MONITORING MATTERS
FABRY DISEASE

Fabry disease progresses silently before clinical manifestations and irreversible organ damage become evident. Therefore, it is essential to monitor patients carefully in order not to miss the appropriate time for initiation of Fabry-specific therapy and assess response to treatment.

BEGIN



MONITORING
MATTERS

MAT-CA-2301436_October 2023

sanofi

RENAL MONITORING
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MULTI-SYSTEMIC MONITORING

Patient management[1]

Patients diagnosed with Fabry disease but not receiving Fabry-specific therapy should be monitored at appropriate intervals to determine disease progression.

For patients on Fabry-specific therapy, regular assessment should be carried out in order to understand the impact of treatment on all affected organ systems.

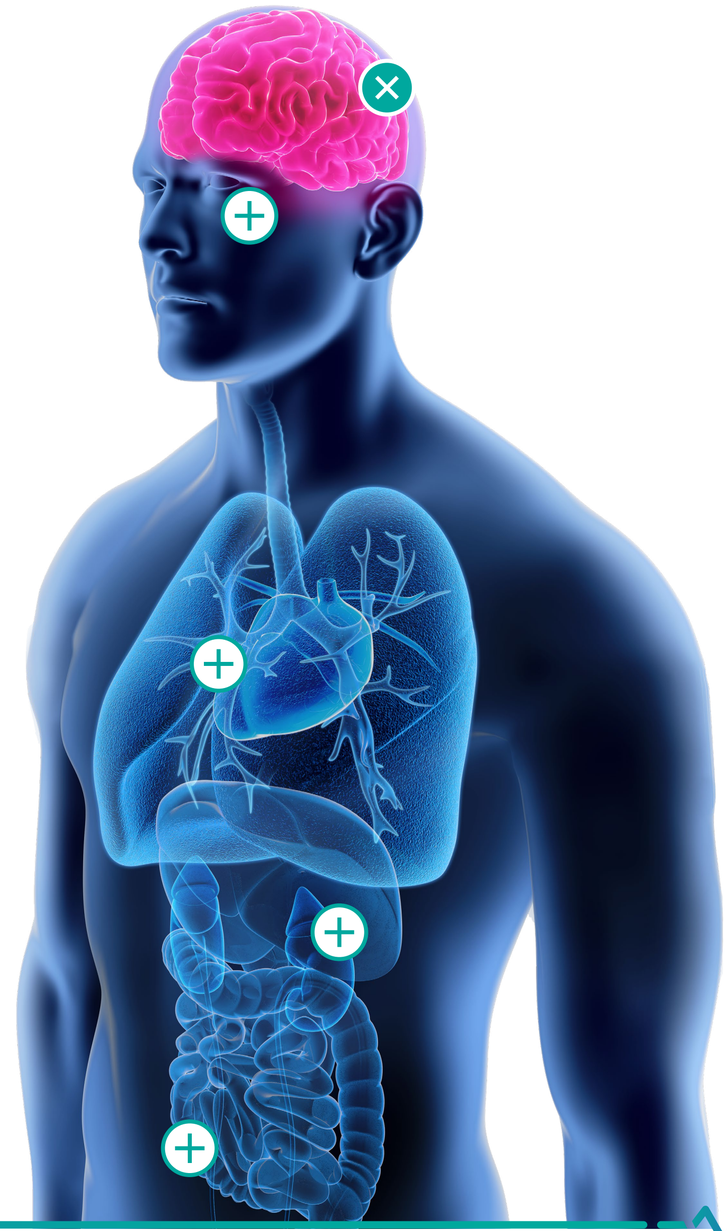
These assessments should be handled by a multidisciplinary clinical team, including a neurologist, a nephrologist, a cardiologist, a medical geneticist/genetic counsellor, a psychologist, and a nurse, and supervised by a physician with experience in Fabry disease.

Select the buttons on the hightlighted areas of the body to discover...



Neurological Manifestations[1-3]

- Neuropathic pain
- Pain crises
- Atypical pain (chronic or episodic)
- Heat/cold intolerance
- Hyperhydrosis/hypohydrosis
- Hearing loss/tinnitus
- Dizziness/vertigo
- White matter lesions
- Development of TIA
- Stroke (often recurrent)



TIA, transient ischaemic attack.

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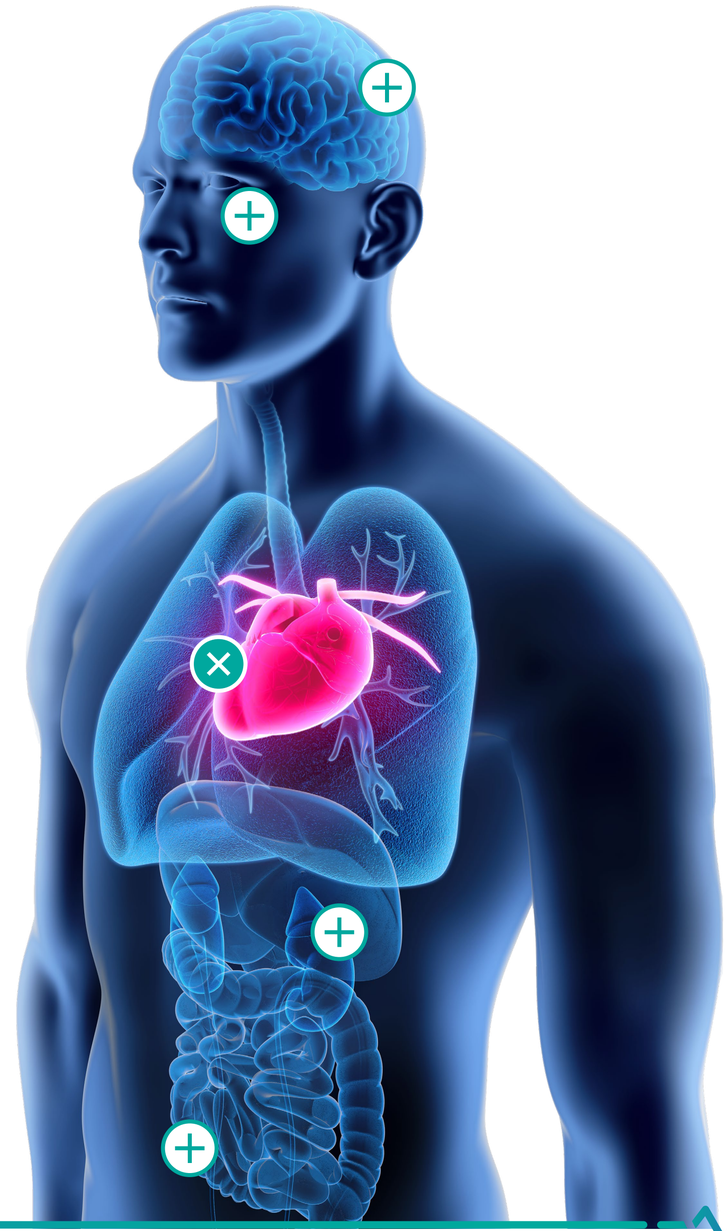
Cardiac Manifestations[1,3,4]

- Cardiomyopathy
- Impaired heart rate variability
- Arrhythmias
- Chest pain and other symptoms
- Ventricular tachycardia
- ECG abnormalities (shortened PR interval)
- Reduced exercise tolerance
- Heart failure
- Sudden cardiac death



EGC, electrocardiogram

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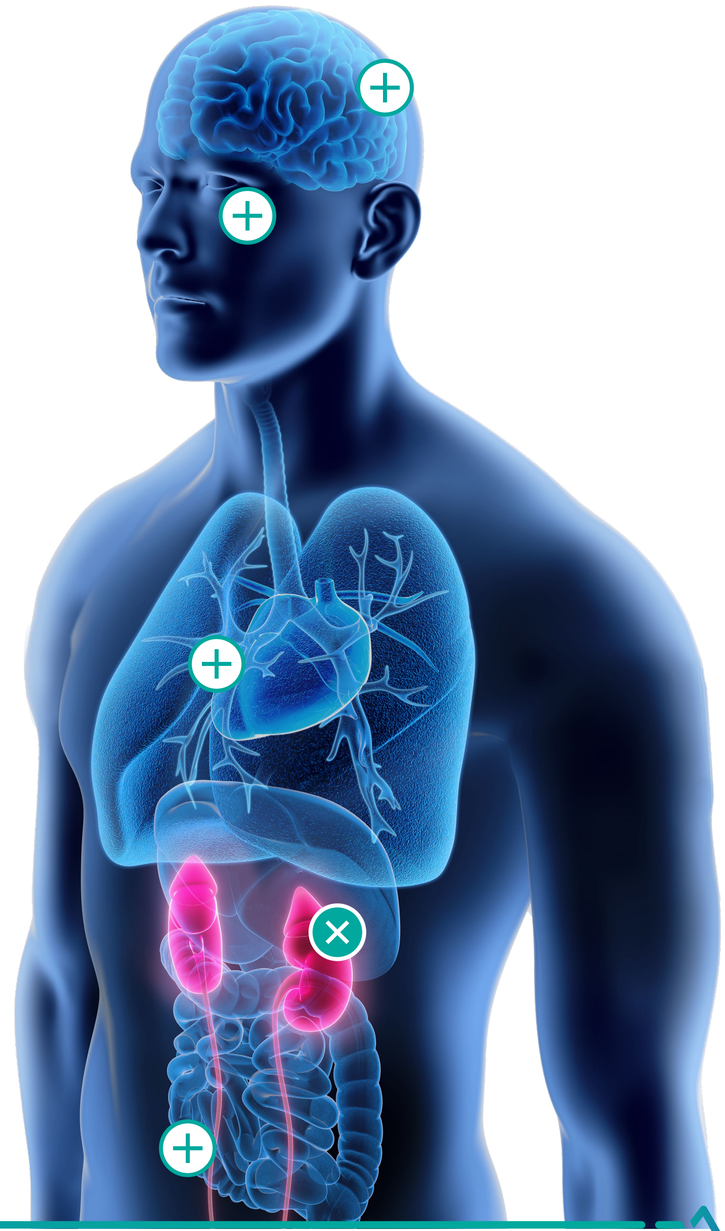
Renal Manifestations[1-3]

- Hyperfiltration
- uACR increase
- eGFR decline
- Impaired concentration ability
- Increased urinary GL-3 excretion
- Chronic kidney disease
- End-stage renal disease



eGFR, estimated glomerular filtration rate; GL-3, globotriaosylceramide; uACR, urine albumin:creatinine ratio.

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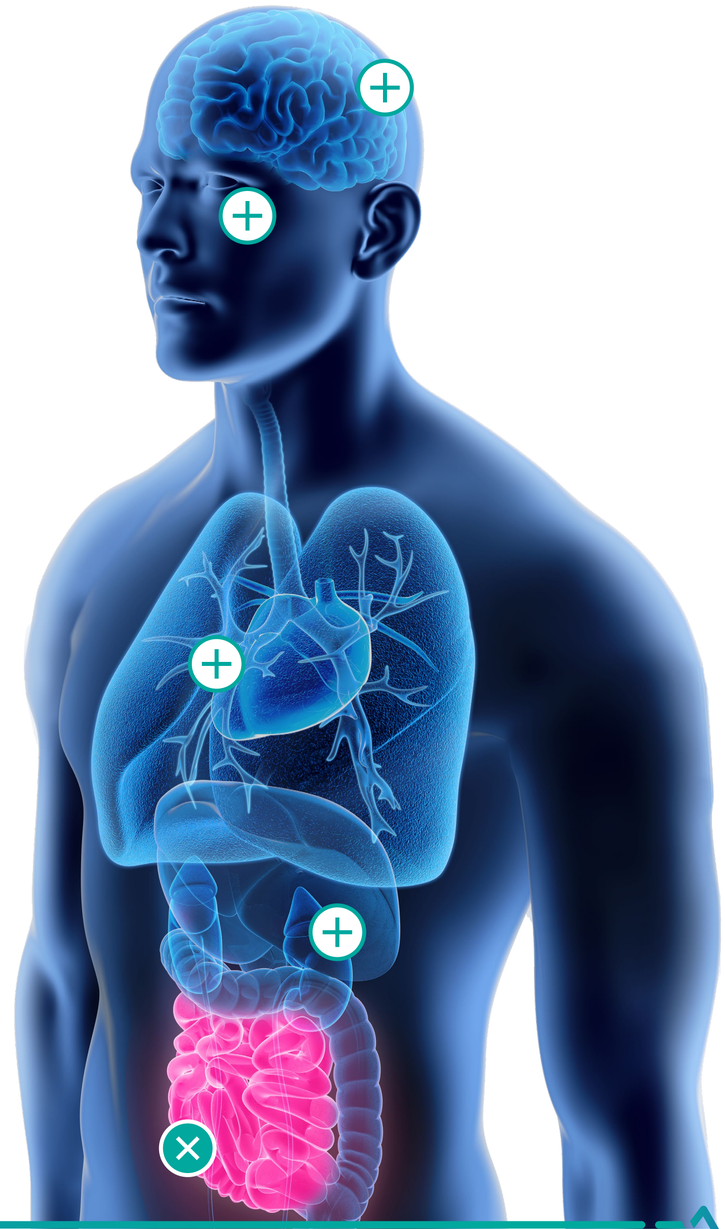
Gastrointestinal Manifestations[1-3]

- Nausea/vomiting
- Diarrhoea/constipation
- Postprandial bloating and pain
- Early satiety
- Difficulty gaining weight



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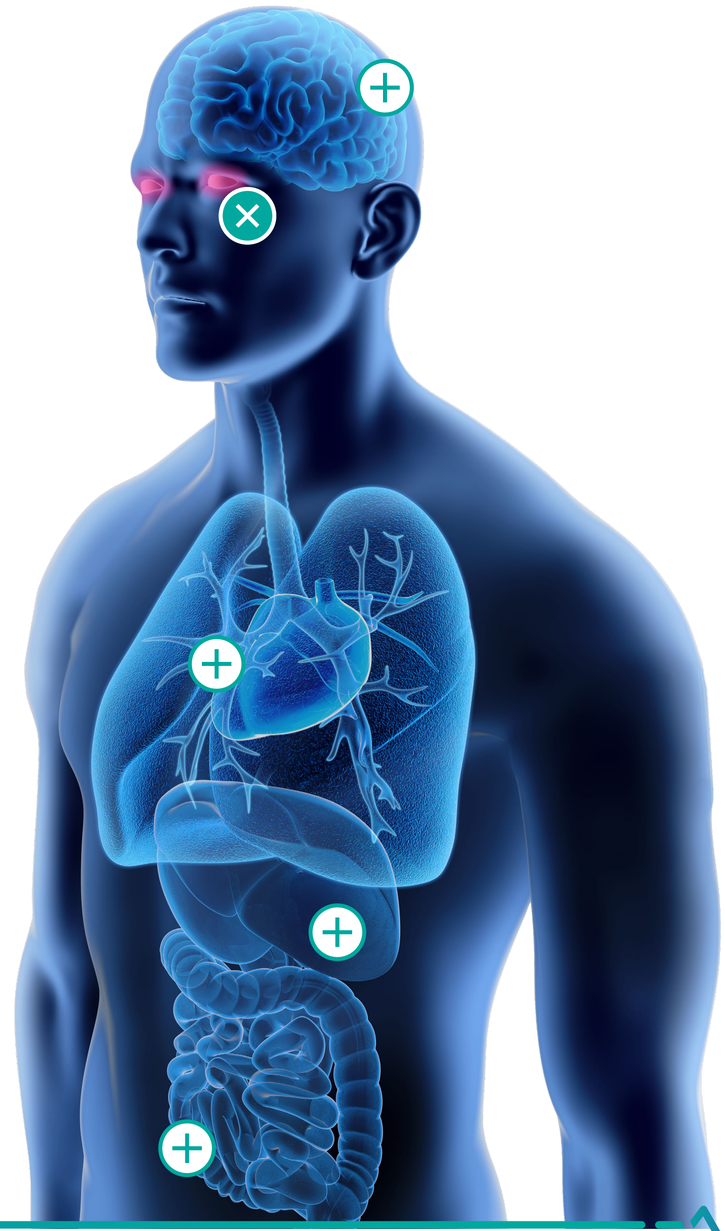
Other Manifestations[1-3]

- Elevated lyso-GL-3
- Angiokeratoma
- Cornea verticillata
- Lymphoedema



Lyso-GL-3, globotriaosylsphingosine.

RENAL MONITORING[1]

Measured GFR (Preferred)

ANNUALLY
Because of complexity

or

Estimated GFR (Using appropriate formulae)

Risk of adverse outcomes[+]:

Low	Moderate	High to very high
ANNUALLY	**EVERY 6 MONTHS**	**EVERY 3 MONTHS**

Albuminuria (Preferred, more sensitive)

or

Proteinuria (24-h or spot urine for total protein/creatinine and albumin/creatinine ratios)

Risk of adverse outcomes[+]:

Low	Moderate	High to very high
ANNUALLY	**EVERY 6 MONTHS**	**EVERY 3 MONTHS**

Proteinuria only increases as albuminuria progresses

Kidney biopsy

AS CLINICALLY INDICATED

Podocyte foot process effacement may precede pathological albuminuria

25-OH vitamin D

AS CLINICALLY INDICATED

Vitamin D levels in late autumn/early winter

+RISK OF ADVERSE OUTCOMES STRATIFICATION

RECOMMENDATIONS FOR TREATMENT INITIATION

25-OH, 25-hydroxy; ERT, enzyme replacement therapy; GFR, glomerular filtration rate.

RENAL MONITORING

RISK OF ADVERSE OUTCOMES STRATIFICATION

Risk of adverse outcomes by GFR and albuminuria categories: KDIGO 2012[5]

GFR categories (mL/min/min/1.73 m²) Description and range			Persistent albuminuria categories description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–300 mg/g 3–30 mg/mmol	A3 Severely increased >300 mg/g <30 mg/mmol
G1	Normal or high	≥90			
G2	Mildly decreased	60–89			
G3a	Mildly to moderately decreased	45–59			
G3b	Moderately to severely decreased	30–44			
G4	Severely decreased	15–29			
G5	Kidney failure	<15			

Risk of adverse outcomes: Low risk* | Moderately increased risk | High risk | Very high risk

*If no other marker of kidney disease, no CKD
CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

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Recommendations for the initiation of ERT[1]:

Patients with classic Fabry disease phenotype			Patients with later-onset Fabry disease phenotype and patients with missense *GLA* VUS
Male patients	**Female Patients**		
Symptomatic or Asymptomatic	**Symptomatic**	**Asymptomatic**	**Male and female patients**
ERT should be considered and is appropriate in all patients at any age of presentation	ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, even in the absence of typical Fabry symptoms. The abnormalities should be attributable to Fabry disease; this may require histological assessment or biochemical evidence of GL-3 accumulation	ERT should be considered if there is laboratory, histological, or imaging evidence of injury to the kidney renal disease: • decreased GFR (category≥G2) • persistent albuminuria (category A2 or A3) podocyte FPE or glomerulosclerosis on renal biopsy, moderate or severe • GL-3 inclusions in a range of renal cell types	Signs/symptoms suggesting major organ involvement, warranting initiation of ERT proteinuria/albuminuria NOT attributable to other causes, evidence of renal impairment (may require renal biopsy if isolated)

Chaperone therapy is indicated only for patients with amenable alpha-galactosidase A gene mutations.

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ERT, enzyme replacement therapy; FPE, foot process effacement; GFR, glomerular filtration rate, GL-3, globotriaosylceramide; VUS, variant of unknown significance.

CARDIOLOGICAL MONITORING[1,4,6,7]

BP and cardiac rhythm

EVERY CLINIC VISIT

Cardiac MRI with gadolinium

REGULARLY
at an interval >2 years

or

Whenever there is evidence of clinical disease progression

ECG and echocardiography

ANNUALLY
and as clinically indicated

T1 Mapping

Allows non-invasive tissue characterization and can be used to assess disease progression

NT-proBNP

to assess the severity of cardiac involvement before overt hypertrophy

ANNUALLY
at least

It can be difficult to interpret NT-proBNP level in chronically dialyzed patients

48 h-Holter

to detect intermittent rhythm abnormalities

or

Implantable loop recorder

recommended for patients with significant HCM

ANNUALLY
(dependent on risk factors such as age or arrhythmias)

More frequent or detailed rhythm surveillance to be initiated if arrhythmias are detected (schedule determined individually)

RECOMMENDATIONS FOR TREATMENT INITIATION

BP, blood pressure; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro B-type natriuretic peptide.

CARDIOLOGICAL MONITORING

RECOMMENDATIONS FOR TREATMENT INITIATION

Recommendations for the initiation of ERT[1]:

Patients with classic Fabry disease phenotype			Patients with later-onset Fabry disease phenotype and patients with missense *GLA* VUS
Male patients	**Female Patients**		
Symptomatic or Asymptomatic	**Symptomatic**	**Asymptomatic**	**Male and female patients**
ERT should be considered and is appropriate in all patients at any age of presentation	ERT should be considered and is appropriate if there are signs/symptoms suggesting major organ involvement, such as symptomatic cardiac disease NOT due to other causes: • dyspnea • palpitations • syncope • chest pain	ERT should be considered if there is laboratory, histological, or imaging evidence of injury to the heart, such as asymptomatic cardiac disease: • cardiomyopathy or arrhythmia • cardiac fibrosis on contrast cardiac MRI	Signs/symptoms suggesting major organ involvement, warranting initiation of ERT, even in the absence of typical Fabry symptoms, such as asymptomatic cardiac disease NOT attributable to other diseases: • this may require histological or biochemical evidence

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ERT, enzyme replacement therapy; MRI, magnetic resonance imaging; VUS, variant of unknown significance.

NEUROLOGICAL MONITORING

PERIPHERAL NERVOUS SYSTEM[1]

Pain evaluation and history

ANNUALLY

Pain measurement scale (SF-36, BPI, FD-PRO)

Cold and heat intolerance, vibratory thresholds

quantitative sensory testing, if available

ANNUALLY
and as clinically indicated

Autonomic symptom evaluation

by orthostatic blood pressure

ANNUALLY
and as clinically indicated

Skin biopsy

(for IENFD assessment)

CONSIDER

CEREBROVASCULAR[1]

Brain MRI

EVERY 3 YEARS
or when clinically needed*

At first assessment in male patients >21 years old and female patients >30 years old

*E.g., presence of neurological changes that could potentially relate to stroke

CT Imaging

only if MRI is contraindicated due to cardiac pacing

ANNUALLY

PAIN MEASUREMENT SCALES
RECOMMENDATIONS FOR TREATMENT INITIATION

BPI, Brief Pain Inventory; IENFD, intraepidermal nerve fibre density, MRI, magnetic resonance imaging; NPSI, Neuropathic Pain Symptom Inventory.

NEUROLOGICAL MONITORING

RECOMMENDATIONS FOR TREATMENT INITIATION

Recommendations for the initiation of ERT[1]:

Patients with classic Fabry disease phenotype			Patients with later-onset Fabry disease phenotype and patients with missense *GLA* VUS
Male patients	**Female Patients**		
Symptomatic or Asymptomatic	**Symptomatic**	**Asymptomatic**	**Male and female patients**
ERT should be considered and is appropriate in all patients at any age of presentation	ERT should be considered and is appropriate if there are signs/symptoms suggesting major organ involvement, such as: • neuropathic pain • pain crises • FD neuropathy	ERT should be considered if there is laboratory, histological, or imaging evidence of injury to the CNS, such as: • silent strokes • cerebral white matter lesions (on brain MRI)	Signs/symptoms suggesting major organ involvement, warranting initiation of ERT, even in the absence of typical Fabry symptoms: • strokes or white matter lesions NOT attributable to other diseases (this may require histological or biochemical evidence)

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CNS, central nervous system; FD, Fabry disease; ERT, enzyme replacement therapy; MRI, magnetic resonance imaging; VUS, variant of unknown significance.

QUALITY OF LIFE MONITORING[8]

PATIENTS UNDER 18 YEARS OF AGE

Pediatric QoL Assessment *In (PedsQL™ Pediatric QoL Inventory and Multidimensional Fatigue Scale)* **EVERY 6–12 MONTHS*** following initial baseline	*and at time of event or therapy change
Pediatric pain Assessment *(PedsQL™ Pediatric Pain Questionnaire™)* **EVERY 6–12 MONTHS*** following initial baseline	*and at time of event or therapy change

PATIENTS AGE 18 AND OVER

QoL Assessment *(SF-36®, BPI, FD-PRO)* **EVERY 6–12 MONTHS*** following initial baseline	*and at time of event or therapy change

FACTORS IMPACTING QoL

PEDIATRIC QoL MEASURING TOOLS

ADULT QoL MEASURING TOOLS

BPI, Brief Pain Inventory; QoL, quality of life; SF-36, 36-Item Short Form Survey.

QUALITY OF LIFE MONITORING

FACTORS IMPACTING QOL

FACTORS IMPACTING QoL[9,10]:

Pain
(chronic pain, pain crisis)

Kidney failure
(renal replacement therapy)

GI symptoms
(diarrhoea, abdominal pain)

60+

Older age

Physical inactivity, fatigue
(exercise intolerance, impact on sexual activity)

Hearing loss
(vestibular and hearing disturbance, tinnitus)

GI, gastrointestinal; QoL, quality of life.

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PEDIATRIC QoL ASSESSMENT TOOLS

PedsQL™

Modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions.

Pediatric QoL Inventory[11]

Designed to measure the core dimensions of health as delineated by the WHO, as well as role (school) functioning. The multidimensional scales and summary scores are:

Scales
- Physical Functioning (8 items)
- Emotional Functioning (5 items)
- Social Functioning (5 items)
- School Functioning (5 items)

Summary Scores
- Total Scale Score (23 items)
- Physical Health Summary Score (8 items)
- Psychosocial Health Summary Score (15 items)

Multidimensional Fatigue Scale[12]

Designed as a generic symptom-specific instrument to measure fatigue in patients with acute and chronic health conditions as well as healthy school and community populations

Child self-report and Parent proxy-report (total of 36 items)
- General fatigue (6 items)
- Sleep/rest fatigue (6 items)
- Cognitive fatigue (6 items)
- Total fatigue (18 items)

Pediatric Pain Questionnaire™[13]

Designed as a generic symptom-specific instrument to measure pain in patients with acute and chronic health conditions.

Scales
- Present pain (1 item)
- Worst pain (1 pain)

Not scored
- Localisation of pain

QoL, quality of life. WHO, World Health Organization.

NEUROLOGICAL and QoL MONITORING

ADULT QoL ASSESSMENT TOOLS

NEUROLOGICAL PAIN MEASUREMENT SCALES and ADULT QoL ASSESSMENT TOOLS

SF-36®[14]

SF-36 is a set of generic, coherent, and easily administered QoL measures.

Patients report on:
- vitality
- physical functioning
- bodily pain
- general health perceptions
- physical role functioning
- emotional role functioning
- social role functioning
- mental health

BPI[15,16]

Rapidly assesses the severity of pain and its impact on functioning.

The BPI is available in two formats:
- short form
- long form (contains items that expand the descriptors of pain and other additional descriptive items)

Sections of the scale include:
- worst pain in the last 24 hours
- least pain in the last 24 hours
- pain on average
- pain right now

Patients also report on:
- general activity
- mood
- walking ability
- normal work
- relations with other people
- sleep
- enjoyment of life

FD-PRO[17,18]

The FD-PRO instrument is a novel Fabry disease-specific instrument that assesses classic and non-classic symptoms.

19-items measuring the severity of symptoms in the past 24 h:
- pain
- burning feeling
- numbness
- tingling
- headache pain
- abdominal pain
- heat intolerance
- swelling in the lower extremities
- ringing or buzzing in ears
- tiredness
- hearing impairment
- vision impairment
- sweating (yes/no)
- sweating (score)
- impact on physical activities

QoL, quality of life. WHO, World Health Organization.

BIOMARKERS MONITORING[6]

Lyso-GL-3		
In patients not on therapy:	*In patients on therapy:*	*in patients on therapy, routinely monitor at baseline and then every 6 months after treatment initiation or switch to evaluate longitudinal changes.
REGULARLY following initial baseline	**EVERY 6 MONTHS*** after treatment initiation	

RECOMMENDATIONS FOR TREATMENT INITIATION

Lyso-GL-3, globotriaosylsphingosine.

BIOMARKERS MONITORING

RECOMMENDATIONS FOR TREATMENT INITIATION

Recommendations for the initiation of ERT[1]:

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Symptomatic or Asymptomatic	**Symptomatic**	**Asymptomatic**	**Male and female patients**
ERT should be considered and is appropriate in all patients at any age of presentation	ERT should be considered and is appropriate if there are signs/ symptoms suggesting major organ involvement	ERT should be considered if there is laboratory, histological, or imaging evidence of moderate or severe GL-3 inclusions in a range of renal cell types	ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS, even in the absence of typical Fabry symptoms. • these abnormalities should be attributable to Fabry disease (e.g. following biochemical evidence of GL-3 accumulation)

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CNS, central nervous system; ERT, enzyme replacement therapy; GL3, globotriaosylceramide; VUS, variant of unknown significance.

MONITORING SCHEDULES SUMMARY[1,6]

MONITORING	MEASURES	AT BASELINE	EVERY VISIT	EVERY 3 MONTHS	EVERY 6 MONTHS	ANNUALLY	≥ EVERY 2 YEARS	AS CLINICALLY INDICATED
RENAL	eGFR			X High/Very high[a]	X Moderate[a]	X low[a]		
	mGFR					X		
	ALBUMINURIA and PROTEINURIA			X High/Very high[a]	X Moderate[a]	X Low[a]		
	25-OH VITAMIN D							X
	KIDNEY BIOPSY							X
CARDIOLOGICAL	BLOOD PRESSURE AND CARDIAC RHYTHM		X					
	ECG AND ECHOCARDIOGRAPHY					X		X
	48-H HOLTER/IMPLANTABLE LOOP RECORDER					X[c]		
	cMRI WITH GADOLINIUM						X	X
	T1 MAPPING							X
	NT-proBNP					X[c,d]		
NEUROLOGICAL	BRAIN MRI	X[e]					X Every 3 years	
	CT IMAGING							X[f]
	PAIN EVALUATION					X[g]		
	COLD/HEAT INTOLERANCE, VIBRATORY THRESHOLDS					X		
	AUTONOMIC SYMPTOM EVALUATION					X		
	SKIN BIOPSY							X
BIOMARKERS	LYSO-GL-3	X			X[h]			X[i]
QUALITY OF LIFE	PEDIATRIC QoL and PAIN ASSESSMENT (PedsQL™ Pediatric QoL Inventory and Pain Questionnaire™)	X			X[j]			X
	PEDIATRIC QoL ASSESSMENT (PedsQL™ Multidimensional Fatigue Scale)	X			X[j]			X
	ADULT QoL ASSESSMENT (SF-36®, BPI, FD-PRO)	X			X			X

[a]Risk of adverse outcomes; [b]due to complexity; [c]at least; [d]can be difficult to interpret in chronically dialyzed patients, [e]in male patients >21 years old and female patients >30 years old; [f]in case of acute stroke and only if MRI is contraindicated; [g]less frequently with age; [h]in patients on therapy; [i]in patients not on therapy, [j]every 6–12 months. 25-OH, 25-hydroxy; BPI, Brief Pain Inventory; CT, computed tomography; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; lyso-GL-3, globotriaosylsphingosine; mGFR, measured glomerular filtration rate; MRI, magnetic resonance imaging; NT-proBNP, B-type natriuretic peptide; QoL, quality of life; SF-36, 36-Item Short Form Survey.



RENAL MONITORING



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NEUROLOGICAL MONITORING



QUALITY OF LIFE



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REFERENCES

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