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Consensus

2021 TSOC Expert Consensus on the Clinical Features, Diagnosis, and Clinical Management of Cardiac Manifestations of Fabry Disease

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Fabry disease (FD) is an X-linked, rare inherited lysosomal storage disease caused by α-galactosidase A gene variants resulting in deficient or undetectable α-galactosidase A enzyme activity. Progressive accumulation of pathogenic globotriaosylceramide and its deacylated form globotriaosylsphingosine in multiple cell types and organs is proposed as main pathophysiology of FD, with elicited pro-inflammatory cascade as alternative key pathological process. The clinical manifestations may present with either early onset and multisystemic involvement (cutaneous, neurological, nephrological and the cardiovascular system) with a progressive disease nature in classic phenotype, or present with a later-onset course with predominant cardiac involvement (non-classical or cardiac variant; e.g. IVS4+919G>A in Taiwan) from missense variants. In either form, cardiac involvement is featured by progressive cardiac hypertrophy, myocardial fibrosis, various arrhythmias, and heart failure known as Fabry cardiomyopathy with potential risk of sudden cardiac death. Several plasma biomarkers and advances in imaging modalities along with novel parameters, cardiac magnetic resonance (CMR: native T1/T2 mapping) for myocardial tissue characterization or echocardiographic deformations, have shown promising performance in differentiating from other etiologies of cardiomyopathy and are presumed to be helpful in assessing the extent of cardiac involvement of FD and in guiding or monitoring subsequent treatment. Early recognition from extra-cardiac red flag signs either in classic form or red flags from cardiac manifestations in cardiac variants, and awareness from multispecialty team work remains the cornerstone for timely managements and beneficial responses from therapeutic interventions (e.g. oral chaperone therapy or enzyme replacement therapy) prior to irreversible organ damage. We aim to summarize contemporary knowledge based on literature review and the gap or future perspectives in clinical practice of FD-related cardiomyopathy in an attempt to form a current expert consensus in Taiwan.

Key Words: Cardiac magnetic resonance (CMR) • Cardiac variant • Chaperone • Enzyme replacement therapy (ERT) • Fabry disease (FD) • Globotriaosylsphingosine (Lyso-Gb3) • Globotriaosylceramide (Gb3) • IVS4+919G>A • α-galactosidase A (*GLA*) gene

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GENERAL INTRODUCTION AND PREVALENCE

Fabry disease (FD) has an estimated prevalence of 1 in 40,000 to 1 in 117,000 live births for males,[1-3] and presents as an abnormal accumulation of glycosphingolipids within lysosomes due to deficient or absent α-galactosidase A (α-GAL A) enzyme activity in various cell types and organs (Figure 1). As a rare X-linked inherited metabolic disease, FD has been increasingly recognized in recent years.[4,5] To date, more than 1,000 *GLA* gene variants have been identified and are categorized as pathogenic, benign without clinical relevance, or of unclear significance.[6,7] Nonsense, missense variants, and premature stop codons that lead to absent or low α-GAL A enzyme activity are usually associated with classic early-onset FD, presenting with a male predominance as a multisystemic disorder with earlier onset, and progressive clinical picture (in childhood or adolescence) as the classic FD phenotype (Figure 2). Initial clinical manifestations may involve multiple organs including neuropathic pain, anhidrosis or hypohidrosis, and skin lesions known as angiokeratoma[8] with the heart and kidneys being more prominent by the third decade of life, eventually leading to premature death from renal failure, stroke and cardiac disease.[1,9] Some missense genetic variants have been identified, including p.N215S in North America and Europe, p.F113L in Portugal, and IVS4+919G→A in Taiwan. These variants have been associated with residual α-GAL A activity and may manifest with late-onset FD affecting the heart as the predominant clinical picture (cardiac variant) (Figure 2).[7,10,11]

Random X-chromosome inactivation likely results in mosaicism in female patients, with some cells expressing the normal allele and others the mutated allele. This likely causes heterogeneous manifestations[12] ranging from an asymptomatic or mild symptomatic course later in life to a more severe phenotype resembling classic FD. With advances in cardiac imaging techniques and enhanced awareness of cardiomyopathy, the actual prevalence of FD in high-risk patients may not be as rare as

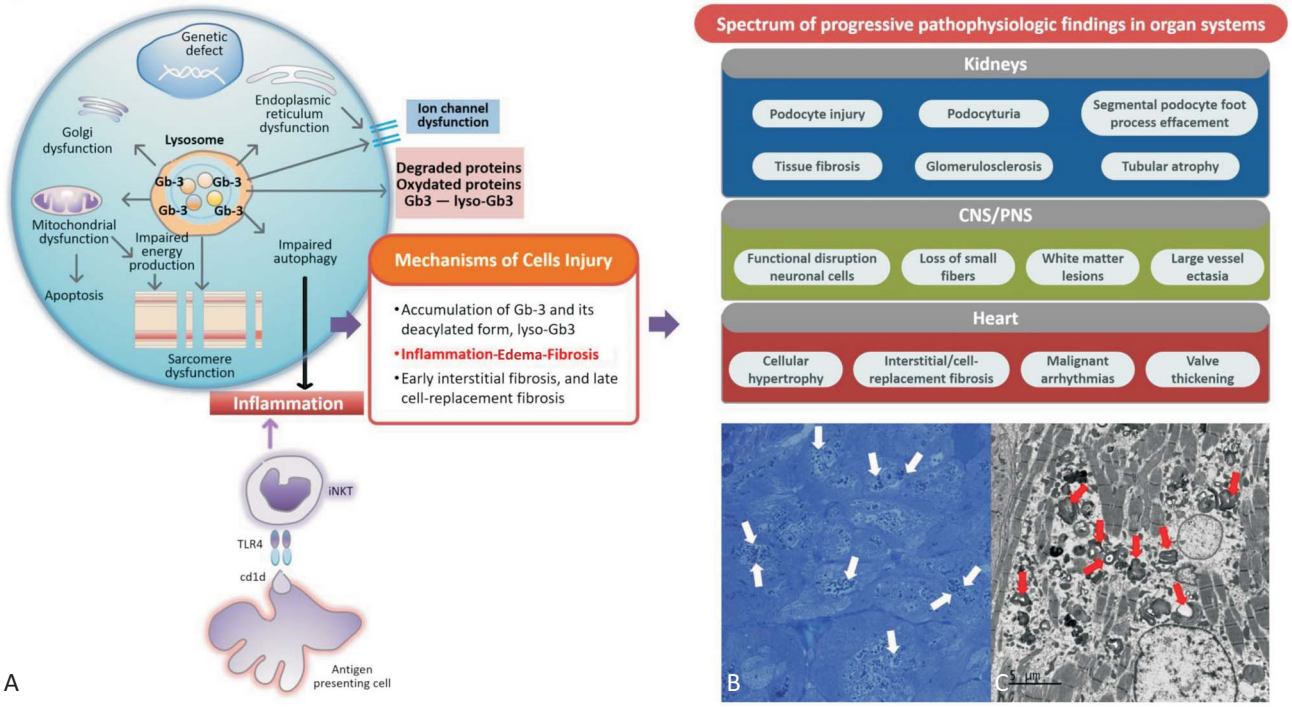

Figure 1. *(A) Typical pathophysiology of Fabry disease (FD) as a storage disease with cardiac involvement and recently reported secondary pathways operating in FD. Figure was adapted and modified from reference 30. (B) Endomyocardial biopsy from a 86-year-old female Fabry patient of cardiac variant (IVS4+919G>A mutation) presenting with hypertrophic cardiomyopathy. Toluidine blue staining demonstrating abundant granular inclusions (white arrows) caused by Gb3 accumulation within cardiomyocytes. (C) Electron microscopy showing enlarged secondary lysosomes packed with lamellated membrane structures (zebra bodies) and myofibrillar loss in cardiomyocytes. CNS, central nervous system; Gb3, globotriaosylceramide; iNKT, invariant natural killer T; lyso-Gb3, globotriaosylsphingosine; PNS, peripheral nervous system; TLR4, toll-like receptor-4. (Pathology shown by courtesy of Dr. Chen, Tung-Ying. MacKay Memorial Hospital, Division of Pathology).*

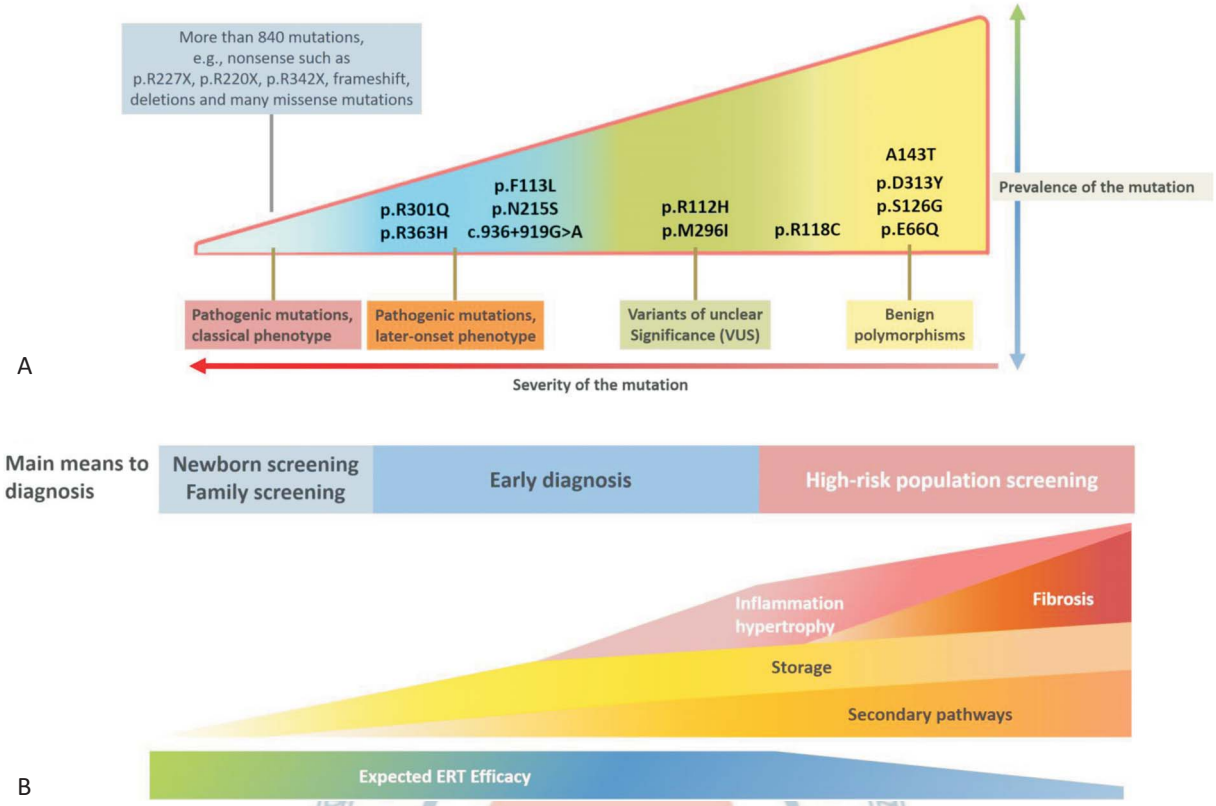

Figure 2. *(A) Several key GLA mutations associated with classic or later-onset (or cardiac variant) Fabry disease phenotype, variants of unclear significance (VUS), and benign variants. The triangular shape presented illustrates higher frequency of GLA mutations involving benign or benign variants with such mutations probably seen during screening yet less related to Fabry-related clinical manifestations. c.936+919G>A refers to IVS4+919G>A. (B) Proposed stages of Fabry disease (FD) of cardiac involvement evolution along with clinical progression in relation to expected enzyme replacement treatment (ERT) efficacy. Figure was adapted and modified from references 30 and 47.*

previously reported,[4] especially for late-onset (as a non-classic phenotype) or atypical FD[8,13] with predominant cardiac involvement (phenotypes) (e.g. in certain Asian regions) (Table 1). One European multicenter cross-sectional Anderson-Fabry survey by Elliott et al. including 1386 hypertrophic cardiomyopathy (HCM) patients reported a 0.5% prevalence rate of pathogenic *GLA* mutations.[14] In comparison, another study reported a pathogenic mutation rate of around 1% during screening trials,[15] and a newborn screening survey conducted in Italy suggested a prevalence of up to 1 in 8,800 newborns.[6,16] There is a high prevalence of the cardiac variant (IVS4+919G→A) (≈1 in 1600 males) of FD in Taiwan as revealed by newborn screening programs[17,18] and patients with idiopathic HCM.[11]

As a disease with multisystemic involvement, early pathological changes in FD are thought to predominantly involve the microvasculature[19] (endothelial dysfunction) due to affected clearance of globotriaosylceramide (Gb3). A combination of cardiogenic embolism formation or vascular wall changes due to Gb3 accumulation and abnormal reactivity/signaling contributes to the activation of coagulation pathways predisposing to cerebrovascular events.[20,21] These complex pathophysiological conditions likely explain why juvenile and/or cryptogenic transient ischemic attack and cerebrovascular complications are the major causes of morbidity and early mortality in both male and female patients with FD.[22-24]

Owing to the high prevalence of cardiovascular involvement, the leading cause of death in FD is cardiovascular death in both men and women.[25] Cardiac involvement is a common clinical manifestation in FD patients, with hallmark features including increased myocardial inflammation, myocardial fibrosis,[26-28] and left ventricular hypertrophy (LVH). Several cellular components of the heart have been shown to be involved due to chronic intracellular accumulation of Gb3, including

Table 1. Fabry disease red flags for differential diagnosis

Diagnostic tool		Cardiac red flags	Extra-cardiac red flags	Presenting decades of age
	History	Family history of LVH, particularly if no evidence of male-to-male transmission	Family history of renal failure and/or stroke	Any time
			Neuropathic pain	1-2
	Electrocardiography	Short PQ interval[#]	Gastrointestinal symptoms	1-2
		Bradycardia	Angiokeratomas	1-2
		Chronotropic incompetence	Cornea verticillata*	1-2
		Atrioventricular blocks[#]	Hypohidrosis, heat/cold, and exercise intolerance	1-2
	2D-Echo	LVH with normal systolic function	Albuminuria	1-2
		Reduced global longitudinal strain	Juvenile and/or cryptogenic TIA/stroke	3-4
		Mild-to-moderate aortic root dilation	Hearing loss (either progressive or sudden)	3-4
		Mitral and aortic valve thickening with mild-to-moderate regurgitation	Dolichoectrasia of the basilar artery, chronic white matter hyperintensities at brain MRI	3-4
	CMR Imaging	Hypertrophy of papillary muscles	Proteinuria	3-4
		Mid-layer posterolateral late gadolinium enhancement	Renal failure	3-4
		Low native T1	Lymphedema	3-4

Fabry disease red flags for differential diagnosis of patients with idiopathic left ventricular hypertrophy (LVH) and/or hypertrophic cardiomyopathy.
* In the absence of iatrogenic causes (chloroquine/amiodarone). [#] Short PQ interval in early stages; atrioventricular and bundle branch blocks are more common in advanced disease.
2D-Echo, 2-dimensional echocardiography; CMR, cardiac magnetic resonance; TIA, transient ischemic attack.
Table was adapted and modified from reference 30.

endothelial cells, vascular smooth muscle cells, cardiomyocytes, conduction system cells and valvular fibroblasts.[4] Excessive Gb3 deposits within cardiomyocytes may also elicit sarcomeric myofilament dysfunction and myofibrillolysis.[29] Given the relatively low percentage of complex lipids (1-2%) in total cardiac mass, accumulating data suggest that pathological cardiac involvement in FD typically begins with in Gb3 deposition as the initial step, followed by provoked alternative pathological signaling of subsequent inflammation, hypertrophy, and interstitial fibrotic processes over time (Figure 1).[4,30] Furthermore, coronary microvascular ischemia from endothelial dysfunction, impaired endocytosis/autophagy processes and mitochondrial dysfunction may also play a role in progressively diseased myocardium,[31-33] leading to chest pain, heart failure symptoms and arrhythmic events (Figure 2) (~60%).[34] Various cardiac arrhythmias have been identified, including bradyarrhythmia, conduction block, and ventricular tachycardia. The degree of LVH and the presence of myocardial fibrosis are risk factors for more malignant form of ventricular tachyarrhythmia or sudden cardiac death in both FD and non-FD HCM.[35]

Renal involvement is one of the main complications of FD and may affect podocytes, glomerular, vascular smooth muscle and tubular cells at an early stage,[36,37] possibly since early childhood and early adolescence.[38,39] High amounts of Gb3 deposits have been found in several types of renal cells,[40] with segmental podocyte foot process effacement in young classic FD, which is an early

marker of nephropathy prior to albuminuria or decline of estimated glomerular filtration rate. Podocyturia due to continuous podocyte loss may antedate proteinuria in FD, whereas proteinuria likely indicates a more advanced stage with glomerular involvement.[41] A study from a US dialysis registry reported that FD may account for 0.01% of patients with end-stage kidney disease,[42] probably due to continued and irreversible cellular loss of both glomerulus and podocytes without early enzyme replacement therapy (ERT).[43]

SCREENING CRITERIA IN CARDIOLOGY

As a multisystemic disease with relatively rare clinical prevalence, multiple diagnostic approaches are helpful for the early recognition and referral in highly suspected subjects. Apart from the typical clinical manifestations of extra-cardiac red flag picture in classic FD with multisystemic involvement (Table 1) (e.g. skin, peripheral/central nervous system, renal dysfunction or stroke), more patients are likely to have late onset (non-classic) than the classic type of FD manifesting with first presentations of unexplained LVH, especially in men.[9] Cardiac involvement in FD may present with unexplained LVH, preserved ejection fraction heart failure and ventricular arrhythmias starting from the third decade of life (> 30 years in males, > 40 years in females.[11,30,44] Therefore, routine screening of α-GAL A enzyme activity (in males) and *GLA* sequencing (in females) for individuals with unexplained LVH older than 40 years and with unknown family background may be recommended (Figure 3).[44] In classic FD, confirmation of severely reduced or absent plasma or leukocyte α-GAL A activity is often sufficient for a diagnosis in males.[45] Apart from several typical clinical manifestations or markers as cardiac red flags, identifying the unique features of extra-cardiac red flags relevant to the pathophysiological findings of FD may also be helpful.[30] One large prospective, multidisciplinary, multicenter screening program conducted in multispecialty clinics (including cardiology, neurology, nephrology, pediatrics, ophthalmology, dermatology, gas-

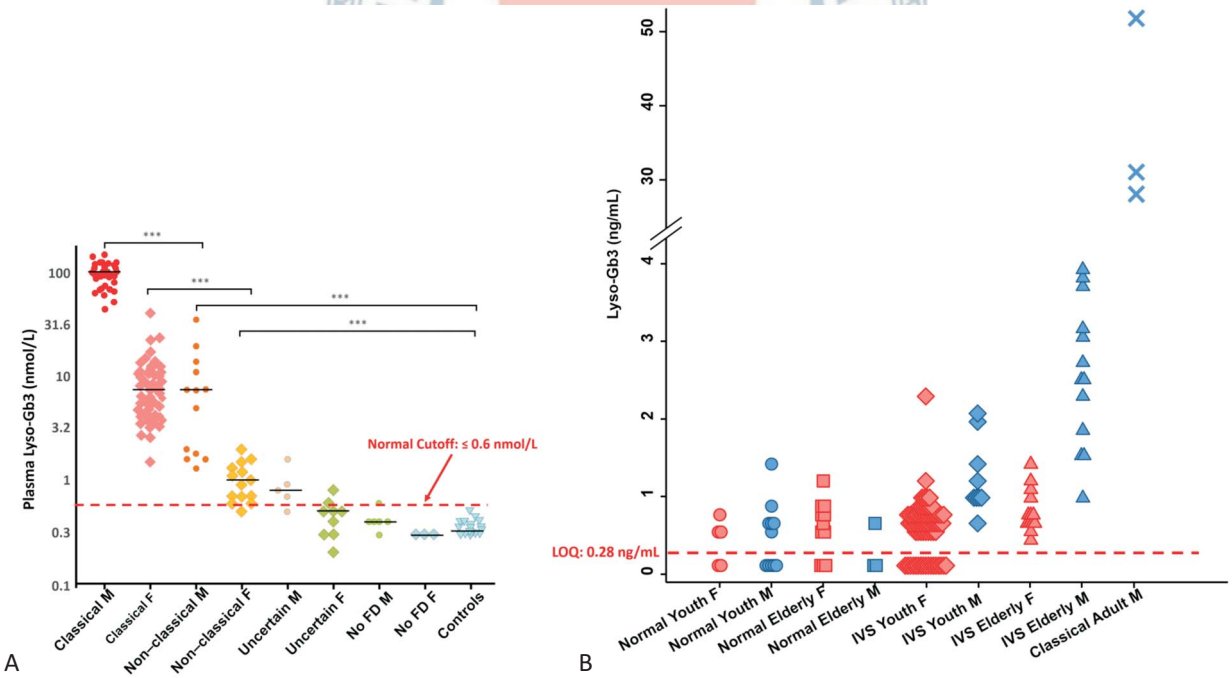

Figure 3. *(A) Plasma globotriaosylsphingosine (lyso-Gb3) levels stratified by disease phenotype and sex on a logarithmic scale. Dotted horizontal red line refers to the upper limit of normal cutoff defined as 2 SDs above the mean in healthy controls (≤ 0.6 nmol/L, mean 0.4 nmol/L, SD: 0.1, n = 20). Male subjects (M) are depicted as circles, female subjects (F) are depicted in diamonds, and controls depicted as triangles. Horizontal line per group represents the median group value. Figure was adapted and modified from reference 48. *** p < 0.01. Of note, plasma lyso-Gb3 in classical M and F subjects differed significantly from healthy controls (both p < 0.01). (B) Lyso-Gb3 levels in adults with the later-onset FD (GLA IVS4+919G>A mutation) stratified by sex and disease phenotypes from ethnic Taiwanese population. Adapted and modified from reference 46. with permission granted from Dr. Chien, Yin-Hsiu. FD, Fabry disease; SD, standard deviation.*

troenterology, internal medicine, and genetics clinics) reported that 37 (1.8%) patients who fulfilled the inclusion criteria incorporating clinical, genetic, and biochemical indices were carriers of *GLA* mutations among 2,034 probands.[45] The most commonly involved organ systems were the heart (69%), peripheral nerves (46%), kidneys (45%), eyes (37%), brain (34%), skin (32%), gastrointestinal tract (31%), and auditory system (19%). The male patients with late-onset FD had higher residual α-GAL A activity compared to those with classic FD, although its level is far below normal. In comparison, plasma or leukocyte α-GAL A activity may be normal or slightly deficient in heterozygous females.[45,46] Hence all FD diagnoses should be confirmed by genetic testing, with cascade family genetic screening according to X-linked inheritance.[47] Assessment of more highly specific biomarkers of FD, such as circulating Gb3 and globotriaosylsphingosine (lyso-Gb3) levels in plasma and Gb3 levels in urine, can be useful and highly specific in establishing the diagnosis and clinical phenotype (e.g. high levels in classical patients and lower levels in non-classical patients) of FD, particularly in female patients in whom partial enzyme activity is present (Figure 4).[48-50]

ELECTROCARDIOGRAPHY (ECG)

A variety of ECG parameters have been reported including macroscopic myocardial changes compatible with pathological ventricular hypertrophy including left ventricular (LV) strain pattern, T-wave inversion and left atrial enlargement in precordial leads.[51] These features are also common in other forms of advanced and progressive HCM.[52] The presence of posterolateral fibrosis may cause ST-T segment depression and T-wave inversion in the inferolateral leads in some FD patients.[53] Additionally, recent studies have shown multiple ECG abnormalities in FD.[54] A shortened PR interval has been reported in the earlier stage of FD,[55] probably due to altered cellular conductive properties from intracardiac Gb3 deposition.[56] In contrast, due to the pathological and progressive burden of Gb3, PR prolongation and subsequent AV block is not uncommon in the later stage of FD,[57] making these novel findings helpful in identifying FD.

IMAGING FOR FABRY DISEASE

Cardiac ultrasonography is a convenient bedside imaging modality and remains a fundamental tool in determining the precise geometry (e.g. concentric hypertrophy), phenotypic LVH or the presence of HCM. Conventional geometric echocardiography measures in FD include wall thickness, ventricular dimension, atrial/ventricular volumes by using linear measurements and several functional hemodynamic assessments, standard 2D and hemodynamic Doppler measurements.[9,11,30,27,28,57] A maximum LV wall thickness of 15 mm not explained by pressure overload indicates typical phenotypic HCM, whereas in those manifesting a borderline value (13-14 mm) of maximum wall thickness, other demographic elements (including family history, other clinical systemic manifestations such as renal, neurological, or dermatological involvement, and electrocardiographic findings) should be used to guide the clinical diagnosis.[58] A recently published study combining several key clinical indices (including PR interval on ECG, arrhythmia history, LVH pattern on echocardiography, and autonomic dysfunction) reported high[28] sensitivity for classifying patients at high risk of FD in a Korean HCM cohort. Right ventricular hypertrophy (defined as RV wall thickness > 5 mm using echocardiography) is not uncommon (71% reported by Niemann et al.;[59] 31% reported by Graziani et al.[60]) in Fabry cardiomyopathy.

Advanced echocardiographic imaging modalities using tissue Doppler imaging, strain and strain rate through either tissue Doppler-based imaging or speckle-tracking techniques, may allow for the identification of the early stages of FD prior to the development of LVH.[61] In this regard, echocardiography is particularly useful in identifying diastolic dysfunction (as prevalent as 79% in phenotypic LVH compared to 7% with normal LV wall thickness), impaired pre-clinical systolic function prior to LVH,[61] and impaired atrial compliance.[62] Doppler-based myocardial strain and strain rate are promising to allow for early detection for cardiomyopathy progression in FD, which may be able to guide early ERT in such patients.[63,64] Novel speckle tracking-based echocardiography, irrespective of degree of LV remodeling, has greater sensitivity and specificity than conventional echocardiographic parameters[65] and can be used to assess regional myocardial longitudinal dysfunction which cor-

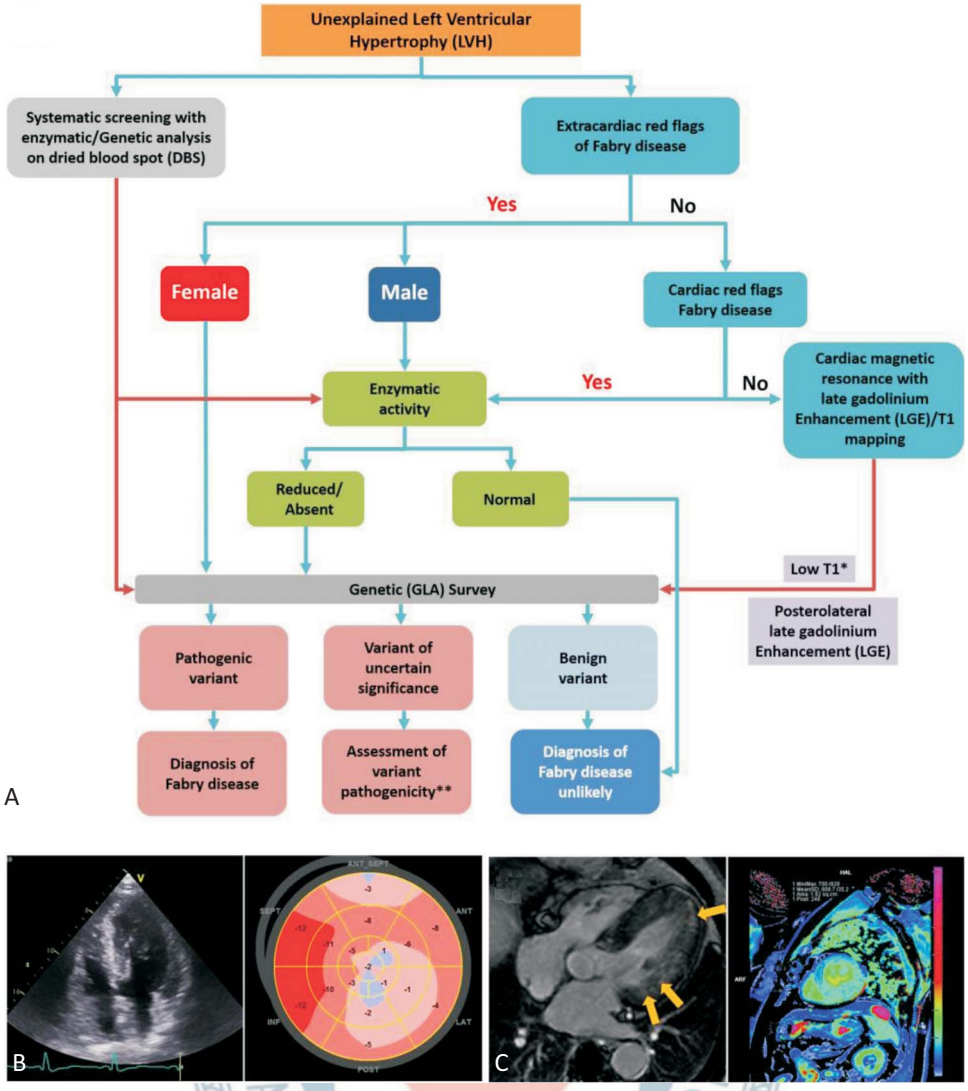

Figure 4. *(A) Proposed flowchart and red flag signs for diagnosis of Fabry disease (FD) in patients with idiopathic, unexplained left ventricular hypertrophy (LVH). * Low native non-contrast cardiac magnetic resonance (CMR) imaging T1 values reinforce or generate suspicion of FD, however, normal T1 values do not exclude FD which can occasionally and rarely be seen in untreated patients with mild LVH (mostly females) or in more advanced disease stage due to "pseudo-normalization". With normal native T1 values, genetic analysis remains indicated if other clinical findings are in favor of FD. ** By lyso-Gb3 levels assessment and endomyocardial biopsy. Figure was adapted and modified from reference 30. (B) Echocardiography including 2D (Left, 4 chamber view) and severely deteriorated global longitudinal strain (-6.8%) (Right, bull eye view) from a 61-year-old, male cardiac variant FD (GLA IVS4+919G>A mutation) patient presenting clinical HFpEF. (C) In same patient, CMR imaging showed diffuse myocardial fibrosis including basal lateral segment using LGE technique (Left) and native T1 imaging demonstrated relatively low T1 values (808.7 ms) at septal region. (CMR imaging by courtesy of Dr. Yun, Chun-Ho. MacKay Memorial Hospital, Division of Radiology).*

relates with segmental fibrosis by late gadolinium enhancement (LGE) using cardiac magnetic resonance (CMR) imaging.[66] Marked global reduction in deformational strain measures, especially longitudinal strain, has been observed in FD which may be either due to a regional (e.g. basal inferolateral segment) decrease caused by myocardial fibrotic changes or a deterioration in global longitudinal systolic function despite preserved LV ejection fraction (Figure 4).[66] This pattern is distinct from amyloid cardiomyopathy which mainly affected longitudinal strain in the basal and mid regions leading to apical sparing.[67] Furthermore, a segmental myocardial longitudinal strain worse than -12.5% has been shown to be an excellent indicator of region-specific fibrosis, while a

segmental strain better than -16.5% excludes the presence of fibrosis. Compared to FD, HCM patients tend to have reduced regional longitudinal strain in segments of greatest hypertrophy (e.g. septal region).[68] Interestingly, decreased global circumferential strain accompanied by loss of the normal base-to-apex gradient may be able to differentiate FD from other types of HCM.[69] In hypertensive cardiomyopathy, the worst longitudinal strain has been observed in basal septal segments of the hypertrophic part, or in most of the basal regions,[70] although a more heterogeneous reduced global longitudinal strain pattern has been observed in aortic stenosis.[71]

CMR imaging is a novel imaging modality that features myocardial tissue characteristics and is increasingly being used in FD. As a more accurate non-invasive imaging tool in determining ventricular volume, wall thickness and LV mass, CMR imaging also allows for more clear characterization of pathologic myocardial processes (e.g. infiltration, replacement fibrosis, or inflammation) and enables assessment of the extracellular volume fraction and differentiation of pathological cardiomyocyte and myocardial interstitial involvement (Figure 4).[72,73] These features may be helpful in differentiating FD from LVH with different underlying etiologies.[72,73] In particular, CMR imaging can supplement echocardiography in determining the extent of sphingolipid accumulation, edema, and interstitial fibrosis (presence of LGE), and thereby is able to evaluate changes in the stages of FD. Low native T1 myocardial values may represent a higher burden of sphingolipid storage from Gb3 accumulation, and a lower native T1 value has been observed in patients with FD compared to controls or patients with concentric LVH from other etiologies. In addition, it has been shown to be correlated with ECG changes and likely serves as a novel predictor of worsening disease, especially in pre-hypertrophic FD.[74-76] A reduction in native T1 value prior to the development of LVH has thus been correlated with early LV functional changes detected by echocardiography,[77] and more closely associated with the extent of LV remodeling compared to strain measure.[78] By assessing increased T2 myocardial relaxation time in FD, the presence of myocardial edema can be evaluated and determined, especially in segments with LGE, which is common in basal inferolateral segments.[30,79,80]

BIOMARKERS

Circulating biomarkers including N terminal pro B type natriuretic peptide (NT-proBNP) and cardiac troponin I/T (cTNI/cTNT) have been proposed to be alternative surrogate markers of cardiac involvement in FD. NT-proBNP level has been shown to correlate with overall disease severity in FD,[81] given the high prevalence of LV dysfunction and myocardial damage from multiple pathological mechanisms as mentioned, resulting in an excessive degree of LV remodeling or the presence of impaired diastolic mechanics.[82] Overall, NT-proBNP has been shown to be meaningful and useful both in experimental models and clinical scenario earlier than overt pathological cardiac remodeling stage, suggesting its pre-clinical screening role in subjects with suspicious profiles.[83,84] Likewise, cardiac troponins reflecting cardiac muscular necrosis and damage, can be helpful in assessing active and continuous cardiac involvement in FD. cTNT/cTNI have been correlated with the presence of LGE by CMR independently of coronary lesions,[85] as a predictor of progressive cardiomyopathy, and thereby helpful in clinical staging in FD.[86,87] Several biomarkers or cytokines, such as interleukin-6 and high sensitivity C-reactive protein, reflecting elicited pro-inflammatory pathways/signaling in FD,[88] have also been reported to be markers in the evaluation, monitoring and prognosis of FD.[89-91] The utilization of these biomarkers were listed in Table 2.

TREATMENT EFFECTS AND MONITORING OF FD

Several treatment options are currently available for FD. Table 3 shows detailed information of these therapies along with their advantages and disadvantages. Among them, ERT remains the main therapeutic intervention for FD.[30,92,93] Other potential and novel therapies for FD are evolving and currently under development, including chaperone therapy, substrate reduction therapy, and stem cell-, gene-, and messenger ribonucleic acid-based therapies.[92] Lack of effective treatment in this patient population may result in reduced life expectancy of nearly 20 years in male carriers and 15 years in female carriers compared to the general population.[94,95] Two recombinant enzyme preparations of α-galactosi-

Table 2. Biomarkers and their potential clinical utilities in Fabry disease

Organ Involvement	Biomarkers	Potential clinical utilization (organ specificity)
Systemic	Plasma and leukocytes a-galactosidase A (a-Gal) plasma activity	Diagnosis, disease activity, organ damage
	Plasma and *urinary* Gb3	Diagnosis, disease activity, efficacy of ERT, monitor disease progression, organ damage
	Plasma and *urinary* Lyso-Gb3	
	Neutralizing antibodies	Prognosis, disease severity
	MiRNA (miR21, miR210, miR29, miR200, miR21-5p, miR19a-3p, etc.)	Diagnosis, disease activity, response to treatment, prognosis
Kidney	Proreinuria, albuminuria, eGFR	Renal involvement
	Uromodulin, N-acety-β-D-glucosaminidase, beta2 microglobulin	Renal involvement (under investigation)
	Urinary lyso-Gb3 analogues	Diagnosis (detectable in case not in control)
	Cystatin C	Early renal involvement
Heart	3-NT	Cardiac and vascular involvement
	Longitudinal strain distribution	Cardiac involvement, prognosis
	TNF, IL-6, TNFR1, TNFR2	Cardiac involvement, prognosis
	Cardiac-specific scores, left ventricular hypertrophy, diastolic dysfunction	Cardiac involvement, prognosis
	Late gadolinium enhancement on CMR imaging, non-contrast T-1 mapping	Cardiac involvement (detect pre-hypertrophic stages), prognosis
	NT-proBNP, BNP, MRproANP, MMP2, MMP9, galectin-1, galectin-3	Cardiac involvement (remodeling. diastolic dysfunction), prognosis

BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; eGRF, estimated glomerular filtration rate; ERT, enzyme replacement therapy; IL, interleukin; Lyso-Gb3, globotriaosylsphingosine; MiRNA, microRNA; MMP, matrix metalloproteinases; MRproANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; 3-NT, 3-nitrotyrosine.
Table was adapted and modified from reference 106.

dase A (r-αGAL A) are commercially available (agalsidase-alfa [Replagal, Takeda, Japan] at a dose of 0.2 mg/kg biweekly, and agalsidase-beta [Fabrazyme, Sanofi Genzyme, France] at a dose of 1.0 mg/kg biweekly) for the treatment of FD for over 15 years, with variations in the efficacy, partly due to the timing of treatment initiation, duration and distinct clinical phenotypes.[92-95] Despite the lack of head-to-head comparison from randomized control trials, long-term observational clinical studies have shown a slightly better ERT on both cardiovascular and renal events with agalsidase-beta at higher dose compared to agalsidase-alfa.[96,97] The effects observed were probably dose-dependent, with benefits mainly in those who received treatment before irreversible organ damage,[98,99] since presence of decreased renal function, proteinuria and/or cardiac fibrosis at the time of treatment initiation are associated with disease progression despite treatment with ERT.[93] ERT has profoundly changed or modulated the natural history of FD and improved the patients' quality of life by decreasing neurological symptoms (e.g. neuropathic pain), gastrointestinal manifestations, as well as heat and exercise intolerance.[44,47,100,101] Close following of the treatment response is essential to assess disease progression and requires a multidisciplinary approach. Recently, expert consensus on the management and monitoring of FD has been documented.[44] A multiparametric clinical scoring system for the treatment effects has also been proposed and well validated.[102]

Lyso-Gb3 is a degradation product of Gb3 and a surrogate biomarker of FD, and it has been shown to be an effective monitoring marker for ERT in FD treatment and to serve as a useful indicator for treatment outcomes., although its role in the late-onset cardiac variant (e.g. IVS4 + 919G > A) remains less clear.[103-105] Furthermore, some new biomarkers, including microRNAs and lyso-

Table 3. Contemporary approved and under development therapies for Fabry disease

A. ERT/SRT and Chaperone Therapy

Approved			
Mechanism of action	ERT		Pharmacological chaperone
Drug name	Agalsidase (Alfa)	Agalsidase (Beta)	Migalastat
Route of Administration	IV	IV	Oral
Dose	0.2 mg/kg/every other week	1.0 mg/kg/every other week	123 mg/every other day
Notes	Agalsidase alfa is the human protein a-galactosidase A produced in a human cell line by genetic engineering technology.*	Agalsidase beta is a recombinant form of human a-galactosidase A and is produced by recombinant DNA technology using a mammalian Chinese hamster ovary cell culture. The amino acid sequence of the recombinant form, as well as the nucleotide sequence that encoded it, are identical to the natural form of a-galactosidase A.†	Indicated only for adult patients with migalastat-amenable a-galactosidase variants (i.e., a GLA variant translating into a-Gal A proteins that may be stabilized by migalastat, thereby restoring their trafficking to lysosomes and their intralysosomal activity). No food 2 h before and after intake.§

Ongoing or under development (phase III trials)‖*				
Mechanism of action	ERT		SRT	
Drug name	Pegunigalsidasealfa	Moss-aGal	Venglustat	Lucerastat
Route of Administration	IV	IV	Oral	Oral
Dose	1 mg/kg/every other week	Being tested as 0.2 mg/kg to measure pharmacokinetics and safety	15 mg/once daily	1.0 g/twice daily (dose adjusted for renal function)
Notes	Produced in tobacco cells and chemically modified with polyethylene glycol Three ongoing phase III clinical trials.	Produced in moss. Phase I trial completed. Plans for phase II and III studies in progress.	Ongoing long-term, phase II trial. Plans for phase III trials in progress.	Ongoing phase III trial for patients with Fabry disease with neuropathic pain.

ERT, enzyme replacement therapy; IV, intravenous; SRT, substrate reduction therapy.
Adapted and modified from references 30 and 47‡.
* Shire Pharmaceuticals Limited. Agalsidase alfa. Summary of product characteristics. † Sanofi Genzyme. Agalsidase beta. Summary of product characteristics. § Amicus Therapeutics UK Limited. Migalastat hydrochloride. Summary of product characteristics.
‖ Information taken from ClinicalTrials.gov.
Note: These therapies are not recommended in those patients with well-characterized benign a-galactosidase benign variants.
‡ In the absence of demonstrable Fabry disease related tissue pathology or clinical symptoms, ERT may not be appropriate, particularly in heterozygous female patients; however, these patients should be monitored regularly by a multidisciplinary care team. ‡ In patients with late-onset Fabry disease, ERT should be considered in the presence of laboratory, histological, or imaging evidence of injury to the heart, kidney, or central nervous system, even in the absence of typical Fabry symptoms. In Taiwan, the information about ERT for late-onset Fabry disease (e.g. IVS4+919G→A) can be obtained at https://pse.is/3hg2wz, or Supplement information as English version.

B. Gene-based Therapy

Mechanism of gene transference	Experimental animal model	
	In vivo	Ex vivo
Types of administration	Systemic or local administration of viral vectors carrying GLA gene. AAV (adeno-associated viruses) intramuscular injection.	Cultures of extracted and patient stem cells transfected using virus vectors and reimplanted.
Virus used for vectors	Adenovirus or Lentivirus	
Mechanism of gene transference	Human Trials Ex vivo (HSC) transduced stem cell with in vivo transplant.	
Types of administration	CD34+ stem cell from the patients infected with autologous cell transplant.	
Virus used for vectors	Lentivirus	

These data were adapted and modified from references 113-116.

Gb3 isoforms, are currently under investigation. Several other proposed markers, including clinical manifestations, systemic, urine or circulating plasma, and cardiac remodeling biomarkers have been widely used to monitor the treatment effect and response to ERT in FD (Table 2).[106]

Long-term follow-up studies and registry data have shown that ERT may alter and delay cardiac disease progression and reduce the cardiovascular event rate.[44,47,92,100] Excessive LV remodeling or LVH is an important phenotype in FD, and it has gained attention as a potential therapeutic monitoring index or marker in ERT. Prior reports have shown that early ERT may prevent the development of LVH, and regression at the earlier stage of LVH has been reported in patients with both classic and cardiac phenotypes, although relatively few studies have reported on late-onset cardiac FD variants.[30,44,47,92,100] Notably, the therapeutic response to ERT regarding myocardial fibrosis and LVH progression is uncertain and probably less prominent in advanced cardiac FD. Several factors have been proposed to predict the cardiac response to ERT, including phenotype, sex, timing and dosage of ERT, and antidrug antibody development against exogenous α-GAL A.[11,92,107] In one longitudinal Fabry Registry study (by Germain et al.[108]) conducted to determine the effect of Fabrazyme on the progression of LVH in male patients, untreated group had a 3.4-fold higher risk of having faster increases in LV mass compared to treated group [odds ratio: 3.43, 95% confidence interval (CI): 1.05-11.22, p = 0.042] after more than 2 years of treatment. In the same study, higher baseline age (≥ 40 years) was also associated with LVH progression (odds ratio: 5.03; 95% CI: 1.03-24.49; p = 0.046) compared to men younger than 30 years. Attenuated T1 lowering after ERT has been shown to be accompanied by small reductions in maximum wall thickness and stabilization of the LV mass index.[109] In one prospective long-term CMR imaging study, long-term therapy with agalsidase-beta at 1 mg/ kg every 2 weeks was effective in significantly reducing LVH and myocardial T2 relaxation times and improving overall cardiac performance.[110] The summary of cardiac imaging in monitoring response to therapy in FD was listed in Table 4. The flowchart of cardiac monitoring in treated and untreated FD patients

Table 4. The role of cardiac imaging including echocardiography and cardiac magnetic resonance in monitoring response to therapy in Fabry disease

The role of echocardiography in monitoring response to therapy in Fabry disease		
Echocardiographic parameter	Response to Treatment	Comments
LV wall thickness or mass	Variable	More reduction seen in patients with baseline LVH and little or no LGE
Diastolic function	No change or minor improvement	E/e' may be more sensitive than mitral inflow alone
Tissue Doppler imaging	Improvement in strain and strain rate	Improvement only seen in patients without LGE
Tei index	No change	
Speckle tracking strain	Improvement in LA strain High quality LV strain data not available	LA strain improvement correlates with decreased left atrial volume index LV inferolateral regional strain predicted progress of LGE

The role of cardiac magnetic resonance (CMR) imaging in monitoring response to therapy in Fabry disease		
CMR parameter	Response to treatment	Comments
LV wall thickness/mass	Variable	More reduction seen in patients with baseline LVH and little/no LGE
LGE	No change (ERT)*	Absence predicts regression of LV mass
T1 mapping	Reduction of lowering T1 value	Correlates with small reduction in wall thickness and LV mass index
T2 mapping	Reduction in T2 relaxation time	Correlates with reduction in LV mass
RV mass	No change	

CMR, cardiac magnetic resonance; E/e', ratio of early mitral inflow to early diastolic tissue Doppler e' velocity; ERT, enzyme replacement therapy; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; RV, right ventricular.

Table was adapted and modified from reference 80, 109.

* *Pending results* of the Effect of Migalastat on Cardiac Involvement in Fabry Disease (MAIORA) study (ClinicalTrials.gov Identifier: NCT03838237).

is further illustrated in Figure 5.

Despite huge efforts, several limitations have been observed in ERT for FD. For example, even though progressive LV mass remodeling has been shown to be partially ameliorated in FD patients who receive ERT, meaningful events including sudden cardiac death continue to develop even after long-term treatment.[62,109] Therefore, risk stratification for the need of implantable cardioverter-defibrillator (ICD) in patients with FD presenting with overt hypertrophic phenotype is indicated.[58] Furthermore, as most of the administered recombinant enzyme may end up in the liver, two of the most severely affected cell types in FD including the heart (mainly cardiomyocytes) and kidney (mainly podocytes) may only take up very limited amounts of recombinant enzymes, leading to inefficient bio-distribution.[37,111,112]

SOCIAL RESOURCES AND REFERRAL

The National Health Insurance (NHI) program was launched in Taiwan to provide universal health coverage more than two decades ago. Once the diagnosis of a rare disease is confirmed by physicians and the Health Promotion Administration of the Ministry of Health and Welfare is informed, the patient will receive a major ill-

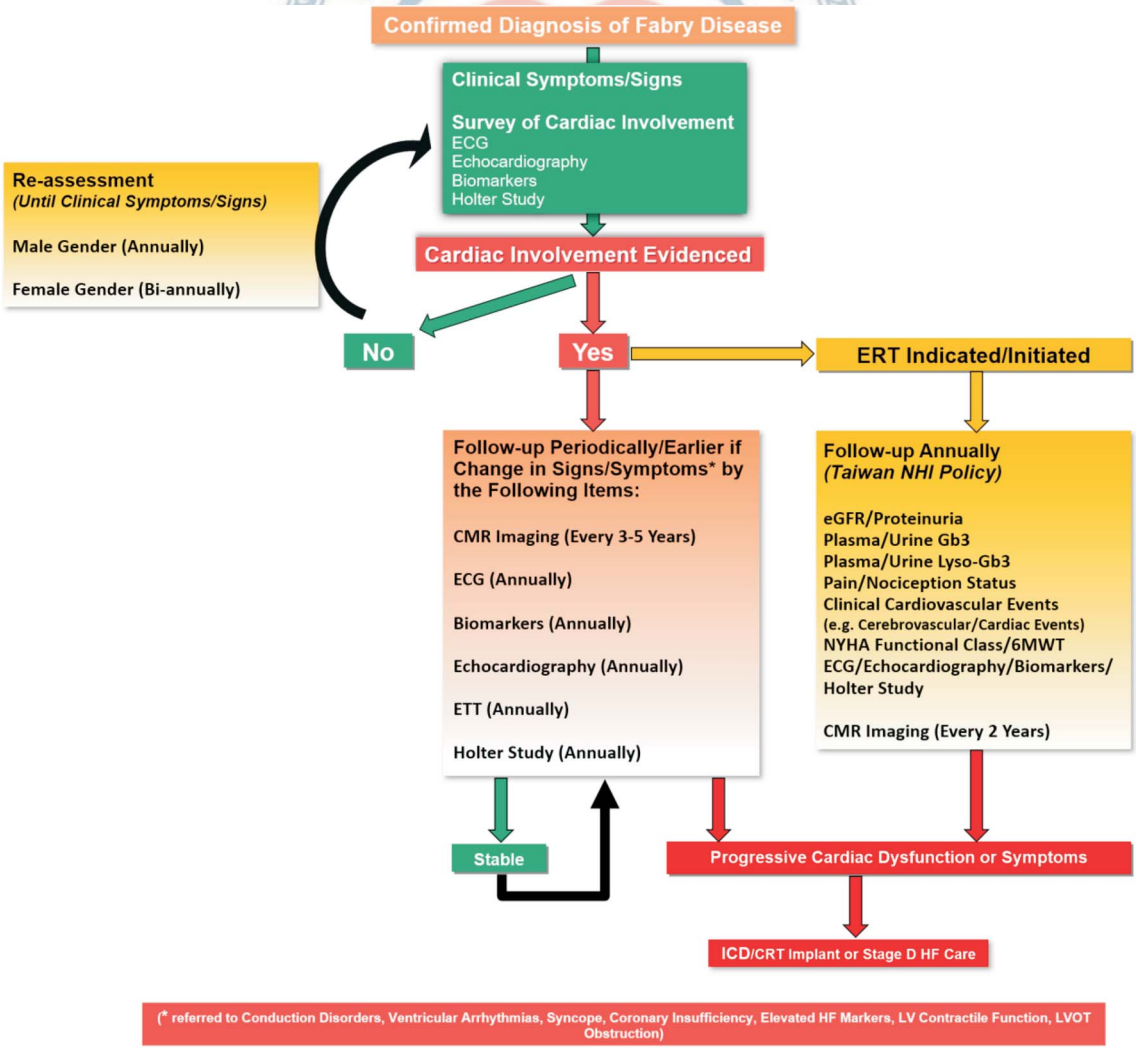

Figure 5. *Flowchart for clinical management and treatment monitoring approach for confirmed FD with or without cardiac involvement. Figure was adapted and modified from reference 44. CAD, coronary artery disease; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; ERT, enzyme replacement therapy; ETT, exercise treadmill test; ICD, implantable cardioverter-defibrillator; LV, left ventricle; LVOT, left ventricular outflow tract.*

Table 5. Recommended requirements on medical subdivisions/subspecialty, technical and hardware facilities/equipment for the clinical care of FD patients

Suggested facility and taskforce to become hub for main centers	Capacity/capability and markers	Potential clinical utilization (organ subspecialty)	Optional
Laboratory	Plasma and Leukocytes a-galactosidase A (a-Gal) plasma activity	Diagnosis, disease activity, organ damage	
	Plasma/urine Lyso-Gb3	Diagnosis, disease activity	
	DBS	Diagnosis	
6MWT	Cardiopulmonary functional capacity	Prognosis, disease severity	
CMR Imaging	Cine	Chamber/structure assessments	
	LGE	Cardiac fibrosis	
	Native T1 mapping	Glycolipid storage	
	ECV	Diffuse fibrosis/inflammation	V
	T2 mapping (relaxation time)	Myocardial edema	
Echocardiography	2D	Chamber/structure assessment	
	Color Doppler imaging	Hemodynamic assessment	
	Tissue Doppler imaging	s', e', and strain/strain rate assessment	
	Speckle tracking techniques	Chamber-specific strain/strain rate assessment	
	Exercise Stress Test	Functional study during exercise	V
Biomarkers	NT-proBNP/BNP	Cardiac involvement (remodeling. Diastolic dysfunction), response to treatment and prognosis	
EMB	Myocardial Gb3/Lyso-Gb3 staining	Diagnosis, disease activity, organ damage	
Genetic counseling	Clinical genetics	Diagnosis/genotyping	V

BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; DBS, dry blood smear; ECV, extracellular volume fraction; EMB, endomyocardial biopsy; FD, Fabry disease; LGE, late gadolinium enhancement; NT-proBNP, N-terminal pro-B-type natriuretic peptide; 6MWT, 6-minute Walking Test.

ness certificate which exempts them from co-payments. As the classic FD phenotype is a rare disease, the NHI Administration reimburses these patients through specially earmarked funds to receive ERT at NHI-contracted healthcare institutions. Additional criteria are required to apply for reimbursements for ERT in those with non-classic FD (Table 3). Additionally, the Taiwan Foundation for Rare Disorders has established social networks engaged in funding, counseling, and research of rare disorders in Taiwan (http://www.tfrd.org.tw/tfrd/). Further, as an evolving rare disease with high diagnostic and management threshold with multiple co-morbid conditions, multidiscipline teamwork is essential for the clinical diagnosis, management and follow-up of FD. The emerging need for a systematic approach, subspecialty care, technical requirement, and advanced equipment for diagnostic accuracy, management and disease monitoring is rapidly growing, hence an adequate referral system is thus required to improve the clinical care. In Table 5, we recommend requirements (including relevant medical specialties, techniques and hardware) for the care of patients with FD in detail.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPLEMENT

Taiwan National Health Insurance Administration Ministry of Health and Welfare Fabry Reimbursement Criteria (Effective from May 1st, 2019)

- For the Fabry patient with **classic genotype**, need to fulfill one of the criteria
  (I) With renal or cardio biopsy evidence related to Fabry disease
    1. Acroparesthesia, hypohidrosis, or stroke
    2. Proteinuria and microalbuminuria
    3. Myocardial and rhythmic abnormalities or ventricular hypertrophy

- For the Fabry patient with **non-classic genotype**, need to fulfill one of the criteria (either I or II):
  (I) With renal or cardio biopsy evidence related to Fabry disease
  (II) Patient being regarded as a "**Fabry disease IVS4+919G>A genotype Patient**" should meet at least two indicators as stated in "cardiac function assessment indicators of Fabry's disease cardiac variant type" with cardiac biopsy confirmed GL3 or lyso-Gb3 lipid accumulation.

The "Cardiac function assessment indicators of Fabry's disease cardiac variant type" have described as below:

(1) The thickness of left ventricle (LV) more than 12 mm,

(2) LVH on electrocardiogram (ECG) being diagnosed by Romhilt-Estes score > 5 or meet the Cornell's criteria,

(3) Echocardiographic left ventricular mass index (LVMI) more than 51 g/$m^{2.7}$ in male and 48 g/$m^{2.7}$ in female,

(4) Echocardiographic diastolic dysfunction (E/A ratio > 2.0 and deceleration time < 150 ms) or tissue doppler abnormality (early transmitral flow velocity to early diastolic velocity of the mitral annulus [E/e'] > 15 at the septum or E/e' > 12 at the lateral wall),

(5) Left ventricular mass (LVM) increased more than 5 g/m^2 at the interval of 12 months,

(6) Left atrium (LA) volume increased (> 34 ml/m^2 body surface area),

(7) Arrhythmia not medicine induced or related, such as atrioventricular (AV) block, short PR interval, left bundle branch block (LBBB), ventricular or atrial tachyarrhythmias, sinus bradycardia,

(8) Moderate to severe mitral/aortic regurgitation (MR/AR),

(9) Mild to moderate LV fibrosis detected by delayed enhancement of magnetic resonance imaging (MRI).