Preventing the consequences:
An evidence-driven proposal for a change in the treatment paradigm for Fabry disease to ensure timely and equitable access to treatment after confirmatory diagnosis

Fabry Australia Medical Advisory Committee

Dr Drago Bratkovic
Metabolic Clinic, Women's and Children's Hospital, Adelaide, SA

A/Prof Charles Denaro
Department of Internal Medicine and Aged Care, Royal Brisbane and Women's Hospital, Herston, QLD

A/Prof Carolyn Ellaway
Paediatric Specialist Genetic Metabolic Disorders Service, Sydney Children's Hospital Network, Sydney, NSW

A/Prof Kathy Nicholls
Department of Nephrology, Royal Melbourne Hospital, Parkville, VIC

Dr Michel Tchan
Department of Genetic Medicine, Westmead Hospital, NSW

Prof Mark Thomas
Department of Nephrology, Royal Perth Hospital, Perth, WA

Fabry Australia Committee

Megan Fookes OAM
Former Managing Director, Fabry Australia, NSW

Sheridan Campbell
Chair, Fabry Australia, VIC

Funding and support

This report has been funded by an unrestricted education grant from Amicus Therapeutics, Sanofi Aventis Australia Pty Ltd, and Takeda Pharmaceuticals Australia Pty Ltd. Editorial assistance was provided by Hazel Palmer MSc, ISMPP CMPP™ of Scriptix Pty Ltd. The working group members are responsible for all content and interpretation of the data; they received no honoraria related to the development of this report.

CONTENTS

ABBREVIATIONS **3**

BACKGROUND AND RATIONALE **3**

LITERATURE SEARCH STRATEGY **4**

DEFINITION OF PATIENT GROUPS FOR TREATMENT ELIGIBILITY **4**

Background 4
Contemporary considerations for the classification of Fabry disease 6
Fabry Australia Working Group: Recommendations (1) 6

CHOICE OF TREATMENT **8**

Background 8
Fabry Australia Working Group: Recommendations (2) 9

SENSITIVITY OF TREATMENT INITIATION CRITERIA **9**

Background 9
Fabry disease: New data, consensus and expert opinions 10
Rationale for early treatment initiation 13
Treatment initiation in paediatric patients 14
Treatment initiation in patients with classical Fabry disease 14
Treatment initiation in patients with non-classical Fabry disease 15
Fabry-related organ involvement and the need for confirmatory biopsy 15
Fabry Australia Working Group: Recommendations (3) 17

SUMMARY **20**

REFERENCES: **20**

WORKING GROUP – PROFILES **27**

APPENDICES **31**

Appendix 1: Search Strategy 31
APPENDIX 2. Summary of organ involvement criteria to trigger initiation of Fabry-specific therapy. 33
Appendix 3: Comparison of treatment guidelines in Australia, UK, and Canada 36

LIST OF TABLES

Table 1. Recommendation: Contemporary classification criteria. 7
Table 2. Current LSDP criteria for treatment access 10
Table 3. Summary of published consensus and expert opinions. 11
Table 4. Recommendation: Fabry-specific treatment initiation criteria 17

LIST OF FIGURES

Figure 1. Clinical signs and symptoms suggestive of Fabry disease. 5

ABBREVIATIONS

alpha-Gal A	alpha-galactosidase A
cMRI	cardiac magnetic resonance imaging
eGFR	estimated glomerular filtration rate
ERT	Enzyme replacement therapy
GB3	Globotriaosylceramide [also referred to as GL3]
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLA	Galactosidase Alpha
LGE	Late gadolinium enhancement
LSDP	Life Saving Drug Program
LVMI	Left ventricular mass index
Lyso-GB3	Globotriaosylsphingosine [also referred to as lyso-GL3)
MWT	Mean wall thickness
VUS	Variant of unknown significance

BACKGROUND AND RATIONALE

Fabry disease is a rare, inherited X-linked disease caused by pathogenic variants of the galactosidase alpha (*GLA*) gene encoding the enzyme, alpha-galactosidase A (alpha-Gal A).[1] Reduction in enzyme activity causes accumulation of toxic metabolites, globotriaosylceramide (GB3) and the deacylated form globotriaosylsphingosine (lyso-GB3), leading to progressive kidney disease, cardiomyopathy, and cerebrovascular, and reduced life expectancy.[2 3]

Fabry disease is underdiagnosed.[4] Prevalence is geographically variable and subject to founder effect, current prevalence is estimated as 1 to 5/10,000, but increases to 1 in 3,000 when late-onset variants are accounted for.[5] Fabry disease is a chronic, slowly progressive disorder. In the absence of a cure, the aim of treatment is to delay progression or stabilise current symptoms.[6] However, the early symptoms of Fabry disease are non-specific and diagnostic delay is common, with published median delays of between of 14.0 [Fabry Outcome Survey][7] to 21.0 years [German dataset of 39 patients].[8] This delay often results in progressive, irreversible tissue damage prior to treatment commencement.[9 10]

Fabry disease is characterised by a wide spectrum of heterogeneously progressive clinical phenotypes. Disease specific treatments aim to delay progression or stabilise current symptoms. In Australia access to available treatments is managed via the Life Saving Drug Program (LSDP) Committee and each patient must meet pre-specified diagnostic and eligibility criteria in order to access treatment. Despite significant progress in the understanding of Fabry disease[11] and its management ,[12] these LSDP criteria have not been reviewed for more than 15 years.

The Australian patient organisation, Fabry Australia, and its Medical Advisory Committee of six experts who manage the majority of the known cases of Fabry disease in Australia, draw on the published literature and current clinical practices to provide contemporary

recommendations to guide clinical management of patients diagnosed with Fabry disease. It is hoped that these recommendations will help to inform updated treatment access for patients with Fabry disease in Australia.

LITERATURE SEARCH STRATEGY

A search strategy (Appendix 1) was constructed based on the methodology/search strategy in Casis 2015.[13] The search returned a total of 938 citations (when limited to 5 years) and 1582 citations (when limited to the last 10 years). The resultant outputs from the 5-year search strategy were imported into excel, and of these, 125 were selected based on a review of their titles and abstract content.

The available literature has been used to inform three core considerations:

1. the definition of patient groups for treatment eligibility
2. choice of treatment
3. the sensitivity of the treatment initiation criteria in terms of the symptomology it encompasses and the flexibility to adapt to emerging evidence

These considerations have been applied to the Australian setting and relevant recommendation statements developed.

DEFINITION OF PATIENT GROUPS FOR TREATMENT ELIGIBILITY

Background

Fabry disease is best described as a disease with a wide spectrum of heterogeneously progressive clinical phenotypes, ranging from the classic severe phenotype in males to a benign course in some asymptomatic females, with a variety of clinical presentations in-between. Other than the timing of presentation of clinical features, the criteria for establishing a diagnosis of Fabry disease are not age dependent.[14 15]

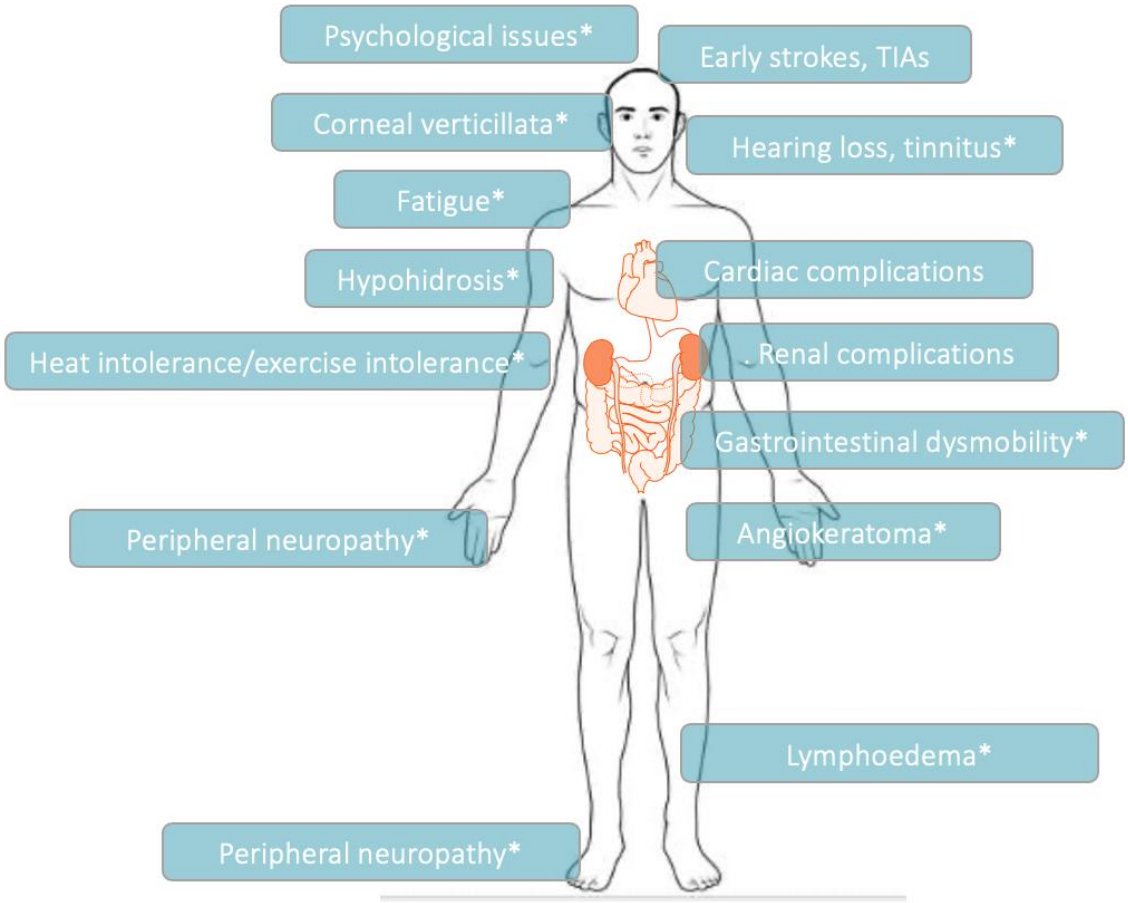
Intermittent episodes of burning pain in the extremities (acroparesthesias), cutaneous vascular lesions (angiokeratomas), diminished perspiration (hypo- or anhidrosis), corneal verticillata, and gastrointestinal symptoms (abdominal pain, nausea, and/or diarrhoea of unknown aetiology) are often the first clinical manifestations of Fabry disease.[16] However, the spectrum of clinical features prompting suspicion of Fabry disease are diverse (Figure 1).

Patient Perspectives:

Australian experience suggests that inheritance is a key driver of Fabry diagnosis in Australia, family screening/cascade testing played a role in diagnosis in 48% of males and 80% of women. As a consequence, diagnostic delay is reduced with 37% having had their diagnosis confirmed diagnosed prior to symptom onset and a further 23% within 6 months of symptom onset.[17]

Consistent with this, pain, renal, cardiovascular or gastrointestinal involvement were the most frequent contributors of symptom-driven diagnosis reported amongst Australian patients.[17]

Figure 1. Clinical signs and symptoms suggestive of Fabry disease.
Adapted from: Yousef Z, et al. 2013 [16]



*Denotes symptom onset in childhood/adolescence. TIA, transient ischaemic attack.

Contemporary considerations for the classification of Fabry disease

In patients with clinically suspected Fabry disease, diagnosis can be confirmed based on either demonstration of reduced alpha-Gal A enzyme activity (in males ≤5% of the mean reference value confirms classical Fabry disease[18]) or identification of a pathogenic *GLA* gene variant.[15]

In non-classical Fabry disease, manifestations may be limited to a single organ (e.g. variant-specific cardiac or kidney involvement).[19] Cardiac variant Fabry disease is the most common late-onset variant, and patients may be asymptomatic until cardiomyopathy is diagnosed later in adult life. Heterozygous females can be affected as classical Fabry disease, but the range of symptoms varies.[20] Females usually have a milder phenotype than males, but they may have severe organ (kidneys, heart, and/or brain) involvement,[21] [22] which occurs on average around a decade later than the male patients.[22]

While hundreds of different *GLA* gene variants have been described,[22] most are private.[23] Patients with clinical symptoms suggestive of Fabry disease but with a variant of unknown significance (VUS) on *GLA* gene testing therefore pose a diagnostic challenge. In such cases, diagnosis would require the patient to meet the criteria within three of the four categories: biochemical, molecular, clinical, and histopathologic.[24]

Biopsy of an affected organ provides definitive evidence of Fabry disease by showing vacuolization and typical lysosomal inclusions or zebra bodies on electron microscopy. However, it is not required for confirmation of diagnosis in all patients. Current consensus suggests that evidence of GB3 accumulation in renal or cardiac biopsies may be of value to confirm a diagnosis in patients with VUS, particularly in patients whose clinical signs are nonspecific and alternative or additional diagnoses are under consideration.[24]

However, to avoid unnecessary risks, the indication for conducting a tissue biopsy should be strongly supported by convincing arguments, such as cases of atypical presentations, cases in which it is necessary to rule out other pathologies or overlapping diseases, and patients with 30- to 300mg/g albumin-to-creatinine ratio and normal kidney function.[25] Renal biopsy is rarely indicated as a requirement to determine disease-specific treatment commencement. Similarly, cardiac biopsy can be used to confirm or exclude Fabry disease as the cause of left ventricular hypertrophy in patients with VUS (particularly in females) after genetic sequencing. However, it should not be used to determine treatment efficacy or to follow-up cardiac involvement.[26] A recent review of cardiac involvement in Fabry disease further supports restricting the use of cardiac biopsy to diagnosis in patients with VUS and low lyso-GB3 levels, and has highlighted the emerging role of cardiac imaging, particularly cardiac magnetic resonance imaging (cMRI), for diagnosis and staging.[27]

Fabry Australia Working Group: Recommendations (1)

- After confirmation of diagnosis, evidence-based criteria should be applied for phenotypic classification of Fabry disease[15]
- Fabry disease should be categorised as classic or non-classical disease. [14]

- The current literature supports the phenotypic classification of Fabry disease for treatment eligibility (Table 1).
- In patients in whom classification based on these criteria is not feasible, the final classification judgement should be made by the Fabry specialist.[15]
- In non-classical Fabry disease, biopsy is not required for diagnosis; its use should be reserved for excluding other treatable diseases or when dealing with GLA VUS.
- The advice of an expert in genetics and management of Fabry disease should be sought for interpretation of the pathogenicity of a variant of unknown significance.[15]

Table 1. Recommendation: Contemporary classification criteria.

Classification	Criteria

Classical male	• A likely pathogenic or pathogenic variant in the *GLA* gene
	• One or more of the following characteristic symptoms of Fabry disease:
	  ○ Fabry neuropathic pain
	  ○ Corneal verticillate
	  ○ Angiokeratomas
	  ○ Severely decreased or absent leucocyte alpha-Gal A enzyme activity (≤5% of the mean reference value*)

Classical female	• A likely pathogenic or pathogenic variant in the *GLA* gene
	• One or more of the following characteristic symptoms of Fabry disease:
	  ○ Fabry neuropathic pain
	  ○ Corneal verticillate
	  ○ Angiokeratomas

Non-classical male	• A likely pathogenic or pathogenic variant in the *GLA* gene • Not fulfilling the criteria for classical Fabry disease
Non-classical female	• A likely pathogenic or pathogenic variant in the *GLA* gene • Not fulfilling the criteria for classical Fabry disease

* alpha-Gal A reference range: 2.0 to 6.9 nmol/h/mL [≤5% = ≤1.0 nmol/h/mL]
alpha-Gal A, alpha-galactosidase A; GLA, Galactosidase Alpha

CHOICE OF TREATMENT

Background

Fabry disease is a chronic, slowly progressive disorder. In the absence of a cure, the aim of treatment is to delay progression or stabilise current disease/symptoms.[6] The current available therapeutic options for eligible individuals are:

- Enzyme replacement therapy (ERT):
  - Agalsidase alfa (Replagal)
  - Agalsidase beta (Fabrazyme)
- Oral therapy with a chaperone that facilitates trafficking of alpha-Gal A to lysosomes in patients with a migalastat-amenable *GLA* variant.
  - Migalastat (Galafold)

The clinical efficacy of the available treatment options is established in the literature and is not in question.[12] No compelling evidence exists to consider one therapy superior to another. The impact of the available therapies on mortality is unknown.

ERT:

- Systematic literature reviews demonstrate significant decreases in GB3 accumulation and improvement in Fabry symptoms and quality of life in paediatric,[28] adult male,[29] and adult female[30] Fabry patients.
- Studies have found that both available ERT preparations can stabilise or improve Fabry symptomatology.[31 32]
- Agalsidase beta may be considered as the first option in male patients with a classic phenotype (based on Arends 2018,[33] CFDI/Sirrs, 2018[34], El Dib, 2017[35])

Migalastat:

- Approved for the treatment of Fabry disease in adult patients with an amenable *GLA* gene variant (https://www.galafoldamenabilitytable.com/hcp).[36 37]
- Available data support that migalastat should not be used in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2.
- Pivotal clinical trial data [38 39] and open-label extension follow-up[40 41] and real-world data[42] demonstrate improvement in Fabry symptoms.
  - FACETS included both ERT-naïve and ERT-experienced patients[39]
  - ATTRACT included only ERT-experienced patients[38]

Symptomatic improvement has been established with ERT in paediatric,[28] adult male,[29] and adult female[30] Fabry patients and with migalastat in both ERT-naïve and ERT-experienced patients.[39]

As of January 2022, the LSDP criteria restrict the use of migalastat to second-line therapy after a minimum 12-month trial of ERT, despite data from the FACETS trial demonstrating efficacy in a population of ERT-naïve patients. More recently updated guidelines in the UK and Canada do not include this restriction (See Appendix 3).

A recent Italian consensus suggests that on the basis of currently available evidence, "*Migalastat can be considered either as a first-line therapy – given its efficacy, extensive*

tissue penetration, convenient oral regimen, and the current limited therapeutic options available – or in patients on ERT who experience side effects, poor compliance to chronic i.v. therapy, or in the case of unstable disease."[43]

Fabry Australia Working Group: Recommendations (2)

- No compelling evidence exists to consider one therapy superior to another
- No compelling evidence exists to support a better treatment response to migalastat in patients who have previously received 12 months of ERT as opposed to ERT-naïve patients.
- Choice of therapy should be individualized for each patient in discussion with their physician.
- Consideration of choice of migalastat therapy in patients with migalastat-amenable GLA variants should include:
    - Degree of organ involvement
    - Patient compliance (with pre-agreed thresholds)
    - Need for increased surveillance of response to treatment
    - Desire for pregnancy in the next 12 months

SENSITIVITY OF TREATMENT INITIATION CRITERIA

Background

Initiation of Fabry-specific treatment is contingent upon a fully confirmed diagnosis of Fabry disease.[24]

The current LSDP application form for Fabry-specific treatment requires a patient to meet at least one of a range of criteria (Table 2).

The current LSDP treatment initiation criteria do not distinguish between classical and non-classical patients with Fabry disease, who have different prognoses and different severity of symptoms. The current criteria do not take into account other important symptoms of Fabry disease that can greatly affect quality of life, such as gastrointestinal symptoms.

This creates considerable and unnecessary difficulty in ensuring timely treatment initiation to optimise outcomes and avoid irreversible damage to organs in those patients with most severe symptoms (i.e. male and female patients with classical disease).

Patient Perspectives:

Amongst Australian patients surveyed, 42% reported that they were not receiving disease-specific treatment, reasons given included not having many symptoms (60% of respondents) and not meeting eligibility criteria (34% of respondents).[17] This is despite the fact that very few patients (6%) reported experiencing no symptoms at

all, and those experiencing symptoms reported having more than one (average 3.34 symptoms).

Table 2. Current LSDP criteria for treatment access

Fabry-related renal disease	Male Fabry patients: abnormal albumin excretion rate (> 20µg/min), as determined by 2 timed urine collections, at least 24 hours apart. and/or abnormal protein excretion (>150mg/24 hours). and/or albumin: creatinine ratio greater than upper limit of normal, in 2 separate samples, at least 24 hours apart. and/or renal disease due to long-term accumulation of glycosphingolipids in the kidneys. Female Fabry patients: proteinuria >300mg/24 hours with clinical evidence of progression. and/or renal disease due to long-term accumulation of glycosphingolipids in the kidneys.
Fabry-related cardiac disease	Left ventricular hypertrophy, as evidenced by cardiac MRI or echocardiogram data, in the absence of hypertension. (If hypertension is present, it should be treated optimally for at least 6 months prior to the submission of an application through this criterion) and/or Significant life-threatening arrhythmia or conduction defect.
Ischaemic vascular disease	Shown on objective testing with no other cause or risk factors identified.
Uncontrolled chronic pain	Uncontrolled chronic pain despite the use of optimal doses of appropriate analgesia and antiepileptic medications for peripheral neuropathy.

Fabry disease: New data, consensus and expert opinions relating to when specific treatment should be initiated

Prior guidelines have recommended initiation of treatment for all patients either at the onset of symptoms or onset of organ involvement; for example, those of the European Fabry Working Group published in 2015.[44] However, there has been a substantial advancement in knowledge, as is evidenced by the volume of published consensus and expert opinions now available (Table 3). Relevant criteria (Appendix 2) and management guidelines (Appendix 3) have been tabulated and used as background to inform the Fabry Australia Working Group recommendations.

The increasing body of contemporary data, consensus and expert opinion supports that:

- Timely treatment initiation is important to avoid irreversible damage to organs.
- Risk factors for progression of disease while on therapy include – male gender, classical phenotype, older age at treatment initiation, reduced renal function, proteinuria, cardiac hypertrophy and fibrosis, hypertension and the occurrence of events before the start of treatment.[3]
- Early initiation of therapy, especially in males with classical Fabry disease, improves treatment outcomes.[45 46]
- Treatment late in the course of the disease may have limited efficacy.[47]
- New imaging techniques offer the means to detect Fabry-related organ damage earlier than was previously possible, their adoption would facilitate treatment initiation before advanced or irreversible organ damage occurs.[47]

Table 3. Summary of published consensus and expert opinions.

Region	Theme	Title	Year	Reference
Global	Renal	Chronic kidney disease and an uncertain diagnosis of Fabry disease: approach to a correct diagnosis	2015	[48]
Global	Management	Early indicators of disease progression in Fabry disease that may indicate the need for disease-specific treatment initiation: findings from the opinion-based PREDICT-FD modified Delphi consensus initiative	2020	[47]
Global	Outcomes	Standardising clinical outcomes measures for adult clinical trials in Fabry disease: A global Delphi consensus	2021	[49]
International	Management	Fabry disease: guidelines for the evaluation and management of multi-organ system involvement	2006	[50]
International	Renal	Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference	2017	[51]
International	Management	Fabry disease revisited: Management and treatment recommendations for adult patients	2018	[24]

Europe	Renal	Fabry nephropathy: indications for screening and guidance for diagnosis and treatment by the European Renal Best Practice	2013	[52]
Europe	Cardiac (LVH & VUS)	Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance	2014	[18]
Europe	ERT	Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document	2015	[44]
Europe	Cardiac	Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI)	2017	[53]
Europe	Management/ outcomes	European expert consensus statement on therapeutic goals in Fabry disease	2018	[54]
Europe	Cardiac	An expert consensus document on the management of cardiovascular manifestations of Fabry disease.	2020	[26]
Europe	Other (stroke)	Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology	2020	[55]
France	Paediatric	Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients	2019	[4]
France	Cardiac	Fabry disease in cardiology practice: Literature review and expert point of view	2019	[56]
Italy	Cardiac	[Heart involvement in Anderson-Fabry disease: Italian recommendations for diagnostic, follow-up and therapeutic management]	2015	[57]
Italy	Paediatric/Renal	Renal involvement in paediatric Fabry disease	2019	[58]
Netherlands	Other	Uncertain diagnosis of fabry disease in patients with neuropathic pain, angiokeratoma or cornea verticillata: consensus on the approach to diagnosis and follow-up	2014	[59]

Poland	ERT	Enzyme replacement therapy in Fabry disease in Poland: a position statement.	2020	[60]
Portugal	Management tools	Biomarkers and Imaging Findings of Anderson-Fabry Disease-What We Know Now	2017	[61]
Spain	Management	Spanish multidisciplinary clinical practice guidelines for Anderson-Fabry Disease in Adults. I. Method and recommendations	2019	[62]
Spanish	ERT	Gender Differences in the Application of Spanish Criteria for Initiation of Enzyme Replacement Therapy for Fabry Disease in the Fabry Outcome Survey	2016	[63]
USA	ERT	Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy	2003	[64]
USA	Paediatric	The management and treatment of children with Fabry disease: A United States-based perspective	2016	[65]
USA	Management	Fabry Disease practice resource: Focused revision.	2020	[66]

Rationale for early treatment initiation

Disease specific treatment would be most successful when started early in the course of the disease.[30] This concept is supported by data to suggest that early initiation of therapy, especially in males with classical Fabry disease, improves treatment outcomes[45 46] while treatment late in the course of the disease may have limited efficacy.[47]

There is now a better understanding of the risk factors for progression of disease while on therapy, which include – male gender, classical phenotype, older age at treatment initiation, reduced renal function, proteinuria, cardiac hypertrophy and fibrosis, hypertension and the occurrence of events before the start of treatment.[3] The PREDICT-FD initiative has captured global opinion regarding 27 early clinical indicators of disease progression that could be used to prompt disease-specific treatment initiation earlier than is currently practiced, in particular in classical males patients aged >16 years who are either asymptomatic or have no overt organ involvement.[47]

Importantly, new imaging techniques offer the means to detect Fabry-related organ damage earlier than was previously possible, their adoption would facilitate treatment initiation before advanced or irreversible organ damage occurs.[47] For example, advanced cardiac MRI imaging includes the use of gadolinium T1 mapping and T2 mapping. In addition, troponin levels are positively correlated with increasing T2 times.[67-69]

Treatment initiation in paediatric patients

The available paediatric data (to January 2017), including 6 clinical trials (Grade 1c) and 10 observational studies, have been reviewed by Spada, 2019,[28] supports significantly reduced or normalised plasma GB3 levels, relieved pain*, improved gastrointestinal (GI) symptoms, and increased quality of life.

Repeating the search (as described in Elliot, 2019[70]) with dates from 01-Jan2017 to 31-Mar-2021 and limiting for children and adolescents identified 57 references of which 3 contained data from clinical trials involving paediatric patients:

- Parini, 2020: A retrospective review of data from the Fabry Outcome Survey (FOS) included a cohort of patients (N=151; median [range] age at symptom onset :7.5 [0.0–16.0] years) who were initiated on ERT (agalsidase alfa) at median 13.7 years (range 2.5-18 years). At baseline (initiation of ERT), the mean eGFR was 113.8 ± 26.9 mL/min/1.73 m^2 and only 15 (17.0%, N=88) had pathological eGFR. No significant annual changes in eGFR, proteinuria, or LVMI were observed throughout the 10-year follow-up period.[71]
- Ramaswami, 2019: open-label, parallel-group, phase 3b study. Asymptomatic (no clinical signs or symptoms or laboratory findings due to complications involving the kidneys, heart, or brain at study enrolment) classical male patients (N=31; ERT initiated at median 12 years, range 5-18 years). Results support treatment with agalsidase beta (1.0 mg/kg 2-weekly) in patients being considered for ERT.[72]
- Kritzer, 2019: data from two classical male cases who were commenced on ERT at ages 3 and 5 years, showed both to have sustained normalisation of previously elevated biomarkers (plasma Lyso-GB3) within one year of treatment with agalsidase beta (1.0 mg/kg 2-weekly).[73]

*Some patients were able to reduce or discontinue pain medications. This is particularly important in paediatric patients, because reduced use of pain medications for symptomatic control of neuronopathic pain had positive outcomes such as reduced sedation, improved concentration, and fewer school absences.[74]

Contemporary International,[50] European,[44] and country specific (France,[4] USA[65]) paediatric consensus papers are aligned on their recommendations for treatment initiation in all symptomatic children, but differ with respect to the age of ERT initiation in asymptomatic boys with classical Fabry disease. The most recent consensus provides clear criteria to help guide the commencement of ERT in children.[4] Most notably, it is recommended that in asymptomatic patients, Fabry-specific therapy should be considered from age 7 years in patients who have either a pathogenic *GLA* variant responsible for the classic phenotype, or <3% of the mean levels of normal alpha-Gal A enzyme activity in peripheral blood leukocytes, or plasma Lyso-GB3 over 20 nmol/L.[4]

Treatment initiation in patients with classical Fabry disease

All males with classical Fabry disease develop organ failure, there is no reason to wait for irreversible fibrosis before commencing treatment. Treatment should be available at diagnosis, or as soon as practicable after disease confirmation, when they are either

asymptomatic or have no overt organ involvement. This aligns with prior recommendations from the US[65] and Europe,[44] the more recent global consensus initiatives,[24 47] and clinical evidence demonstrating that these patients may benefit from treatment that starts early, before major organ damage has developed.[41 75]

While there have been relatively fewer clinical studies specifically evaluating the effects of disease-specific therapy in female patients,[63] data support that women are as likely to respond to therapy as are men.[76] However, unlike males diagnosed with classical Fabry disease, initiation of treatment in females with classical Fabry disease should commence when there is evidence of organ involvement.[4]

While progressive nephropathy is more prominent in males Fabry patients, both males and females should initiate treatment if they have evidence of renal involvement.[77] On this basis, recent guidance recommends that females with classical Fabry disease mutations should commence therapy if there is evidence of early organ involvement, based on the results of laboratory, histological or imaging tests.[24] With respect to renal involvement, this is defined based on KDIGO-recommended threshold estimates for glomerular filtration rate (<90 mL/min/1.73 m^2 after adjustment for age > 40 years; [GFR category ≥ G2]), or persistent abnormal albumin (albuminuria >30 mg/g [albuminuria category A2 or A3]) with evidence of podocyte foot process effacement or glomerulosclerosis on renal biopsy or moderate or severe GB3 inclusions in a range of renal cell types.[24]

Similarly, females with classical Fabry disease should initiate treatment when there is evidence of cardiac involvement from symptoms or detected by investigations.

Treatment initiation in patients with non-classical Fabry disease

As with classical females, patients diagnosed with non-classical Fabry disease should not commence disease-specific therapy when asymptomatic for organ involvement.[24] Therapy should be initiated if there are any signs or symptoms that are suggestive of major organ involvement.[24] Fabry-specific treatment should be considered on an individual basis, particularly if patients experience quality-of-life issues such as neuropathic pain or gastrointestinal symptoms.[29 51], though these symptoms are rare or usually only mild in non-classical disease

Fabry-related organ involvement and the need for confirmatory biopsy

The current LSDP criteria state that where Fabry-related renal or cardiac disease is used as the treatment eligibility criterion:

- Renal: confirmation by renal biopsy is recommended for all patients.
- Cardiac: Confirmation by myocardial biopsy is recommended to exclude other causes of cardiac hypertrophy.

Biopsy of an affected organ provides definitive evidence of Fabry disease by showing vacuolization and typical lysosomal inclusions or “zebra” bodies on electron microscopy. However, it is not required for confirmation of diagnosis in all patients. The literature

supports that evidence of lysosomal GB3 accumulation in renal or cardiac biopsies may be of value (1) to confirm a diagnosis in patients with VUS (particularly when the clinical signs are nonspecific, alternative or additional diagnoses are under consideration) or (2) in cases in which there is uncertainty over whether therapy should be started.[24]

Renal biopsy

While renal disease is common in patients with Fabry disease, case reports have shown alternative treatable causes for patients who had renal dysfunction based on biopsy;[78] these are usually drug induced (e.g. hydroxychloroquine/quinine/amiodorone). Other causes of reduced GFR and proteinuria, such as auto-immune disease, should therefore be excluded as best as possible. However, the recent Canadian guideline suggests that renal biopsy is not required as a prelude to therapy. A recent review suggests that the indication for conducting a renal biopsy should be supported by convincing arguments to avoid unnecessary risks, and summarises the reasonable indications as follows:[25]

- To assess the degree of glomerulosclerosis and interstitial damage.
- In patients with 30- to 300-mg/g urinary albumin-to-creatinine ratio and normal kidney function, to detect and quantify GB3 deposits
- In patients with subclinical Fabry nephropathy, the presence of significant renal deposits may serve as an indicator to start specific therapy.
- Cases of atypical presentations.
- Cases in which it is necessary to rule out other nephropathies or overlapping/concomitant diseases.
- Cases with suspected or confirmed presence of antibodies against the enzyme to evaluate the response to ERT.

NOTE: In 2018, a European consensus continued to support the role of renal biopsy and clearance of renal GB3 as a therapeutic treatment goal.[54]

Cardiac biopsy

The recent Canadian guideline suggests that consideration should be given to a left ventricular biopsy if there is any doubt as to the diagnosis (for example in patients with VUS).

This is in concert with the review by Linhart et al, which supports a role for cardiac biopsy to confirm or exclude Fabry disease as the cause of LVH in patients with VUS (and particularly in women with VUS) after *GLA* sequencing and states that it should not be used to determine treatment efficacy or to follow-up cardiac involvement.[26] A recent review of cardiac involvement in Fabry disease further supports restricting the use of cardiac biopsy to diagnosis in patients with VUS and low Lyso-GB3 levels, and has highlighted:[27]

- The cardiomyopathy associated with Fabry disease manifests mainly as LVH.
- In addition to GB3 accumulation, secondary mechanisms of cardiac damage include inflammation and immune activation

- Cardiac imaging, particularly cMRI, is essential for diagnosis and staging.

Fabry Australia Working Group: Recommendations (3)

The Fabry Working Group has reviewed all the international recommendations in the literature, international guidelines when to initiate therapy as well as relevant trial data. Our conclusions are as follows:

- Timely treatment initiation is important to avoid irreversible organ damage. [47]
- In the absence of a cure, the aim of Fabry-specific treatment is to prevent the consequences of this progressive disorder.
- Initiation criteria should distinguish between classical and non-classical Fabry disease:
    - Classical males:
      All classical males develop organ involvement, Fabry-specific therapy should be considered and is appropriate in all patients at any age of presentation.[24]
    - Classical females:
      Fabry-specific therapy should be considered and is appropriate if there is evidence of injury to the kidney, heart or central nervous system that is attributable to Fabry disease or if the patient has significant symptoms from Fabry disease that are affecting their quality of life.
    - Non-classical males or females:
      Fabry-specific therapy should be considered and is appropriate if there is evidence of injury to the kidney, heart or central nervous system that is attributable to Fabry disease.[24]
      Fabry-specific therapy may not be appropriate in the absence of demonstrable Fabry-related tissue pathology or clinical symptoms; these patients should be monitored by a multidisciplinary team experienced in Fabry therapies.[24]

Table 4. Recommendation: Fabry-specific treatment initiation criteria

Classification	Treatment initiation criteria
Classical male	Fabry specific therapy is appropriate and should be considered in all patients at any age
Classical female	Signs/symptoms suggesting major organ involvement: One or more the following: • Fabry neuropathic pain or pain crises; after review by a consultant physician or paediatrician to ensure all common causes are excluded. • Proteinuria/albuminuria [category A2 or A3] not attributable to other causes; evidence of renal

	impairment [GFR category G2 or higher] *NOTE: may require biopsy if isolated* • Stroke or transient ischaemic attack, not attributable to other causes • Severe GI symptoms [recurrent diarrhoea/gastrointestinal dysfunction] due to Fabry disease; after review by a consultant physician or paediatrician to ensure all common causes for GI symptoms are excluded.
OR	Evidence of injury to the heart: Asymptomatic cardiac disease One or more the following: • Electrocardiography: Complete heart block, ventricular tachycardia (non-sustained or not), atrial fibrillation not otherwise explained • 2D echocardiography: LVMI above normal for age (>mean + 2SD), cardiac hypertrophy (MWT>12mm), abnormal strain • Cardiac MRI: Low myocardial T1 relaxation time, High myocardial T2 relaxation time, LGE, LVMI above normal for age (>mean + 2SD) and cardiac hypertrophy (MWT>12mm), Abnormal papillary muscles • Histological: Abnormal cardiac biopsy demonstrating Fabry disease
OR	Evidence of injury to the kidney: renal disease One or more the following: • Reduced GFR due to Fabry nephropathy, having definitively excluded other causes of chronic kidney disease • Histological: Confirmatory biopsy showing podocyte foot process effacements, evidence of damage (e.g. glomerulosclerosis) and moderate to severe GB3 inclusions in a range of renal cell types
OR	Evidence of injury to other organs One or more the following • Silent strokes • Cerebral white matter lesions out of keeping with age-related changes, not attributable to other causes • Chronic or sudden, severe hearing loss or tinnitus where no other contributing causes can be found
Non-classical male or Female	Evidence of injury to the heart: Asymptomatic cardiac disease One or more the following: • Electrocardiography: Complete heart block, ventricular tachycardia (non-sustained or not), atrial fibrillation not otherwise explained

- 2D echocardiography: LVMI above normal for age (>mean + 2SD), cardiac hypertrophy (MWT>12mm), abnormal strain
- Cardiac MRI: Low myocardial T1 relaxation time, High myocardial T2 relaxation time, LGE, LVMI above normal for age (>mean + 2SD) and cardiac hypertrophy (MWT>12mm), Abnormal papillary muscles
- Histological: Abnormal cardiac biopsy demonstrating Fabry disease

OR Evidence of injury to the kidney: renal disease

One or more the following:

- Proteinuria/albuminuria [category A2 or A3] not attributable to other causes; evidence of renal impairment [GFR category G2 or higher] *NOTE: may require biopsy if isolated*
- Reduced GFR due to Fabry nephropathy, having definitively excluded other causes of chronic kidney disease
- Histological: Confirmatory biopsy showing podocyte foot process effacements, evidence of damage (e.g. glomerulosclerosis) and moderate or severe GB3 inclusions in a range of renal cell types

OR Evidence of injury to other organs

One or more the following

- Ischaemic vascular disease (stroke/transient ischaemic attack), with no risk factors identified or not attributable to other causes
- Cerebral white matter lesions out of keeping with age-related changes, not attributable to other causes
- Sudden, severe hearing loss or tinnitus not attributable to other causes

GB3, Globotriaosylceramide; GFR glomerular filtration rate, GI, gastrointestinal, LVMI, left ventricular mass index, LGE, late gadolinium enhancement, MWT, mean wall thickness

Chronic kidney disease classification: CGA staging

GFR	Category	GFR (mL/min/1.73m2)	Terms
	G1	≥ 90	Normal or high
	G2	60-89	Mildly decreased*
	G3a	45-59	Mildly to moderately decreased
	G3b	30-44	Moderately to severely decreased
	G4	15-29	Severely decreased
	G5	<15	Kidney failure
Albuminuria	**Category**	**ACR (mg/g) [mg/mmol]**	**Terms**
	A1	<30 [<3]	Normal to mildly increased
	A2	30-300 [3-30]	Moderately increased*

A3	>300 [>30]	Severely increased**

*Relative to young adult level; **Including nephrotic syndrome (albumin excretion ACR >2220 mg/g)

SUMMARY

The published literature supports an extensive impact of Fabry disease beyond its clinical manifestations, with patients demonstrating a significantly worse overall quality of life compared with the general population.[79] Recent insights demonstrate that patients' perceptions of the negative impact of Fabry disease spans disease-related problems (predominantly fatigue and pain), concerns about the future (organ impairment, increasing symptom severity and the potential impact on work prospects), and mental health (depression, anxiety, loneliness).[80] Moreover, self-perceived health status has been observed to improve after diagnostic confirmation and subsequent access to disease-specific therapy.[8]

The impetus behind this publication has been, in part, a need to answer questions surrounding disease-specific treatment access for patients with Fabry disease and their families. As has been demonstrated, the current access criteria have not been updated in step with the mounting clinical evidence supporting earlier treatment with reduced barriers to access in some circumstances.

On this basis the Fabry Australia Working Group have proposed an updated framework for defining patient groups, alongside more comprehensive treatment initiation criteria that:

- differentiate classical from non-classical Fabry patients
- facilitate more timely access to Fabry-specific treatment for classical male patients
- propose relevant organ involvement criteria in classical female patients and in patients with non-classical disease.

The intention is that these recommendations (as described in table 4) raise awareness of a wider range of clinical scenarios that could be considered to prompt the initiation of disease-specific therapy in patients with Fabry disease.

REFERENCES:

1. Michaud M, Mauhin W, Belmatoug N, et al. [Fabry disease: A review]. *La Revue de medecine interne / fondee par la Societe nationale francaise de medecine interne* 2021;42(2):110-19. doi: 10.1016/j.revmed.2020.08.019 [published Online First: 2020/11/12]
2. Lenders M, Brand E. Fabry Disease: The Current Treatment Landscape. *Drugs* 2021 doi: 10.1007/s40265-021-01486-1 [published Online First: 2021/03/16]
3. Kok K, Zwiers KC, Boot RG, et al. Fabry Disease: Molecular Basis, Pathophysiology, Diagnostics and Potential Therapeutic Directions. *Biomolecules* 2021;11(2) doi: 10.3390/biom11020271 [published Online First: 2021/03/07]

4. Germain DP, Fouilhoux A, Decramer S, et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. *Clinical genetics* 2019;96(2):107-17. doi: 10.1111/cge.13546 [published Online First: 2019/04/04]
5. OrphaNet. Fabry Disease 2021 [
6. Ortiz A, Abiose A, Bichet DG, et al. Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: data from the Fabry Registry. *Journal of medical genetics* 2016;53(7):495-502. doi: 10.1136/jmedgenet-2015-103486 [published Online First: 2016/03/20]
7. Reisin R, Perrin A, García-Pavía P. Time delays in the diagnosis and treatment of Fabry disease. *International journal of clinical practice* 2017;71(1) doi: 10.1111/ijcp.12914 [published Online First: 2017/01/18]
8. Mengel E, Gaedeke J, Gothe H, et al. The patient journey of patients with Fabry disease, Gaucher disease and Mucopolysaccharidosis type II: A German-wide telephone survey. *PloS one* 2020;15(12):e0244279. doi: 10.1371/journal.pone.0244279 [published Online First: 2021/01/01]
9. Mallett A, Kearey P, Cameron A, et al. The Ckd. Qld fabRy Epidemiology (aCQuiRE) study protocol: identifying the prevalence of Fabry disease amongst patients with kidney disease in Queensland, Australia. *BMC nephrology* 2020;21(1):58. doi: 10.1186/s12882-020-01717-9 [published Online First: 2020/02/24]
10. Jahan S, Sarathchandran S, Akhter S, et al. Prevalence of Fabry disease in dialysis patients: Western Australia Fabry disease screening study - the FoRWARD study. *Orphanet journal of rare diseases* 2020;15(1):10-10. doi: 10.1186/s13023-019-1290-3
11. Miller JJ, Kanack AJ, Dahms NM. Progress in the understanding and treatment of Fabry disease. *Biochim Biophys Acta Gen Subj* 2020;1864(1):129437. doi: 10.1016/j.bbagen.2019.129437 [published Online First: 2019/09/19]
12. Castelli V, Stamerra CA, d'Angelo M, et al. Current and experimental therapeutics for Fabry disease. *Clinical genetics* 2021;100(3):239-47. doi: 10.1111/cge.13999 [published Online First: 2021/05/25]
13. Cassis L, Cortès-Saladelafont E, Molero-Luis M, et al. Review and evaluation of the methodological quality of the existing guidelines and recommendations for inherited neurometabolic disorders. *Orphanet journal of rare diseases* 2015;10(1):164. doi: 10.1186/s13023-015-0376-9
14. Michaud M, Mauhin W, Belmatoug N, et al. When and How to Diagnose Fabry Disease in Clinical Pratice. *Am J Med Sci* 2020;360(6):641-49. doi: 10.1016/j.amjms.2020.07.011 [published Online First: 2020/07/30]
15. Arends M, Wanner C, Hughes D, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study. *Journal of the American Society of Nephrology : JASN* 2017;28(5):1631-41. doi: 10.1681/asn.2016090964 [published Online First: 2016/12/17]
16. Yousef Z, Elliott PM, Cecchi F, et al. Left ventricular hypertrophy in Fabry disease: a practical approach to diagnosis. *European heart journal* 2013;34(11):802-08. doi: 10.1093/eurheartj/ehs166 [published Online First: 2012/06/26]
17. Stollznow N, Stollznow G, Curran K. The Australian Experience of Fabry Disease, a patients' perspective. In: Stollznow Research N, Australia, ed. Fabry Australia, NSW, Australia, 2020.
18. Smid BE, van der Tol L, Cecchi F, et al. Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. *Int J Cardiol* 2014;177(2):400-8. doi: 10.1016/j.ijcard.2014.09.001

19. Hsu T-R, Hung S-C, Chang F-P, et al. Later Onset Fabry Disease, Cardiac Damage Progress in Silence: Experience With a Highly Prevalent Mutation. *Journal of the American College of Cardiology* 2016;68(23):2554-63. doi: https://doi.org/10.1016/j.jacc.2016.09.943
20. Chimenti C, Pieroni M, Morgante E, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circulation* 2004;110(9):1047-53. doi: 10.1161/01.CIR.0000139847.74101.03
21. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *Journal of medical genetics* 2001;38(11):750-60.
22. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. *Molecular genetics and metabolism* 2008;93(2):112-28. doi: 10.1016/j.ymgme.2007.09.013
23. van der Tol L, Smid BE, Poorthuis BJ, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. *Journal of medical genetics* 2014;51(1):1-9. doi: 10.1136/jmedgenet-2013-101857 [published Online First: 2013/08/08]
24. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. *Molecular genetics and metabolism* 2018;123(4):416-27. doi: 10.1016/j.ymgme.2018.02.014 [published Online First: 2018/03/14]
25. Silva CAB, Moura-Neto JA, dos Reis MA, et al. Renal Manifestations of Fabry Disease: A Narrative Review. *Canadian Journal of Kidney Health and Disease* 2021;8:2054358120985627. doi: 10.1177/2054358120985627
26. Linhart A, Germain DP, Olivotto I, et al. An expert consensus document on the management of cardiovascular manifestations of Fabry disease. *Eur J Heart Fail* 2020;22(7):1076-96. doi: 10.1002/ejhf.1960 [published Online First: 2020/07/09]
27. Pieroni M, Moon JC, Arbustini E, et al. Cardiac Involvement in Fabry Disease: JACC Review Topic of the Week. *J Am Coll Cardiol* 2021;77(7):922-36. doi: 10.1016/j.jacc.2020.12.024 [published Online First: 2021/02/20]
28. Spada M, Baron R, Elliott PM, et al. The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease - A systematic literature review by a European panel of experts. *Molecular genetics and metabolism* 2019;126(3):212-23. doi: 10.1016/j.ymgme.2018.04.007 [published Online First: 2018/05/23]
29. Germain DP, Elliott PM, Falissard B, et al. The effect of enzyme replacement therapy on clinical outcomes in male patients with Fabry disease: A systematic literature review by a European panel of experts. *Mol Genet Metab Rep* 2019;19:100454. doi: 10.1016/j.ymgmr.2019.100454 [published Online First: 2019/02/19]
30. Germain DP, Arad M, Burlina A, et al. The effect of enzyme replacement therapy on clinical outcomes in female patients with Fabry disease - A systematic literature review by a European panel of experts. *Molecular genetics and metabolism* 2019;126(3):224-35. doi: 10.1016/j.ymgme.2018.09.007 [published Online First: 2018/11/11]
31. Banikazemi M, Desnick RJ. Does enzyme replacement therapy improve symptoms of Fabry disease in patients undergoing dialysis? *Nature clinical practice Nephrology* 2006;2(2):72-3. doi: 10.1038/ncpneph0100
32. Schiffmann R, Kopp JB, Austin HA, 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *Jama* 2001;285(21):2743-9. doi: 10.1001/jama.285.21.2743 [published Online First: 2001/06/21]
33. Arends M, Biegstraaten M, Wanner C, et al. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort study. *Journal of medical genetics*

2018;55(5):351-58. doi: 10.1136/jmedgenet-2017-104863 [published Online First: 2018/02/14]
34. Sirrs SM, Bichet DG, Iwanochko M, et al. Differential effects of agalsidase alfa and agalsidase beta in Fabry outcomes: 10 year outcomes from the Canadian Fabry Disease Initiative. *J Inherit Metab Dis* 2018;41:S188 (abstract 373).
35. El Dib R, Gomaa H, Ortiz A, et al. Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. *PloS one* 2017;12(3):e0173358. doi: 10.1371/journal.pone.0173358 [published Online First: 2017/03/16]
36. Benjamin ER, Della Valle MC, Wu X, et al. The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat. *Genetics in medicine : official journal of the American College of Medical Genetics* 2017;19(4):430-38. doi: 10.1038/gim.2016.122 [published Online First: 2016/09/23]
37. McCafferty EH, Scott LJ. Migalastat: A Review in Fabry Disease. *Drugs* 2019;79(5):543-54. doi: 10.1007/s40265-019-01090-4 [published Online First: 2019/03/16]
38. Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *Journal of medical genetics* 2017;54(4):288-96. doi: 10.1136/jmedgenet-2016-104178 [published Online First: 2016/11/12]
39. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat. *The New England journal of medicine* 2016;375(6):545-55. doi: 10.1056/NEJMoa1510198 [published Online First: 2016/08/11]
40. Feldt-Rasmussen U, Hughes D, Sunder-Plassmann G, et al. Long-term efficacy and safety of migalastat treatment in Fabry disease: 30-month results from the open-label extension of the randomized, phase 3 ATTRACT study. *Molecular genetics and metabolism* 2020;131(1):219-28. doi: https://doi.org/10.1016/j.ymgme.2020.07.007
41. Germain DP, Nicholls K, Giugliani R, et al. Efficacy of the pharmacologic chaperone migalastat in a subset of male patients with the classic phenotype of Fabry disease and migalastat-amenable variants: data from the phase 3 randomized, multicenter, double-blind clinical trial and extension study. *Genetics in medicine : official journal of the American College of Medical Genetics* 2019;21(9):1987-97. doi: 10.1038/s41436-019-0451-z [published Online First: 2019/02/07]
42. Lenders M, Nordbeck P, Kurschat C, et al. Treatment of fabry disease with migalastat-outcome from a prospective 24 months observational multicenter study (FAMOUS). *Eur Heart J Cardiovasc Pharmacother* 2021 doi: 10.1093/ehjcvp/pvab025 [published Online First: 2021/03/17]
43. Chimenti C, Nencini P, Pieruzzi F, et al. The GALA project: practical recommendations for the use of migalastat in clinical practice on the basis of a structured survey among Italian experts. *Orphanet journal of rare diseases* 2020;15(1):86. doi: 10.1186/s13023-020-1318-8 [published Online First: 2020/04/09]
44. Biegstraaten M, Arngrímsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. *Orphanet journal of rare diseases* 2015;10(1):36. doi: 10.1186/s13023-015-0253-6
45. Svarstad E, Marti HP. The Changing Landscape of Fabry Disease. *Clinical journal of the American Society of Nephrology : CJASN* 2020;15(4):569-76. doi: 10.2215/cjn.09480819 [published Online First: 2020/03/07]

46. van der Veen SJ, Hollak CEM, van Kuilenburg ABP, et al. Developments in the treatment of Fabry disease. *Journal of inherited metabolic disease* 2020;43(5):908-21. doi: 10.1002/jimd.12228 [published Online First: 2020/02/23]
47. Hughes DA, Aguiar P, Deegan PB, et al. Early indicators of disease progression in Fabry disease that may indicate the need for disease-specific treatment initiation: findings from the opinion-based PREDICT-FD modified Delphi consensus initiative. *BMJ open* 2020;10(10):e035182. doi: 10.1136/bmjopen-2019-035182 [published Online First: 2020/10/12]
48. van der Tol L, Svarstad E, Ortiz A, et al. Chronic kidney disease and an uncertain diagnosis of Fabry disease: approach to a correct diagnosis. *Molecular genetics and metabolism* 2015;114(2):242-7. doi: 10.1016/j.ymgme.2014.08.007
49. Moreno-Martinez D, Aguiar P, Auray-Blais C, et al. Standardising clinical outcomes measures for adult clinical trials in Fabry disease: A global Delphi consensus. *Molecular genetics and metabolism* 2021;132(4):234-43. doi: 10.1016/j.ymgme.2021.02.001 [published Online First: 2021/03/02]
50. Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genetics in medicine : official journal of the American College of Medical Genetics* 2006;8(9):539-48. doi: 10.109701.gim.0000237866.70357.c6
51. Schiffmann R, Hughes DA, Linthorst GE, et al. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney international* 2017;91(2):284-93. doi: 10.1016/j.kint.2016.10.004 [published Online First: 2016/12/22]
52. Terryn W, Cochat P, Froissart R, et al. Fabry nephropathy: indications for screening and guidance for diagnosis and treatment by the European Renal Best Practice. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2013;28(3):505-17. doi: 10.1093/ndt/gfs526 [published Online First: 2012/12/14]
53. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017;19(1):75. doi: 10.1186/s12968-017-0389-8 [published Online First: 2017/10/11]
54. Wanner C, Arad M, Baron R, et al. European expert consensus statement on therapeutic goals in Fabry disease. *Molecular genetics and metabolism* 2018;124(3):189-203. doi: 10.1016/j.ymgme.2018.06.004 [published Online First: 2018/07/19]
55. Mancuso M, Arnold M, Bersano A, et al. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. *Eur J Neurol* 2020;27(6):909-27. doi: 10.1111/ene.14183 [published Online First: 2020/03/21]
56. Hagège A, Réant P, Habib G, et al. Fabry disease in cardiology practice: Literature review and expert point of view. *Arch Cardiovasc Dis* 2019;112(4):278-87. doi: 10.1016/j.acvd.2019.01.002 [published Online First: 2019/03/04]
57. Pieruzzi F, Pieroni M, Zachara E, et al. [Heart involvement in Anderson-Fabry disease: Italian recommendations for diagnostic, follow-up and therapeutic management]. *G Ital Cardiol (Rome)* 2015;16(11):630-8. doi: 10.1714/2066.22434
58. Sestito S, Falvo F, Sallemi A, et al. Renal involvement in paediatric Fabry disease. *J Biol Regul Homeost Agents* 2019;33(5 Suppl. 1):59-63. [published Online First: 2019/10/22]
59. van der Tol L, Cassiman D, Houge G, et al. Uncertain diagnosis of fabry disease in patients with neuropathic pain, angiokeratoma or cornea verticillata: consensus on the

approach to diagnosis and follow-up. *JIMD reports* 2014;17:83-90. doi: 10.1007/8904_2014_342
60. Nowicki M, Bazan-Socha S, Błażejewska-Hyzorek B, et al. Enzyme replacement therapy in Fabry disease in Poland: a position statement. *Pol Arch Intern Med* 2020;130(1):91-97. doi: 10.20452/pamw.15117 [published Online First: 2019/12/24]
61. Beirão I, Cabrita A, Torres M, et al. Biomarkers and Imaging Findings of Anderson-Fabry Disease-What We Know Now. *Diseases* 2017;5(2) doi: 10.3390/diseases5020015 [published Online First: 2017/09/22]
62. Calderón Sandubete EJ, Briones Pérez de la Blanca E, Alonso-Ortiz Del Río C, et al. Spanish multidisciplinary clinical practice guidelines for Anderson-Fabry Disease in Adults. I. Method and recommendations. *Rev Clin Esp* 2019;219(4):200-07. doi: 10.1016/j.rce.2018.09.017 [published Online First: 2019/01/30]
63. Barba-Romero M, Pintos-Morell G. Gender Differences in the Application of Spanish Criteria for Initiation of Enzyme Replacement Therapy for Fabry Disease in the Fabry Outcome Survey. *Int J Mol Sci* 2016;17(12) doi: 10.3390/ijms17121965 [published Online First: 2016/11/26]
64. Desnick RJ, Brady R, Barranger J, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Annals of internal medicine* 2003;138(4):338-46. doi: 10.7326/0003-4819-138-4-200302180-00014 [published Online First: 2003/02/15]
65. Hopkin RJ, Jefferies JL, Laney DA, et al. The management and treatment of children with Fabry disease: A United States-based perspective. *Molecular genetics and metabolism* 2016;117(2):104-13. doi: 10.1016/j.ymgme.2015.10.007
66. Henderson N, Berry L, Laney DA. Fabry Disease practice resource: Focused revision. *Journal of Genetic Counseling* 2020;29(5):715-17. doi: https://doi.org/10.1002/jgc4.1318
67. Vijapurapu R, Baig S, Nordin S, et al. Longitudinal Assessment of Cardiac Involvement in Fabry Disease Using Cardiovascular Magnetic Resonance Imaging. *JACC: Cardiovascular Imaging* 2020;13(8):1850-52. doi: 10.1016/j.jcmg.2020.03.004
68. Nordin S, Kozor R, Vijapurapu R, et al. Myocardial Storage, Inflammation, and Cardiac Phenotype in Fabry Disease After One Year of Enzyme Replacement Therapy. *Circ Cardiovasc Imaging* 2019;12(12):e009430. doi: 10.1161/circimaging.119.009430 [published Online First: 2019/12/13]
69. Vijapurapu R, Nordin S, Baig S, et al. Global longitudinal strain, myocardial storage and hypertrophy in Fabry disease. *Heart* 2019;105(6):470-76. doi: 10.1136/heartjnl-2018-313699 [published Online First: 2018/10/05]
70. Elliott PM, Germain DP, Hilz MJ, et al. Why systematic literature reviews in Fabry disease should include all published evidence. *European journal of medical genetics* 2019;62(10):103702. doi: 10.1016/j.ejmg.2019.103702 [published Online First: 2019/06/14]
71. Parini R, Pintos-Morell G, Hennermann JB, et al. Analysis of Renal and Cardiac Outcomes in Male Participants in the Fabry Outcome Survey Starting Agalsidase Alfa Enzyme Replacement Therapy Before and After 18 Years of Age. *Drug design, development and therapy* 2020;14:2149-58. doi: 10.2147/dddt.S249433 [published Online First: 2020/06/26]
72. Ramaswami U, Bichet DG, Clarke LA, et al. Low-dose agalsidase beta treatment in male pediatric patients with Fabry disease: A 5-year randomized controlled trial. *Molecular genetics and metabolism* 2019;127(1):86-94. doi: 10.1016/j.ymgme.2019.03.010 [published Online First: 2019/04/17]
73. Kritzer A, Siddharth A, Leestma K, et al. Early initiation of enzyme replacement therapy in classical Fabry disease normalizes biomarkers in clinically asymptomatic pediatric

patients. *Mol Genet Metab Rep* 2019;21:100530. doi: 10.1016/j.ymgmr.2019.100530 [published Online First: 2019/10/30]
74. Wraith JE, Tylki-Szymanska A, Guffon N, et al. Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. *The Journal of pediatrics* 2008;152(4):563-70, 70 e1. doi: 10.1016/j.jpeds.2007.09.007
75. Wanner C, Germain DP, Hilz MJ, et al. Therapeutic goals in Fabry disease: Recommendations of a European expert panel, based on current clinical evidence with enzyme replacement therapy. *Molecular genetics and metabolism* 2019;126(3):210-11. doi: 10.1016/j.ymgme.2018.04.004 [published Online First: 2018/05/05]
76. Hughes DA, Barba Romero M, Hollak CE, et al. Response of women with Fabry disease to enzyme replacement therapy: comparison with men, using data from FOS--the Fabry Outcome Survey. *Molecular genetics and metabolism* 2011;103(3):207-14. doi: 10.1016/j.ymgme.2011.03.022 [published Online First: 2011/05/06]
77. Pisani A, Visciano B, Imbriaco M, et al. The kidney in Fabry's disease. *Clinical genetics* 2014;86(4):301-9. doi: 10.1111/cge.12386 [published Online First: 2014/03/22]
78. Maixnerová D, Tesař V, Ryšavá R, et al. The coincidence of IgA nephropathy and Fabry disease. *BMC nephrology* 2013;14:6-6. doi: 10.1186/1471-2369-14-6
79. Arends M, Hollak CEM, Biegstraaten M. Quality of life in patients with Fabry disease: a systematic review of the literature. *Orphanet journal of rare diseases* 2015;10(1):77. doi: 10.1186/s13023-015-0296-8
80. Polistena B, Rigante D, Sicignano LL, et al. Survey about the Quality of Life of Italian Patients with Fabry Disease. *Diseases* 2021;9(4) doi: 10.3390/diseases9040072
81. Esposito R, Santoro C, Mandoli GE, et al. Cardiac Imaging in Anderson-Fabry Disease: Past, Present and Future. *Journal of Clinical Medicine* 2021;10(9) doi: 10.3390/jcm10091994

WORKING GROUP – PROFILES

Dr Drago Bratkovic is a paediatrician, metabolic physician and clinical geneticist who received training in both metabolic medicine and clinical genetics through the Children's Hospital at Westmead in Sydney and the Women's and Children's Hospital in Adelaide. He took on the position of Head of the Metabolic Clinic in 2008 after completing his specialist training in 2006. Dr Bratkovic's clinical and research interests include the use of array technology in cytogenetics, enzyme replacement therapy, newborn screening and the investigation of patients with autism.

Associate Professor Charles Denaro trained at Princess Alexandra Hospital in Brisbane and University of California, San Francisco. Currently is the Director of Internal Medicine & Aged Care, Royal Brisbane & Women's Hospital and Associate Professor of Medicine with the University of Queensland. He has a Doctorate of Medicine in Clinical Pharmacology. A member of the Queensland Health Medicines Advisory Committee and Chair since 2002. Dr Denaro has been looking after patients with Fabry Disease for Queensland and Northern NSW since 2002, and was a member of the Fabry Disease Advisory Committee for the Life Saving Drug Program from 2004 to 2014.

Associate Professor Carolyn Ellaway is a Clinical Associate Professor at the University of Sydney and has been working as a Pediatrician and Clinical Geneticist at the Genetic Metabolic Disorders Service, Children's Hospital, Westmead, NSW since 2001 and Sydney Children's Hospital, Randwick, since 2014. In her clinical role, Carolyn is responsible for the care of children with a range of genetic metabolic disorders including lysosomal storage disorders, such as Fabry disease. Carolyn currently cares for the majority of children with Fabry disease in NSW / ACT. Carolyn is a member of the Human Genetics Society of Australasia (HGSA), Australian Society For Inborn Errors of Metabolism (ASIEM), the Society for the Study of Inborn Errors of Metabolism (SSIEM), the Society of Inherited Metabolic Disorders (SIMD) and the American Society of Human Genetics (ASHG). Her clinical and research interests include treatments and clinical trials for lysosomal storage disorders, Rett syndrome and other inborn errors of metabolism and the genetic diagnosis of children with developmental delay.

Associate Clinical Professor Kathy Nicholls MBBS, MD, FRACP, Grad Cert University teaching is a kidney specialist at The Royal Melbourne Hospital. She coordinates Fabry-related clinical care for over 100 Victorian patients, working with Dr Andrew Talbot and colleagues from other specialties. The Royal Melbourne Hospital unit has treated Fabry patients with enzyme replacement therapy since 2000, and more recently has actively participated in trials of chaperone molecule therapy. Linked with clinical care is an ongoing departmental clinical and basic science research interest in Fabry disease. Current research interests include using stem cells to study the effects of Fabry mutations on the function of kidney and heart cells, accessing gene therapy, effects of enzyme replacement of different types, and oral therapies for Fabry disease.

Dr Michel Tchan is a clinical and metabolic geneticist looking after adults with genetic disorders. He is currently responsible for the NSW Adult Genetic Metabolic Disorders Clinic as well as the Centre of Expertise supervising enzyme replacement therapy for Fabry disease, Pompe disease and the Mucopolysaccharidoses. Dr Tchan has active research interests in clinical aspects of the lysosomal storage disorders, particularly Fabry and Pompe diseases. He is involved in a number of collaborative programmes looking into neurological function in these diseases. He also has a strong interest in neurogenetic and renal genetic disorders.

Clinical Professor Mark Thomas is a nephrologist working at Royal Perth Hospital, supervising the WA Statewide Fabry Service for around 70 patients, including a quarterly multidisciplinary clinic. The unit participates in Fabry Disease research trials, including pharmacokinetics of combined chaperone and enzyme replacement therapy, substrate reduction therapy and gene therapies. He is a member of Fabry Disease advisory boards assisting industry, NXT global registry and local patients' association.

Megan Fookes, OAM, former Managing Director of Fabry Australia has been involved with Fabry Australia since 1999. She also served as founding Executive Director of a National Alliance for Rare Diseases in Australia; Rare Voices Australia for five years. Her professional association with Rare Diseases stems from a very personal connection. Her late father; David Davie waited 48 years to receive a diagnosis of Fabry disease. Her parents who were very keen to learn more and helped form the patient organisation and establishing the first Fabry Clinic in Melbourne in 1994. Megan was awarded the Medal of the Order (OAM) in 2016 for her services to the Australian rare disease community.

Sheridan Campbell (VIC) serves as **Chair of Fabry Australia** and is pleased to be involved with such a proactive group, to improve the lives of those affected by Fabry disease. Her father Rick Butler, was the first in her family to be diagnosed with the Fabry gene and she, along with other family members, are affected. Sheridan lives with her husband and three young boys in Northern Victoria, where she works as an osteopath.

APPENDICES

Appendix 1: Search Strategy

Search terms:	Fabry disease, management, therapeutic, treatment, guideline, consensus, criterion, review
Search strategy:	(("fabry"[All Fields] OR "fabry s"[All Fields] OR ("fabry disease"[MeSH Terms] OR ("fabry"[All Fields] AND "disease"[All Fields]) OR "fabry disease"[All Fields]) OR ("fabry disease"[MeSH Terms] OR ("fabry"[All Fields] AND "disease"[All Fields]) OR "fabry disease"[All Fields] OR ("anderson"[All Fields] AND "fabry"[All Fields] AND "disease"[All Fields]) OR "anderson fabry disease"[All Fields]) OR ("fabry disease"[MeSH Terms] OR ("fabry"[All Fields] AND "disease"[All Fields]) OR "fabry disease"[All Fields] OR ("fabry s"[All Fields] AND "disease"[All Fields]) OR "fabry s disease"[All Fields])) AND ("manage"[All Fields] OR "managed"[All Fields] OR "management s"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "managment"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields] OR "therapeutic*"[All Fields] OR "treatment*"[All Fields] OR "guideline*"[All Fields] OR ("consensual"[All Fields] OR "consensually"[All Fields] OR "consensus"[MeSH Terms] OR "consensus"[All Fields]) OR ("reference standards"[MeSH Terms] OR ("reference"[All Fields] AND "standards"[All Fields]) OR "reference standards"[All Fields] OR "standardization"[All Fields] OR "standard"[All Fields] OR "standard s"[All Fields] OR "standardisation"[All Fields] OR "standardisations"[All Fields] OR "standardise"[All Fields] OR "standardised"[All Fields] OR "standardises"[All Fields] OR "standardising"[All Fields] OR "standardization s"[All Fields] OR "standardizations"[All Fields] OR "standardize"[All Fields] OR "standardized"[All Fields] OR "standardizes"[All Fields] OR "standardizing"[All Fields] OR "standards"[MeSH Subheading] OR "standards"[All Fields]) OR ("criterion"[All Fields] OR "criterions"[All Fields]) OR ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]))) AND (y_5[Filter])

Translations of terms:	Fabry: "fabry"[All Fields] OR "fabry's"[All Fields]+D13:D21
	Fabry disease: "fabry disease"[MeSH Terms] OR ("fabry"[All Fields] AND "disease"[All Fields]) OR "fabry disease"[All Fields]
	Anderson-Fabry disease: "fabry disease"[MeSH Terms] OR ("fabry"[All Fields] AND "disease"[All Fields]) OR "fabry disease"[All Fields] OR ("anderson"[All Fields] AND "fabry"[All Fields] AND "disease"[All Fields]) OR "anderson fabry disease"[All Fields]
	Fabry's disease: "fabry disease"[MeSH Terms] OR ("fabry"[All Fields] AND "disease"[All Fields]) OR "fabry disease"[All Fields] OR ("fabry's"[All Fields] AND "disease"[All Fields]) OR "fabry's disease"[All Fields]
	Management: "manage"[All Fields] OR "managed"[All Fields] OR "management's"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager's"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "management"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields]
	consensus: "consensual"[All Fields] OR "consensually"[All Fields] OR "consensus"[MeSH Terms] OR "consensus"[All Fields]
	standard: "reference standards"[MeSH Terms] OR ("reference"[All Fields] AND "standards"[All Fields]) OR "reference standards"[All Fields] OR "standardization"[All Fields] OR "standard"[All Fields] OR "standard's"[All Fields] OR "standardisation"[All Fields] OR "standardisations"[All Fields] OR "standardise"[All Fields] OR "standardised"[All Fields] OR "standardises"[All Fields] OR "standardising"[All Fields] OR "standardization's"[All Fields] OR "standardizations"[All Fields] OR "standardize"[All Fields] OR "standardized"[All Fields] OR "standardizes"[All Fields] OR "standardizing"[All Fields] OR "standards"[Subheading] OR "standards"[All Fields]

	criterion: "criterion"[All Fields] OR "criterions"[All Fields]
	review: "review"[Publication Type] .or. "review literature as topic"[MeSH Terms] .or. "review"[All Fields]

APPENDIX 2. Summary of organ involvement criteria to trigger initiation of Fabry-specific therapy.

NOTES

- The table below contains data derived from various literature sources. The recommendations support that Fabry-specific therapy should be considered and is appropriate in all males with classical Fabry disease at any age of presentation. Hence, there is no column for males with classic Fabry disease because these patients do not need to meet specific organ involvement criteria to be eligible for treatment.

Data sources:

- GREEN: Early organ involvement criteria (PREDICT-FD Hughes, 2020)
- BLUE: Established organ involvement criteria [Current European Fabry Working Group guideline, Biegstraaten, 2015][44]
- Pink: Wording in the January 2020 UK treatment guidelines

	Females with classical FD<16 years	Females with classical FD>16 years	Non-classical males/females (any age)
	• Do not initiate treatment if the patient is asymptomatic for organ involvement	• Do not initiate treatment if the patient is asymptomatic for organ involvement	• Do not initiate treatment if the patient is asymptomatic for organ involvement or in individuals with well-characterised benign *GLA* polymorphisms[24]
	• Fabry-specific therapy should be considered from the age of 7 if the child	• Fabry-specific therapy should be considered if the patient has any ONE or	• Fabry-specific therapy should be considered if the patient has any ONE or

	has any ONE or more of the following Fabry-related clinical manifestations:	more of the following Fabry-related clinical manifestations:	more of the following Fabry-related clinical manifestations:
Evidence of Fabry related renal disease*	• Persistent microalbuminuria (3 consecutive early morning urine samples or 3 random early morning urine samples over a period of 6 months)	• Persistent microalbuminuria (3 consecutive early morning urine samples or 3 random early morning urine samples over a period of 6 months)	• Chronic kidney disease (CKD) stage 3: at least 2 consistent estimates or measured GFR over a minimum of 6 months
	• Reduction in estimated / measured GFR (after a review by nephrologist and other causes have been excluded). • OR eGFR >130 mL/min/1.73m^2 • OR eGFR <90 mL/min/1.73m^2	• Reduction in estimated / measured GFR (after a review by nephrologist and other causes have been excluded). • OR Measured GFR<90 mL/min/1.73m^2	• CKD stage 2: at least 3 consistent estimates or measured GFR over at least 12 months with a GFR slope greater than age-related normal (0.8-1.0 ml/min/year) • OR eGFR <90 mL/min/1.73m^2
	• Proteinuria/albuminuria NOT attributable to other causes: ACR<16.95 mg/mmol + confirmatory biopsy	• Proteinuria/albuminuria NOT attributable to other causes: ACR ratio 16.95 – 33.9 mg/mmol + confirmatory biopsy	• Persistent proteinuria: increased albumin/creatinine or protein/creatinine ratio for males • OR Proteinuria/albuminuria NOT attributable to other causes: ACR<16.95-33.9 mg/mmol + confirmatory biopsy
	• Confirmatory biopsy: podocyte foot process effacement or glomerulosclerosis on renal biopsy, moderate or severe GB3 inclusions in a range of renal cell types	• Confirmatory biopsy: podocyte foot process effacement or glomerulosclerosis on renal biopsy, moderate or severe GB3 inclusions in a range of renal cell types	• Confirmatory biopsy: podocyte foot process effacement or glomerulosclerosis on renal biopsy, moderate or severe GB3 inclusions in a range of renal cell types
Evidence of Fabry related cardiac disease*	• Electrocardiography: ○ Arrhythmias ○ Shortening or prolonged PR interval on age-appropriate ECG analysis, ○ Symptomatic bradycardia	• Electrocardiography: ○ Arrhythmias ○ Shortening or prolonged PR interval on age-appropriate ECG analysis, ○ Symptomatic bradycardia	• Electrocardiography: ○ Arrhythmias ○ Shortening or prolonged PR interval on age-appropriate ECG analysis, ○ Symptomatic bradycardia
	• 2D echocardiography: ○ LVMI above normal for age (>mean ± 2SD)	• 2D echocardiography: ○ LVMI above normal for age (>mean ± 2SD)	• 2D echocardiography: ○ LVMI above normal for age (>mean ± 2SD)

	○ Cardiac hypertrophy (MWT>12mm) without or with only minimal fibrosis ○ LVH with normal systolic function	○ Cardiac hypertrophy (MWT>12mm) without or with only minimal fibrosis	○ Cardiac hypertrophy (MWT>12mm) without or with only minimal fibrosis ○ Early signs of LVH (males)
	• Cardiac MRI: ○ Low myocardial T1 relaxation time ○ High myocardial T2 relaxation time ○ LGE without LVH (rare in <16 years) ○ Disproportionate papillary muscle hypertrophy without LVH[81]	• Cardiac MRI: ○ Low myocardial T1 relaxation time ○ High myocardial T2 relaxation time ○ LGE without LVH ○ Disproportionate papillary muscle hypertrophy without LVH[81]	• Cardiac MRI: ○ Low myocardial T1 relaxation time ○ High myocardial T2 relaxation time ○ LGE without LVH ○ Disproportionate papillary muscle hypertrophy without LVH[81]
Evidence of general symptoms of Fabry disease*	Neuropathic pain/pain in extremities: • Acroparesthesia confirmed by the LSD physician to be Fabry specific should be sufficient to consider ERT • *NOTE: Analgesia for acroparesthesia must be considered for a minimum period of 6 months in a child less than ten years of age.*	Neuropathic pain/pain in extremities: • Symptoms leading to a need to alter lifestyle or significantly affecting quality of life after review by a specialist pain team to be Fabry related • *NOTE: Patients whose sole eligibility criterion is pain should have been assessed first by a specialist pain team, with a trial of conventional pain therapy.*	Neuropathic pain/pain in extremities: • Symptoms leading to a need to alter lifestyle or significantly affecting quality of life after review by a specialist pain team to be Fabry related • *NOTE: Patients whose sole eligibility criterion is pain should have been assessed first by a specialist pain team, with a trial of conventional pain therapy.*
	Gastrointestinal: • Unexplained severe GI symptoms affecting quality of life after review by a gastroenterologist to ensure all common causes for GI symptoms are excluded.	Gastrointestinal: • Unexplained severe GI symptoms affecting quality of life after review by a gastroenterologist to ensure all common causes for GI symptoms are excluded. • *NOTE: Patients whose sole eligibility criterion is gastrointestinal symptoms should have been assessed first by a gastrointestinal team, with a trial of conventional GI therapy.*	Gastrointestinal: • Unexplained severe GI symptoms leading to a need to alter lifestyle or significantly affecting quality of life after review by a gastroenterologist to ensure all common causes for GI symptoms are excluded. • *NOTE: Patients whose sole eligibility criterion is gastrointestinal symptoms should have been assessed first by a*

			gastrointestinal team, with a trial of conventional GI therapy.
	Ischaemic vascular disease: • Stroke/TIA with no other cause or risk factors identified (rare in <16 years)	Ischaemic vascular disease: • Stroke/TIA with no other cause or risk factors identified	Ischaemic vascular disease: • Stroke/TIA with no other cause or risk factors identified
	• Cerebral white matter lesions	• Cerebral white matter lesions	• Cerebral white matter lesions
	• Sudden severe hearing loss, corrected for age	• Sudden severe hearing loss, corrected for age	• Sudden severe hearing loss, corrected for age

* Organ involvement should be consistent with Fabry disease and not fully explained by other pathology.

Appendix 3: Comparison of treatment guidelines in Australia, UK, and Canada

Country	Australia	UK	Canada
Date last reviewed	September 2018	January 2020	October 2019
Available treatments & dosage	Agalsidase alfa (Replagal), 0.2 mg/kg per fortnight. Agalsidase beta (Fabrazyme), 1.0 mg/kg per fortnight. Migalastat (Galafold), 150 mg every second day	Adults and children (<16 years): Agalsidase alfa (Replagal), 0.2 mg/kg per fortnight. Agalsidase beta (Fabrazyme), 1.0 mg/kg per fortnight (Adults: 0.3 mg/kg in some circumstances) Adults: Migalastat (Galafold), 123 mg every second day	Agalsidase alfa (Replagal) Agalsidase beta (Fabrazyme) Migalastat (Galafold)

Choice of treatment	Treating physicians can request the most appropriate drug to treat their patient. Migalastat can only be used for patients who have been treated with agalsidase alfa or agalsidase beta for at least 12 months. All patients who are initiated on a drug or transitioned to a different drug through the LSDP are required to remain on the same drug for a period of at least 12 months, unless there is objective clinical evidence of ongoing clinical deterioration or significant adverse reactions.		Once a diagnosis of Fabry disease is confirmed, there should be a thorough evaluation of whether disease-specific therapy, either ERT or chaperone, is likely to provide clinical benefit. The indication for therapy should pre-cede the decision on which type of therapy should be used. The first decision about any patient with a confirmed diagnosis of Fabry disease is SHOULD the patient receive disease specific therapy. In those patients in whom benefit from disease specific therapy can be anticipated, then the next question is WHICH therapy should be used. Disease specific therapy should be considered in all patients with documented Fabry disease, of any age and either sex, who meet the criteria outlined below for disease-specific therapy. Choice of therapy needs to be individualized for each patient in discussion with their physician. ERT is the only therapy appropriate for patients who do not have amenable mutations. Agalsidase beta may be considered as the first option in male patients with a classic phenotype (based on Arends 2018,[33] CFDI/Sirrs, 2018[34], El Dib, 2017[35])
Home infusion	Suitability assessment required At least 12 in-hospital infusions		

	Medically stable (wrt IAR)		
General criteria	A patient must: Satisfy the initial and ongoing eligibility criteria (see below) Participate in the evaluation of effectiveness of the drug by periodic assessment (see below) or have an acceptable reason not to participate Not be suffering from any other medical condition, including complications or sequelae of Fabry disease, that might compromise the effectiveness of the drug treatment Be an Australian citizen or permanent Australian resident who qualifies for Medicare.		Indications for disease specific therapy are designed to target patients for such therapies at early stages of disease progression. Primary prevention is not supported (based on Ramaswami, 2019).[72] They note this study has limitations and accept that disease specific therapy will likely be of more benefit in patients in whom irreversible manifestations of Fabry disease (e.g. cardiac fibrosis) have not yet developed and recommend regular assessment so that therapy can be started as early as possible.
Exclusion criteria	Patients with related Fabry disease conditions which may compromise response to Enzyme Replacement Therapy (ERT) or migalastat. Patients with a presence of another life-threatening or severe disease where the long term prognosis is unlikely to be influenced by ERT or migalastat. The presence of another medical condition that might reasonably be expected to compromise a response to ERT or migalastat.	Patients with Fabry disease who are deemed too severely affected to benefit from Fabry-specific therapy (e.g. severely incapacitated following stroke / dementia). The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by Fabry-specific therapy. End stage renal failure requiring dialysis in the absence of other starting criteria.	Contraindications: Pregnancy and lactation. Pregnancy is a relative contraindication to ERT but patients on migalastat therapy should be advised to stop the chaperone therapy prior to conception and remain off it while breastfeeding and to use adequate contraception while taking migalastat therapy. Severe disease or concomitant medical condition in which death is expected within a year (absolute contraindication)

	Patients participating in a clinical trial are not eligible for subsidised treatment through the LSDP.		Presence of a severe co-morbid condition such that ERT for Fabry disease is unlikely to significantly improve quality of life (absolute contraindication) Other conditions in which the benefit to risk ratio for ERT use is not favourable (absolute contraindication) Presence of IgE antibody to ERT; this may be associated with anaphylaxis (absolute contraindication)
Diagnosis/patient group	Confirmation of disease via: alpha-galactosidase enzyme activity in blood or white cells genetic mutations known to result in deficiency of alpha- galactosidase enzyme activity	All adult and paediatric patients with a GLA gene variant of documented pathogenicity. GLA gene variants of uncertain significance (VUS) in subjects with single organ involvement pose a diagnostic challenge. If the diagnosis remains uncertain, the following may provide supportive evidence of pathogenicity: • biopsy of the affected organ (e.g. kidney or heart) to demonstrate the characteristic storage pattern by electron microscopy. • characteristic Fabry cardiomyopathy findings on cardiac magnetic resonance imaging (cMRI) • plasma lyso-GB3 levels ≥ 2.7 nM (diagnostic sensitivity and specificity of 100% in patients with "non-classic' GLA variants).	Confirmation by having 3 of 4 criteria (based on van der Tol, 2014)[23] • Clinical criteria • Biochemical criteria • Molecular criteria • Pathologic criteria Note they have included a table, and used an adaptation of the diagnostic criteria (ie a score of 3 or more points) based on Smid, 2014.[18]

Eligibility requirements (initial)	Patients must satisfy at least one of the following criteria a) Fabry-related renal disease Confirmation by renal biopsy is recommended for all patients to: • _provide prognostic information • exclude other causes of nephropathy • demonstrate evidence of focal glomerular sclerosis or fibrosis greater than that expected for age, once other causes of nephropathy have been excluded • document significant histological changes related to Fabry disease. Male Fabry patients: • abnormal albumin (>20 µg/min), as determined by 2 separate samples, at least 24 hours apart; and/or • abnormal protein excretion (>150 mg/24 hours); and/or • _albumin: creatinine ratio greater than upper limit of normal, in 2 separate samples, at least 24 hours apart; and/or • renal disease due to long-term accumulation of glycosphingolipids in the kidneys.	In males with "classical variants" (leucocyte enzyme activity <5% and a classical phenotype) Fabry-specific therapy should be considered at diagnosis. In adult females and males with 'later onset' disease, Fabry-specific therapy should commence when one of the following criteria are fulfilled: 5.1 Evidence of Fabry-related renal disease (one of): • Chronic kidney disease (CKD) stage 3: at least 2 consistent estimates or measured GFR over a minimum of 6 months. • CKD stage 2: at least 3 consistent estimates or measured GFR over at least 12 months with a GFR slope greater than age-related normal (0.8-1.0 ml/min/year) • Persistent proteinuria: increased albumin:creatinine or protein:creatinine ratio for males (https://renal.org/information-resources/the-uk-eckd-guide/proteinuria/). Females seldom progress to end stage renal failure (ESRF). In females, if proteinuria is the only presentation – anti-proteinuria medications (ACEi/ARB) should be tried in the first instance for a minimum period of 12 months. 5.2 Evidence of Fabry-related cardiac disease (one of):	Renal disease 1 major criterion or 2 minor criteria required Major criteria: • Fabry nephropathy with reduced GFR For GFR < 60 ml/min/1.73m^2 chronic kidney disease (CKD) stages 3-5: at least 2 consistent estimates or measurements of GFR over a minimum of 2 months For GFR 60 - 90 ml/min/1.73m^2, CKD stage 2: at least 3 consistent estimates or measurements of GFR over at least 4 months with a GFR slope greater than age-related normal. For GFR >135 ml/min/1.73m^2: a 15% decrease in GFR or a GFR slope greater than age-related normal as measured by nuclear medicine technique. Estimated GFR is not accurate in this range and thus cannot be used. Persisting proteinuria of 500 mg/day/1.73m^2 or greater without other cause. Findings of high risk pathology (glomerular sclerosis, tubulointerstitial atrophy, fibrosisor vascular sclerosis) on renal biopsy are a major criterion in males only (see comments).

	Female Fabry patients: • proteinuria >300 mg/24 hours with clinical evidence of progression. • renal disease due to long-term accumulation of glycosphingolipids in the kidneys. b) Fabry-related cardiac disease Confirmation by myocardial biopsy is recommended to exclude other causes of cardiac hypertrophy. Left ventricular hypertrophy, as evidenced by cardiac MRI or echocardiogram data, in the absence of hypertension. If hypertension is present, it should be treated optimally for at least 6 months prior to the submission of an application through this criterion. Significant life-threatening arrhythmia or conduction defect. c) Ischaemic vascular disease Shown on objective testing with no other cause or risk factors identified. d) Uncontrolled chronic pain	• LV wall thickness >13 mm in males and >12 mm in females. • LV mass index by 2D echo / cMRI above normal for age and sex. • Late gadolinium enhancement on cMRI. 5.3 General symptoms of Anderson-Fabry disease: • Uncontrolled pain or gastrointestinal symptoms leading to a need to alter lifestyle or which significantly interferes with quality of life. Patients whose sole eligibility criterion is gastrointestinal symptoms should have been assessed first by a gastrointestinal team, with a trial of conventional GI therapy. • Patients whose sole eligibility criterion is pain should have been assessed first by a specialist pain team, with a trial of conventional pain therapy. • If Fabry related symptoms are the only indication for consideration of Fabry-specific therapy a trial could be given for a year with pre-specified outcomes agreed as to what would constitute a positive effect for symptom control. Such outcomes may include: o Reduction in the need for analgesia	Minor criteria: • Hyperfiltration: There should be at least two (2) consistent measurements of GFR by nuclear medicine techniques at least one month apart when GFR reaches or exceeds 135 ml/min/1.73m2. Hyperfiltration by eGFR as calculated by any formula is not accurate and thus not acceptable. • Isolated proteinuria of 300 mg/day/1.73m2 or greater than normal for age and gender and persistent for at least one year with exclusion of other causes. • Renal tubular dysfunction. Fanconi syndrome and/or nephrogenic diabetes insipidus confirmed usually with abnormal water deprivation test and resistance to DDAVP. • Hypertension of at least one year duration. • Renal pathology in women may be taken into account as a minor criterion if the patient has indications for renal biopsy. If a renal biopsy is done, the presence of glomerular sclerosis, tubulointerstitial atrophy and fibrosis or vascular sclerosis

	Uncontrolled chronic pain despite the use of maximum doses of appropriate analgesia and antiepileptic medications for peripheral neuropathy. Patients meeting this criterion must provide ongoing evidence of effect, through analgesic intake, pain diary, summary letter from treating physician.	o Reduction in time lost from work o Significant Improvements in validated pain scores and / or quality of life measures.	should be considered a minor criterion in women. Cardiac disease (2 criteria required) • LV wall thickness >12 mm in males and >11 mm in females • LV hypertrophy (LVH) by Estes ECG score must be greater than 5 • LV mass index by 2D echo 20% above normal for age • Increase of LV mass of at least 5 g/m2/year, with three measurements over a minimum of 12 months • Diastolic filling abnormalities by 2D echocardiogram, Grade 2 or Grade 3 diastolicdysfunction as outlined by ASE and/or the presence of speckle tracking abnormalities • Abnormal base to apex circumferential strain gradient • Increased LA size on 2D echo. In parasternal long axis view (PLAX) >40 mm; Left atrial volume index > 34 ml/m^2 • Cardiac conduction and rhythm abnormalities: AV block, short PR interval, left bundle branch block (LBBB), ventricular or atrial tachyarrhythmias, sinus bradycardia

			(inthe absence of drugs with negative chronotropic activity or other causes) • Moderate to severe mitral or aortic insufficiency • Late enhancement of left ventricular wall on cardiac MRI • T1 values using a 1.5 Tesla magnet in males below 901 ms and females below 916ms • Increase of either N-terminal pro-natriuretic brain peptide (NT-proBNP) above the upper limit of normal for age and gender OR an increase of high sensitivity troponin (a surrogate marker of fibrosis) more than 2 times the upper limit of the normal range Neurological disease 1 major criterion required • Stroke or TIA documented by a neurologist diagnosed on the basis of clinical features (TIA) and/or CNS imaging criteria consistent with the diagnosis of stroke . • Sudden onset unilateral hearing loss when other possible causes have been excluded. • Acute ischemic optic neuropathy when all other possible causes have

			been excluded Neuropathic Pain • Pain is NOT considered an isolated indication for disease specific therapy in most patients. • If pain is the only indication for consideration of disease specific therapy, then consideration for a one year trial of disease specific therapy could be given as long as all of the following criteria are met: A. Prespecified outcomes as to what would constitute a positive effect of disease specific therapy for this symptom are agreed to prior to the trial by the treating physician and the patient. Such outcomes may include tangible benefits such as: • Significant reduction in the need for analgesics • Significant reduction in time lost from work or school due to pain • Significant reduction in the frequency of pain crises requiring hospital admission etc. Gastrointestinal Disease

			• Significant gastrointestinal symptoms unresponsive to other measures for at least 6 months or associated with poor growth or significant reduction in quality of life.
Migalastat (additional criteria)	Patients must meet the above criteria as well as have an amenable genetic mutation. Patients must have been treated with agalsidase alfa or agalsidase beta for at least 12 months or must be intolerant to agalsidase alfa or agalsidase beta.	Not indicated in patients with an eGFR < 30 ml/min. • As a precautionary measure, it is recommended to avoid the use of Migalastat during pregnancy. This should be discussed prior to commencing therapy.	Not indicated in patients with an eGFR < 30 ml/min. Consideration of choice of therapy in patients with amenable mutations should include: Degree of organ involvement Patient compliance (pre-agreed thresholds) Patient age (18-65 yrs) Need for increased surveillance of response to treatment
Ongoing eligibility criteria	Annual reapplication by 1 May each year Reapplication must demonstrate clinical improvement in the patient or stabilisation of the patient's condition Evidence to support ongoing eligibility for the treatment of Fabry disease must be provided.	Patient receiving Fabry-specific therapy should have at least a 12 monthly review in person at an LSD centre, with an additional review every 6 months (in person, or by telephone as clinically indicated) Efficacy measures Biochemical:	Consideration should be given to discontinuation of disease specific therapy if there is evidence that the patient is not responding to treatment after a reasonable period of observation, of at least a year.

		• Plasma lyso-GB3 concentration (reduction from baseline by 20% after ≥ 12 months of therapy). Renal: • eGFR change (decline by < 4 ml/min/1.73m2/year) • Initiation of renal replacement therapy (no requirement) • Renal transplant (no requirement) Cardiac: • LVMI (gain < 6 gm / m2 over the previous 3 year period • Cardiac rhythm monitoring (no requirement for therapeutic device insertion) • Systolic and diastolic function (to prevent dysfunction with worsening of heart failure symptoms). Other: • Neurological endpoints (no new TIA / stroke) • Brief Pain Inventory score (improvement) • EQ5D Quality of Life score (Improvement) • Composite clinical endpoint - to include	

		new renal end stage renal disease, arrhythmia requiring pacemaker or defibrillator, stroke or death (improvement)	
Discontinuation	Subsidised treatment may continue unless one or more of the following situations apply: • failure to comply adequately with treatment or measures • failure to provide data, copies of the test results and the Excel spreadsheet for Fabry disease, evidencing the effectiveness of the therapy • therapy fails to relieve the symptoms of disease that originally resulted in the patient being approved for subsidised treatment • the patient has severe infusion-related adverse reactions which are not preventable by appropriate pre-medication and/or adjustment of infusion rates and has a non-amenable mutation to migalastat • the patient develops another life threatening or severe disease where the long term prognosis is unlikely to be influenced by LSDP subsidised treatment • the patient develops another medical condition that might reasonably be expected to compromise a response to LSDP subsidised treatment	Fabry specific therapy may be withdrawn under the following circumstances: 9.1 General: Intolerable and unavoidable adverse effects. Intercurrent illness, where either long-term quality of life or expected survival is such that the patient will gain no significant benefit from specific treatment for Fabry disease. At the request of the patient, or properly allocated guardian acting in the patient's best interests, if the patient is properly deemed not competent. If the circumstances of the patient's lifestyle are such that sufficient compliance with treatment is not possible. If the health and wellbeing of medical and / or nursing staff are placed under significant threat as a result of the actions or lifestyle of the patient. Emigration of the patient outside the jurisdiction of the UK, when administration and funding of the treatment becomes the responsibility of Health Services in the new	

	• presentation of conditions listed in the exclusion criteria.	country of residence / domicile. Specific Objective evidence of progression in measured clinical criteria which are not: Attributable to a secondary pathology Commensurate with natural age-related decline Remediable by changing product or institution of other simple therapeutic measure Within the normal measured variation of that laboratory parameter Out-weighed in clinical significance by stabilisation or improvement in one of the other criteria On the basis of current major criteria these might include: Deterioration of eGFR by more than 4 ml/min/1.73m2/year and / or requiring renal replacement therapy Progressive impairment of systolic or diastolic dysfunction resulting in worsening heart failure symptoms Gain in LVMI > 6 gm / m2 over a three year period	

		Rhythm disturbance requiring therapeutic device insertion in the absence of other demonstrable benefit New presentation of clinically significant neurovascular disease in the absence of other demonstrable benefit Worsening of pain or gastrointestinal symptoms beyond baseline or no improvement if these are the only reasons to start treatment Failure of reduction of plasma lyso-GB3 or increase after initial response	
Other		For children (< 16 years), ERT dose will be calculated based on body weight and capped at a BMI that is increased +2SD above the median (98th centile) for age. For adult patients with an increased BMI the dose will be capped as for a BMI of 27 kg/m2. Vials will be used in integer units with alternating vials if needed to ensure the most cost effective use. No drug will be wasted.	
Paediatric patients		Starting criteria Children < 16 years: Disease-modifying therapies should be considered when there are documented Fabry related clinical manifestations. There is no evidence currently that treating asymptomatic children prevents disease progression in classical and later onset	

		variants. 5.1 Evidence of Fabry related renal disease (one of): Persistent microalbuminuria (3 consecutive early morning urine samples or 3 random early morning urine samples over a period of six months) Reduction in estimated / measured GFR (after a review by nephrologist and other causes have been excluded). 5.2 Evidence of Fabry related cardiac disease (one of): LV mass index by 2D echo / cMRI above normal for age or increased by 2SD over a 12 to 24 month period ECG: arrhythmias, shortening or prolonged PR interval on age appropriate ECG analyses 5.3. Evidence of general symptoms of Fabry disease: 5.3.1 Isolated neuropathic pain: Acroparesthesia confirmed by the LSD physician to be Fabry specific should be sufficient to consider ERT. Whilst analgesia for acroparesthesia must be considered for a minimum period of 6 months in a child less than ten years of age,	

		neuropathic pain is frequently the first Fabry symptom in children and hence defines a more severe cohort. This occurs in approximately 60% of children with “classic” GLA gene variants. 5.3.2 Unexplained gastrointestinal (GI) symptoms affecting quality of life Common causes for childhood GI symptoms such as food allergies, coeliac disease, or infections must be excluded first; prior to considering ERT for GI symptoms in children. Review by a gastroenterologist to ensure all common causes for GI symptoms are excluded with / without GI endoscopy is recommended. Efficacy measures: Children < 16 years: • Age appropriate paediatric pain tools / devices (improvement)(examples could include VAS, BPI, NRS-11, FPHPQ) • School attendance (improvement) • Pain medications (reduction) • Age appropriate quality of life score (improvement)(examples could include EQ-ED or FPHPQ) • Growth and development (improvement / or stabilisation if normal)	

		Monitoring Boys and girls < 5 years: Arrange clinical review if indicated. 8.2. Children ≥ 5 years and < 10 years: 8.2.1 Boys with classic pathogenic variants: Frequency of review as clinically indicated by the treating clinician eg. 12 to 24 monthly. 8.2.2. Girls and boys with late-onset variants: Frequency of review as clinically indicated by the treating clinician eg. 24 to 36 monthly. • Clinical review • School attendance • Growth and development • Pain and QOL questionnaires • Urine protein/creatinine ratio (random spot urine) • Plasma lyso-GB3 • ECG; cardiac ECHO (baseline and thereafter as indicated) • Urine albumin/creatinine ratio (spot urine; 3 x consecutive urine samples	

		if random early morning spot urine abnormal) • Ophthalmology with slit lamp examination (baseline and thereafter once every 2 to 3 years as indicated) • Age specific audiology (baseline and thereafter as indicated) 8.2.3 Boys and girls ≥ 10 and < 14 years: Monitor as above (every 12 months) and include: • Calculated GFR (Counahan-Barratt [CB] method or Schwartz) • MRI brain if clinically indicated only (stroke/symptoms of TIA/other neurological symptoms. Arrange review by a paediatric neurologist and other causes excluded) 8.2.4 Boys and girls ≥ 14 and <16 years: Monitor as above (every 12 months) and include: • Cardiac MRI (optional but preferred) • Measured GFR once every 3 years, with calculated GFR (CB method) annually	

		• Baseline MRI brain (if clinically indicated) • Audiology at 14 years and thereafter as clinically indicated 9.0 Stopping Criteria in children • Severe life threatening infusion associated reactions that cannot be managed by standard protocols, including desensitisation • Other life threatening / life limiting illness • Poor compliance – consider a safe-guarding referral if deemed appropriate • End stage renal failure due to other causes that cannot be treated, or that is not suitable for renal transplant when there are no other Fabry specific symptoms.	