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The new 2023 ESC guidelines for the management of cardiomyopathies: a guiding path for cardiologist decisions

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In the ESC 2023 guidelines, cardiomyopathies are conservatively defined as 'myocardial disorders in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality'. They are morpho-functionally classified as hypertrophic, dilated, restrictive, and arrhythmogenic right ventricular cardiomyopathy with the addition of the left ventricular non-dilated cardiomyopathy that describes intermediate phenotypes not fulfilling standard disease definitions despite the presence of myocardial disease on cardiac imaging or tissue analysis. The new ESC guidelines provide 'a guide to the diagnostic approach to cardiomyopathies, highlight general evaluation and management issues, and signpost the reader to the relevant evidence base for the recommendations'. The recommendations and suggestions included in the document provide the tools to build up pathways tailored to specific cardiomyopathy (phenotype and cause) and define therapeutic indications, including target therapies where possible. The impact is on clinical cardiology, where disease-specific care paths can be assisted by the guidelines, and on genetics, both clinics and testing, where deep phenotyping and participated multi-disciplinary evaluation provide a unique tool for validating the pathogenicity of variants. The role of endomyocardial biopsy remains underexploited and confined to particular forms of restrictive cardiomyopathy, myocarditis, and amyloidosis. New research and development will be needed to cover the gaps between science and clinics. Finally, the opening up to disciplines such as bioinformatics, bioengineering, mathematics, and physics will support clinical cardiologists in the best governance of the novel artificial intelligence-assisted resources.

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Introduction

The new ESC 2023 guidelines for the management of cardiomyopathies[1] are entering the clinical activity of the cardiology community after 15 years of intense scientific collaborative activity, which led to the publication of the ESC position statement on the classification of cardiomyopathies[2] followed by key documents on genetic counselling and testing,[3] diagnostic workup on cardiomyopathies,[4] guidelines on hypertrophic cardiomyopathy (HCM),[5] proposal of hypokinetic non-dilated cardiomyopathy (DCM),[6] statement on cardiac amyloidosis,[7] and interpretation and actionability of genetic variants in cardiomyopathies.[8] The new guidelines conservatively maintain the morpho-functional definition and the classification of the four main types of cardiomyopathies, namely HCM, DCM, restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC), each sub-grouped as familial/non-familial. In addition, they introduce a new phenotype, the 'non-dilated left ventricular cardiomyopathy' (NDLVC), which was originally proposed in 2016 as 'hypokinetic non-dilated cardiomyopathy'.[6] The guidelines clarify the experts' position regarding left-ventricular non-compaction as a dynamic trait, different in each individual, which can be present in phenotypically healthy hearts, in congenital heart diseases, cardiomyopathies, haematological disorders, especially anaemias, renal diseases, but also in athletes, in pregnancy, and in many other conditions, different for causes and pathogenesis, which lead to an adaptive, persistent or transient and reversible, trabecular remodelling. The Task Force does not recommend the classification of Tako-Tsubo as a cardiomyopathy, given the transient nature of the phenomenon.

In new guidelines, advanced imaging and genetics emerge as key contributors to the diagnostic workup of cardiomyopathy and are now considered essential to the diagnostic and therapeutic path of patients and families with cardiomyopathy.

This text collects the multi-disciplinary and inter-disciplinary considerations of cardiologists, internal medicine specialists, pathologists, geneticists, biologists/biotechnologists, and biomedical engineers, each from their point of view, and highlights the advantages offered by the document for the clinical management of the patient and families, the unmet needs, as well as the possibility of simplifying diagnostic processes foreseeing the future implementation of artificial intelligence (AI)-assisted deep learning facilities for the global management of cardiomyopathies.

The impact of guidelines on clinical workup

Faced with a document including hundreds of recommendations, the clinician can plan personalized diagnostic paths for the individual patient and family in the case of hereditary-familial cardiomyopathy, not necessarily identical for all patients when rigidly grouped under the phenotypic umbrella of their 'cardiomyopathy phenotype'. The diagnostic path must include a clinical offer, shared for all cardiomyopathies, including medical-cardiological examination, electrocardiographic tools, echocardiography, first-level and second-level biochemical tests/biomarkers, multi-modality advanced imaging, and activation of the genetic path to explore hereditary familial cardiomyopathy. On the one hand, the low number of Level I-A recommendations may appear as a limitation of the document; on the other hand, it allows for reasoned clinical governance of the console guiding the diagnostic and therapeutic decisions for patients suffering from cardiomyopathies.

The guidelines acknowledge the four main phenotypes (HCM, DCM, RCM, and ARVC), their genocopies, and their phenocopies and seek to fill the gap between fully manifested phenotypes for those genetic and acquired disorders that manifest as intermediate phenotypes that do not meet standard cardiomyopathy definitions despite the presence of structural myocardial disease on cardiac imaging or tissue analysis. In 2016, these latter phenotypes were described with the term 'hypokinetic non-DCM',[6] which is now replaced with 'NDLVC'. Non-dilated left ventricular cardiomyopathy describes any conditions with structural myocardial alterations proven with imaging [cardiac magnetic resonance (CMR)] even if not necessarily hypokinetic, as well as hypokinetic forms, irrespective of LV dilation or structural alterations (fibrosis) detectable on CMR. This latter condition can represent a substrate for arrhythmic events,[9] even potentially fatal ones, and seems to recur in carriers of defects in some preferential genes (*FLNC*, *DSP*, *DES*, *PLN*, *TMEM43*, and *RBM20*).[1]

The impact of guidelines on genetic workup

Clinical genetics should drive appropriate indications for genetic testing. The risk that genetic tests drive clinics is high, favoured by the availability of new sequencing technologies. On the one hand, the identification of causative genetic defects can confirm a clinical diagnosis and clarify the precise cause of the cardiomyopathy; on the other hand, both the affected gene and the type of variant must be carefully evaluated before labelling the defect as the unique and sufficient cause of the observed phenotype. Only in this case does the genetic information also take on a pre-clinical diagnostic role in not-yet-affected family members, especially when the patients show uncertain phenotypes, and clinical family screening excludes other affected relatives.[8,10] The strong clinical advocacy of these guidelines promotes the advantages of deep phenotyping of patients with cardiomyopathies and their corresponding genocopies and phenocopies. In the complex diagnostic path of cardiomyopathies, genetics plays a key diagnostic and research role. The cardiologist should govern the path and eventually tailor each multi-disciplinary evaluation to the clinical suspect. The diagnostic workup may include not only the genetic visit, counselling, and testing but also a multi-disciplinary evaluation tailored to a diagnostic hypothesis, in particular for syndromic cardiomyopathies. Planning a personalized diagnostic workup (for each patient and family) implies an added organizational load for the cardiologist, easy to say and difficult to implement in a discipline-centred healthcare system. Cardiologists may face syndromic, multi-organ, or systemic diseases in which: (i) the cardiomyopathy is the

major clinical problem (e.g. Danon disease)[11]; (ii) the severity of the involvement of other organs prevents cardiological clinical decisions [e.g. mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and heart transplantation][12]; and (iii) the cardiomyopathy is a limit to the therapeutic options needed for the management of other affected organs (e.g. kidney–liver transplant in primary hyperoxaluria).[13] The new guidelines offer the combination of all needed investigations to provide a precise diagnosis and appropriate treatment for each patient.

The impact of guidelines on cardio-pathology

The pathological study of affected hearts still finds limited exploitation. These new guidelines provide a unique general recommendation for endomyocardial biopsy (EMB) in patients with cardiomyopathy (Level IIa C): 'In patients with suspected cardiomyopathy, endomyocardial biopsy (EMB) should be considered to aid in diagnosis and management when the results of other clinical investigations suggest myocardial inflammation, infiltration, or storage that cannot be identified by other means'. Endomyocardial biopsy is a precision diagnostic tool in restrictive cardio-desminopathies[14]; iron myocardial overload, both intra-myocyte in HFE haemochromatosis[15] and mitochondrial in Friedreich ataxia cardiomyopathy[11]; cystinosis[16]; and lysosomal storage diseases, e.g. Fabry disease.[17] Myocardial tissue studies may strongly contribute to the characterization of the effects of genetic defects in cardiomyopathies associated with neuromuscular diseases.[18,19] In addition, invasive diagnostic criteria including EMB apply to all forms of cardiac amyloidosis, whereas non-invasive criteria are accepted only for transthyretin amyloidosis (ATTR). The first EMB studies in cardiac amyloidosis date back to 1985 (morphology)[20] and to 1995 (immuno-characterization of myocardial amyloid).[21] Today, the demonstration of amyloid fibrils within cardiac tissue remains the diagnostic gold standard; alternatively, amyloid deposits have to be demonstrated in an extracardiac biopsy accompanied by characteristic features of cardiac amyloidosis on echocardiography or imaging.[9]

The impact of guidelines on research

These new guidelines repeatedly mention research with several major orientations. For example, the use of advanced imaging tools that cannot yet be used for practical clinical application or are possibly indicated in particular conditions, e.g. H2 15O or 13NH3 dipyridamole or regadenoson positron emission tomography to evaluate microvascular dysfunction in HCM, an important predictor of adverse outcome. However, this test does not currently have a role in aetiological diagnosis (e.g. in distinguishing phenocopies) and is largely confined to research purposes. The reader's attention is repeatedly drawn to the intense research activity relating to phenotype heterogeneity also in the context of cardiomyopathies associated with defects in the same genes, sometimes even within the same families in which the disease segregates with the genetic defect but the severity, course, and outcome differ in the affected members of the same family. A particular mention concerns the so-called 'secondary findings' in whole exome or whole genome genetic tests performed to identify possible causes of diseases that are not sufficiently characterized on a clinical level: these tests may identify genetic defects potentially associated with diseases that are not correlated to the one for which the genetic test was performed.[8] Among the areas of unmet clinical needs, the guidelines underline the lack of evidence regarding controlled randomized trial, e.g. in patients with HCM. Much remains to be done to clarify the pathophysiology of cardiomyopathies. At the point of 'gaps in evidence', the guidelines state: '…there are several areas where robust evidence is still lacking and deserve to be addressed in future clinical research'.

The guidelines open to novel disciplinary collaborations

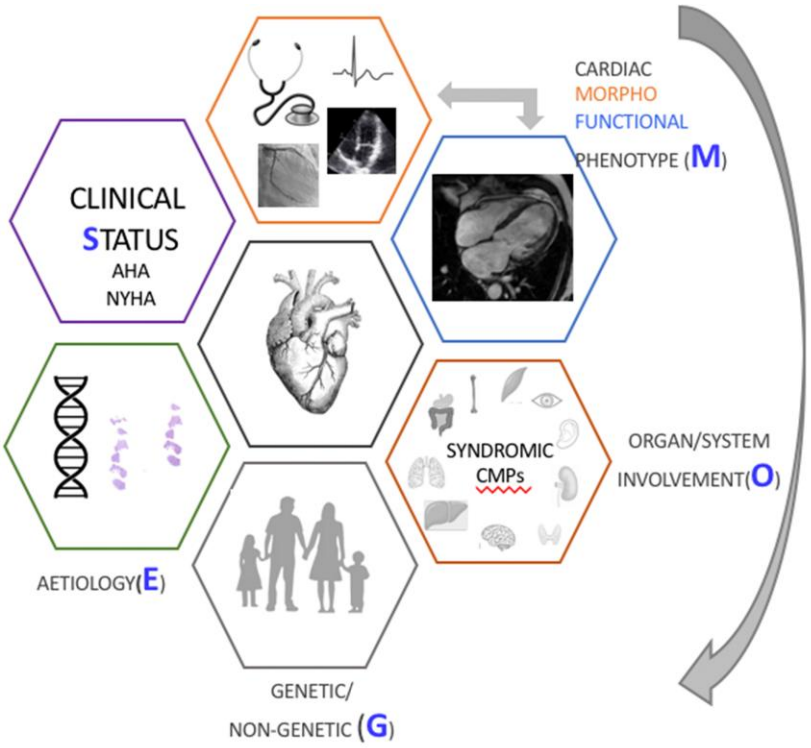
While not included in any recommendations, AI appears almost a preview of the near future.

'Artificial intelligence enhanced electrocardiography and imaging for cardiomyopathy evaluation has been proving a novel tool to dramatically improve diagnosis and prognosis; further studies are needed for routine introduction in clinical practice'.[1] Spaces for participatory interactions are opened up to disciplinary developments in new biomedical areas that will become, with ever greater force, a part of complex medical care and management. More specifically, cardiomyopathies will take advantage of developments in the field of AI (machine learning and deep learning) with electrocardiographic reading, digital biomarkers, advanced imaging, and multimodal integration of the resulting information from the various available tools. Innovative systems/pipelines will be implemented to improve diagnostic specificity, simplify procedures, and reduce times and costs, in favour of optimized and personalized care. Bioinformatic engineers, chemists, physicists, and mathematicians will progressively be called upon to support cardiologists (as well as other medicine specialists) in their clinical activity: the increase in knowledge not only increases complexity but also requires the cardiologist to govern innovation and technological expansion.

The 'cardiomyopathy path' launches a personalized advanced care model of precision medicine

The integration of deep clinical cardiological and multi-disciplinary expertise, advanced diagnostic tools, and their combination governed by the clinics and longitudinally applied to the study and care of patients and families with cardiomyopathies provide a novel model of care for rare, complex genetic diseases. The new guidelines recapitulate the MOGE(S) nosology system proposed by the World Heart Foundation in 2013: the Morpho-functional characterization of the cardiomyopathy; the involvement of non-cardiac Organ/tissues in syndromic cardiomyopathies; the Genetic/non-genetic, familial/non-familial status; and the precise aEtiology (genetic or no genetic) of the cardiomyopathy (*Figure 1*).[11] Decades of clinical and

A



B

PRIMARY (MAIN, KNOWN)	PHENOTYPES (ESC, 2023)	GENOCOPIES -SYNDROMIC	PHENOCOPIES
SARCOMERIC HCM MYH7, MYBPC3, ACTC1, FHL1, MYL2, MYL3		DANON DISEASE, FABRY DISEASE, FRIEDERICH ATAXIA MITOCHONDRIAL D. AMYL. TTRv, APOA1 RASOPATHIES GLYCOGENOSES	ATHLETE'S HEART HYPERTENSIVE HEART DISEASE SARCOIDOSIS (?) AORTIC DISEASES HYPERKINETIC CONDITIONS
DCM LMNA, EMD, DMD, TAZ, RBM20, TNNT2		DCM IN IN NMD IN MANY SYNDROMIC CONDITIONS NEUROMUSCULAR DISORDERS (NUMEROUS AUTOSOMAL RECESSIVE)	INFLAMMATORY AUTOIMMUNE ALCOHOLIC CYRROTIC PERIPARTUM? DRUG TOXICITY
LVNDC DSP, LMNA, DES, FLNC, PLN, TMEM43,		FUTURE DEVELOPMENTS ANNOTATIONS	
ARVC PKP2 DSG2 DSC2 TMEM43 JUP TGFB3		GENETIC MIMICS: CHANNELOPATHIES RV OUTFLOW TRACT TACHYCARDIA	SARCOIDOSIS CHRONIC INFLAMMATORY MYOCARDIAL DISEASE PULMONARY HYPERTENSION ATHELETE
RCM TNNI3, DES FLNC, BAG3, RASOPATHIES		HEMOCHROMATOSIS PXE CYSTINOSIS IRON OVERLOAD PRIMARY OXALURIA (...ECM EXAPNSION)	CHOLOQUINE SEROTONIN, METHYSERGIDE, ERGOTAMINE, MERCURIAL AGENTS, BUSULFAN HEAVY METALS

Figure 1 (*A*) Summarizes the obligate diagnostic steps for cardiomyopathies and recapitulates the strategy of the MOGE(S) nosology system as a descriptor of the multi-disciplinary integration needed to provide a precise diagnosis for all cardiomyopathies. (*B*) Shows the main primary genetic causes of the four types of cardiomyopathies, as well as major known genocopies and phenocopies.

basic research have changed the diagnostic and therapeutic landscape of cardiomyopathies by not only exploiting the most advanced biotechnologies but also empowering the clinical role of the cardiologist. Many achievements are consolidated, while others are still uncertain. The guidelines arise from this background: they provide evidence, indications, recommendations, and suggestions; they dynamically accompany clinical practice, but … they are not laws.

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Data availability

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

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