SANOFI GENZYME

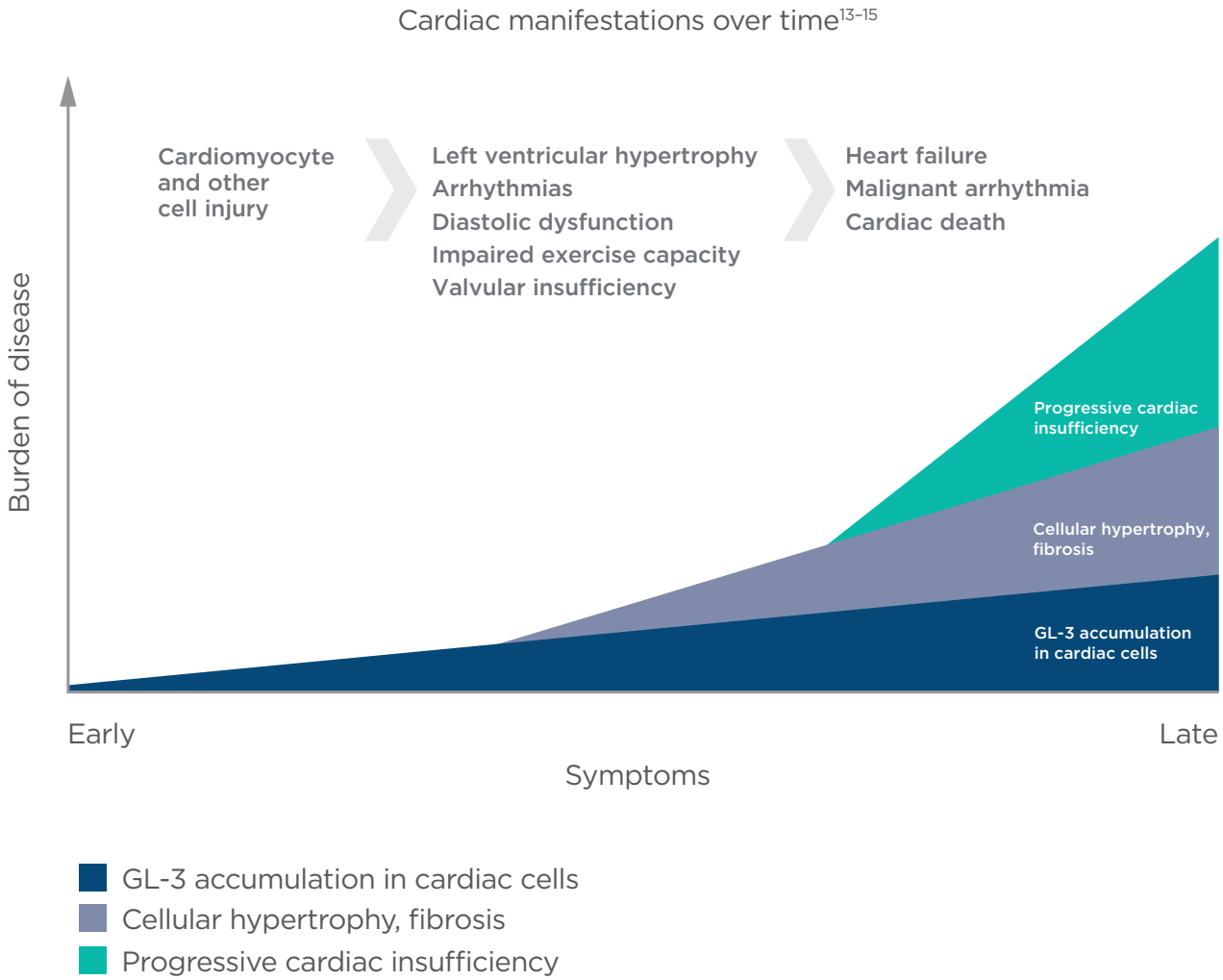
ARE YOU LOOKING FOR FABRY DISEASE?

YOU AS A CARDIOLOGIST
PLAY AN IMPORTANT ROLE in identifying patients with this progressive, often life-altering genetic disease.[1-6]

THE HALLMARK OF FABRY DISEASE IS GL-3 ACCUMULATION[7]

- Fabry disease is caused by mutations in the *galactosidase alpha* (*GLA*) gene that cause deficiency of the enzyme α-galactosidase A (α-GAL A)[8]
- This results in continuous, progressive cellular accumulation of lysosomal globotriaosylceramide (GL-3) and its deacetylated form (Lyso-GL3) throughout the body[8]
- GL-3 buildup starts in utero and continues throughout life[7,9–11]

Cardiac damage as a result of GL-3 accumulation often precedes laboratory abnormalities and clinical symptom onset[5,12]



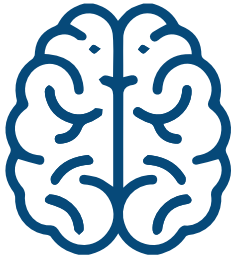
Adapted from Yousef Z, et al., Weidemann F, et al., and Linhart A and Elliott PM.

THE PREVALENCE OF FABRY DISEASE

Based on prevalence estimates in Canada (1 in 40,000 to 60,000 people), there should be >500 patients diagnosed with Fabry disease[16]

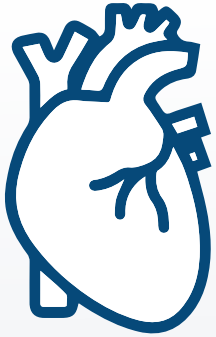
Clinical manifestations of Fabry disease include stroke, cardiomyopathy (LVH and/or HCM) and renal insufficiency[3]

The prevalence of Fabry disease in patients who present with these manifestations is:[17]



~0.13%

in patients with stroke



~0.93%

in patients with LVH or HCM

~0.19%

in patients with ESRD

A "cardiac variant" of Fabry disease may include patients who present with LVH and conduction disease but without the classic extracardiac symptoms of Fabry disease[15]

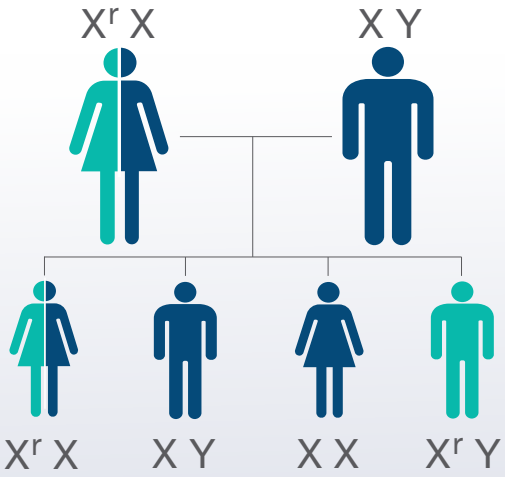
ESRD=end-stage renal disease; HCM=hypertrophic cardiomyopathy; LVH=left ventricular hypertrophy.

CARDIOLOGISTS CAN PLAY A CRITICAL ROLE IN THE EARLY DETECTION OF FABRY DISEASE

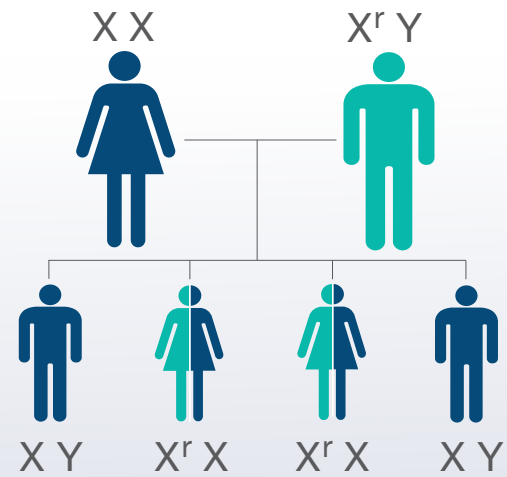
Fabry disease: Progressive. Often life-altering.[1–5]

- A multisystemic disease that impacts essential organs, such as the kidneys, heart and brain[18,19]
- An X-linked disorder that affects men, women and children[1,2]

Inheritance is X-linked[2]



Affected mothers have a 50% risk of passing along the defective gene (X^r) to their children, regardless of gender.



Affected fathers pass along the defective gene (X^r) to all their daughters. There is no male-to-male transmission.

Affected (X^r) chromosome with Fabry disease
Not affected (X) chromosome

Adapted from Germain DP (2010).

Random X chromosome inactivation in Fabry disease means females with the defective gene are affected to varying degrees

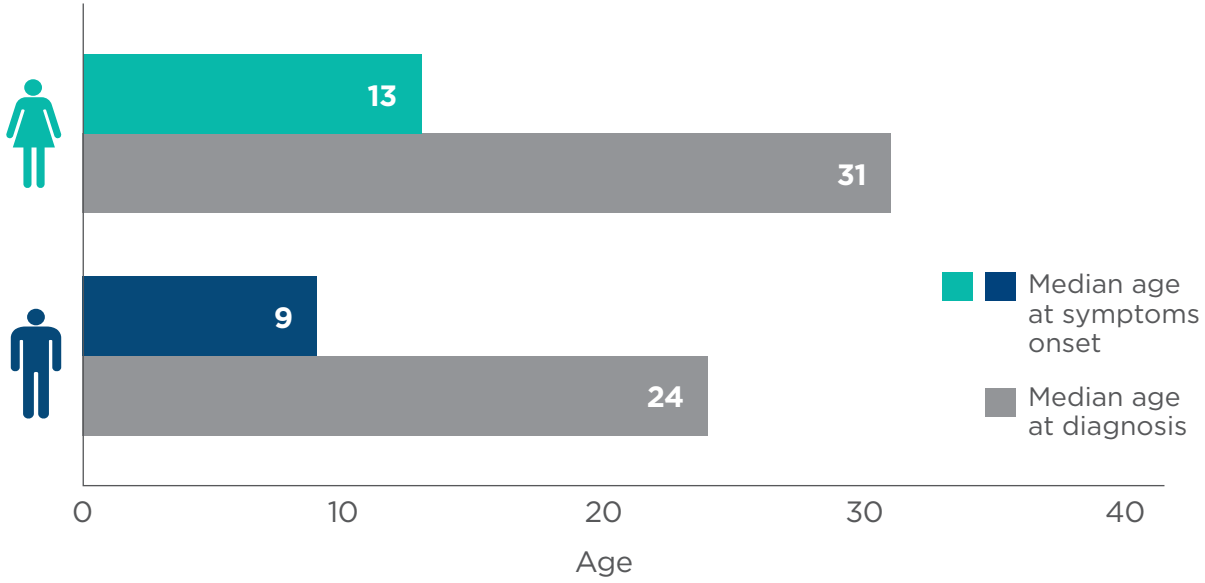
For every index patient diagnosed, an average of 5 additional affected family members may be identified[20]

THE IMPACT OF FABRY DISEASE ON YOUR PATIENT

Diagnostic delays are common due to the heterogeneous nature of the disease and the fact that many symptoms are nonspecific[21,22]

Median age of onset was 13 years for females and 9 years for males in an analysis of Fabry Registry patients

- From symptoms onset to a diagnosis of Fabry disease, there was a delay of at least 15 years in both males and females



Fabry disease can have a serious impact on essential organs, including the heart[16,17]

Patients with Fabry disease are at high risk of experiencing heart failure and myocardial infarction at a relatively young age[23]

Cardiac disease is a major cause of morbidity and mortality in patients with Fabry disease:[24]

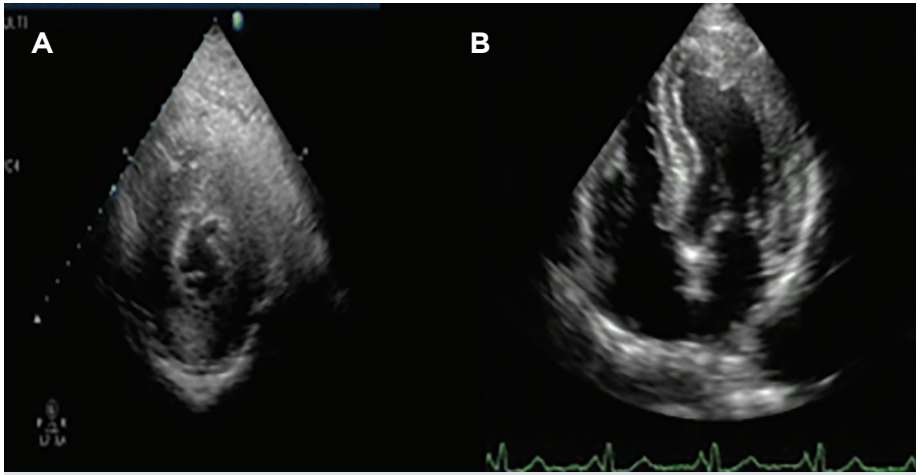
49% of males and 35% of females with Fabry disease were found to have had a cardiac event (myocardial infarction, cardiac procedure, angina, cardiac failure, arrhythmia) **by an average of 36 and 44 years,** respectively—events may appear as early as the teen years in males.[24]

Undiagnosed or unmanaged Fabry disease reduces life expectancy by 15 years in women and 20 years in men[21,22]

CARDIOLOGISTS CAN IDENTIFY FABRY DISEASE BEFORE SERIOUS COMPLICATIONS OCCUR

Progressive accumulation of GL-3 in the cardiomyocytes, endothelial cells and other cells of the heart contribute to the cardiac symptoms of Fabry disease[15]

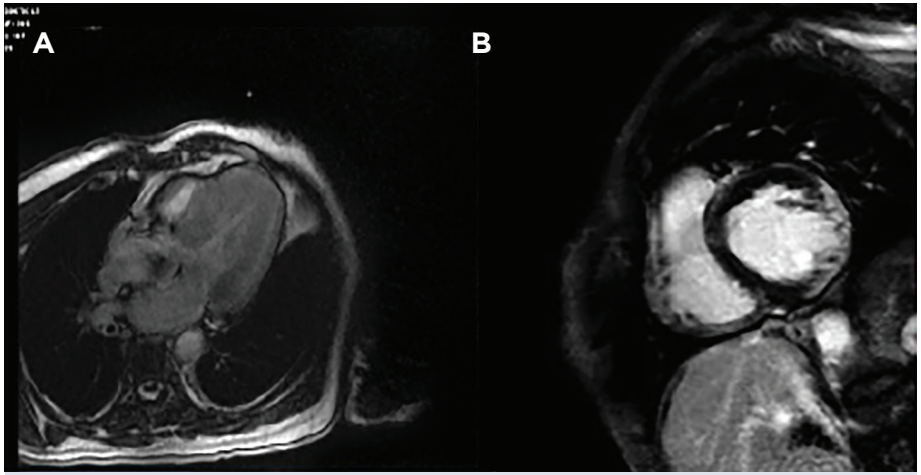
Cardiac imaging may include:



Concentric ventricular hypertrophy on echocardiography

Echocardiogram showing ventricular hypertrophy via the left chamber (A) and 4-chamber apical (B)

Adapted from Serra W and Marziliano N.[25]



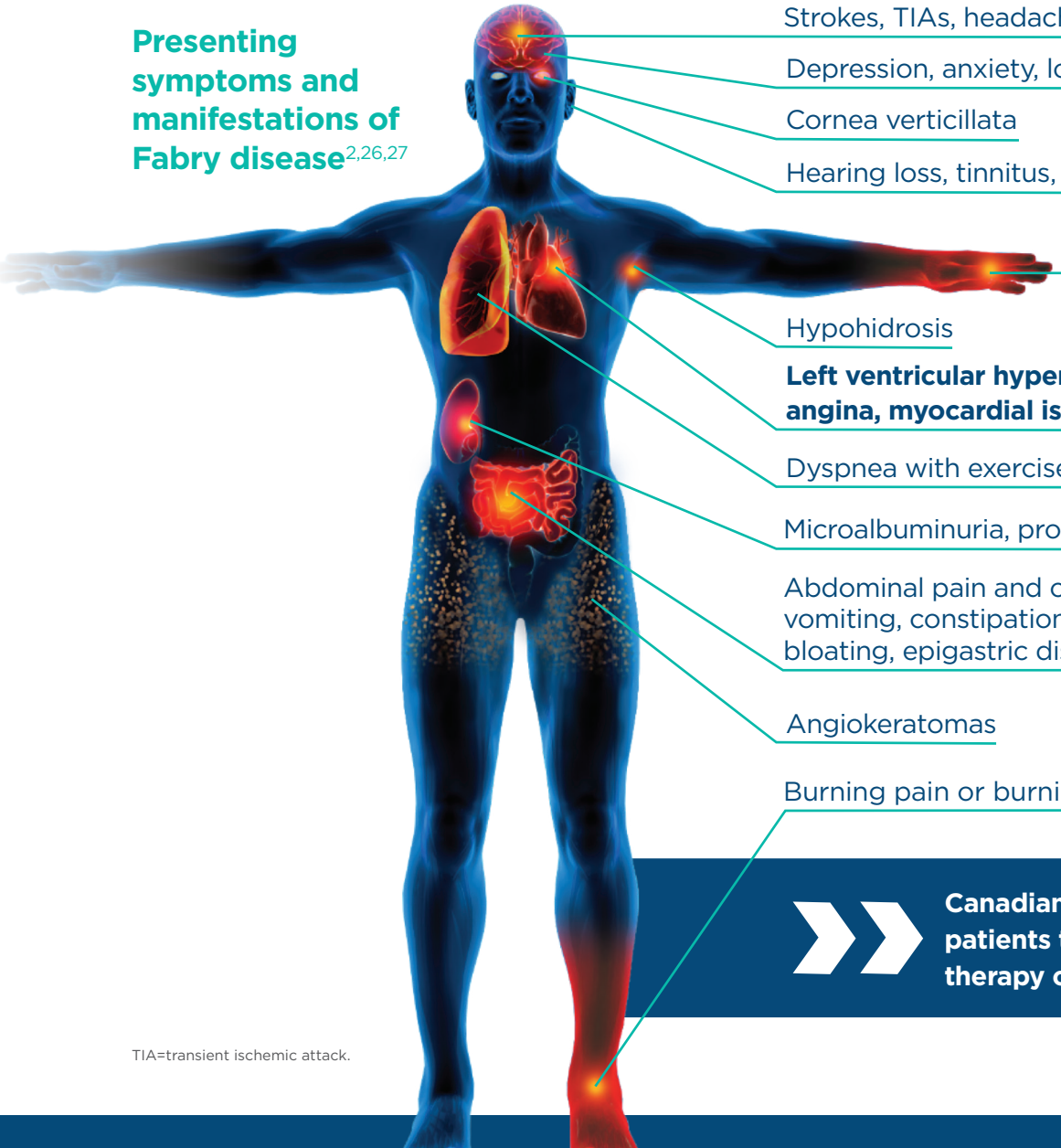
Hypertrophic cardiomyopathy on cardiac magnetic resonance

Cardiac magnetic resonance (T1) showing hypertrophic cardiomyopathy with hyper-enhancement relief at the left ventricular wall

Adapted from Serra W and Marziliano N.[25]

DIAGNOSTIC DELAYS ARE COMMON DUE TO THE HETEROGENEOUS NATURE OF THE DISEASE AND THE FACT THAT MANY SYMPTOMS ARE NONSPECIFIC[2,21]

Presenting symptoms and manifestations of Fabry disease[2,26,27]



- Strokes, TIAs, headaches
- Depression, anxiety, low mood, sleep disturbances, fatigue
- Cornea verticillata
- Hearing loss, tinnitus, vertigo
- Burning pain or burning and tingling paresthesia in the limbs, heat intolerance
- Hypohidrosis
- **Left ventricular hypertrophy, arrhythmias, angina, myocardial ischemia and infarction**
- Dyspnea with exercise, chronic cough, wheezing
- Microalbuminuria, proteinuria, renal lesions, renal failure
- Abdominal pain and cramping, diarrhea, nausea, vomiting, constipation and early satiety after meals, bloating, epigastric discomfort
- Angiokeratomas
- Burning pain or burning and tingling paresthesia in the limbs, heat intolerance

Canadian guidelines recommend regular follow-up of diagnosed patients to assess organ involvement, so that disease-specific therapy can begin at an early phase in the disease, if needed[28]

TIA=transient ischemic attack.

RULE OUT FABRY DISEASE IN YOUR PATIENTS WITH CARDIOMYOPATHIES

Cardiovascular imaging provides key insights when diagnosing heart diseases[29]

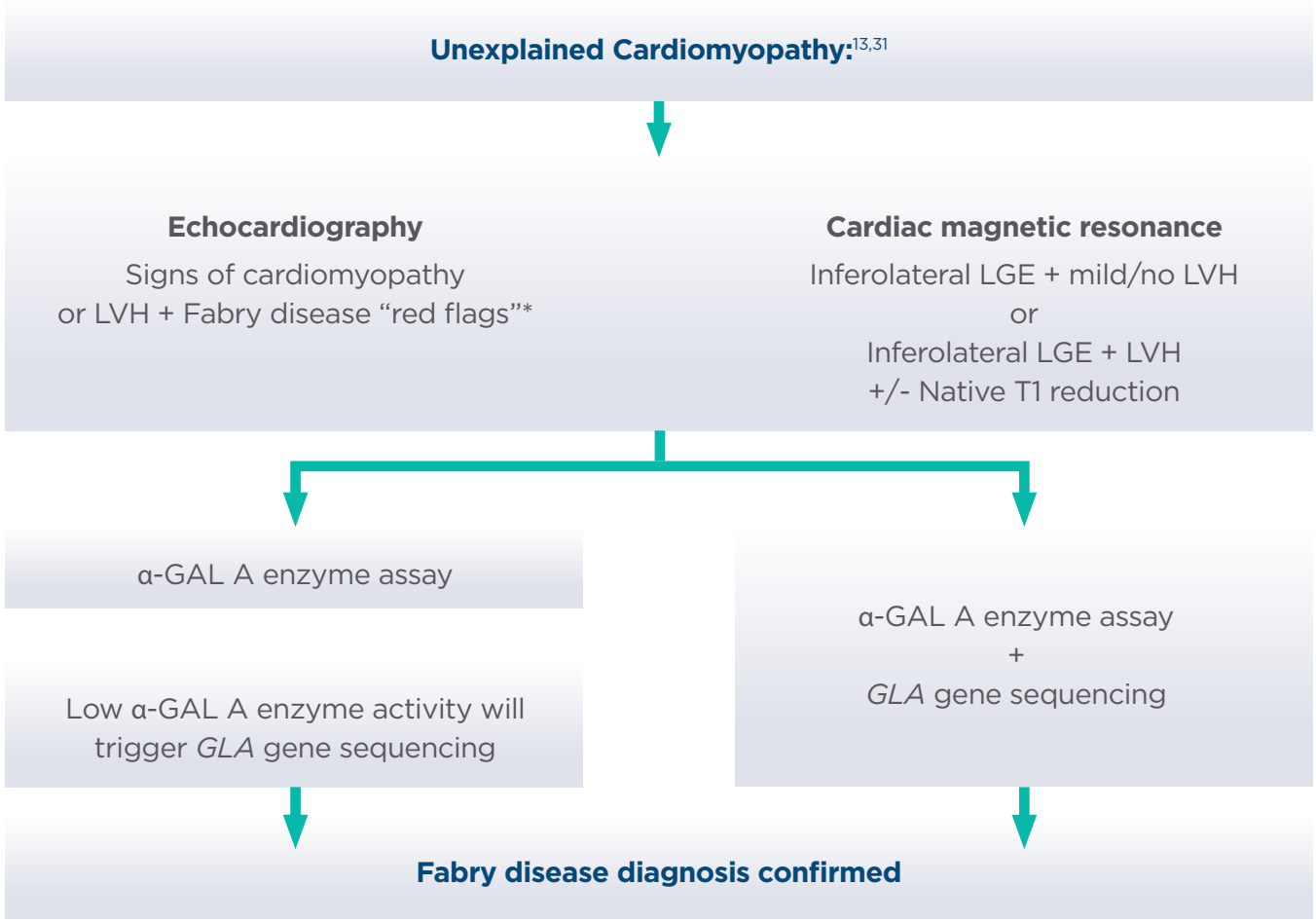
Echocardiography and CMR criteria that identify the different forms of hypertrophic cardiomyopathies[29]

	HCM	Amyloidosis	Fabry Disease	Athlete's Heart
Hypertrophic pattern	• Asymmetric • Symmetric • Midventricular • Apical	• Symmetric	• Symmetric	• Symmetric
Increased LVM	+++	+++	+++	+
LVOT obstruction	Frequent	Very rare	Rare	Absent
LGE	• Focal • Intramyocardial junction	• Subendocardial • Frosted glass • Valves • Atria • Heterogeneous pattern	• Inconstant • Intramyocardial • Inferolateral wall	• Rare
Native T1 mapping	Increased	Greatly increased	Reduced	Normal
Myocardial annulment at LGE	Annulled	Not annulled	Annulled	Annulled
ΔT1 (myocardium/blood) in LGE	High	Low	High	High
Other characteristics	• SAM • Accessory papillary muscles • Apical aneurysms	• IAS hypertrophy • RV hypertrophy • Valves leaflet thickening • Pericardial effusion	• Papillary muscles[30]	• Diastolic wall thickness to volume ration <0.15 • Normal LVM after deconditioning

Adapted from Savino K, et al.[29]

ΔT1=changes in T1; AS=atrial septum; HCM=hypertrophic cardiomyopathy; CMR=cardiac magnetic resonance; IAS=interatrial septum; LGE=late gadolinium enhancement; LVM=left ventricular mass; LVOT=left ventricular outflow tract obstruction; RV=right ventricle; SAM=systolic anterior movement.

A DIAGNOSTIC ALGORITHM FOR PATIENTS WITH UNEXPLAINED CARDIOMYOPATHY



Adapted from Yousef Z, et al. and Miltaru S, et al.[13,31]

CS=circumferential strain; GLS=global longitudinal strain; eGFR=estimated glomerular filtration rate; LGE=late gadolinium enhancement; LS=longitudinal strains; LVH=left ventricular hypertrophy.

* Echocardiographic "red flags" for Fabry disease cardiomyopathy includes papillary muscle hypertrophy, longitudinal myocardial velocities, left ventricular GLS, inferolateral basal segment LS, CS, base-to-apex CS gradient, and other (visible hyperechogenic and/or thin posterolateral wall).[31]

Affected males typically have low α-GAL A enzyme activity

Affected females may have normal to low-normal enzyme activity. Therefore, proceed directly to *GLA* gene sequencing.

TEST THE PATIENT, TEST THE FAMILY

Perform a simple blood test and genetic testing to confirm a diagnosis. Then test the family to identify affected relatives early.[2,20,32,33]

CAN YOU SOLVE THIS DIAGNOSTIC CHALLENGE?

CASE STUDY: Julie, a 45-year-old woman presenting with unexplained LVH

Nonspecific signs and symptoms that overlap with more common diseases often make diagnosis of rare diseases a challenge. Additionally, diagnosis can be delayed when manifestations affect multiple organ systems, if they are considered in isolation rather than holistically.

Julie presented with unexplained LVH

Clinical history	
SINCE TEENS	Angiokeratomas and cornea verticillata
IN 20s	Reduced exercise tolerance, recurrent abdominal pain, episodes of diarrhea and constipation
OVER PAST 2 YEARS	Polyuria and development of burning and tingling paresthesia in hands/feet following heavy exercise
Family history	
Julie has a family history of cardiomyopathy and premature stroke	

Do you know a patient like Julie?

Fictitious patient.
LVH=left ventricular hypertrophy.

Pertinent clinical and cardiac-specific findings

CLINICAL FINDINGS

- BP 125/85 mmHg
- BMI and HR in normal ranges
- Abdominal and pelvic angiokeratomas, cornea verticillata

CARDIAC FINDINGS

- ECG: AV block; voltage criteria for LVH
- Echo: Concentric ventricular hypertrophy

Based on general clinical and cardiac-specific findings, the cardiologist suspects Fabry disease

Diagnosis of Fabry disease is confirmed by low plasma α-GAL A activity (less than 25–30% of the mean normal level) followed by gene sequencing

Family screening was conducted after Julie tested positive for Fabry disease

BP=blood pressure; BMI=body mass index; ECG=electrocardiogram; HR=heart rate; LVH=left ventricular hypertrophy.

JULIE EXHIBITED SIGNS AND SYMPTOMS OF FABRY DISEASE SINCE HER TEENS BUT REMAINED UNDIAGNOSED FOR ~30 YEARS

An earlier diagnosis of Fabry could have helped better manage the disease and identify other affected family members sooner

SANOFI GENZYME

EARLY DIAGNOSIS AND INTERVENTION ARE KEY FOR PATIENTS WITH FABRY DISEASE

- **Cardiac disease** is a major cause of morbidity and mortality in patients with Fabry disease[24]
- Undiagnosed or unmanaged Fabry disease can reduce life expectancy in males by 20 years and in females by 15 years[21,22]
- You as a cardiologist are in a unique position because you can identify early signs of Fabry disease, leading to an earlier diagnosis for the patient and any of their affected family members
- Testing for Fabry disease is indicated when the presence of LVH is associated with other red flags on echocardiography[31]

Early diagnosis and treatment of Fabry disease is critical for optimal disease management[32,33]

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Learn more

For more information or to request a complimentary testing kit, please email FabryAwareness@sanofi.com. Simply provide us with your contact information and a Sanofi Genzyme representative will contact your office.

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