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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

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ABSTRACT

Objectives The PRoposing Early Disease Indicators for Clinical Tracking in Fabry Disease (PREDICT-FD) initiative aimed to reach consensus among a panel of global experts on early indicators of disease progression that may justify FD-specific treatment initiation.

Design and setting Anonymous feedback from panellists via online questionnaires was analysed using a modified Delphi consensus technique. Questionnaires and data were managed by an independent administrator directed by two non-voting cochairs. First, possible early indicators of renal, cardiac and central/peripheral nervous system (CNS/PNS) damage, and other disease and patient-reported indicators assessable in routine clinical practice were compiled by the cochairs and administrator from panellists' free-text responses. Second, the panel scored indicators for importance (5-point scale: 1=not important; 5=extremely important); indicators scoring ≥3 among >75% of panellists were then rated for agreement (5-point scale: 1=strongly disagree; 5=strongly agree). Indicators awarded an agreement score ≥4 by >67% of panellists achieved consensus. Finally, any panel-proposed refinements to consensus indicator definitions were adopted if >75% of panellists agreed.

Results A panel of 21 expert clinicians from 15 countries provided information from which 83 possible current indicators of damage (kidney, 15; cardiac, 15; CNS/PNS, 13; other, 16; patient reported, 24) were compiled. Of 45 indicators meeting the importance criteria, consensus was reached for 29 and consolidated as 27 indicators (kidney, 6; cardiac, 10; CNS/PNS, 2; other, 6; patient reported, 3) including: (kidney) elevated albumin:creatinine ratio, histological damage, microalbuminuria; (cardiac) markers of early systolic/diastolic dysfunction, elevated serum cardiac troponin; (CNS/PNS) neuropathic pain, gastrointestinal symptoms suggestive of gastrointestinal neuropathy; (other) pain in extremities/neuropathy, angiokeratoma; (patient-reported) febrile crises, progression of symptoms/signs. Panellists revised and approved proposed chronologies of when the consensus indicators manifest. The panel response rate was >95% at all stages.

Conclusions PREDICT-FD captured global opinion regarding current clinical indicators that could prompt FD-specific treatment initiation earlier than is currently practised.

Strengths and limitations of this study

- ► A globally representative panel of clinician-experts in Fabry disease (FD) was recruited.
- ► Group interaction bias was minimised by the anonymous consensus process.
- ► The response rate was >95% at each round of the consensus process.
- ► Scoring of FD indicators reflects the real-world views of clinicians.

INTRODUCTION

Fabry disease (FD) affects individuals deficient in lysosomal alpha-galactosidase A. The disease is X-linked, with an estimated prevalence of up to 1 in 40 000, and its multisystem pathology is caused by intracellular accumulation of globotriaosylceramide (Gb3).[1] FD presents with highly variable symptomatology ranging from patients who are asymptomatic to those severely affected with multiorgan

damage.[1] The rate at which FD progresses also varies considerably.[1] This poses a major challenge for physicians in determining prognosis, and consequently a diagnosis of FD does not automatically merit initiation of FD-specific treatment with enzyme replacement therapy (ERT) or chaperone therapy. Instead, physicians must monitor patients regularly to identify signs that may warrant treatment initiation. The decision whether to treat may be complicated by the high costs of FD-specific treatments[2] and by the considerable patient burden associated with hospital treatment if home therapy is unavailable or inappropriate.[3 4]

In 2015, the European Fabry Working Group (EFWG) published consensus criteria for initiation and withdrawal of ERT in patients with FD.[1] The general recommendation applied to classically affected males and females and to non-classically affected males, and was to initiate treatment when clinical signs of kidney, heart or central nervous system (CNS) involvement, pain or gastrointestinal symptoms first appeared.[1] Treatment of classically affected males aged ≤16 years could also be considered in the absence of signs or symptoms of organ involvement, as could treatment of non-classically affected females with early clinical signs attributed to FD.[1] Initiation or continuation of FD-specific treatment was to be considered on an individual basis, and certain recommendations were made to withhold treatment (eg, in patients with end-stage renal disease with no option for renal transplant and advanced heart failure, or in patients with severe cognitive decline).[1]

The EFWG guidelines provide a valuable framework for clinical decision making in FD, but important recent advances in the field suggest that revising these recommendations may now be appropriate. An increasing body of evidence supports the early initiation of ERT in patients with FD,[5–8] and several studies show that the best outcomes of ERT are in patients with the least organ damage at treatment initiation.[5 6 9–12] A study comparing response to FD-specific treatment after 1 year among treatment-naïve men starting ERT before the age of 25 years with that among men who started treatment later, found a significantly greater reduction in plasma levels of globotriaosylsphingosine (lyso-Gb3; a marker of disease severity in FD) in the group treated early.[13]

As well as new clinical outcome data, new imaging techniques such as cardiac MRI (cMRI)[14] and ^{123}I-metaiodobenzylguanidine single-photon emission CT[15] will likely offer the means to detect very early FD-related organ damage not identified by traditional assessment methods. Such approaches facilitate FD-specific treatment initiation before more advanced signs appear and irreversible organ damage occurs.

We conducted the international PRoposing Early Disease Indicators for Clinical Tracking in Fabry Disease (PREDICT-FD) modified Delphi initiative to establish expert consensus on early clinical indicators that may prompt when FD-specific treatment should be initiated in treatment-naïve patients. The Delphi process is a widely used, validated technique for developing expert consensus when evidence is limited and has generated simple, robust clinical guidance, including for the diagnosis and management of patients with FD.[1 16–18] The stepwise use of questionnaires and the maintenance of anonymity of the experts consulted minimises data distortion that can arise from the pressure on individuals within a group to conform to a dominant view.[19] As well as examining the most relevant early clinical indicators of FD progression, we also aimed to gain agreement on when to initiate and to stop FD-specific treatment in different patient groups in different scenarios. The intention is that these findings will raise awareness among specialist and general physicians of the early clinical cues that should prompt consideration of disease-specific treatment initiation in patients with FD, so that disease progression and irreversible organ damage in these patients is minimised or avoided.

METHODS

The modified Delphi process used in PREDICT-FD is described below and summarised in figure 1.

Selection of chairs and expert panel

Two leading global experts in FD were invited to be non-voting cochairs of the PREDICT-FD initiative. The cochairs selected an international group of FD experts to form the voting panel. Panel members were nominated based on track record and demonstrated expertise in the field, according to factors such as research activities, participation in national or regional FD management initiatives and authorship of relevant peer-reviewed publications. Nominated panellists were recruited on behalf of the initiative cochairs by an independent third-party administrator (Oxford PharmaGenesis, Oxford, UK).

Modified Delphi process

Under the direction of the PREDICT-FD cochairs, the third-party administrator drafted a study protocol, which was reviewed and approved by both cochairs and by a patient representative before commencement of the initiative. A non-exhaustive literature search was also conducted by the administrator for the cochairs and was used to inform aspects of the initiative (see online supplementary appendix). All stages of the initiative, including content development, data collation, data processing and reporting, were overseen by the cochairs and conducted by the independent third-party administrator. Expert panel responses were gathered anonymously via an online survey platform (SurveyMonkey, SurveyMonkey Europe, Dublin, Ireland). For tracking purposes, the administrator knew the identities of responding panellists, but no identifying information was shared with the cochairs or other panel members. Panellists remained anonymous to each other throughout the Delphi stages. Circulation of the questionnaires, and collection and processing of the panel's responses was conducted between January and

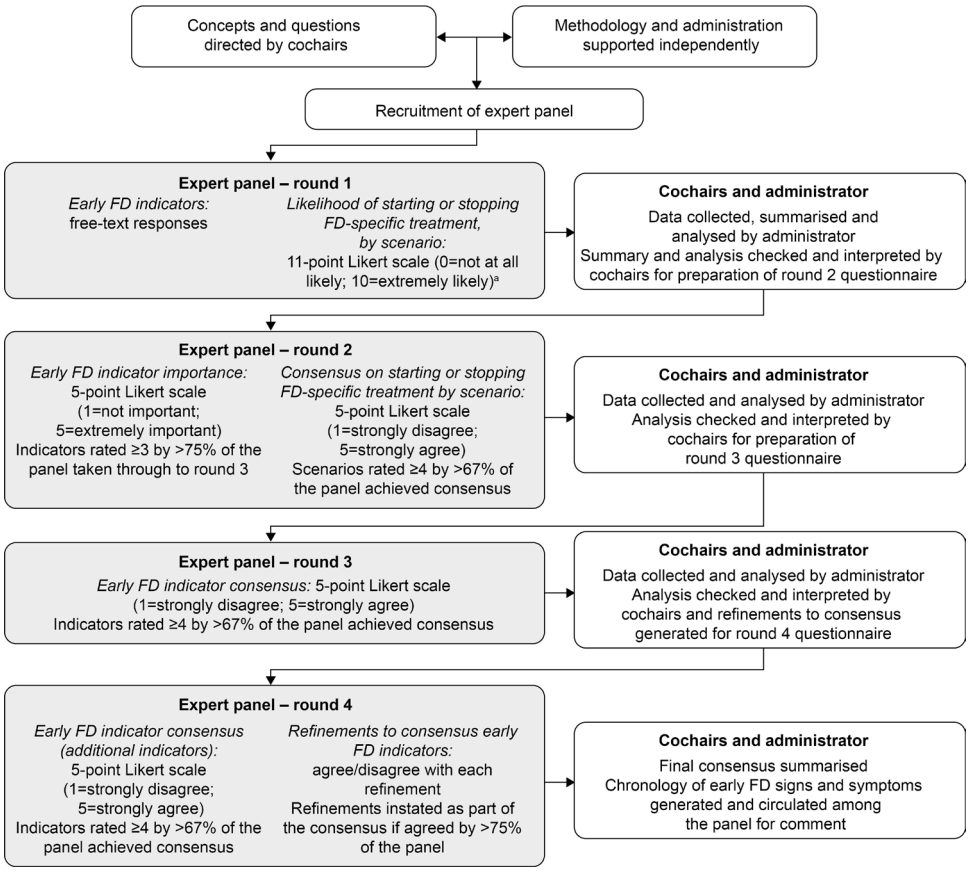

Figure 1 PREDICT-FD modified Delphi consensus methodology. [a]A threshold median likelihood score of 7.5 was set a priori. For questions about the likelihood of initiating treatment, agreement for initiation was sought in round 2 if a scenario was awarded a median score of ≥7.5 and agreement not to initiate treatment sought if the score was <7.5. Similarly, for questions about cessation of treatment, agreement to stop treatment was sought in round 2 if a scenario was awarded a median score ≥7.5 and agreement not to stop treatment sought if the score was <7.5. PREDICT-FD, PRoposing Early Disease Indicators for Clinical Tracking in Fabry Disease.

September 2018. Except for comment fields included in the questionnaires, all questions were compulsory. No controlled feedback was provided to panellists between rounds.

Further details on the design of the modified Delphi initiative, including all questionnaires, are provided in the online supplementary appendix. Achieving consensus with three rounds of questionnaires was planned. In round 1, information was solicited regarding panellists' FD clinical practices, number of years spent treating patients with FD and number of patients with FD typically managed in their practices. Panellists provided free-text responses to open questions soliciting suggestions for early indicators of renal, cardiac and CNS damage that can be assessed in current routine clinical practice, or that are not assessed routinely at present, but might be in the future. Additional round 1 questions explored symptoms experienced by patients with FD that could contribute to initiating FD-specific treatment. Attitudes towards FD-specific treatment initiation or cessation were also investigated by asking panellists to rate on an 11-point scale (0=not at all likely; 10=extremely likely) the likelihood that they would start or stop FD-specific treatment in different patient groups and clinical scenarios proposed by the cochairs.

Among questions in round 1 that solicited free-text responses, the administrator identified similar themes among the responses and created provisional groupings for review by the cochairs. The cochairs checked and revised the groupings to exclude indicators that are not widely used, are known to be of greater relevance in late-stage than in early-stage disease or are poorly indicative of FD status and progression. The administrator generated lists of indicators and compiled responses from the panel regarding attitudes to FD-specific treatment initiation or cessation in different patient groups, determining the panel's median likelihood scores for starting or stopping FD-specific treatment.

In round 2, panellists rated the importance of each indicator on a 5-point Likert scale (1=not important; 2=slightly important; 3=important; 4=very important; 5=extremely important). Regarding scenarios for initiation or cessation of FD-specific treatment, if a scenario was awarded a median likelihood score of ≥7.5 in round 1, agreement was sought whether to start or

to stop FD-specific treatment. In contrast, if the score was <7.5, agreement was sought whether to start or to stop treatment. Panellists rated their level of agreement using a 5-point Likert scale (1=strongly disagree; 2=disagree; 3=neither agree nor disagree; 4=agree; 5=strongly agree). Importance and agreement ratings were compiled by the administrator. It was specified a priori that indicators awarded an importance score of ≥3 by >75% of the panel would be tested for consensus in round 3, and that agreement on treatment recommendations would be reached if an agreement score of ≥4 was awarded by >67% of the panel. All ratings compiled by the administrator were reviewed by the cochairs as per the predefined scores and consistent with previous Delphi initiatives[20 21]; agreement on treatment recommendations concluded in round 2. In round 3, panellists rated their level of agreement with each indicator that had met the designated importance criteria in round 2, using the 5-point Likert scale already described. Consensus was established using the same a priori criteria already described. Agreement scores were compiled by the administrator and reviewed by the cochairs.

Round 4 was included post hoc to capture the panel's level of agreement with certain indicators that met the importance criteria in round 2 but which were inadvertently omitted from round 3. Panel members were also asked whether they agreed or disagreed with refinements proposed for several indicators that achieved consensus in round 3 and these were adopted if >75% of the panel agreed; refinements were informed by comments made by panel members during the first three rounds. Panellists' responses were compiled by the administrator, reviewed by the cochairs, and any new consensus terms combined with those identified in round 3.

Chronology of signs and symptoms

After generating the refined list of consensus indicators, timelines were developed under the direction of the cochairs showing when each indicator typically manifests during the disease course in relation to established indicators currently recommended as triggers for treatment initiation. Indicators manifesting before and after established indicators were termed 'early' and 'late', respectively. Indicators featuring in the chronologies were grouped as renal, cardiac or patient reported/other. The cochairs agreed a draft chronology for each group, and these proposals were submitted to each panel member for comment and amendment. Panel responses were collated, and the chronologies revised by the administrator then approved by the cochairs. The chronologies were developed between December 2018 and January 2019; Delphi consensus techniques were not applied to this part of the initiative.

Statistical analyses

The study was exploratory; no hypotheses were tested and only descriptive statistical analyses were performed.

Patient and public involvement statement

A leadership representative from the Fabry International Network (FIN), JJ, was invited to participate in the project in a non-voting role. The representative reviewed and approved the initial protocol and round 1 questionnaire, and facilitated the involvement of three patients with FD (one from the USA and two from outside the USA) in reviewing these materials. This ensured that any appropriate feedback from the patients could be incorporated into materials before distributing the round 1 questionnaire. Additional roles of the FIN representative included capturing these patients' views on the outcomes of the initiative, and reviewing and approving the final study report.

RESULTS

PREDICT-FD expert panel demographics and clinical experience

In total, 23 experts were invited to join the expert panel; one declined to participate, and one did not complete round 1 and was excluded from the analysis. Thus, the panel comprised 21 physicians representing 15 countries (Argentina, Australia, Canada, Czech Republic, France, Italy, Norway, Portugal, Slovenia, Spain, Switzerland, Taiwan, Turkey, UK, USA). All panellists had managed male and female patients with FD; most panellists had experience of managing both patients with classical and those with non-classical FD (table 1).

The majority of panellists (18 (85.7%)) practised in public teaching hospitals. Panellists had treated patients with FD for a mean of 15.5 years and four panellists (19.0%) had >20 years of clinical experience with FD. Specialties most commonly represented were nephrology (8 (38.1%)), metabolic diseases (5 (23.8%), of whom 3 (14.3%) also specialised in genetics) and cardiology (4 (19.0%)); haematology, immunology, neurology, paediatrics, internal medicine, biochemistry and angiology were also represented. Overall, the panel managed an estimated 2079 patients, 40.7% of whom were male; 64.5% of patients had classical FD (table 1). A response rate of 95.5% (21/22) was achieved during round 1 of the modified Delphi process; thereafter all 21 panellists responded.

Consensus on current and potential future indicators of disease progression in FD

Indicators achieving consensus in round 3 of the modified Delphi process were further refined in round 4 (see section 'Refinements to consensus indicators' for further information); the final list of consensus indicators is summarised in table 2. Results by organ system and category are described below.

Indicators of renal damage

Following consolidation by the cochairs, 15 indicators of early renal damage in current use and 19 potential future indicators were collated from round 1. Of these, seven

Table 1 PREDICT-FD modified Delphi expert panel clinical experience

Clinical experience (n=21)	
Main clinical practice*	
Private teaching hospital	1 (4.8)
Private hospital	0
Public teaching hospital	18 (87.5)
Public non-teaching hospital	0
Research centre	6 (28.6)
Duration of FD clinical experience, years	
Mean (SD)	15.5 (7.5)
0–10	6 (28.6)
11–20	11 (52.4)
21–30	4 (19.0)
Number of patients with FD managed	
Mean (SD)	99 (81)
1–50	4 (19.0)
51–100	12 (57.1)
101–200	3 (14.3)
>200	2 (9.5)
Patient summary†	
Male	847 (40.7)
Female	1232 (59.3)
Classical FD	1341 (64.5)
Non-classical FD	738 (35.5)

Data are shown as number (%) of respondents unless otherwise stated.
*Respondents could select more than one option.
†Patient n (%) values are estimates, derived from total patient numbers and estimated sex and FD-type breakdown reported by each panellist.
FD, Fabry disease; PREDICT-FD, PRoposing Early Disease Indicators for Clinical Tracking in Fabry Disease.

current and two future indicators met the predefined importance criteria in round 2. Consensus was reached for the following current indicators (see online supplementary table S1): elevated urine albumin:creatinine ratio; histological damage (lesions associated with Gb3 deposition); microalbuminuria; abnormal glomerular filtration rate (GFR); decline in iohexol GFR and podocyte inclusions in renal biopsies. Consensus was not achieved for any future indicators.

Indicators of cardiac damage

After consolidation at the end of round 1, 15 current and 14 future indicators of early cardiac damage were identified, and 12 current and 3 future indicators met the importance criteria in round 2. Consensus was reached for 10 current indicators, 3 of which also reached consensus as future indicators (see online supplementary table S2). The indicators deemed important, both currently and in the future, were: reduced myocardial T1 relaxation time on cMRI; elevated serum cardiac troponin; and elevated serum N-terminal probrain natriuretic peptide (NT-pro-BNP). The other important current indicators were: markers of early systolic/diastolic dysfunction; early indicators of left ventricular hypertrophy (LVH); histological damage (lesions associated with Gb3 deposition) in endomyocardial biopsies; late gadolinium enhancement on cMRI; abnormal ECG; abnormal echocardiogram; and, specifically, abnormal wall motion revealed by echocardiogram.

Indicators of peripheral nervous system damage

In round 1 following consolidation, 13 current and 13 future indicators were identified, with 5 and 2 indicators, respectively, subsequently meeting the importance criteria in round 2 (see online supplementary table S3). Consensus was reached for neuropathic pain and gastrointestinal symptoms suggestive of gastrointestinal neuropathy as current indicators; no consensus was achieved for future indicators.

Other indicators

When asked for further information about early indicators of FD, such as non-organ-specific symptoms, consensus was reached for five indicators (see online supplementary table S4): pain in extremities/neuropathy; angiokeratoma; organ biopsy (including skin biopsy for small-fibre neuropathy); gastrointestinal symptoms (including bloating, pain, diarrhoea/frequent diarrhoea or constipation); and sweating abnormalities or heat/exercise intolerance.

Patient-reported indicators

Panellists were asked to list what they considered to be the earliest signs and symptoms relevant to FD progression and FD-specific treatment initiation, and also to list patient-reported signs and symptoms relevant to FD-specific treatment initiation. When the responses were combined, consensus was achieved for the following six patient-reported indicators: stroke/transient ischaemic attack; febrile crises; patient-reported progression of symptoms/signs of FD (such as acral burning paraesthesias, heat intolerance, impaired sweating, fatigue, depression, pain, gastrointestinal symptoms, shortness of breath, palpitations, peripheral oedemas); diarrhoea/frequent diarrhoea; angiokeratoma; and neuro-otological abnormalities (see online supplementary table S5). Based on consensus reached in round 4, stroke/transient ischaemic attack and diarrhoea/frequent diarrhoea were reclassified among 'other indicators', and neuro-otological abnormalities was discarded (see 'Refinements to consensus indicators').

Indicators under research

Of the eight indicators that were the focus of experimental studies or ongoing research, five were deemed important, and two achieved consensus (see online supplementary table S6): reduced quality of life and high gastrointestinal symptom scores.

Table 2 Indicators for which consensus was achieved in PREDICT-FD

Current early indicators of damage				
Kidney	**Cardiac**	**PNS**	**Other**	**Patient reported**
Elevated urine albumin:creatinine ratio*	Markers of early systolic/diastolic dysfunction†‡	Neuropathic pain†§	Pain in extremities/neuropathy¶	Febrile crises
Histological damage (kidney biopsy)*	Elevated serum cardiac troponin†	Painful gastrointestinal symptoms suggestive of gastrointestinal neuropathy related to FD†§	Stroke/transient ischaemic attack**	Patient-reported progression of symptoms/signs††
Microalbuminuria*†	Early indicators of left ventricular hypertrophy		Angiokeratoma	Angiokeratoma
Abnormal glomerular filtration rate	Early indicators of histological damage (heart biopsy)‡‡§§		Organ biopsy¶¶	(Neuro-otological abnormalities)***
Decline in iohexol glomerular filtration rate	Late gadolinium enhancement on cardiac MRI		Non-pain gastrointestinal symptoms (including diarrhoea/frequent diarrhoea) related to FD	
Podocyte inclusions	Elevated serum N-terminal probrain natriuretic peptide†		Sweating abnormalities or heat/exercise intolerance	
	Reduced myocardial T1 relaxation time on cardiac MRI			
	Abnormal ECG‡,‡‡			
	Abnormal echocardiogram†‡			
	Abnormal wall motion on echocardiography			
Early cardiac indicators of FD that may be used in future			**Early indicators of FD subject to ongoing research**	
Reduced myocardial T1 relaxation time on cardiac MRI			Reduced quality of life	
Elevated serum cardiac troponin†			High gastrointestinal symptom scores	
Elevated serum N-terminal probrain natriuretic peptide†				

*It was noted in round 4 that the prognostic significance of this indicator is different in male and female patients.
†It was noted in round 4 that a causal relationship between this indicator and FD is required to justify treatment initiation.
‡Including decreased myocardial strain and strain rate, tissue Doppler abnormalities,enlarged left atrium or pulmonary venous flow abnormalities on echocardiogram.
§Recategorised as PNS in round four because no indicators of CNS damage achieved consensus.
¶Including acroparaesthesias.
**Previously under 'patient-reported indicators of FD', recategorised in round 4 under 'other early indicators of FD' because such indicators would need to be confirmed clinically.
††Renamed 'patient-reported progression of symptoms/signs' from 'symptom/sign progression' in round 4.
‡‡Including a shortened PR interval, non-sustained ventricular tachycardia and symptomatic bradycardia.
§§Cardiac histological changes have been reported in FD, but cardiac biopsy is too invasive to be recommended.
¶¶Including skin biopsy for small-fibre neuropathy, and kidney and heart biopsy nominated in other categories.
***This indicator is included because it achieved consensus but was subsequently excluded in round 4. It refers to a cluster of indicators (vertigo, hearing loss and tinnitus) that did not achieve consensus individually.
†††Originally grouped under 'patient-reported indicators of FD'; combined with 'non-pain gastrointestinal symptoms' under 'other early indicators of FD' in round 4.
‡‡‡Including bloating, pain, diarrhoea/frequent diarrhoea or constipation, that are causally related to FD.
CNS, central nervous system; PNS, peripheral nervous system; PREDICT-FD, PRoposing Early Disease Indicators for Clinical Tracking in Fabry Disease.

Refinements to consensus indicators

During the first three rounds, panellists offered additional information about the indicators, typically to define broad indicators more precisely. Comments on the current indicators that achieved consensus were reviewed by the cochairs, and proposed clarification on 23 of these was circulated to the panel in round 4, either to endorse new information or to provide an opportunity to include additional information. The panel reached agreement on refinements to 19 of these indicators (see online supplementary table S7; 'neuro-otological abnormalities' was excluded from the consensus because it encompassed the other indicators 'vertigo', 'hearing loss' and 'tinnitus' that had not achieved consensus (see online supplementary tables S4,S5). The current and potential future indicators, as well as those under research, that achieved final consensus are summarised in table 2; explanatory table footnotes describe the refinements made in round 4 based on feedback from the panel.

Chronology of manifestation of indicators during the disease course

Indicators that achieved consensus were allocated to three groups: renal; cardiac; and patient reported/other, and a chronology was developed for each group (figure 2A–C).

Initiation and cessation of FD-specific treatment in patients with FD

In round 1, the panel rated the likelihood of initiating FD-specific treatment in different scenarios (patients asymptomatic for organ damage, symptomatic patients not meeting guideline criteria, patients meeting guideline criteria) in five different patient groups (defined by sex, age group, and classical or non-classical FD) (see online supplementary figure S1A). The panel's level of agreement in round 2 with proposals that treatment should or should not be started in different patient groups in different scenarios is summarised in table 3. Agreement was reached in round 2 that FD-specific treatment should be initiated in all males aged ≥16 years with classical disease, and in males of any age with classical disease and with early indicators of organ damage, irrespective of whether these symptoms meet the EFWG recommendations for treatment initiation.[1] Agreement that FD-specific treatment should be initiated was also reached for all female patients and for male patients with non-classical disease with indicators meeting the EFWG guideline criteria.[1] Agreement not to start treatment was reached only for asymptomatic females with non-classical FD (table 3). However, when asked if all patients who meet the EFWG guideline criteria[1] should receive FD-specific treatment, the panel did not reach agreement (mean (median) score, 3.4 (4); score ≥4, 11 (52.4%)), including for female patients with classical FD and male patients with non-classical FD.

The panel's responses regarding starting or stopping FD-specific treatment in scenarios relating to organ damage are summarised in table 4 and online supplementary figure S1B. Agreement was reached that treatment should be initiated in patients with evidence of damage to a single organ system, irrespective of whether that organ system was being treated by a non-Fabry-specific intervention (eg, renal replacement therapy, kidney transplant or cardiac pacemaker, etc), and that FD-specific treatment of such patients should not be stopped, were such a therapy to become necessary. Agreement was also reached that FD-specific treatment should be initiated and should not be stopped in patients receiving separate therapies for damage to multiple organ systems (such as a combination of renal replacement therapy, kidney transplant and/or cardiac pacemaker, etc). The group in which the panel was least likely to initiate or to stop FD-specific treatment was that comprising patients who were receiving no separate therapy for multiple organ system damage. However, no agreement was reached for either scenario. The panel also did not reach agreement on the question of whether all patients with FD should remain on disease-specific treatment, irrespective of organ damage or any related treatment (mean (median) agreement score, 2.2 (2); agreement score ≥4, 6 (28.6%)).

DISCUSSION

The PREDICT-FD panel was convened to identify early clinical indicators that could prompt disease-specific treatment initiation in patients with FD, thereby minimising disease progression. The panel reached consensus on 27 early renal, cardiac, peripheral nervous system (PNS), patient-reported and other indicators of disease progression that can currently be assessed in FD clinics (table 2). Other indicators that were considered important but where no consensus was reached or that were categorised as being of no importance, are summarised in the supplementary tables. Three indicators of cardiac damage were also identified that might be adopted more widely for routine use in future and the utility of two other consensus indicators are the focus of ongoing research. In the opinion of the panellists, treatment should be initiated in any male patients with classical FD aged at least 16 years, and in younger males with classical disease if early signs of organ damage appear. Female patients and male patients with non-classical disease should be treated based on existing guideline recommendations.

Detection of renal histological damage requires a biopsy, which is highly invasive, so the presence of other, less invasive early indicators could be sufficient grounds to start FD-specific treatment without biopsy data. The panel reached a consensus that early indicators of renal damage included microalbuminuria, glomerular hyperfiltration and podocyte inclusions in the presence of other renal lesions, such as signs of glomerulosclerosis or vasculopathy, which may occur even in patients without microalbuminuria (figure 2).[22 23]

Regarding cardiac indicators, consensus was reached on several early indicators of cardiac damage, including ECG

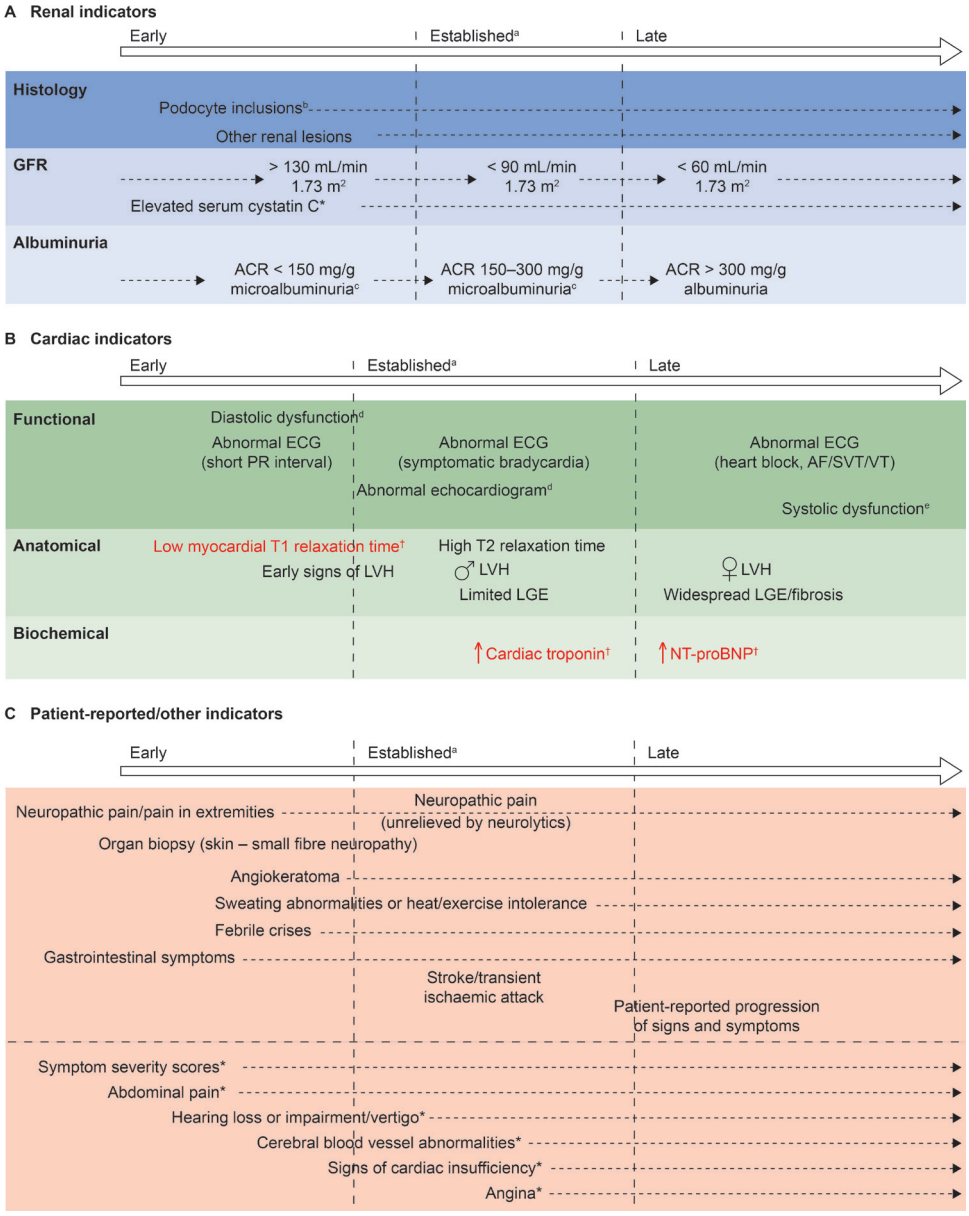

Figure 2 Chronology of consensus indicators. (A) *Indicator tested for, but not achieving, consensus in round 3. (B) †Indicators in red text achieved consensus both as currently used, and suitable for future adoption, because they are not available in all centres. Two further indicators (abnormal PET/MRI and increased serum lyso Gb3) that were included in round 2 of the initiative but were not taken forward to round 3 are not shown here based on guidance from the cochairs. (C) *Indicator tested for, but not achieving, consensus in round 3. Other indicators tested for, but not achieving, consensus, and which are not included here owing to their lack of specificity were: biomarkers; patient-reported outcomes; absenteeism owing to ill health; and palpitations. [a]Indicators that currently would be likely to trigger FD-specific treatment initiation. [b]In isolation, probably insufficient justification for FD-specific treatment initiation. [c]Microalbuminuria could be a trigger for further investigation, such as confirmatory biopsy, and subsequent initiation of disease-specific treatment. [d]Including decreased myocardial strain and strain rate, tissue Doppler abnormalities, enlarged left atrium, abnormal wall motion or pulmonary vein abnormalities. [e]Including shortened PR interval, non-SVT and symptomatic bradycardia. ACR, albumin:creatinine ratio; AF, atrial fibrillation; FD, Fabry disease; GFR, glomerular filtration rate; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; lyso Gb3, globotriaosylsphingosine; NT-pro-BNP, N-terminal probrain natriuretic peptide; PET, positron emission tomography; SVT, sustained VT; VT, ventricular tachycardia.

abnormalities (eg, shortened PR interval) elevated cardiac troponin, elevated NT-pro-BNP and low myocardial T1 relaxation times on cMRI, although the utility of the last may be limited by the low availability of T1 mapping by cMRI in specialist FD centres. Grade 1 diastolic dysfunction in early FD[24] may be a useful indicator of cardiac changes, but perhaps only in young patients. Because LVH is an established sign of cardiac involvement in FD, any tests revealing early stages of hypertrophy could be valuable in informing treatment decisions and could help to slow cardiac disease progression on treatment.[25] Elevated high-sensitivity cardiac troponin and NT-pro-BNP levels are early signs of cardiac damage that might be detectable before signs that can be seen with cMRI. A concern

Table 3 Treatment initiation in different patient groups and scenarios

Scenario	Males aged <16 years with classical FD		Males aged ≥16 years with classical FD		Females with classical FD		Males with non-classical FD		Females with non-classical FD	
Asymptomatic for organ involvement										
Likelihood of starting treatment										
Mean (median) score	5.4 (5)		7.1 (8)		2.8 (2)		3.3 (2)		1.6 (1)	
Agreement	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment
Mean (median) score	2.5 (2)			4.2 (4)	3.2 (3)		3.2 (4)		3.8 (4)	
Score ≥4, n (%)	5 (23.8)			18 (85.7)	10 (47.6)		11 (52.4)		15 (71.4)	
Early indicators of organ involvement										
Likelihood of starting treatment										
Mean (median) score	7.6 (8)		8.6 (10)		6.6 (7)		6.6 (7)		5.3 (5)	
Agreement	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment
Mean (median) score		4.4 (5)		4.8 (5)	1.7 (2)		1.7 (2)		2.1 (2)	
Score ≥4, n (%)		19 (90.5)		21 (100)	0 (0)		1 (4.8)		2 (9.5)	
Guideline indicators for FD-specific treatment initiation										
Likelihood of starting treatment										
Mean (median) score	9.4 (10)		9.7 (10)		9.4 (10)		9.1 (10)		8.5 (10)	
Agreement	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment
Mean (median) score		4.5 (5)		4.6 (5)		4.6 (5)		4.3 (4)		4.1 (4)
Score ≥4, n (%)		20 (95.2)		20 (95.2)		20 (95.2)		19 (90.5)		16 (76.2)

Where the median likelihood score awarded for starting treatment was ≥7.5 in round 1, panellists were asked in round two to rate their level of agreement with starting treatment. Where the median likelihood score awarded for starting treatment was <7.5 in round 1, panellists were asked in round two to rate their level of agreement with not starting treatment.
Green shading: consensus that FD-specific treatment should be initiated. Orange shading: consensus that FD-specific treatment should not be initiated. No shading: no consensus was achieved. n=21.
FD, Fabry disease.

Table 4 Treatment initiation or cessation in patients with organ damage*

	Damage to one organ system, receiving therapy for that organ		Damage to one organ system, not receiving therapy for that organ		Multiorgan damage, receiving therapy for those organs		Multiorgan damage, not receiving therapy for those organs	
Starting treatment								
Likelihood of starting treatment								
Mean (median) score	8.1 (9)		7.0 (8)		7.1 (8)		6.3 (7)	
Agreement	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment	Do not start treatment	Start treatment
Mean (median) score		4.3 (4)		3.8 (4)		4.1 (4)	2.3 (2)	
Score ≥4, n (%)		19 (90.5)		16 (76.2)		18 (85.7)	3 (14.3)	
Stopping treatment								
Likelihood of stopping treatment								
Mean (median) score	2.8 (2)		3.9 (5)		3.9 (3)		4.8 (4)	
Agreement	Do not stop treatment	Stop treatment	Do not stop treatment	Stop treatment	Do not stop treatment	Stop treatment	Do not stop treatment	Stop treatment
Mean (median) score	4.3 (4)		4.0 (4)		4.0 (4)		3.7 (4)	
Score ≥4, n (%)	18 (85.7)		16 (76.2)		16 (76.2)		13 (61.9)	

*For example, renal replacement therapy, kidney transplant or cardiac pacemaker. Where the median likelihood score awarded for starting or stopping treatment was ≥7.5 in round 1, panellists were asked in round 2 to rate their level of agreement with that course of action. Where the median likelihood score awarded was <7.5 in round 1, panellists were asked in round 2 to rate their level of agreement with not taking that course of action. Green shading: scenarios in which consensus was reached that either treatment should start or treatment should not be stopped. n=21.

raised by panellists was that later manifestations of cardiac damage do not typically respond to FD-specific treatment. Histological markers have the potential to reveal very early cardiac tissue changes, but undertaking a cardiac biopsy is too invasive to be recommended as a routine screen for FD progression.

Other clinical and patient-reported early indicators of FD, such as neuropathic pain, gastroenterological symptoms and difficulties with hearing or balance, are well-known signs and symptoms experienced by patients with FD. Such clinical features could contribute to a physician's decision to treat but may respond only partially to FD-specific treatment.

Implications of the consensus indicators for the start of treatment

The panel reached a consensus on initiating FD-specific treatment in predefined patient groups. In particular, the panel agreed that treatment should be initiated for all males ≥16 years of age with the classical FD mutation regardless of symptom status. Similarly, the panel agreed that treatment should be initiated among males <16 years of age with classical FD demonstrating early or guideline-associated indicators. However, there was no consensus on initiating treatment in asymptomatic males <16 years of age. In particular, consensus regarding early renal and cardiac indicators of disease progression could encourage FD centres to monitor for these indicators, pre-empting accrual of irreversible organ damage. Furthermore, agreement among the panel about the most suitable patient groups for FD-specific treatment initiation indicates that the current guideline recommendations[1] could be updated, and the impact of early intervention could be audited for beneficial outcomes. Likewise, policymakers can use observational and longitudinal data to examine the cost–benefit implications of early treatment of patients for avoidable complications, as well as appropriate cessation of therapy in specific patient groups.

Results of the PREDICT-FD initiative in context

The PREDICT-FD modified Delphi initiative represents the broadest evaluation of early indicators of FD-specific treatment initiation to date. Previous Delphi initiatives have evaluated indicators specific to renal or cardiac organ damage,[17 18] with a focus on tissue biopsy evaluation. However, biopsies are invasive and other approaches are available to aid early identification of disease progression. The use of biopsies in the diagnosis of FD was also key in a Delphi initiative exploring diagnosis, treatment and adverse event management.[16] This Delphi panel reached conclusions similar to those of the PREDICT-FD panel regarding initiation of treatment.[16] Both the cardiac and renal Delphi panels recognised serum lyso Gb3 levels as a potential indicator, although it might have limited specificity in kidney damage.[17 18] Lyso Gb3 has also been proposed as a potential primary biomarker for FD in other studies.[26 27] In the PREDICT-FD panel, there was no consensus on the use of lyso Gb3 as an early indicator of organ damage or treatment

initiation, with the strongest marker of the importance of lyso Gb3 observed for cardiac damage.

Strengths and weaknesses of the PREDICT-FD modified Delphi initiative

The anonymised nature of Delphi methodology should minimise the possibility of bias often seen in face-to-face group interactions, thereby strengthening the validity of the consensus process. However, clinicians in a relatively small and highly specialised field may well be aware of the opinions of their peers, which may have influenced the responses provided in our study. With this qualification, the anonymity of the panellists was maintained until the Delphi stages were complete and the disease chronologies circulated for comment. Furthermore, the overall response rate was >95%, indicating that panellists' knowledge and opinions were well represented. However, because the importance- and agreement-rating steps in this Delphi consensus were opinion based, it is possible that a different consensus would have been reached, had the panel comprised different medical specialties. Thus, the generalisability of our findings is influenced by the panel composition and by the degree to which each panellist's perspective represents that of FD specialists not polled. Such shortcomings are implicit in the Delphi process and the findings require further evaluation in real-world clinical practice to confirm their relevance. Weaknesses of the methodology were the absence of a neutral response option for those unfamiliar with the relevance of an indicator during the importance rating stage, and that no controlled feedback was provided to panellists between rounds. Another was that no attempt was made to achieve consensus on the utility of indicators that did not meet the consensus criteria. Conceivably, this would have led to some indicators being completely discounted, leaving others whose utility remains to be proven.

Conclusion and implications for future research

The PREDICT-FD modified Delphi initiative achieved consensus on 27 early renal, cardiac, PNS, patient-reported and other indicators of disease progression that could prompt FD-specific treatment initiation earlier than is currently practised. These findings should raise awareness among physicians of the early clinical cues that should prompt consideration of disease-specific treatment initiation in FD, so that disease progression and irreversible organ damage in these patients is minimised or avoided. Empirically, early treatment is associated with better outcomes than delaying treatment of FD, but there is currently scant information about the responsiveness to treatment of many of the early indicators of disease progression identified in PREDICT-FD. Further evidence is needed to understand the latest stage at which treatment can be initiated to minimise the long-term complications of FD.

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Contributors DAH and SF provided expert clinical insight throughout the development of the PREDICT-FD modified Delphi initiative, advised on the recruitment for the panel members and contributed to the concept, design and development of the initiative and the development of the questions for each round, as well as to the interpretation of the findings. MJR contributed to the design and development of the initiative and the development of the questions for each round, as well as to the interpretation of the findings. JJ provided expert guidance on the initiative design and questions for each round, and the interpretation of the findings. PA, PBD, FE, AF, OL, AL, J-CL, JCM, KN, D-MN, AN, UR, RR, PR, RS, ES, MT, RT, BV, DGW and MLW were voting members of the panel, and provided expert input at each round and on the interpretation of the findings. All authors contributed to the development and approval of the manuscript.

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Supplementary Appendix

Early indicators of disease progression in Fabry disease that may indicate the need for disease-specific treatment initiation: findings from the PREDICT-FD Delphi consensus initiative

Selection of Chairs and expert panel

The panel size selected in this study was based on a previous Delphi study, which aimed to recruit 15–22 panellists (Mehta A, *et al. Intern Med J* 2019;49(5):578-91). This sample size was also informed by a review of the Delphi process (Hsu CC, Sandford BA. *Pract Assess Res Eval* 2007; 12:1–8), which acknowledged that no consensus on the required sample size exists but that 15–20 panellists was typical. It was agreed *a priori* that 23 experts would be invited to participate to provide adequate study power in case of dropouts.

Delphi process

Early indicators were defined as parameters that may be clinically relevant early warnings of organ damage (pathological findings, biomarkers, etc), and which appear before the signs and symptoms currently used to guide initiation of FD-specific treatment. 'Current routine clinical practice' was defined as assessments, tests or techniques readily available now, and which may either be used routinely in some or most FD disease units or could easily be adopted for routine use. 'Future' routine clinical practice was defined as assessments, tests or techniques not used routinely in most or any FD units at present but with the potential to be used routinely. Thresholds for importance and for agreement used in the consensus process were the same as used in Mehta A, *et al. Intern Med J* 2019;49(5):578-91.

Literature review

Before the Delphi consensus stages of the initiative commenced, a non-exhaustive PubMed literature search was performed to compile an evidence base for new data relating to the FD-specific treatment 'start' and 'stop' criteria outlined by the EFWG (Biegstraaten M, *et al. Orphanet J Rare Dis* 2015;10:36), and relevant new developments in the field (e.g. novel biomarkers of early organ damage and new assessment techniques for identifying early organ damage). The findings of the literature search were shared with the Co-Chairs and used to inform questions in the modified Delphi consensus about starting or stopping treatment in different patient groups and scenarios. The literature search also provided a resource to support subsequent development of the study report and materials for publication.

In total, 24 individual literature searches were conducted, using the following strings. 1) 'Fabry[Title] AND (microalbuminuria OR albuminuria[Title/Abstract])'; 2) 'Fabry[Title] AND proteinuria[Title/Abstract]'; 3) 'Fabry[Title] AND (glomerular filtration rate OR kidney disease[Title/Abstract])'; 4) 'Fabry[Title] AND (cardiac hypertrophy OR maximal wall thickness OR left ventricular mass index[Title/Abstract])'; 5) 'Fabry[Title] AND (rhythm OR arrhythmia[Title/Abstract])'; 6) 'Fabry[Title] AND white matter[Title/Abstract]'; 7) 'Fabry[Title] AND (stroke OR ischem* OR ischaem* OR cerebrovascular[Title/Abstract])'; 8) 'Fabry[Title] AND (hearing loss OR audio impair* OR auditory[Title/Abstract])'; 9) 'Fabry[Title] AND (pain OR painful[Title/Abstract])'; 10) 'Fabry[Title] AND (gastrointestinal OR gastro-intestinal OR vomiting OR nausea OR diarrhoea OR diarrhea OR constipat* OR abdominal OR bloating[Title/abstract])'; 11) 'Fabry[Title] AND (status OR quality OR

QoL OR impact OR burden OR utility[Title/Abstract])'; 12) 'Fabry[Title] AND (therapy OR treatment OR ERT) AND (start OR initiate OR initiation OR begin[Title/Abstract])'; 13) 'Fabry[Title] AND (stop OR cease OR withdraw OR withdrawal OR cessation OR discontin*[Title/Abstract])'; 14) 'Fabry[Title] AND (inhibition OR antibody OR antibodies[Title/Abstract])'; 15) 'Fabry[Title] AND N-acetyl-β-glucosaminidase[Title/Abstract]'; 16) 'Fabry[Title] AND implantable loop [Title/Abstract]'; 17) 'Fabry[Title/Abstract] AND (CMR OR T1[Title/Abstract])'; 18) 'Fabry[Title] AND metaiodobenzylguanidine[Title/Abstract]'; 19) 'Fabry[Title] AND (enhance OR enhanced OR enhancement OR enhancing[Title/Abstract])'; 20) 'Fabry[Title] AND (electrocardiogram OR ECG[Title/Abstract])'; 21) 'Fabry[Title] AND (echocardiogram OR ECG[Title/Abstract])'; 22) 'Fabry[Title] AND diffusion tensor imaging[Title/Abstract]'; 23) 'Fabry[Title] AND diffusion tensor imaging[Title/Abstract]'; 24) 'Fabry[Title] AND (marker OR biomarker[Title/Abstract])'.

Titles and abstracts of English language articles published between 1 April 2014 and 31 August 2017 were searched initially for general relevance to the initiative. Case reports and systematic reviews/meta-analyses were included, whereas opinion-based reviews, animal model studies and *in vitro* studies were excluded. Articles identified in one search that were more relevant to another search were categorised accordingly. Abstracts and full text (where available) of identified articles were then read in detail and relevant studies summarised. Additional relevant publications were provided *ad hoc* by the Co-Chairs.

PREDICT-FD Delphi initiative Round 1 questionnaire

PREDICT-FD

An International Delphi Consensus Initiative

Round 1 questionnaire

Thank you for agreeing to participate in the PREDICT-FD (**PR**oposing **E**arly **D**isease **I**ndicators for **Cl**inical **T**racking in **F**abry **D**isease) International Delphi Consensus Initiative.

The aim of this initiative is to reach consensus on the most important early indicators of Fabry disease organ damage that can be assessed readily in routine clinical practice (now or in the future) to guide the early initiation of disease-specific therapy (such as enzyme replacement therapy and chaperone therapy) in treatment-naïve patients.

This questionnaire is the first part of this initiative and comprises 5 sections.

1. General background information
2. Main consensus questions 1: early indicators of Fabry disease organ damage that can be assessed readily now, in current routine clinical practice
3. Main consensus questions 2: early indicators of Fabry disease organ damage that might be assessed readily in future routine clinical practice
4. Attitudes towards initiation and cessation of Fabry disease-specific therapy
5. Potential impact of findings from the PREDICT-FD International Delphi Initiative Consensus

Please answer all questions in each of the sections and provide as much detail as possible for each question. Please base your answers on your clinical knowledge and experience, not on other factors such as costs associated with changes to treatment practice. Although we do acknowledge that such considerations are important, they are outside the focus of this Delphi initiative.

All information that you provide throughout the questionnaire will be reported back to the Co-Chairs anonymously.

1. General background information

The questions in this section are supplemental to the main Delphi consensus initiative. Your answers will provide us with general information about your experiences in the clinical management of patients with Fabry disease. Here, and in subsequent sections of the questionnaire, we ask about 'classical' and 'non-classical' disease. For the purposes of this consensus initiative, please base your answers on the following definitions (from Arends M *et al. J Am Soc Nephrol* 2017; 28(5):1631–41):

Fabry disease subtype	Men	Women
Classical	1) A *GLA* mutation* 2) ≥1 of the following characteristic Fabry disease symptoms: Fabry neuropathic pain, angiokeratoma, and/or cornea verticillata 3) Severely decreased or absent leukocyte α-galactosidase A activity (<5% of the normal mean)	1) A *GLA* mutation* 2) ≥1 of the following characteristic Fabry disease symptoms: Fabry neuropathic pain, angiokeratoma, and/or cornea verticillata
Non-classical	A *GLA* mutation, and not fulfilling criteria for classical Fabry disease	

*The following GLA mutations are considered neutral and therefore not indicative of Fabry disease: A143T, P60L, D313Y, R118C, T385A, IVS0-10 C>T, the complex haplotype: IVS0-10 C>T/IVS4-16A>G/IVS6-22C>T.

To save your answers, click 'OK'. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey before submitting your answers, click 'OK', then click the 'Exit' button (found at the top of the page). Any responses saved already will then be available to view/review at the next session.

Please do not use the 'back' button in your web browser to exit the survey, as your answers may not be saved.

1. Please enter your name (for tracking purposes only, all answers will be reported anonymously)

2. Please select your main medical specialty/specialties (tick the relevant check boxes)

Cardiology ☐
Genetics ☐
Haematology ☐
Immunology ☐
Metabolic diseases ☐
Nephrology ☐
Neurology ☐
Paediatrics ☐
Other (please specify) ☐

3. Please select your type of practice/s (tick the relevant check boxes)

Public non-teaching hospital ☐
Public teaching hospital ☐
Private hospital ☐
Research centre ☐
Other (please specify) ☐

4. Please enter the number of years you have treated patients with Fabry disease

5. Please enter the number of patients with Fabry disease currently in your practice/s

6. Please provide an approximate gender breakdown of patients with Fabry disease typically managed by your practice/s (e.g. 85% male, 15% female)

7. Please provide an approximate breakdown of Fabry disease type among patients typically managed by your practice/s (e.g. 75% classical, 25% non-classical)

The next two sections form the main part of Round 1 of the Delphi consensus initiative. Your answers will inform the statements that will be generated for use in Rounds 2 and 3 of the initiative.

We will be asking you to think about the **early indicators** of Fabry disease organ damage that may make you consider initiating disease-specific therapy (e.g. enzyme replacement therapy or chaperone therapy) in treatment-naïve patients.

We will ask you to consider these early indicators in two separate settings.

- Firstly, early indicators of Fabry disease organ damage that can be assessed readily **now**, in current routine clinical practice.
- Secondly, early indicators of Fabry disease organ damage that might be assessed readily **in future** routine clinical practice.

2. Main Delphi consensus questions 1: early indicators of Fabry disease organ damage that can be assessed readily now, in current routine clinical practice

We would like you to think about the **early indicators** of Fabry disease organ damage that can be assessed readily **now**, in current routine clinical practice, and which may make you consider initiating disease-specific therapy in treatment-naïve patients.

- By '**current routine clinical practice'**, we mean assessments, tests, or techniques that are readily available now, which may be used routinely in some or most Fabry disease units, and could easily be used routinely in others.
- By '**early indicators**', we mean parameters that may be clinically relevant early warnings of organ damage, which appear **before** the signs and symptoms currently used to guide initiation of Fabry disease-specific therapy. These **early indicators** may be biomarkers (e.g. cells, molecules, metabolites etc. that are detectable in the urine, plasma, or body tissues) or pathological findings that can be identified using techniques such as echocardiography, magnetic resonance imaging, and cardiac magnetic resonance imaging.
- Examples of such **early indicators** could include podocytes in the urine, elevated cardiac troponin I levels, or hippocampal atrophy etc.
- By contrast, **signs and symptoms** currently used to guide initiation of Fabry disease-specific therapy represent more advanced markers of organ damage, such as proteinuria, cardiac hypertrophy, and white matter lesions (e.g. for full guidelines on ERT initiation, please see Biegstraaten M, *et al*. *Orphanet J Rare Dis* 2015;10:36; Concolino D, *et al*. *Eur J Intern Med* 2014;25:751–6; and Schiffmann R, *et al*. *Kidney Int* 2017;91:284–93). **This Delphi initiative will not be examining these more advanced signs and symptoms, which are already well established.**

The following questions on **early indicators** are subdivided by organ so that you can provide organ-specific responses.

Please answer the questions based on your own clinical experience, patient management protocols followed within your Fabry disease practice, and your broader knowledge of Fabry disease.

To save your answers, click 'OK'. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey before submitting your answers, click 'OK', then click the 'Exit' button (found at the top of the page). Any responses saved already will then be available to view/review at the next session.

Please do not use the 'back' button in your web browser to exit the survey, as your answers may not be saved.

8. What are the early indicators of kidney damage that can be assessed readily now, in current routine clinical practice in Fabry disease units, and which could prompt initiation of disease-specific therapy?

Possible indicators could include podocyturia, raised serum uric acid, or new biomarkers that have been described recently etc. Please consider all early indicators of kidney damage that you know are used routinely in Fabry disease units, as well as those that you monitor/assess routinely in your own practice.

Your answer should take into account any considerations for patient subtypes and sex, and provide clarity where approaches are specific to your own Fabry disease unit. There is no word count limit for your answer.

9. Please reflect on any perceived barriers to the wider uptake and use of these early indicators of kidney damage in current clinical practice.

You may also like to consider the perspective of your patients and their carers when giving your answer (e.g. the potential burden that undergoing such assessments may impose). There is no word count limit for your answer.

10. What are the early indicators of cardiac damage that can be assessed readily now, in current routine clinical practice in Fabry disease units, and which could prompt initiation of disease-specific therapy?

Possible indicators could include elevated cardiac troponin I or reduced myocardial T1 etc. Please consider all early indicators of cardiac damage that you know are used routinely in Fabry disease units, as well as those that you monitor/assess routinely in your own practice.

Your answer should take into account any considerations for patient subtypes and sex, and provide clarity where approaches are specific to your own Fabry disease unit. There is no word count limit for your answer.

11. Please reflect on any perceived barriers to the wider uptake and use of these early indicators of cardiac damage in current clinical practice.

You may also like to consider the perspective of your patients and their carers when giving your answer (e.g. the potential burden that undergoing such assessments may impose). There is no word count limit for your answer.

12. What are the early indicators of central nervous system damage that can be assessed readily now, in current routine clinical practice in Fabry disease units, and which could prompt initiation of disease-specific therapy?

Possible indicators could, for example, include hippocampal atrophy. Please consider all early indicators of central nervous system damage that you know are used routinely in Fabry disease units, as well as those that you monitor/assess routinely in your own practice.

Your answer should take into account any considerations for patient subtypes and sex, and provide clarity where approaches are specific to your own Fabry disease unit. There is no word count limit for your answer.

13. Please reflect on any perceived barriers to the wider uptake and use of these early indicators of central nervous system damage in current clinical practice.

You may also like to consider the perspective of your patients and their carers when giving your answer (e.g. the potential burden that undergoing such assessments may impose). There is no word count limit for your answer.

14. Please provide any further relevant information on the early indicators of Fabry organ damage that can be assessed readily now, in current routine clinical practice in Fabry disease units, and which could prompt initiation of disease-specific therapy.

Your answer should take into account any considerations not covered by the previous questions. For example, any non-organ-specific early indicators that you are aware of, or early indicators that in isolation would not prompt initiation of disease-specific therapy, but might if they were present with one or more other early indicators. There is no word count limit for your answer.

Some patient-reported signs and symptoms of Fabry disease organ damage (e.g. neuropathic pain and gastrointestinal symptoms etc.) may currently be used to guide initiation of disease-specific therapy. Although these signs and symptoms appear relatively early on in the progression of the disease, it is possible that others may appear even earlier.

15. What do you consider to be the earliest signs and symptoms (e.g. neuropathic pain and gastrointestinal etc.) that are relevant to Fabry disease progression and the initiation of disease-specific therapy?

Your answer should take into account any considerations for patient subtypes and sex, and provide clarity where approaches are specific to your Fabry disease unit. There is no word count limit for your answer.

Other patient-reported signs and symptoms of Fabry disease (e.g. burning sensations in the arms and legs, tinnitus, hearing loss, oedema, changes in sweating, headache etc.) can occur frequently in patients with Fabry disease and may have a significant negative impact on quality of life. However, these signs and symptoms are not currently used to guide initiation of disease-specific therapy.

16. Which (if any) additional patient-reported signs and symptoms do you think are relevant to consider in decisions regarding initiation of disease-specific therapy?

Your answer should take into account any considerations for patient subtypes and sex, and provide clarity where approaches are specific to your Fabry disease unit. There is no word count limit for your answer.

3. Main consensus questions 2: early indicators of Fabry disease organ damage that might be assessed readily in future routine clinical practice

As before, the following questions relate to **early indicators** of Fabry disease organ damage that could prompt consideration to initiate disease-specific therapy (such as enzyme replacement therapy and chaperone therapy) in treatment-naïve patients. However, this time we would like you to limit your answers to the **early indicators** that are **not currently assessed in routine clinical practice**, but which **might be assessed routinely in the future**.

- In this section, we are only interested in assessments, tests, or techniques that are not used routinely in Fabry disease units right now, but may have the potential to be used routinely in the future (e.g. when access to equipment, availability of testing facilities, or training in techniques etc. has improved).
- Examples of **early indicators** that are not assessed routinely at present, but could be in the future, include elevated levels of urinary *N*-acetyl-β-glucosaminidase or raised levels of serum interleukin-6 etc.

The questions are again subdivided by organ so that you can provide organ-specific responses. Please answer the questions based both on your own clinical/research experience and your broader knowledge of Fabry disease.

To save your answers, click ‘OK’. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey before submitting your answers, click ‘OK’, then click the ‘Exit’ button (found at the top of the page). Any responses saved already will then be available to view/review at the next session.

Please do not use the ‘back’ button in your web browser to exit the survey, as your answers may not be saved.

17. What are the early indicators of kidney damage that might be possible to assess readily in future routine clinical practice in Fabry disease units, and which could prompt initiation of disease-specific therapy?

Possible indicators could include raised levels of urinary *N*-acetyl-β-glucosaminidase or uromodulin etc. Please consider all early indicators that you are aware of that are being evaluated as part of experimental studies/ongoing research.

Your answer should take into account any considerations for patient subtypes and sex. There is no word count limit for your answer.

18. Please reflect on any perceived barriers to the uptake of these early indicators of kidney damage in future clinical practice.

You may also like to consider the perspective of your patients and their carers when giving your answer (e.g. the potential burden that undergoing such assessments may impose). There is no word count limit for your answer.

19. What are the early indicators of cardiac damage that might be possible to assess readily in future routine clinical practice in Fabry disease units, and which could prompt initiation of disease-specific therapy?

Possible indicators could include raised levels of serum interleukin-6 or monocyte chemoattractant protein-1 etc. Please consider all early indicators that you are aware of that are being evaluated as part of experimental studies/ongoing research.

Your answer should take into account any considerations for patient subtypes and sex. There is no word count limit for your answer.

20. Please reflect on any perceived barriers to the uptake of these early indicators of cardiac damage in future clinical practice.

You may also like to consider the perspective of your patients and their carers when giving your answer (e.g. the potential burden that undergoing such assessments may impose). There is no word count limit for your answer.

21. What are the early indicators of central nervous system damage that might be possible to assess readily in future routine clinical practice in Fabry disease units, and which could prompt initiation of disease-specific therapy?

Possible indicators could include alterations in thalamic grey matter or posterior white matter etc. Please consider all early indicators that you are aware of that are being evaluated as part of experimental studies/ongoing research.

Your answer should take into account any considerations for patient subtypes and sex. There is no word count limit for your answer.

22. Please reflect on any perceived barriers to the uptake of these early indicators of central nervous system damage in future clinical practice.

You may also like to consider the perspective of your patients and their carers when giving your answer (e.g. the potential burden that undergoing such assessments may impose). There is no word count limit for your answer.

23. Please provide any further relevant information on other early indicators of Fabry disease organ damage that you are aware of that are being evaluated as part of experimental studies/ongoing research.

Please also consider patient-reported early indicators in your answer, if relevant. There is no word count limit for your answer.

4. Attitudes towards initiation and cessation of Fabry disease-specific therapy

We would now like to ask you some further general questions. Your responses to these questions will provide us with information to benchmark the panel's current attitudes towards starting/stopping disease-specific therapy in patients with Fabry disease. All the information that you provide will be anonymous.

To save your answers, click 'OK'. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey before submitting your answers, click 'OK', then click the 'Exit' button (found at the top of the page). Any responses saved already will then be available to view/review at the next session.

Please do not use the 'back' button in your web browser to exit the survey, as your answers may not be saved.

24. In your experience, what are the key drivers of early initiation of disease-specific therapy in patients with Fabry disease?

Example drivers could be related to clinical, logistical, socioeconomic, or other factors (please list as many drivers as necessary). Please also consider the perspective of your patients and their carers when giving your answer. There is no word limit, so please provide as much detail as you think is necessary.

25. In your experience, what are the greatest barriers to early initiation of disease-specific therapy in patients with Fabry disease?

Example barriers could be related to clinical, logistical, socioeconomic, or other factors (please list as many barriers as necessary). Please also consider the perspective of your patients and their carers when giving your answer. There is no word limit, so please provide as much detail as you think is necessary.

The following questions are designed to benchmark how likely you would be to initiate disease-specific therapy in patients with Fabry disease who are **asymptomatic for organ damage.**

- By '**asymptomatic**', we mean patients with Fabry disease who **do not have early indicators** of Fabry organ damage (e.g. podocyturia, elevated cardiac troponin I levels, or hippocampal atrophy) and **do not have the signs and symptoms** currently used to guide initiation of disease-specific therapy (e.g. Biegstraaten M, *et al*. 2015; Concolino D, *et al*. 2014; and Schiffmann R, *et al*. 2017, outlining ERT initiation guidelines).

While acknowledging the need to assess every patient individually, we have stratified patients into 5 different groups to look for possible prescribing trends.

26. How likely would you be to initiate disease-specific therapy in male patients with classical Fabry disease aged < 16 years old who are asymptomatic for Fabry organ involvement?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

27. How likely would you be to initiate disease-specific therapy in male patients with classical Fabry disease aged ≥16 years old who are asymptomatic for Fabry organ involvement?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

28. How likely would you be to initiate disease-specific therapy in female patients with classical Fabry disease who are asymptomatic for Fabry organ involvement?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

29. How likely would you be to initiate disease-specific therapy in male patients with non-classical Fabry disease who are asymptomatic for Fabry organ involvement?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

30. How likely would you be to initiate disease-specific therapy in female patients with non-classical Fabry disease who are asymptomatic for Fabry organ involvement?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

31. If necessary, please provide any additional thoughts or comments relating to your answers.

There is no word limit, so please provide as much detail as you think is necessary.

The following questions are designed to benchmark by patient subgroup how likely you would be to initiate disease-specific therapy in patients with Fabry disease who **have early indicators** of Fabry organ damage (e.g. podocyturia, elevated cardiac troponin I levels, or hippocampal atrophy), **but do not yet have the signs and symptoms** currently used to guide initiation of therapy (e.g. Biegstraaten M, *et al*. 2015; Concolino D, *et al*. 2014; and Schiffmann R, *et al*. 2017, outlining ERT initiation guidelines).

32. How likely would you be to initiate disease-specific therapy in male patients with classical Fabry disease aged <16 years old who have early indicators of Fabry organ damage, but do not yet have signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

33. How likely would you be to initiate disease-specific therapy in male patients with classical Fabry disease aged ≥16 years old who have early indicators of Fabry organ damage, but do not yet have signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

34. How likely would you be to initiate disease-specific therapy in female patients with classical Fabry disease who have early indicators of Fabry organ damage, but do not yet have signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

35. How likely would you be to initiate disease-specific therapy in male patients with non-classical Fabry disease who have early indicators of Fabry organ damage, but do not yet have signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

36. How likely would you be to initiate disease-specific therapy in <u>female</u> patients with <u>non-classical</u> Fabry disease who have early indicators of Fabry organ damage, but do not yet have signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

37. If necessary, please provide any additional thoughts or comments relating to your answers.

There is no word limit, so please provide as much detail as you think is necessary.

38. Do you think that outcomes and/or quality of life could be improved by initiating disease-specific therapy in patients who <u>have early indicators</u> of Fabry organ damage, <u>but do not yet have signs and symptoms</u> currently used to guide initiation of therapy?

There is no word limit, so please provide as much detail in your answer as you think is necessary.

39. Approximately what proportion of patients do you think might respond to this 'earlier than currently recommended' initiation of disease-specific treatment?

There is no word limit, so please provide as much detail in your answer as you think is necessary.

The following questions are designed to benchmark by patient subgroup how likely you would be to initiate disease-specific therapy in patients with Fabry disease who **display the signs and symptoms currently used to guide initiation of therapy** (e.g. Biegstraaten M, *et al*. 2015; Concolino D, *et al*. 2014; and Schiffmann R, *et al*. 2017, outlining ERT initiation guidelines).

40. How likely would you be to initiate disease-specific therapy in male patients with classical Fabry disease aged <16 years old who display the signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

41. How likely would you be to initiate disease-specific therapy in male patients with classical Fabry disease aged ≥16 years old who display the signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

42. How likely would you be to initiate disease-specific therapy in female patients with classical Fabry disease who display the signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

43. How likely would you be to initiate disease-specific therapy in male patients with non-classical Fabry disease who display the signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

44. How likely would you be to initiate disease-specific therapy in female patients with non-classical Fabry disease who display the signs and symptoms currently used to guide initiation of therapy?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

45. If necessary, please provide any additional thoughts or comments relating to your answers.

There is no word limit, so please provide as much detail as you think is necessary.

The following questions are designed to benchmark by patient subgroup how likely you would be to initiate disease-specific therapy in patients with Fabry disease who have **varying degrees of Fabry organ damage** and who **are/are not receiving relevant therapy for that organ**.

46. How likely would you be to initiate Fabry disease-specific therapy in patients who have severe organ damage in <u>one organ system only</u> and who <u>are</u> receiving relevant therapy for that organ (e.g. renal replacement therapy, kidney transplant, or cardiac pacemaker etc.)?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

47. How likely would you be to initiate Fabry disease-specific therapy in patients who have severe organ damage in <u>one organ system only</u> and who <u>are not</u> receiving relevant therapy for that organ (e.g. <u>no</u> renal replacement therapy, <u>no</u> kidney transplant, <u>no</u> cardiac pacemaker etc.)?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

48. How likely would you be to <u>initiate</u> Fabry disease-specific therapy in patients who have severe <u>multi-organ damage</u> and who <u>are</u> receiving relevant therapies for those organs (e.g. renal replacement therapy, kidney transplant, cardiac pacemaker etc.)?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

49. How likely would you be to <u>initiate</u> Fabry disease-specific therapy in patients who have severe <u>multi-organ damage</u> and who <u>are not</u> receiving relevant therapies for those organs (e.g. <u>no</u> renal replacement therapy, <u>no</u> kidney transplant, <u>no</u> cardiac pacemaker etc.)?

Not at all likely — Extremely likely

0	1	2	3	4	5	6	7	8	9	10

50. In your experience, what are the key drivers for <u>not initiating</u> disease-specific therapy in patients with Fabry disease?

Example drivers could be related to clinical, logistical, socioeconomic, or other factors. Please also consider the perspective of your patients and their carers when giving your answer. There is no word limit, so please provide as much detail as you think is necessary.

The following questions are designed to benchmark by patient subgroup how likely you would be to **stop** disease-specific therapy in patients with Fabry disease who have **varying degrees of Fabry organ damage** and who **are/are not receiving relevant therapy for that organ**.

51. How likely would you be to stop Fabry disease-specific therapy in patients who have severe organ damage in one organ system only and who are receiving relevant therapy for that organ (e.g. renal replacement therapy, kidney transplant, cardiac pacemaker)?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

52. How likely would you be to stop Fabry disease-specific therapy in patients who have severe organ damage in one organ system only and who are not receiving relevant therapy for that organ (e.g. no renal replacement therapy, no kidney transplant, no cardiac pacemaker)?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

53. How likely would you be to stop Fabry disease-specific therapy in patients who have severe multi-organ damage and who are receiving relevant therapies for one of those organs (e.g. renal replacement therapy, kidney transplant, cardiac pacemaker)?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

54. How likely would you be to stop Fabry disease-specific therapy in patients who have severe multi-organ damage and who are not receiving relevant therapies for one of those organs (e.g. no renal replacement therapy, no kidney transplant, no cardiac pacemaker)?

Not at all likely										Extremely likely
0	1	2	3	4	5	6	7	8	9	10

55. In your experience, what are the key drivers for stopping disease-specific therapy in patients with Fabry disease?

Example drivers could be related to clinical, logistical, socioeconomic, or other factors. Please also consider the perspective of your patients and their carers when giving your answer. There is no word limit, so please provide as much detail as you think is necessary.

5. Potential impact of findings from the PREDICT-FD International Delphi Consensus Initiative

The aim of the PREDICT-FD initiative is to reach consensus on the most important early indicators of Fabry disease organ damage that can be assessed readily in clinical practice in Fabry disease units (now or in the future) to guide the early initiation of Fabry disease-specific therapy in treatment-naïve patients.

56. Assuming that the PREDICT-FD International Delphi Consensus Initiative achieves this goal, what difference could it make to day-to-day clinical practice?

There is no word limit, so please provide as much detail in your answer as you think is necessary.

57. Assuming that the PREDICT-FD International Delphi Consensus Initiative achieves this goal, what difference could it make to the lives of patients with Fabry disease and their carers?

There is no word limit, so please provide as much detail in your answer as you think is necessary.

Many thanks for the time you have taken to complete this Round 1 questionnaire. If you are satisfied that you have completed all sections, then please click 'DONE'.

We will email you the link to the Round 2 questionnaire over the coming weeks.

We would like to take this opportunity to remind you that owing to the nature of this initiative, your involvement in this Delphi consensus and your responses to the questionnaires should be kept confidential.

PREDICT-FD Delphi initiative Round 2 questionnaire

PREDICT-FD

An International Delphi Consensus Initiative

Round 2 questionnaire

Thank you for your continued participation in the PREDICT-FD (**PR**oposing **E**arly **D**isease **I**ndicators for **Cl**inical **T**racking in **F**abry **D**isease) International Delphi Consensus Initiative.

As described in Round 1, the aim of this initiative is to reach consensus on the most important early indicators of Fabry disease organ damage that can be assessed readily in routine clinical practice (now or in the future) to guide the early initiation of disease-specific therapy (such as enzyme replacement therapy and chaperone therapy) in treatment-naïve patients.

Responses to the Round 1 questionnaire have been reviewed and consolidated into a series of statements. We would now like you to rate these statements for importance, or to indicate the extent to which you agree with them. This questionnaire is considerably shorter than that circulated in Round 1 and comprises three sections.

1. Main consensus questions: early indicators of Fabry disease organ damage that can be assessed readily now or in the future in routine clinical practice
2. Attitudes towards initiation and cessation of Fabry disease-specific therapy
3. Potential impact of findings from the PREDICT-FD International Delphi Initiative Consensus

Please answer all questions in each section, basing your answers on your clinical knowledge and experience, **not on other factors, such as costs associated with changes to treatment practice**. Although we acknowledge that such considerations are important, the purpose of this Delphi initiative is to identify best clinical practice. It is beyond the scope of the initiative to identify how to adapt best clinical practice to meet the requirements of any local reimbursement policies.

Please also note that as in Round 1, when we refer to ‘classical’ and ‘non-classical’ Fabry disease, these are based on the definitions used in Arends M *et al. J Am Soc Nephrol* 2017; 28(5):1631–41.

All responses to this questionnaire will be reported back to the Co-Chairs anonymously. To save your answers, click ‘OK’. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey before submitting your answers, click ‘OK’, then click the ‘Exit’ button (found at the top of the page). Any responses saved already will then be available to view/review at the next session. It is recommended that you use the same computer each time you access the questionnaire. Alternatively, if you are using a device or phone, cookies must be enabled on the browser you are using at the start of the survey. When you return to complete the survey, the same browser and device must be used.

Please do not use the ‘back’ button in your web browser to exit the survey, as your answers may not be saved.

Section 1.

Main consensus questions: early indicators of Fabry disease organ damage that can be assessed readily now or in the future in routine clinical practice

In this section, you will be asked to **rate the importance** of various early indicators of Fabry disease.

We will first ask you to rate the importance of early indicators that can be **assessed readily now in current routine clinical practice**.

After you have completed the section on current use, we will **then** ask you to rate the importance of early indicators that might be assessed readily **in future** routine clinical practice.

- By '**current routine clinical practice**', we mean assessments, tests, or techniques that are readily available now, which may be used routinely in some or most Fabry disease units and could easily be used routinely in others.
- By '**future routine clinical practice**', we mean assessments, tests, or techniques that are **not** readily available now and are **not** used routinely in some or most Fabry disease units, but which may have the potential to be used routinely in the future (e.g. when access to equipment, availability of testing facilities, or training in techniques etc. has improved).
- By '**early indicators**', we mean parameters that may be clinically relevant early warnings of organ damage, which appear **before** the signs and symptoms currently used to guide initiation of Fabry disease-specific therapy. These **early indicators** may be biomarkers (e.g. cells, molecules, metabolites etc. that are detectable in the urine, plasma, or body tissues) or pathological findings that can be identified using techniques such as echocardiography, magnetic resonance imaging, and cardiac magnetic resonance imaging. Examples of such **early indicators** could include podocytes in the urine, elevated cardiac troponin I levels, or hippocampal atrophy etc.
- By contrast, **signs and symptoms** currently used to guide initiation of Fabry disease-specific therapy represent more advanced markers of organ damage, such as proteinuria, cardiac hypertrophy, and white matter lesions (e.g. for full guidelines on ERT initiation, please see Biegstraaten M, *et al*. *Orphanet J Rare Dis* 2015;10:36; Concolino D, *et al*. *Eur J Intern Med* 2014;25:751–6; and Schiffmann R, *et al*. *Kidney Int* 2017;91:284–93). **This Delphi initiative will not be examining these more advanced signs and symptoms, which are already well established.**

Your answers will inform the first stage of consensus, regarding which early indicators of organ damage should be tracked now, and in the future, to provide treating physicians with the information necessary to decide whether to initiate disease-specific therapy (e.g. enzyme replacement therapy or chaperone therapy) in treatment-naïve patients.

1. Please enter your name (for tracking purposes only, all answers will be reported anonymously)

2. For the following early indicators of kidney damage that can be assessed readily NOW in CURRENT routine clinical practice, please rate how important you think each one is in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

Please rate the importance of each indicator based **only** on your perception of its **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Microalbuminuria					
Elevated uric acid					
Histological damage (kidney biopsy)					
Elevated serum globotriaosylceramide					
Elevated urinary globotriaosylceramide					
Elevated urinary retinol binding protein					
Abnormal glomerular filtration rate					
Elevated urinary globotriaosylsphingosine (and analogues)					
Elevated urinary β-2 microglobulin					
Podocyte inclusions					
Elevated urinary *N*-acetyl-β-glucosaminidase					
Decline in iohexol glomerular filtration rate					
Peripelvic cysts					
Elevated albumin:creatinine ratio					
Elevated serum cystatin C					

3. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

4. For the following early indicators of kidney damage that might be possible to assess readily in FUTURE routine clinical practice, please rate how important you think each one is in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate the importance of each indicator based **only** on your perception of its **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Urinary proteomics					
Podocyturia					
Elevated urinary or plasma globotriaosylsphingosine (and analogues)					
Elevated urinary globotriaosylceramide (and analogues)					
Elevated urinary uromodulin					
Faecal calprotectin					
Elevated urinary Kidney Injury Molecule-1					
Elevated urinary collagen type-IV					
Elevated urinary α-1 microglobulin					
Urinary microRNAs					
Proinflammatory cytokines					
Apoptosis					
mRNA					
Elevated urinary β-2 microglobulin					
Decreased urinary GM2-activator protein					
Sortilin					
Cholesteryl esters					
Elevated urinary nephrin					
Elevated urinary bikunin					
Elevated urinary neutrophil gelatinase-associated lipocalin					

5. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

6. For the following early indicators of cardiac damage that can be assessed readily NOW in CURRENT routine clinical practice, please rate how important you think each one is in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate the importance of each indicator based **only** on your perception of its **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Early indicators of left ventricular hypertrophy					
Early indicators of histological damage (heart biopsy)					
Reduced myocardial T1 relaxation time on cardiac magnetic resonance imaging					
Late gadolinium enhancement on cardiac magnetic resonance imaging					
Abnormal positron emission tomography/magnetic resonance imaging					
Abnormal echocardiogram					
Abnormal electrocardiogram					
Markers of early systolic/diastolic dysfunction					
Abnormal wall motion					
Autonomic dysfunction					
Obstructive haemodynamics					
Proinflammatory biomarkers					
Elevated plasma globotriaosylsphingosine					
Elevated cardiac troponin					
Elevated N-terminal pro-brain natriuretic protein					

7. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

8. For the following early indicators of cardiac damage that might be possible to assess readily in FUTURE routine clinical practice, please rate how important you think each one is in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate the importance of each indicator based **only** on your perception of its **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Reduced myocardial T1 relaxation time on cardiac magnetic resonance imaging					
Proinflammatory biomarkers					
Elevated cardiac troponin					
Elevated N-terminal pro-brain natriuretic protein					
Elevated mid-regional pro-atrial natriuretic peptide					
Elevated matrix metalloproteinases					
Elevated monocyte chemoattractant protein-1					
Elevated galectins					
Elevated adrenomedullin					
Elevated procollagen type I C-terminal propeptide					
Elevated interleukin-6					
Elevated 3-nitrotyrosine					
Anti-myosin antibodies					
Micro-RNAs					

9. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

10. For the following early indicators of central nervous system damage that can be assessed readily NOW in CURRENT routine clinical practice, please rate how important you think each one is in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate the importance of each indicator based **only** on your perception of its **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Autonomic dysfunction					
Peripheral sensory nerve abnormalities					
Cranial blood flow abnormalities					
Neuropathic pain					
Hearing impairment					
Tinnitus					
Retinal vessel abnormalities					
Gastrointestinal symptoms suggestive of gut neuropathy					
Migraine-like headaches					
Neuropsychiatric abnormalities					
Cerebral vessel abnormalities					
Abnormal electromyography					
Hippocampal atrophy					

11. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

12. For the following <u>early indicators</u> of <u>central nervous system damage</u> that might be possible to assess readily in <u>FUTURE</u> routine clinical practice, please rate how important you think each one is in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate the importance of each indicator based **only** on your perception of its **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Dynamic imaging abnormalities					
Neuropsychiatric abnormalities					
Cerebral vessel abnormalities (structural)					
Other novel magnetic resonance imaging findings					
Metabolic abnormalities					
Blood–brain-barrier dysfunction					
Elevated neurofilament light chain					
Nitric oxide pathway dysregulation					
Elevated cell adhesion molecule-1					
Elevated high-sensitivity C-reactive protein					
Elevated tumour necrosis factor					
Elevated interleukin-6					
Elevated P-selectin					

13. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

14. The following additional early indicators of Fabry disease include signs and symptoms that may not be organ-specific, or that may co-present with indicators of organ damage. Please rate how important you think each one is in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate the importance of each indicator based **only** on your perception of its **clinical utility**.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Gastrointestinal symptoms					
Sweating abnormalities or heat/exercise intolerance					
Organ biopsy					
Symptom severity scores					
Biomarkers					
Faecal calprotectin					
Pain in extremities/neuropathy					
Vertigo					
T2 elevation in the basal inferolateral wall					
X chromosome inactivation					
Angina					
Eye pathology					
Cornea verticillata					
Angiokeratoma					
Fatigue					
Depression					

15. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

16. The following patient-reported signs and symptoms were nominated in Round 1 as being relevant to Fabry disease progression and the initiation of disease-specific therapy. Bearing in mind that these signs may be indicative of disease activity, please rate how important you think each one is in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate the importance of each indicator based **only** on your perception of its **clinical utility**.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Sensory disturbances					
Neuro-otologic abnormalities					
Hearing loss/impairment					
Tinnitus					
Stroke/transient ischaemic attack					
Diarrhoea/frequent diarrhoea					
Constipation/frequent constipation					
Abdominal pain					
Bloating					
Weight loss					
Dizziness					
Rash					
Headache					
Dyspnoea					
Angina					
Palpitations					
Signs of cardiac insufficiency					
Lymphoedema					
Angiokeratoma					
Aseptic cellulitis					
Febrile crises					
Absenteeism due to ill health					
Patient-reported outcomes					
Symptom/sign progression					

17. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

18. The following indicators are the subject of ongoing research in Fabry disease. Please rate how important you think each one is likely to be in providing information that would help you to manage patients with Fabry disease.

As before, please rate the importance of each indicator based **only** on your perception of its **clinical utility**.

Indicator	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Reduced quality of life					
High gastrointestinal symptom scores					
Low activity levels					
Obstructive lung disease					
Bone abnormalities					
Gene expression levels					
Chest pain					
High number of analgesics					

19. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

Section 2.

Attitudes towards initiation and cessation of Fabry disease-specific therapy

Based on responses you provided in Round 1, this section lists some statements about factors that may drive or impede the decision to offer disease-specific treatment to patients with Fabry disease. The section also examines your responses relating to which groups of patients you would treat and at what stage of their disease.

You will be asked to **rate your level of agreement** with each of these statements.

To save your answers, click 'OK'. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey before submitting your answers, click 'OK', then click the 'Exit' button (found at the top of the page). Any responses saved already will then be available to view/review at the next session.

Please do not use the 'back' button in your web browser to exit the survey, as your answers may not be saved.

20. The following statements have been drafted with the aim of summarizing the feedback you provided relating to the key drivers of early initiation of disease-specific therapy in patients with Fabry disease. Please rate how important you think each statement is in terms of decision-making in your clinical practice.

Statement	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
A family history of FD, especially if severe or with major organ involvement or premature death, is a key driver of early initiation of treatment					
Male sex, young age, and clinical findings, such as severe pain and signs/symptoms of organ involvement, are key drivers of early initiation of treatment					
Improving clinical outcomes and preventing disease progression are key drivers of early initiation of FD-specific treatment					
Meeting eligibility requirements of national treatment/reimbursement guidelines is a key driver of early initiation of treatment					

21. The following statements have been drafted with the aim of summarizing the feedback you provided relating to the key barriers to early initiation of disease-specific therapy in patients with Fabry disease. Please rate how important you think each statement is in terms of decision-making in your clinical practice.

Statement	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
High costs of treatment are a key barrier to early initiation of treatment					
Treatment administration complexity (i.e. infusions) is a key barrier to early initiation of treatment					
The high patient burden of treatment is a key barrier to early initiation of treatment					
Side effects of therapy are a key barrier to early initiation of treatment					
Poor patient compliance is a key barrier to early initiation of treatment					
A lack of robust evidence supporting the efficacy of earlier treatment is a key barrier to early initiation of treatment					
A lack of biomarkers predicting which patients will progress and which will respond to treatment is a key barrier to early initiation of treatment					

Failing to meet eligibility criteria of national treatment/reimbursement guidelines is a key barrier to early initiation of treatment					
A lack of clinical expertise (in the FD centre) to make accurate and appropriate therapeutic decisions is a key barrier to early initiation of treatment					
Misdiagnosis is a key barrier to early initiation of treatment					
Young age and female sex are key barriers to early initiation of treatment					
Poor socioeconomic status can impede early initiation of treatment					

22. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

In Round 1, you were asked to score how likely you would be to **initiate disease-specific therapy** in different patient groups at different stages of Fabry disease. You were asked about patients who **are asymptomatic for Fabry organ damage,** patients who **have early indicators of Fabry organ damage**, and patients who **display the signs and symptoms that currently guide therapy initiation.**

Based on the responses you provided to those questions, we have generated a series of patient profiles in whom treatment should or should not be initiated. Although the decision to initiate disease-specific treatment in any patient should be made on an individual basis, for the purposes of this consensus exercise, we would like to determine the level of agreement among the panel regarding treatment initiation in each of these patient profiles.

Please rate your level of agreement with each of the following statements.

23. Disease-specific therapy <u>SHOULD</u> be initiated in the following patients who <u>are asymptomatic</u> for Fabry organ damage.

Patient profile	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Male patients aged ≥16 years with classical FD					

24. Disease-specific therapy <u>SHOULD NOT</u> be initiated in the following patients who <u>are asymptomatic</u> for Fabry organ involvement.

Patient profile	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Male patients aged <16 years with classical FD					
Female patients with classical FD					
Male patients with non-classical FD					
Female patients with non-classical FD					

25. Disease-specific therapy SHOULD be initiated in the following patients who have early indicators of Fabry organ damage.

Patient profile	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Male patients aged <16 years with classical FD					
Male patients aged ≥16 years with classical FD					

26. Disease-specific therapy SHOULD NOT be initiated in the following patients who have early indicators of Fabry organ damage.

Patient profile	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Female patients with classical FD					
Male patients with non-classical FD					
Female patients with non-classical FD					

27. Disease-specific therapy SHOULD be initiated in the following patients who display the signs and symptoms that currently guide therapy initiation.

Patient profile	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Male patients aged <16 years with classical FD					
Male patients aged ≥16 years with classical FD					
Female patients with classical FD					
Male patients with non-classical FD					
Female patients with non-classical FD					

28. There are no patients in whom disease-specific therapy <u>SHOULD NOT</u> be initiated if they <u>display the signs and symptoms that currently guide therapy initiation</u>.

	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree

In Round 1, you were also asked about your likelihood of **initiating** and **stopping disease-specific therapy** in patients with **severe organ damage** (single organ or multiple organs), who **are receiving** or who **are not receiving adjunctive therapy** for that/those organ(s) (e.g. renal replacement therapy, kidney transplant, or cardiac pacemaker etc.).

Based on the responses you provided to those questions, we have generated a series of patient profiles in whom treatment should or should not be initiated. Although the decision to initiate disease-specific treatment in any patient should be made on an individual basis, for the purposes of this consensus exercise, we would like to determine the level of agreement among the panel regarding treatment initiation in each of these patient profiles.

Please rate your level of agreement with each of the following statements.

29. Disease-specific therapy SHOULD be initiated in the following patients.

Patient profile	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Single organ damage and receiving adjunctive organ therapy					
Single organ damage and not receiving adjunctive organ therapy					
Multiple organ damage and receiving adjunctive organ therapy					

30. Disease-specific therapy SHOULD NOT be initiated in the following patients.

Patient profile	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Multiple organ damage and not receiving adjunctive organ therapy					

31. There are no patients in whom disease-specific therapy SHOULD be stopped, regardless of whether they have single or multiple organ damage, or whether they are receiving adjunctive organ therapy or not

	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree

32. Disease-specific therapy SHOULD NOT be stopped in the following patients.

Patient profile	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Single organ damage and receiving adjunctive organ therapy					
Single organ damage and not receiving adjunctive organ therapy					
Multiple organ damage and receiving adjunctive organ therapy					
Multiple organ damage and not receiving adjunctive organ therapy					

Section 3.

Impact of the PREDICT-FD International Delphi Consensus Initiative

33. The following statements have been drafted with the aim of summarizing the feedback you provided on the impact that the PREDICT-FD International Delphi Consensus could have on day-to-day clinical practice and on the lives of patients with Fabry disease. Please rate how important you think the scenario described in each statement is to your clinical practice

Statement	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Findings from the initiative could lead to the achievement of consensus on when to start (and stop) disease-specific treatment in patients with FD					
Findings from the initiative could lead to the modification of national treatment guidelines to include predictive biomarkers of disease progression					
Findings from the initiative could lead to the earlier initiation of disease-specific treatment in patients with FD					
Findings from the initiative could help to improve outcomes and/or quality of life of patients with FD					
Findings from the initiative could help to improve clinical practice and the overall management of patients with FD					
Findings from the initiative could help to stimulate research, for example, into predictive biomarkers of disease progression					
Findings from the initiative could increase pressure on existing healthcare resources and personnel					
Findings from the initiative could help support negotiations relating to reimbursement of treatment					
If more patients receive treatment because of findings from the initiative, this could lead to increased treatment costs					
Findings from the initiative could help to reduce the burden placed on families and carers of patients with FD					
Findings from the initiative could help to reduce unnecessary FD-specific treatment (and associated costs)					
Findings from the initiative could help to increase HCP awareness and understanding of the need for individualized assessment and regular multi-disciplinary follow-up of patients with FD					
Findings from the initiative could help to improve communication between HCPs and patients with FD regarding when to start (and stop) disease-specific therapy					
I don't know/it is too early to tell what the impact of findings from this initiative will be for day-to-day clinical practice					

34. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

Many thanks for the time you have taken to complete this Round 2 questionnaire. If you are satisfied that you have completed all sections, then please click 'DONE'.

We will email you the link to the Round 3 questionnaire over the coming weeks.

We would like to take this opportunity to remind you that owing to the nature of this initiative, your involvement in this Delphi consensus and your responses to the questionnaires should be kept confidential.

PREDICT-FD Delphi initiative Round 3 questionnaire

PREDICT-FD

An International Delphi Consensus Initiative

Round 3 questionnaire

Thank you for your continued participation in the PREDICT-FD (**PR**oposing **E**arly **D**isease **I**ndicators for **Cl**inical **T**racking in **F**abry **D**isease) International Delphi Consensus Initiative.

As described in Round 1, the aim of this initiative is to reach consensus on the most important early indicators of Fabry disease organ damage that can be assessed readily in routine clinical practice (now or in the future) to guide the early initiation of disease-specific therapy (such as enzyme replacement therapy and chaperone therapy) in treatment-naïve patients.

Responses to the Round 2 questionnaire have been processed to determine which indicators of Fabry disease you rated as most important. The subgroup of indicators that met threshold criteria for importance are presented here in Round 3. To reach a final consensus, we would like you to rate your level of agreement that these are the most important early indicators of organ damage in Fabry disease.

In Round 2, you also rated the importance of key drivers of therapy initiation and of various statements of the potential impact of the PREDICT-FD initiative. We would like you to rate your level of agreement with those statements identified as important.

This questionnaire is considerably shorter than those circulated in earlier rounds and comprises three sections.

1. Main consensus questions: early indicators of Fabry disease organ damage that can be assessed readily now or in the future in routine clinical practice
2. Key drivers of therapy initiation in Fabry disease
3. Potential impact of findings from the PREDICT-FD International Delphi Initiative Consensus

Please answer all questions in each section, basing your answers on your clinical knowledge and experience, **not on other factors, such as costs associated with changes to treatment practice**. Although we acknowledge that such considerations are important, the purpose of this Delphi initiative is to identify best clinical practice. It is beyond the scope of the initiative to identify how to adapt best clinical practice to meet the requirements of any local reimbursement policies.

All responses to this questionnaire will be reported back to the Co-Chairs anonymously.

To save your answers, click ‘OK’. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey before submitting your answers, click ‘OK’, then click the ‘Exit’ button (found at the top of the page). Any responses saved already will then be available to view/review at the next session.

It is recommended that you use the same computer each time you access the questionnaire. Alternatively, if you are using a device or phone, cookies must be enabled on the browser you are using

at the start of the survey. When you return to complete the survey, the same browser and device must be used.

Please do not use the 'back' button in your web browser to exit the survey, as your answers may not be saved.

Finally, for information, you were asked in Round 2 to rate your level of agreement with statements pertaining to initiation and cessation of Fabry-disease specific therapy in different patient groups. Your responses have allowed us to build a consensus for these points, and this consensus will be included in a final summary report that will be circulated for your review and comment at the end of the initiative. Thank you again for your continued participation.

Section 1.

Main consensus questions: early indicators of Fabry disease organ damage that can be assessed readily now or in the future in routine clinical practice

In this section, you will be asked to **rate your level of agreement** that early indicators of Fabry disease are important.

We will first ask you to rate the early indicators that can be **assessed readily now in current routine clinical practice**.

After you have completed the section on current use, we will **then** ask you to rate the importance of early indicators that might be assessed readily **in future** routine clinical practice.

- By '**current routine clinical practice**', we mean assessments, tests, or techniques that are readily available now, which may be used routinely in some or most Fabry disease units and could easily be used routinely in others.
- By '**future routine clinical practice**', we mean assessments, tests, or techniques that are **not** readily available now and are **not** used routinely in some or most Fabry disease units, but which may have the potential to be used routinely in the future (e.g. when access to equipment, availability of testing facilities, or training in techniques etc. has improved).
- By '**early indicators**', we mean parameters that may be clinically relevant early warnings of organ damage, which appear **before** the signs and symptoms currently used to guide initiation of Fabry disease-specific therapy. These **early indicators** may be biomarkers (e.g. cells, molecules, metabolites etc. that are detectable in the urine, plasma, or body tissues) or pathological findings that can be identified using techniques such as echocardiography, magnetic resonance imaging, and cardiac magnetic resonance imaging. Examples of such **early indicators** could include podocytes in the urine, elevated cardiac troponin I levels, or hippocampal atrophy etc.
- By contrast, **signs and symptoms** currently used to guide initiation of Fabry disease-specific therapy represent more advanced markers of organ damage, such as proteinuria, cardiac hypertrophy, and white matter lesions (e.g. for full guidelines on ERT initiation, please see Biegstraaten M, *et al*. *Orphanet J Rare Dis* 2015;10:36; Concolino D, *et al*. *Eur J Intern Med* 2014;25:751–6; and Schiffmann R, *et al*. *Kidney Int* 2017;91:284–93). **This Delphi initiative will not be examining these more advanced signs and symptoms, which are already well established.**

Your answers will inform the final stage of consensus, regarding which early indicators of organ damage should be tracked now, and in the future, to provide treating physicians with the information necessary to decide whether to initiate disease-specific therapy (e.g. enzyme replacement therapy or chaperone therapy) in treatment-naïve patients.

1. Please enter your name (for tracking purposes only, all answers will be reported anonymously)

2. For the following <u>early indicators</u> of <u>kidney damage</u> that can be assessed readily <u>NOW</u> in <u>CURRENT</u> routine clinical practice, please rate your level of agreement that each is important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

Please rate your agreement based **only** on your perception of each indicator's **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Microalbuminuria					
Histological damage (kidney biopsy)					
Abnormal glomerular filtration rate					
Podocyte inclusions					
Decline in iohexol glomerular filtration rate					
Elevated albumin:creatinine ratio					
Elevated serum cystatin C					

3. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

4. For the following early indicators of kidney damage that might be possible to assess readily in FUTURE routine clinical practice, please rate your level of agreement that each will be important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate your agreement based **only** on your perception of each indicator's **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Podocyturia					
Elevated urinary or plasma globotriaosylsphingosine (and analogues)					

5. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

6. For the following early indicators of cardiac damage that can be assessed readily NOW in CURRENT routine clinical practice, please rate your level of agreement that each is important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate your agreement based **only** on your perception of each indicator's **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Early indicators of left ventricular hypertrophy					
Early indicators of histological damage (heart biopsy)					
Reduced myocardial T1 relaxation time on cardiac magnetic resonance imaging					
Late gadolinium enhancement on cardiac magnetic resonance imaging					
Abnormal positron emission tomography/magnetic resonance imaging					
Abnormal echocardiogram					
Abnormal electrocardiogram					
Markers of early systolic/diastolic dysfunction					
Abnormal wall motion					
Elevated cardiac troponin					
Elevated N-terminal pro-brain natriuretic protein					

7. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

8. For the following early indicators of cardiac damage that might be possible to assess readily in FUTURE routine clinical practice, please rate your level of agreement that each will be important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate your agreement based **only** on your perception of each indicator's **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Reduced myocardial T1 relaxation time on cardiac magnetic resonance imaging					
Elevated cardiac troponin					
Elevated N-terminal pro-brain natriuretic protein					

9. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

10. For the following early indicators of central nervous system damage that can be assessed readily NOW in CURRENT routine clinical practice, please rate your level of agreement that each is important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate your agreement based **only** on your perception of each indicator's **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Neuropathic pain					
Hearing impairment					
Tinnitus					

Gastrointestinal symptoms suggestive of gut neuropathy					

11. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

12. For the following early indicators of central nervous system damage that might be possible to assess readily in FUTURE routine clinical practice, please rate your level of agreement that each will be important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate your agreement based **only** on your perception of each indicator's **clinical utility**. Your answer **should not** take into consideration other factors, such as barriers to the uptake/use of these indicators. This information has been captured already in the Round 1 questionnaire and will be taken into consideration when compiling the final consensus.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Dynamic imaging abnormalities					
Other novel magnetic resonance imaging findings					

13. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

14. The following additional early indicators of Fabry disease include signs and symptoms that may not be organ-specific, or that may co-present with indicators of organ damage. Please rate your level of agreement that each is important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate your agreement based **only** on your perception of each indicator's **clinical utility**.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Gastrointestinal symptoms					
Sweating abnormalities or heat/exercise intolerance					
Organ biopsy					
Symptom severity scores					
Pain in extremities/neuropathy					
Vertigo					

15. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

16. The following patient-reported signs and symptoms were rated as important in Round 2 in terms of their relevance to Fabry disease progression and the initiation of disease-specific therapy. Please rate your level of agreement that each is important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate your agreement based **only** on your perception of each indicator's **clinical utility**.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Neuro-otologic abnormalities					
Hearing loss/impairment					
Stroke/transient ischaemic attack					
Diarrhoea/frequent diarrhoea					
Abdominal pain					
Angina					
Signs of cardiac insufficiency					
Febrile crises					
Absenteeism due to ill health					
Patient-reported outcomes					
Symptom/sign progression					

17. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

18. The following indicators are the subject of ongoing research in Fabry disease. Please rate your level of agreement that each is likely to be important in providing information that would help you to decide whether to initiate Fabry disease-specific therapy.

As before, please rate your agreement based **only** on your perception of each indicator's **clinical utility**.

Indicator	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
Reduced quality of life					
High gastrointestinal symptom scores					
Low activity levels					
Chest pain					
High number of analgesics					

19. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

Section 2.

Drivers of Fabry disease-specific therapy initiation

Based on responses you provided in Round 1, this section lists some statements about key drivers of disease-specific treatment initiation among patients with Fabry disease. Please **rate your level of agreement** with each of these statements.

To save your answers, click 'OK'. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey before submitting your answers, click 'OK', then click the 'Exit' button (found at the top of the page). Any responses saved already will then be available to view/review at the next session.

Please do not use the 'back' button in your web browser to exit the survey, as your answers may not be saved.

20. The following statements have been drafted with the aim of summarizing the feedback you provided relating to the key drivers of early initiation of disease-specific therapy in patients with Fabry disease. Please rate your level of agreement that each statement is important in terms of decision-making in your clinical practice.

Statement	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
A family history of FD, especially if severe or with major organ involvement or premature death, is a key driver of early initiation of treatment					
Male sex, young age, and clinical findings, such as severe pain and signs/symptoms of organ involvement, are key drivers of early initiation of treatment					
Improving clinical outcomes and preventing disease progression are key drivers of early initiation of FD-specific treatment					
Meeting eligibility requirements of national treatment/reimbursement guidelines is a key driver of early initiation of treatment					

21. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

Section 3.

Impact of the PREDICT-FD International Delphi Consensus Initiative

22. The following statements have been drafted with the aim of summarizing the feedback you provided on the impact that the PREDICT-FD International Delphi Consensus could have on day-to-day clinical practice and on the lives of patients with Fabry disease. Please rate your level of agreement that each scenario described is important to your clinical practice.

Statement	1 Not important	2 Slightly important	3 Important	4 Very important	5 Extremely important
Findings from the initiative could lead to the achievement of consensus on when to start (and stop) disease-specific treatment in patients with FD					
Findings from the initiative could lead to the modification of national treatment guidelines to include predictive biomarkers of disease progression					
Findings from the initiative could lead to the earlier initiation of disease-specific treatment in patients with FD					
Findings from the initiative could help to improve outcomes and/or quality of life of patients with FD					
Findings from the initiative could help to improve clinical practice and the overall management of patients with FD					
Findings from the initiative could help to stimulate research, for example, into predictive biomarkers of disease progression					
Findings from the initiative could increase pressure on existing healthcare resources and personnel					
Findings from the initiative could help to reduce unnecessary FD-specific treatment (and associated costs)					
Findings from the initiative could help to increase HCP awareness and understanding of the need for individualized assessment and regular multi-disciplinary follow-up of patients with FD					
Findings from the initiative could help to improve communication between HCPs and patients with FD regarding when to start (and stop) disease-specific therapy					

23. OPTIONAL: if you want to leave a comment about any of your answers, please use the text box below. There is no word count limit for your answer.

Many thanks for the time you have taken to complete this Round 3 questionnaire. If you are satisfied that you have completed all sections, then please click 'DONE'.

We would like to take this opportunity to remind you that owing to the nature of this initiative, your involvement in this Delphi consensus and your responses to the questionnaires should remain confidential.

PREDICT-FD Round 4 questionnaire

Thank you for your participation in the PREDICT-FD initiative. On behalf of the Co-Chairs, I am pleased to inform you that we have had a 100% response rate to all three rounds conducted so far. We are writing to you because we need to conduct a fourth round, which was not anticipated at the start of the program. This is not uncommon when running Delphi consensus exercises, because unforeseen ambiguities can arise during the process. Accordingly, we would be most grateful if you can respond to the questions listed in the table and text below.

We expect this to be the last questionnaire that we will send to you before a draft report of the initiative and its findings is circulated for your review. Thank you in advance for your continued support of this important initiative.

1. For each of the following indicators, please would you **rate your level of agreement** that each is an important early indicator in Fabry disease by **placing an 'X' in one box per row**

Category and indicator	**1** Strongly disagree	**2** Disagree	**3** Neither agree nor disagree	**4** Agree	**5** Strongly agree
Current early indicators of cardiac damage					
Elevated plasma globotriaosylsphingosine					
Current early indicators of CNS damage					
Cerebral vessel abnormalities					
Non-organ-specific early indicators of FD					
Angiokeratoma					
Biomarkers, e.g. lysoGb3					
Patient-reported early indicators of FD					
Angiokeratoma					
Palpitations					
Barriers to initiation of FD-specific treatment					
A lack of biomarkers predicting which patients will progress and which will respond to treatment is a key barrier to early initiation of treatment					
Misdiagnosis is a key barrier to early initiation of treatment					
The impact of PREDICT-FD on clinical practice					
Findings from the initiative could help support negotiations relating to reimbursement of treatment					

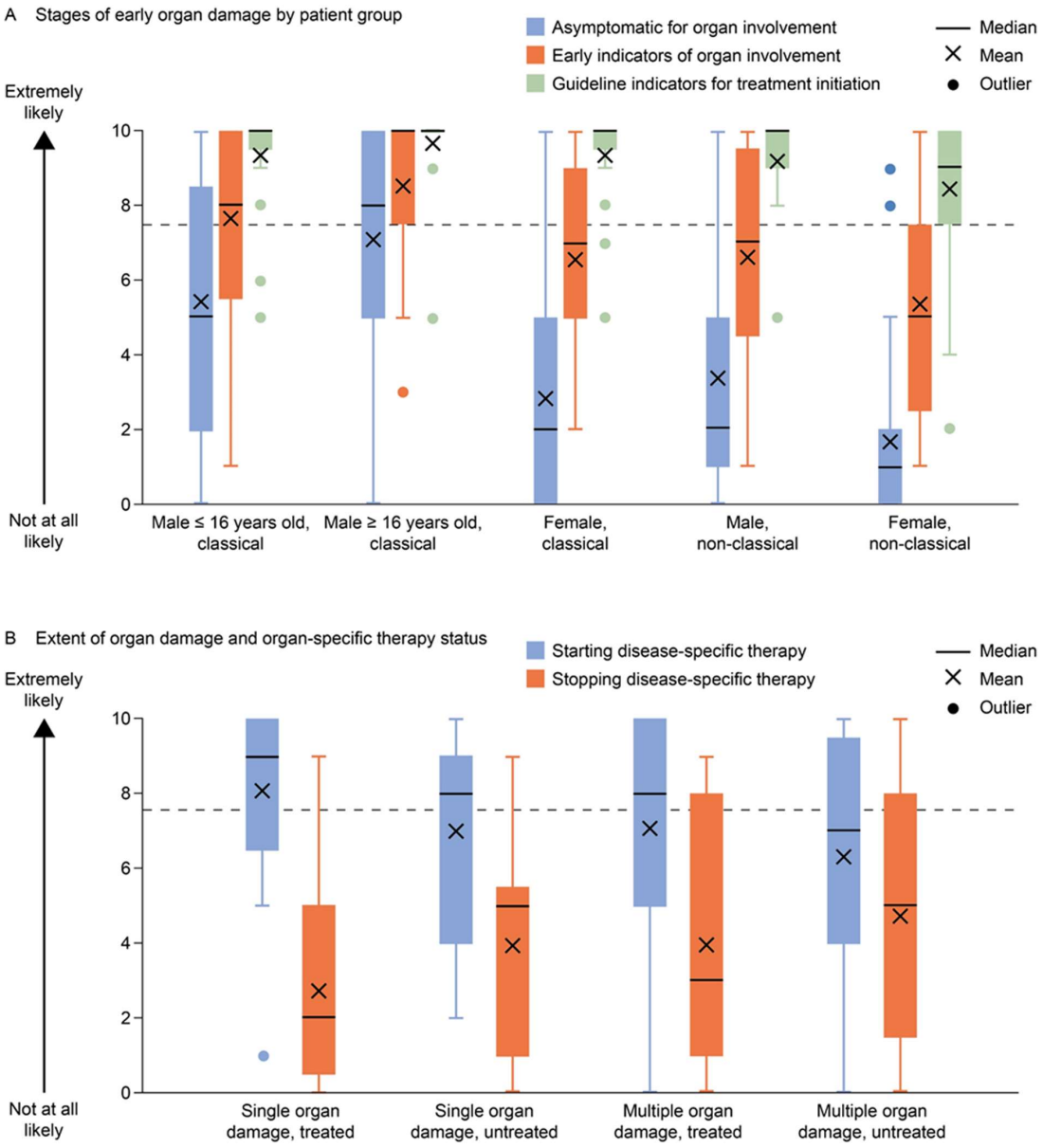
2. Based on feedback received during PREDICT-FD, we propose that some of the indicator descriptions may need to be refined. In light of your specialist knowledge of FD and your clinical expertise (e.g. nephrology, cardiology, neurology, metabolic diseases), please would you state whether you agree or disagree with the additional information provided for each of the following

indicators relevant to your specialist knowledge, and add any changes that you would like to see made to this information.

Category and indicator	Additional information	1 Agree	2 Disagree	Comments about additional information
Current early indicators of renal damage				
Histological damage (kidney biopsy)	The prognostic significance of these renal indicators is different in male and female patients			
Elevated urinary albumin:creatinine ratio				
Microalbuminuria				
Abnormal glomerular filtration rate				
Decline in iohexol glomerular filtration rate				
Podocyte inclusions				
Current early indicators of cardiac damage				
Markers of early systolic/diastolic dysfunction	Including decreased myocardial strain and strain rate, tissue Doppler abnormalities, enlarged left atrium, or pulmonary vein abnormalities on echocardiogram			
Elevated cardiac troponin	None			
Early indicators of histological damage (heart biopsy)	None			
Abnormal electrocardiogram	Including a shortened PR interval, non-sustained ventricular tachycardia, symptomatic bradycardia			
Elevated N-terminal pro-brain natriuretic protein	None			
Abnormal wall motion	Combine with 'Abnormal echocardiogram'			
Current early indicators of CNS damage				
Neuropathic pain	Reclassify as PNS; causal relationship with FD is needed			
Gastrointestinal symptoms suggestive of gut neuropathy				

Category and indicator	Additional information	1 Agree	2 Disagree	Comments about additional information
	to justify FD-specific treatment			
Other early indicators of FD				
Pain in extremities/neuropathy	Including acroparaesthesia			
Organ biopsy	Including skin biopsy for small-fibre neuropathy			
Gastrointestinal symptoms	Including bloating, pain, diarrhoea, or constipation, that are causally related to FD			
Sweating abnormalities or heat/exercise intolerance	None			
Patient-reported indicators of FD				
Stroke/transient ischaemic attack	Reclassify as an 'Other early indicator of FD'			
Febrile crises	None			
Symptom/sign progression	Should be termed 'Patient-reported progression of symptoms/signs'			
Diarrhoea/frequent diarrhoea	Combine with 'Gastrointestinal symptoms'			
Neuro-otologic abnormalities	Exclude if referring to hearing loss, tinnitus, and vertigo, because these indicators did not achieve consensus			

Figure S1 Likelihood of FD-specific treatment initiation



Dotted line, threshold score=7.5; N=21.

FD, Fabry disease.

Table S1 Consensus at round 3 on early indicators of kidney damage that are used in current, or may be used in future, routine clinical practice

Current indicators of kidney damage	Importance*		Agreement†	
	Mean (median) score	Score ≥3 n (%)	Mean (median) score	Score ≥4 n (%)
Elevated urine albumin:creatinine ratio	4.1 (4)	20 (95.2)	4.5 (5)	21 (100)
Histological damage (kidney biopsy)	4.4 (5)	21 (100)	4.5 (5)	20 (95.2)
Microalbuminuria	4.1 (4)	20 (95.2)	4.5 (5)	20 (95.2)
Abnormal glomerular filtration rate	4.3 (5)	19 (90.5)	4.5 (5)	19 (90.5)
Decline in iohexol glomerular filtration rate	4.3 (5)	19 (90.5)	4.1 (4)	16 (76.2)
Podocyte inclusions	3.8 (4)	18 (85.7)	4.1 (4)	15 (71.4)
Elevated serum cystatin C	3.6 (3)	18 (85.7)	3.8 (4)	13 (61.9)
Elevated urinary globotriaosylsphingosine (and analogues)	3.0 (3)	14 (66.7)	–	–
Elevated serum globotriaosylceramide	2.7 (3)	12 (57.1)	–	–
Elevated urinary globotriaosylceramide	2.8 (3)	12 (57.1)	–	–
Elevated urinary N-acetyl-β-glucosaminidase	2.3 (2)	7 (33.3)	–	–
Elevated serum uric acid	1.9 (2)	6 (28.6)	–	–
Elevated urinary β-2 microglobulin	2.2 (2)	6 (28.6)	–	–
Elevated urinary retinol binding protein	1.9 (2)	5 (23.8)	–	–
Peripelvic cysts	1.7 (2)	4 (19.0)	–	–

Future indicators of kidney damage				
Podocyturia	3.4 (3)	18 (85.7)	3.7 (4)	13 (61.9)
Elevated urinary or plasma globotriaosylsphingosine (and analogues)	3.6 (4)	18 (85.7)	3.6 (4)	12 (57.1)
Urinary proteomics	2.8 (3)	13 (61.9)	–	–
Proinflammatory cytokines	2.5 (2)	9 (42.9)	–	–
Apoptosis	2.4 (2)	8 (38.1)	–	–
mRNA	2.3 (2)	8 (38.1)	–	–
Elevated urinary uromodulin	2.2 (2)	7 (33.3)	–	–
Elevated urinary collagen type IV	2.1 (2)	7 (33.3)	–	–
Elevated urinary β-2 microglobulin	2.3 (2)	7 (33.3)	–	–
Urinary microRNAs	2.2 (2)	6 (28.6)	–	–
Faecal calprotectin	1.9 (2)	5 (23.8)	–	–
Elevated urinary neutrophil gelatinase-associated lipocalin	2.0 (2)	5 (23.8)	–	–
Elevated urinary kidney injury molecule-1	1.9 (2)	4 (19.0)	–	–
Elevated urinary α-1 microglobulin	2.0 (2)	4 (19.0)	–	–
Sortilin	2.0 (2)	4 (19.0)	–	–
Elevated urinary nephrin	1.9 (2)	4 (19.0)	–	–
Decreased urinary GM2-activator protein	1.8 (2)	3 (14.3)	–	–
Cholesteryl esters	1.7 (2)	3 (14.3)	–	–
Elevated urinary bikunin	1.7 (2)	3 (14.3)	–	–

*Importance was rated using a 5-point Likert scale (1=not important; 5=extremely important); indicators awarded an importance score of ≥3 by >75% of the panel were rated for agreement; N=21.

†Agreement that an indicator was important was rated using a 5-point pivoted Likert scale (1=strongly disagree; 5=strongly agree); indicators awarded an agreement score of ≥4 by >67% of the panel achieved consensus; N=21.

Indicators reaching consensus are shaded grey.

GM2, monosialic-ganglioside 2; mRNA, messenger ribonucleic acid.

Table S2 Consensus at round 3 on early indicators of cardiac damage that are used in current, or may be used in future, routine clinical practice

Current indicators of cardiac damage	Importance*		Agreement†	
	Mean (median) score	Score ≥3 n (%)	Mean (median) score	Score ≥4 n (%)
Markers of early systolic/diastolic dysfunction	3.8 (4)	19 (90.5)	4.4 (4)	21 (100)
Elevated serum cardiac troponin	3.9 (4)	20 (95.2)	4.1 (4)	18 (85.7)
Early indicators of left ventricular hypertrophy	4.1 (4)	20 (95.2)	4.1 (4)	18 (85.7)
Early indicators of histological damage (heart biopsy)	3.9 (4)	18 (85.7)	4.0 (4)	17 (81.0)
Late gadolinium-enhancement on cardiac magnetic resonance imaging	4.1 (4)	19 (90.5)	4.0 (4)	17 (81.0)
Elevated serum N-terminal pro-brain natriuretic peptide	3.7 (4)	16 (76.2)	4.0 (4)	17 (81.0)
Reduced myocardial T1 relaxation time on cardiac magnetic resonance imaging	3.9 (4)	21 (100)	3.9 (4)	17 (81.0)
Abnormal electrocardiogram	3.9 (4)	18 (85.7)	3.9 (4)	16 (76.2)
Abnormal echocardiogram	3.9 (4)	18 (85.7)	3.9 (4)	15 (71.4)
Abnormal wall motion	3.4 (4)	17 (81.0)	3.7 (4)	15 (71.4)
Abnormal positron emission tomography/magnetic resonance imaging	3.2 (3)	17 (81.0)	3.3 (3)	9 (42.9)
Elevated plasma globotriaosylsphingosine‡	3.1 (3)	16 (76.2)	2.8 (3)	7 (33.3)
Autonomic dysfunction	3.1 (3)	15 (71.4)	–	–
Obstructive haemodynamics	2.9 (3)	15 (71.4)	–	–
Proinflammatory biomarkers	2.5 (3)	12 (57.1)	–	–

Future indicators of cardiac damage				
Reduced myocardial T1 relaxation time on cardiac magnetic resonance imaging	4.0 (4)	21 (100)	4.0 (4)	19 (90.5)
Elevated serum cardiac troponin	4.0 (4)	20 (95.2)	4.0 (4)	17 (81.0)
Elevated serum N-terminal pro-brain natriuretic peptide	3.7 (4)	18 (85.7)	3.9 (4)	15 (71.4)
Proinflammatory biomarkers	2.9 (3)	13 (61.9)	–	–
Elevated mid-regional pro-atrial natriuretic peptide	2.7 (3)	12 (57.1)	–	–
Elevated matrix metalloproteinases	2.2 (2)	10 (47.6)	–	–
Elevated interleukin-6	2.4 (2)	10 (47.6)	–	–
Micro-RNAs	2.4 (2)	10 (47.6)	–	–
Elevated 3-nitrotyrosine	2.2 (2)	7 (33.3)	–	–
Elevated procollagen type I C-terminal propeptide	1.9 (2)	6 (28.6)	–	–
Anti-myosin antibodies	2.0 (2)	6 (28.6)	–	–
Elevated monocyte chemoattractant protein-1	2.0 (2)	5 (23.8)	–	–
Elevated adrenomedullin	1.8 (2)	5 (23.8)	–	–
Elevated galectins	1.9 (2)	4 (19.0)	–	–

*Importance was rated using a 5-point Likert scale (1=not important; 5=extremely important); indicators awarded an importance score of ≥3 by >75% of the panel were rated for agreement; N=21.
†Agreement that an indicator was important was rated using a 5-point pivoted Likert scale (1=strongly disagree; 5=strongly agree); indicators awarded an agreement score of ≥4 by >67% of the panel achieved consensus; N=21.
‡This indicator was inadvertently omitted from round 3 and was therefore submitted to the panel for agreement rating in round 4.
Indicators reaching consensus are shaded grey.

RNA, ribonucleic acid.

Table S3 Consensus at round 3 on early indicators of CNS damage that are used in current, or may be used in future, routine clinical practice

	Importance*		Agreement†	
Current indicators of CNS damage	**Mean (median) score**	**Score ≥3 n (%)**	**Mean (median) score**	**Score ≥4 n (%)**
Neuropathic pain	4.1 (5)	21 (100)	4.3 (5)	19 (90.5)
Gastrointestinal symptoms suggestive of gut neuropathy	3.5 (3)	17 (81.0)	4.1 (4)	18 (85.7)
Hearing impairment	3.9 (4)	20 (95.2)	4.0 (4)	14 (66.7)
Cerebral vessel abnormalities‡	3.0 (3)	16 (76.2)	3.8 (4)	13 (61.9)
Tinnitus	3.4 (3)	19 (90.5)	3.7 (4)	12 (57.1)
Autonomic dysfunction	3.2 (3)	15 (71.4)	–	–
Cranial blood flow abnormalities	2.8 (3)	15 (71.4)	–	–
Retinal vessel abnormalities	3.0 (3)	15 (71.4)	–	–
Peripheral sensory nerve abnormalities	3.3 (3)	14 (66.7)	–	–
Neuropsychiatric abnormalities	2.7 (3)	11 (52.4)	–	–
Hippocampal atrophy	2.5 (3)	11 (52.4)	–	–
Migraine-like headaches	2.4 (2)	10 (47.6)	–	–
Abnormal electromyography	1.9 (1)	6 (28.6)	–	–
Future indicators of CNS damage				
Dynamic imaging abnormalities	3.0 (3)	17 (81.0)	3.3 (3)	8 (38.1)

Other novel magnetic resonance imaging findings	3.0 (3)	17 (81.0)	3.4 (3)	7 (33.3)
Neuropsychiatric abnormalities	3.0 (3)	15 (71.4)	–	–
Cerebral vessel abnormalities (structural)	3.2 (3)	15 (71.4)	–	–
Metabolic abnormalities	2.5 (3)	11 (52.4)	–	–
Nitric oxide pathway dysregulation	2.6 (3)	11 (52.4)	–	–
Elevated interleukin-6	2.4 (3)	11 (52.4)	–	–
Elevated tumour necrosis factor	2.4 (2)	9 (42.9)	–	–
Blood–brain barrier dysfunction	2.3 (2)	8 (38.1)	–	–
Elevated neurofilament light chain	2.1 (2)	8 (38.1)	–	–
Elevated high-sensitivity C-reactive protein	2.2 (2)	7 (33.3)	–	–
Elevated cell adhesion molecule-1	2.0 (2)	6 (28.6)	–	–
Elevated P-selectin	1.9 (2)	5 (23.8)	–	–

*Importance was rated using a 5-point Likert scale (1=not important; 5=extremely important); indicators awarded an importance score of ≥3 by >75% of the panel were rated for agreement; N=21.
†Agreement that an indicator was important was rated using a 5-point pivoted Likert scale (1=strongly disagree; 5=strongly agree); indicators awarded an agreement score of ≥4 by >67% of the panel achieved consensus; N=21.
‡This indicator was inadvertently omitted from round 3 and was therefore submitted to the panel for agreement rating in round 4.
Indicators reaching consensus are shaded grey.

CNS, central nervous system.

Table S4 Consensus at round 3 on additional early indicators of FD that are used in current routine clinical practice

Current additional early indicators	Importance*		Agreement†	
	Mean (median) score	Score ≥3 n (%)	Mean (median) score	Score ≥4 n (%)
Pain in extremities/neuropathy	4.0 (4)	20 (95.2)	4.4 (4)	20 (95.2)
Angiokeratoma‡	3.4 (4)	16 (76.2)	4.1 (4)	17 (81.0)
Organ biopsy	4.2 (4)	21 (100)	4.1 (4)	16 (76.2)
Gastrointestinal symptoms	3.7 (3)	21 (100)	4.0 (4)	16 (76.2)
Sweating abnormalities or heat/exercise intolerance	3.8 (4)	19 (90.5)	4.0 (4)	15 (71.4)
Biomarkers‡	3.1 (3)	16 (76.2)	3.9 (4)	14 (66.7)
Symptom severity scores	3.5 (4)	17 (81.0)	3.7 (4)	13 (61.9)
Vertigo	3.1 (3)	16 (76.2)	3.3 (3)	9 (42.9)
T2 elevation in the basal inferolateral wall	3.3 (3)	15 (71.4)	–	–
Angina	3.2 (3)	15 (71.4)	–	–
Cornea verticillata	3.2 (3)	14 (66.7)	–	–
X-chromosome inactivation	2.8 (3)	14 (66.7)	–	–
Eye pathology	2.9 (3)	13 (61.9)	–	–
Fatigue	2.7 (3)	13 (61.9)	–	–
Depression	2.7 (3)	12 (57.1)	–	–
Faecal calprotectin	2.0 (2)	5 (23.8)	–	–

*Importance was rated using a 5-point Likert scale (1=not important; 5=extremely important); indicators awarded an importance score of ≥3 by >75% of the panel were rated for agreement; N=21.

†Agreement that an indicator was important was rated using a 5-point pivoted Likert scale (1=strongly disagree; 5=strongly agree); indicators awarded an agreement score of ≥4 by >67% of the panel achieved consensus; N=21.
‡This indicator was inadvertently omitted from round 3 and was therefore submitted to the panel for agreement rating in round 4.
Indicators reaching consensus are shaded grey.

FD, Fabry disease.

Table S5 Consensus at round 3 on patient-reported indicators of FD

Current patient-reported indicators	Importance*		Agreement†	
	Mean (median) score	Score ≥3 n (%)	Mean (median) score	Score ≥4 n (%)
Stroke/transient ischaemic attack	4.3 (5)	20 (95.2)	4.3 (4)	18 (85.7)
Febrile crises	4.0 (4)	20 (95.2)	4.2 (5)	17 (81.0)
Symptom/sign progression	4.2 (4)	20 (95.2)	4.1 (4)	17 (81.0)
Diarrhoea/frequent diarrhoea	3.6 (4)	18 (85.7)	4.1 (4)	16 (76.2)
Angiokeratoma‡	3.2 (3)	16 (76.2)	4.0 (4)	16 (76.2)
Neuro-otologic abnormalities	3.2 (3)	17 (81.0)	3.9 (4)	15 (71.4)
Signs of cardiac insufficiency	3.7 (4)	17 (81.0)	4.0 (4)	14 (66.7)
Hearing loss/impairment	3.5 (3)	19 (90.5)	4.0 (4)	13 (61.9)
Abdominal pain	3.4 (3)	16 (76.2)	4.0 (4)	13 (61.9)
Angina	3.4 (3)	18 (85.7)	3.7 (4)	12 (57.1)
Patient-reported outcomes	3.6 (4)	18 (85.7)	3.6 (3)	10 (47.6)
Absenteeism due to ill health	3.2 (3)	17 (81.0)	3.6 (3)	10 (47.6)
Palpitations‡	3.3 (3)	16 (76.2)	2.6 (3)	3 (14.3)
Tinnitus	3.1 (3)	15 (71.4)	–	–
Sensory disturbances	3.1 (3)	15 (71.4)	–	–
Lymphoedema	3.1 (3)	15 (71.4)	–	–
Bloating	2.8 (3)	14 (66.7)	–	–

Dyspnoea	2.9 (3)	14 (66.7)	–	–
Weight loss	2.6 (3)	12 (57.1)	–	–
Constipation/frequent constipation	2.6 (3)	11 (52.4)	–	–
Dizziness	2.7 (2)	10 (47.6)	–	–
Headache	2.1 (2)	8 (38.1)	–	–
Aseptic cellulitis	2.0 (2)	7 (33.3)	–	–
Rash	2.0 (2)	6 (28.6)	–	–

*Importance was rated using a 5-point Likert scale (1=not important; 5=extremely important); indicators awarded an importance score of ≥3 by >75% of the panel were rated for agreement; N=21.

†Agreement that an indicator was important was rated using a 5-point pivoted Likert scale (1=strongly disagree; 5=strongly agree); indicators awarded an agreement score of ≥4 by >67% of the panel achieved consensus; N=21.

‡This indicator was inadvertently omitted from round 3 and was therefore submitted to the panel for agreement rating in round 4.

Indicators reaching consensus are shaded grey.

FD, Fabry disease.

Table S6 Consensus at round 3 on indicators of FD that are the focus of ongoing research

Current indicators subject to ongoing research	Importance*		Agreement†	
	Mean (median) score	Score ≥3 n (%)	Mean (median) score	Score ≥4 n (%)
Reduced quality of life	3.9 (4)	20 (95.2)	4.1 (4)	17 (81.0)
High gastrointestinal symptom scores	3.8 (4)	20 (95.2)	4.1 (4)	16 (76.2)
High number of analgesics	3.5 (4)	17 (81.0)	3.8 (4)	14 (66.7)
Chest pain	3.2 (3)	17 (81.0)	3.8 (4)	12 (57.1)
Low activity levels	3.1 (3)	18 (85.7)	3.6 (4)	12 (57.1)
Obstructive lung disease	2.8 (3)	14 (66.7)	–	–
Gene expression levels	2.9 (3)	13 (61.9)	–	–
Bone abnormalities	2.3 (2)	8 (38.1)	–	–

*Importance was rated using a 5-point Likert scale (1=not important; 5=extremely important); indicators awarded an importance score of ≥3 by >75% of the panel were rated for agreement; N=21.

†Agreement that an indicator was important was rated using a 5-point pivoted Likert scale (1=strongly disagree; 5=strongly agree); indicators awarded an agreement score of ≥4 by >67% of the panel achieved consensus; N=21.

Indicators reaching consensus are shaded grey.

FD, Fabry disease.

Table S7 Agreement in round 4 on refinements to consensus indicators

Category and indicator	Refinement	Agreement* n/N (%)
Current early indicators of renal damage		
Histological damage (kidney biopsy)	The prognostic significance of these renal indicators is different in male and female patients	15/18 (83.3)
Elevated urinary albumin:creatinine ratio		15/18 (83.3)
Microalbuminuria		16/18 (88.9)
Abnormal glomerular filtration rate		11/18 (61.1)
Decline in iohexol glomerular filtration rate		11/18 (61.1)
Podocyte inclusions		12/18 (66.7)
Current early indicators of cardiac damage		
Markers of early systolic/diastolic dysfunction	Including decreased myocardial strain and strain rate, tissue Doppler abnormalities, enlarged left atrium or pulmonary vein abnormalities on echocardiogram	17/18 (94.4)
Elevated serum cardiac troponin	None	12/17 (70.6)
Early indicators of histological damage (heart biopsy)	None	12/17 (70.6)
Abnormal electrocardiogram	Including a shortened PR interval, non-sustained ventricular tachycardia, symptomatic bradycardia	13/17 (76.5)
Elevated serum -terminal pro-brain natriuretic peptide	None	12/16 (75.0)
Abnormal wall motion	Combine with ‘Abnormal echocardiogram’	8/15 (53.3)
Current early indicators of CNS damage		
Neuropathic pain	Reclassify as PNS; causal relationship with FD is needed to justify FD-specific treatment	14/17 (82.4)
Gastrointestinal symptoms suggestive of gut neuropathy		14/18 (77.8)
Other early indicators of FD		

Pain in extremities/neuropathy	Including acroparesthesia	17/17 (100.0)
Organ biopsy	Including skin biopsy for small-fibre neuropathy	13/18 (72.2)
Gastrointestinal symptoms	Including bloating, diarrhoea or constipation, that are causally related to FD	14/18 (77.8)
Sweating abnormalities or heat/exercise intolerance	None	16/18 (88.9)
Patient-reported indicators of FD		
Stroke/transient ischaemic attack	Reclassify as an 'Other early indicator of FD'	13/17 (76.5)
Febrile crises	None	13/16 (81.3)
Symptom/sign progression	Should be termed 'Patient-reported progression of symptoms/signs'	14/18 (77.8)
Diarrhoea/frequent diarrhoea	Combine with 'Gastrointestinal symptoms'	16/17 (94.1)
Neuro-otologic abnormalities	Exclude if referring to hearing loss, tinnitus and vertigo, because these indicators did not achieve consensus.	13/18 (72.2)

*Panellists were asked whether they agreed with the proposed refinements relating to indicators in their own specialty, but many panellists indicated whether they agreed with each refinement under each specialty, therefore 'n'=the number who agreed and 'N'=the number who responded. Agreement was reached if >67% of panellists who responded agreed with a refinement.

CNS, central nervous system; FD, Fabry disease; PNS, peripheral nervous system.