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New perspectives in diagnosis and risk stratification of non-ischaemic dilated cardiomyopathy

Carola Pio Loco detto Gava, Marco Merlo, Alessia Paldino, Renata Korcova, Laura Massa, Aldostefano Porcari, Massimo Zecchin, Maria Perotto, Maddalena Rossi, and Gianfranco Sinagra*

Cardiothoracovascular Department, Cardiology, Giuliano Isontina University Health Authority (ASUGI), European Reference Network for rare, low-prevalence, or complex diseases of the Heart (ERN GUARD-Heart), University of Trieste, Via Pietro Valdoni, 7, 34149 Trieste (TS), Italy

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Dilated cardiomyopathy is a primitive heart muscle condition, characterized by structural and functional abnormalities, in the absence of a specific cause sufficient to determine the disease. It is, though, an 'umbrella' term that describes the final common pathway of different pathogenic processes and gene–environment interactions. Performing an accurate diagnostic workup and appropriate characterization of the patient has a direct impact on the patient's outcome. The physician should adapt a multiparametric approach, including a careful anamnesis and physical examination and integrating imaging data and genetic testing. Aetiological characterization should be pursued, and appropriate arrhythmic risk stratification should be performed. Evaluations should be repeated thoroughly at follow-up, as the disease is dynamical over time and individual risk might evolve. The goal is an all-around characterization of the patient, a personalized medicine approach, in order to establish a diagnosis and therapy tailored for the individual patient.

Introduction

Cardiomyopathies (CMPs) are myocardial disorders in which the heart muscle has structural and functional abnormalities, in the absence of a specific cause sufficient to determine the disease. Dilated cardiomyopathy (DCM), in particular, is defined as an impaired left ventricular systolic function (frequently but not invariably associated to dilation), in the absence of coronary heart disease, abnormal loading conditions or ischaemia proportional to the systolic disfunction level.[1] It is, though, an 'umbrella' term that describes the final common pathway of different pathogenic processes and gene–environment interactions: microscopical modifications impact on myocardial contractility and, with persistence of the underlying condition, determine a macroscopic variation, which finally occurs as a visible change in heart chambers, resulting dilated and globular in shape, with normal or thinned walls and with an impaired ejection fraction. Despite the heterogenous clinical spectrum of DCM, the systolic dysfunction is the common representative sign of the process.

DCM usually affects relatively young male patients, without relevant comorbidities, and with long theoretical life expectancy, that is influenced mostly by cardiovascular (i.e. mostly ventricular arrhythmias or heart failure) events. DCM prognosis significantly improved in the last decades, nevertheless it still remains one of the first causes of heart transplantation (HTx) in the Western World.[2]

Definitions and classifications of DCM changed over time in order to better characterize the disease, exploiting advances in pathophysiology, pathology, in genetics and molecular medicine, in imaging techniques as echocardiography and cardiac magnetic resonance (CMR). The variety of pathogenetic mechanisms explains the lack of uniformity in clinical presentation, functional status, complications, and response to treatment. In order to reflect the kaleidoscopic spectrum of this disease and the increasing impact of the aforementioned features, definitions and classifications became increasingly complex, too.

*Corresponding author. Tel: +39 0403994477, Fax: +39 0403994878, Email: gianfranco.sinagra@asugi.sanita.fvg.it

Historically, classifications of cardiomyopathies were mainly based on phenotype. The 2006 American Heart Association (AHA) classification divided CMPs into primary (further divided into genetic, mixed and acquired) and secondary, and, for the first time, channelopathies were mentioned among genetic CMPs. In 2008, the European Society of Cardiology (ESC) presented an updated classification mainly focused on clinical elements and morphological and functional phenotypes.[3] In this context, though, heterogenous presentations may undergo the same definition, and overlapping forms become increasingly relevant. The 2013 morphofunctional MOGE(S) classification, instead, focused on inheritance, effects of gene mutation on function, and functional status, providing the basis for a genotype–phenotype correlation and pushing physicians to deeply analyze aetiology and familial background, but it has been scarcely used in clinical practice. However, it was a step forward, as it proposed those actions that physicians should perform when facing a newly discovered non-ischemic DCM patient. The goal was a precise diagnosis, with direct impact on clinical management and therapeutic strategies, and it was associated with an increased attention to family members and the early signs of the disease that might be shown, too. Lastly, in 2016, Pinto tried to enclose the broad clinical features and the changes of the disease over time, and introduced the hypokinetic non-dilated cardiomyopathy (HNDC) definition, in which decreased left ventricle ejection fraction (LVEF) is mandatory, but combination with dilation is not fundamental.[4]

Despite the great efforts that were put in encoding DCM, and despite the rapidly increasing and evolving knowledge in pathophysiology, aetiology, diagnostic workup and prognostic stratification, the clinical management of the disease, addressed to every specific patient, remains extremely challenging in daily practice.

DCM diagnosis

It is important to underline the central role the clinician has in assembling all the patient's characteristics: keeping a critical mindset is of the utmost importance to properly evaluate every detail for a precise diagnosis and clinical management. Above all, the physician should focus on a careful anamnesis: arrhythmic events or sudden cardiac death (SCD) and CMPs should be deeply searched in familial history; palpitation or syncope, as possible expression of arrhythmias, should not be underestimated symptoms. An accurate physical evaluation should be performed and red flags searched for, also outside the heart system (i.e. muscle weakness, neurosensorial abnormalities, mental disability).

Focusing on the clinical presentation, usually DCM first manifestation is often advanced heart failure (75–85% of cases), with New York Heart Association (NYHA) Class III or IV, predominantly left heart failure symptoms and possibly peripheral hypoperfusion, with cardiogenic shock being the most severe manifestation. Rarely, the fist manifestation of the disease might be syncope or sudden death.

The fist instrumental tests, as electrocardiogram (ECG) or echocardiography, should be carefully analyzed, through a cardiomyopathy-oriented assessment. In particular, ECG is a powerful tool, highly accessible and reproducible, that in DCM has a particular importance: usually there are no specific ECG findings that alone help in the diagnosis of the disease, but a 'cardiomyopathy-oriented' ECG interpretation is required, as it may suggest clinical scenarios requiring a specific approach and management.[5] The most relevant anomalies, when present, are left ventricular hypertrophy, pathological Q waves, T wave inversion in infero-lateral leads, poor R wave progression in chest leads or abnormalities of conduction (i.e. left bundle branch block, atrioventricular block). Enlarged QRS complexes have been identified as a predictive sign of negative prognosis and response to resynchronization therapy. Sopra-ventricular arrhythmias, especially atrial fibrillation, are common and they are an expression of advanced disease if developed at follow-up; non-sustained ventricular tachycardia might present in 20–30% of patients over time. In the last years, moreover, specific ECG patterns have been found to be linked to genetic mutations: e.g. the first manifestation of laminopathies, emerin or SCN5A mutations might be seen as prolongation of the PR interval.

Echocardiography is the first imaging modality to assess DCM patients; left ventricular dilation and an impaired ejection fraction are typical of the disease, and measurements are repeated at follow-up in order to monitor therapeutic effects, reverse remodelling or progression of the disease. Many findings are useful in prognostic stratification, such as right heart function and pulmonary pressures evaluation, restrictive filling pattern or left atrial volume.[6,7] A helpful prognostic tool could come from global longitudinal strain (GLS): it could help in evaluating arrhythmic risk in DCM patients, by identifying those with mechanical dispersion, which reflects a higher arrhythmic predisposition. Additionally, GLS seems to be a promising tool for cardiac screening of relatives[8]: in Verdonschot *et al.*, relatives of DCM patients had a significantly higher prevalence of systolic dysfunction detected by GLS despite normal LVEF, and it was associated with adverse cardiac events.[9]

Cardiac magnetic resonance (CMR) is an advanced technique that has been demonstrated to improve risk prediction at individual level across a wide array of cardiomyopathies through accurate tissue characterization.[10] Following administration of gadolinium agents, this imaging technique characterises the presence, distribution and extent of myocardial fibrosis reflected by late gadolinium enhancement (LGE), which can be found in up to 40% of DCM patients. Midwall distribution is the most frequent and specific LGE pattern in DCM.[10] LGE presence showed a strong prognostic value in the identification of high-risk patients[11]: its presence and extent are specific predictors of ventricular arrhythmias and sudden death independently from LVEF. Moreover, LGE is the only independent predictor of arrhythmic events in DCM with LVEF >35% and specific distributions are associated with further elevated arrhythmic risk.[12]

Right heart catheterization and endomyocardial biopsy (EMB) are invasive tests: the latter is the only tool for tissue characterization and for differential diagnosis with phenocopies or inflammatory cardiopathies (e.g. sarcoidosis or active myocarditis), that otherwise could not be diagnosed.[13,14] EMB, according to histologic findings, can guide the physician in therapeutic options, and is becoming pivotal in 'hot phase' clinical presentation in arrhythmogenic cardiomyopathy and acute myocarditis with high-risk syndromes.[15]

Table 1 Main red flags in the diagnosis of dilated cardiomyopathy

Red flag	Finding	Suggested cause
Clinical history and physical examination	Mental retardation	Dystrophinopathies
	Neurosensory disorders	Mitochondrial disease
	Skeletal muscle involvement	Mitochondrial disease
	Carpal tunnel and macroglossia	Dystrophinopathies
	Skin pigmentation	Desminopathies
	History of severe hypertension	Laminopathies
	Pregnancy	Infiltrative DCM
		Haemocromatosis
		DCM secondary to hypertension
		Peripartum DCM
Biohumoral findings	Creatine kinase	Dystrophinopathies
	Proteinuria	Desminopathies
	Hyperferritinaemia	Myofibrillar myopathy
		Laminopathies
		Infiltrative DCM
		Haemochromatosis
ECG	P-wave alterations	Emerinopathies
	AV blocks	Laminopathies
	Low voltages	Laminopathies
	Posterolateral pseudonecrosis	Desminopathies
	Intraventricular conduction delays	Post-inflammatory DCM
		Sarcoidosis
		Infiltrative DCM
		Active myocarditis
		Dystrophinopathies
		Laminopathies
Echocardiography	Cardiac hypertrophy	DCM secondary to hypertension
		Infiltrative DCM
CMR	Posterolateral akinesia	Dystrophinopathies
	Subendocardial/transmural LGE	Ischaemic DCM
	Subepicardial LGE	Post-inflammatory DCM
	Septal LGE	Post-inflammatory DCM
	Midwall LGE	Sarcoidosis
	LV aneurysm	Arrhythmogenic phenotype
		Sarcoidosis

From Merlo M *et al*. Evolving concepts in dilated cardiomyopathy. Eur J Heart Fail 2018;20(2):228-39. 1111-1121. (Granted Licence no. 5438271282950).[2]

All these powerful tools, guided by clinical suspicion and a red flags approach, help the physician in narrowing the DCM diagnosis towards an aetiologic assessment. Progresses have been made over time, nevertheless about 20-30% of DCM seen in clinical practice continues to be identified as 'idiopathic' (*Table 1*).

Etiological characterization and genetics

At present, the term 'idiopathic' DCM is progressively indicating a smaller group of patients, as 'secondary' cardiomyopathies, induced by specific triggers (i.e. tachyarrhythmias, hypertension, alcohol, chemotherapy, inflammation), are better characterized and ruled out.

'Secondary' CMPs should be considered disease subtypes, each one with a different evolution and outcome. Tachycardia-Induced CMP, in fact, might be reversible after the trigger elimination; it appears to have a benign prognosis, whereas Alcoholic CMP and Post-chemotherapy CMP have lower survival rates, when confronted with other types of DCM. Chemotherapy-related cardiac dysfunction (CRCD), and especially anthracyclines type I CRCD, provokes oxidative damage to the cardiac myocyte, mitochondrial dysfunction and necrosis; it has cumulative, dose-related effects, cardiac dysfunction appears to be irreversible and may progress in heart failure and subsequent death. Instead, Type II CRCD induces myocyte disfunction, but there is a high likelihood of recovery. Inflammatory CMPs play their role, too: approximately 20% of patients with proven myocarditis develop DCM.

The complex interaction between environmental factors and genetic background, moreover, is increasingly emerging, as DCM recognizes a complex genetic background: it is far from being a monogenic disease, there are multiple unknown epigenetic interactions, and it introduces the possibility of the relevance of a 'second hit' on an already predisposed patient (*Figure 1*).

Genetic testing is acquiring relevance in the diagnosis and classification of DCM: it is recommended in guidelines and position papers (level C of evidence); it provides diagnostic and prognostic information, guides targeted therapy, unveals predisposition in developing DCM in relatives thanks to familial screening and promotes and

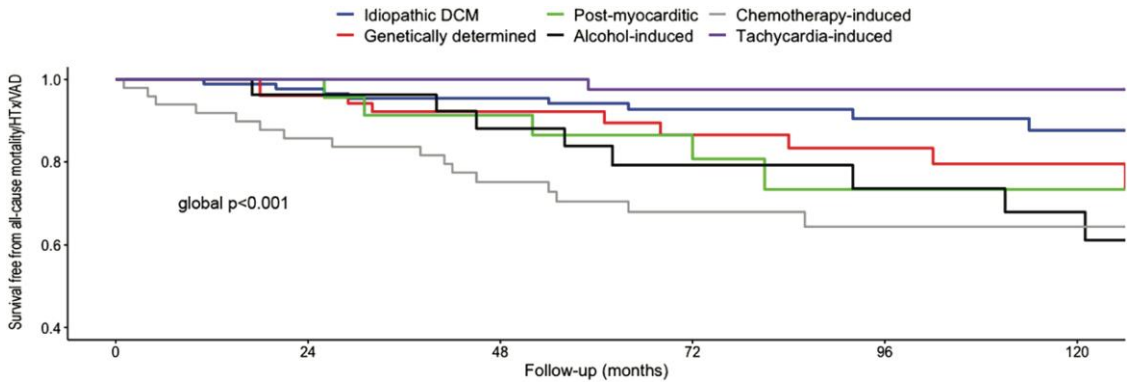

Figure 1 Kaplan-Meier curves according to the specific aetiologies of dilated cardiomyopathy (DCM). Adapted from Merlo M *et al*. Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. Eur J Heart Fail, 2020;22:1111–1121. (Granted Licence no. 5438271110540).[16]

early diagnosis even in a pre-clinical stage of the disease.[17] Familial patterns and genetic mutations have been identified as pathogenic in nearly 50% of previously defined idiopathic DCM.

On the other side, genetic background of DCM is a very complex and rapidly evolving issue. So far, more than 50 genes have been found to be involved in DCM: they encode for sarcomeric proteins, cytoskeleton, sarcolemma, nuclear envelope ion channels, and intercellular junctions, and several more genes are jet to be discovered. The real extent and impact of these mutations on developing DCM is still unknown. Furthermore, the same gene mutation may cause different phenotypic CMPs: it underlines the significant genetic overlap among dilated, hypertrophic, restrictive, arrhythmogenic right ventricular cardiomyopathy and channelopathies, and it also highlights that a precise correlation between clinical presentation and genetic mutation is still lacking (*Figure 2*).

Differentiating genetically determined DCMs from inflammatory cardiomyopathies, identifying possible mechanisms of correlation between genotype and environmental factor in phenotype expression appears to be the way towards precision medicine in DCM and should be the focus of the next future research in DCM.

The abovementioned effort towards an aetiological classification as a component of the multiparametric global stratification in DCM, underline the need for physicians to thoroughly pursue an all-around evaluation of the patients and of their background. An aetiological characterization appears, in fact, fundamental in order to stratify patients according to their specific risk of adverse events and might help clinicians in considering different treatment strategies (including targeted therapy in the near future) and follow-up evaluation.

Furthermore, keeping in mind the dynamic nature of DCM over time is also essential and, in the light of this, follow-up should always be pursued. It allows a longitudinal monitoring of patients, of their therapeutic response and clinical status, and even to offer the right therapeutic option at the right time. In selected relatives, in asymptomatic or mildly affected patients, follow-up grants an early detection of pathological signs and the subsequent prevention of cardiovascular events. At follow-up, almost 40% of DCM patients, under optimal medical and device therapy, experience a significant left ventricular reverse remodelling (LVRR). A complete re-evaluation, including a repeated aetiological classification of disease in long term follow-up, appears pivotal as risk factors evolve and change over time, with possible development of coronary artery or valve disease in advanced ages.

Arrhythmic risk assessment

It should be underlined that 30% of DCM patients show an arrhythmic pattern at presentation, and it significantly changes the prognostic evaluation. Among CMPs, the relevance of an arrhythmogenic trait associated with increased risk of SCD is well known in arrhythmogenic right ventricular cardiomyopathy (ARVC) or in left-dominant arrhythmogenic cardiomyopathy, as well as in hypertrophic cardiomyopathy and LV noncompaction, and it is an important element that should be considered in risk stratification.

Ventricular arrhythmias in DCM were historically considered a manifestation of systolic dysfunction of the left ventricle; guidelines for implantable cardioverter defibrillator implantation (ICD) were established on this basis, and ICDs dramatically reduced the risk of SCD and mortality in patients with reduced ejection fraction heart failure on optimal medical treatment. However, ventricular arrhythmias may be the first symptom that occur, or they might present early in the disease course: approximately 50% of SCD occur in patients without severely depressed left ventricular ejection fraction. Therefore, an accurate characterization of the arrhythmic risk in DCM patients, other than LVEF and NYHA class, is crucial. Moreover, it appears that DCM might overlap with Arrhythmogenic Cardiomyopathy. It is now clear that there may be a shared genetic background, especially in desmosomal gene mutations, as DSP. Filamin C truncating variants, also, lead to a clinical presentation with both DCM and ARVC phenotypic aspects; as shown in Gigli *et al*.[18] mutation carriers have a significant risk of arrhythmic-related major outcomes, and an ICD might be considered regardless of the LVEF.

The DANISH trial results,[19] preceded by SCDHEFT and DEFINITE, put in discussion the effects on global survival after ICD implantation in patients with non-ischaemic DCM heart failure and ejection fraction $\leq$35%, despite acknowledging the significant impact on SCD among younger

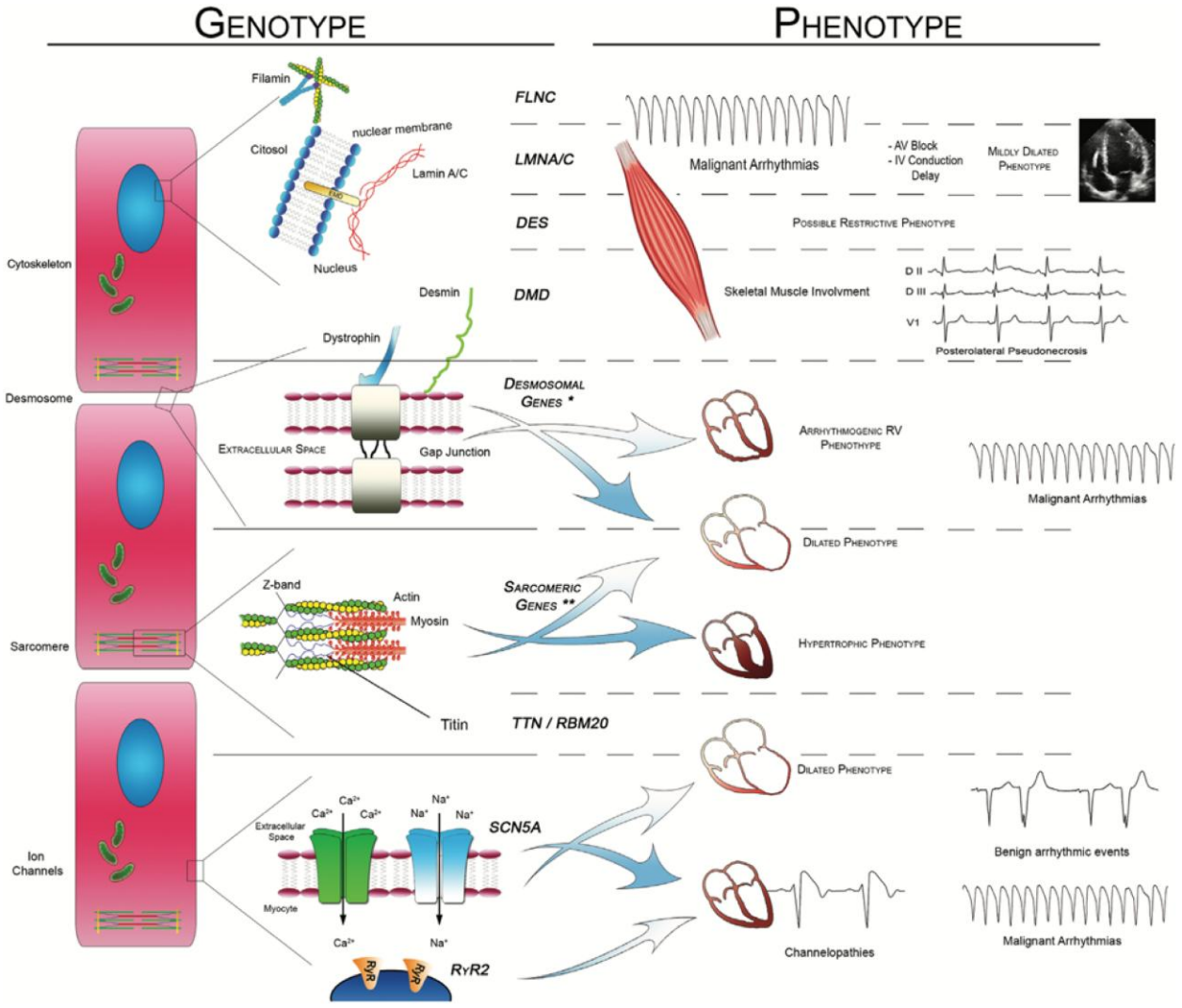

Figure 2 Genotype–Phenotype correlation. Adapted from Merlo M *et al*. Evolving concepts in dilated cardiomyopathy. Eur J Heart Fail 2018;20(2):228–39. (Granted Licence no. 5438271282950).[2]

patients. In the latest 2022 ESC guidelines, according to these results, primary prevention ICD implantation in non-ischemic DCM grade of recommendation was lowered from IA to IIa-A; it must be underlined, although, that subgroups at high risk of SCD exist, and the indication to implantation should be individually evaluated and tailored on the patient. A multiparametric approach and a thorough evaluation, guided by clinical suspicion and supported by the abovementioned instruments, should be pursued; all prognostic predictors must be taken into account and properly weighted, and going beyond guidelines and trials is essential in order to offer the best solution for the patient.

The approach to DCM patients evaluation should be multiparametric, but also dynamical over time. LVRR, for example, has important prognostic implications, in particular in those candidates for ICD implantation in primary prevention; approximately only one third of cases on optimal medical therapy, with the criteria for ICD implantation at baseline, maintain those criteria over a 6-month follow-up. A wait-and-see period of about 3–9 months on optimal medical treatment is recommended before the ICD implantation, even though approximately 2% of patients with DCM die suddenly in the first 6 months after the diagnosis. Despite standardized predictors of early arrhythmic events are not systematically available, some elements may identify arrhythmogenic traits and patients at elevated risk of SCD: a severe LV dilatation at baseline with prolonged QRS duration and a long duration of symptoms, a familial history of SCD, cardiac syncope, or arrhythmic expression at Holter ECG monitoring, an extensive fibrotic pattern at CMR.[20]

Conclusions and future perspectives

At present, one of the major challenges in DCM is the complex and heterogeneous aetiologies and presentations of the disease, with overlapping characteristics among the fundamental elements that define different CMPs.

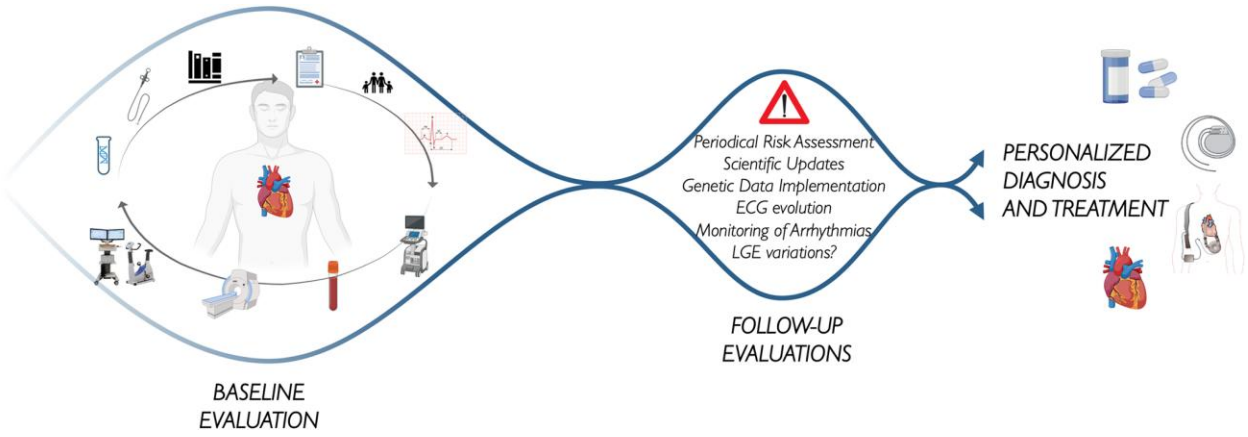

Figure 3 Multiparametrical approach to DCM diagnosis and dynamical adaptation and re-evaluation over time (created with BioRender.com).

Thus considered, the present classification of cardiomyopathies appears to be outdated, as it does not adequately include all possible forms of CMPs, and especially leaves a 'void' for those cardiomyopathies with overlapping elements that do not exactly fit within present definitions. It is becoming a relevant and pressing matter, as the more we know, the harder it gets to fit cardiomyopathies within rigid definitions; we should aim towards a different approach and a different type of diagnostic workup, including advanced echocardiography and CMR, 3D echo, mapping and GLS, and polygenic risk score search, and possibly artificial intelligence and machine learning in order to elaborate a multiparametric and detailed evaluation (*Figure 3*).

Each patient should be individually and fully characterized and our efforts should be aimed towards a personalized medicine approach, in which the focus is set on the patient and on its own disease manifestation, instead of a generic definition; the ultimate goal is the step from a 'personalized classification' to a 'personalized therapy', in which both diagnosis and treatment are perfectly tailored on the patients and on their changes over time.

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