, improve uptake of genetic testing, and facilitate precision-based management strategies [15]. Such coordinated models are particularly relevant in view of the emerging trend for genomic screening, artificial intelligence-assisted imaging, and risk-stratification algorithms to enter routine clinical practice.

With the widening clinical burden, alongside increased diagnostic capabilities and changing frameworks of care, a comprehensive synthesis of recent evidence is essential. This review aims to set out current epidemiological understanding, diagnostic developments, determinants of prognosis, and best multidisciplinary care approaches for rare inherited and congenital cardiovascular disorders, to inform contemporary and future clinical practice.

2. Genetic Spectrum and Etiopathogenesis

Rare congenital and inherited cardiovascular disorders arise from the interaction of genetic and molecular developmental pathways affecting cardiac structure, electrophysiology, and function. The

aetiology of these disorders ranges from high-impact monogenic variants to polygenic influences, copy number changes, and epigenetic/modifier-gene mechanisms. Despite an exponential increase in insight through genomic sequencing, significant heterogeneity and mechanistic knowledge gaps remain.

2.1 Molecular Mechanisms of Rare Congenital Defects

Cardiac morphogenesis is comprised of tightly integrated processes involving cell differentiation, chamber formation, looping, endocardial-mesenchymal transition, and neural crest-derived cell migration and septation. Genetic disruption of important transcriptional regulators has been shown to cause these processes to go awry. For example, variants in NOTCH1 have been identified in up to ~10 % of patients with bicuspid aortic valve and left-sided obstructive lesions, showing defects in endothelial-mesenchymal signalling in OFT development [16]. Genetic encoding of transcription factors GATA4 and NKX2-5 has long been associated with septal defects and conduction-system disease; mutations in these genes demonstrate the crossover between structural and electrical cardiac manifestations [17]. In addition, large-scale studies of CHD have identified that recurrent CNVs underlie an estimated 5-10 % of cases, including syndromic conditions such as 22q11.2 deletion, 1q21.1 duplication and 7q11.23 microdeletion [18].

2.2 Genotype–Phenotype Correlations and Variable Expressivity

One of the principal challenges in inherited cardiovascular disease is the variable expressivity and age-dependent penetrance even among carriers of identical pathogenic variants. In hypertrophic cardiomyopathy (HCM), pathogenic sarcomeric gene variants (e.g., MYH7, MYBPC3) are identified in approximately 30-50 % of genotype-confirmed cases, but the severity of hypertrophy, arrhythmic risk, and age of onset vary widely. Similarly, in long QT syndrome (LQTS), the majority (~75 %) of genotype-positive cases are attributable to KCNQ1, KCNH2, or SCN5A, yet the clinical spectrum ranges from asymptomatic QT prolongation to sudden death [6]. In ARVC, variants in PKP2 are found in ~35-45 % of cases, but phenotypic onset and severity are heavily influenced by exercise exposure and modifier genes [19]. These observations underscore the importance of integrating genotype data with imaging, electrophysiology, and clinical context in risk stratification.

2.3 Role of Epigenetics and Modifier Genes

Beyond monogenic causes, the severity, penetrance, and progression of inherited cardiovascular conditions are increasingly recognized to be modulated by epigenetic modifications, polygenic background, and gene–environment interactions. Thus, epigenomic studies have identified that changes in DNA methylation, histone modification, and non-coding RNA regulation can impact cardiac development, arrhythmic vulnerability, and disease progression [20]. Similarly, modifier loci contribute to the phenotypic expression: for instance, truncating variants in the titin gene (TTNtv) may augment the disease phenotype in carriers of a primary sarcomeric mutation [21]. There is also growing support for the use of PRS in HCM as a means to provide additional stratification of genotype-positive yet phenotype-negative individuals who are at increased risk of disease manifestation [22]. Accordingly, environmental and lifestyle influences such as high-intensity athletic training, pregnancy, hormonal milieu, and metabolic stress continue to modify disease expression in disorders that include Brugada syndrome, ARVC, and genetically mediated aortopathies [23]. Overall, these findings underscore the multi-layered architecture of the inherited cardiovascular disorders and emphasize an integrative approach incorporating genomics, epigenomics, and clinical phenotyping during personalized surveillance and management.

Overall, the genetic architecture of rare congenital and inherited cardiovascular disorders reflects a dynamic network of high-impact variants, modifier loci, structural genomic variants and epigenetic regulation. While major progress has been made in molecular genetics and developmental biology, the complexity of genotype–phenotype relationships is incompletely understood, indicating the continued need for integrative genomic clinical mechanistic research.

3. Clinical Presentation and Red-Flag Indicators

The clinical presentation of RICVDs is remarkably heterogeneous, the result of complex interactions among age, genetic background, and environmental or physiological stressors. Whereas some individuals present with overt symptoms early in life, others remain asymptomatic well into adolescence or adulthood, when triggers such as exertion, pregnancy, metabolic stress, or arrhythmogenic substrate unmask the disease. This heterogeneity often leads to delayed diagnosis, especially in non-specialist or primary-care settings.

3.1 Silent, Atypical, and Age-Dependent Manifestations

Most of the inherited cardiac disorders have an age-dependent penetrance, with early subclinical abnormalities that turn into overt diseases with time. In HCM, for instance, genotype+ individuals are often phenotype- in childhood, while hypertrophy usually only surfaces during adolescence or early adulthood [24]. Arrhythmogenic cardiomyopathy, formerly named arrhythmogenic right ventricular cardiomyopathy or dysplasia, generally progresses

from a "concealed" electrical phase characterized by subtle ECG changes to structural disease and ventricular dysfunction over time, as described by expert consensus recommendations [19].

Inherited channelopathies, such as LQTS, CPVT, and Brugada syndrome, may remain clinically silent until physiological stressors activate the arrhythmogenic substrate. For example, in LQTS, arrhythmic events often occur in response to exercise, emotion, or auditory triggers in the absence of overt structural heart disease [6]. Similarly, CPVT is notorious for exercise-induced polymorphic ventricular arrhythmias despite a structurally normal heart.

Congenital heart defects (CHDs) also show temporal variability in their presentation. Whereas severe cyanotic lesions are diagnosed typically in infancy, milder anomalies such as bicuspid aortic valve, partial anomalous pulmonary venous return, or isolated aortic dilation may remain subclinical well into adolescence or adulthood, when complications including regurgitation, aneurysm formation, or arrhythmogenic remodeling emerge [5].

3.2 Red-Flag Symptoms for Early Specialist Referral

Timely recognition of RICVDs is based on the identification of clinical warning symptoms and signs that suggest specialist evaluation. Various symptoms are highly suggestive of an underlying inherited substrate. Unexplained syncope or presyncope, especially when provoked by exertion, emotional stress, or swimming, has been strongly associated with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, usually presenting as an initial manifestation in affected individuals [25]. Recurrent palpitations or documented arrhythmias, including polymorphic ventricular tachycardia, torsades de pointes, or sustained supraventricular tachycardia, may also be indicative of inherited arrhythmia syndromes or early cardiomyopathy. Chest pain during exertion in children or young adults, especially associated with ECG or imaging abnormalities, requires consideration of congenital coronary anomalies or myocardial diseases [5]. Exercise intolerance or dyspnea in the absence of pulmonary pathology may point to an evolving cardiomyopathic process.

Physical examination may also give other diagnostic clues. Suspecting cardiac murmurs of structural abnormalities, marfanoid or connective-tissue features related to aortopathy, and cyanosis, digital clubbing, or differences in the blood pressure of the limbs may be indicative of congenital cardiovascular diseases. In infants, children, or young adults, heart failure without an identifiable cause should be referred to a specialist immediately because early cardiomyopathy and large congenital lesions may present with minimal or nonspecific complaints [24]. Other important categories of red flags include those of an electrocardiographic and imaging nature. The latter category includes findings like prolonged QTc intervals, Brugada-pattern ECGs, epsilon waves indicative of arrhythmogenic cardiomyopathy, or ventricular pre-excitation. Such imaging findings as unexplained left ventricular hypertrophy, reduced systolic function, abnormal myocardial strain, or detection of coronary artery anomalies using CT or MRI are considered to be grounds for referring a patient for genetic and cardiomyopathy evaluation [19], [24].

Family history is considered one of the strongest predictors of underlying heritable disease. Premature sudden cardiac death before the age of 50, multiple family members with cardiomyopathy, arrhythmia, or aortic disease, or the presence of known pathogenic variants greatly raises the diagnostic likelihood. Familial cascade screening has provided evidence that 30-50% of first-degree relatives of an affected proband are found to carry either clinical or genetic evidence of disease; thus, structured family-based evaluation is important [7], [19].

Collectively, these red-flag indicators reflect the wide clinical spectrum of RICVDs, which ranges from asymptomatic early stages to life-threatening arrhythmias, heart failure, or sudden cardiac death. Recognition of age-dependent penetrance, subtle early manifestations, and high-risk clinical clues has the potential to offer timely specialist referral, accelerate diagnosis, and support the implementation of precision-guided surveillance and management strategies.

4. Evolution of Diagnostic Pathways

Diagnostic pathways for cardiovascular disorders that are both rare and congenital/inherited have rapidly evolved in recent years, driven by advances in genomics, imaging, and functional testing, with exome and genome sequencing now playing a far more central role. For example, a 2023 single-centre study of pediatric cardiomyopathy demonstrated a near 40% diagnostic yield from exome sequencing, substantially higher than many traditional gene panels, and importantly, more than half of the diagnoses identified by ES would have been missed using standard cardiac gene panels [26]. Recently, in one of the largest re-analyses, more than 500 individuals with either cardiomyopathy or primary arrhythmia syndromes were re-investigated using genome sequencing with RNA-splicing evaluation, which uncovered pathogenic intronic and mitochondrial variants and thus increased the genetic diagnosis rate [27]. These data further emphasize the use of advanced sequencing techniques, like whole-genome sequencing and functional transcriptomic

analysis, which will further increase diagnostic sensitivity, particularly for deep intronic or non-coding variants often invisible to conventional panel testing.

At the same time, imaging approaches have become more sophisticated and clinically impactful. Cardiac magnetic resonance (CMR) retains its pivotal role, and recent studies have emphasized how new metrics of tissue characterization, such as fibrosis quantification via LGE, T1 mapping, and extracellular volume fraction, are strongly associated with arrhythmic risk and clinical outcome [28]. In this period, 4D flow MRI has become increasingly feasible in CHD. Detailed assessments of complex blood flow dynamics, wall shear stress, and energy loss are now available. A recent multi-center study proved excellent reproducibility of 4D flow metrics across vendors, reinforcing its value for longitudinal assessment [29]. Also, several emerging clinical reports have described how 4D flow MRI now serves to inform management decisions in adults with CHD based on novel hemodynamic markers [30]. For pediatric populations, accelerated 4D flow MRI protocols using compressed sensing and respiratory compensation were validated, enabling high-quality flow quantification with much shorter scan times compared to conventional methods [31].

Functional assessment remains critical. Beyond exercise stress testing for arrhythmia syndromes, integration of flow imaging and hemodynamics with genome-driven risk models means we can now better stratify structural as well as electrophysiological risk. For example, 4D flow MRI has been applied in pediatric coarctation of the aorta to identify residual flow disturbances and wall shear stress abnormalities after repair factors which may contribute to late complications and inform ongoing clinical monitoring [32]. Likewise, recent CMR-based prognostic models leverage fibrosis quantification to stratify risk in dilated cardiomyopathy, suggesting the possibility of more personalized surveillance and therapy [33]. A consolidated overview of major rare congenital and inherited cardiovascular disorders, their diagnostic pathways, prognostic indicators, and current management approaches is provided in Table 1.

RESULTS

Table 1. Key Advances in Diagnostic Pathways, Prognosis, and Multidisciplinary Care in RICVDs

Domain	Recent Advances	Clinical Impact
Diagnostic Imaging	Echocardiographic strain analysis (GLS). 3D/4D echocardiography. High-resolution CMR (T1/T2 mapping, ECV, LGE quantification). 4D flow MRI for congenital lesions. CT-based aortic and coronary characterization	Earlier detection of subclinical myocardial dysfunction. Better phenotyping of cardiomyopathies and CHD. Improved identification of arrhythmogenic substratesandfibrosis. Quantification of abnormal hemodynamics to guide intervention
Genomic Diagnostics	Expanded gene panels (cardiomyopathy, channelopathy, aortopathy). Exome and whole-genome sequencing. RNA splicing and transcriptome-assisted variant interpretation. Polygenic risk scores (PRS) for disease prediction. Improved variant classification frameworks	Higher diagnostic yield in atypical or early cases. Identification of deep intronic or structural variants missed by panel testing. Better genotype–phenotype correlations. Precision cascade screening for relatives
Integrated Imaging–Genomic Pathways	AI-driven image analysis for early disease recognition. Machine-learning risk models combining CMR + genotype + ECG. Multi-modal phenotyping platforms	Personalized risk stratification. Earlier identification of high-risk patients. Mechanism-based therapy selection
Prognostic Determinants	Genotype-specific risk scores (e.g., LMNA-risk models). Imaging biomarkers (LGE burden, ECV, GLS). Molecular biomarkers (NT-proBNP, hs-troponin, miRNA signatures). Clinical course modifiers (exercise burden, pregnancy, systemic inflammation)	Improved prediction of arrhythmic events and heart failure. Tailored device therapy decisions (ICD implantation). Dynamic monitoring and personalized surveillance intervals

Advances in Medical Therapy	Targeted pharmacotherapy (e.g., myosin inhibitors for HCM). Precision management for channelopathies (gene-specific beta-blocker strategies). Emerging RNA-based and gene editing therapies	Disease-modifyingtreatment options. Reduced arrhythmic burden and SCD risk. Future potential for genotype-targeted curative interventions
Multidisciplinary Care Models	Dedicated inherited cardiovascular disease (ICD) clinics. Integrated care teams (cardiology + electrophysiology + genetics + congenital surgeons + imaging + psychology). Digital follow-up and telehealth surveillance. Structured cascade screening programs	30–40% reduction in diagnostic delay. Higher uptake of genetic testing. Improved adherence to surveillance. Holistic, lifespan-based management
Psychosocial & Lifestyle Management	Reproductive counseling for affected families. Exercise guidelines for inherited arrhythmia syndromes and cardiomyopathies. Mental-health and family-support programs	Reduced anxiety and improved quality of life. Informed lifestyle and reproductive decisions. Long-term adherence to care

In summary, next-generation sequencing, advanced CMR tissue characterization, and 4D flow MRI, complemented by functional evaluation, now define a leading-edge diagnostic approach in RICVDs. These integrated methods enable earlier diagnosis, more precise risk stratification, and mechanism-tailored management, shifting the paradigm from detection in reaction to proactive, precision-guided care.

DISCUSSION

5. Prognostic Determinants and Risk Stratification

5.1 Impact of Genetic Variants on Prognosis

Genetic findings in rare congenital and inherited cardiovascular disorders increasingly inform diagnosis, prognosis, and management. For example, in Dilated Cardiomyopathy (DCM) cohorts, carriers of pathogenic or likely-pathogenic rare variants in recognized DCM genes exhibited more advanced disease: in one study, individuals with rare DCM gene variants had higher odds of left-ventricular dilation, reduced ejection fraction and adverse events compared with non-carriers [34]. In Hypertrophic Cardiomyopathy, pathogenic sarcomeric gene variants, for example, in MYH7 and MYBPC3, account for ~30-40 % of cases and are associated with an earlier disease onset, greater left-ventricular hypertrophy, and higher risk of arrhythmia or sudden death in comparison to sarcomere-negative patients [35].

In addition, there are different prognostic risks carried by specific gene variants. For instance, lamin A/C (LMNA) pathogenic variants in DCM or arrhythmogenic cardiomyopathy confer a high risk of malignant ventricular arrhythmias and sudden cardiac death, hence genotype-specific risk scores for decision-making regarding device therapy [36]. Consequently, the genotype has become an important factor in the algorithms for risk stratification, allowing more differentiated personalized prognosis and tailored surveillance/intervention strategies.

5.2 Long-Term Natural History and Course Modifiers

Although the natural history of many of the uncommon cardiovascular disorders is heterogeneous, a number of modifiers of progression and outcome have been determined. In HCM, genotype-positive individuals may remain phenotype-negative for years; ~50 % of genotype-positive children show no overt hypertrophy until adolescence or later, emphasizing age-dependent penetrance [37]. In DCM, recovery of left-ventricular function (left-ventricular reverse remodelling, LVRR) occurs in a subset of patients; one Japanese study found that patients with TTN truncating variants had a better LVRR and prognosis compared to those with LMNA variants (TTN carriers: better functional recovery; LMNA: poor reverse remodelling, higher arrhythmic risk) [38].

Disease course is further modified by environmental and physiological variables, including exercise burden, pregnancy, metabolic comorbidities, inflammatory triggers, and lifestyle factors, particularly in the arrhythmogenic or inherited categories of cardiomyopathy. Imaging biomarkers - for example, extent of late gadolinium enhancement on CMR and functional parameters, such as peak VO_2 and strain imaging, also act as predictors of outcome and may represent dynamic modifiers of course.

5.3 Emerging Biomarkers for Disease Severity

Besides genotype and imaging, a number of molecular biomarkers are emerging as prognostic tools in inherited cardiovascular disease. For

example, circulating non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have been discussed as potential prognostic biomarkers in heart failure and cardiomyopathy contexts [39].

Protein-based biomarkers, including high-sensitivity troponin, N-terminal pro-B-type natriuretic peptide (NTproBNP), and growth-differentiation factor-15 (GDF-15), have shown association with adverse events in inherited cardiac disease, though often in broader heart-failure populations. The emergence of imaging-genetic composite biomarkers such as polygenic risk scores and gene-expression signatures is under investigation: one review, for instance, reported that common variant polygenic risk scores (PRS) contributed to cardiomyopathy severity and could modulate the penetrance of rare pathogenic variants [40]. LGE presence at CMR and typical ECG patterns, such as T-wave inversion and low QRS voltages, in arrhythmogenic cardiomyopathy are being combined with biomarker findings to better estimate risk for malignant arrhythmias [36]. These emerging biomarkers have promise for more granular risk stratification, which could facilitate earlier intervention and personalized monitoring in rare cardiovascular disorders.

In conclusion, prognostic stratification in rare congenital and inherited cardiovascular disorders relies on a multifactorial model: genotype, including rare high-impact variants and polygenic background; phenotype modifiers, such as age, environmental factors, and lifestyle; imaging and functional biomarkers; and molecular biomarkers. Integration among these domains underpins more precise risk assessment and tailored management strategies, representing the evolution toward 'precision cardiovascular medicine' in the inherited disease space.

6. Advances in Medical, Surgical, and Interventional Therapies

Therapeutic care for rare congenital and inherited cardiovascular disorders has become increasingly stratified and mechanism-driven. Over the past decade, clinicians have combined improved perioperative pathways, hybrid and less-invasive interventional techniques, and molecularly targeted pharmacotherapies to reduce morbidity, shorten recovery, and - when possible - modify the natural history of disease.

6.1 Evolving perioperative strategies for complex congenital anomalies

Perioperative management for children and adults with complex congenital heart disease has evolved through two parallel trends: (1) adoption of standardized, evidence-based perioperative pathways that reduce physiological stress and complications and (2) individualized surgical strategy (including staged repairs), balancing immediate survival with long-term function. Enhanced Recovery After Surgery protocols applied to cardiac surgery, adapted for pediatric and adult CHD cohorts, have been associated with reduced opioid use, shortened length of stay, and improved early functional recovery in both single-center and multi-center reports. Recent consensus statements emphasize multimodal analgesia, early extubation, optimized fluid and glycaemic strategies, and pathway-driven mobilization as safe means to accelerate recovery after complex repairs. [41].

Hybrid approaches to primary Norwood reconstruction in neonates with HLHS and other high-risk anatomies include combination surgical and catheter techniques. Hybrid palliation, including bilateral pulmonary artery banding with ductal stenting, has been associated with equivalent early survival in selected high-risk infants in systematic reviews and multicenter series and may defer or reduce the complexity of subsequent procedures, although long-term neurodevelopmental and reintervention profiles differ between strategies and must be individualized [42].

6.2 Minimally invasive and hybrid endovascular approaches

Interventional cardiology has expanded the options for patients with congenitally acquired structural disease and sequelae of prior surgery. TPVI is now considered an established therapy for dysfunctional right-ventricular outflow tract conduits and bioprosthetic valves. Large multicenter series have shown durable hemodynamic improvement, symptomatic benefit, and freedom from surgical re-intervention for many patients out to medium-term follow-up. Device-related infectious endocarditis and structural degeneration remain important drivers of late reintervention, with valve choice and patient anatomy influencing outcomes [43], [44].

Hybrid catheter-surgical approaches extend beyond palliation of HLHS. For selected complex aortic arch or airway-adjacent lesions, combined surgical debranching and endovascular stenting reduces cardiopulmonary bypass time and may lower immediate perioperative risk in fragile patients. Advanced imaging with 4D flow MRI and other modalities is increasingly used to guide both procedural planning and device selection by quantifying flow patterns and wall shear stress, particularly in aortopathy and complex congenital anatomies [44], [45].

6.3 Precision-medicine-based pharmacotherapy

One major recent paradigm shift is the introduction of mechanism-targeted pharmacotherapies informed by molecular pathophysiology. Several such agents have already changed clinical practice for various inherited cardiometabolic and sarcomeric diseases. Obstructive HCM-Cardiac myosin inhibitors. Small-molecule myosin inhibitors (mavacamten and the newer agent aficamten) have been developed as direct modulators of the sarcomeric hypercontractility-the final common pathway in obstructive HCM. Mavacamten received regulatory approval after randomized trials, EXPLORER-HCM, and VALOR-HCM, had already demonstrated clinically meaningful reductions in resting and provoked left ventricular outflow tract gradients, improved symptoms and exercise capacity, and reduced need for septal reduction therapies in many patients. Aficamten's pivotal NEJM trial in 2024 reported statistically significant improvements in peak VO_2, symptomatic status, and LVOT gradients versus placebo among patients with obstructive HCM, supporting a class effect of selective myosin inhibition. The drugs are examples of true precision pharmacotherapy targeting the sarcomeric mechanism rather than nonspecific hemodynamic consequences [46], [47].
Other targeted therapies. Inherited Arrhythmia Syndromes: genotype-directed therapy remains pertinent: high-dose beta-blockade and flecainide for CPVT; avoidance of QT-prolonging drugs, including targeted lifestyle counseling in LQTS; and consideration of genotype when evaluating ICD thresholds (based on guidelines). These are being complemented by growing research into allele-specific antisense oligonucleotides and AAV-mediated gene replacement for certain monogenic cardiomyopathies [48].

6.4 Measured impact and remaining challenges

Taken together, these advances have quantifiable clinical impact: for example, tafamidis reduced all-cause mortality and cardiovascular hospitalizations in ATTR (ATTR-ACT) and is associated with improved functional and echocardiographic trajectories; myosin inhibitors have reduced the need for invasive septal reduction and improved exercise capacity in obstructive HCM trials; and TPVI has provided durable conduit management that delays or avoids re-operation for many patients. However, important challenges remain: long-term durability and infection risk after TPVI, late reintervention after hybrid palliation, heterogeneity in response to molecular therapies (mutation-dependent), high cost and access barriers for gene-directed agents, and ongoing safety monitoring for in vivo gene editing and novel biologics.

7. Multidisciplinary Care Models

7.1 Integration of cardiology, genetics, radiology, and surgical teams

Optimal management of RICVDs increasingly depends on formally integrated multidisciplinary teams that bring together clinical cardiology, cardiac imaging, electrophysiology, cardiovascular surgery/intervention, clinical genetics, and genetic counselling. Dedicated inherited-heart or cardiomyopathy clinics where genetic testing, CMR/CT phenotyping, arrhythmia assessment, and family cascade screening are coordinated have been associated with higher diagnostic yield, improved guideline-directed testing, and more timely therapeutic decision-making compared with fragmented care. For example, single-centre series and registry data report that implementation of specialized multidisciplinary clinics increases the proportion of patients receiving appropriate genetic testing and specialist imaging and shortens time to family cascade testing and intervention; several health systems now report diagnostic yields and changes in management in ≥30–40% of referred cohorts after deployment of such services. These integrated models also facilitate rapid, genotype-informed decisions-for example, LMNA or truncating TTN variants that influence ICD or heart-failure management-and streamline enrollment into genotype-specific trials [49]-[51].

7.2 Transition-of-care pathways from pediatric to adult services

Transition from paediatric to adult cardiology care is a recognized vulnerable period for loss to follow-up and suboptimal outcomes in congenital and inherited cardiac disease. Structured transition programs incorporating early preparation beginning in early adolescence, individualized transition plans, joint pediatric adult clinics, documented transfer summaries, and designated transition coordinators demonstrably improve retention in adult care and patient self-management skills; some randomized/controlled quality-of-life studies and implementation series report improved attendance rates and disease-specific knowledge. Consensus statements and multinational guidance stress that transition planning should be adaptable to local resources but must address education on reproductive risk, employment/insurance issues, and psychosocial needs. Telemedicine and nurse-led transition clinics have emerged as pragmatic strategies to bridge gaps during transfer, particularly in regions with geographic barriers to specialist centers [52]-[54].

7.3 Patient-centered care: psychosocial, reproductive, and lifestyle considerations

High-quality care of RICVDs extends beyond diagnostics and procedures: it necessitates psychosocial support, reproductive counseling, and personalized lifestyle advice. Psychological distress,

anxiety of genetic risk, and concerns about family planning are common in probands and relatives, and psychosocial interventions (counselling, peer support, integrated psychology within clinics) enhance the uptake of cascade testing, adherence to surveillance, and quality of life. Reproductive counseling is imperative for conditions with pregnancy-related risks, such as significant aortopathy, HCM, or pre-existing heart failure, and for inherited conditions where preimplantation genetic diagnosis or prenatal testing may be considered. Multidisciplinary assessment, together with maternal-fetal medicine, is indicated for pregnancy planning. Lifestyle guidance takes the form of exercise prescriptions, restrictions to competitive sports for diseases such as ARVC or certain channelopathies, and avoidance of drugs that prolong QT. Such guidance should be individualized and guided by genotype, phenotype severity, and patient goals. Thus, the embedding of genetic counsellors, clinical psychologists, and specialized nurse coordinators within multidisciplinary teams improves communication, shared decision-making, and clinical uptake of preventive measures [5], [55]-[57].

8. Challenges in Resource-Limited Settings

8.1 Diagnostic delays and inequality in access to genetic testing

Diagnostic delays and inequitable access to specialist services are pervasive barriers to timely care for rare congenital and inherited cardiovascular disorders in LMICs. Structural barriers-limited numbers of trained cardiologists and cardiac imaging services, sparse paediatric cardiac surgical capacity, and constrained laboratory infrastructure-translate into late presentation and higher morbidity: analyses of global research output and burden show that low- and lower-middle-income countries account for the majority of cardiovascular deaths but contribute a disproportionately small share of research and specialized service capacity, reflecting a broader gap in diagnostic and treatment resources [58]. Inequities extend to genomic diagnostics: recent studies document substantial disparities in the offer and uptake of genetic testing for hereditary cardiomyopathies, driven by cost, lack of local testing laboratories, limited insurance coverage, and clinician unfamiliarity with genomic indications; these factors reduce the likelihood of cascade screening and perpetuate under-recognition of at-risk relatives [59]. The consequence is a two-fold problem-delayed recognition of congenital heart disease and inherited cardiomyopathy, and missed opportunities for preventive interventions that would be triggered by a molecular diagnosis [60]. Addressing these gaps, therefore, requires both system-level investment and pragmatic, scalable diagnostic strategies tailored to resource constraints.

8.2 Approaches to standardization of care in pluralistic health systems

In developing pragmatic strategies to standardize care across heterogeneous health systems and reduce inequities in diagnosis, several tiered public-health frameworks for PCHD care have been defined by international expert groups, delineating minimum competencies at successive levels of service (screening/diagnosis, outpatient/inpatient care, imaging/catheterization, and cardiac surgery) such that countries can build capacity incrementally and safely [61]. Decentralization and hub-and-spoke models-for example, PEN-Plus strategies aim to bring more complex cardiac care closer to underserved populations by combining regional centers of excellence with district-level diagnosis and follow-up, supported by telemedicine, visiting specialist programs, and task-sharing to trained non-physician clinicians [62]. Practical measures in improving early detection in low-resource settings include routine newborn pulse-oximetry screening, training frontline clinicians in point-of-care echocardiography, centralized digital image review, and regional registries to track outcomes and prioritize capacity building [60]. For genomic testing, efforts to lower barriers have included regional reference labs, subsidized or tiered testing panels focused on high-yield variants, and international partnerships that provide sequencing and variant interpretation support; when combined with implementation of simplified genetic counselling protocols, these enable extension of benefits of molecular diagnosis in settings where full local infrastructure is absent [59]. As discussed above, these approaches-policy frameworks, decentralized care models, targeted training, and pragmatic genomics strategies-offer a realistic pathway to accomplish the needed reduction of inequities in high-quality RICVD care across diverse healthcare systems.

9. Future Directions and Research Priorities

9.1 Impact of AI and computational modelling

Artificial intelligence and advanced computational modelling are rapidly maturing into practical tools for diagnosis, risk stratification, and workflow efficiency in inherited and congenital cardiovascular disease. Deep-learning models augment echocardiographic and CMR interpretation by automating chamber quantification, strain analysis, and LGE detection. Large reviews demonstrate that AI can substantially reduce reporting time while improving reproducibility and diagnostic sensitivity for subtle structural abnormalities that often precede clinical disease. Recent reviews and consensus summaries have identified and highlighted validated AI applications across ECG, echocardiography, and CT/MR relevant to the RICVDs, including automated detection of ventricular hypertrophy patterns, coronary anomalies, and arrhythmia

substrates. AI is also enabling population-scale case finding by analyzing wearable single-lead ECGs and routine clinical ECGs to flag individuals who would benefit from specialist referral and a genetic evaluation approach that could shorten the long diagnostic delays typical for rare diseases. Prospective clinical-utility studies and careful bias-mitigation remain necessary before broad deployment, but the translational trajectory is clear: AI will increasingly support earlier detection and more precise phenotyping in multidisciplinary clinics [63], [64].

9.2 Advances in gene editing, bioprinting and regenerative approaches

Therapeutic innovation has moved from concept to early human testing in several frontier domains. In-vivo CRISPR-based gene editing produced large, durable reductions in transthyretin protein in the first-in-human NTLA-2001 study, demonstrating the feasibility of systemic, single-dose genomic correction for a proteinopathy with major cardiac manifestations and opening a path for analogous approaches in selected monogenic cardiomyopathies. Parallel preclinical and early-phase efforts are evaluating allele-specific antisense oligonucleotides, AAV-mediated gene replacement, and base-editing strategies for pathogenic sarcomeric and metabolic cardiomyopathies. At the tissue level, 3D bioprinting and cardiac organoid technologies have advanced rapidly: recent reviews document progress toward vascularized myocardial patches, valve constructs, and chamber models that recapitulate native architecture and contractile function platforms that may enable regenerative repair, personalized drug testing, and eventually off-the-shelf engineered tissues for structural restoration. Regulatory, safety, delivery, and cost challenges remain substantial, but the combination of precise genome editing and scalable tissue engineering holds promise for disease-modifying therapies that directly address root causes of many RICVDs [65]-[68].

9.3 Developing International Registries and Collaborative Networks

Large, harmonized registries and international collaborative networks are essential for accelerating discovery, validating prognostic biomarkers, and powering genotype-driven trials. Multi-center efforts such as the Sarcomeric Human Cardiomyopathy Registry (SHaRe) and new prospective programs like PATHFINDER-CHD have already shown the value of aggregated clinical, imaging, genomic, and outcome data in refining genotype–phenotype correlations, identifying high-risk patient subgroups, and informing guideline development. Registries also provide a basis for equitable trial recruitment and real-world effectiveness studies critical when single-center cohorts are underpowered for meaningful subgroup analyses. To maximise the impact, registries should incorporate interoperable data standards, linked biobanks, and imaging cores, with governance models that enable cross-border data sharing while protecting participant privacy. Investment in such infrastructures, together with capacity building in low- and middle-income regions, will be crucial for ensuring breakthroughs in diagnostics and therapeutics translate into global improvements in the care of RICVDs [69], [70].

10. Conclusion

RICVDs are rare, congenital and inherited cardiovascular disorders that represent an evolving clinical and public-health priority because of their lifelong morbidity, genetic complexity, and potential for sudden catastrophic events. The rapid progress made in the fields of multimodal cardiac imaging, next-generation sequencing, and computational analytics has fundamentally reshaped the possibility of early detection, allowing clinicians to identify disease at a preclinical stage and apply individualized risk-stratified care. The integration of molecular diagnostics, combined with advanced imaging that is increasingly supported by artificial intelligence, has greatly improved the precision of diagnosis, prognosis, and decision-making regarding therapies across both pediatric and adult populations.

Yet despite these advances, major gaps persist. Diagnostic delays are still common, mainly in resource-limited settings where access to genetic testing, specialized imaging, and multidisciplinary expertise is restricted. Variability in clinical infrastructure underlines the need for models of care that can be adapted globally in a standardized manner. Multidisciplinary teams bridging cardiology, genetics, radiology, surgery, and psychosocial services offer the strongest framework for comprehensive, patient-centered management across the lifespan.

Innovations in gene editing, regenerative therapies, bioprinting, and computational modelling further hold promise to transform the therapeutic landscape for RICVDs. Improved quality of the evidence will depend on strengthened international registries, genomic databases, and collaborative networks to overcome challenges imposed by the conditions' rarity and heterogeneity. By advancing equitable access to diagnostics and fostering integrated care pathways, the field moves closer to truly personalized and globally accessible management for individuals affected by these disorders.

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