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The contemporary role of genetics in cardiovascular medicine: from phenotypes to precision diagnoses

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The diagnostic work-up of cardiovascular genetic diseases is emerging as a reference model for precision (cause and phenotype) and personalized medicine (tailored individual management). This approach is expanding across all areas of cardiovascular medicine, ranging from monogenic diseases to multifactorial disorders where 'risk factors' such as familial hypercholesterolaemia may play a role in the risk profile. In this context, cardiomyopathies provide an ideal reference because they are monogenic yet genetically heterogeneous diseases, much like many other cardiovascular genetic disorders. In this model, the genetic path starts with deep phenotyping of the patient and relatives and progresses with genetic testing including extensive multigene panels, up to whole-exome sequencing and whole-genome sequencing. Although genetic work-ups are increasingly successful, several unresolved challenges and limitations remain. These include the interpretation and reinterpretation of variants, as many pre-American College of Medical Genetics variants previously classified as likely pathogenic or pathogenic are now recognized as variants of uncertain significance or benign/likely benign; pathogenic variants missed with short-read next generation sequencing (NGS) technologies (e.g. deep intronic variants or Copy Number Variations); gene-specific issues such as pseudogenes and pseudo-exons; and differing interpretations of pathogenicity for the same gene defects by commercial pipelines. Despite widespread NGS-based testing, about half of suspected Mendelian conditions still lack a precise molecular diagnosis. New organizational models are needed to integrate emerging knowledge and innovations incorporating both clinical and genetic data into intelligent platforms that may support shared management pathways.

Introduction

Genetics is a medical discipline that encompasses phenotypic traits and manifestations, possible familial aggregation (e.g. Mendelian or mitochondrial genetic diseases), and molecular genetic causes. Beyond its disciplinary or academic definitions, genetics is a model for precision (linking cause to phenotype) and personalized medicine (individualized medical management tailored to clinical needs), entering many areas of cardiovascular medicine—from monogenic

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diseases to multifactorial disorders, where risk can also be influenced by monogenic factors. The current clinical applications address: cardiomyopathies and their genocopies, both syndromic and non-syndromic[1]; primary, non-cardiomyopathy arrhythmogenic diseases[2]; heritable arteriopathies[3]; autoinflammatory diseases with myo-pericardial involvement [e.g. Familial Mediterranean Fever (FMF)][4]; pulmonary hypertension (PH)[5]; monogenic risk factors such as familial hypercholesterolaemia[6,7]; and ultrarare multiorgan syndromes/diseases in which the cardiovascular system is involved, often determining the outcome. In these diseases, the goal is to identify pathogenic defects in validated disease-specific genes in patients with well-defined phenotypes, and that these defects are sufficient to explain the phenotypes observed in probands and their families. This brief overview focuses on the diagnostic work-up model and monogenic cardiovascular diseases encountered in daily cardiology practice, highlighting recent advancements, and ongoing challenges.

A shared work-up model for genetic cardiovascular diseases

In clinical practice, we are witnessing exponential advancements in genetic work-up targeting cardiovascular monogenic diseases. Simple yet fundamental rules provide for clinical models whose primary objectives are to frame the phenotypes and the family contexts and evaluate the possibility that the observed phenotypes are potentially referable to known genetic causes or suggest a genetic origin of familiar aggregation. Even before genetic counselling, the role of the cardiologist is to assign the phenotypes to their nosology, annotate and collect individual traits in probands and relatives, and then guide the search for the precise cause of the disease.[1,8] The patterns of inheritance in familial cardiovascular diseases may substantially contribute. The new ESC guidelines on cardiomyopathies offer a practical framework for managing diagnostic work-up,[1,9] considering not only the possibility of genetic cardiac or vascular diseases that primarily involve the heart and vessels, but also syndromic diseases, affecting multiple organs and systems (*Figure 1*).

The concept of 'deep phenotyping', emphasized in the ESC Cardiomyopathies guidelines 2023[1] and previously anticipated by ESC position statements[10-13] and guidelines for hypertrophic cardiomyopathy (HCM),[14] can be extended to all isolated or syndromic 'cardiovascular genetic diseases'. Most inherited cardiovascular diseases are genetically heterogeneous: many disorders allelic at the same locus may phenotypically 'overlap', and are not specific enough to be attributed to a unique gene/defect. The rule 'one gene, one disease' is respected, i.e. for some genocopies of primary cardiomyopathies. The simplest examples are Danon Disease and Fabry Disease. Defects in *LAMP2* gene cause only Danon Disease, those in *GLA* gene only cause Fabry Disease, both classical and late-onset forms, but defects in genes such as *LMNA* or *MYH7* may manifest with different phenotypes. However, new horizons are opening up that are capable of explaining how the same defective gene can cause different phenotypes (e.g. *BAG3*, *DES*, or *DMD*): defects causing gain of function or loss of function may be associated with different clinical manifestations. This new knowledge should meet an equally deep clinical characterization of the phenotype similarities and differences to make comprehensible differently actionable causative genetic defects. Since symptoms are rarely disease-specific, multiparametric data-incorporating genetic, clinical and imaging information are essential for addressing clinically oriented diagnostic hypotheses.

Genetic cardiovascular diseases

Cardiomyopathies

Cardiomyopathies represent one of the most advanced models of integration of clinical and molecular genetics in cardiovascular diseases. In the ESC Cardiomyopathy 2023 guidelines,[1] the diagnostic approach has retained the morpho-functional basis; the classification has conservatively maintained the four main phenotypes (HCM; DCM, dilated cardiomyopathy; restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy).[10] Additionally, a new group of cardiomyopathies defined as non-dilated left ventricular cardiomyopathy (NDLVC) has been introduced to encompass early or intermediate forms, especially 'early' DCM with imaging proving the structural changes (e.g. fibrosis), eventually supported by genetic testing. NDLVC should prevent the inclusion of confusing conditions alternatively classifiable, for example, hereditary arrhythmias or chronic granulomatous and non-granulomatous inflammatory diseases, which can benefit from their own specific diagnostic decision-making algorithms and targeted therapies, independent or additional to those of cardiomyopathies.

The new guidelines offer the cardiologist a management console to combine the most appropriate clinical-instrumental multimodality assessments with the possible disease-specific traits addressing the indications for genetic, clinical, and molecular pathways.[9] Specific recommendations guide genetic counselling/visit, and genetic testing in probands and relatives for each type and subtype of cardiomyopathy, including genocopies, and phenocopies. All diagnostic pathways share a common baseline that includes clinical evaluation, ECG, 24H ECG, 2-Dimensional Transthoracic Echocardiography (2DTTE). Depending on available facilities, these baseline tools may be expanded with cardiac magnetic resonance imaging, right heart catheterization, endomyocardial biopsy, functional imaging, and disease-specific biomarkers testing when available.

Heritable arteriopathies

This complex and large group of syndromic and non-syndromic diseases shares severe cardiovascular manifestations such as thoracic aortic aneurism (TAA) and dissection (TAAD), extra-aortic arterial aneurysms, valve diseases and, less commonly, spontaneous coronary artery dissection.[3] TAA is easily diagnosed with simple cardiac ultrasound imaging. 2DTTE is the first-line diagnostic tool for ascending aorta aneurysms, which recur in the vast majority of these diseases and is a matter of cardiology care, irrespective of the primary

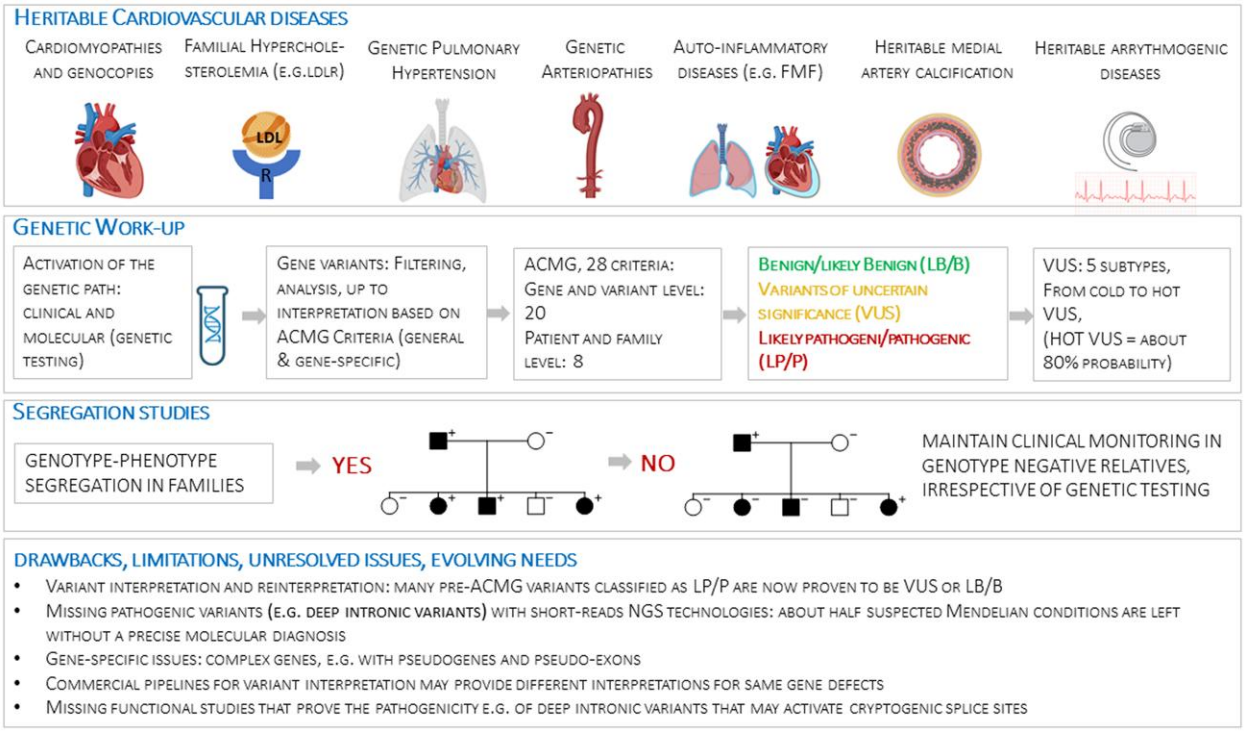

Figure 1 Heritable cardiovascular diseases, diagnostic work-up, limitations. (Partially obtained with BioRender.)

clinical indication to the cardiological evaluation. Although deep phenotyping of patients with syndromic TAA/TAAD may involve specialties beyond cardiovascular and imaging settings, the indications to genetic paths are largely based on individual data and deep phenotyping as well as family history and screening. Multispecialty teams needed to manage complex syndromic disorders can be organized by cardiologists, or vice versa cardiologists may be involved in teams led by cardiac or vascular surgeons or by geneticists. These teams always originate from initiatives that may initially appear mono-disciplinary, but progressively evolve into multi-disciplinary collaborations. They extend beyond strictly biomedical fields to include areas like bioengineering or physics, enabling advancements in artificial intelligence-assisted diagnostics, particularly in application such as multimodal imaging.

Heritable arrhythmias syndromes

Primary arrhythmia syndromes are one the most advanced groups of cardiovascular disease that benefited from genetic research and its clinical translation.[2] Clinical genetics and genetic testing are now an integral part of the diagnostic work-up for patients with primary rhythm disorders. Genetic work-up for patients with cardiac channelopathies (Long-QT, Short-QT, Brugada Syndrome, etc.) is clinical routine. Genetic counselling and testing are offered to both probands and relatives; clinical monitoring, medical, and non-medical treatment options are now largely available in specialized tertiary arrhythmias centres. The 2022 ESC guidelines addressing the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death provide the most advanced indications about genetic investigation in these patients.[2] Supraventricular arrhythmias are receiving more attention either as isolated disorders or in the context of cardiac, valvular, metabolic, and systemic diseases. The 2024 ESC guidelines for the management of atrial fibrillation (AF)[15] address the emerging role of genetics in AF, including lone AF, AF complicating other heart diseases, and atrial cardiomyopathies.

Primary arterial calcifications

Monogenic diseases associated with non-atherosclerotic artery calcifications are complex genetic syndromes that cause non-atherosclerotic mineralization of the arterial elastic lamina and tunica media.[16] In the broad groups of arterial calcifications, calcium deposits can localize at the level of intima (intimal artery calcification, IAC), internal elastic lamina-artery (IEL-AC), and tunica media (MAC). Historically, research focused on IAC in atherosclerosis and therefore developed in the context of multifactorial diseases. However, in recent years, non-atherosclerotic IEL-AC and MAC gained novel attention based on the growing detection of monogenic disorders manifesting in infancy (e.g. the autosomal recessive potentially fatal Generalized Arterial Calcification of Infancy) and in adulthood (e.g. the autosomal recessive Pseudoxanthoma Elasticum with ocular, cutaneous and arterial manifestations). In these disorders, the genetic diagnosis plays a key indication for novel treatments that mitigate medial artery mineralization.

Pulmonary hypertension

A key diagnostic role of genetics concerns the precise diagnosis and risk stratification of PH, which is classified into five main groups: (i) Pulmonary arterial hypertension; (ii) PH associated with left heart disease; (iii) PH associated with lung diseases and/or hypoxia (repositioning in this group the PH in lymphangioleiomyomatosis caused by defects in *TSC1* and *TSC2* genes); (iv) PH associated with pulmonary artery obstructions (mainly chronic thromboembolic PH; CTEPH); (v) PH with unclear and/or multifactorial mechanisms.[5] The precise diagnosis is mandatory because the therapeutic strategies are substantially different. Group 1 includes heritable PH, with six known disease genes (the most common is *BMPR2*), and pulmonary veno-occlusive disease, with the autosomal dominant (*BMPR2*) and the autosomal recessive (*EIF2AK4*) forms. Group 5 includes cases/families with genetic metabolic disorders, where a precise diagnosis can be essential when target treatments enter the clinical scenarios, allowing patients to receive treatments tailored to the underlying cause.

Heritable autoinflammatory diseases

In the large group of these disorders, monogenic periodic fever syndromes (PFS) may affect the heart, in particular the pericardium and epicardium. The most common monogenic PFS include FMF, cryopyrin-associated periodic syndrome (Mukle–Well Syndrome), and tumour necrosis factor receptor-associated periodic syndrome.[4,17] In addition to the epi-pericardial inflammation, a major complication in these diseases is AA amyloidosis, which typically affects kidneys and joints but can also involve the heart. In addition, the complex cascade of vascular inflammation-related damage may influence the risk of atherosclerosis and complications. Genetic testing identifies the cause of the disease and supports treatments that may control disease manifestations and disease progression.

Monogenic risk factors

Malignant, early atherosclerosis may manifest in young people due to the effects of monogenic risk factors such as the ultrarare homozygous familial hypercholesterolaemia (HoFH) (1:300 000). HoFH is underdiagnosed and undertreated leading to significant premature cardiovascular morbidity and mortality, despite recommendations for universal paediatric lipid screening in children.[6,7] HoFH is eventually diagnosed later on in the life course, after the occurrence of potentially life-threatening events. Children/adolescents with high cholesterol levels can receive education to life styles, biochemical and clinical monitoring, and aggressive medications. Clinicians should complement biochemical diagnosis with genetic testing. Heterozygous forms of familial hypercholesterolaemia similarly deserve precise diagnosis both biochemical/clinical and genetic.

Strategies, limitations, unresolved issues

Genetic work-up: phenotype-first or genotype-first?

Genetic work-ups for heritable cardiovascular diseases are particularly complex because, with a few exceptions, most major groups of diseases are genetically heterogeneous meaning that multiple defective genes can cause similar phenotypes. Whether the diagnostic driver should be the phenotype or the genotype is the subject of two different interpretations of the role of the cardiologist. On one hand, the phenotype-first approach supported by current guidelines for cardiomyopathies,[1] relies on the clinical diagnosis as the foundation of the diagnostic pathway. On the other hand, the genotype-first approach[18] advocates for broad genetic testing (up to whole-exome or whole-genome sequencing) to search of genetic defects possible causing the observed phenotype. The choice of strategy depends on the clinician's expertise, that is, the ability to formulate pre-test diagnostic hypotheses.

Pertinence of the work-up organization

A recurring question on the organization and management of diagnostic pathways in these diseases is who has this role. This is straightforward for cardiac (cardiomyopathy) or vascular (TAA/TAAD) non-syndromic diseases whose clinical and disciplinary relevance is attributable to one (cardiology) or a few disciplines (cardiology, cardiac surgery, vascular surgery, radiology). However, it may be more challenging to assign the role of work-up organization in syndromic diseases, when the first clinical manifestations are neurological, nephrological, ophthalmological, dermatological, pulmonary, or others. In these cases, patients can refer to cardiovascular care after the first or multiple evaluations by specialists from other disciplines. Each work-up organization can vary in different hospitals according to logistical reasons. There is a lack of shared organizational models that, trained on guidelines, define the diagnostic platforms for the different cardiovascular genetic diseases. In any case, the activation of multidisciplinary operative platforms (tailored for the different pathologies and cases) requires 'flexible and sustainable' plans, more dependent on the initiatives of the specialists involved in the care of these diseases, than foreseen and planned at an institutional level.

Workup-related limitations

Limitations exist at both at clinical and genetic testing levels. The clinical genetics pathway should include counselling performed by geneticists. In syndromic diseases with manifest phenotypic traits (e.g. Marfan Syndrome), the geneticist performs the visits and frames the phenotypes. In genetic diseases such as cardiomyopathies, channelopathies, or PH, the clinical skills needed to evaluate the phenotypes require a highly specialized profile. Although joint (cardiologist and geneticist) counselling is suggested by guidelines, professional cardio-geneticists educated in both cardiology and genetics are missing.

Limitations related to genetic testing are linked to technologies, types of tests, interpretation of results, and incomplete testing. Despite the widespread use of next generation sequencing (NGS) (multigene commercial or customized multigene panels, MGP, WES, or WGS), and other tests, such as Array-CGH, and MLPA, approximately half of patients with suspected Mendelian cardiomyopathy are left without a precise molecular

diagnosis after the completing the genetic evaluation. The diagnostic yield tends to be higher in children[19] than adults[20], with WES adding little to the diagnostic yield of MGP. Missing detection of pathogenic variants, in particular CNV and deep intronic splice variants, remains an open issue when tests are only based on current short-reads NGS technologies.

Variants of uncertain significance

The increasing use of genetic testing has significantly increased the burden of variants of uncertain significance (VUS) resulting in substantial interpretative challenges, often complicating clinical decisions without providing actionable benefits for patients and families. According to American College of Medical Genetics guidelines, VUS are rare variants with uncertain possible effects on the observed phenotype, with a probability ranging from 10 to 90%. Vice versa, Pathogenic/Likely Pathogenic (P/LP) variants have a 90–99% probability of being the cause of the observed phenotype, particularly when identified in validated disease genes. On the opposite, Likely Benign/Benign (LB/B) variants have very low or negligible probability of causing the phenotype (<5% for LB and <0.1% for B). Whereas LP/P variants in disease genes are rare and directly relevant to the disease, VUS are individually rare but so numerous across genetic tests that they have become a major limitation in interpreting results. In patients with proven familial disease, the identification of a VUS hinders the benefits of cascade genetic testing within families. This often shifts the burden of diagnosis back to clinical evaluation, which genetic testing was intended to support by providing a precise aetiological diagnosis for personalized patient management.

Concluding comment

The contemporary genetic diagnostic work-up for monogenic heritable cardiovascular diseases cannot be considered complete unless the specific cause—the defect underlying the phenotype—is integrated with the clinical phenotype. The complexity of the work-up increases at the clinical level, where deeper phenotyping is needed to move beyond groups of genes (e.g. sarcomeric, desmosomal, etc.) and address single disease genes, while also considering emerging gene-based risk stratification (e.g. *LMNA*, or *DSP*). This process, which gradually shifts from gene groups to individual genes, requires a renewed clinical effort to thoroughly characterize phenotypes by gene and type of defect. New organizational models are needed to integrate innovations in clinical observations, genetics, and multiparametric data into sustainable, streamlined intelligent systems, ensuring equitable access to care in the face of the increasing clinical demand.

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Data availability

No new data were generated or analysed in support of this research.

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