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Expert review in diagnostic, therapeutic and follow-up of Fabry disease in Latin America based on patient care standards

Roberto Giugliani [a], Juan Politei [b], Ana Martins [c], Nelson Murillo [d], Paula Rozenfeld [e], Mauricio Lopera [f], Sergio Salgado [g], Gustavo Quirós [h], Charles Marques [i], Osvaldo Vieira [j], Hernán Amartino [k], Fernando Perretta [l], Sandra Marques e Silva [m], Joseph Brooks [n], Laura Titievsky [o], Jacobo Villalobos [p], Cassiano Braga [q], Harris A. Peñaranda [r,*]

[a] PPGBM UFRGS, HCPA, DASA Genomics and Casa dos Raros, Rua Ramiro Barcelos 2350, 90035-903, Porto Alegre, RS, Brazil
[b] Departamento de neurología, FUNDACION SPINE. Bs As, Argentina
[c] Universidade Federal de São Paulo, Departamento de Pediatria Rua Botucatu, 598 Vila Clementino 04023-062, Sao Paulo, SP, Brazil
[d] Clínica de Occidente, Calle 19 N # 5N-35, Cali, Colombia
[e] Instituto de Estudios Inmunológicos y Fisiopatológicos (IIFP), UNLP, CONICET, asociado CIC PBA, Facultad de Ciencias Exactas, Departamento de Ciencias Biológicas, La Plata, Argentina
[f] Hospital Pablo Tobón Uribe, Cl. 78b #69-240, Medellín, Colombia
[g] Centro internacional de especialistas (CIE), valle de menzuly Km 7, Piedecuesta, Colombia
[h] Nefrouros, Carrera 11 No 27-27, Tunja, Colombia
[i] Neurogenetics Unit - Inborn Errors of Metabolism Clinics, National Reference Center for Rare Diseases Faculdade de Medicina de São José do Rio Preto, SP, Brazil
[j] Servicio De Nefrologia De Ribeirao Preto, Av Vereador Manir Calil, 880, Ribeirão Preto, Brazil
[k] Instituto Neurogenia, Hospital Universitario Austral, Buenos Aires, Argentina
[l] NEFRA Medical Care Escobar, Provincia de Buenos Aires, Argentina
[m] Instituto Hospital de Base do Distrito Federal at SMHS - Área especial, Q 101, Brasília, DF, Brazil
[n] Universidade Metropolitana de Santos- UNIMES, Av. Gal. Francisco Glycerio, 8 - Encruzilhada, 11045-002, Santos, São Paulo, Brazil
[o] Cardiología e Imagen Cardiovascular, Instituto de Cardiología de Corrientes., Argentina
[p] Servicio de Medicina Interna, Hospital Regional de Antofagasta., Chile
[q] Clinica Senhor do Bonfim, Av Getulio Vargas, 744Centro44001496, Feira de Santana, Brazil
[r] Pint Pharma Colombia, Crr 13 85-39 of. 306, Bogotá, Colombia

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ABSTRACT

Background: Fabry disease (FD) is an X-linked lysosomal sphingolipidosis. It is caused by pathogenic variants in the GLA gene with a consequent deficiency of the enzyme α-galactosidase A, resulting in the pathological accumulation of glycolipids - mainly globotriosyl ceramide (GL-3, GB3) and its deacylated product, globotriaosylsphingosine (Lyso-Gb-3) - in plasma and in a wide variety of cell types throughout the human body; it is characterized as a chronic, multisystemic disease with progressive evolution, which causes deterioration of the patient's quality of life and decreases survival and life expectancy.

In Latin America there are different limitations to the management of patients with Fabry disease, in most countries, access to diagnostic tools and treatment on time is complex and can sometimes suffer delays in its implementation. This situation is due to the high costs to health systems of follow-up and pharmacological therapy for Fabry patients, creating barriers to timely access.

Conclusions: Although medical criteria are fundamental in the choice of pharmacological therapy, the final decision should also rely on the patient's choice according to their expectations and the adherence and compliance with the treatment that they are willing to follow. As it has been described, there are currently three therapeutic options, for which the appropriate profile must be defined to achieve the best clinical outcomes, considering that it is a permanent treatment; experts consider that Fabry patients need comprehensive and interdisciplinary management to stop the progression and functional deterioration of the affected organs by its multiple systemic manifestations. In Latin-American countries, it is difficult to guarantee this comprehensive and coordinated management, due to limited public policies related to orphan diseases diagnosis, treatment and follow up.

* Corresponding author at: Crr 13 85-39 of. 306, Bogotá, Colombia.
E-mail addresses: harris.penaranda@pint-pharma.com, harris.penaranda@doctorado.unini.edu.mx (H.A. Peñaranda).

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It is considered crucial to structure support networks specialized in Fabry disease and generate partnerships with health institutions and other health system stakeholders, that would articulate and coordinate patients and relatives counseling and management, establish the specific pharmacological treatment to reduce the progression of the disease and the systemic involvement, deciding between the administration of enzyme replacement therapy or the most recent option of oral management with pharmacological chaperone both with proven effectiveness. This will be the decision of the attending physician, who will propose and advise the therapeutic choice that best suits the patient's needs.

1. Background

Fabry disease (FD) is an X-linked lysosomal sphingolipidosis. It is caused by pathogenic variants in the GLA gene [1] with a consequent deficiency of the enzyme α-galactosidase A, resulting in the pathological accumulation of glycolipids - mainly globotriosyl ceramide (GL-3, GB3) and its deacylated product, globotriaosylsphingosine (Lyso-Gb-3) - in plasma and in a wide variety of cell types throughout the human body [2].

It is characterized as a chronic, multisystemic disease with progressive evolution, which causes deterioration of the patient's quality of life and decreases survival and life expectancy [3,4].

There are different variants of the disease according to its phenotype, ranging from a "classic" phenotype, this being the variant with onset in infancy and with multi-organ involvement, to a late-onset phenotype, with cardiac manifestations. In female patients, this is explained by X-chromosome inactivation patterns [5]. The X-chromosome inactivation pattern in women results in the presence of more severe symptoms or attenuated forms, which defines the need for treatment [6,7].

The diagnosis of Fabry disease is based on the presence of clinical, biochemical, molecular, and pathological criteria. Given the challenges with each of these criteria, it is recommended that a patient has at least three of the four criteria before a definitive diagnosis of Fabry disease is made, although, if there are characteristic pathologic findings, fewer criteria may be needed [7,8].

Patient treatment with Fabry disease can be divided into specific therapeutics such as enzyme replacement therapy (ERT) or pharmacological chaperones, and symptomatic supportive care [9].

ERT was the first disease-specific therapy developed for Fabry disease and is designed as a genetically engineered enzyme that replaces the deficient enzyme [10].

Migalastat is another therapeutic choice for the treatment of patients with Fabry disease, it is a novel molecule intended for patients with amenable pathogenic variants of the GLA gene [1]. It is a first-in-class orally administered pharmacological chaperone that binds to amenable mutant forms of α-Gal, leading to enhanced physical stability of the enzyme, improved intracellular transport, and enhanced lysosomal activity. It is estimated that 35–50 % of patients diagnosed with Fabry disease have variants amenable to migalastat treatment [11,12].

Both migalastat and ERT have proved benefits in long-term follow-up studies in Fabry patients [13,14].

A retrospective study showed that among male patients treated with ERT with Fabry disease, those who developed antibodies against the replacement enzyme had significantly higher plasma Lyso-Gb3 levels than those without ERT antibodies ($P = 0.02$) [15,16]. Furthermore, ERT decreased the presence of Gb3 inclusions in glomerular cells after 6 months of treatment in patients with FD [17,18]. Similarly, migalastat has been shown to decrease podocyte volume and partially eliminate Gb3 inclusions in podocytes after 6 months of treatment in male and female patients with Fabry disease [18].

Specific treatment will look to prevent the onset of irreversible organ damage, while at the same time, when showed in first stages, it may reverse some of the pathophysiological mechanisms that lead to cellular death. Treatment should be supervised by a multidisciplinary team of experts in the disease including, among others, pediatricians (in the case of initiating treatment in children), neurologists, cardiologists, nephrologists, ophthalmologists, dermatologists, otorhinolaryngologists and clinical geneticists [2].

This article presents the context and current situation of some countries from Latin America (Argentina, Chile, Colombia and Brazil) regarding how the diagnosis, treatment and follow-up of Fabry disease patients is currently addressed, access to health services for these patients, as well as other dimensions such as regulation, patient participation and research that are relevant to the Fabry disease environment.

Finally, this article proposes policy recommendations that address the main challenges for the benefit of patients living with Fabry disease and opportunities for improvement in patient's care to improve their quality of life, supported by ethical considerations.

2. Status of Fabry disease in Latin America

Rare diseases are a large group of diverse conditions which individually have a low prevalence, but which together can affect 6 % of the world population [6]. Latin America is a region with about 640 million inhabitants, being a significantly large population, there is no certainty of data about the global prevalence of rare diseases, a situation that is not alien to Fabry disease. According to expert knowledge about the Fabry registry, Latin-American patients tend to be younger than patients registered in the rest of the world, documenting an average age in years of 35.5 versus 39.2 for men and 37.8 versus 43.6 for women, with a lower percentage of Latin-American patients who have received ERT compared to patients in the rest of the world, being 67 % versus 80 % for men and 19 % versus 39 % for women, respectively [7]. Thirty-one percent of men and 22 % of women in Latin America reported having experienced a clinically significant cardiovascular, renal, or cerebrovascular event, at a mean age of 35 ± 12.6 years in men and 44 ± 12.3 years in women, being the most common clinical events [7,8].

In Latin America, the management of patients with Fabry disease faces various limitations. In most countries in the region, access to diagnostic tools and prompt treatment is complex and often suffers delays in implementation. This situation is due to the high costs that health systems incur for the follow-up and pharmacological therapy of Fabry patients, creating barriers to timely access.

In countries such as Brazil and Colombia, based on patient follow-up experiences, patients must resort to legal resources to ensure that the health system provides them with the necessary medications for their treatment on time. This needs to appeal to legal means reflects the systemic and economic difficulties faced by patients.

Additionally, it is important to highlight that there is still little dissemination of knowledge about rare diseases among the medical and scientific community in the region. This underscores the need to strengthen medical education in the clinical identification and treatment of conditions like Fabry disease. Improving training and knowledge about these diseases is crucial to ensure more effective and prompt diagnosis and treatment.

3. Barriers to Fabry disease in Latin America

The following barriers were found among the experts involved in this review for the diagnosis and treatment in patients with Fabry, as well as proper follow-up (Table 1):

4. Diagnosis

The diagnosis of Fabry disease in Latin America faces several significant barriers. Firstly, there is a lack of knowledge in the medical field about the manifestations of the disease, which makes early and correct identification difficult. This lack of information results in misdiagnoses or delayed diagnoses, negatively affecting patient outcomes. Secondly, in some countries, insurers do not guarantee access to the necessary diagnostic tests, preventing many patients from receiving an adequate and prompt diagnosis. This lack of coverage is partly due to the high costs associated with these specialized tests. Finally, few primary healthcare professionals are trained in the clinical manifestations of rare diseases, including Fabry disease. This lack of specific training limits the ability of frontline doctors to recognize and appropriately refer patients who could receive help from more detailed and specialized evaluations. These combined barriers create a challenging environment for the effective diagnosis and treatment of Fabry disease in the region [8].

5. Treatment

The treatment of Fabry disease in Latin America faces multiple challenges. Firstly, in some countries in the region, treatment is not authorized or covered on time, delaying the initiation of therapy, and negatively affecting patients' health. Additionally, ensuring continuity in pharmacological management is complicated due to the high costs associated with these treatments, which can lead to interruptions in therapy and worsen patient outcomes. Cultural barriers also play a significant role, as some patients may not fully adhere to treatment due to beliefs or cultural practices that interfere with the therapeutic regimen. Finally, none of the available therapies are included in the health system coverage in many countries, forcing patients to seek costly alternatives or rely on legal resources to obtain the necessary treatment. These combined barriers create a challenging environment for the effective management of Fabry disease in the region [8,19].

6. Follow Up

The follow-up of patients with Fabry disease in Latin America faces several significant challenges. Firstly, patients often do not visit the same healthcare professionals during their follow-up due to the organization of healthcare providers, leading to inconsistencies in care and potential gaps in treatment [8]. Secondly, there are no specialized centers dedicated to the care of patients with this disease, which means that patients may not receive the comprehensive and specialized care they need. Lastly, there is a general lack of interest in the supportive care for patients with Fabry disease, which can result in inadequate management of the disease and poorer health outcomes. These factors combined create a challenging environment for the effective follow-up and management of Fabry disease in the region [19].

7. Suspecting patients with Fabry disease: clinical manifestations and screening

Recently, different reviews of the strategies for the detection of Fabry disease have been conducted based on the detailed knowledge of the natural history of the disease and the genetic alterations of the disease [20,21].

The family tree in Fabry disease has been shown to be very relevant in the screening of this disease and identification of affected subjects. Nonspecific manifestations are often found in several members of the patient's family. In addition, family tree analysis allows early detection of cases [22].

Detection of the disease requires the use of different tools such as screening and clinical diagnosis (Fig. 1). (See Fig. 2.)

Patients with Fabry disease presents symptoms that can be common and not very specific to the disease, such as the classic clinical, cardiological and nephrological manifestations of Fabry [26], and other more specific, but infrequently presented, such as neurological, psychiatric, auditory, and gastroenterological manifestations [27]. Nephrologists state that the first marker of the disease in classical forms is the presence of proteinuria; in addition, parapelvic cysts in Fabry disease can be confused with those of polycystic disease, being present in up to 90 % of patients; the presence of these in the study of a patient with renal disease (RD) should raise suspicion of Fabry [28]. In cardiology, hypertrophic heart disease and alterations of the interventricular septum, cardiac rhythm disturbances are found early, such as extreme bradycardias, tachyarrhythmias with short PR segments, dysautonomia pictures, palpitations, and elevation of NT-proBNP levels [29].

This group of experts suggest that any patient with unexplained proteinuria is potentially a candidate for consideration of this entity as a differential diagnosis, and in patients who do not have traditional risk factors, since there is no familial inheritance to suspect hereditary proteinuria. Another ideal type of patient to be screened are patients under 50 years of age who are not hypertensive, who have presented an ischemic CVD and patients with ventricular hypertrophy without clear etiology and not associated with valvopathies [30].

There are a significant number of patients on renal replacement therapy and peritoneal dialysis whose cause of renal disease cannot be decided. It is important to consider the diagnosis of this entity in these patients, because, although renal function is being replaced, there are organs such as heart and brain whose function must be preserved and therefore the presence of Fabry disease should be ruled out. [31]

Another important group that should be considered are patients with small fiber sensory neuropathy of non-filial cause, even, thinking about this, as a debutant manifestation. In this group there are a considerable number of patients in whom Fabry disease should be ruled out as a cause [32].

Finally, once the diagnosis of Fabry is considered in a patient, the performance of a multidisciplinary approach is needed in order to evaluate possible target organs impact of the disease by different diagnostic methods such as: electrocardiogram, magnetic resonance imaging

Table 1
Barriers found to Fabry disease in Latin America.

1. ***Diagnosis***
A. Lack of knowledge of the medical area about the manifestations of the disease.
B. Some insurers do not guarantee access to diagnostic tests.
C. Few primary healthcare professionals are trained in the clinical manifestations of rare diseases, including Fabry.
2. ***Treatment***
A. Treatment is not authorized/covered on time in some Latin American countries.
B. Difficulties in guaranteeing continuity in pharmacological management due to its high cost.
C. Cultural barriers of patients do not guarantee full adherence to treatment.
D. None of the therapies are included in the coverage of the health system.
3. ***Follow-up***
A. Patients do not usually visit the same professionals during their follow-up due to healthcare providers organization.
B. There are no specialized centers for the care of patients with this disease.
C. Lack of interest about the supportive care for patients with Fabry disease.

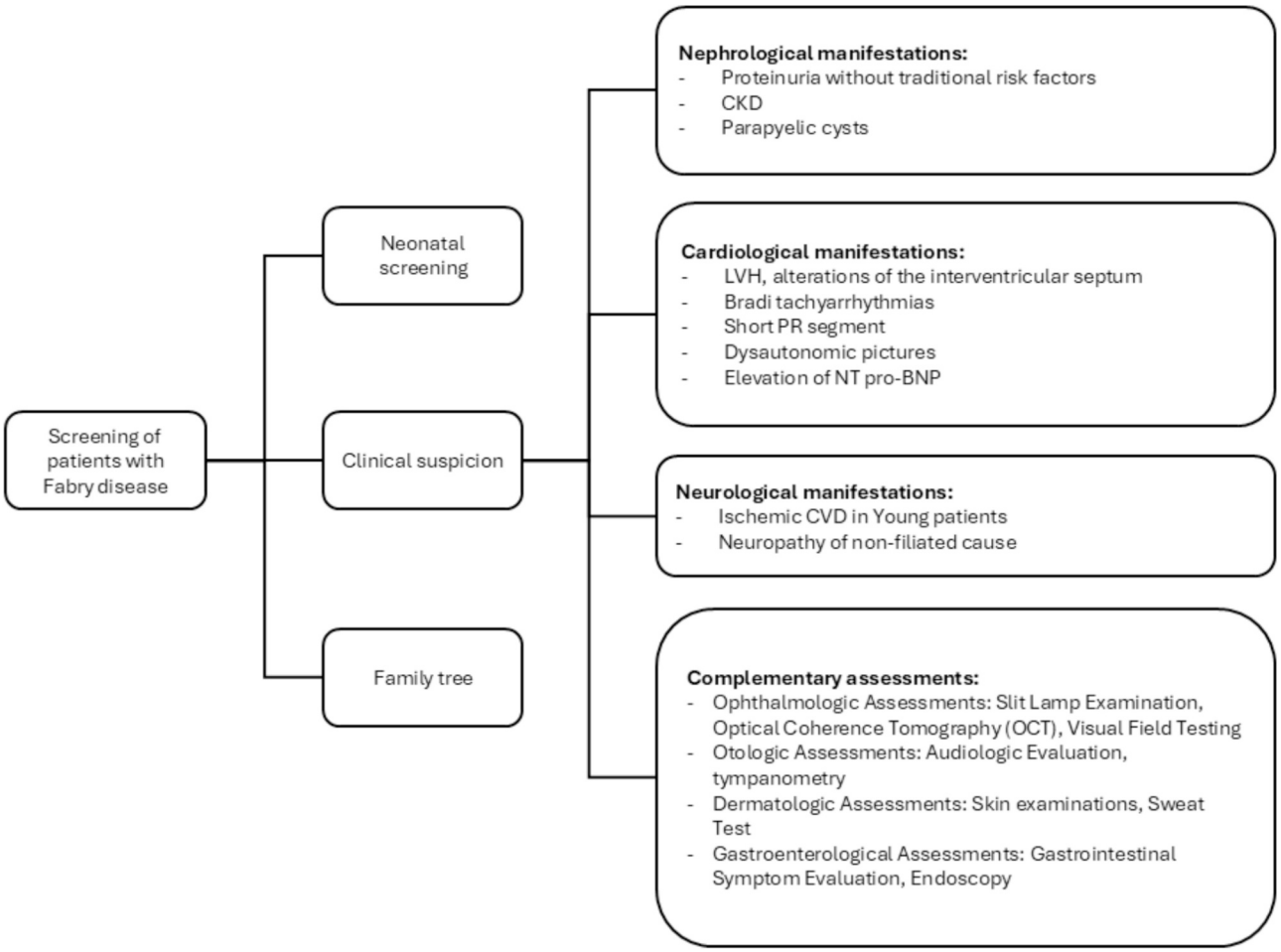

Fig. 1. Screening scenarios for patients with Fabry disease [23,24,25]

with gadolinium (with T1 MAP) in order to detect cardiac fibrosis, echocardiogram to evaluate systolic function and biomarkers such as troponin and NT-proBNP; an evaluation of renal function should also be made with measurement of proteinuria, ultrasound of the urinary tract and renal biopsy in selected cases. Finally, for neurological evaluation, tests such as non-contrast cranial MRI and quantitative sensory test (if available) should be performed to exclude differential diagnoses.

8. Laboratory diagnosis and monitoring of the disease

Different publications and clinical practice guidelines agree in setting up that the biochemical diagnosis of Fabry disease in affected males is performed by measuring of alpha-Galactosidase A (α-Gal A) activity in leukocytes taken from peripheral blood or, cultured fibroblasts [33,34].

Although laboratory tests are used for diagnostic confirmation, clinical suspicion is the first and most important tool to make the diagnosis of the patient with Fabry disease and according to the clinical suspicion, biochemical and molecular tests will be performed [35]. Interdisciplinary groups are key for follow-up and early identification of target organ complications. In Latin America, clinical, genetic, pathological and biomarker tools are available for the diagnosis and follow-up of Fabry patients; however, in most cases the local health system may set longer timelines in their administrative steps to diagnose these patients, leading to patient and physicians' frustration.

In Fabry disease, molecular diagnosis plays several important roles as a tool to identify the different genetic variants and in some cases to evaluate whether it is a classic or non-classic Fabry [36]; in addition, it allows for the follow-up and identification of female heterozygotes and enables an adequate genetic counseling can be carried out. In Latin America, the necessary tools are available to make the diagnosis by enzymatic and genetic studies, which has made it possible to conduct prevalence studies of the disease in population groups at risk by these analytical techniques [37].

Experts agree that diagnostic confirmation varies according to sex as follows: the confirmatory method in males is the enzymatic study that demonstrates a severe enzymatic deficiency in leukocytes, in females the measurement of enzymatic activity is not reliable because many female carriers have normal activity, being the genetic study the most reliable method for the diagnosis of heterozygous females [38]. In several countries of the region these tests are covered by health plans; however, there are barriers on the part of the system's payers so that they can be performed in a timely manner in many patients, as it is the case in Colombia, in contrast to countries such as Argentina and Chile, which do not face this limitation. Molecular diagnosis is a tool that allows Fabry patients to choose the treatment, the need to adjust it and finally to define the need to change the pharmacological treatment [39].

Detecting the genetic variant in the *GLA* gene is useful in some cases to predict the phenotype of the disease [1]. In female patients, the demonstration of a pathogenic variant in *GLA* gene is needed for the diagnosis of Fabry disease since the enzyme activity can be in the normal range [40]. For patients with variants of uncertain significance in the *GLA* gene, clinical, biochemical, and histopathological demonstration of Fabry disease is needed to set up the pathogenic nature of the variant [23].

Although it is an X-linked disease, to make a correct diagnosis

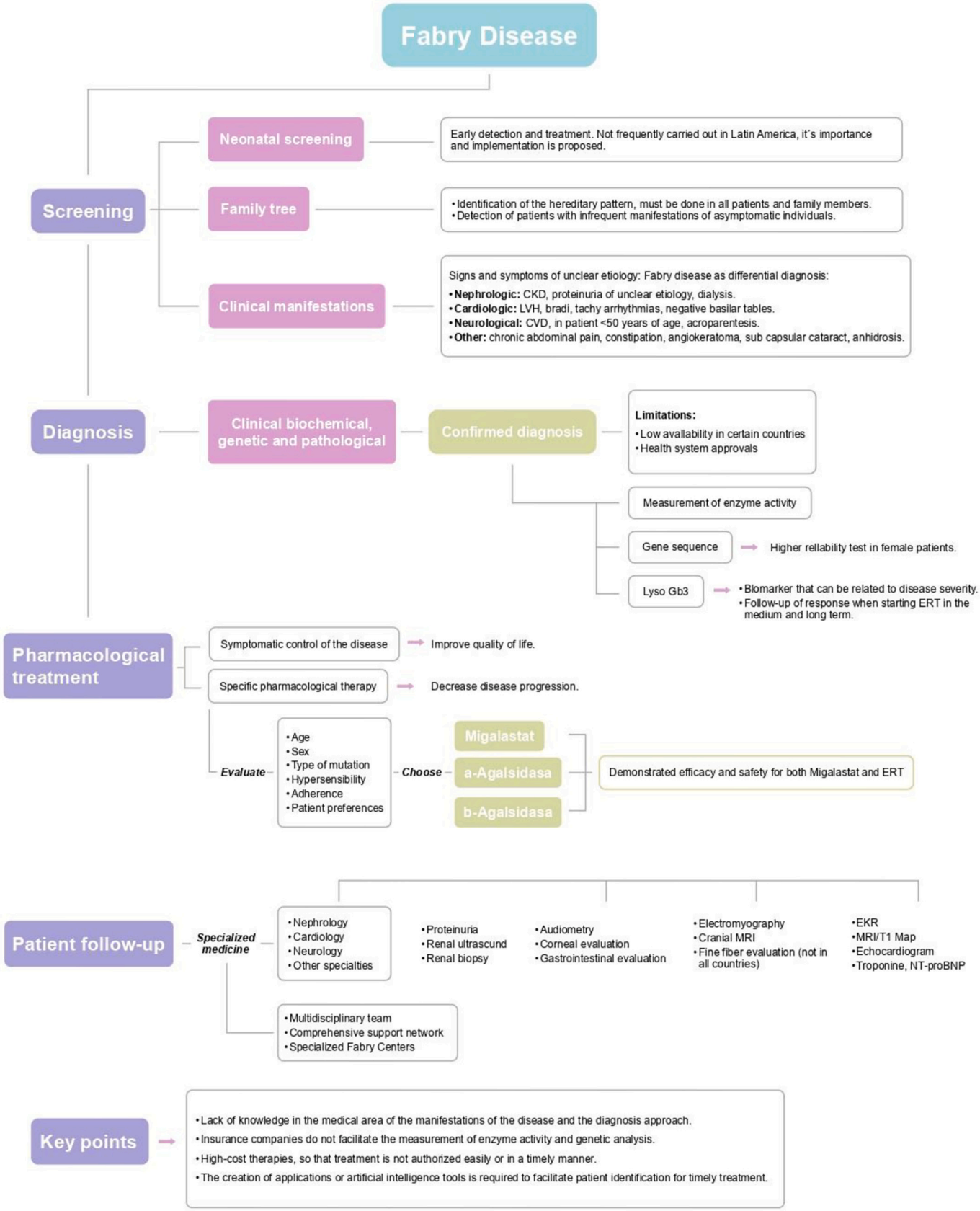

Fig. 2. Key points in Latin America for Fabry disease.

professionals recommend enzyme activity measurement and sequencing. With this data therapeutic decisions can be made, such as the use of oral pharmacological chaperones if the variant is amenable [41].

For follow up and response to treatment, globotriaosylsphingosine or Lyso-Gb3 has been used as a biomarker which can correlate to the risk progression of renal disease and cardiovascular events such as cardiac arrhythmias and stroke [42–44].

However, the use of Lyso-Gb3 as a follow-up marker in patients receiving pharmacological treatment with migalastat has not been shown to be effective; studies have proved that the concentrations of Lyso-Gb3 in patients treated with migalastat do not correlate with measures of disease progression such as the size of the left ventricle and the glomerular filtration rate, nor it is useful to predict associated clinical events. In 2022, an international expert consensus concluded that the hypothesis that plasma lyso-Gb3 may not be a suitable biomarker for monitoring treatment response in migalastat-treated patients was based on the analysis of a predominantly female and late onset population [42] and may not apply to classic phenotype males Furthermore, the disease is independent of characteristics such as earlier treatment or patient gender [21,44].

In prespecified analyses, patients who were switched from placebo to migalastat at month 6 (stage 2) experienced a significant reduction in the mean number of GL-3 inclusions/KIC (− 0.33 GL-3 inclusions/KIC; $p = 0.01$; $n = 17$) and plasma lyso-Gb3 levels (− 15.5 ng/ml; $p < 0.001$; $n = 13$) after 6 months of therapy (i.e., at month 12) [45]. The beneficial effects of 6 months' migalastat therapy on these two surrogate endpoints during the double-blind period were kept during a further 6 months of open label migalastat treatment [46].

In evaluable patients in the mITT (Modified intent to treat) population, plasma lyso-Gb3 levels were kept at the same low levels in the migalastat and ERT groups, and comparable results were seen between male and female patients [12]. Conversely, in two patients with non-amenable GLA variants, plasma lyso-Gb3 levels increased after switching from ERT to migalastat [12].

The mean change from baseline in 24 h urine protein was fourfold lower in migalastat recipients than ERT recipients after 18 months (49.2 vs. 194.5 mg) [44]. Clinical outcomes for GL-3 inclusions/KIC, plasma lyso-Gb3 levels and the LVMi (Left Ventricular Mass Index) were not affected by renal function at baseline [47].

There are also other limitations around the use of this test to monitor the patients with Fabry disease; first, concerning the need for this test, in some countries the health system payers are unaware of the nature of this test and its indications (as in the case of Brazil). Secondly, obtaining the result of this lab test can be delayed, so it does not provide an approximation in real time. Sometimes, private sector projects such as DPS (diagnosis patient support), have supported the process to perform the test and obtain its result in brief period.

9. Pharmacological treatment

On the management of Fabry disease, an international panel of experts with experience in the clinical management of patients with this pathology collaborated in the development of therapeutic guidelines of this condition. The authors belong to different subspecialties and perform a comprehensive review of the relevant medical literature on Fabry disease [20].

Although there are several guidelines and consensus recommendations for the treatment of the disease, there have been changes in the aims looked-for in-patient management. This was motivated by a better understanding that early initiation of ERT or migalastat can prevent organ damage in later life, improving both morbidity and mortality [44]. The mindset has shifted from a focus on treatment alone to one of prevention, with the aim of keeping organ function and improving patient's quality of life. Consequently, there is a need for updated recommendations for the management of patients with Fabry disease.

The heterogeneity in disease severity observed among female patients is attributable to factors such as X-chromosome inactivation, which significantly impacts the clinical manifestation and progression of Fabry disease. Consequently, this variability necessitates a tailored approach to treatment and monitoring to optimize patient outcomes [48].

About the pharmacological alternatives available for the management of Fabry disease, ERT with a-agalsidase and b-agalsidase have shown consistent efficacy and safety results; experts in the region have experienced with their use in the treatment of patients and are familiar with the characteristics of the molecule. Table 2 reflects the recommendations for treatment with ERT and migalastat. (See details on indications on migalastat on Table 3.)

Regarding the use of migalastat, phase 3 clinical studies have demonstrated that this drug is able to effectively decrease the substrates of the disease, stabilizes the renal function, reduces the LVMi and consequently reduces ventricular hypertrophy, also, improves gastrointestinal symptoms in patients with Fabry disease with variants able to migalastat treatment [42].

Oral therapy with pharmacological chaperone such as migalastat, offers among its main advantages the greater convenience of administration, the low frequency of occurrence of adverse effects derived from the use of the drug [46]; the experts consider that compliance and adherence to oral therapy needs narrow supervision and relies almost entirely on the patient's compliance in not omitting drug doses. Some specialists reinforce the importance of making patients aware of treatment adherence and the importance of patient support programs, as there is no direct supervision.

During therapy with Migalastat, the therapeutic goals are:

(1) Stabilization of organ deterioration, i.e., kidney insufficiency.

(2) Organ function improved, i.e., decrease in left ventricular mass in patients with a hypertrophic cardiomyopathy,

(3) Overall reduction in Fabry related symptoms.

(4) Improvement of quality of life.

(5) Decrease of lyso-Gb3 in parallel to an increase of AGAL activity. (1)

Using all this information, it must be decided if the therapeutic goals are achieved and thus the patient is clinically amenable [49].

Patients must have specific characteristics to be candidates for this treatment choice, such as being older than 12 years, weight equal or superior to 45 kg with amenable variants and GFR >30 ml/min/1.73 m^2 [50].

Although medical criteria are fundamental in the choice of pharmacological therapy, the final decision should also rely on the patient's choice according to their expectations and the adherence and compliance with the treatment that they are willing to follow. As has been described, there are currently three therapeutic options, for which the proper profile must be defined to achieve the best clinical outcomes, considering that it is permanent treatment [51].

For the initiation of treatment in Fabry disease, it is emphasized that the decision goes beyond the efficacy and safety proved by the available therapies, which are satisfactory [51]. They recommend that each case should be evaluated individually according to gender, age, family history, the condition of the most often affected organs, the patient's place of residence, intellectual and cognitive level, and finally the patient's preferences.

About the suspension or change of pharmacological treatment, criteria such as stabilization or deterioration of renal function, inadequate responses, presence of adverse events, presence of antibodies, progressive cardiovascular compromise, abdominal pain or Acro paresthesia that do not improve should be evaluated. Patient criteria that are also important relate to preference for oral or intravenous therapy, travel, ease of administration, and quality of life. They consider that the decision to drop or change a treatment in Fabry patients should not only be consensual but based on the lab test result, considering that withdrawal of treatment would worsen the patient's clinical condition

Table 2
Recommendations for the initiation of ERT and Migalastat in adult patients with Fabry disease.

Population		Recommendations for the start of ERT and Migalastat
Classic Fabry	**Male patient, symptomatic or asymptomatic**	1. Consider ERT in any patient and at all ages. 2. Consider Migalastat in any patient Older than 12 years, weight equal or superior to 45 kg with amenable variants and GFR >30 ml/min/1.73 m^2
	Female patient, symptomatic	1. Signs/Symptoms suggesting major organ involvement a) Neuropathic pain, pain crises, neuropathy secondary to Fabry's disease. b) Proteinuria/albuminuria of unknown cause, evidence of renal injury (may require biopsy) c) Stroke or TIA d) Cardiac disease not attributable to other causes (dyspnea, palpitations, syncope, chest pain) e) Chronic diarrheal disease; gastrointestinal dysfunction (diagnosis of exclusion) f) exercise, profuse sweating 2. Consider Migalastat in any patient Older than 12 years, weight equal or superior to 45 kg with amenable variants and GFR >30 ml/min/1.73 m^2
	Female patient, asymptomatic	1. Consider ERT if there is laboratory, histological or imaging evidence of renal, cardiac or CNS injury. a) Renal disease: decreased GFR (<90 ml/min/1.73m^2 adjusted for age > 40 years (GFR category >G2), persistent albuminuria >30 mg/g (category A2 or A3), podocytopathy or glomerulosclerosis in renal biopsy moderate to severe GL-3 inclusions in diverse types of renal cells. b) Silent stroke, cerebral white matter lesions (cerebral MRI). c) Asymptomatic cardiac disease (cardiomyopathy or arrhythmias), cardiac fibrosis (contrasted cardiac MRI). 2. Consider ERT if there is a pattern of X-chromosome inactivation with predominant expression of the GLA gene variant with or without demonstration of low levels of alpha-galactosidase A activity in the presence of signs and symptoms of the disease. 3. Consider Migalastat in patients Older than 12 years, weight equal or superior to 45 kg with amenable variants and GFR >30 ml/min/1.73 m^2, if there is a pattern of X-chromosome inactivation with predominant expression of the GLA gene variant with or without demonstration of low levels of alpha-galactosidase A activity in the presence of signs and symptoms of the disease.
Late-onset Fabry variant or GLA variant of unknown onset variant	**Male or female patient**	1.Consider ERT if there is laboratory, histologic or imaging evidence of renal, cardiac or CNS injury according to the above criteria. Alterations should be attributed to Fabry, this will require a histological evaluation of GL-3 accumulation. 2. Counseling by a genetic expert in the management of Fabry disease is needed to interpret the pathogenicity of any variant of uncertain significance. 3. Patients with well-characterized benign GLA polymorphisms should not be treated with ERT. 4. In the absence of histological demonstration, ERT is not a proper management particularly in heterozygous female patients. These patients need follow-up by a multidisciplinary team. 5. Consider Migalastat in patients Older than 12 years, weight equal or superior to 45 kg with amenable variants and GFR >30 ml/min/1.73 m^2 if there is laboratory, histologic or imaging evidence of renal, cardiac or CNS injury according to the above criteria. Alterations should be attributed to Fabry, this will require a histological evaluation of GL-3 accumulation.

ERT: enzyme replacement therapy; **CVA**: cerebrovascular attack; **TIA**: transient ischemic attack; **CNS**: central nervous system.
GFR: glomerular filtration rate**; GL-3**: globotriosyl ceramide; **MRI**: magnetic resonance imaging.
Source: Changed from Ortiz et al. (2018).

and the progression of the disease. They have seen that mild to moderate adverse reactions secondary to infusions most of the time can be resolved and do not require discontinuation of treatment [52]. They should not be considered drug allergies.

10. Migalastat versus ERT

There are several attributes of migalastat that make it an attractive alternative to ERT for treating Fabry disease. First, migalastat has a convenient oral regimen, thereby eliminating the requirement for life-long IV infusions and complications that have been associated with IV ERT (a-agalsidase and b-agalsidase), such as infusion-related reactions (e.g., fever, chills, flushing, headache, pruritus, and nausea) and hypersensitivity reactions (e.g., allergic, or anaphylactic-type reactions) [53]. The non-immunogenic nature of migalastat means that such antibody-related tolerability issues, which have been described for several ERTs, are not expected [54]. Secondly, as a small molecule, migalastat is likely to have enhanced cellular and tissue distribution and the potential to cross the blood-brain barrier [as shown in Fabry transgenic mice], which may help in the treatment of disease symptoms originating in the central nervous system [55]. The improved efficacy of migalastat compared with ERT in reducing cardiac mass suggests that migalastat may be more effective than ERT at penetrating cardiac tissue [56]. As an orally administered therapy, migalastat may also ease earlier benefit than ERT in patients with Fabry disease.

Migalastat, a small molecule pharmacological chaperone therapy has important advantages over parenteral therapy; starting with a simpler administration, which minimally interferes with the patient's daily life as it can be administered autonomously without requiring additional

Table 3
Indications to start Oral Therapy with Migalastat.

Indications for treatment with Migalastat
Older than 12 years old
Weight equal or superior to 45 kg
GFR >30 ml/min/1.73 m^2
Have an amenable variant consulted in the web portal: https://www.galafoldamenabilitytable.com/hcp

GFR: glomerular filtration rate

interventions prior to infusion; in addition, it is a therapy with a low frequency of adverse effects [12] and of course the probability of generating allergic reactions and anaphylaxis is minimal with this therapy compared to ERT infusion. Patients with a treatment-amenable variant may be eligible for migalastat and more than one treatment, unlike the non-amenable variant, which is limited to ERT. Amenable mutation does not always mean clinically amenable patient – adherence should be checked -, but there are other factors that can interfere in the response [57].

With ERT, infusion can be verified and thus ensure adherence, however, because of the requirement to go every two weeks to an intravenous infusion administration center leads to a greater impact on the patient's quality of life. In recent years, the infusion of ERT at home has been implemented as a strategy to avoid transfer the patient to the hospital to receive the intravenous infusion; some experts in the region have experienced with this practice for more than 10 years, however, the real life in all Latin-American countries is different and it is not a widely spread practice, especially due to different barriers by the local health systems, therefore not all patients with Fabry treated with ERT can access this advantage.

About ERT, these have important characteristics, the infusion guarantees quicker bioavailability of the drug and its distribution. The disadvantages include the fact that since it is an intravenous drug, it requires the use of frequent venous access [58].

In terms of efficacy and safety (adverse events and drug-drug interactions) the following is concluded: the studies performed for both therapies have shown efficacy and a wide safety margin, some evidence suggests that migalastat may have a slight edge in safety [59,60,61]. ERT has long-term studies that support its safety and the management of adverse events; during long-term therapy, these beneficial effects on endogenous α-Gal A activity levels were sustained, renal function was kept across a wide spectrum of baseline function, and cardiac mass was reduced. [62]. To date, no antibodies against oral therapy with migalastat have been reported.

During long-term therapy, these beneficial effects on endogenous α-Gal A activity levels were sustained, renal function was kept across a wide spectrum of baseline function, and cardiac mass was reduced. In summary, the results of this post hoc analysis suggest that patients with Fabry disease and amenable *GLA* variants had stable renal function during long-term migalastat treatment (≤8.6 years) irrespective of treatment status, sex, or phenotype. Prompt treatment should be encouraged to stabilize or slow the decline in renal function in patients with Fabry disease [63,64].

A recent review focused on the safety and efficacy of switching from ERT to migalastat in Fabry patients with "amenable" GLA variants based on currently available literature. The authors concluded that, due to its proven efficacy in the reduction of LVMi and stabilization of renal function and disease biomarkers, migalastat offers a safe alternative for switching from ERT or starting therapy in patients with FD and "amenable" variants [65,64].

11. Patient follow-up

Clinical practice guidelines define that the clinical course will decide the frequency of testing and clinical evaluation needed for follow-up of the Fabry patient. Follow-up information and data on all Fabry patients should be transferred to a central national and regional registry [60].

At least one annual assessment should be considered for asymptomatic Fabry disease patients and should be more frequent for symptomatic patients by a multidisciplinary medical team, including cardiology, neurology, and nephrology diagnostics [1,66].

Experts consider that Fabry patients need comprehensive management to stop the progression and functional deterioration of the organs affected by its multiple systemic manifestations [64,67]. In some Latin-American countries, it is difficult to guarantee this comprehensive and coordinated management, so they advise the patients themselves to keep a schedule that allows the treating physicians to see the follow-ups of other specialties. They consider that institutions specialized in the management of Fabry would optimize its management in general an "integral support network" and it is considered crucial to have centers specialized in the treatment of Fabry patients.

The Fabry disease patient pathway must be improved. Education is the first pillar. In addition, it is necessary to create academic clusters or specialized Fabry support networks to improve the care network and ensure that the diagnosis can be guaranteed in a correct, quick, prompt, and reliable manner. The experts consider that for Fabry disease, local data collection should be strengthened to generate a greater number of scientific publications, conduct epidemiological analyses, and achieve the interpretation of local variants. In this way, it is possible to make the disease visible, define its course in our context and specify routes and recommendations for the patient.

Table 4 summarizes the recommended interventions to be performed and the periodicity in which they should be evaluated according to each system or organ that may be compromised in the patient with Fabry disease.

12. Conclusions

Fabry disease is a heterogeneous and multisystemic disease; in Latin America, there are barriers in the local health systems that limit the possibility to diagnose, treat and follow up the patients properly.

It is considered crucial to structure support networks specialized in Fabry disease and generate partnerships with health institutions that would articulate and coordinate patient management. Create multidisciplinary groups under the context of comprehensive evaluation in Fabry disease, in favor of the authorization of certain medical prescription.

It is important to establish the specific pharmacological treatment to reduce the progression of the disease and the systemic involvement, deciding between the administration of ERT or option of oral management with a migalastat, which has proven effectiveness (will be a decision of the treating physician within the patient to consider the therapeutic option that meets the best requirements for the patient).

There should be more intervention from health authorities through its policies, providing more resources towards rare diseases and encouraging awareness on these clinical conditions.

It is necessary to create a consensus with key opinion leaders that allows the development of an algorithm for this disease that can be implemented by physicians in Latin America and serve as starting point for the review of treatments approved by the local health system.

Table 4
Recommendations for the evaluation and follow-up of organ involvement in adult patients with Fabry disease.

System/Organ	Intervention	Frequency
General	Complete history and clinical examination	Each medical visit
	Family history, assessing quality of life	
	Work/academic performance	
	Symptoms of depression or anxiety	
	Assessment of α-Gal A activity	If they have not been previously
	GLA gene variant analysis	previously
Renal	Assessment of GFR (ideally measured)	According to risk: low: yearly
	or estimated according to formula (eGFR)	Intermediate: semi-annually
	Albuminuria or proteinuria in 24 h; or	High and very high: every 3 months
	25 OH Vitamin D	Expert's criteria
	Renal biopsy	Expert's criteria
Cardiac	Blood pressure and heart rate	Every medical visit
	ECG and echocardiogram	Annual
	48-h Holter monitoring	Annual or according to risk factors
	Cardiac MRI with gadolinium	If there is evidence of disease progression disease progression or > 2 years
	Cardiac MRI with T1 mapping	Screening tool
	BNP	Annually for patients with cardiomyopathy or bradycardia
Cerebrovascular	Brain MRI (resonance angiography)	Every 3 years thereafter according to clinical requirement in male patients older than 21 years and female patients older than 30 years
	Cranial computed tomography	In case of stroke
Nervous System	Evaluation of pain clinical history and application of scales such as:	Annual
	Neuropathic Pain Symptom Inventory	
	Pain Symptom Inventory or Brief Pain Inventory	
	Evaluation of heat and cold tolerance	
	Orthostatic blood pressure, autonomic symptoms	
	Neuropsychological evaluation according to the patient or informant complaint	
Skin and adnexa	Skin biopsy	According to the expert's criteria
Hearing	Audiometry	According to clinical manifestations
Pulmonary	Spirometry and bronchodilator response	Every 2 years
	Chest X-ray	
Gastrointestinal	Refer to gastroenterologist for endoscopic and	According to symptoms
	endoscopic and radiographic evaluation	
Glycolipids	Lyso-Gb3, GL-3 in plasma and urinary sediment	Initial and then annual assessment
Bone	Bone densitometry	According to expert's criteria
Vision	Ophthalmologic evaluation	According to expert's criteria

GFR: glomerular filtration rate; eGFR: estimated glomerular filtration rate; GLA: alpha-galactosidase A; ECG: electrocardiogram; MRI: magnetic resonance imaging; BNP: brain natriuretic peptide; CVA: cerebrovascular attack; stroke; Lyso-GL-3: globotriaosylsphingosine.
Source: taken from Ortiz et al. (2018).

Abbreviations

Abbreviation	Definition
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CVA	Cerebrovascular Attack
CVD	Cardiovascular disease
DPS	Diagnosis Patient Support
ERT	Enzyme Replacement Therapy
FD	Fabry Disease
GFR	Glomerular Filtration Rate
GL-3, GB3	globotriosyl ceramide
ITT	Intent To treat
KIC	Kidney Interstitial Capillary
LVH	Left Ventricular Hypertrophy
LVMi	Left Ventricular Mass Index
Lyso-Gb3	globotriaosylsphingosine
mITT	Modified Intent To treat
MRI	Magnetic Resonance Imaging
NT-proBNP	N-terminal pro-B type natriuretic peptide
TIA	Transient Ischemic Attack
α-Gal A	alpha-galactosidase A

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Data sharing is not applicable to this article as no data was generated or analyzed during the development of this study.

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Authors' contributions

This work was carried out using a qualitative focus group technique with review by experts and as such should consider the potential bias of the participants, coming from their experience and work environment, which may determine their opinion in each section; however, the opinion of a group of specialists, from different medical specialties, would always be of higher quality than the opinion of a single professional, for which all the participants add their opinions and the support bibliography of each aspect involved. RG, AM, CM and PR compiled and added the Laboratory diagnosis and monitoring of the disease section and contributed to the pharmacological treatment and barriers from their expertise in genetics and diagnosis, as well as JP, SS, JB, HA who did add the resources related to neurological manifestations, follow up and treatment. ML, GQ, OV, FP, JV, CB contributed for the creation of the diagnosis pathway and the barriers identifications, also contributed to the diagnosis, and follow up of renal impairment. NM, SM, LT contributed to the diagnostic and follow up related to the cardiology matters, HP contributed gathering and organizing the authors contributions and added the information about health systems limitations, the conclusions section was constructed between all the authors at the end of the focus group.

CRediT authorship contribution statement

Roberto Giugliani: Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Juan Politei:** Writing – review & editing, Writing – original draft, Conceptualization. **Ana Martins:**

Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Nelson Murillo:** Writing – review & editing, Validation. **Paula Rozenfeld:** Writing – original draft, Validation, Supervision, Conceptualization. **Mauricio Lopera:** Writing – original draft, Validation, Supervision. **Sergio Salgado:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Gustavo Quirós:** Writing – original draft. **Charles Marques:** Writing – original draft, Validation, Methodology. **Osvaldo Vieira:** Writing – review & editing, Validation. **Hernán Amartino:** Writing – review & editing, Methodology. **Fernando Perretta:** Methodology, Investigation, Conceptualization. **Sandra Marques e Silva:** Methodology, Investigation, Conceptualization. **Joseph Brooks:** Writing – review & editing, Writing – original draft. **Laura Titievsky:** Writing – review & editing, Conceptualization. **Jacobo Villalobos:** Writing – review & editing. **Cassiano Braga:** Writing – review & editing. **Harris A. Peñaranda:** Writing – original draft, Resources, Project administration, Funding acquisition.

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Data availability

No data was used for the research described in the article.

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