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Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

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ABSTRACT

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene leading to deficient α-galactosidase A activity, glycosphingolipid accumulation, and life-threatening complications. Phenotypes vary from the "classic" phenotype, with pediatric onset and multi-organ involvement, to later-onset, a predominantly cardiac phenotype. Manifestations are diverse in female patients in part due to variations in residual enzyme activity and X chromosome inactivation patterns. Enzyme replacement therapy (ERT) and adjunctive treatments can provide significant clinical benefit. However, much of the current literature reports outcomes after late initiation of ERT, once substantial organ damage has already occurred. Updated monitoring and treatment guidelines for pediatric patients with Fabry disease have recently been published. Expert physician panels were convened to develop updated, specific guidelines for adult patients. Management of adult patients depends on 1) a personalized approach to care, reflecting the natural history of the specific disease phenotype; 2) comprehensive evaluation of disease involvement prior to ERT initiation; 3) early ERT initiation; 4) thorough routine monitoring for evidence of organ involvement in non-classic asymptomatic patients and response to therapy in treated patients; 5) use of adjuvant treatments for specific disease manifestations; and 6) management by an experienced multidisciplinary team.

1. Introduction

Fabry disease (OMIM 301500) is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene. Markedly reduced or absent activity of the enzyme α-galactosidase A (α-Gal A, EC 3.2.1.22) [1,2] results in progressive accumulation of glycolipids, primarily

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; α-Gal A, α-galactosidase A; CKD, chronic kidney disease; CNS, central nervous system; CT, computed tomography; DBS, dried blood spots; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; ENT, ear, nose, and throat; ERT, enzyme replacement therapy; GFR, glomerular filtration rate; GI, gastrointestinal; GL-3, globotriaosylceramide; IENFD, intra-epidermal nerve fiber density; IgG, immunoglobulin G; IV, intravenous; LV, left ventricular; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; lyso-GL-3, globotriaosylsphingosine; MBD, metabolic bone disorder; MRI, magnetic resonance imaging; TIA, transient ischemic attack; TOF MRA, time-of-flight magnetic resonance angiography (head and neck); TRPV1, transient receptor potential vanilloid 1; VUS, variants of unclear significance

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globotriaosylceramide (GL-3, Gb_3) and its deacylated form, globotriaosylsphingosine (lyso-GL-3), in plasma and in a wide range of cells throughout the body. This includes those particularly relevant to disease pathology (e.g., vascular endothelial cells, podocytes, cardiomyocytes, arterial smooth muscle cells) and other cell types in the kidneys, nervous system, and other organs [1,2]. Currently, there are 15 years of clinical experience with enzyme replacement therapy (ERT) [3,4] for Fabry disease.

Fabry disease was initially described in male patients with a severe clinical phenotype, now known as "classic" Fabry disease [1,2]. These patients are characterized by absent or severely reduced (< 1% of mean normal) α-Gal A activity, marked GL-3 accumulation in vascular endothelial cells, cardiomyocytes, smooth muscle cells, and podocytes, and childhood or adolescent onset of symptoms followed by progressive multi-organ failure, and eventually death [1,2]. However, a larger group of patients has later-onset phenotypes with varying levels of residual α-Gal A activity, age of onset, and manifestations [2]. Newborn screening (NBS) studies revealed frequencies of the classic and later-onset phenotypes of up to 1 in 22,570 males and 1 in 1390 males, respectively [5]. The spectrum of disease severity in heterozygous female patients ranges from asymptomatic to a severe phenotype that resembles that observed in male patients with the classic phenotype and is in part dependent on the mutation and the X chromosome inactivation (Lyonization) profile [2,6–8]. Severe clinical manifestations have been reported in at least 43% of obligate carrier women [7,9,10]. Numerous *GLA* mutations have been reported [11–15] and efforts are underway to correlate *GLA* mutations with the major phenotypic subtypes [16].

The past decade has witnessed an increased understanding of the pathogenesis, natural history, and prevalence of Fabry disease, and the effectiveness and limitations of ERT. The advances have changed our approach to disease monitoring and therapeutic intervention, necessitating an appraisal and update of monitoring and treatment guidelines for the multisystemic involvement in adult patients with Fabry disease published in 2006 [17]. The present document complements specific documents that have addressed controversial areas (KDIGO [18]) or aspects of diagnosis and management usually focused around individual organs [19–28]. Furthermore, these updated recommendations underline the importance of early treatment initiation in both males and females, and stress the importance of patient-specific care and a multidisciplinary approach to disease management. Recommendations for the cessation of treatment have not been included here as the clinical consequences of treatment cessation, compared with ERT continuation, remain to be clarified [29].

The development of these recommendations was initiated in July 2014 at a meeting of an international panel of Fabry disease experts from seven subspecialties, including nephrology, cardiology, neurology, genetics, genetic counseling, pediatrics, and metabolic disorders convened in Atlanta, GA, USA, to review existing treatment guidelines for adults with Fabry disease [17]. Subsequent discussions were held during a panel meeting in February 2015 in Orlando, FL, USA. Treatment of pediatric patients was not part of the discussions; recommendations for the monitoring and management of pediatric/adolescent patients were being developed by a panel of experts in pediatric Fabry disease and have recently been published [30]. Based on these face-to-face panel discussions, an independent coordinator prepared a draft set of updated recommendations for clinical management of adult patients with Fabry disease. Each member of the panel amended the recommendations based on his/her long clinical experience and in-depth knowledge of the literature; therefore, no systematic review of the literature on clinical outcome was performed, and the recommendations were not graded. Several revision rounds were performed until a consensus was reached by all panelists, taking important newly published data and perspectives into account.

2. Disease manifestation

In classic Fabry disease, the first symptoms, including chronic neuropathic pain and episodic severe pain crises, typically emerge during childhood (Table 1). Symptoms such as hypohidrosis, skin abnormalities (angiokeratomas), gastrointestinal (GI) disturbances (bloating, diarrhea, abdominal pain), and a characteristic asymptomatic corneal opacity (cornea verticillata) are additional common early manifestations [1,2]. Occult kidney injury may occur at a young age, including albuminuria (a defining feature of chronic kidney disease [CKD]) and glomerulosclerosis [33,43,44]. Symptomatic organ complications typically emerge in young adult patients, including CKD progression to renal failure and left ventricular hypertrophy (LVH) associated with myocardial fibrosis and arrhythmias, auditory loss, transient ischemic attacks (TIAs), strokes, and eventually premature death [7,32,45–50]. Accumulation of GL-3 in cardiac tissues, as well as inflammatory and neurohormonal mechanisms leading to cardiac cellular and vascular dysfunction are likely contributors to cardiac manifestations [45]. Lung manifestations have been reported (e.g., dyspnea, wheezing, dry cough) [39]. In patients with the later-onset phenotype, typical cardiac symptoms (e.g., LVH, arrhythmia, abnormalities on cardiac magnetic resonance imaging [MRI]) and, exceptionally, decreased glomerular filtration rate (GFR) present in the fourth to seventh decades of life, reflecting delayed onset and slower disease progression [2,51,52]. The spectrum of disease in heterozygous female patients ranges from being asymptomatic or having mild, later-onset phenotypes that usually affect only a few or one organ(s) to the severe phenotype (as observed in male patients with the classic disease phenotype) [2,6–8]. Registry data provide evidence that cardiomyopathy and strokes are also common among female patients, and that female patients typically develop disease complications at older ages than male patients, although renal failure may manifest at a similar mean age [53,54] in female patients with a skewed X inactivation pattern and predominant expression of the mutant *GLA* allele [6,7,34,46–48,53,54]. More detailed descriptions of the clinical signs and symptoms of Fabry disease are provided in Table 1 and online Appendices A, B, C, D, and E (renal, cardiac, peripheral nervous system, central nervous system (CNS), and other organ systems, respectively).

3. Genetics

α-Gal A is a homodimeric glycoprotein encoded by the *GLA* gene which is located on the long arm of the X chromosome [1,2]. Numerous *GLA* mutations are currently reported in gene mutation databases [11–15] Missense, nonsense, consensus splice site, cryptic splicing, and frameshift mutations (small and large deletions and insertions) cause Fabry disease (Fig. 1). In general, nonsense, consensus splice site, and most frameshift mutations result in little or no α-Gal A enzyme activity, and are associated with the classic phenotype. In contrast, a proportion of the missense mutations and rare cryptic splicing mutations can encode enzymes with residual α-Gal A activity, which may explain the later-onset phenotypes. Except in the most recent publications [55], general registries and clinical studies have not stratified Fabry patients by genotype.

Random X chromosome inactivation occurs in heterozygous female patients, and prediction of their ultimate disease course is challenging. A largely skewed X chromosome inactivation pattern (reported in 29% of a female Fabry patient population in a recent study [6]), either preferentially expressing or suppressing the disease-causing Fabry mutation, significantly contributes to phenotypic variability, in addition to other factors [6]. Thus, heterozygous female patients who preferentially express the normally functioning *GLA* ("wild-type") allele will experience few, if any symptoms, while female patients who preferentially express the mutant *GLA* allele have a disease course which may mimic the male disease phenotype (either classic or later-onset), depending on the underlying *GLA* mutation in their family [2,6].

Table 1
Clinical manifestations of classic Fabry disease.

Organ system	Characteristics	Abnormalities	Usual age at onset (decade)
Peripheral nervous system	Neuropathic pain (formerly called "acroparesthesia"), pain crises, atypical (for pain characteristics and localization) chronic or episodic pain; heat and/or cold intolerance; impaired sweat function (hypohidrosis)	Small fiber neuropathy, loss of small myelinated and unmyelinated fibers, GL-3 accumulation in dorsal root ganglia, ectopic discharges possibly due to upregulation of Na+ channels (Nav1.8) and TRPV1; [31] axonal degeneration due to ischemia secondary to massive microvascular endothelial GL-3 accumulation; hypohidrosis can also be due to GL-3 deposition in the sweat glands	1st [19]
	Hearing loss, tinnitus; dizziness, vertigo	Potentially due to narrowing of cochlear and vestibular vessels, GL-3 deposition in spiral ganglia and vestibular structures; ischemic auditory neuropathy	Begins in 3rd and increases with age [32]
Dermatological	Angiokeratomas	Weakened capillary walls and ectasia in dermis due to microvascular endothelial GL-3 accumulation	1st/2nd [2]
Gastrointestinal	Nausea, vomiting, intermittent diarrhea and constipation; abdominal pain and/or bloating; difficulty gaining weight in childhood	Narrowing of mesenteric blood vessels due to microvascular endothelial GL-3 accumulation; mesenteric and submucosal plexus involvement; GL-3 accumulation in the autonomic ganglia of the bowel; autonomic neuropathy	1st [2,30]
Ophthalmological	Cornea verticillata; conjunctival and retinal vasculopathy, cataract, central retinal artery occlusion (rarely), reduced tear secretion	Streaks in corneal epithelium, vasculopathy	1st/2nd (usually present from birth) [1]
Renal	Pathological albuminuria/proteinuria	GL-3 accumulation in podocytes and multiple kidney cell types; podocyte injury (foot process effacement precedes pathological albuminuria)	1st/2nd [33]
	Decreased glomerular filtration rate progressing to kidney failure	Glomerular sclerosis secondary to podocyte loss, tubular atrophy, interstitial fibrosis, microvascular endothelial GL-3 accumulation, and arteriolar injury	Mean age at kidney failure: 40 years [34]
Cardiac	Cardiomyopathy (particularly hypertrophic cardiomyopathy with concentric hypertrophy and minimal/absent outflow obstruction); reduced exercise tolerance; syncope; cardiac fibrosis; heart failure (mostly with preserved ejection fraction). Bradycardia – chronotropic incompetence; atrial fibrillation, ventricular tachycardia; sudden cardiac death	ECG abnormalities (shortened PR interval only in early stages, T-wave inversion), LVH (echo and cardiac MRI) leading to hypertrophic cardiomyopathy and myocardial fibrosis (late enhancement of the posterior inferobasilar wall on cardiac MRI)	4th/5th (usually asymptomatic until well into adulthood) [35]
Vascular	Aortic stiffness	Increased intima media thickness	Unknown [36]
Cerebrovascular	TIA; ischemic stroke and (less frequently) hemorrhagic stroke; cerebral venous thrombosis; cervical carotid dissection	Small vessel occlusion, dolichoectasia (particularly of the basilar artery), chronic white matter hyperintensities, TIAs and stroke due to cardiac arrhythmias	3rd and 4th [37]
Neuro-psychological	Common: depression; anxiety; panic attacks; social adaptive function difficulties. Rarely: cognitive decline and dementia	Potentially related to living with chronic disease, plus neuropathic pain and small vessel occlusions, as well as reduced hippocampal volume, multiple infarcts, and small vessel occlusions; white matter lesions	3rd and 4th [38]
Pulmonary	Dyspnea, wheezing; dry cough; sleep-disordered breathing	Obstructive airway limitation (with or without restrictive limitation), reduced spirometric parameters; if advanced, chest X-ray/CT scan abnormalities (pulmonary infiltrations, fibrosis, air trapping); accumulation of glycolipids in small-medium sized airway cells	Unknown [39]
Lymphatic	Lymphedema in all or part of a limb (also below eyes), pitting edema	Accumulation of glycolipids in the lymph vessels; fragmentation of the microlymphatic network	4th [40]
Skeletal	Osteopenia, osteoporosis	Reduced bone mineral density of lumbar spine and femoral neck	2nd and 3rd [2,41]
Other	Mild facial dysmorphism	Potentially due to continuous GL-3 accumulation in growing facial bones and developing facial connective tissues	Unknown [42]

CT, computed tomography; ECG, electrocardiography; GL-3, globotriaosylceramide; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; TIA, transient ischemic attack; TRPV1, transient receptor potential vanilloid 1.

Methods to assess the skewing of X chromosome inactivation hold particular promise in predicting future clinical severity for women with a classic mutation [6].

Most of the pathogenic *GLA* mutations are private, occurring in a single or few families; intra-familial phenotypic variability has been observed, complicating the study of genotype–phenotype correlations [2]. Some correlations have been suggested, such as for the missense mutation p.N215S, which has been found consistently in patients with predominantly cardiac manifestations (LVH and hypertrophic cardiomyopathy) [51,52]. Overt renal involvement appears to be rare in patients with this mutation and, if present, causes other than Fabry disease should be excluded [51].

Disease manifestations in patients with the same gene mutation, even males from the same family, may vary, making counseling difficult. Factors that will likely alter the impact of a given gene mutation include the presence of additional deleterious *GLA* variants or variants of unknown significance (VUS; either on the *GLA* allele in *cis* male and female patients, or on the other *GLA* allele in *trans* female patients), the genetic background of the patient, concomitant diseases, and environmental modifiers. For example, it has recently been shown that the −10T polymorphism found in *cis* within the mutation p.A143T may impact disease severity and the timing of disease manifestations, and research is currently underway to validate this finding [56].

Some mutations, such as IVS4 + 919G > A (c.936 + 919G > A), very common in Taiwan and southern China, appear to have reduced penetrance [57]. Similarly, a number of *GLA* mutations, such as p.D313Y,

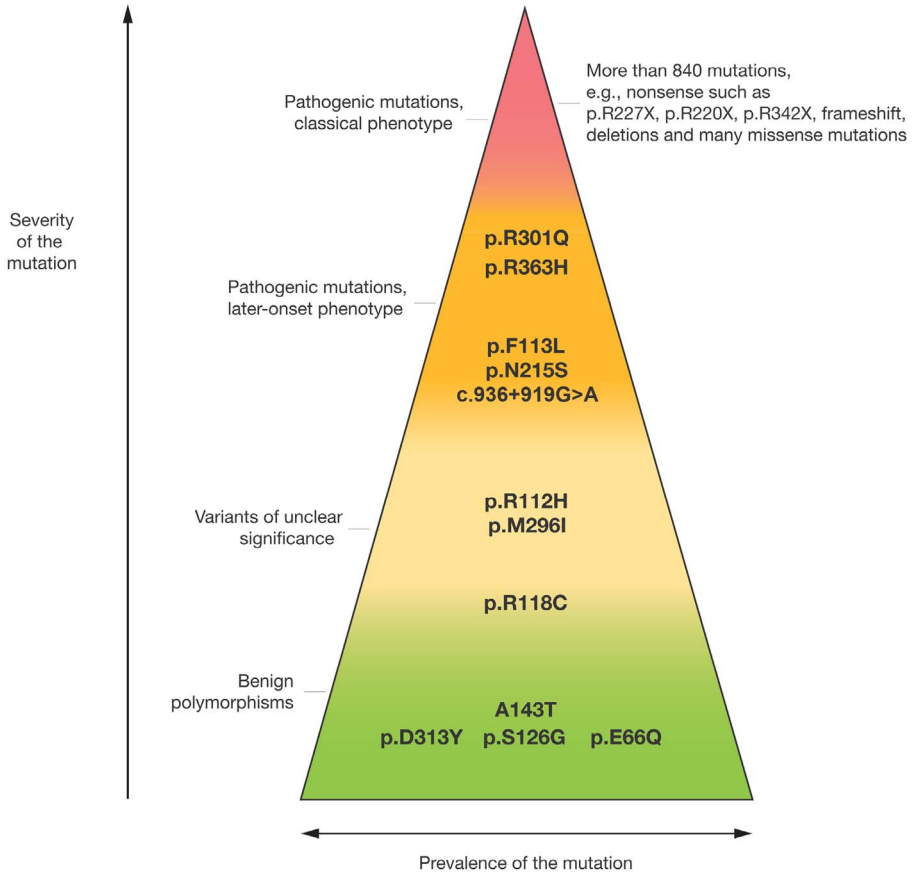

Fig. 1. Some key mutations associated with the classic or later-onset Fabry disease phenotype, *GLA* variants of unclear significance (VUS), and benign variants. The triangular form illustrates the higher frequency of benign and probably benign variants. Physicians should be aware that, due to this higher frequency, such mutations may be seen in screening studies but may not be related to actual Fabry-related manifestations.

p.E66Q, and probably p.R118C, have a higher or similar prevalence among certain general populations than among clinical or registry populations [57–60]. These mutations are likely benign polymorphisms, as there is no published evidence of lysosomal substrate accumulation in the tissues expressing them. Screening studies for Fabry disease may reveal individuals with genetic variants of yet unknown significance [60].

4. Diagnostic confirmation

α-Gal A activity testing alone is diagnostic for male patients; however, confirmation of the disease-causing *GLA* mutation is important to help establish the disease phenotype, rule out benign polymorphisms that cause reduced levels of α-Gal A activity, and it permits the testing of at-risk family members. In female patients, demonstration of the presence of a disease-causing mutation in the *GLA* gene is required as the plasma enzyme activity is often found within the normal range, although leukocyte α-Gal A activity may be low [6]. Enzymatic activity is usually measured in plasma, leukocytes, or dried blood spots (DBS) [2]. For patients with a *GLA* VUS, clinical, biochemical, or histopathological evidence of Fabry disease is required to determine the pathogenic nature of the mutation. In addition, family history can predict pathogenicity for a *GLA* VUS. The “gold standard” to clarify if a novel mutation is pathogenic or likely benign includes in vitro *GLA* mutation expression assays (only available at specialized research laboratories) [5]. Characteristic clinical features of Fabry disease (neuropathic pain, cardiomyopathy, renal insufficiency) should be assessed. The finding of increased plasma and/or urinary GL-3, or plasma lyso-GL-3 and its analogues in the evaluation of male or female patients with a VUS and normal (in female patients) or lowered α-Gal A activity provides additional diagnostic information, but the role of biomarkers in such patients still requires validation [61,62]. Male patients with a VUS and normal α-Gal A activity do not have Fabry disease.

Evidence of lysosomal GL-3 accumulation in renal or cardiac biopsies, although invasive, may be required when interpretation of genetic *GLA* mutation is challenging [26–28], particularly when the clinical signs are nonspecific, alternative or additional diagnoses are under consideration, or in cases in which there is uncertainty over whether ERT should be started. Therefore, the advice of an expert in genetics and management of Fabry disease should be sought for interpretation of the pathogenicity of any VUS.

In individuals with an uncertain diagnosis of Fabry disease and no renal, cardiac, or cerebral manifestations, characteristic patterns of neuropathic pain, angiokeratomas, and/or cornea verticillata can support a diagnosis. Fabry disease can be confirmed in the presence of small fiber neuropathy characterized by pain in the hands and feet starting at childhood and increasing with heat/fever, angiokeratomas localizations clustered in the bathing trunk area, umbilicus and/or perioral region, or cornea verticillata [27]. Of note, cornea verticillata is observed in most male and female patients with classic Fabry disease [63] and demonstration of cornea verticillata by slit-lamp examination supports the diagnosis [27]. However, cornea verticillata is also known to be associated with the use of various drugs (e.g., amiodarone, chloroquine) [2].

5. Clinical management of adult patients with Fabry disease

It has become increasingly clear that comprehensive and timely treatment of adult patients with Fabry disease should be directed toward prevention of (further) progression to irreversible tissue damage and organ failure. Care should include ERT and adjunctive therapies to treat symptoms that arise due to tissue injury and prevent non-specific progression of tissue injury. Treatment and follow-up assessments to evaluate treatment responses should ideally be supervised by a

physician experienced in the management of patients with Fabry disease, with input from sub-specialists who also have Fabry disease experience, as part of a multidisciplinary clinical team that includes a neurologist, nephrologist, cardiologist, medical geneticist, genetic counselor, psychologist, and nurse.

5.1. Available enzyme replacement therapies

ERT is presently available in the form of agalsidase alfa (Replagal®, Shire HGT, Inc., Cambridge, MA, USA) and agalsidase beta (Fabrazyme®, Sanofi Genzyme, Cambridge, MA, USA). Agalsidase alfa is given at 0.2 mg/kg body weight every other week by intravenous (IV) infusion [4] and is approved in many countries throughout the world, though not by the US Food and Drug Administration. Agalsidase beta is administered at 1.0 mg/kg body weight once every 2 weeks as an IV infusion [3] and is approved in Europe, the USA, and many other countries. In 2014, Fabagal®, an agalsidase beta manufactured by ISU Abxis (Seongnam-si, Gyeonggi-do, South Korea), ISU Global, was approved in South Korea only.[1] The ERT infusion setting including home infusions, tolerability, and infusion-associated adverse reactions is discussed in online Appendix F.

5.2. Initiation of enzyme replacement therapy

The levels of effectiveness in the management of Fabry disease of both agalsidase alfa and agalsidase beta, including data from pivotal trials and related open-label extension studies [64–68], has been documented in the clinical literature, though it is outside the scope of this article to provide detailed information on the entire body of literature available. One vital area of focus, however, is the timing for ERT initiation. The importance of early initiation of ERT has been highlighted in treatment guidelines for pediatric patients with Fabry disease (developed by a Fabry Expert Panel of United States Fabry specialists [30]). In line with the recommendations for initiation and cessation of ERT developed by the European Fabry working group [25], these treatment guidelines indicate that ERT should be considered in asymptomatic classical males before adulthood (< 18 years).

A systematic renal biopsy study has evaluated the long-term effect of ERT on early renal Fabry pathologic features in young Fabry patients with the classic phenotype ($n = 12$, median age 16.5 years, range 7–33 years) [43]. This study showed that ERT with agalsidase alfa or agalsidase beta can result in complete GL-3 clearance of mesangial and glomerular endothelial cells and in a cumulative dose-dependent GL-3 clearance of podocytes over 5 years of treatment [43]. The correlation between podocyte GL-3 clearance and the cumulative agalsidase dose has been recently confirmed in a larger group of patients ($n = 20$) with higher median age (21 years), wider age range (7–62 years), and longer treatment duration (9.4 years) with agalsidase alfa and/or beta [44]. Better renal outcomes have been achieved by patients who started agalsidase beta soon after the emergence of symptoms, and before the urine protein-to-creatinine ratio was ≥1 g/g [69]. Similarly, modest kidney function deterioration has been reported in patients with lower estimated glomerular filtration rate (eGFR) and lower proteinuria levels who received agalsidase alfa, whereas a greater loss of GFR was observed in patients with higher baseline levels [70,71]. Improvement in left ventricular mass was greater in men who started agalsidase beta treatment before the age of 40 years than in those who started at an older age [72], and patients who started ERT before developing cardiac fibrosis had greater improvement in LVH and cardiac function than those who already have cardiac fibrosis [73]. Improvements were apparent after 1 year of treatment in patients with left ventricular mass index (LVMI) ≥50 g/m$^{2.7}$ before the start of agalsidase alfa treatment; benefits in male patients continued after 10 years, while deterioration in females was controlled [74]. In a 10-year outcomes study of 52 patients with classic Fabry disease from the original pivotal clinical trial, starting agalsidase beta at a younger age in patients with less kidney damage was associated with more clinical benefit [68].

Finally, a recent observational study found that increasing time on agalsidase beta over 5 years was associated with decreasing incidence rates of severe events, despite patient aging [55]. This decrease in incidence was observed in both higher risk (i.e., patients with pre-ERT severe clinical events, patients > 40 years of age, and male patients) and lower risk groups (i.e., patients without pre-ERT severe clinical events, patients < 40 years of age, and female patients). Overall, the observations were in line with the positive results of the placebo-controlled trial of agalsidase beta that included a composite endpoint of severe clinical events as a primary endpoint [75]. With regard to biochemical responses, improved outcomes were achieved in male patients with classic Fabry disease that started ERT before the age of 25 years as compared to those who initiated treatment at older age. The higher lyso-GL-3 levels in the latter group may reflect a greater residual disease burden [76]. Further discussion of head-to-head studies and meta-analyses is available in online Appendix G.

5.2.1. Expert panel recommendations for initiation of enzyme replacement therapy in adult patients with Fabry disease

Recommendations for initiation of ERT in patients who present to a clinician at adult age, or have been diagnosed late via Fabry screening among populations at high-risk or family screening, are presented in Table 2. Initiation of ERT requires a fully confirmed diagnosis of Fabry disease; the impact of treatment should first be discussed with the patient/patient's family.

5.2.1.1. Patients with classic Fabry mutations. In male patients with classic Fabry disease diagnosed in childhood (aged < 18 years), ERT has usually been initiated in childhood [30]. Indications for ERT initiation in males with classic mutation who have reached adulthood without having started ERT, and for adult females are summarized in Table 2.

5.2.1.2. Patients with later-onset Fabry mutations or GLA variants of unknown significance. In adult male and female patients with later-onset Fabry mutations or missense *GLA* VUS, ERT should be considered and is appropriate once there is biochemical, histological, or imaging evidence of injury to the kidney, heart, or CNS attributable to Fabry disease, even in the absence of other typical Fabry symptoms (Table 2).

5.2.2. Further considerations for initiation of enzyme replacement therapy

The amino-acid sequences of agalsidase beta and alfa are similar with comparable specific activities per mg, but the glycosylation patterns are different [77,78]. Periodic monitoring of the patient's immunoglobulin G (IgG) anti-agalsidase antibody status is recommended. IgG antibody formation is relatively common and has been reported with both forms of recombinant agalsidase in male patients with more severe mutations (especially in those with absent α-Gal A production) [79]. International antibody testing standards are lacking and different criteria have been used to assess antibody formation in response to the two agalsidase preparations in clinical studies, hampering the comparison of data. Studies have shown that male patients' titers of immunoreactivity toward either agalsidase alfa or agalsidase beta do not appear to be significantly different [80–82]. Moreover, complete cross-reactivity of antibodies has been demonstrated [81], although the impact of IgG antibodies on the clinical effectiveness of the two dose regimens requires further study. Results from a recent study suggest that serum-mediated ERT inhibition does not depend on the initial ERT formulation used, and that in males the main risk factor for the development of inhibition is harboring a nonsense mutation [83]. Testing patients with poor clinical outcome on ERT for agalsidase inhibition is

[1] Any further mention of agalsidase beta in this paper and its appendices refers only to Fabrazyme® as no data on Fabagal® have yet been published in peer-reviewed literature.

Table 2
Recommendations for initiation of ERT in adult male and female patients with classic or later-onset mutations, or *GLA* VUS.

Adult patient population	Recommendation for the initiation of ERT
Classic Fabry mutation	
• Male patient, symptomatic or asymptomatic	• ERT should be considered and is appropriate in all patients at any age of presentation[a]
• Female patient, symptomatic	• Signs/symptoms suggesting major organ involvement, warranting initiation of ERT - neuropathic pain, pain crises, Fabry disease neuropathy - proteinuria/albuminuria NOT attributable to other causes, evidence of renal impairment (may require renal biopsy if isolated) - stroke or TIA - symptomatic cardiac disease not due to other causes (dyspnea, palpitations, syncope, chest pain) - recurrent diarrhea, chronic, disabling GI dysfunction (excluding alternative causes) - exercise intolerance and impaired sweating
• Female patient, asymptomatic[b]	• ERT should be considered if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS - renal disease: decreased GFR (< 90 mL/min/1.73 m^2 adjusted for age $>$ 40 years [GFR category $\geq$ G2], persistent albuminuria $>$ 30 mg/g [albuminuria category A2 or A3]), podocyte foot process effacement or glomerulosclerosis on renal biopsy, moderate or severe GL-3 inclusions in a range of renal cell types - silent strokes, cerebral white matter lesions (on brain MRI)[c] - asymptomatic cardiac disease (cardiomyopathy or arrhythmia, cardiac fibrosis on contrast cardiac MRI) • ERT should also be considered if a skewed X chromosome inactivation pattern with predominant expression of the mutant *GLA* allele with or without very low α-Gal A activity have been demonstrated in the presence of signs and symptoms of disease
Later-onset Fabry mutation or missense *GLA* VUS	
• Male and female patients	• ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS, as detailed above, even in the absence of typical Fabry symptoms. The abnormalities should be attributable to Fabry disease; this may require histological assessment or biochemical evidence of GL-3 accumulation • The advice of an expert in genetics and management of Fabry disease should be sought for interpretation of the pathogenicity of any VUS • Individuals with well characterized benign *GLA* polymorphisms should not be treated with ERT • In the absence of demonstrable Fabry disease-related tissue pathology or clinical symptoms, ERT may not be appropriate, particularly in heterozygous female patients. These patients should be monitored regularly by a multidisciplinary care team

CNS, central nervous system; ERT, enzyme replacement therapy; α-Gal A, α-galactosidase A; GFR, glomerular filtration rate; GI, gastrointestinal; GL-3, globotriaosylceramide; MRI, magnetic resonance imaging; TIA, transient ischemic attack; VUS, variant of unknown significance.

[a] Treatment decisions may be influenced by advanced elderly age of the patient and severe comorbidity.

[b] Treatment decisions in female patients may be guided by the X chromosome inactivation profile, if assessed. Predominant expression of the mutant *GLA* allele is generally associated with rapid disease progression, requiring closer monitoring and early therapeutic intervention [6].

[c] See also online Appendix D.

recommended by the investigators who also suggested that the higher 1.0 mg/kg every 2 weeks formulation may be necessary to overcome the impact of antibodies in patients with greater disease severity [83].

In a few patients, agalsidase beta administration resulted in the development of IgE antibodies [74,84,85]. Agalsidase beta treatment could be safely reinstated in patients with previous IgE-antibody or skin-test reactivity to agalsidase beta using a rechallenge infusion protocol [86].

Given the biochemical similarity of the products, the five-fold difference in the labeled doses (and related difference in infusion duration), and the need for effective early treatment to prevent or mitigate disease progression, the choice of ERT formulation should be based on the dose necessary to optimize clinical outcomes (online Appendix G).

5.3. Adjunctive therapies

Treatment with ERT should be combined with supportive interventions, if indicated, to clinically manage the renal, cardiac, neurological, and other complications of Fabry disease-induced chronic tissue injury (Table 3). The rationale for the recommendations and further details are provided in online Appendices A (renal), B (cardiac), C (peripheral nervous system), D (central nervous system), and E (involvement of other organs). It should be stressed that it is inappropriate to manage active clinical symptoms of Fabry disease with only symptomatic therapies such as pain relief, as these do not target the underlying Fabry disease pathogenesis. Preventative measures (e.g., stroke prophylaxis with an antithrombotic agent) and lifestyle modifications (e.g., avoiding extremes of temperature) are also important considerations for patient care [2,19] and should be considered in addition to symptomatic treatments.

5.4. Non-ERT approaches for patients with specific mutations

While this manuscript was under development, the oral small-molecule pharmacological chaperone migalastat (Galafold™; Amicus Therapeutics, Cranbury, NJ, USA) received approval in Europe and Canada for the treatment of a subset of Fabry patients with mutations predicted as "amenable" according to their response to migalastat in an in vitro assay of human embryonic kidney (HEK) cells transfected with mutant *GLA* cDNA.

In a 6-month, double-blind, randomized (1:1), placebo-controlled study, 67 patients (64% female, mean age 42 years, mean $eGFR_{CKD\text{-}EPI}$ 95 mL/min/1.73 m^2) with potentially "amenable" *GLA* mutations received either migalastat or placebo [91]. Eligible patients had either never received ERT or not received ERT for $\geq$6 months and had an eGFR $>$ 30 mL/min/1.73 m^2. The primary endpoint (the percentage of patients who had a response at 6 months defined as a $\geq$50% reduction in the number of GL-3 inclusions in endothelial cells per kidney interstitial capillary [IC]) did not show a significant treatment effect (migalastat 41% of patients, placebo 28%; $p = 0.30$). Based on a modified "suitability" HEK assay developed during the trial [91,92], *GLA* mutations from 17 of the 67 patients (25%) did not meet the new "suitability" criteria. Post-hoc analysis focusing on the non-randomized patients with "suitable" mutations ($n = 50$) showed a significant reduction in GL-3 IC inclusions for patients receiving migalastat for 6 months compared with those receiving placebo (-0.25 ± 0.10 vs 0.07 ± 0.13 GL-3 inclusions in endothelial cells per kidney IC, respectively; $p = 0.008$), but the primary endpoint was not reported for these patients. In the migalastat-only follow-up of up to 24 months of patients with "suitable" mutations, renal function remained stable, LVMI decreased significantly with a trend toward a larger reduction in patients with LVH at baseline, and the severity of GI symptoms decreased.

Table 3
Adjunctive support for the management of adult patients with Fabry disease.

Organ/system	Adjunctive/symptomatic therapy and preventative measures
General	• Genetic counseling (at diagnosis and at adolescence/pre-pregnancy, during pregnancy, or periodically for new issues) [20]
Renal	• Standard management approach for CKD - ACEI or ARB to target albuminuria level < 30 mg/g creatinine if baseline 30–300 mg/g or < 300 mg/g if baseline > 300 mg/g (roughly equivalent to proteinuria > 500 mg/g); great care should be taken if patient has baseline hypotension; dietary salt restriction - general management of CKD regarding statin indication and CKD-MBD prevention and management according to guidelines [87–90] - consider assessment of 25 OH vitamin D levels and replacement therapy if deficient [87] - dialysis or kidney transplantation for patients entering renal failure (donor screened negative for Fabry disease if living related)
Cardiac	• Consider ACEI or ARB; beta blockers should be used with caution and amiodarone avoided in patients receiving ERT[a] • If symptomatic bradycardia/chronotropic incompetence or significant AV conduction impairment, consider permanent cardiac pacing • If evidence of atrial fibrillation, lifetime anticoagulation should be initiated, maintenance of sinus rhythm should be preferred while the use of amiodarone should be avoided, if possible • If evidence or strong suspicion of malignant arrhythmias, consider implantable cardioverter-defibrillator
Cerebrovascular	• Stroke prophylaxis with antithrombotic agents (aspirin or clopidogrel) is indicated as secondary prevention; no data are currently available regarding primary prevention • Stroke prophylaxis with anticoagulants (warfarin or the new anticoagulant drugs in absence of kidney failure), when needed, e.g., patients with atrial fibrillation [17]
Peripheral nervous system	• Individualize strategy for neuropathic pain management • First-line agents include anticonvulsants (e.g., carbamazepine, gabapentin, pregabalin); other drugs can be considered according to current international recommendations for neuropathic pain [19] • Pain crises: consider opioid agonists (care needed to avoid worsening GI disturbances) [19] • Avoid pain triggers with lifestyle modifications (e.g., avoid temperature extremes, maintain proper hydration, use air conditioning, cooling vests, facial mist/spray) [19]
Gastrointestinal	• Delayed gastric emptying and dyspepsia symptoms may be successfully treated with metoclopramide and H-2 blockers, respectively; dysmotility and diarrhea may be treatable with dietary changes (increased fiber intake, more frequent and smaller meals) and pharmacotherapy
Pulmonary	• Bronchodilators to provide relief of airway obstruction
Ophthalmological	• Polarized glasses can help manage difficulty in driving at night (headlight splaying); artificial tears ointment
Auditory	• Hearing aids, cochlear implants
Dermatological	• Laser/cosmetic treatment for angiokeratomas not proven effective; compression stockings can improve lymphedema

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; CKD, chronic kidney disease; GI, gastrointestinal; MBD, metabolic bone disorder.
[a] The use of beta blockers requires careful monitoring due to the risk of bradycardia exacerbation and chronotropic incompetence. The use of amiodarone should also be limited, as it may have an inhibitory effect on α-GAL activity. See also online Appendix B, Section 3.2.

An 18-month, randomized, open-label study assessed the effects of migalastat on renal function in patients with "amenable" *GLA* mutations previously treated with ERT [93]. Fifty-seven patients (56% female, mean age 49 years, baseline mean $eGFR_{CKD\text{-}EPI}$ 92 mL/min/1.73 m^2, mean proteinuria 0.3 g/day) who had received ERT (65% agalsidase alfa 0.2 mg/kg every other week, 33% agalsidase beta 1.0 mg/kg every other week) for ≥12 months prior to the study were randomized (1.5:1) to receive migalastat (without a washout period) or remain on ERT. Patients taking angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) had to be on a stable dose for ≥4 weeks. Primary efficacy analysis was performed using data only from subjects with "suitable" mutations based on a modified HEK assay (migalastat $n = 34$, ERT $n = 19$) instead of the initial HEK assay. Pre-specified criteria were developed to define comparability of GFR results. Renal function, normal at baseline, remained stable on migalastat and ERT at 18 months; proteinuria and albuminuria had increased from baseline in both groups. LVMI decreased significantly in patients switched to migalastat, whereas a smaller, non-significant change was observed in those who continued on ERT. There was no significant difference in percentages of patients experiencing renal, cardiac, or cerebrovascular events. Plasma lyso-GL-3 remained low and stable in both groups and patient-reported outcomes remained stable. A 12-month open-label extension with migalastat showed that the effects were maintained.

These results show that migalastat can have significant effects on some aspects of the course of Fabry disease in a subset of patients with "suitable" mutations, though treatment responses were variable. Interpretation of the migalastat study results in this group of patients is affected by the fact that data from agalsidase alfa- and agalsidase beta-treated patients were pooled, and the study populations consisted mostly of non-classic Fabry patients who are expected to have a slower rate of disease progression than classic patients.

Because migalastat has only been approved in a limited number of countries, Fabry disease experts have not yet gained sufficient clinical experience to make recommendations about the use of this drug at this time. At this point, the different clinical characteristics between patients enrolled in pivotal ERT trials (mostly males) and those enrolled in pivotal migalastat trials (mostly females) and the different spectrum of mutations that may respond to either therapy (all for ERT and a subset for migalastat) complicate generalizations and placement of this therapy in the treatment of Fabry disease.

5.5. Monitoring of adult patients with Fabry disease

Each organ system potentially affected by the disease should be thoroughly evaluated at diagnosis. Patients not (yet) initiated on ERT should be monitored at appropriate intervals, incorporating measures that effectively capture the expected progression of disease, if genotype-phenotype correlation data are available (Table 4). For patients initiated on ERT, it is strongly recommended to regularly assess the impact of ERT on all affected organ systems. A baseline tissue biopsy, especially of the kidney, can serve as a potential marker to assess disease progression if the patient experiences deterioration in his/her condition [97]. Rationales and details of the proposed assessment and monitoring methods are provided in online Appendices A (renal), B (cardiac), C (peripheral nervous system), D (central nervous system), and E (involvement of other organs).

In ERT-naïve patients with later-onset Fabry disease close monitoring may be particularly challenging because signs and symptoms may develop at an age when the incidence of non-Fabry kidney disease, heart disease, and CNS disease in the general population is already increasing. Thus, in some already-symptomatic cases, a tissue biopsy may help distinguish renal or cardiac involvement due to Fabry disease from that due to alternative etiologies.

As mentioned above, the presence of a *GLA* mutation in a female heterozygote woman does not allow for the prediction of her ultimate disease course, although methods to assess the skewing of X chromosome inactivation hold promise in this regard [6]. In general, female

Table 4
Recommended assessments and schedule for monitoring organ involvement in adult patients with Fabry disease.

Organ/system	Assessment(s)	Monitoring schedule
General	Complete history and physical examination including family history and evaluation of quality of life [94], gastrointestinal symptoms, work/study performance, level of depression/anxiety	Every clinic visit
	α-Gal A enzyme activity and *GLA* mutation analysis	If not previously determined
Renal	Glomerular filtration rate (measured GFR [preferred] or estimated [eGFR] using appropriate formulae)	Annually if low risk, every 6 months if moderate risk, and every 3 months if high to very high risk;[a] measured GFR only once yearly because of complexity
	Albuminuria (preferred, more sensitive) and/or proteinuria (24-h or spot urine for total protein/creatinine and albumin/creatinine ratios)	Annually if low risk, every 6 months if moderate risk, and every 3 months if high to very high risk
	25 OH vitamin D	As clinically indicated; vitamin D levels in late fall/early winter
	Kidney biopsy	As clinically indicated. Podocyte foot process effacement may precede pathological albuminuria
Cardiac	Blood pressure and cardiac rhythm	Every clinic visit
	ECG and echocardiography	Annually, and as clinically indicated
	48-h Holter monitoring to detect intermittent rhythm abnormalities; [95] implantable loop recorder recommended for patients with significant hypertrophic cardiomyopathy [96]	Annually, but may be assessed more or less frequently depending on age and other risk factors; if arrhythmias detected, more frequent/detailed rhythm surveillance should be instituted (schedule determined individually)
	Cardiac MRI with gadolinium	If available, whenever there is evidence of clinical progression of disease or regularly at an interval > 2 years
	Cardiac MRI with T1 mapping	Investigational tool, should be interpreted with caution
	Brain natriuretic peptide	At least annually for patients with cardiomyopathy or bradycardia
Cerebrovascular	Brain MRI (TOF MRA at first assessment in male patients aged over 21 and female patients over 30, then according to the clinical picture)	Every 3 years and when clinically needed (e.g., presence of neurological changes that could potentially relate to stroke) [37]
	CT imaging	In case of acute stroke and only if MRI is contraindicated due to cardiac pacing
Peripheral nervous system	Pain evaluation and history: pain measurement scale such as the Neuropathic Pain Symptom Inventory or Brief Pain Inventory	Annually
	Cold and heat intolerance, vibratory thresholds (quantitative sensory testing, if available)	Annually (less frequently in older patients)
	Autonomic symptom evaluation by orthostatic blood pressure	Annually
	Skin biopsy (for IENFD assessment, if available)	Consider
ENT	Audiometry [17]	As required [17]
Pulmonary	Spirometry, including response to bronchodilators, treadmill exercise testing, oximetry, chest X-ray	Every 2 years or more frequently for clinical indications; [17] chest X-ray according to clinical indications
Gastrointestinal	Referral to gastroenterology specialist for endoscopic or radiographic evaluation	If symptoms persist or worsen despite treatment
Overall glycolipid burden	Plasma and urinary sediment lyso-GL-3, GL-3	At baseline and then annually (at the moment, this is for research purposes only); biobanking of plasma/serum samples recommended if feasible
Skeletal	Bone dual-energy X-ray absorptiometry (DEXA)	Consider
Ophthalmological	Ophthalmological screening	Ophthalmological screening as clinically indicated

Rationale and details for each organ system are provided in online Appendices A (renal), B (cardiac), C (peripheral nervous system), D (central nervous system), and E (involvement of other organs). Baseline values should always be obtained; longer intervals between more complex organ assessments can be considered in asymptomatic female patients with a normal initial evaluation and/or favorable X chromosome inactivation pattern.

CKD, chronic kidney disease; CT, computed tomography; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; ENT, ear, nose, and throat; GFR, glomerular filtration rate; IENFD, intra-epidermal nerve fiber density; MRI, magnetic resonance imaging; TOF MRA, time-of-flight magnetic resonance angiography (head and neck).

[a] Risk levels based on KDIGO 2012 chronic kidney disease classification scheme. Low risk, CKD Stage G1/2 A1; moderate risk, CKD stage G3a A1, G1/2 A2; high to very high risk CKD Stage G4 or 5, G3b A1, G3 A3 [90]. See also online Appendix A, including Fig. 1S.

patients should be assessed and monitored (Table 4) in a manner similar to that recommended for men (i.e., a full baseline evaluation followed by annual assessments) although longer intervals between assessments can be considered for asymptomatic women, particularly when a skewed X chromosome inactivation profile with predominant expression of the wild type *GLA* allele has been demonstrated [6]. By contrast, for asymptomatic women with later-onset mutations, initial evaluation may be normal and longer intervals between disease-monitoring tests may be considered. It is important to remain aware that clinical vigilance and regular monitoring are essential, as an absence of symptoms at baseline or at follow-up assessment does not preclude subsequent development of organ complications. For example, women with Fabry disease can have cardiac fibrosis without the appearance of LVH [98]. For this reason, cardiac MRI with gadolinium (to detect late enhancement suggestive of fibrosis) should be considered the first-line diagnostic approach in the cardiac evaluation of women with Fabry disease. Although most female patients have uneventful pregnancies [99], signs such as proteinuria should be monitored closely by a specialist, as they may progress during pregnancy [99], and genetic counseling should be provided in line with current guidance [2,20]. Further details on pregnancy and lactation are provided in online Appendix H.

6. Recommendations for screening

Clinical and genetic screening of the at-risk members of families of newly diagnosed patients is of critical importance, as additional family members with Fabry disease may be identified from each individual index patient. One pedigree review study found that, on average, there were at least five family members diagnosed with Fabry disease following the diagnosis of a proband [100]. These family members may be diagnosed relatively early in the disease process. NBS programs based on enzymatic assays for α-Gal A activity allow for the identification and monitoring of individuals (mostly male) with Fabry disease mutations from an early age [5,101], and permits identification of affected adults in the family. Such programs have been initiated in some states in the USA [20,102], several European countries [20,103,104], and Taiwan [57,105]. Though the use of NBS for the identification of Fabry disease

remains an ethical issue, several publications on patient experiences with NBS for Fabry disease indicate that most patients would prefer to be informed [106–108]. The most prevalent reasons include the elimination of "feeling misunderstood" by parents, teachers, and physicians – usually due to pain symptoms, the opportunity to begin early treatment and prevent complications, and better reproductive decision making [106,107]. However, female patients also indicated that having the genetic knowledge resulted in a feeling of "being labeled as a patient", even though they were asymptomatic [106]; some patients, both male and female, indicated that the early diagnosis also led to a loss of a carefree life and increased worrying about the future [106]. Appropriate genetic counseling should be provided for patients identified via NBS [30]. However, counseling individuals (and families) who have a missense VUS identified through such screening programs remains challenging (see also Section 4 Diagnostic confirmation).

7. Recommendations for genetic counseling

Fabry disease has a profound emotional and physical impact on affected individuals and their families. In order to provide patients with a better understanding of Fabry disease, genetic counseling for patients and their families/partners by a medical geneticist or a counselor with Fabry disease expertise is critical following diagnosis, and forms a vital part of the multidisciplinary approach to the management of Fabry disease.

An initial genetic counseling session should be focused on Fabry disease's X-linked pattern of inheritance, genetic testing options available for the patients, and identification of at-risk family members through the creation and interpretation of a detailed family history. It is also important to ensure that patients understand that female patients can be significantly affected by the disease, and should not be regarded simply as carriers of it [6,7,20]. As appropriate, genetic counseling sessions should also address the psychosocial issues that can arise following a diagnosis of Fabry disease, such as anxiety concerning disease progression, guilt related to passing the disease on to children, denial of disease progression, and other strong emotions such as anger, grief, blame, hopelessness, and impacts on self-esteem and self-identity. Where applicable, economic, social, disability, employment, and life insurance impacts should also be addressed/discussed [20,101]. Provision of Fabry support group information and informational resources to patients and their families can help them to further understand their diagnosis and provide a means of reducing a potential sense of isolation. Pre-conception or prenatal genetic counseling should be offered to all male and female patients of reproductive age, discussing Fabry disease's X-linked pattern of inheritance, availability of both prenatal diagnosis using cultured amniocytes or chorionic villi for molecular testing and preimplantation genetic diagnosis for selection of unaffected embryos. Pre-conception genetic counseling is important when pregnancy is being considered, as some adjunctive therapies routinely used to treat Fabry symptoms are teratogenic and may pose a risk to fetal development [99].

8. Discussion

The clinical heterogeneity of Fabry disease mandates an individualized approach to patient care that reflects the genotype, gender, family history, phenotype, and specific clinical symptom severity of a given patient. ERT with agalsidase is a cornerstone of therapy, and there is growing evidence that the clinical response to treatment is improved with early ERT initiation. Ideally, adult male patients with a classic Fabry mutation should initiate ERT promptly, regardless of Fabry symptoms, with appropriate adjunctive treatment for symptomatic management. Adult female patients with classic mutations should be considered for ERT if they present with symptoms suggesting major organ involvement or, if still asymptomatic, if there is laboratory, histological, or imaging evidence of injury to the major organs. The latter requirement is also applicable for patients with later-onset Fabry mutations or *GLA* VUS. Thus, tissue-based assessment of Fabry disease pathology may assist the decision to initiate ERT and may occasionally be helpful in assessing disease progression and response to treatment during follow-up. Adult female patients without signs or symptoms of Fabry disease should be monitored regularly for evidence of organ involvement. In conclusion, the long-term management of adult patients with Fabry disease should involve timely ERT, regular assessment of disease progression in all patients, and the use of appropriate adjunctive therapies by a multidisciplinary care team to assist in the management of organ-specific complications.

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Conflicts of interest

A.O. is a consultant for Sanofi Genzyme and has received speaker fees from Shire HGT and Amicus Therapeutics.
D.P.G. has received honoraria from Amicus Therapeutics, Sanofi Genzyme, and Shire HGT, and fees for consulting from Sanofi Genzyme and Shire HGT.
R.J.D. has founder stock in Amicus Therapeutics, consults for Amicus Therapeutics, Kiniksa Pharmaceuticals, and Sangamo BioSciences, and receives royalties from Sanofi Genzyme and Shire HGT.
J.P. has received honoraria for presentations and board meetings from Amicus Therapeutics, Sanofi Genzyme, and Shire HGT.
M.M. consults for Sanofi Genzyme and receives research funding from Sanofi Genzyme. This interest has been reviewed and managed by the University of Minnesota in accordance with its conflict of interest policy. He also consults for and has a service contract with Amicus Therapeutics and has reviewed research grants from Shire HGT.
A.B. has received honoraria for presentations and board meetings from Amicus Therapeutics, Merck-Serono, Nutricia, and Sanofi Genzyme; he is a member of the European Advisory Board of the Fabry Registry, which is sponsored by Sanofi Genzyme, and of the Nutricia International Advisory Board.
C.E. is on the Fabry Registry Board of Advisors, has been on a speaker's bureau with Sanofi Genzyme and has been an investigator in clinical trials sponsored by Sanofi Genzyme and Shire HGT.
R.J.H. consults with Sanofi Genzyme and Shire HGT, and has been an investigator in clinical trials sponsored by Amicus Therapeutics, Sanofi Genzyme, and Shire HGT. These activities have been monitored and found to be in compliance with the conflict of interest policies at Cincinnati Children's Hospital Medical Center.
D.L. is on the Fabry Registry Board, consults with Sanofi Genzyme, and has been an investigator and coordinator in clinical trials sponsored by Alexion, Amicus Therapeutics, Protalix BioTherapeutics, Pfizer, Retrophin, Sanofi Genzyme, Shire HGT, and Synageva. These activities have been monitored and found to be in compliance with the conflict of interest policies at Emory University School of Medicine.
A.L. is a member of the Fabry Registry Board. He has received honoraria and fees for consulting from Amicus Therapeutics, Sanofi

Genzyme, and Shire HGT.

S.W. has been a member of the Fabry Registry Board. He has received honoraria from Amicus Therapeutics, Sanofi Genzyme, and Shire HGT and fees for consulting from Sanofi Genzyme and Shire HGT.

E.W. has received honoraria for presentations and board meetings from Sanofi Genzyme. He has been an investigator in clinical trials sponsored by Sanofi Genzyme. These activities have been monitored and found to be in compliance with the conflict of interest policies at the University of Alabama at Birmingham.

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Appendices A–H. Supplementary data

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