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POSITION PAPER

Diagnosis and management of patients with left ventricular hypertrophy: Role of multimodality cardiac imaging. A scientific statement of the Heart Failure Association of the European Society of Cardiology

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Left ventricular (LV) hypertrophy consists in an increased LV wall thickness. LV hypertrophy can be either secondary, in response to pressure or volume overload, or primary, i.e. not explained solely by abnormal loading conditions. Primary LV hypertrophy may be due to gene mutations or to the deposition or storage of abnormal substances in the extracellular spaces or within the cardiomyocytes (more appropriately defined as pseudohypertrophy). LV hypertrophy is often a precursor to subsequent development of heart failure. Cardiovascular imaging plays a key role in the assessment of LV hypertrophy. Echocardiography, the first-line imaging technique, allows a comprehensive assessment of LV systolic and diastolic function. Cardiovascular magnetic resonance provides added value as it measures accurately LV and right ventricular volumes and mass and characterizes myocardial tissue properties, which may provide important clues to the final diagnosis. Additionally, scintigraphy with bone tracers is included in the diagnostic algorithm of cardiac amyloidosis. Once the diagnosis is established, imaging findings may help predict future disease evolution and inform therapy and follow-up. This consensus document by the Heart Failure Association of the European Society of Cardiology provides an overview of the role of different cardiac imaging techniques for the differential diagnosis and management of patients with LV hypertrophy.

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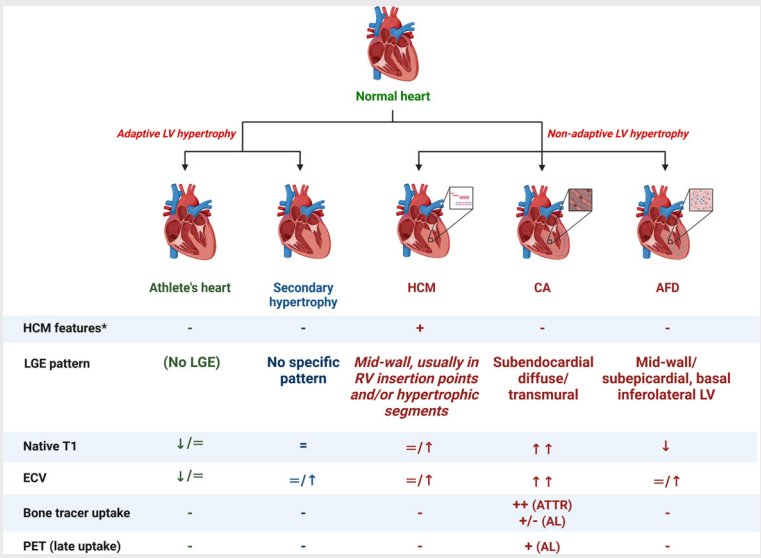
Graphical Abstract



Main imaging findings that may guide the differential diagnosis among hypertrophic disorders. +, present; −, absent; =, unchanged; ↑, increased; ↑↑, much increased; ↓, decreased; AFD, Anderson–Fabry disease; AL, amyloid light-chain; ATTR, amyloid transthyretin; CA, cardiac amyloidosis; ECG, electrocardiogram; ECV, extracellular volume; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle; PET, positron emission tomography; RV, right ventricle. *Asymmetrical hypertrophy, left ventricular obstruction, papillary muscle hypertrophy.

Keywords Imaging • Hypertrophy • Cardiomyopathy • Diagnosis • Consensus document

Left ventricular (LV) hypertrophy consists in an increased LV wall thickness. LV hypertrophy can be classified according to the pattern of wall thickening (symmetrical vs. asymmetrical), the presence of LV dilatation (concentric vs. eccentric), and possibly based on the occurrence of right ventricular (RV) hypertrophy. Furthermore, increased LV wall thickness can be a compensatory response to abnormal loading conditions, as in athletes' heart, severe aortic stenosis or arterial hypertension. Alternatively, no cause of LV hypertrophy may be apparent, or the degree of hypertrophy may be excessive compared to the pro-hypertrophic stimulus.[1,2] While helpful, this distinction can be complicated when we consider that certain genetic mutations may need an environmental trigger such as hypertension to develop into hypertrophic cardiomyopathy (HCM).[3] Primary hypertrophy may be due to gene mutations or to an accumulation of abnormal substances in the extracellular spaces or within the cardiomyocytes, which is defined more correctly as pseudo-hypertrophy.[4] The 2014 European Society of Cardiology (ESC) guidelines on HCM nicely classified the causes of primary LV hypertrophy as follows: sarcomeric protein gene mutations (40–60%), unknown causes (25–30%), and other genetic and non-genetic causes (5–10%: inborn errors of metabolism, neuromuscular diseases, mitochondrial diseases, malformation syndromes, amyloidosis, newborn of diabetic mother, or drug-induced).[1]

The same identification of LV wall thickening requires the use of imaging techniques. Echocardiography is the first-line technique, and enables a sophisticated assessment of systolic and diastolic function and cardiac valves. The strengths of cardiovascular magnetic resonance (CMR) include more accurate measurement of LV and RV volumes and mass, as well as the characterization of myocardial tissue properties, which may provide important clues to the diagnosis. As for other imaging techniques, we must remember at least scintigraphy with bone tracers, which plays an essential role in the diagnostic workup of cardiac amyloidosis (CA). Once the diagnosis is established, imaging findings may help predict future disease trajectories. For example, the extent of late gadolinium enhancement (LGE) on CMR (in terms of total amount of LGE) has been associated with a worse outcome in HCM,[5] and transmural LGE with worse outcome in CA.[6] Finally, serial imaging studies could provide clues on disease evolution and the response to treatment, as recently suggested by the relationship between CMR-derived extracellular volume (ECV), the haematologic response and final outcome in patients with amyloid light-chain (AL) CA.[7]

In this consensus document by the Heart Failure Association of the ESC we reappraise the role of different imaging techniques for the differential diagnosis and management of patients with LV hypertrophy.

Imaging findings as diagnostic tools

Echocardiography

Standard transthoracic echocardiography

Many echocardiographic findings can help differentiate physiological from pathological hypertrophy, and then between the different forms of hypertrophy (*Table 1*).[8] Patients with HCM display more often asymmetric LV hypertrophy involving just the interventricular septum, but other morphologic variants have been described.[9] In 70% of the cases, HCM is associated with LV outflow tract obstruction at rest or during exercise, mainly because of the systolic anterior movement of the anterior mitral valve leaflet. In rare cases, the obstruction occurs at the mid-ventricular level. The continuous-wave Doppler show a typical 'dagger-shaped' morphology in the sites of obstruction.[10] Most patients show mitral regurgitation due to poor leaflet apposition (with posteriorly directed jets). Left atrial (LA) enlargement and diastolic dysfunction are common.

The echocardiographic pattern of CA is characterized by concentric hypertrophy with non-dilated left ventricle, and usually extends to the right ventricle. The atria are typically enlarged, and the interatrial septum is often thickened, particularly in late disease stages.[11] To our knowledge, no definition of interatrial septal thickening has been proposed so far. Based on the experience of the Authors, interatrial septal thickening could be defined by a septal thickness >5 mm during atrial diastole, measured preferentially with CMR also to exclude lipomatous hypertrophy. Diastolic dysfunction is present from the early disease stages, and a restrictive pattern appears in advanced stages. LV ejection fraction (LVEF) is usually preserved until the very late stages.

Right ventricular hypertrophy is a pathologic increase in RV wall thickness in response to pressure overload (e.g. because of pulmonary hypertension), but possibly also cardiomyocyte hypertrophy due to a gene mutation, or even infiltration of the RV wall. RV hypertrophy in HCM is extremely heterogeneous, varying from mild concentric hypertrophy to more severe obstructive disease, either isolated or associated with LV hypertrophy.[12] RV hypertrophy is common in CA and may show an apical sparing pattern.[13,14] In Anderson–Fabry disease (AFD), RV and LV hypertrophy are often associated.[15] Few data are available on the prevalence of RV hypertrophy in these three settings. The patterns of RV hypertrophy are nonetheless quite similar and do not help differentiate between different disorders.

Speckle-tracking echocardiography

Speckle-tracking echocardiography (STE) is a very sensitive tool for identifying the early stages of HCM. A decrease in longitudinal deformation in single segments precedes the deterioration of global longitudinal strain (GLS). Segmental longitudinal strain is typically reduced in the site of maximal LV hypertrophy, which is also the site with most fibrosis.[16] A more severely impaired GLS predicts a higher risk of ventricular arrhythmias[17] and worse post-operative outcome after septal myectomy.[18]

Speckle-tracking echocardiography is very useful for early diagnosis as it detects a systolic dysfunction from the early stages and often an 'apical sparing pattern', which is a sensitive but not very specific marker for CA, as it can also be seen in other forms of LV hypertrophic phenotype like HCM.[19,20] Mild-to-moderate pericardial effusion is common.[21]

Speckle-tracking echocardiography also enables early detection of LA and RV involvement in CA, which may be useful for differential diagnosis.[22–24] LA strain is more severely depressed in patients with transthyretin (ATTR)-CA than those with AL-CA or those without CA,[25] and RV strain shows a basal-to-apical strain reduction distribution similar to the left ventricle.[23] Many diagnostic scores have been developed to improve the diagnosis of CA in patients with unexplained LV hypertrophy. Multiparametric echocardiographic diagnostic scores have also been proposed, such as the increased wall thickness (IWT)[26] and AMYLoidosis Index (AMYLI) scores,[27] the latter not requiring STE imaging.

In patients with AFD, cardiac remodelling is due to replacement fibrosis (starting in the basal inferolateral wall) and vasculopathy.[28] LV GLS in the basal inferolateral wall is typically decreased,[29] and the loss of normal circumferential strain base-to-apex gradient may represent an early marker of cardiac involvement in AFD.[30] Compared with patients with HCM, those with AFD typically show a greater impairment in free wall RV strain and a lower difference between free wall and global RV strain.[31]

Cardiovascular magnetic resonance

Morphology assessment

Cardiovascular magnetic resonance provides an assessment of ventricular mass, chamber volume, cardiac function, pattern and distribution of hypertrophy and tissue characterization without ionizing radiation.[32–35] In detail, CMR allows absolute mass quantification[36] and the detection of unusual patterns of LV hypertrophy.[37] Moreover, CMR can detect early markers of HCM in gene carriers, such as myocardial crypts, elongated anterior mitral leaflets, abnormal apical trabeculae and smaller LV ventricular volumes[38] (*Figure 1*).

T1 mapping

A variable combination of tissue characterization sequences may help distinguish different disorders.[33,38,39] Native (i.e. pre-contrast) T1-mapping is useful to evaluate myocardial tissue changes (both intracellular and extracellular) that are increased by presence of oedema, fibrosis, amyloidosis and decreased by iron or fat deposition. ECV mapping is a quantitative index of ECV expansion, and has been validated against histology,[40] similarly to LGE.[41] Both native T1-mapping and ECV mapping are slightly increased in HCM patients, particularly in regions of hypertrophy.[42–45]

Native T1-mapping has high positive and negative predictive values in patients with suspected CA.[46] Although native T1-mapping is less specific than ECV mapping because the latter reflects ECV only, rather than both intra- and extracellular volume. ECV represents the best parameter for quantifying amyloid and has shown the best diagnostic accuracy when compared to other CMR parameters.[47] In patients with AFD, intracellular accumulation of sphingolipids

Table 1 **Imaging features for the differential diagnosis of left ventricular hypertrophy**

Aetiology	Hypertrophy pattern	Morphology and valve function	LVEF	GLS	Diastolic function	ECV	LGE	Bone tracer uptake
Athlete's heart	Eccentric LVH with MWT <14 mm	Balanced LV and RV dilatation	Normal	Preserved	Normal or supernormal	15–30%	Usually absent	Absent
Sarcomeric HCM	Asymmetrical hypertrophy with MWT often >15 mm	Possible LVOTO and/or SAM with secondary MR	Normal/ supernormal or reduced	Preserved or abnormal	Abnormal	20–45%	No specific pattern	Absent
Hypertensive heart disease	Asymmetrical hypertrophy (≫basal IVS)		Normal or reduced	Preserved or abnormal	Abnormal	20–35%	No specific pattern	Absent
Aortic stenosis	Concentric LVH	Valvular cusp calcification with reduced opening, increased valve pressure gradient	Normal or reduced	Preserved or abnormal	Abnormal	20–35%	No specific pattern	Absent
Cardiac amyloidosis	Concentric LVH, often RV hypertrophy	Progressive reduction in LV volumes; biventricular involvement; bi-atrial enlargement; pericardial effusion	Normal or reduced	Preserved or abnormal, apical sparing	Abnormal	35–75%	Subendocardial diffuse/transmural	Present (ATTR)
Anderson–Fabry disease	Severe concentric LVH	Progressive increase in LV volume	Normal or reduced	Altered basal LS	Abnormal	20–35%	Midmyocardial LGE in the basal to mid-inferolateral wall	Absent

ECV values are derived from Sado *et al.*[8]

ATTR, transthyretin amyloidosis; ECV, extracellular volume; GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LGE, late gadolinium enhancement; LS, longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; MWT, maximal wall thickness; RV, right ventricle; SAM, systolic anterior motion.

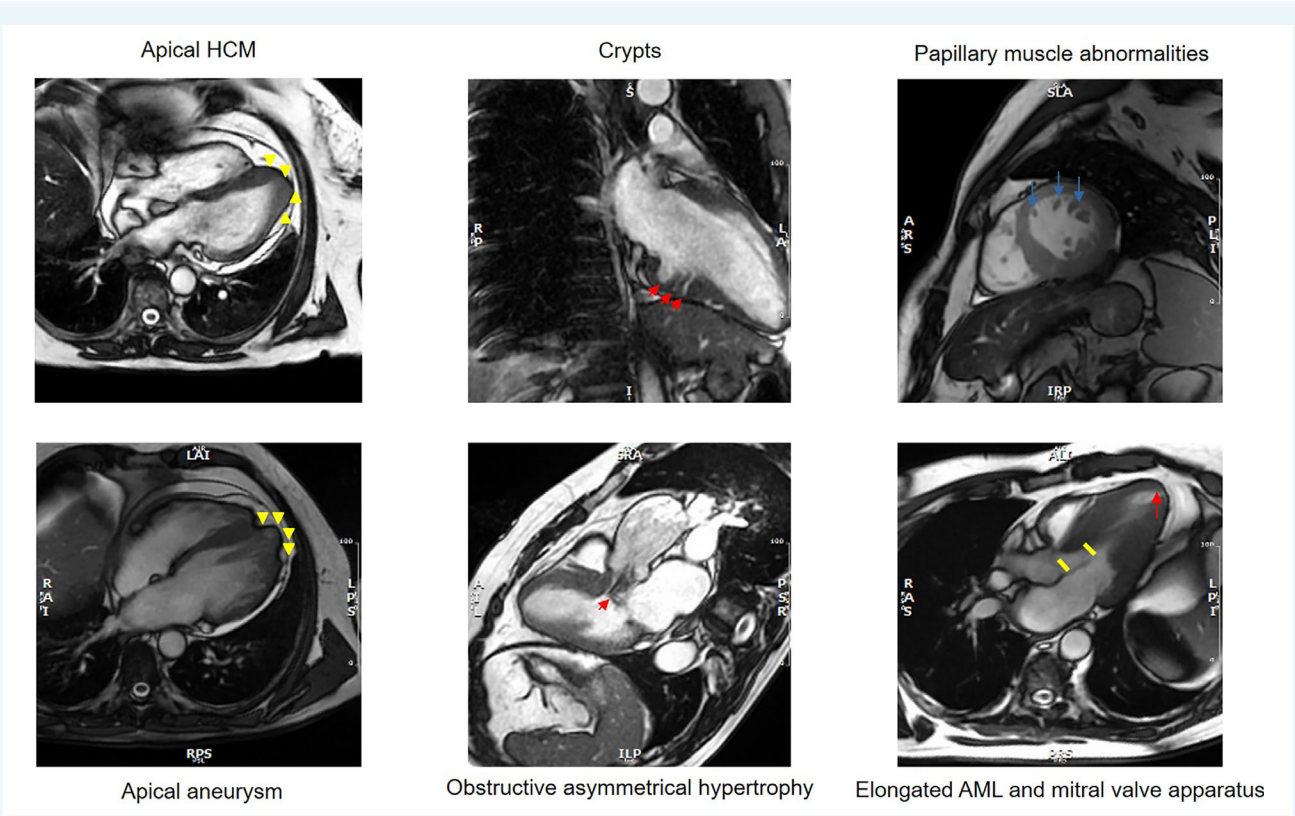


Figure 1 Main features of hypertrophic cardiomyopathy (HCM). AML, anterior mitral leaflet.

causes a typical shortening of native T1 relaxation times, even before the development of hypertrophy, which allows to distinguish AFD from other conditions such as CA or HCM despite similar morphological features[48] (*Figure 2*). The development of myocardial fibrosis in later disease stages, secondary to cardiomyocyte necrosis, balances the effect of sphingolipids on T1 relaxation times leading to a pseudo-normalization of native T1-mapping, at least in myocardial regions involved by fibrosis. Similarly, ECV is typically normal in AFD because of the intracellular accumulation of sphingolipids, as compared to other cardiomyopathies characterized by interstitial infiltration (such as CA),[49] although it might increase in later disease stages in myocardial areas involved by fibrosis.

Late gadolinium enhancement

Cardiovascular magnetic resonance is a possible additional exam when CA is suspected, and is also particularly useful in patients with a monoclonal protein and no bone tracer uptake in the heart (Perugini grade zero).[21] A diffuse subendocardial LGE pattern is highly specific for CA (94%). LGE imaging can be challenging due to the diffuse nature of amyloid infiltration.[50] However, the typical alterations in inversion times responsible for the difficult myocardial nulling, partially overcome by the development of phase-sensitive inversion recovery sequences, are also strongly suggestive of CA.[46,50,51]

The main findings in patients with AFD are concentric LV hypertrophy[52] and non-ischaemic mid-wall or subepicardial LGE pattern mainly involving the basal inferolateral LV segment.[53] In male patients, LGE does not precede the development of LV hypertrophy, while it has been reported in a significant proportion of female patients without hypertrophy.[54]

Cardiovascular magnetic resonance may also be helpful in the assessment of glycogen storage diseases (e.g. Pompe, PRKAG2, Danon); for instance, Danon disease is characterized by extensive subendocardial LGE in the left ventricle, particularly in the apex and sparing the basal septum.[55]

T2-mapping, T2*-weighted imaging, diffusion tensor imaging

Quantitative T2-mapping analysis has been used to detect myocardial oedema in HCM patients,[56] which might be explained by acute ischaemic bouts, inflammatory injuries, myocyte disarray, scar heterogeneity, and has been proposed as a marker of disease activity. In patients with AFD, T2-mapping has been used to demonstrate the presence of myocardial inflammation, which is thought to contribute to disease progression.[49,57,58]

Myocardial T2* values, an index of magnetic field inhomogeneities usually utilized to detect myocardial iron overload in hereditary haemochromatosis or haemoglobinopathies, may be slightly reduced even in HCM patients, possibly providing further information to characterize myocardial fibrosis.[59]

Diffusion tensor imaging is a novel technique that shows the microstructure of myocardial fibres and myocardial disarray. It

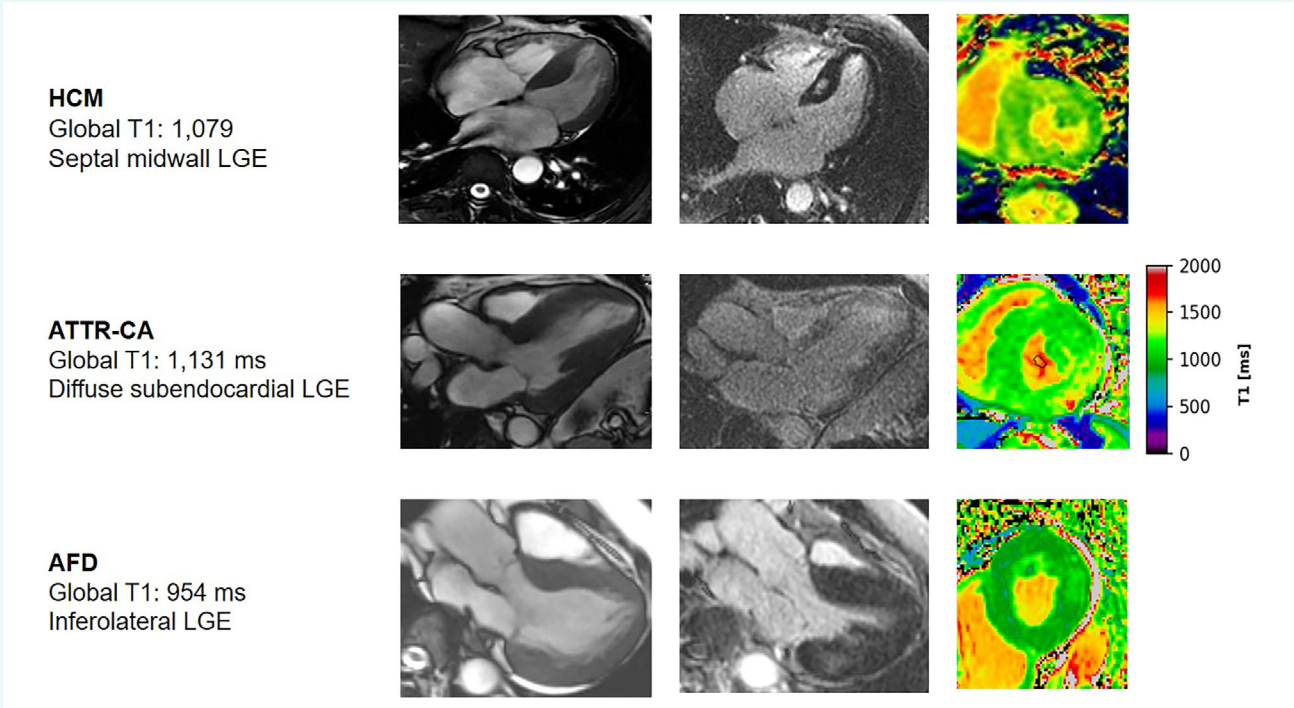


Figure 2 Similar morphology but different native T1-mapping in hypertrophic cardiomyopathy (HCM), transthyretin cardiac amyloidosis (ATTR-CA) and Anderson–Fabry disease (AFD). LGE, late gadolinium enhancement.

holds some promise to provide further insight on the myocardial substrate and potentially refine risk prediction, but is currently just a scientific and research tool.[60]

Nuclear imaging

Scintigraphy

Cardiac scintigraphy with bone tracers is the only nuclear cardiology technique used in clinical practice to establish the aetiology of LV hypertrophy. The mechanism of the more intense myocardial uptake of ^{99m}Tc-labelled bone tracers in ATTR- than AL-CA is not well understood, although may be related to the presence of microcalcifications in the heart.[61] Although these radiotracers are generally considered to have a similar diagnostic yield, very limited evidence is available.[62,63]

Scintigraphy with bone tracers involves the intravenous administration of 370 to 740 MBq of ^{99m}Tc-labelled bone-seeking radiotracer followed by planar and possibly single-photon emission computed tomography (SPECT) imaging after 2–3 h. The intensity of myocardial radiotracer uptake can be analysed either by visual grading or by quantifying radiotracer uptake using the heart-to-contralateral lung (H/CL) ratio. The Perugini grading system is based on a visual analysis of cardiac uptake on planar images (*Figure 3*).[64] A grade 2 or 3 uptake has a high sensitivity (>85%) for ATTR-CA, but a lower specificity (around 30%), as patients with AL-CA may show a grade 1–2 uptake.[65]

Semi-quantitative analysis of myocardial uptake can be performed using the heart-to-whole body (H/WB) or H/CL ratio. H/WB ratio is calculated by drawing a rectangular region of interest (ROI) for the heart and irregular ROIs for the whole body except urinary tract. Mean H/WB ratio of ATTR-CA was 10.0% versus 5.4% in controls.[66] An H/CL ratio ≥1.5 is highly suggestive for ATTR-CA, and therefore can be used in the diagnosis of ATTR-CA.[67,68] Other cut-off points have been proposed and incorporated in the diagnostic algorithms by different scientific societies.[69]

Patients with specific *TTR* gene mutations (Phe84Leu, Ser97Tyr) may not display an uptake of bone tracers. Moreover, differentiation of myocardial uptake from blood pool uptake, rib fractures, valvular or annular mitral calcifications may be challenging in patients with Perugini grade 1. In these patients, additional SPECT imaging is necessary to achieve more accurate localization of radiotracer uptake.[65] Moreover, combination between SPECT and computed tomography (CT) imaging allows accurate quantitative measures of the standardized uptake value (SUV) through attenuation correction. SUV-based quantitative SPECT/CT parameters have shown excellent correlations with conventional visual scores.[70]

Positron emission tomography

The differential diagnosis between AL- and ATTR-CA is clinically important because of different treatments and prognoses. Besides differences in clinical features and laboratory findings, some imaging findings help distinguish ATTR- from AL-CA on bone scintigraphy. First, the degree of myocardial uptake is usually significantly higher

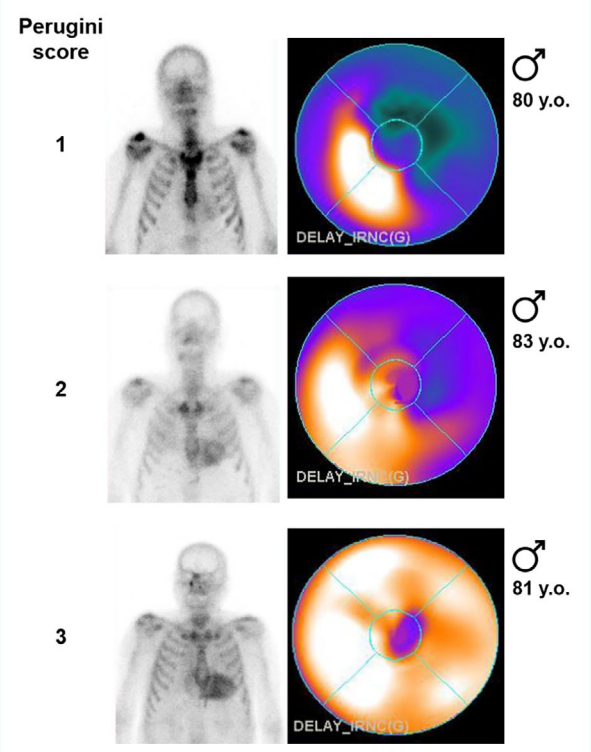


Figure 3 Cardiac uptake of bone tracers on planar scintigraphy (*left*) and tomographic acquisitions (*right*). A visual grade of 0, 1, 2, and 3 indicates no myocardial uptake, or uptake less than, equal to, and greater than rib uptake, respectively. Reprinted with permission from Grigoratos *et al.*[64]

in ATTR than in AL[71]; second, diffuse uptake in soft tissue is more common in ATTR-CA.

Several positron emission tomography (PET) tracers, such as ^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben, and ^{11}C-Pittsburgh B (^{11}C-PiB), have been investigated for CA imaging.[72–74] All these tracers are analogues of thioflavin-T, a histological dye binding to the beta-pleated motif of the amyloid fibril. These tracers bind to any type of amyloid fibril, even if they seem to have a higher affinity for AL than for ATTR.[73] This may explain why delayed acquisitions (from 50 to 60 min) highlight amyloid deposits in AL, but not in ATTR-CA (*Figure 4*).[72] Therefore, PET imaging might allow to reliably differentiate AL- from ATTR-CA, which is not possible based on echo or CMR imaging.

Myocardial tissue remodelling in AFD leads to a significant reduction of hyperaemic myocardial blood flow (MBF).[75] For example, a study reported a 60% reduction in hyperaemic MBF regardless of LV mass. Such reduction is more prominent in males, but it is common also in females, where it may be the only sign of cardiac involvement.[76]

Computed tomography

Cardiac CT is routinely performed in patients referred to transcatheter aortic valve replacement. In a small case series, ECV measurements by CT and CMR were well correlated ($r^2 = 0.85$). ECV_{CT} was higher in amyloidosis than aortic stenosis (0.54 ± 0.11 vs. 0.28 ± 0.04, $p < 0.001$), with no overlap. ECV_{CT} also tracked clinical markers of cardiac amyloid severity (N-terminal pro-B-type natriuretic peptide, troponin, LVEF, LV mass, LA and right atrial area), and bone scintigraphy amyloid burden ($p < 0.001$).[77]

Integration of imaging and clinical data

The first step to make the diagnosis in a patient with LV hypertrophy is to assess the personal and family history. Age at diagnosis is an important element. For example, inborn errors of metabolism and congenital syndromes are much more common in neonates or infants than in older children or adults, and ATTRwt-CA affects elderly individuals.[78–80] When collecting the clinical history, an important goal is to exclude common causes of LV hypertrophy, while keeping in mind that they may coexist with primary cardiomyopathies.[81] The family history should be detailed to identify other family members with known or suspected cardiomyopathy or other elements such as a history of sudden cardiac death (SCD), heart failure, heart transplantation, pacemaker or defibrillator implantation, stroke in a young individual, or neuromuscular disease.[81] When this is the case, the likely pattern of inheritance and other clinical features possibly pointing towards a specific diagnosis should be searched.[81] A negative family history does not rule out a genetic aetiology because the disease may be the result of a *de novo* mutation, or the manifestations of the genetic disorders may have gone unnoticed.[81]

Signs and symptoms of systemic disorders should be searched. The mechanisms of multi-organ involvement include: the expression of the mutated protein in multiple organs (e.g. dystrophin), infiltration of multiple organs (e.g. amyloidosis), mitochondrial dysfunction (e.g. MELAS), or developmental abnormalities (e.g. cardiofaciocutaneous syndrome).[81] Some features of systemic involvement may be readily detected (such as a dysmorphic appearance), while others require specific investigations (e.g. carpal tunnel syndrome) or laboratory testing, such as an increment of transaminase levels and creatine kinase for glycogen storage diseases, mitochondrial and muscular disorders. Skeletal muscle weakness usually precedes cardiac involvement and dominates the clinical picture, but is occasionally subtle and less prominent than cardiac disease.[81]

An abnormal electrocardiogram may be the only manifestation of a cardiomyopathy. Many electrocardiographic features can suggest the underlying diagnosis, in association with other specific clinical and imaging features. Progressive atrioventricular conduction delay due to disease of the atrioventricular node or His–Purkinje system is common in many genetic diseases including laminopathies,[82] mitochondrial disorders,[83] and storage or infiltrative diseases.[80,84] Ventricular pre-excitation is a common feature of storage diseases[85] and some mitochondrial disorders.[83] Repolarization abnormalities are common but not specific. Abnormalities of the ST segment and T wave are usually the expression of ventricular strain or a specific location of the disease process; an example is giant T-wave inversion in the precordial and/or inferolateral leads in patients with apical HCM. Extremely large QRS voltage is typical

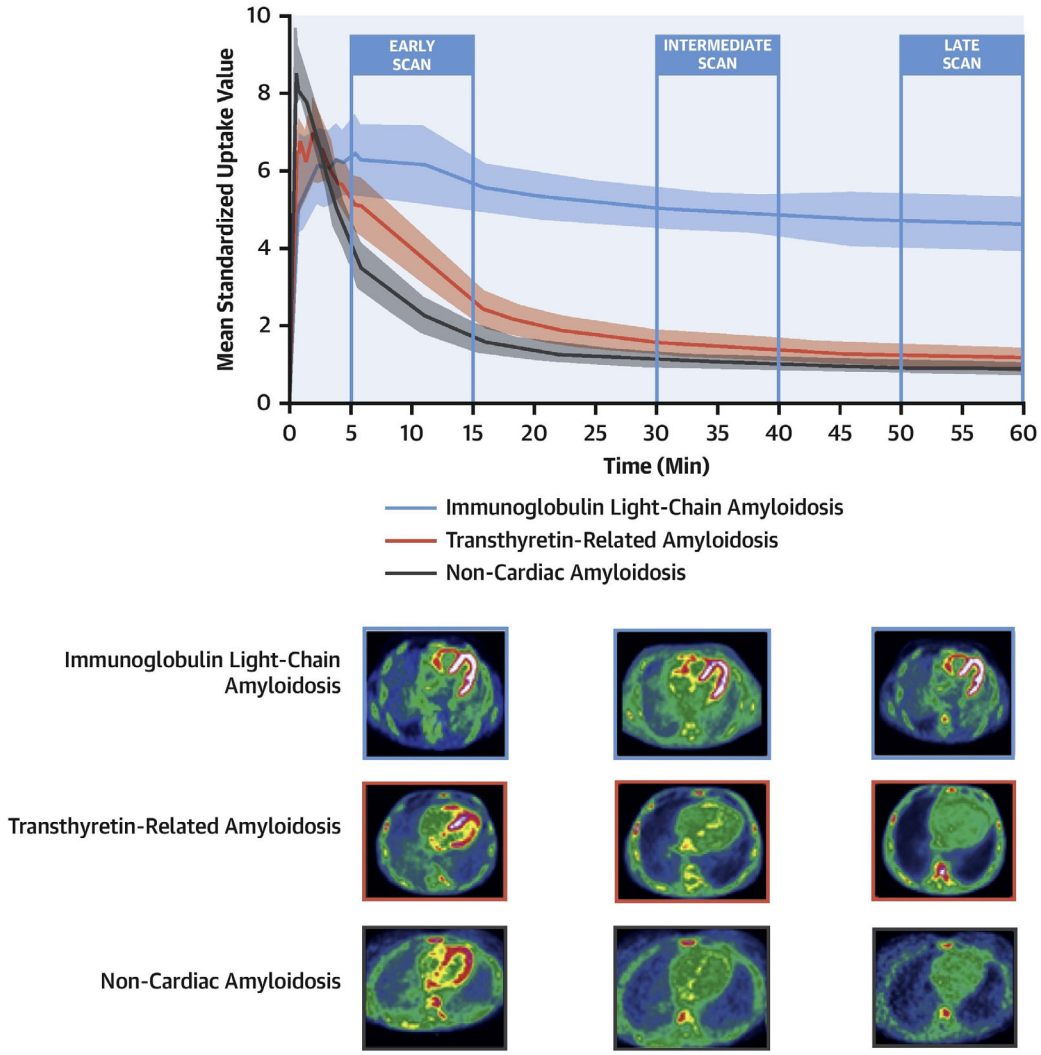


Figure 4 Cardiac ^{18}F-florbetaben uptake in patients with and without cardiac amyloidosis. *Upper panel*: ^{18}F-florbetaben cardiac positron emission tomography myocardial time–activity curves in patients with immunoglobulin light-chain amyloidosis, transthyretin-related amyloidosis, and non-cardiac amyloidosis. The 95% confidence interval is represented as a shaded area for each curve. *Lower panel*: early (5–15 min), intermediate (30–40 min), and late (50–60 min) ^{18}F-florbetaben cardiac positron emission tomography scans in patients with amyloid light-chain and transthyretin-related cardiac amyloidosis and in those with non-cardiac amyloidosis. SUV, standardized uptake value. Reprinted with permission from Genovesi *et al.*[72]

of storage diseases.[85] Low QRS voltage is frequent in CA but has low sensitivity; the relation of the total or peripheral QRS voltages to LV mass is more important.[86] A low ratio in the presence of a hypertrophic phenotype is consistent with CA, whereas it is rare in patients with sarcomeric disease.[80] A pseudo-infarction pattern (due to asymmetric hypertrophy or a myocardial scar) is particularly common in HCM and CA.[80,87] In patients with severe aortic stenosis, the discrepancy between the degree of hypertrophy and QRS voltages may also be informative,[88] while the classical apical sparing pattern may be concealed.[89] Myocardial ECV quantification can help identify CA, particularly ATTR-CA.[88,90]

The value of routine laboratory testing lies mostly in the assessment of organ dysfunction or in the detection of non-specific markers of disease severity such as natriuretic peptides. The possibility of metabolic disorders such as Danon or mitochondrial disease should be considered. Measurement of alpha galactosidase A can be considered in male patients with unexplained LV hypertrophy over the age of 30 years, as most cardiovascular signs of AFD develop from the third decade of life onwards.[91] In female patients with AFD, plasma and leucocyte enzyme levels are often within the normal range, and genetic testing may be more appropriate.[92] When CA is suspected, a monoclonal protein must be searched in the serum and urine.[21] It is important to remember that up to 5% of the general population of elderly people have monoclonal gammopathy of uncertain significance, which is not necessarily an abnormal condition.[93]

Imaging findings for risk stratification

Imaging findings may help predict future disease trajectories and patient outcomes. This topic has been extensively investigated in HCM and CA (*Table 2*).

Risk stratification in HCM cannot rely only on LVEF. Current ESC guidelines stratify the risk of SCD using a score based on qualitative and quantitative parameters obtained by clinical and echocardiographic data, and LGE as modulating factor in selected cases.[1] The echocardiographic findings used for risk stratification are maximal wall thickness ≥30 mm, maximum (rest/Valsalva) gradient of the LV outflow tract (>30 mmHg), and LA size.[1] Areas of myocardial LGE are present in up to 80% of patients.[37] Quantitative evaluation of LGE is mandatory, and a LGE threshold ≥15% of LV mass identifies patients at high risk of SCD, even in the absence of other major risk factors.[33,94,95] LGE presence has been listed among the criteria for patient selection in the recently updated HCM guidelines by the American Heart Association/American College of Cardiology.[33] Scar heterogeneity with islands of viable myocardium within the fibrotic tissue may be a better marker of poor prognosis than LGE presence or extent, being a substrate for malignant ventricular arrhythmias.[96]

Myocardial oedema may be detected in up to 40% of HCM patients using either T2-weighted imaging (i.e. conventional T2-STIR or T2-FAT-SAT)[97] or quantitative T2-mapping.[56] The most plausible mechanism of regional T2-signal hyperintensity in HCM is myocardial ischaemia due to supply–demand imbalance in the hypertrophic myocardium, but tissue remodelling is another possible cause. T2 imaging has been proposed as a marker of disease activity in HCM, and has been investigated as a marker of disease progression and prognosis. Indeed, myocardial oedema on T2 imaging has been associated with established markers of adverse remodelling and prognosis, including LGE, elevated troponin levels and non-sustained ventricular tachycardia.[97] Among patients with extensive LGE, those with hyperintense areas at T2-weighted sequences experienced more life-threatening ventricular arrhythmias than those without.[98] Higher T2-mapping values were associated with increased levels of troponin T and B-type natriuretic peptide in HCM, reflecting active myocardial injury and probably cardiac stiffness and diastolic dysfunction.[56] This mechanism may explain the progressive phenomenon of myocardial fibrosis over time in HCM, justifying a follow-up based also on CMR.[1,33,99] Diffusion tensor sequences, despite their complexity and limited availability, are able to visualize the microstructure of myocardial fibres and myocardial disarray,[98] potentially providing additional markers of arrhythmic risk in HCM. Single studies have reported that nuclear imaging techniques revealing myocardial ischaemia, heterogeneity of myocardial blood flow or innervation could help predict SCD.[100] Finally, apical aneurysms (particularly those ≥2 cm) predict a higher risk of malignant ventricular arrhythmias.[101]

In up to 10% of HCM patients, the disease process is characterized by faster rate of adverse remodelling and development of progressive dysfunction.[102] Two patterns of remodelling have been described: a progressive dilatation with spherical remodelling and a worsening diastolic dysfunction culminating in severe restriction.[102] Serial imaging investigations can follow disease progression, but the prediction of future ventricular remodelling at the time of diagnosis remains challenging.

In patients with AL-CA, GLS has emerged as a strong predictor of major adverse cardiac events in AL amyloidosis with preserved LVEF, independently of serum biomarkers.[103,104] Stroke volume index, right atrial area index, GLS and E/e' have been independently associated with mortality in patients with ATTR-CA.[105] The function of all cardiac chambers holds prognostic significance, as suggested by a study on 136 patients with CA (80% with AL-CA) reporting that strain data from all cardiac chambers

Table 2 Risk stratification in hypertrophic cardiomyopathy and cardiac amyloidosis

	Echocardiography	Cardiac magnetic resonance
Sarcomeric HCM	- Maximal wall thickness ≥30 mm, maximum (rest/Valsalva) gradient of the LV outflow tract (>30 mmHg), and LA size are part of the standardized recommendations on risk stratification of SCD (European vs. American guidelines). - Apical aneurysms predict a higher risk of malignant ventricular arrhythmias. - LS, LV mechanical dispersion and LA volume index as predictors of arrhythmic events.	• LGE ≥15% of LV mass identifies patients at high risk of SCD. • Myocardial oedema on T2-imaging is associated with higher rates of ventricular arrhythmias.
CA	- GLS is a strong predictor of major adverse cardiac events in AL-CA with preserved LVEF. - Stroke volume index, right atrial area index, GLS and E/e' have been independently associated with mortality in ATTR-CA. - Strain data from all the cardiac chambers are associated with all-cause mortality.	• A transmural LGE pattern is associated with a five-fold increased risk of events. • Higher ECV is associated with worse patient outcomes. • ECV changes over time could allow the assessment patients' response to treatment.

AL-CA, amyloid light-chain cardiac amyloidosis; ATTR-CA, transthyretin-related cardiac amyloidosis; CA, cardiac amyloidosis; ECV, extracellular volume; GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; LA, left atrial; LGE, late gadolinium enhancement; LS, longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

are associated with all-cause mortality.[106] As for CMR imaging, subendocardial diffuse or transmural LGE pattern signals extensive amyloid deposition and a more advanced disease; a transmural LGE pattern was associated with a five-fold increased risk of events.[6] Marked elevation of native T1-mapping and ECV values were associated with a poor prognosis.[6] ECV emerged as the parameter with the highest hazard ratio in predicting patient outcomes, and its changes over time could allow the assessment patients' response to treatment.[47,107,108] Ideally, CMR should be repeated every 6 months to track treatment response, and clinically significant changes in the cardiac amyloid burden should be considered when there is an absolute increase or decrease of 5% of ECV, based on previous studies on ECV repeatability.[7] The role of T2-mapping, adenosine stress perfusion and CMR feature tracking imaging have also been shown to provide additional information in patients with CA, but further studies are needed to validate these findings.[19,109–112]

In both CA and AFD, LVEF is preserved until late disease stages. Therefore, the assessment of LV diastolic function and GLS is crucial in the evaluation of symptoms, disease staging and risk stratification.[113] RV hypertrophy and systolic dysfunction have been associated with a worse outcome in patients with HCM,[114] CA,[13,14] and AFD.[15]

Imaging for therapy decision-making

Echocardiography has an established role in the assessment of LV outflow tract obstruction in patients with HCM. Symptomatic patients with significant resting or provoked gradient (≥50 mmHg) are usually treated with non-vasodilating beta-blockers and disopyramide. Non-dihydropyridine calcium channel blockers such as verapamil or diltiazem are alternatives to beta-blockers. Surgical myectomy and alcohol septal ablation are two viable invasive therapies for symptomatic patients despite optimized medical therapy. The feasibility for alcohol septal ablation is generally assessed through myocardial contrast echocardiography with selective injection of contrast agent into a septal perforator branch of the left anterior descending artery.[115] Echocardiography can disclose septal thinning and LV outflow tract gradient decrease after septal reduction.[116] In HCM patients, the evidence of structural abnormalities such as massive LV hypertrophy (>30 mm), LV apical aneurysm or LV systolic dysfunction is a risk factor for SCD, and may help to select patients for implantable cardioverter-defibrillator implantation.[33] The extent of LGE is also associated with an increased risk of arrhythmias, and of progression toward end-stage HCM with systolic dysfunction.[94] In the

Table 3 Imaging in primary hypertrophic disorders: possible perspectives for future research

	Diagnosis	Risk stratification	Therapy decision-making
Sarcomeric HCM	• Creation of reliable algorithms for diagnosis based on AI, possibly integrating imaging findings with other clinical and laboratory data • Technological enhancement to find the obstructive forms in CMR using 4D flow for evaluation of cardiovascular haemodynamics • Virtual native enhancement from 'cine' and native T1-mapping images	• Standardized recommendations on risk stratification of SCD (European vs. American guidelines) • Role of novel imaging modalities for further risk stratification in HCM: T2-mapping, tensor imaging, etc. • LS, LV mechanical dispersion and LA volume index as predictors of arrhythmic events	• Optimal ways to screen for early disease in gene mutation carriers and timing of treatment start • Serial imaging to assess treatment response
CA	• Standardization of diagnostic algorithms by different societies • PET imaging for the non-invasive diagnosis of AL-CA • Identification of imaging markers useful to screen patients being tested for other reasons (e.g. ECV expansion in patients undergoing cardiac CT before TAVR) • Creation of reliable algorithms for diagnosis based on AI	• Creation of reliable algorithms for risk prediction based on AI	• Optimal ways to screen for early disease in gene mutation carriers and timing of treatment start • Serial imaging to assess treatment response
AFD	• Identification of imaging markers useful to screen patients being tested for other reasons • Creation of reliable algorithms for diagnosis based on AI	• Creation of reliable algorithms for risk prediction based on AI	• Serial imaging to assess treatment response

4D, four-dimensional; AFD, Anderson–Fabry disease; AI, artificial intelligence; AL-CA, amyloid light-chain cardiac amyloidosis; CA, cardiac amyloidosis; CMR, cardiovascular magnetic resonance; CT, computed tomography; ECV, extracellular volume; HCM, hypertrophic cardiomyopathy; LA, left atrial; LS, longitudinal strain; LV, left ventricle; PET, positron emission tomography; SCD, sudden cardiac death; TAVR, transcatheter aortic valve replacement.

EXPLORER-HCM trial, mavacamten was associated with a greater reduction in LV outflow tract gradient and with improved symptoms and exercise capacity compared to placebo.[117] A positive effect in terms of reduction of LV mass has also been reported.[118]

Enzyme replacement therapy (ERT) has dramatically changed the natural history of AFD. Data suggest that mild LV hypertrophy can partially regress after treatment initiation.[119] Conversely, response to therapy can be less pronounced at later disease stages. The presence of LGE is associated with increased LV mass and is linked to the failure of attaining significant regression of hypertrophy on ERT.[120] One-year treatment with ERT attenuates T1 lowering, and is associated with small reductions in maximum wall thickness and stabilization of LV mass index.[121]

Assessment of LV function in AL-CA can be useful to identify high-risk subsets and to select the most appropriate treatment regimen.[122] A recent study on 915 patients with newly diagnosed AL-amyloidosis has shown that improvement in longitudinal strain is present in patients achieving a complete haematological response.[123] A complete or very good response is also associated with a reduction in ECV.[107] The role of imaging for treatment selection and monitoring in ATTR is less well defined. ECV has been demonstrated to stabilize with tafamidis treatment[124] and to decrease after initiation of patisiran, a transthyretin-specific small interfering RNA, in a small group of patients with hereditary ATTR-CM, thus possibly reflecting cardiac amyloid regression.[108] In this last study, patients also displayed a reduction in cardiac uptake by bone scintigraphy. Quantitative assessment of bone tracer uptake may also prove useful to assess the response to tafamidis, a transthyretin tetramer stabilizer.[125]

Conclusions and future perspectives

Several imaging findings have an established role in the differentiation between the physiological response to exercise (athlete's heart), LV hypertrophy secondary to pathological stimuli such as pressure overload, or primary cardiac disorders, and in the identification of the specific disease condition (*Graphical Abstract*). Recent advances in echocardiography, CMR and nuclear medicine as well as their increased accessibility allow a precise assessment of ventricular volumes, thickness, systo/diastolic function and non-invasive tissue characterization. In particular, CMR and nuclear medicine, thanks to their ability to provide crucial information on tissue characterization, are usually able to replace (or guide) invasive endomyocardial biopsy. On the other hand, advance myocardial imaging should always be interpreted and integrated with clinical, electrocardiographic, genetic and laboratory information, and endomyocardial biopsy is still needed for specific infiltrative/storage diseases. Still, there are several grey zones in the optimal application of imaging findings, many potential applications of imaging techniques have limited supporting evidence or may be envisaged based on theoretical considerations, in the absence of dedicated studies. *Table 3* summarizes the main perspectives for future research on three forms of primary hypertrophy (sarcomeric HCM, cardiac amyloidosis, AFD). Novel technical improvements (including new CMR sequences and new nuclear tracers) are being developed, together with an increasing use of artificial intelligence tools to help the clinician to interpret and integrate such a growing amount of clinical and imaging information. In conclusion, an integrated clinical and imaging approach seems to be essential to guide diagnosis, to distinguish the different hypertrophic phenotypes by unravelling specific underlying aetiologies, as well as to predict patient prognosis and to ensure a tailored therapeutic management.

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