

MONITORING MATTERS FABRY DISEASE

Fabry disease may progress silently before clinical manifestations and irreversible organ damage become evident. Therefore, it is essential to monitor patients carefully in order to not miss the appropriate time for initiation of Fabry-specific multi-organ management.

BEGIN



MONITORING
MATTERS



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MULTI-SYSTEMIC MONITORING



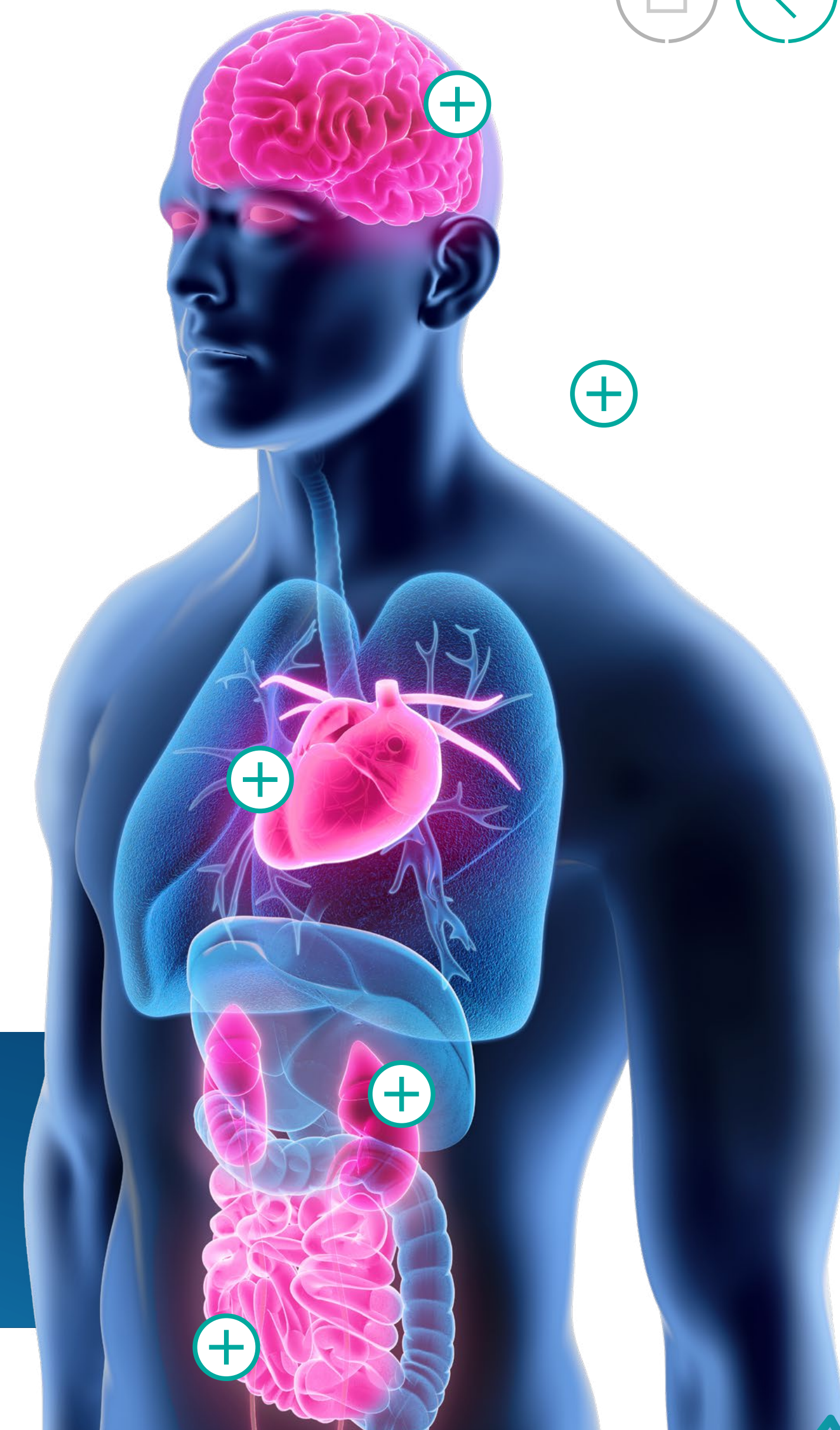
Patient management¹

Patients diagnosed with Fabry disease should be monitored at appropriate intervals to determine disease progression.

In order to detect disease progression across organ systems, regular assessments should be carried out for all patients with Fabry disease.

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.

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RENAL
MONITORING



CARDIOLOGICAL
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NEUROLOGICAL
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QUALITY OF LIFE



BIOMARKERS
MONITORING

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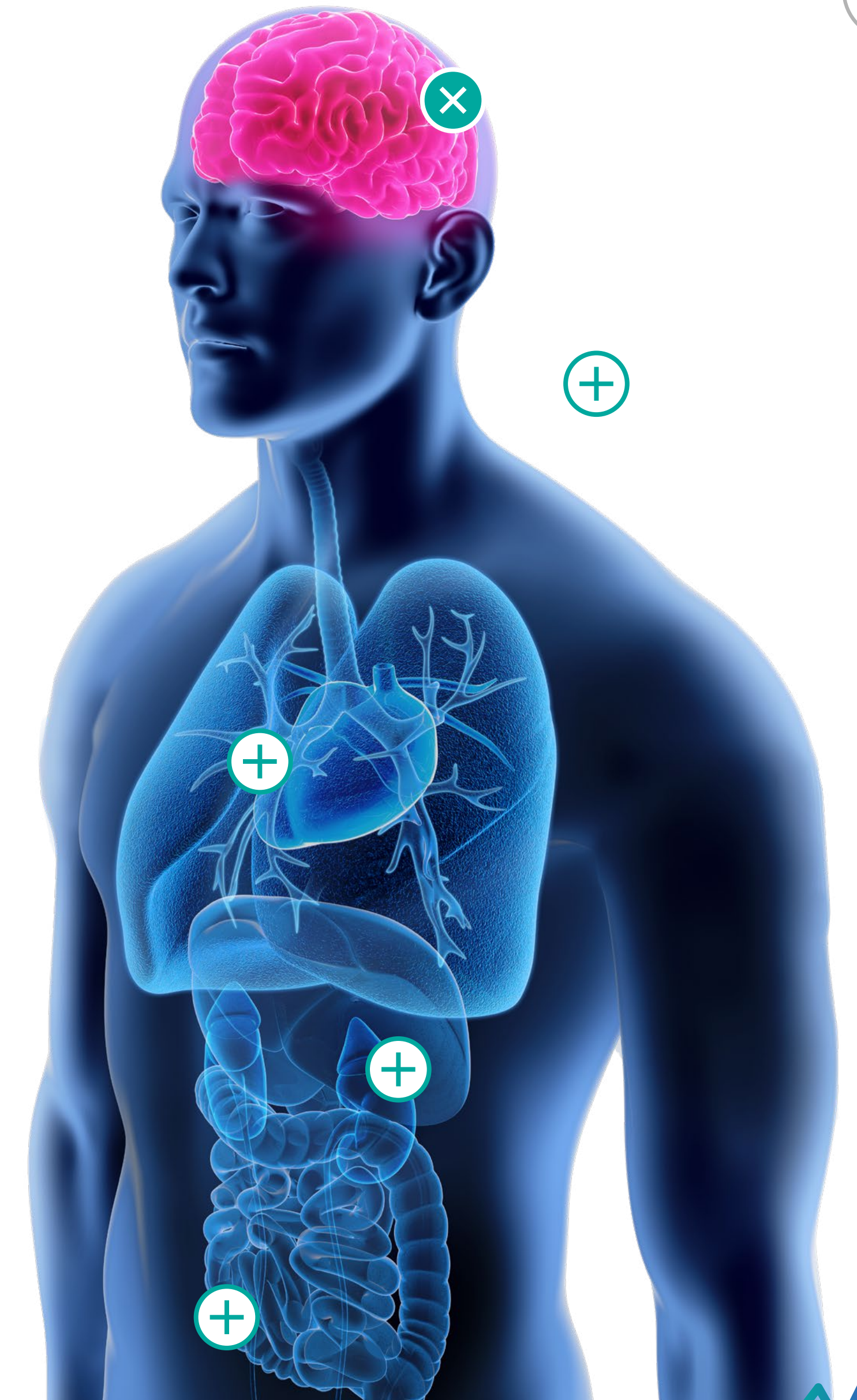
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Neurological Manifestations¹⁻³

- Neuropathic pain, acroparesthesia
- Pain crises
- Atypical pain (chronic or episodic)
- Heat/cold intolerance
- Hyperhidrosis/hypohidrosis
- Hearing loss/tinnitus
- Dizziness/vertigo
- White matter lesions
- Development of transient ischemic attack (TIA)
- Stroke (often recurrent)





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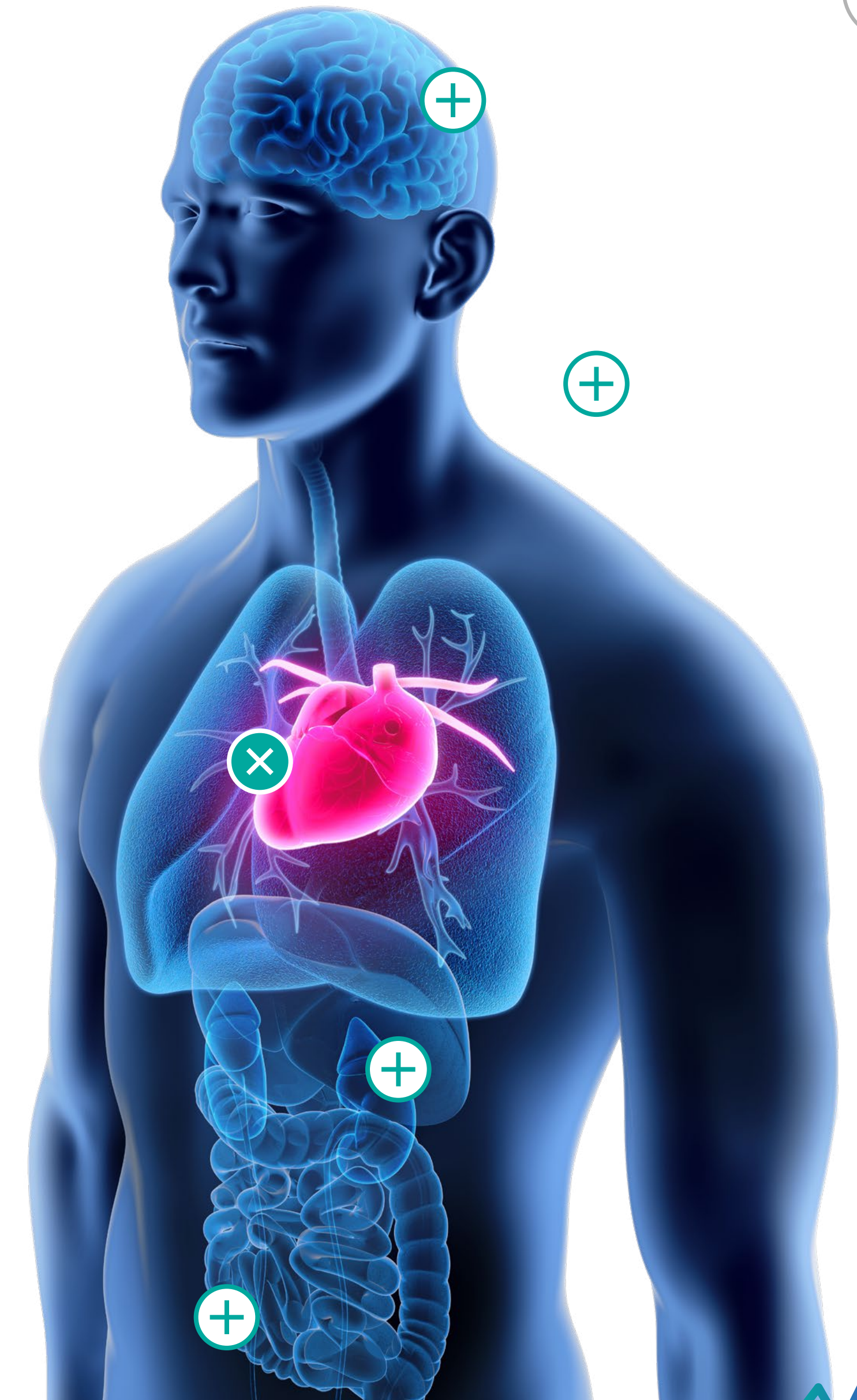
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Cardiac Manifestations^{1,3-5}

- Cardiomyopathy
- Impaired heart rate variability
- Arrhythmias
- Chest pain and other symptoms
- Ventricular tachycardia
- ECG abnormalities
 - Shortened PR interval or QRS prolongation
- Mild valvular insufficiency
- Reduced exercise tolerance
- Heart failure
- Cardiac fibrosis
- Sudden cardiac death



ECG, electrocardiogram.



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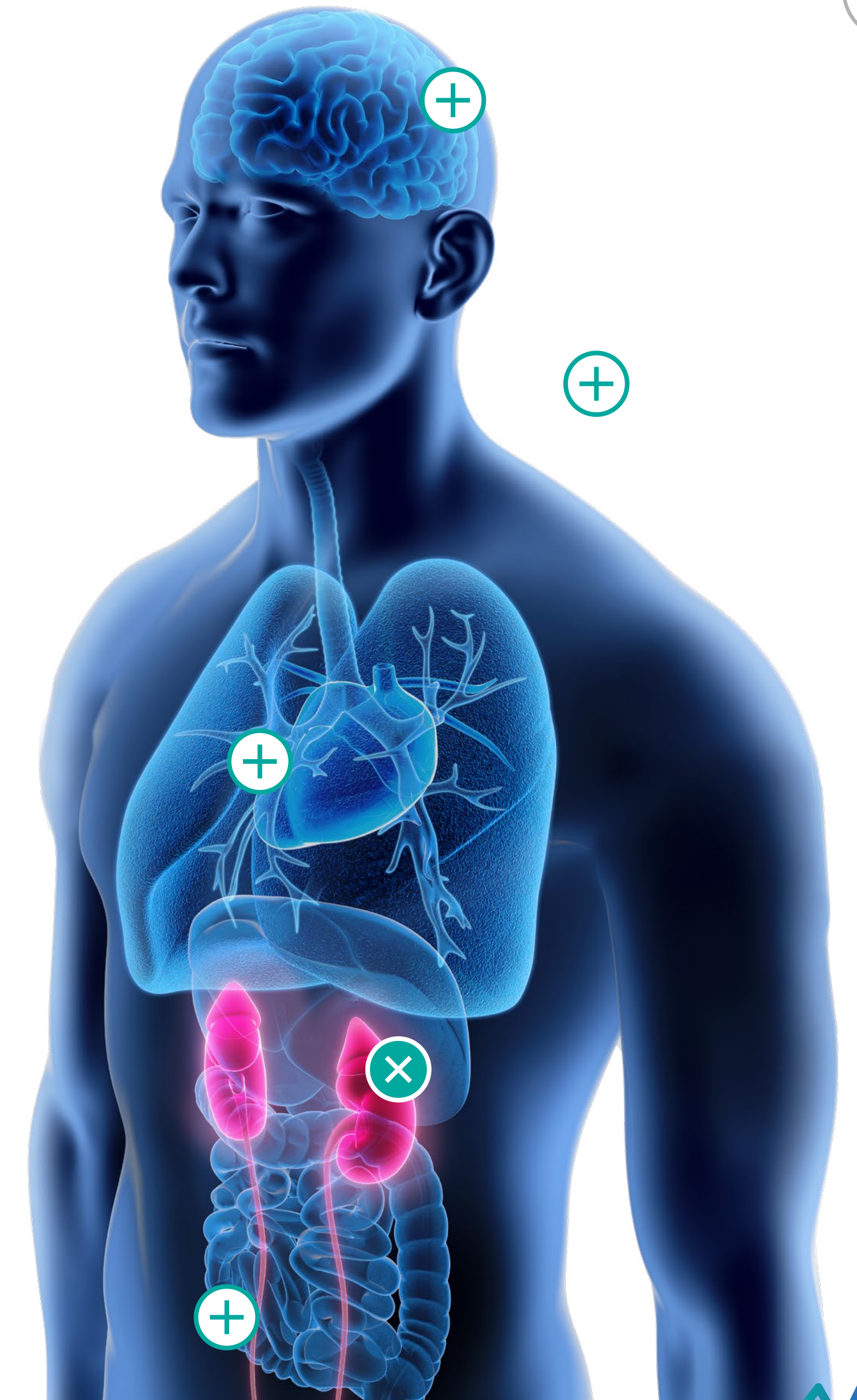
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Renal Manifestations¹⁻³

- Hyperfiltration
- Microalbuminuria, proteinuria
- 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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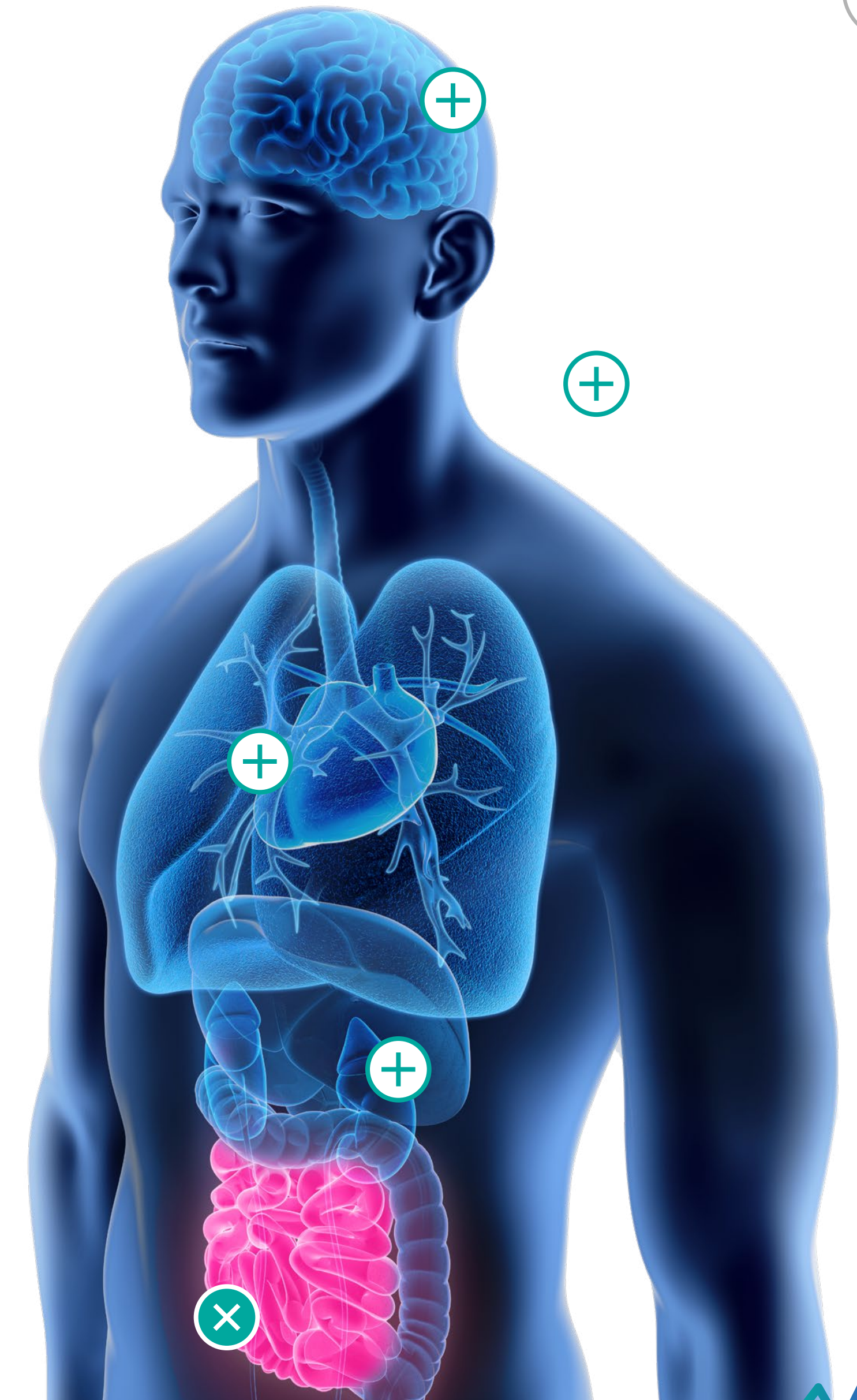
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Gastrointestinal Manifestations¹⁻³

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





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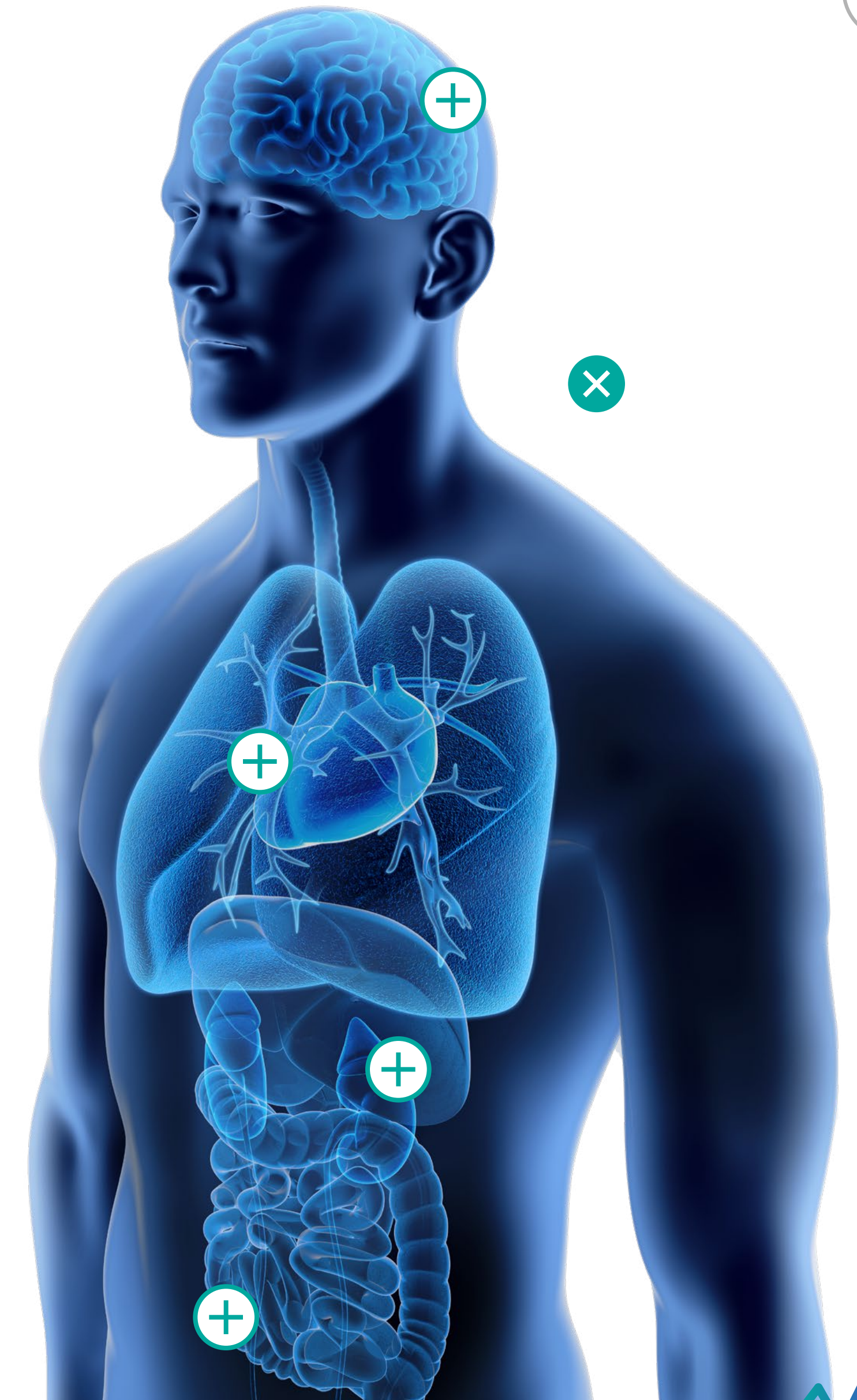
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Other Manifestations¹⁻³

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





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RENAL MONITORING IN ADULTS WITH FABRY DISEASE¹



Measured GFR (preferred)	or	Estimated GFR (using appropriate formulae)	
ANNUALLY Due to complexity		Risk of adverse outcomes ^a : Low ANNUALLY	Moderate EVERY 6 MONTHS
			High to very high EVERY 3 MONTHS
Albuminuria (preferred, more sensitive)	or	Proteinuria (24 h or spot urine for total protein/creatinine and albumin/creatinine ratios)	Proteinuria only increases as albuminuria progresses
Risk of adverse outcomes ^a : Low ANNUALLY	Moderate EVERY 6 MONTHS	High to very high EVERY 3 MONTHS	
Kidney biopsy			Podocyte foot process effacement may precede pathological albuminuria
AS CLINICALLY INDICATED			
25-OH vitamin D			Vitamin D levels in late autumn/early winter
AS CLINICALLY INDICATED			

+ RISK OF ADVERSE OUTCOMES STRATIFICATION

¹25-OH, 25-hydroxy; GFR, glomerular filtration rate; h, hour.



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RISK OF ADVERSE OUTCOMES STRATIFICATION



Risk of adverse outcomes by GFR and albuminuria categories: KDIGO 2012 ⁶			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		
GFR categories (mL/min/1.73m ²) Description and range	G1	Normal or high	≥90	Low risk ^a	Moderately increased risk	High risk	Very high risk
	G2	Mildly decreased	60–89	Low risk ^a	Moderately increased risk	High risk	Very high risk
	G3a	Mildly to moderately decreased	45–59	Moderately increased risk	High risk	Very high risk	Very high risk
	G3b	Moderately to severely decreased	30–44	High risk	Very high risk	Very high risk	Very high risk
	G4	Severely decreased	15–29	Very high risk	Very high risk	Very high risk	Very high risk
	G5	Kidney failure	<15	Very high risk	Very high risk	Very high risk	Very high risk
	Risk of adverse outcomes:			Low risk ^a	Moderately increased risk	High risk	Very high risk

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

CARDIOLOGICAL MONITORING IN ADULTS WITH FABRY DISEASE^{1,4,7,8}



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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

elevated in patients with cardiac manifestations, and may be used to assess the severity of cardiac involvement before overt hypertrophy

ANNUALLY
at least, for patients with cardiomyopathy or bradycardia

The level of NT-proBNP can be difficult to interpret in chronically dialyzed patients, as decreased GFR can cause accumulation

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)

NEUROLOGICAL MONITORING IN ADULTS WITH FABRY DISEASE



PERIPHERAL NERVOUS SYSTEM¹

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

CEREBROVASCULAR¹

Brain MRI

EVERY 3 YEARS
or when clinically needed^a

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

^aE.g., presence of neurological changes that could potentially relate to stroke

CT imaging

in case of acute stroke and only if MRI is contraindicated due to cardiac pacing

ANNUALLY



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PAIN MEASUREMENT
SCALES



BPI, Brief Pain Inventory; CT, computerized tomography; FD-PRO, Fabry Disease Patient-Reported Outcome; IENFD, intraepidermal nerve fibre density; MRI, magnetic resonance imaging; NPSI, Neuropathic Pain Symptom Inventory; SF-36, 36-Item Short Form Survey.

QUALITY OF LIFE MONITORING⁹



PATIENTS AGE 18 AND OVER

QoL assessment

(SF-36[®], BPI, FD-PRO)

EVERY 6–12 MONTHS^a
following initial baseline

^aand at time
of event or
therapy change



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ADULT QoL
MEASURING TOOLS



BPI, Brief Pain Inventory; FD-PRO, Fabry Disease Patient-Reported Outcome; QoL, quality of life; SF-36, 36-Item Short Form Survey.



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NEUROLOGICAL PAIN MEASUREMENT SCALES and ADULT QoL ASSESSMENT TOOLS

SF-36 ¹⁰	BPI ^{11,12}	FD-PRO ^{13,14}
<p>SF-36 is a set of generic, coherent, and easily administered QoL measures.</p> <p>Patients report on:</p> <ul style="list-style-type: none"> • vitality • physical functioning • bodily pain • general health perceptions • physical role functioning • emotional role functioning • social role functioning • mental health 	<p>Rapidly assesses the severity of pain and its impact on functioning.</p> <p>The BPI is available in two formats:</p> <ul style="list-style-type: none"> • short form • long form (contains items that expand the descriptors of pain and other additional descriptive items) <p>Sections of the scale include:</p> <ul style="list-style-type: none"> • worst pain in the last 24 hours • least pain in the last 24 hours • pain on average • pain right now <p>Patients also report on:</p> <ul style="list-style-type: none"> • general activity • mood • walking ability • normal work • relationships with other people • sleep • enjoyment of life 	<p>The FD-PRO instrument is a novel Fabry disease-specific instrument that assesses classic and non-classic symptoms.</p> <p>19 items measuring the severity of symptoms in the past 24 h:</p> <ul style="list-style-type: none"> • pain^a • burning feeling^a • numbness^a • tingling^a • 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

^aMeasured in both upper and lower extremities
BPI, Brief Pain Inventory; FD-PRO, Fabry Disease Patient-Reported Outcome; SF-36, 36-Item Short Form Survey; QoL, quality of life; WHO, World Health Organization.

BIOMARKERS MONITORING^{7,15}



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Lyso-GL-3

EVERY 6–12 MONTHS
after treatment initiation^a

^aIt is recommended that patients with classic FD should have their plasma lyso-GL-3 levels routinely monitored at baseline, then every 6–12 months after treatment initiation or switch to evaluate longitudinal changes.

There is no single consensus around the timing for lyso-GL-3 monitoring in all patients with non-classic variants.

- For example, in later-onset FD patients carrying the c.644A>G; p.(Asn215Ser)/p.N215S variant, lyso-GL-3 levels correlated with left ventricular mass, glomerular filtration rate, and overall disease severity¹⁶. Healthcare providers should determine the frequency of monitoring lyso-GL-3 in patients with non-classic variants.

MONITORING SCHEDULES SUMMARY FOR ADULTS WITH FABRY DISEASE^{1,7,9}



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 ^b		
	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		
	CARDIAC MRI 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		
	COLD/HEAT INTOLERANCE, VIBRATORY THRESHOLDS					X ^g		
	AUTONOMIC SYMPTOM EVALUATION					X		
	SKIN BIOPSY							X
BIOMARKERS	LYSO-GL-3	X			X ^h			X ⁱ
QUALITY OF LIFE	ADULT QoL ASSESSMENT (SF-36®, BPI, FD-PRO)	X			X			X

^aRisk of adverse outcomes; ^bdue to complexity; ^cat least; ^dcan be difficult to interpret in chronically dialyzed patients; ^ein male patients >21 years of age and female patients >30 years of age; ^fin case of acute stroke and only if MRI is contraindicated; ^gless frequently with age; ^hin patients on therapy; ⁱin patients not on therapy. 25-OH, 25-hydroxy; BPI, Brief Pain Inventory; CT, computed tomography; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; FD-PRO, Fabry Disease Patient-Reported Outcome; 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.

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