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Cardiology and Fabry disease

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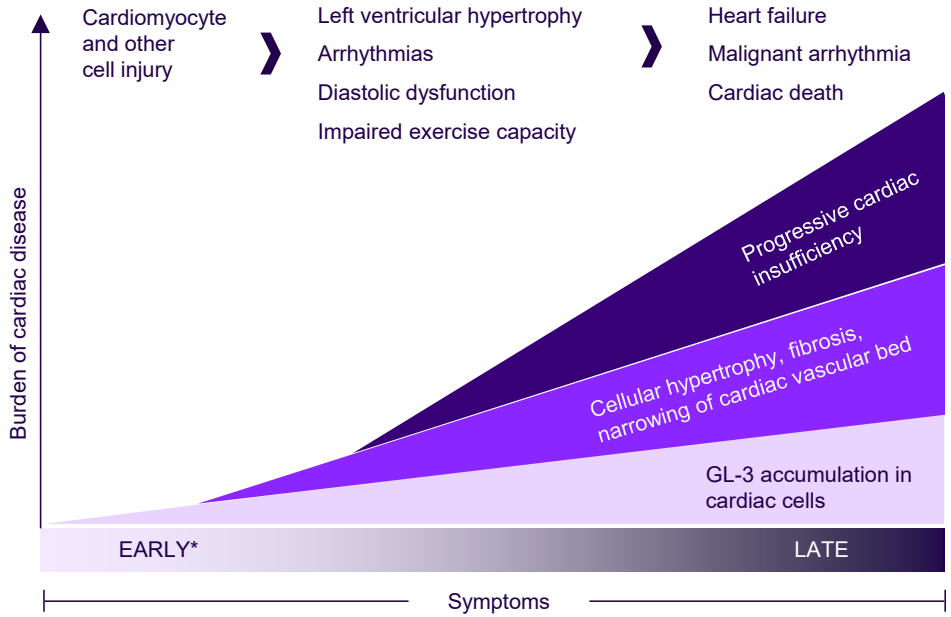
If untreated, cardiac involvement in Fabry disease is life-limiting and may be fatal, however it can be treated[1]

Fabry disease is a multi-systemic, life-limiting X-linked lysosomal storage disorder that results from deficient α-Gal A activity, which causes progressive accumulation of GL-3 in various cells, including cardiac cell types and tissues. Early diagnosis and treatment are essential to reduce disease progression and improve patient outcomes[1–5]

- Damage to the heart **starts early** in the disease course and may progress before significant symptoms occur[6]
- Accumulation of GL-3 in the myocardium usually manifests as **left ventricular hypertrophy presenting similarly to hypertrophic cardiomyopathy[6]**



*Accumulation of GL-3 starts in utero[12]
Adapted from 6–11

α-Gal A, α-galactosidase A; GL-3, globotriaosylceramide

1. Elliott PM, et al. Eur Heart J. 2014;35:2733–79; 2. Desnick RJ, et al. Ann Intern Med. 2003;138(4):338–46; 3. Laney DA, et al. J Genet Couns. 2008;17(1):79–83; 4. Germain DP. Orphanet J Rare Dis. 2010;5:30; 5. Wanner C, et al. Clin J Am Soc Nephrol. 2010;5(12):2220–8; 6. Tsutsumi O, et al. Asia Oceania J Obstet Gynaecol. 1985;11(1):39–45; 7. Pieroni M, et al. J Am Coll Cardiol. 2021;77:922–36; 8. Schiffmann R et al. Nephrol Dial Transplant. 2009;24(7): 2102–11; 9. Patel MR et al. J Am Coll Cardiol. 2011;57(9):1093–9; 10. Linhart A, Elliott PM. Heart. 2007;93(4):528–35; 11. Kampmann C et al. Int J Cardiol. 2008;130(3):367–73; 12. Weidemann F et al. Orphanet J Rare Dis. 2013;8:116; 13. Desnick RJ, Ioannou YA, Eng CM. a-Galactosidase A deficiency: Fabry disease. In: Valle D, Beaudet AL, Vogelstein B, et al, eds. OMMBID—The Online Metabolic and Molecular Bases of Inherited Diseases. New York, NY: McGraw-Hill; 2014. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546984#1181465996 [Accessed 19 February 2024].

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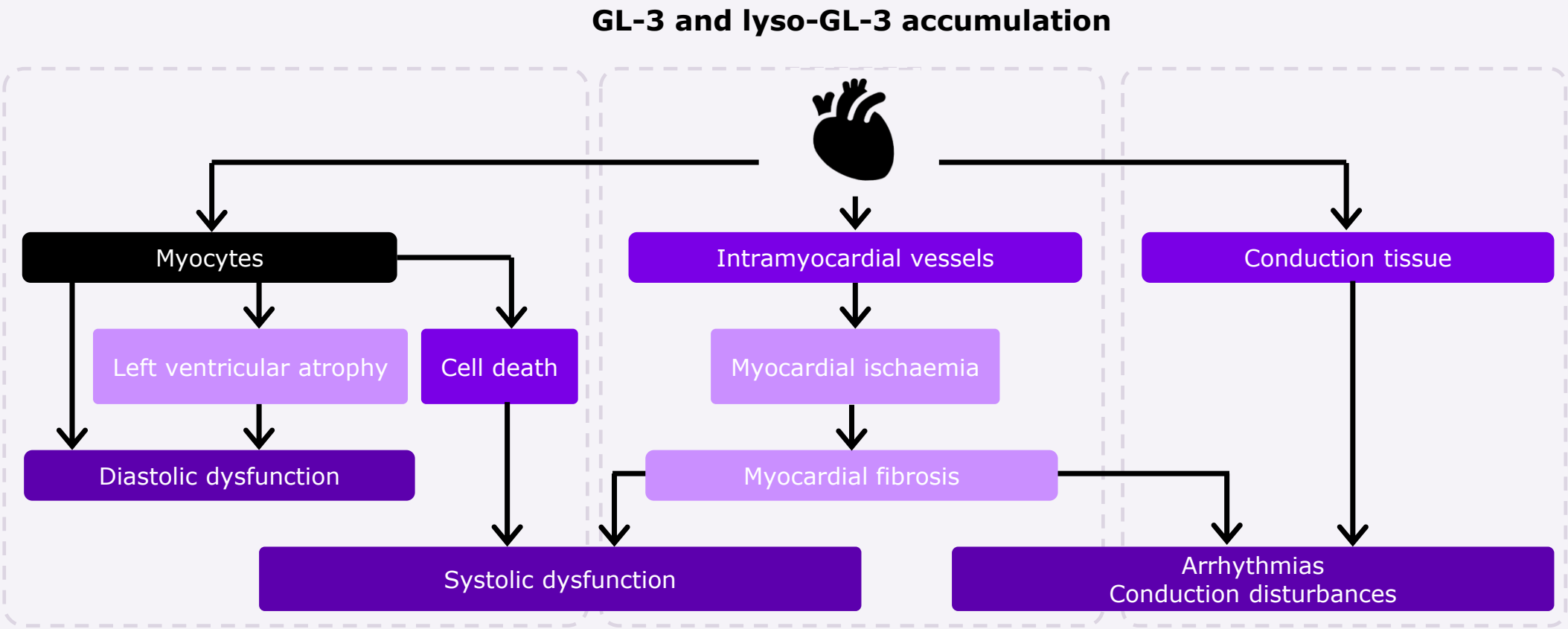
GL-3 accumulation leads to cardiac disturbances in Fabry disease



GL-3, globotriaosylceramide; LVH, left ventricular hypertrophy; lyso-GL-3, globotriaosylsphingosine

Pieroni M, et al. J Am Coll Cardiol. 2021;77:922–36

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It is essential to diagnose and treat early in order to slow progression of the disease and to prevent major cardiac complications

Click here for extra-cardiac red flags

		Cardiac red flags
Diagnostic Tool	History	Family history of LVH, particularly no evidence of male-to-male transmission
	Electrocardiography	Short PQ interval
		Bradycardia
		Chronotropic incompetence
		Atrioventricular blocks
	2D-echocardiography	LVH with normal systolic function
		Reduced global longitudinal strain
		Mild-to-moderate aortic root dilation
		Mitral and aortic valve thickening with mild-to-moderate regurgitation
		Hypertrophy of papillary muscles
	Cardiac Magnetic Resonance	Mid-layer posterolateral late gadolinium enhancement
		Low native T1

LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; TIA, transient ischaemic attack

Pieroni M, et al. J Am Coll Cardiol. 2021;77:922–36; Desnick RJ, Ioannou YA, Eng CM. a-Galactosidase A deficiency: Fabry disease. In: Valle D, Beaudet AL, Vogelstein B, et al, eds. OMMBID—The Online Metabolic and Molecular Bases of Inherited Diseases. New York, NY: McGraw-Hill; 2014. https://ommbid.mhmedical.com/content.aspx?sectionid=225546984&bookid=2709. [Accessed 19 February 2024].

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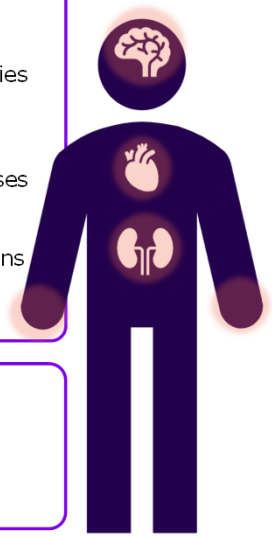
Click here for extra-cardi flags

CONNECT SYMPTOMS ACROSS MULTIPLE ORGAN SYSTEMS FOR A CLEAR DIAGNOSIS

In addition to cardiac manifestations, Fabry disease presents in multiple organ systems[2]

Signs and symptoms that present at any age:

Arrhythmias
Corneal and lenticular opacities
Heat and cold/exercise intolerance
Peripheral neuropathy of extremities/episodic pain crises
Hearing loss, tinnitus
Hypohidrosis
Gastrointestinal manifestations
Angiokeratomas



Clinical events

Progressive renal disease
Progressive cardiac disease
Early ischemic stroke

Extra-cardiac red flags[1]		
Family history renal failure and/or stroke	Any time	Presenting decades of age
Neuropathic pain	1–2	
Gastrointestinal symptoms	1–2	
Angiokeratomas	1–2	
Cornea verticillata	1–2	
Hypohidrosis, heat/cold, and exercise intolerance	1–2	
Albuminuria	1–2	
Juvenile and/or cryptogenic TIA/stroke	3–4	
Hearing loss (either progressive or sudden)	3–4	
Dolichoectasia of the basilar artery, chronic white matter hyperintensities at brain MRI	3–4	
Proteinuria	3–4	
Renal failure	3–4	
Lymphedema	3–4	

Adapted from: Desnick RJ, Ioannou YA, Eng CM. a-Galactosidase A deficiency: Fabry disease. In: Valle D, Beaudet AL, Vogelstein B, et al, eds. OMMBID—The Online Metabolic and Molecular Bases of Inherited Diseases. New York, NY: McGraw-Hill; 2014. https://ommbid.mhmedical.com/content.aspx?sectionid=225546984&bookid=2709. Accessed August 16, 2022.

LVH
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Molecular Bases of Inhe

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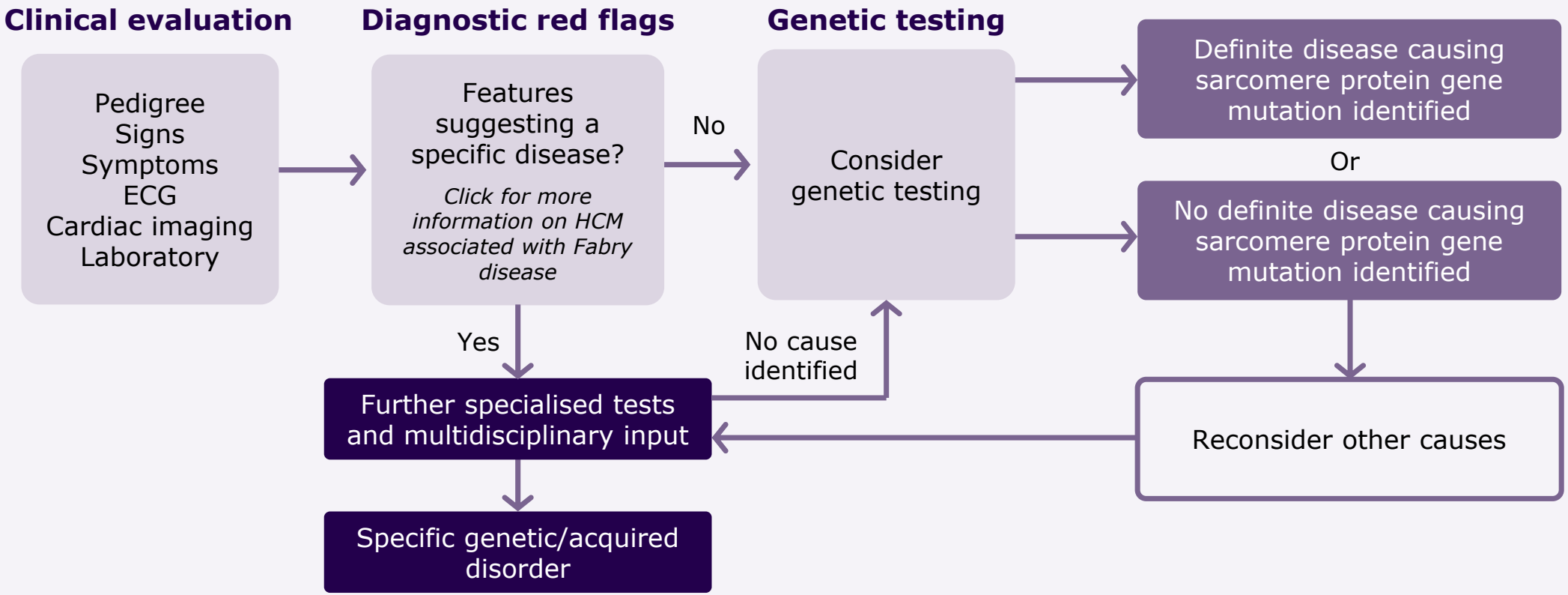
ESC guidelines recommend testing for Fabry disease in patients with HCM[1]



ECG, electrocardiogram; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle

1. Elliott PM, et al. Eur Heart J 2014:35(39):2733-2779; 2. van der Tol L, et al. J Med Genet. 2014;51(1):1–9; 3. Nakao S. N Engl J Med. 1995;333(5):288–93; 4. Elliot PM, et al. Heart. 2011;97(23):1957–60

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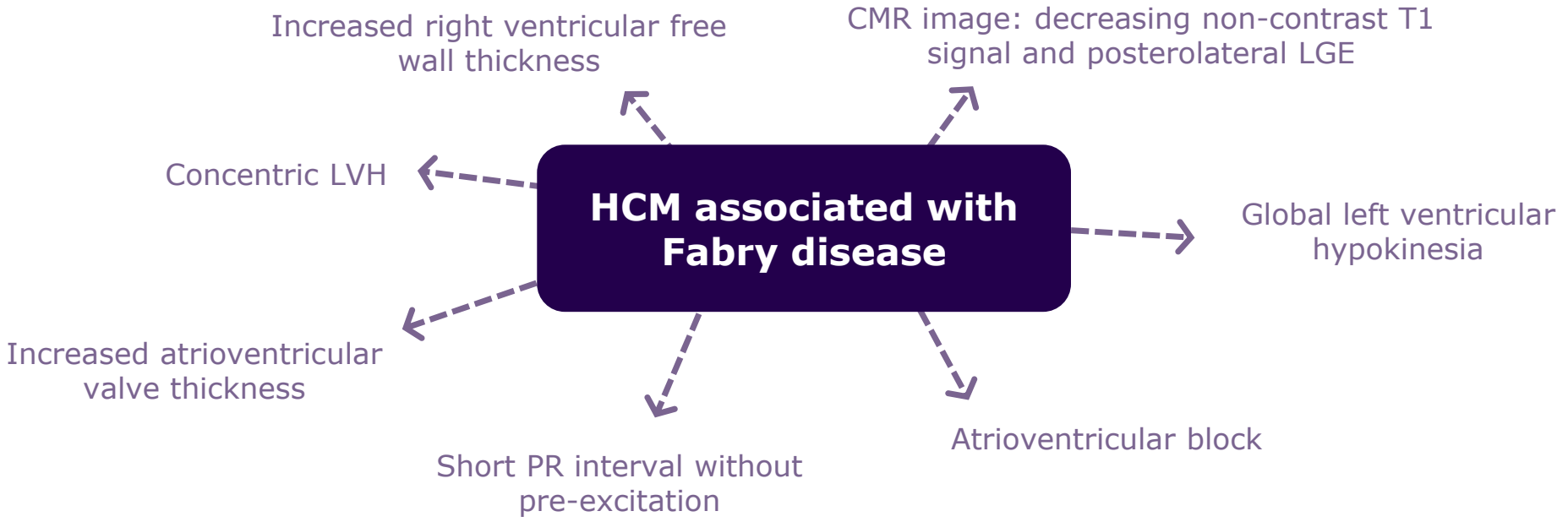
ESC guidelines recommend testing for Fabry disease in patients with HCM1

Fabry disease accounts for **0.5–3% of idiopathic HCM** and is the most common metabolic disease associated with LVH, with a prevalence of around **0.5–1% in patients older than 35–40 years**[1–4]



CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; LGE, Late gadolinium enhancement; LVH, left ventricular hypertrophy

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1. E
4. Elliot PM, et al. Heart. 2011;97(23):1957–60

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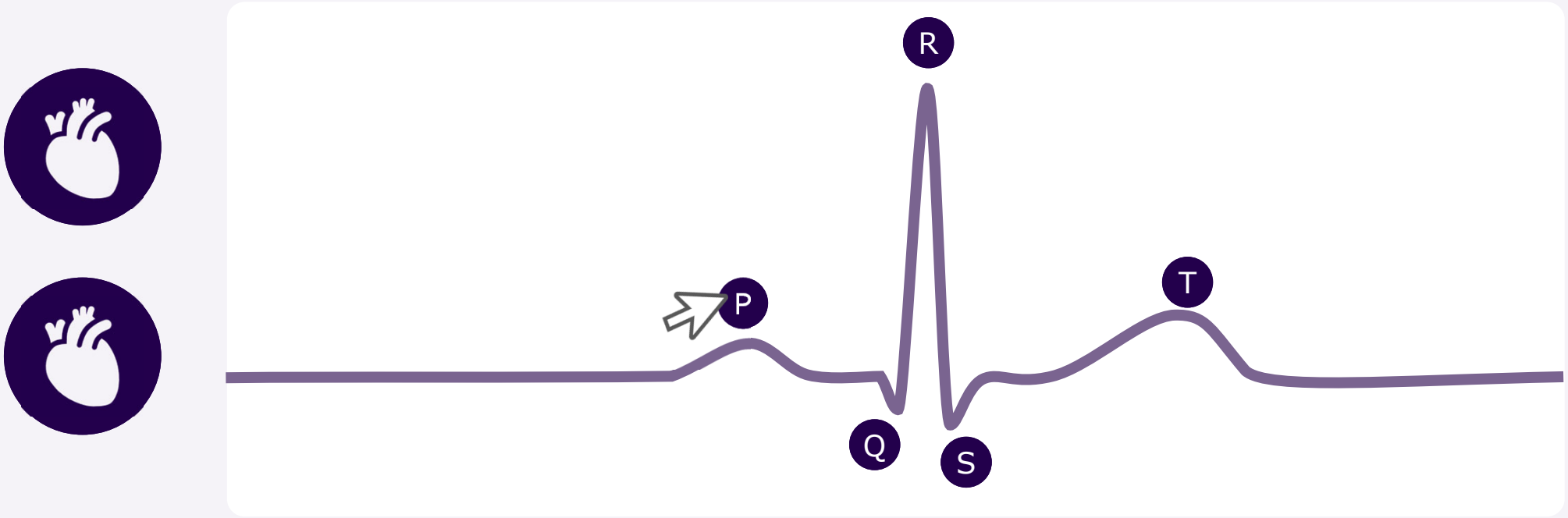
Recognition of pre-hypertrophic cardiac involvement in Fabry disease using automated ECGs

An analysis comparing ECGs from 1496 healthy individuals to 142 patients with Fabry disease (without LVH) **identified nine ECG parameters that were significantly different** between the groups and could be useful for the purpose of screening the very early stages of cardiomyopathy in Fabry disease. *Click the hotspots below to see the parameters:*



ECG, electrocardiogram; LVH, left ventricular hypertrophy

Namdar M, *et al. Int J Cardiol.* 2021;338:121–6

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AI indicators of cardiomyopathy in Fabry disease using ECGs

Ar
pa
ea

P wave morphology in the precordial lead V3
(categorical classification: 1=single upright,−1=single inverted,2=biphasic, leading positive, −2=biphasic, leading negative)

Amplitude of the positive component of the P wave in lead DI
(P+ Amp I, μV)

P wave area in the precordial lead V1
(P Area V1, μV-milliseconds [μV. ms], defined as the algebraic sum of both the positive and negative areas or either alone if the P wave is not biphasic)

LV
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AI indicators of cardiomyopathy in Fabry disease using ECGs

Ar
pa
ea

QT dispersion (ms)
defined as the difference between the shortest and longest QT interval in the 12 lead ECG

4/8 QRS
(time-normalized QRS spatial velocity at 4/8 of the total QRS duration, μV/ms)

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AI indicators of cardiomyopathy in Fabry disease using ECGs

Ar
pa
ea

Amplitude of the ST segment in the precordial lead V2
(ST60 Amp V2, µV)

Duration of the S wave in the precordial lead V1
(S Dur V1; ms)

LV
Namdar M, *et al. Int J Cardiol.* 2021;338:121–6

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AI indicators of cardiomyopathy in Fabry disease using ECGs

An
pa
ea

Amplitude of the ST segment in the precordial lead V2
(ST60 Amp V2, µV)

QT dispersion (ms)
defined as the difference between the shortest and longest QT interval in the 12 lead ECG

LV
Namdar M, *et al. Int J Cardiol.* 2021;338:121–6

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AI indicators of cardiomyopathy in Fabry disease using ECGs

An
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Heart rate
(beats/min)

LV
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AI indicators of cardiomyopathy in Fabry disease using ECGs

Ar
pa
ea

Left ventricular hypertrophy (LVH) Score
(derived from an age and sex based modified Romhilt-Estes score, dimensionless)

LV
Namdar M, *et al. Int J Cardiol.* 2021;338:121–6

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