Early Detection of Genetic Cardiomyopathies in Relatives Using Echocardiographic Deformation Imaging: JACC Review Topic of the Week

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Brief title: Early detection of genetic cardiomyopathies in relatives

Tweet: Deformation imaging can unmask early signs of disease in relatives of DCM, HCM and ACM patients. The presence or absence of mechanical alterations may be helpful for determining follow-up strategies. #familyscreening #imaging

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Abstract

Clinical screening of the relatives of patients with genetic cardiomyopathies is challenging as they often lack detectable cardiac abnormalities at presentation. Life-threatening adverse events can already occur in these early stages of disease, so sensitive tools to reveal the earliest signs of disease are needed. The utility of echocardiographic deformation imaging for early detection has been explored for this population in multiple studies, but has not been broadly implemented in clinical practice. This article discusses contemporary evidence on the utility of deformation imaging in relatives of patients with genetic cardiomyopathies. The available body of data shows that deformation imaging reveals early disease-specific abnormalities in dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic cardiomyopathy. Deformation imaging seems promising to enhance the screening and follow-up protocols in relatives, and we propose measures to accelerate its implementation in clinical care.

Key words: genetic cardiomyopathy, family screening, early detection, deformation imaging, speckle tracking

Condensed abstract

Clinical screening of the relatives of patients with genetic cardiomyopathies is challenging because they often have no detectable cardiac abnormalities at presentation. We conducted a systematic review to evaluate the utility of echocardiographic deformation imaging for early detection of disease in this population. Available literature indicates that deformation imaging enables identification of an early disease substrate in these relatives. With regard to risk stratification, the prognostic value of several deformation parameters is promising. The presence or absence of mechanical alterations may be helpful for determining follow-up strategies in these relatives.

Abbreviations

ACM	arrhythmogenic cardiomyopathy
DCM	dilated cardiomyopathy
GLS	global longitudinal strain
HCM	hypertrophic cardiomyopathy
LA	left atrium/atrial
LV	left ventricle/ventricular
LVMD	left ventricular mechanical dispersion
NCCM	non-compaction cardiomyopathy
RV	right ventricle/ventricular

Introduction

It is recommended to screen relatives of patients with genetic cardiomyopathies, as they are at risk of developing a similar disease as the index patient (1–3). If a (likely-)pathogenic genetic variant has been identified in the index patient, targeted genetic testing can be performed to identify relatives who carry the same variant and are therefore at high risk of developing the disease (4). However, management of these relatives is complicated as they often have no symptoms nor detectable cardiovascular abnormalities at presentation. In addition, penetrance is often incomplete, which implies that not all carriers of the (likely-)pathogenic variant will eventually develop the disease (3,5–7). It is important to identify the relatives who are at highest risk to develop the disease, as they may potentially benefit from early therapeutic intervention to prevent detrimental adverse events such as sudden cardiac death. To identify these relatives in an early stage, sensitive diagnostic tools that reveal the earliest signs of disease meet an important clinical need.

Cardiac imaging has a major role in genetic cardiomyopathies (8–10). It contributes not only to the diagnostic criteria of these cardiomyopathies, but also has important prognostic value. Unfortunately, conventional imaging modalities often lack sensitivity to detect early disease in relatives without overt disease expression (11). This can be attributed to the fact that imaging parameters and their cut-off values are typically derived from affected individuals and therefore represent more established disease. Most relatives at early stages of disease fall in the grey zone or are even classified as normal when conventional imaging parameters are used.

Over the last decade, deformation imaging has emerged as more sensitive compared to conventional imaging for quantification of cardiac function (12–14). This allows quantification of global and regional myocardial deformation and may reveal subtle changes in the early stages of many cardiac diseases (13,14). Echocardiographic two-dimensional (2D)

speckle tracking is the most commonly used tool for myocardial deformation imaging, and has been standardized for all cardiac chambers: the left and right ventricles (LV/RV), and the left and right atria (LA/RA) (15,16). Echocardiographic speckle tracking is particularly attractive for routine clinical use because of its non-invasive nature, wide availability and low cost compared to other imaging modalities. Furthermore, speckle tracking derived indices have superior inter- and intra-observer reproducibility compared to conventional functional measurements (17).

Deformation imaging has unequivocal diagnostic and prognostic value in patients with established genetic cardiomyopathies (18–21). Multiple studies suggest that it may also identify subtle mechanical alterations in the relatives of patients. However, deformation imaging has not been broadly implemented in the routine clinical screening of relatives. We conducted a systematic literature search on the use of echocardiographic deformation imaging in the screening of relatives, with the goals of evaluating the current evidence, identifying knowledge gaps, and determining future directions.

Methodology

A systematic search was conducted in the MEDLINE, Embase and Cochrane databases. The search queries included keywords and synonyms for (i) deformation imaging and (ii) the most common genetic cardiomyopathies, including dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (ACM) and non-compaction cardiomyopathy (NCCM) (22,23). Full search queries for the different databases are provided in the **Supplemental methods**. The search was conducted on April, 1, 2021. After removing duplicates, records were independently screened by two observers (K.T. and F.K.) based on title and abstract. Studies were eligible when 2D speckle tracking was performed in relatives at risk for genetic cardiomyopathy, irrespective of their age and irrespective of whether genotyping was performed. Studies in cardiac storage diseases (e.g. Amyloidosis, Fabry), muscular dystrophy (e.g. Duchenne, Becker) or congenital heart diseases were excluded. Disagreement in abstract selection between the two observers was solved by consensus. Full papers were screened for eligibility and reference lists were screened to identify additional relevant articles that were not identified by the primary search. Abstracts without available full papers in English language, case reports/series, feasibility studies, reviews and editorials were excluded. Study quality and consequent risk of bias was assessed by two observers using the Newcastle-Ottowa scale for case-control studies and/or cohort studies (**Supplemental material**).

Description of included studies

In all, 29 studies were identified which were all published between 2009 and 2021 (flowchart in **Figure 1**). The studies are summarized per disease in **Tables 1-4**. Most studies included relatives who are at risk for HCM (11 studies) (24–34) and ACM (11 studies) (35–45), followed by DCM (6 studies) (46–51) and NCCM (1 study) (52). All studies were case-control studies and/or longitudinal cohort studies, except for one which was a cross-sectional cohort study (36). The number of included subjects at risk varied from 14 to 251 (median 41, interquartile range 24-73). The mean/median age of subjects at risk varied between 20 and 50 years in most studies, except for one study that included genotype-positive children at risk for HCM with a mean age of 9.8 ± 4.5 years (26). Genetic data were reported in 26 studies.

Dilated cardiomyopathy

Most studies in DCM classified relatives as phenotype-negative on the basis of a preserved left ventricular ejection fraction (LVEF, **Table 1**). All studies showed that global deformation parameters of the LV, in particular global longitudinal strain (GLS), are reduced in relatives compared to controls (**Figure 2**). The largest study by Verdonschot et al. (46) investigated 251 first-degree relatives of genotyped DCM patients who all had normal LVEF (≥55%) at baseline. The majority of these relatives was related to an index patient without a proven (likely-)pathogenic variant. GLS was reduced in relatives compared to matched controls. Abnormal baseline GLS in relatives was associated with deterioration of LVEF <55% (with a minimum decrease of 5%) at a median follow-up of 36 months. Abnormal GLS at baseline was also associated with more cardiac hospitalizations and more deaths after a median follow-up of 40 months. While the results suggest that GLS can be used for risk stratification in relatives of DCM patients, occurrence of hard clinical endpoints during follow-up was infrequent, which is a common issue encountered in longitudinal studies of preclinical

relatives. Studies with longer follow-up would strengthen the prognostic value of GLS in relatives at risk for DCM. Moreover, the role of GLS within multi-modality risk calculators should be explored to define its added value on top of validated risk models.

Regional deformation in DCM was investigated in one study. Taha et al. (47) evaluated 139 preclinical relatives who carried the pathogenic phospholamban (PLN) p.(Arg14del) variant, causing a risk of DCM with features of ACM. In one-third of presymptomatic genotype-positive relatives, regional post-systolic shortening was found in the LV apex (**Figure 2**), which was absent in controls. Presence of apical post-systolic shortening was the strongest echocardiographic predictor of ventricular arrhythmias in presymptomatic relatives. This genotype-specific approach has led to the identification of deformation patterns which are characteristic of individuals with a specific genetic variant, allowing a more tailored approach. It would be interesting to characterize genotype-specific strain patterns in other variants, for example *TTN* and *LMNA*, to optimize early detection in relatives with a particular pathogenic variant.

Paldino et al. (50) investigated atrial strain and showed impaired peak atrial longitudinal strain in 18% of the genotype-positive relatives of DCM patients, which possibly reflects early diastolic dysfunction (**Figure 2**). However, the additional value of this parameter on top of GLS has not been studied.

Hypertrophic cardiomyopathy

Most studies in HCM classified relatives as phenotype-negative when LV wall thickness was <12 or 13 mm (**Table 2**). Nine studies evaluated GLS, of which seven found no difference between genotype-positive relatives and controls. Haland et al. (25) observed reduced GLS in relatives without hypertrophy compared to healthy controls. In contrast, van Velzen et al. (24) reported higher GLS in relatives compared to controls, which was not associated with

development of HCM during 5.6 ± 2.9 years of follow-up. The cause of these contradicting results remains speculative and may be explained by the continuum of HCM disease rather than the binary affected-not affected; the relatives could have been in different stages of disease when examined. Moreover, the considerable heterogeneity in HCM phenotypes may also have contributed to the inconsistent findings (53). While GLS has an unequivocal prognostic value in patients with overt HCM (18), its prognostic value in relatives represents a knowledge gap based on these results. A large multicenter study with in-depth multi-modality phenotyping could elucidate the precise role of GLS in genotype-positive HCM relatives.

Global circumferential and rotational function was investigated in five studies. Forsey et al. (26) and Williams et al. (28) reported enhanced systolic LV rotational function in mutation carriers without hypertrophy (**Figure 3**). This may be a consequence of increased Ca^{2+}affinity due to genetic variants in sarcomeres, as indicated in previous experimental studies (54). However, Ho et al. (27), Yiu et al. (30), and Kauer et al. (31) showed no systolic differences in rotation/twist. On the basis of available data, the added clinical value of circumferential and rotational function is unclear.

Six studies reported segmental strain parameters, of which four reported significantly lower strain in the basal septum (**Figure 3**) (29,30,32,34). This was most pronounced in the basal anteroseptum. Early mechanical dysfunction in the basal septum is conceivable, as it has previously been identified as the most affected region in HCM (55). Only one study found no difference in strain in the basal anteroseptum (24). Forsey et al. (26) found no differences in 14 children who had an HCM-related genetic variant, but only the inferoseptum was evaluated. Reduced basal (antero)septal strain appears to be an early sign of disease in HCM relatives. This may not directly translate into reduced GLS in the early stage, presumably due to the typical focal character of the disease.

Arrhythmogenic cardiomyopathy

Early detection in relatives at risk for ACM is of particular interest, because these relatives are at risk of developing life-threatening ventricular arrhythmias before the onset of overt structural disease. Most studies on ACM and its right dominant subform arrhythmogenic right ventricular cardiomyopathy (ARVC) included relatives with (likely-)pathogenic variants in desmosomal genes (typically plakophilin-2, **Table 3**). Global RV deformation was investigated in four studies. Sarvari et al. (42) and Reant et al. (43) found reduced RV free wall strain in genotype-positive relatives compared to control subjects (**Figure 4**). Lie et al. (35) investigated RV free wall strain in a subgroup of genotype-positive relatives and it was reduced in all four relatives who developed life-threatening ventricular arrhythmia during follow-up.

The reduction in RV free wall strain seems to be driven by regional alterations, particularly in the subtricuspid region. Mast et al. (44) described three distinct morphologies of regional deformation patterns in the RV: a type I pattern represents normal deformation while type II/III represents abnormal deformation. An abnormal deformation pattern was found in half of the preclinical relatives in the subtricuspid area (**Figure 4**). A follow-up study noted that normal deformation in the subtricuspid area could exclude disease progression with a high negative predictive value in relatives (39). The role of the subtricuspid region is in line with cardiovascular magnetic resonance (CMR) and electrophysiological data that identified the subtricuspid region as one of the first affected regions in the disease (56).

Besides regional deformation patterns, the regional abnormalities can also be detected by measurement of contraction heterogeneity, expressed by RV mechanical dispersion (**Figure 4**). Sarvari et al. (42) showed greater RV mechanical dispersion in genotype-positive relatives compared to healthy controls. RV mechanical dispersion was found to be an

independent predictor of arrhythmic events in a mixed group of ACM patients and asymptomatic genotype-positive relatives. Leren et al. (36) showed that greater RV mechanical dispersion was associated with arrhythmic events in genotype-positive relatives, and had incremental value on top of electrical parameters according to the 2010 Task Force Criteria for ARVC.

The aforementioned methods of RV deformation were developed and tested in two centers and recently externally validated (57). Both showed independent associations with life-threatening ventricular arrhythmias, and the combination of these methods increased the association with arrhythmia outcome. External validation has been a key step towards clinical implementation of deformation imaging in relatives at risk for ACM.

LV deformation has also been investigated in ACM relatives (**Figure 4**). Reduced GLS (42,43), impaired regional LV deformation (37,43), and increased LV mechanical dispersion (LVMD) (42) was seen in relatives with (likely-) pathogenic variants of desmosomal genes. LVMD was greater in relatives who developed a life-threatening ventricular arrhythmia during follow-up (35), and predicted structural disease progression during follow-up (38).

Non-compaction cardiomyopathy

Relatives of NCCM patients were investigated in one study (**Table 4**) (52). In 30 relatives, many deformation imaging parameters were slightly more abnormal compared to controls, including GLS, global circumferential and rotational strain. These results have not yet been replicated by other studies.

Clinical implications and future perspectives

Early detection of disease expression in relatives of patients with a genetic cardiomyopathy is of great importance, as these relatives are at risk of detrimental adverse events such as sudden cardiac death. Based on currently available literature, deformation imaging enables identification of an early disease substrate in these relatives. This seems to be true across the various genetic cardiomyopathies, possibly reflecting early cardiomyocyte loss in DCM, myocardial disarray and interstitial fibrosis in HCM, and desmosomal dysfunction in ACM. Multiple deformation parameters are available, but the main findings reproduced by the different studies are: (i) reduced GLS in relatives at risk for DCM, (ii) reduced basal (antero)septal strain in relatives at risk for HCM and (iii) reduced RV free wall strain in relatives at risk for ACM (**Central Illustration**).

With regard to risk stratification, the prognostic value of deformation imaging has most extensively been investigated in DCM and ACM, showing a benign prognosis when deformation abnormalities are absent. Prognostic data for deformation imaging in HCM relatives are limited, making its role in clinical risk stratification uncertain. Since life-threatening arrhythmias rarely occur in early stages of HCM (58), follow-up of septal thickness may be sufficient for arrhythmic risk stratification. At this point, the presence or absence of deformation abnormalities may be helpful for determining follow-up strategies in DCM and ACM relatives. Considering the high negative prognostic value of deformation imaging in the available studies, relatives who have normal findings by deformation imaging may be offered lower follow-up intensity than relatives who have subclinical deformation abnormalities. The exact follow-up strategies, including the required intervals, remain to be investigated in longer longitudinal studies. In addition, more studies in younger subjects are needed to gain further knowledge about the penetrance in the pediatric population and the required age to start screening, since our systematic search only yielded one pediatric study.

Identification of an early disease substrate has the most potential to lead to therapeutic strategies in relatives at risk for DCM or ACM. Thereby, these relatives can potentially be offered early heart failure medication to prevent end-stage heart failure (46), or antiarrhythmic medication and implantable cardioverter defibrillator implantation to prevent sudden cardiac death (35). However, since the numbers of hard end-points are low in the published studies, the prognostic value of deformation imaging should be confirmed in larger studies, preferably with longer follow-up intervals. Deformation imaging may also soon become relevant for patient selection in HCM, given the promising trials on medical treatment of early stage HCM (59,60).

We encourage the authors of reported studies to investigate and publish the long term (>10 years) outcomes of their cohorts whenever possible. Moreover, we strongly encourage collaborations between different research groups to create larger cohorts and to create a platform for external validation. We would like to emphasize that deformation imaging should not be used as stand-alone parameter, but interpreted in the context of other clinical variables, and in conjunction with other examinations such as electrocardiography and CMR. Studies implementing relevant deformation imaging parameters into multi-modality risk prediction models are therefore of great interest.

Finally, we would like to encourage the use of machine learning approaches to improve the classification of deformation curves of relatives (61). Machine learning models may detect hidden patterns in deformation curves and improve the classification of these curves, potentially leading to earlier identification of high-risk relatives. Besides using machine learning merely for classification purposes, specific techniques can be applied to visualize the features that are detected by the machine learning model (62). The application of such techniques will enrich our knowledge of hidden features in the deformation curves of relatives, which will enhance the clinical utility of deformation imaging in this population.

Limitations

All studies included in this review are retrospective observational studies, mostly with small sample sizes. The majority of the studies were performed in single centers, and the authors of this review were involved in 10 of the 29 included studies, particularly in the field of ACM. An inherent limitation of studies in relatives is that the rates of hard end-points are generally low. To investigate the clinical significance of deformation imaging in relatives with regard to hard end-points, larger studies with longer follow-up are needed. Due to the heterogeneity in definitions and methods between the studies, we could not perform a meta-analysis, nor could we extract cut-off values from the published data. Finally, when applying these results into clinical practice, it should be taken into account that different software packages were used among the different studies. While the inter-vendor differences for global measurements are small (17), there is still considerable variability in the detection of regional functional abnormalities among different vendors (63).

Conclusion

Deformation imaging can unmask early signs of disease in relatives of DCM, HCM and ACM patients. The main observations in these relatives are (i) reduced GLS in relatives at risk for DCM, (ii) reduced basal (antero)septal strain in relatives at risk for HCM, and (iii) reduced RV free wall strain in relatives at risk for ACM. Considering the prognostic value in early stages of DCM and ACM, we recommend routine measurement of disease-specific deformation parameters in these relatives. Collaborations between research groups are needed to create opportunities for larger studies and to create a platform for external validation.

Highlights

- Screening relatives for genetic cardiomyopathies is challenging due to the absence of overt cardiac abnormalities.
- Disease-specific parameters by deformation imaging may reveal early signs of disease in relatives.
- Deformation imaging has useful prognostic value in DCM and ACM relatives.
- Larger cohorts and longer follow-up studies are needed to investigate the value for predicting hard end-points.

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Disclosures

SK serves as consultant for GE Healthcare and scientific advisor for OP2 Drugs. The remaining authors have nothing to disclose.

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Tables

Table 1: Included DCM studies

	First author, year, journal	Design	Study population	Number	Age (years)	Genotype	Software	Global deformation parameters	Regional deformation parameters	Control group	Main result(s)
DCM	Verdonschot, 2020, JACC cvi	CCS + LCS	First-degree relatives with LVEF ≥55%	251	46 ± 17	Genetic testing in 44 relatives (18%), of which 32 (13%) genotype-positive (predominantly *TTN*)	TomTec	GLS	none	251 patients referred for chest pain, dyspnea or palpitations, with LVEF ≥55%	GLS reduced in relatives (P<0.001). Reduced GLS associated with LVEF deterioration and adverse events (cardiac hospitalization and death) during follow-up
DCM	Taha, 2021, JACC cvi	CCS + LCS	Genotype-positive relatives (PLN p.Arg14del) without a history of VA, premature ventricular complex count <500/24h, LVEF ≥45%	139	33 [IQR 21-41]	All *PLN* p.(Arg14del)	GE Echopac	GLS, LVMD, RVFWLS	post-systolic shortening	70 healthy volunteers and patients from the outpatient clinic without cardiac disease	Post-systolic shortening present in the LV apex in 31% of relatives with the *PLN* p.(Arg14del) variant; presence associated with nonsustained VA during follow-up.
DCM	Okten, 2017, Herz	CCS	First-degree relatives with LVEF ≥55%	77	35 [IQR 15]	Not reported	GE EchoPAC	GLS, GLS rate, GCS, GCS rate, GRS, GRS rate, peak torsion	none	86 healthy subjects with normal ECG and echo, and no family history of heart failure	All global parameters significantly reduced in relatives
DCM	van der Bijl, 2019, EHJ cvi	CCS	Genotype-positive relatives with LVEF ≥55%	50	50 ± 15	Predominantly *TTN* (48%) and *LMNA* (20%)	GE EchoPAC	GLS	none	28 genotype-negative relatives	GLS reduced in genotype-positive relatives (P=0.036)
DCM	Paldino 2021, Int J Cardiology	CCS + LCS	Genotype-positive relatives with normal ECG and echocardiographic findings	41	37 ± 14	*TTN, LMNA, FLNC, MYH7, TNNT2, MYBPC3, DSP, SCN5A, TMEM43, RBM20*	TomTec	GLS, peak atrial longitudinal strain	none	52 healthy volunteers and 17 genotype negative relatives	GLS and peak atrial longitudinal strain reduced in genotype-positive relatives

DCM	Lakdawala, 2012, Circ Cardiovasc Img	CCS	Genotype-positive relatives with LVEF ≥55% and normal dimensions	12	25 ± 19	*MYH7* (75%) and *TPM1* (25%)	GE EchoPAC	GLS, GLS rate, GCS, GCS rate, GRS, GRS rate	none	29 genotype-negative relatives	All parameters (except for GCS rate) reduced in genotype-positive relatives (P=0.018 for GLS)

Abbreviations: CCS = case-control study, DCM = dilated cardiomyopathy, ECG = electrocardiogram, GCS = global circumferential strain, GLS = global longitudinal strain, GRS = global radial strain, IQR = interquartile range, LCS = longitudinal cohort study, LV = left ventricle/ventricular, LVEF = left ventricular ejection fraction, LVMD = left ventricular mechanical dispersion, RVFWLS = right ventricular free wall longitudinal strain VA = ventricular arrhythmia.

Table 2: Included HCM studies

	First author, year, journal	Design	Study population	Number	Age (years)	Genotype	Software	Global deformation parameters	Regional deformation parameters	Control group	Main result(s)
HCM	van Velzen, 2019, Neth Heart J	CCS + LCS	HCM genotype-positive individuals with LV wall thickness <13 mm and LVEF ≥50%	120	41 ± 13	Predominantly *MYBPC3* (77%)	TomTec	GLS, average basal, mid and apical longitudinal strain	LV basal anteroseptal longitudinal strain	110 volunteers with normal physical examination, normal ECG and LVEF ≥50%	GLS increased in mutation carriers (P<0.001), but not associated with development of HCM phenotype during follow-up (5.6 ± 2.9 years)
HCM	Haland, 2017, Open Heart	CCS	Sarcomere mutation carriers with LV wall thickness <13 mm and no symptoms	100	36 ± 15	Predominantly *MYBPC3* (58%) and *MYH7* (29%)	GE EchoPAC	GLS	none	80 healthy volunteers	GLS reduced in mutation carriers (P=0.001)
HCM	Ho, 2009, Circ Cardiovasc Genet	CCS	Genotype-positive relatives with LV wall thickness <12 mm	68	24 ± 12	Predominantly *MYH7* (50%) and *MYBPC3* (37%)	GE EchoPAC	GLS, GLS rate, GCS, GRS	LV septal, lateral, inferior and anterior longitudinal strain and strain rate (averaged over wall)	38 genotype-negative relatives	No significant differences between genotype-positive and genotype-negative relatives. GLS reduced in relatives with *MYBPC3* variant compared to *MYH7* (P<0.001)
HCM	Williams, 2018, Am J Cardiol	CCS	Genotype-positive relatives with LV wall thickness <12 mm	60	30 ± 10	Majority *MYBPC3* and *MYH7* (rates not specified)	Siemens VVI	GLS, GLS rate, GCS (multi-layer), global mechanical synchrony index, rotation, twist	none	60 healthy subjects without family history of HCM and normal echocardiogram	Enhanced circumferential systolic function (P<0.001), increased twist (P<0.001) and more myocardial dyssynchrony (P<0.001) in relatives
HCM	Baudry, 2020, EHJ cvi	CCS	Genotype-positive relatives with LV wall thickness <13 mm	53 (20 derivation cohort, 33 validation cohort)	Derivation cohort: 31 [IQR 24-44], validation cohort: 42 [IQR 34-47]	Predominantly *MYBPC3* (53%) and *MYH7* (28%)	GE EchoPAC	GLS	Longitudinal strain in 17 LV segments	49 genotype-negative relatives and healthy volunteers with no history of cardiovascular disease and normal	Regional strain reduced in genotype-positive relatives in basal anteroseptal wall and basal inferoseptal wall (P=0.035 and

										echocardiography (21 in derivation cohort, 28 in validation cohort)	P=0.002 in validation cohort)
HCM	Yiu, 2012, PLoS one	CCS	Genotype-positive first-degree relatives without HCM diagnosis	47	42 ± 17	*MYBPC3* (83%) and *MYH7* (17%)	GE EchoPAC	GLS, GCS, GRS	LV basal anteroseptal and basal posterior peak longitudinal systolic strain	25 subjects referred for atypical chest pain, palpitations or syncope with normal echo	Basal anteroseptal longitudinal strain reduced in relatives (P<0.01)
HCM	Kauer, 2017, EHJ cvi	CCS	Genotyped relatives without major or minor criteria for HCM	41	37 ± 11	Mutations in 56%, predominantly *MYBPC3* (46%).	Philips QLAB	Twist, twist rate, untwist, untwist rate, unstrain, unstrain rate	LV inferoseptal, anterolateral, inferolateral and anteroseptal unstrain, unstrain rate and longitudinal strain (averaged over wall)	41 healthy, non-obese volunteers, with normal LA/LV volumes and function, and normal ECG	Early diastolic untwist rate reduced in relatives (P<0.05), untwist delayed (P<0.005). Late diastolic unstrain rate increased and delayed in all walls, except for anterolateral wall
HCM	De, 2011, Am Heart J	CCS	Genotype-positive relatives (*MYBPC3* c.3330+2T>G) with LV wall thickness <13 mm and no clinical signs or symptoms consistent with obstructive HCM	35	30 ± 14	All *MYBPC3* c.3330+2T>G	GE EchoPAC	GLS	Longitudinal strain in 18 LV segments	30 healthy volunteers with normal echo	Basal septal longitudinal strain reduced in relatives (P=0.02), whereas basal posterior and mid posterior longitudinal strain increased (both P=0.001)
HCM	Grover, 2019, EHJ cvi	CCS	Genotype-positive relatives (*MYBPC3*) without LVH	18	38 ± 14	All *MYBPC3*	GE EchoPAC	GLS	Longitudinal strain in 6 LV walls (averaged over wall)	11 genotype-negative siblings and 11 volunteers without cardiac disease or cardiovascular risk factors	No significant differences reported
HCM	Peyrou, 2016, Int J Cardiovasc Img	CCS	Genotype-positive first-degree relatives with LV wall thickness <13 mm	14	43 ± 16	*MYH7* (57%), *MYBPC3* (29%) and *TNNT2* (14%)	GE EchoPAC	GLS	Longitudinal strain in 18 LV segments	32 healthy volunteers without LVH, without hypertension and without family history of HCM	Basal inferoseptal and basal anteroseptal longitudinal strain reduced in relatives (p<0.05)
HCM	Forsey, 2014, JASE	CCS	Genotype-positive first-degree	12	10 ± 5	*MYBPC3* (43%), *MYH7*	GE EchoPAC	Mean circumferential	Circumferential strain in 18	28 healthy volunteers from a	Mean apical circumferential

			relatives (children) without LVH			(36%), *MYHC* (14%) and *TPM1* (7%)		strain (basal/mid/apical), mean longitudinal strain (apical 4-chamber), basal/apical rotation and rotation rate, twist	segments, longitudinal strain in 6 segments (apical 4-chamber)	normal control database	strain increased in relatives (P=0.04). Basal and apical rotation and LV twist increased in relatives, most marked at the apex (P=0.0001).

Abbreviations: CCS = case-control study, ECG = electrocardiogram, GCS = global circumferential strain, GLS = global longitudinal strain, GRS = global radial strain, HCM = hypertrophic cardiomyopathy, IQR = interquartile range, LCS = longitudinal cohort study, LA = left atrium/atrial LV = left ventricle/ventricular, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy.

Table 3: Included ACM studies

	First author, year, journal	Design	Study population	Number	Age (years)	Genotype	Software	Global deformation parameters	Regional deformation parameters	Control group	Main result(s)
ACM	Lie, 2018, JACC CVI	LCS	Genotype-positive relatives without life-threatening VA at baseline	83	39 ± 16 for total cohort (including 34 probands)	All desmosomal mutation carriers (not specified)	GE EchoPAC	GLS, LVMD, RVMD, RVFWLS	none	N/A	4 relatives with VA during follow-up. LVMD higher and RVFWLS lower in these relatives
ACM	Leren, 2017, JACC CVI	CSCS	Early ACM (possible/borderline diagnosis), of which 79% are genotype-positive relatives	73	41 ± 16 for total cohort (also including 86 probands)	All desmosomal mutation carriers (not specified)	GE EchoPAC	GLS, LVMD, RVGLS (6 segments), RVMD	None	N/A	15 subjects with arrhythmic events. RVMD lower in subjects with arrhythmic events (P = 0.003).
ACM	Chivulescu, 2019, EHJ	LCS	Genotype-positive relatives without major structural TFC	73	38 ± 18 for all relatives (also including 3 relatives with major structural TFC)	*PKP2* (92%), *DSP* (4%), *DSG2* (4%)	GE EchoPAC	GLS, LVMD	None	N/A	25 relatives had structural progression during follow-up. Higher LVMD at baseline predicted structural progression in relatives (P = 0.02).
ACM	Mast, 2019, JACC cvi	LCS	First-degree relatives without electrical or structural TFC (possible ACM)	37	26 ± 14	Predominantly *PKP2* (65%). Also 22% relatives of gene-elusive index patients	GE EchoPAC	none	Basal RV deformation pattern	N/A	Basal RV deformation patterns have high negative predictive value for disease progression during 3.7 ± 2.1 years follow-up
ACM	Taha, 2020, JACC cvi	LCS	Genotype-positive relatives without definite TFC diagnosis (possible and borderline ACM)	34	Not reported	Predominantly desmosomal (not specified)	GE EchoPAC	none	Basal, mid, apical RV deformation pattern	N/A	Basal RV deformation patterns reveal disease progression during 6.6 ± 3.1 years follow-up, conventional measurements remain unchanged

ACM	Mast, 2016, J Cardiovasc Electrophysiol	CCS + LCS	Genotype-positive first-degree relatives without definite TFC diagnosis and without VA or symptoms (possible and borderline ACM)	31	30 ± 14	*PKP2* (90%) and *DSG2* (10%)	GE EchoPAC	none	Basal, mid, apical RV electromechanical interval	30 healthy volunteers without history of heart disease	Electromechanical interval prolonged in relatives in RV basal area (P<0.001). Prolonged electromechanical interval associated with arrhythmic outcome during 4.2 ± 3.1 years follow-up
ACM	Sarvari, 2011, EHJ	CCS	Genotype-positive first-degree relatives without palpitations, syncopes, arrhythmias or heart failure (possible and borderline ACM)	27	38 ± 18	*PKP2* (89%), *DSP* (11%)	GE EchoPAC	GLS, LVMD, RVFWLS, RVMD	none	10 genotype-negative relatives and 30 healthy volunteers	All parameters impaired in relatives (P<0.001). RVMD strongest association with arrhythmias.
ACM	Reant, 2016, Int J Cardiovasc Img	CCS	Genotype-positive relatives without TFC (possible ACM)	27	40 ± 20	All desmosomal mutation carriers (not specified)	GE EchoPAC	GLS (multilayer), RVFWLS	Longitudinal strain in 17 LV segments (multilayer) and basal, mid and apical RV longitudinal strain	26 healthy volunteers, asymptomatic without history of premature cardiovascular disease	Global parameters reduced in relatives. Regional parameters also reduced in LV free wall segments (epicardial more than endocardial), septal segments and RV mid and apical segments.
ACM	Mast, 2016, JACC	CCS	Genotype-positive relatives without TFC (possible ACM)	21	27 ± 14	*PKP2* and *DSG2* (not specified)	GE EchoPAC	none	Basal RV time to onset shortening, (systolic) peak strain, post-systolic shortening and deformation pattern	84 healthy unrelated controls	Abnormal deformation patterns more frequent in relatives than in controls (48% vs. 4%)
ACM	Aneq, 2012, cardiovascular ultrasound	CCS	First degree male relatives not fulfilling TFC diagnosis (possible	19	median 29 (range 19-73)	Not reported	GE EchoPAC	none	Longitudinal strain in basal/mid segments of LV lateral wall,	Asymptomatic healthy male volunteers without family history of	Reduced strain in basal septum of relatives

			or borderline ACM)						septum and RV lateral wall	premature cardiovascular disease, no ECG abnormalities and no cardiac medication	
ACM	Mast, 2015, JASE	CCS	Mutation-positive relatives without definite Task Force diagnosis (possible or borderline ACM)	16	32 ± 14	*PKP2* (75%), *PLN* (12.5%), *DSG2* (6.25%), *DSC2* (6.25%)	GE EchoPAC	Mean LV systolic peak strain (mean of 18 segments)	Systolic peak strain and strain rate, and post-systolic shortening in 18 LV segments	Healthy control subjects free of any cardiovascular disease (volunteers, unrelated to cases)	Global strain equal, LV involvement in 25% relatives (vs 0% in controls)

Abbreviations: ACM = arrhythmogenic cardiomyopathy, CCS = case-control study, CSCS = cross-sectional cohort study, ECG = electrocardiogram, GLS = global longitudinal strain, LCS = longitudinal cohort study, LV = left ventricle/ventricular, LVMD = left ventricular mechanical dispersion, RV = right ventricle/ventricular, RVFWLS = right ventricular free wall longitudinal strain, RVMD = right ventricular mechanical dispersion, TFC = Task Force Criteria, VA = ventricular arrhythmia.

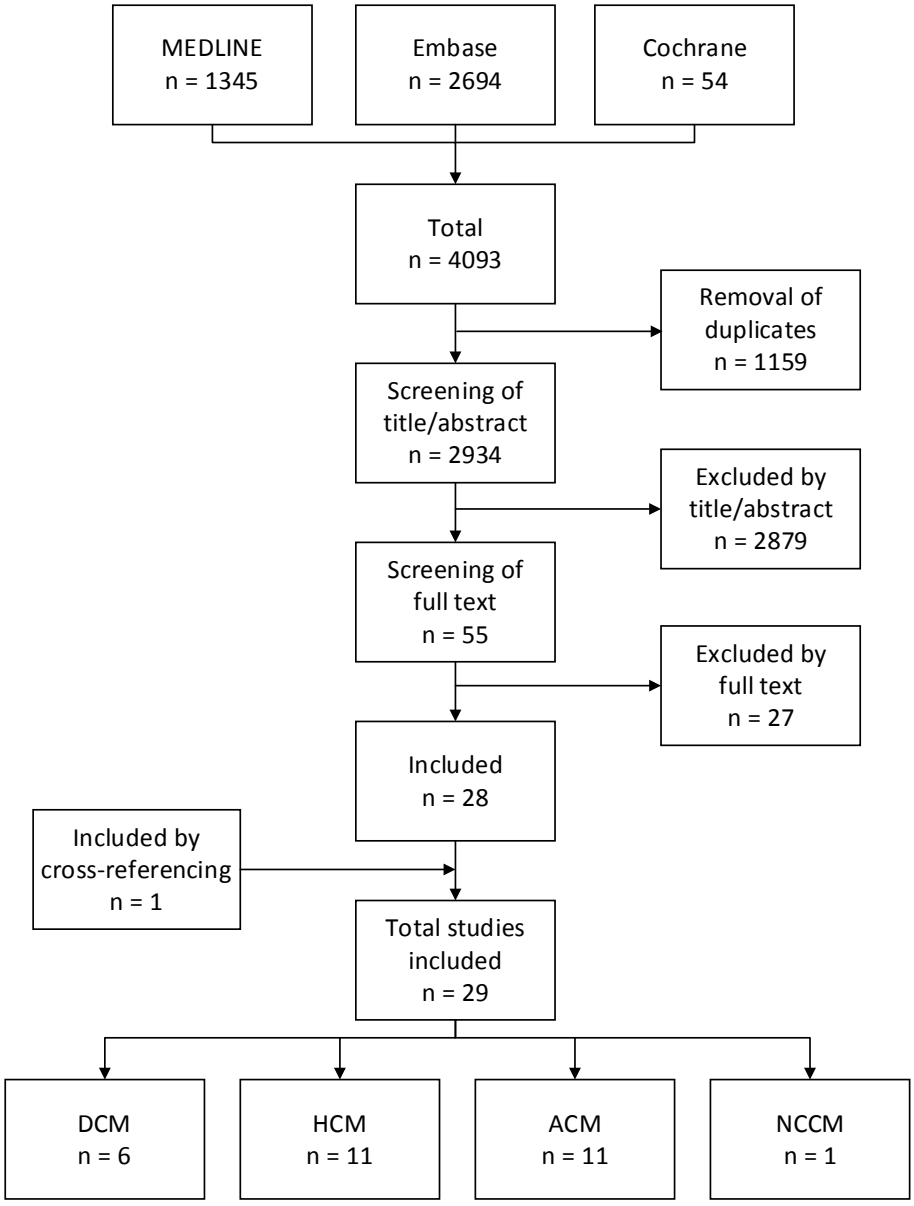
Table 4: Included NCCM studies

	First author, year, journal	Design	Study population	Number	Age (years)	Genotype	Software	Global deformation parameters	Regional deformation parameters	Control group	Main result(s)
NCCM	Akhan, 2021, Int J Cardiovasc Img	CCS	First-degree relatives of NCCM patients	30	46 ± 17	Not reported	GE EchoPAC	GLS, GLS rate, GCS, GCS rate, GRS, GRS rate	none	31 healthy volunteers	Many conventional parameters and all strain parameters impaired in relatives compared to controls

Abbreviations: CCS = case-control study, GCS = global circumferential strain, GLS = global longitudinal strain, GRS = global radial strain, NCCM = noncompaction cardiomyopathy

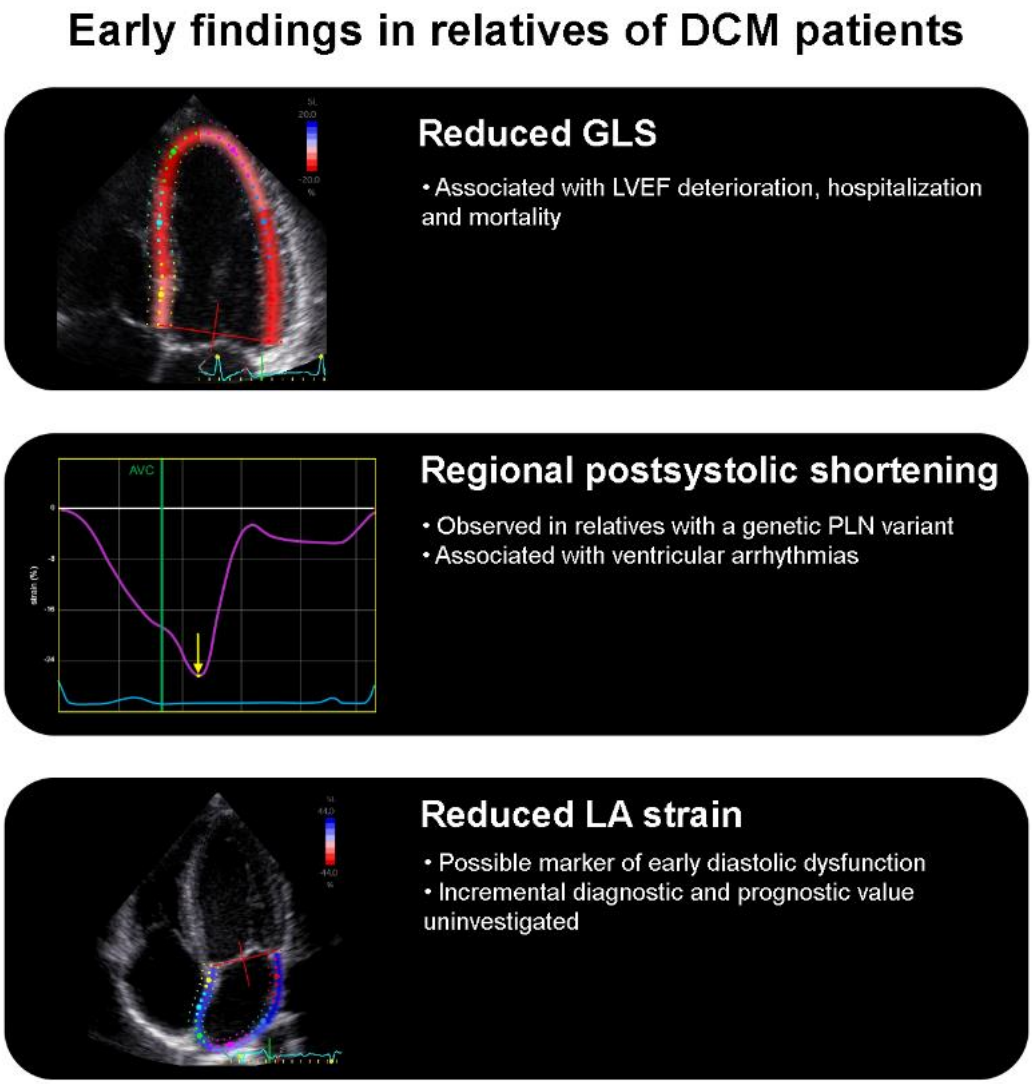
Figures

Figure 1: Flowchart



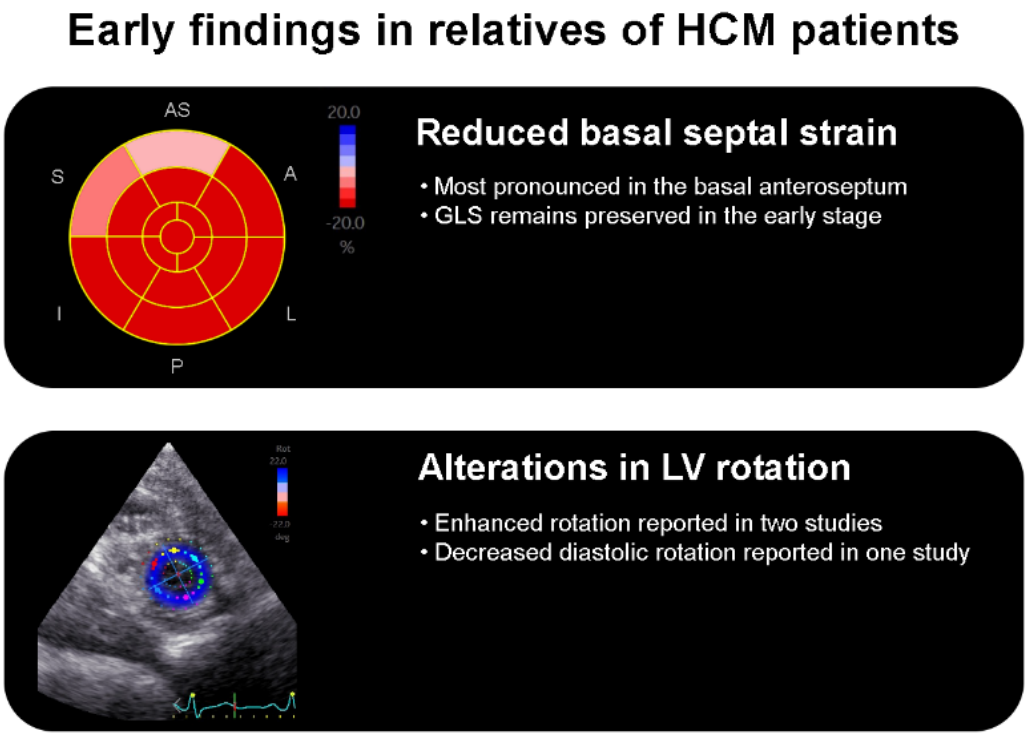
A systematic search was conducted in MEDLINE, Embase and Cochrane databases. After applying the in- and exclusion criteria, 29 studies were included, of which 6 were performed in DCM, 11 in HCM, 11 in ACM and 1 in NCCM. ACM, arrhythmogenic cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy, NCCM, noncompaction cardiomyopathy.

Figure 2: Reported early findings in relatives of DCM patients



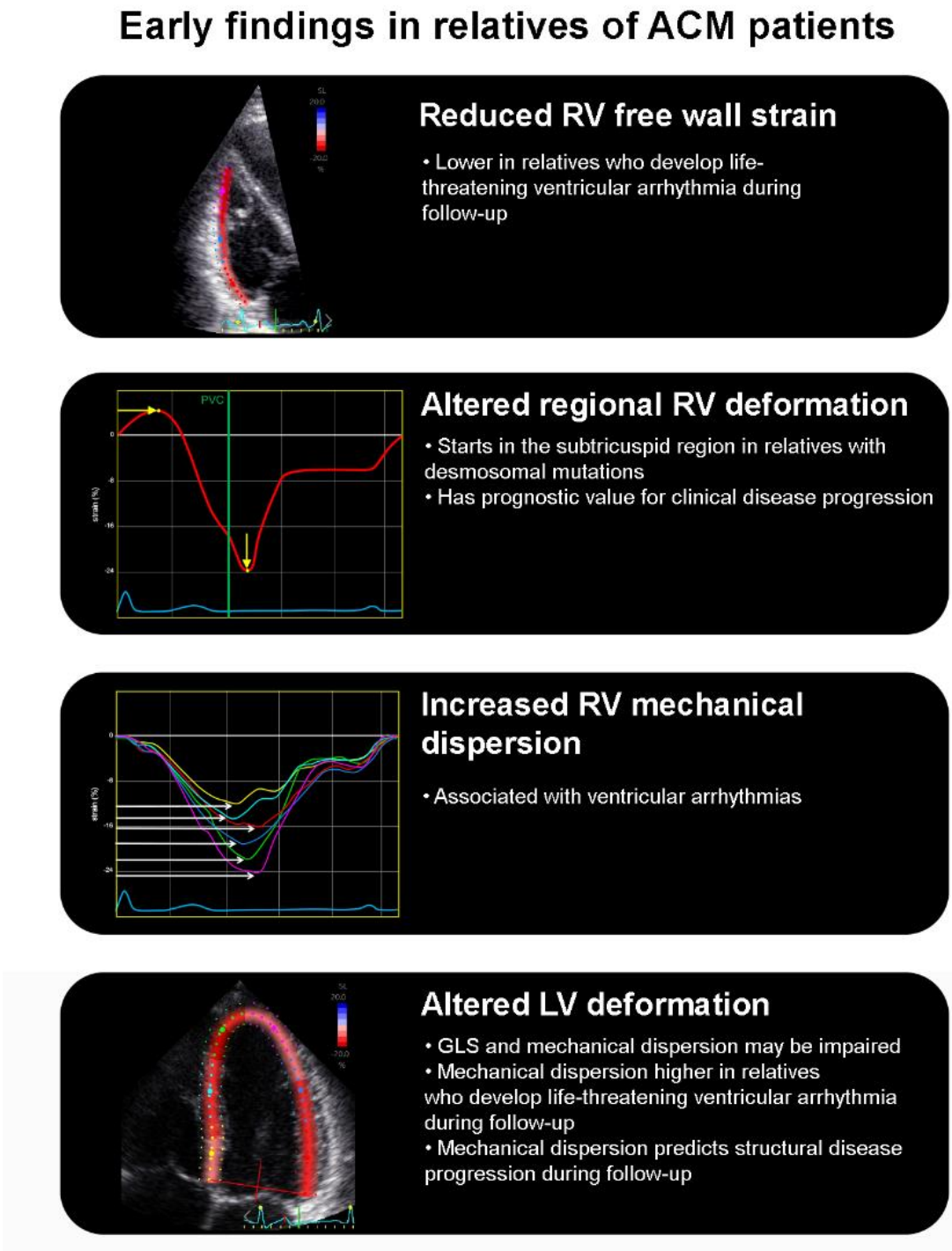
The findings with echocardiographic defromation imaging that are reported in relatives of DCM patients are reduced GLS, regional postsystolic shortening and reduced LA strain. DCM, dilated cardiomyopathy; GLS, global longitudinal strain; LA, left atrium/atrial; PLN, phospholamban.

Figure 3: Reported early findings in relatives of HCM patients



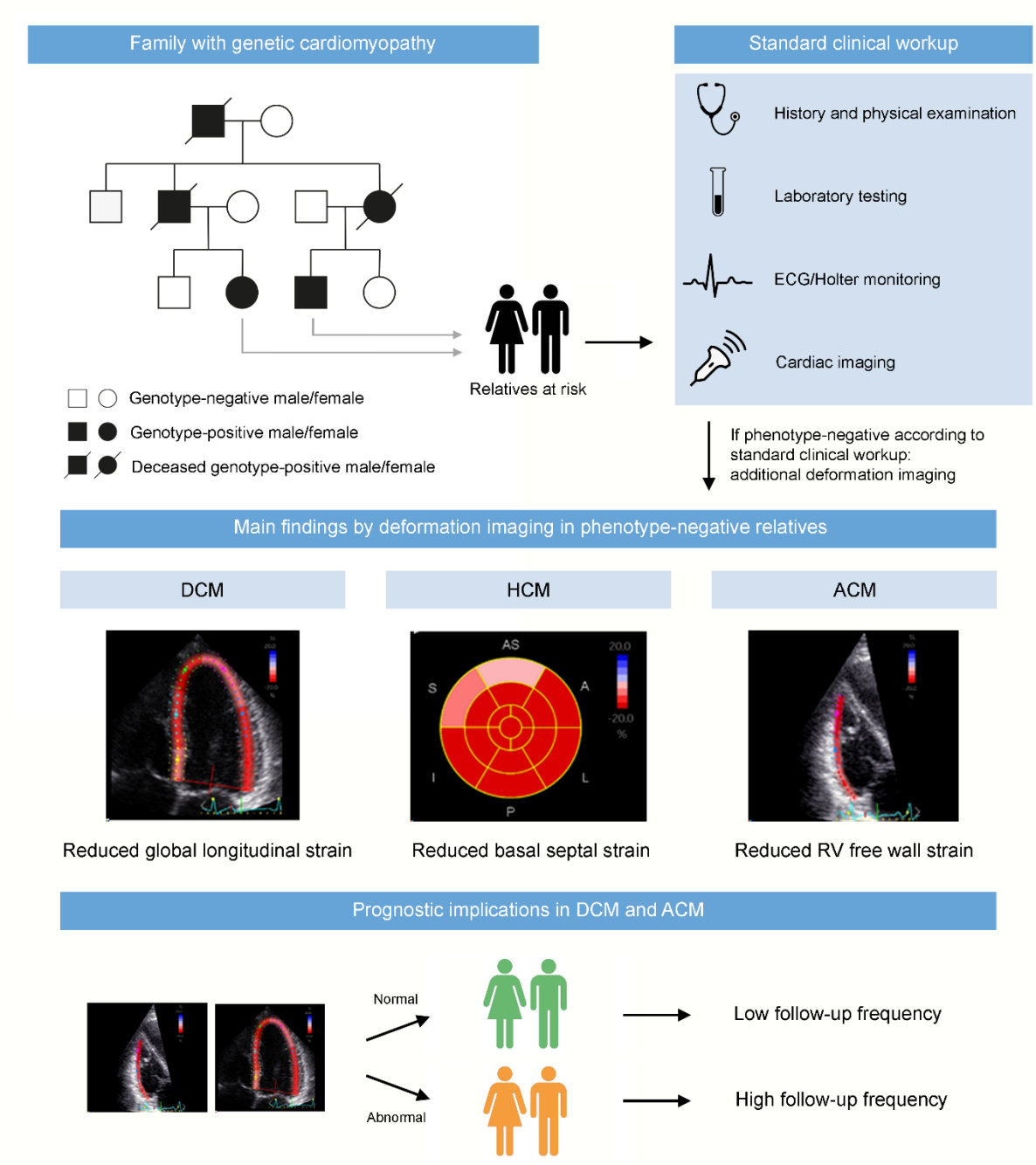
The findings with echocardiographic defromation imaging that are reported in relatives of HCM patients are reduced basal septal strain and alterations in LV rotation. HCM, hypertrophic cardiomyopathy; LV, left ventricle/ventricular.

Figure 4: Reported early findings in relatives of ACM patients



The findings with echocardiographic defromation imaging that are reported in relatives of ACM patients are reduced RV free wall strain, increased RV mechanical dispersion, alterations in regional RV deformation, and alterations in LV deformation. ACM, arrhythmogenic cardiomyopathy; GLS, global longitudinal strain; LV, left ventricle/ventricular; RV, right ventricle/ventricular.

Central illustration: The clinical utility of deformation imaging in relatives at risk for genetic cardiomyopathies



Deformation imaging on top of the standard clinical workup reveals early signs of disease in relatives of patients with genetic cardiomyopathy. These early mechanical abnormalities have prognostic value in DCM and ACM, and may be used in these relatives to tailor follow-up protocols. ACM, arrhythmogenic cardiomyopathy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; RV, right ventricle/ventricular.