



## Fabry patients' experiences with the timing of diagnosis relevant for the discussion on newborn screening

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### ABSTRACT

This study aimed to explore Fabry disease (FD) patients' experiences with the timing of their diagnosis and identify important patient-oriented themes relevant to discussions about the need for newborn screening (NBS) for this disorder.

Thirty FD patients (13 males) were included in a qualitative study involving semi-structured interviews. The interviews were audiorecorded and transcribed, and the transcripts were analyzed to identify themes that captured the patients' experiences.

The interview analysis revealed six relevant themes. One of these was the impact of a delayed diagnosis on severely affected patients, who often felt misunderstood and were frequently misdiagnosed. In contrast, some patients mentioned the drawbacks of presymptomatic diagnosis, which was associated with labeling and medicalization. In addition, the ability to anticipate future FD-related problems was considered both an advantage and a disadvantage of early diagnosis. Still, patients reported that they felt that an early FD diagnosis could prevent disease progression through the timely initiation of treatment.

This study identified several relevant themes that reflect both the phenotypic heterogeneity of the disease and the substantial differences between patients' experiences with and without FD symptoms before diagnosis and among the patients in each group. These results add considerable nuances to the discussion about NBS programs for FD and should be incorporated into the debate.

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### 1. Introduction

Newborn population screening (NBS) aims to provide early presymptomatic diagnosis of treatable disorders that require treatment initiation before the onset of clinical signs and symptoms to prevent severe and irreversible sequelae or death. In the late 1960s and early 1970s, phenylketonuria, was the first disorder for which NBS became available in many countries and it serves as the undisputed example of a successful NBS strategy [1]. As a result of advances in disease-modifying therapy and screening techniques, the number of diseases included in NBS programs has expanded in recent decades. Many countries currently screen for more than 10 disorders, most of them are inborn errors of metabolism. With the introduction of intravenous enzyme replacement therapy (ERT) for several lysosomal storage disorders (LSDs), the inclusion of these

LSDs in NBS programs became a topic of discussion [2–5]. These disorders include Fabry disease (FD), the subject of this study.

FD, an X-linked LSD, is caused by a deficiency of the lysosomal hydrolase alpha-galactosidase A, which leads to globotriaosylceramide (Gb3) accumulation in many cell types [6]. FD usually presents during childhood with severe pain in the hands and feet (acroparesthesia) and gastrointestinal symptoms [7]. Disease progression may result in renal, cardiac and neurological disease with severe morbidity and reduced life expectancy in adults [8]. The diagnosis is often not established until adulthood because of nonspecific signs and symptoms and the rarity of the disease [9–11]. FD treatment was only symptomatic until in 2001, when disease-modifying treatment with ERT became available. ERT was shown to reduce tissue Gb3 and stabilize renal and cardiac disease [8,12,13], however, disease progression despite therapy has also been observed [14–16]. Recent studies suggest that early initiation of treatment might improve efficacy [14,17], however, the optimal timing of enzyme replacement therapy has not been elucidated.

Furthermore, there is a lack of well-established biomarkers for disease severity and progression, although progress has been made recently [18]. This, combined with a poor genotype–phenotype correlation, hampers predictions about the course of the disease.

*Abbreviations:* FD, Fabry disease; NBS, newborn screening; ERT, enzyme replacement therapy; LSD, lysosomal storage disorder.

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To date, the debate about the potential benefits and drawbacks of FD screening has focused on technical aspects and expert opinions. A number of studies have focused on the feasibility of NBS for FD, including studies analyzing enzyme activity in dried blood spots [19–26]. This resulted in three pilot studies of NBS for FD, in which an unexpectedly high number of newborns with low enzyme activity and mutations in the GLA gene were identified, presumably as a result of detecting later-onset FD [27–29].

Until now, the opinions of FD patients have not been taken into account in studies and commentaries about screening for FD. The importance of exploring the opinions of patients and their families about the expansion of NBS programs has been demonstrated in several studies on cystic fibrosis, Duchenne's muscular dystrophy, mucopolysaccharidoses and 22q11 deletion syndrome for example [30–34]. These studies invariably indicate that patients and their parents are highly supportive of the inclusion of a disease in NBS programs. Because we know from the literature that patients' attitudes towards genetic testing do not necessarily reflect their actual behavior [35,36], investigating patients' experiences rather than their opinions may thus provide valuable input for the discussion of expanding NBS to include FD.

Therefore, we conducted an interview-based study to explore FD patients' experiences, focusing on the timing of their diagnosis, with the primary goal to identify important patient-oriented themes relevant to discussions about the need for newborn screening (NBS) for this disorder to fuel that discussion.

## 2. Materials and methods

### 2.1. Patients

This study was conducted at the Academic Medical Center (AMC) in Amsterdam, the national referral center for patients with FD in the Netherlands.

Patients were recruited by one of the authors (MGB), an MD involved in clinical care of children with FD and FD-related research. The patients received an information letter explaining the study's aim and the voluntary nature of the interviews. For this study, we randomly approached patients throughout the entire spectrum of the disease, to include both males and females, asymptomatic, mildly and severely affected patients. In addition, we included patients who were diagnosed early as a result of family screening as well as patients diagnosed after a considerable delay. When patients were younger than 18 years, their parents (all parents being also patients) were also interviewed. The study was approved by the Medical Ethical Committee of the AMC.

### 2.2. Data collection

Semi-structured interviews were conducted between September 2009 and January 2010. All interviews were conducted by a single researcher (MGB) who was trained in qualitative research methods. The interviews took place either at the patient's home or at the hospital, depending on the patient's preferences. Each interview lasted approximately 30 min. At the beginning of the interview, the voluntary nature of participation was emphasized, and patients were informed that the interview would be completely confidential and anonymously analyzed. A topic list (Table 1) was used to guide the interview. The questions were open-ended, and the interviewer encouraged the patients to share their experiences. The interviewer kept field notes describing the interview setting and other reflections to facilitate reproducing the interview context. All interviews were audiorecorded.

After the first six interviews, the patient information letter and topic list were adjusted, to emphasize our special interest in the patients' personal experiences, rather than their opinions about NBS for FD. In

**Table 1**  
Topic list for interviews.

A. Introduction by researcher
– Emphasis on voluntary participation
– Emphasis on confidentiality
– Short explanation aim of the study
B. Open ended questions
– Report on course of disease
– How was the timing of diagnosis experienced?
– What were the benefits or disadvantages of the timing of your diagnosis of FD?
– How do you experience the burden of the disease?
– How did you experience the period before diagnosis?
– What if diagnosis would have been earlier/later?

addition, we noticed that the topic list was difficult for young teenagers to reflect upon; therefore we decided to include only patients aged of 16 years and older from that point forward. We enrolled patients in the study until we felt that no new information related to the research question was obtained. The last five interviews were analyzed specifically to determine whether they provided new insights.

### 2.3. Data analysis

SPSS Version 16.0 was used to calculate descriptive statistics of patients' characteristics. Data are presented as medians with ranges.

The interviews were audiorecorded and transcribed. The transcripts were uploaded in MAXqda 10 ([www.maxqda.com](http://www.maxqda.com)), a software program for qualitative research analysis. Five interviews were openly coded by two researchers independently (MGB and MHdeR, pediatrician). MGB performed axial coding to develop a code tree [37]. After that, the codes were used to identify the main themes most relevant to the research question. These steps were discussed with three other researchers (GEL, internist-endocrinologist/FD expert; FAW, pediatrician/FD expert; and MCBvZ, medical ethicist/qualitative researcher). Six themes were identified, and they are presented in the Results section.

### 2.4. Results

Patient characteristics are summarized in Table 2. Thirty-two patients with FD were approached, and 30 were interviewed (13 males, 17 females). Two patients, aged 16 and 54 years, were not willing to participate because of lack of interest and lack of time, respectively. The median age of the participating patients at time of

**Table 2**  
Characteristics of FD patients.

	n (%)
Gender, male	13 (43%)
Age (range)	43 (12–68)
Treatment with ERT <sup>a</sup>	25 (83%)
MSSI (range) <sup>b</sup>	13.5 (0–37)
Age at diagnosis (range)	25.5 (5–55)
Symptoms pre-diagnosis	23 (77%)
Age at onset symptoms (range)	8 (3–40)
Physician consulted for symptoms	15 (65%)
Time from symptoms to diagnosis in years (range)	13 (0–39)
Diagnosis through family	17 (57%)
Diagnosis following analysis of symptoms	9 (30%)
Diagnosis 'by chance'	4 (13%)

Data are medians and ranges.

<sup>a</sup> ERT: enzyme replacement therapy.

<sup>b</sup> MSSI: Mainz severity score index, pre- treatment with ERT.

the study was 43 years (range: 12 to 68 years). Five children were interviewed, including three patients under the age of 16 years. Of four children, the affected parents were interviewed as well (see Table 3).

Seventeen patients, mostly females (n = 12), had been diagnosed with family screening, after a family member's FD diagnosis. Nine patients, predominantly males (n = 7), were diagnosed with FD as a result of the diagnostic workup based on clinical signs and symptoms of FD. The remaining four patients had been diagnosed by chance (see Tables 2 and 3, patients 12, 14, 15 and 17).

The patients were diagnosed with FD at a median age of 25.5 years (range: 5 to 55 years). The majority of patients had experienced FD-related symptoms before diagnosis (n = 23, 77%). The median time between the onset of symptoms and diagnosis was 13 years (range: 0 to 39 years). Sixteen patients experienced a diagnostic delay of more than five years. Within this group, the perceived severity of symptoms varied from mild (n = 9) to severe (n = 7). The patients who were diagnosed presymptomatically (n = 7) were all diagnosed through family screening and were mostly females (n = 6) (see Table 3).

From the qualitative analysis, we identified six themes relevant to the aim of this study. These themes were (1) feeling misunderstood, (2) misdiagnosed, (3) reproductive planning, (4) medicalization and labeling, (5) anticipating the future, and (6) preventing disease progression with treatment.

#### 2.4.1. Feeling misunderstood

From the interviews, a vivid picture emerged of the impact of growing up with severe and unrecognized clinical symptoms. In general, the patients with severe symptoms and a delayed diagnosis (n = 7) reported that their symptoms, mainly consisting of acroparesthesia, fatigue and heat intolerance, were misunderstood and not taken seriously by parents, physicians and teachers at

school. The patients were frequently told that they “were being overdramatic”.

*“Yes, pain, pain, pain, pain, hands, legs, feet. It's been that way since childhood. When I was about four or five years old, the pain started, and it never really disappeared. Back then, it felt so extreme, it seemed there was no way out. (...) If I had been diagnosed earlier, I would have been able to say: 'this is what I have and, yes, this is happening to me', and there would have been a lot more understanding from others. I would not have had to battle against everything; it would have made things much easier.”*

[(Resp. #13, male with FD)]

*“And they thought I was being overdramatic. (...) I was in such pain and asked for a painkiller, but I did not get it because they didn't know what was wrong with me and thought I was just acting like a baby.”*

[(Resp. #25, male with FD)]

*“And then, at some point, people would say – if I had to go cycling or play handball – I used to play handball – and then every time I'd be in pain and people would say: 'stop being so over dramatic. That's impossible; five minutes ago you were just fine.' You know, like that.”*

[(Resp. #17, female with FD)]

These experiences of feeling misunderstood affected patients' self-esteem:

*“I mean, if people constantly think you're being overly dramatic or just trying to get attention, you yourself start believing you're a little strange, and I think that really affects your self-esteem. On the other hand I think it makes you a fighter.”*

[(Resp. #27, female with FD)]

**Table 3**  
Overview of participants.

Resp.	Age diagnosis	Age symptoms	Gender	Diagnosis	Symptoms pre-diagnosis	Mutation
1	5	–	Male	Family	Presymptomatic diagnosis	F18S
2	5	5	Male	Family	Acroparesthesia	R342Q
3	8	3	Male	Family (mother with FD, resp 10)	Acroparesthesia	p.Asn53fs
4	10	–	Female	Family	Presymptomatic diagnosis	R227Q
5	10	–	Female	Family	Presymptomatic diagnosis	IVS6-2(a>t)
6	11	8	Male	Symptoms	Severe angiokeratoma	R342Q
7	11	5	Male	Symptoms	Acroparesthesia	p.Leu268Ser
8	11	11	Female	Family	Acroparesthesia	p.Tyr134MetfsX31
9	13	–	Female	Family	Presymptomatic diagnosis	F18S
10	15	–	Female	Family	Presymptomatic diagnosis	p.Asn53fs
11	17	3	Female	Family (mother, resp. 24)	Mild acroparesthesia and nausea	L243X
12	18	6	Female	By chance (cornea verticillata)	Acroparesthesia and anhydrosis	R301X
13	18	4	Male	Symptoms	Severe acroparesthesia	W226X
14	18	10	Male	By chance (cornea verticillata)	Acroparesthesia and anhydrosis	R342Q
15	26	15	Male	By chance (cornea verticillata)	Acroparesthesia	E358 frameshift
16	25	3	Male	Symptoms	Angiokeratoma, acroparesthesia	p.Ile319LeufsX10
17	26	10	Female	By chance (renal biopsy glomeronephritis)	Acroparesthesias	C202W
18	29	29	Female	Symptoms	Skin lesions, recognized from father with FD	p.Leu347Phefs28
19	29	3	Female	Family	Mild acroparesthesia pre-diagnosis	R342Q
20	34	20	Female	Family	Mild acroparesthesia during deliveries and fever	R227X
21	35	7	Male	Family	Acroparesthesia	Q416X
22	37	–	Female	Family	Presymptomatic diagnosis	F18S
23	39	?	Female	Family (son, resp. 6)	Mild acroparesthesia, palpitations and dizziness	R342Q
24	40	40	Female	Symptoms	Cardiac complaints	L243X
25	40	8	Male	Symptoms	Severe acroparesthesia	IVS6-2(a>t)
26	41	–	Female	Family (son, resp. 7)	Presymptomatic diagnosis	p.Leu268Ser
27	44	10	Female	Family	Acroparesthesia, CVA, LVH	D136Y
28	49	–	Male	Symptoms	Atypical poly-neuropathy	R122H
29	51	12	Male	Symptoms	Acroparesthesia, renal failure	R342Q
30	55	–	Female	Family	Presymptomatic diagnosis	R227X

#### 2.4.2. Misdiagnosed

Patients with severe symptoms were frequently seen by different doctors and admitted to hospitals before the correct diagnosis was made. Misdiagnoses were common and included juvenile rheumatoid arthritis, muscular dystrophy and infectious mononucleosis. In addition, symptoms were often attributed to psychological problems instead of somatic diseases. When the correct diagnosis was finally made, the patients generally felt relieved to have their symptoms acknowledged. These patients felt that an earlier diagnosis “would have made things much easier”.

*“I have always been in and out of hospitals, but they were never able to determine what it was. Yes, I have been treated by different physicians and GPs and they always said it was all in my mind. But, well, that appeared not to be the case.”*

[(Resp. #13, male with FD)]

*“Yes, and what I was predominantly told was that it was all in my head. And my hearing started to deteriorate. And, well, there were many things that they were unable to comprehend or thought were purely psychological. (...) And that is why it was so comforting to see all the symptoms listed, as it made me think, all right, they all belong together. Yes, all of this is because of the disease. Yes, for me, it was more comforting than thinking it was all just randomly happening to me.”*

[(Resp. #27, female with FD)]

*“Well, that is very frustrating. That's why, at a certain point, we said we're not going to the hospital anymore, because he gets weighed and measured and asked how he's doing. Well then usually everything's fine, it's always like that ... And then you think, 'Well here I am again.' And well, what's the point, if nobody seems to know what he has? And in retrospect I understand, I mean it's so rare, they hadn't seen it before. But it's very frustrating. And we also started to get a little anxious, like I just said; 'Here we are again with our child.'”*

[(Resp. #26, female with FD, mother of Resp. #7)]

However, patients who were only mildly symptomatic before diagnosis and were diagnosed five years or more after the onset of symptoms ( $n = 9$ ) had never visited a doctor because of these symptoms. They only had experienced mild acroparesthesia during fever or exercise. They had never felt worried because of these symptoms and considered these symptoms as either “normal” or due to “growing pains” or “muscle pain”. Some patients had recognized that these symptoms were also present in other family members. These patients did not experience any limitations as a result of these symptoms.

*“Yes, the pain and not being able to sweat, but I cannot remember being worried so much about why I have it while others don't. It was just what it was. And my uncle had it too, so I wasn't the only one.”*

[(Resp. #14, male with FD)]

*“If I didn't have the flu or a cold or something like that, I didn't notice it much, because I was able to play sports and do everything. Yes, go out and so on: that wasn't a problem. (...) Because, well, for me, it didn't affect my health. I could do everything anyone else could do. So I wasn't much hindered, either with my studies or, later on, with work.”*

[(Resp. #15, male with FD)]

#### 2.4.3. Medicalization and labeling

Females who were diagnosed presymptomatically with FD as a children ( $n = 4$ ) grew up with the knowledge that they were only “carriers”, as that was the belief about FD at that time. Generally

speaking, this knowledge did not have any major impact on their lives other than their reproductive choices. However, several female patients reported having negative experiences as a result of being diagnosed presymptomatically with FD. They felt that they were “being labeled as a patient”, when they had no symptoms at all.

*“I very much got the feeling I was immediately labeled as a patient, and I really didn't like that. I got the feeling that I was being labeled from a medical point of view.”*

[(Resp. #4, female with FD)]

In addition, they felt that the diagnosis and the enrollment in follow-up protocols had made them feel ill.

*“I feel like I've been filed along with other Fabry patients; that is how I feel. Well, if you say to me: 'You are a Fabry patient, I will say: 'Well, I'm not'. But that is how you are treated. You have to undergo all kinds of tests, fill in questionnaires and discuss things, while it all just seems so irrelevant for me, like I have to sit and wait until something goes wrong. And that's a feeling I don't like. Why should I be subjected to MRI scans every year? It makes me feel so ... it almost makes me feel sick. (...) So, as far as I'm concerned, I'm glad I didn't know before now, because I have been healthy all my life, and still am, actually. So, because you cannot prepare yourself for it, there isn't anything you can do to prevent things from happening. So yeah, that makes it difficult. What would be the benefit of knowing early on?”*

[(Resp. #26, female with FD)]

*“Well, how can I explain it? As far as I am concerned, I didn't need to know yet, because it made a really big impact on my life. For me, it could have been 20 years later. Because then you ... you receive a lot of information, and you're really confronted with what you've got. Because I ... well, then you become aware of the fact that you have something that will cause certain limitations in life. (...) And well, I think that what I'm experiencing now is less severe than I initially anticipated.”*

[(Resp. #22, female with FD)]

#### 2.4.4. Reproductive planning

Overall, patients' experiences with making reproductive choices were diverse. Half of the patients with children were aware that they had FD when they decided to have children and were thus able to make reproductive choices. One patient described the difficulty and impact of making reproductive choices.

*“Well, I was aware of the fact that I'm a carrier of Fabry disease. I would, by definition, pass it on. The consequences of that — how does one make a decision? And should people be informed? (...) I think that is something; I would say the impact of that is even greater than the impact of the diagnosis, being a carrier and how to deal with it. And informing people adequately, because these are delicate matters. (...) It did have an impact on the joy of having a girl, because, well, although she is a carrier, she will not be affected negatively by it. And for me, it also played a part in my thinking, would I want more children? Well no, I would rather not, because there is a chance that it might be a boy, with all its negative implications.”*

[(Resp. #4, female with FD)]

For two interviewed patients, the hereditary nature of their disease was a reason to have no biological children at all.

*“Then I decided, I would not have more children. Yes, that still bothers me a lot, because all around me women are getting pregnant. (...) Because I knew what my father had been through. And he eventually died from it, so yeah, I thought, not for me. Then I would rather have a life without children.”*

[(Resp. #18, female with FD)]

*“No, that’s what I said the moment I was diagnosed, that is a closed chapter for me. If it stops somewhere ... well, I just don’t want to pass it on through me. I’m aware of all the negative effects, and I could not bear to put another child on this earth with possibly the same problem. I myself know how one can be hampered in life and I don’t want to inflict the same on somebody else.”*

[(Resp. #13, male with FD)]

One interviewed patient decided to have no more children when both her children appeared to have FD.

*“Yes, the question of how many children you want and how much you can handle ... For me, now that I know I have two children with Fabry disease, we decided that two is enough. Because I have Fabry disease myself, I have been able to make a choice.”*

[(Resp. #8, female with FD)]

However, most of the patients, especially the males, just decided to have children without taking any specific measures, e.g., prenatal testing.

*“No, but I can remember that, yes. But you are not so aware of what it really is and I didn’t have any complaints. Yes, and at that time there was not much that could be done so, well, it became something we knew, but didn’t do anything about it. And I knew that if I were to become pregnant genetic testing would have been an option, but I didn’t do that either.”*

[(Resp. #10, female with FD)]

Some patients did decide to perform prenatal testing, and for one interviewed patient, it resulted in the termination of a pregnancy with an affected male fetus.

*“And then I got pregnant, and they needed to do an amniotic fluid test. We had decided beforehand that if it was a boy, we would terminate the pregnancy. Because I could just see my father and I wouldn’t wish that kind of life for my child. And at the same time I didn’t think it would ever happen to me. They had to induce labor, because it was too late for an abortion, of course. (...) Yes, I had many sleepless nights, but, well, life goes on. And I was also very happy. Because I’ve actually never regretted doing it.”*

[(Resp. #9, female with FD)]

In contrast, some patients who were not aware that they had FD before they had children were relieved to be ignorant at when their children were conceived.

*“On the one hand I think how fortunate I am that I was not aware I had Fabry disease before I had children, because I do not know what decision I would have made. There would have been the dilemma and feelings of guilt that you had possibly passed it on to your child and now I, well, now I just didn’t know. That makes you feel less guilty, I think.”*

[(Resp. #20, female with FD)]

#### 2.4.5. Anticipating the future

When the participants were asked about their views of the timing of their diagnosis and on the question what it would have meant for them if their diagnosis had been made earlier, the anticipation of the future was reported as both an advantage and disadvantage. Some patients felt that an “early” diagnosis made it possible to anticipate future FD-related problems, which allowed them to make choices in life.

*“Well, at least now I know what the future has in store for me, and what I have, and what I can take into account.”*

[(Resp. #5, female with FD)]

*“So you can make conscious decisions: What will I do in life? (...) I am a pharmacist now, so that is not so hard, but what if you have to do something else? (...) If it involves heavy physical activity, you will not be able to do it at a certain point in time. So that is why I feel it is of interest to know.”*

[(Resp. #2, male with FD)]

On the other hand, more patients indicated that a disadvantage of an early diagnosis was the loss of carefree life and increased worrying about the future.

*“Yes, because I have two boys (...) and because I was aware of the medical history in the family, and it’s like, well, this is what’s in store. My uncle had a couple of kidney transplants and he eventually died of heart failure (...) and then hearing the stories about my grandmother’s brothers - three of them I believe, dying at 35 years of age. Okay, we’re talking the turn of the last century of course, but it was disheartening to hear, all the same, and although knowledge of the disease has improved, you still think if you have to go through what my uncle went through, that’s not easy.”*

[(Resp. #20, female with FD)]

*“Other facts that surfaced with the diagnosis of Fabry disease, well, they scare me a little. I mean, if you look at the brain, the white matter lesions are increasing. The cardiac muscle is enlarged, hearing deteriorates. Well, I don’t know if I would have wanted to be made aware of all that earlier.”*

[(Resp. #29, male with FD)]

In addition, some parents reported that not knowing their child had the disease was a positive experience.

*“Well, I think that there was a certain kind of peace while raising our children ... that there was a time when we were more calm. Because since diagnosis, well, things have changed. So in that respect, life was carefree for many years.”*

[(Resp. #24, female with FD)]

*“Well, we didn’t know, and thus he was able to grow up as a normal boy without a medical history. For us as parents and for him as a child, I think it was a carefree childhood, but I don’t know how things would have been if he had known since birth and how we would have responded to that. (...) But I still appreciate the time we had without knowing.”*

[(Resp. # 23, parent of Resp. #6 with FD)]

Worrying about the future was also mentioned in relation to the heterogeneity of the disease and the insecurity of the diagnosis.

*“And there are a lot of people like me, who may have some complaints, but are nonetheless capable of living a rather normal life. And there are some who are severely affected and have a lot more difficulty coping with it. You just have to wait and see in which category you end up.”*

[(Resp. #14, male with FD)]

#### 2.4.6. Preventing disease progression with treatment

Most patients mentioned early treatment and the prevention of complications as an important advantage of an early diagnosis. They felt that complications might have been prevented if they would have been treated earlier.

*“Well, concerning treatment and all. Yes, I may not have fallen into some kind of limbo; then things may have been different, yes. Yes, things may have been a lot easier and maybe I wouldn’t have been*

*as severely physically affected as I am now. But well, that's all in retrospect, because you just don't know for sure."*

[(Resp. #13, male with FD)]

However, patients' experiences also illustrate the uncertainty about treatment efficacy.

*"Yes, there are still many uncertainties surrounding Fabry disease. Then, at a certain point, there were also doubts about the effectiveness of the treatment. Well, then you wonder if it's worth getting hooked up to an intravenous drip every two weeks if there are so many doubts? Why should I keep doing that? But, well, you don't know what the impact would be if you didn't take the treatment, what that would mean in the long run. But well, those are things that I think about regularly; you know, should I continue?"*

[(Resp. #15, male with FD)]

In addition, the benefit of early treatment was weighed against the possible burden of treatment.

*"Maybe, but then we're heading into treatment territory; maybe you'll be able to prevent damage to the organs. I see that as an advantage. But on the other hand, the question is: should you start at an early age? Because it is quite a burden, every two weeks."*

[(Resp. #15, male with FD)]

### 3. Discussion

In this study, we explored FD patients' experiences with the timing of their diagnosis, with the primary aim of identifying relevant themes to fuel the discussion about expanding NBS programs to include FD. We used a qualitative, open approach and interviewed 30 patients with FD. The interview analysis revealed six relevant themes. This study illuminates the impact of a delayed diagnosis on some severely affected patients, who felt misunderstood and were misdiagnosed. On the other hand, the study also illustrates the drawback of a presymptomatic diagnosis for some patients, who felt labeled and overmedicalized. Though an early diagnosis was seen as an advantage for anticipation of the future, increased worrying was also frequently noted as a disadvantage. Finally, the possible prevention of FD complications with adequate, timely treatment was considered as an important reason to receive an early diagnosis; however, the respondents also mentioned the uncertainty of treatment efficacy as an important factor. Overall, the interviewed patients' experiences varied remarkably.

A delay between the onset of symptoms and diagnosis was common in the studied patients (mean delay: 14.0 years  $\pm$  13.0 for males; 14.4  $\pm$  12.2 for females) and was comparable to the delay described in 194 index patients in the Fabry Outcome Survey (mean delay: 13.7  $\pm$  12.7 years for males; 16.3  $\pm$  14.7 for females) [11]. Similar results are obtained from another Fabry disease postmarketing registry (14.2  $\pm$  13 and 15.7  $\pm$  14.8 in 778 males and 473 females respectively) [38]. The results of our study once again demonstrate the significant impact of a diagnostic delay, which by Hayes and co-workers also reported for patients with mucopolysaccharidoses (MPS), another LSD [30]. It is important to note however, that the negative experiences in our study seemed to depend on the severity of symptoms before diagnosis in a subset of patients. Approximately half of the patients with a delay in diagnosis did not visit a doctor for their FD-related symptoms and did not report limitations caused by these symptoms. It is of interest that some patients did not regard their symptoms as 'abnormal', because some family members experienced the same symptoms.

The themes identified in this interview study highlight important patient perceptions about the timing of the FD diagnosis, and reflect the heterogeneity of the disease. Females were formerly labeled as "carriers", based on the X-linked mode of FD inheritance. In this study, for

females who grew up with this paradigm and were aware of their carrier status, this had few implications at that time, apart from reproductive planning. During the last decade, it has become clear that females can have significant disease-related symptoms, even to the same extent as male FD patients [38]. Consequently, females with FD are now included in follow up programs aimed at detecting early organ damage. Our results highlight the drawback of this approach, which may lead to medicalization and labeling in asymptomatic patients. Furthermore, a frequently mentioned disadvantage of an early diagnosis was the loss of a carefree life and increased anxiety about the future.

The lack of routinely applied biomarkers and the poor genotype-phenotype correlation of FD, which has numerous private mutations and variable disease severity even within families, generally preclude the prediction of the disease course in individual patients. Consequently, asymptomatic patients diagnosed with FD do not know what to expect, which may enhance anxiety. Previous experiences in recently expanded NBS programs, e.g., medium-chain acyl-CoA dehydrogenase deficiency [39], and the aforementioned results of NBS for FD [27–29], have shown that a large number of individuals with presumed mild mutations or novel missense changes of unknown clinical significance will be diagnosed through NBS. The potential burden of a presymptomatic FD diagnosis needs to be weighed carefully against the benefits of early access to treatment. This again emphasizes the importance of studies aimed at predicting the FD phenotype, enabling the identification of those patients who will benefit most from early treatment.

Previous reports on the opinions of parents and patients with other diseases on NBS reveal some similarities to our study results. Detmar et al., found that the availability of "medical treatment options" was the most commonly cited argument favoring the expansion of NBS programs in focus group discussions of parents-to-be, parents of healthy children and parents of patients with CF, PKU and Duchenne muscular dystrophy. This indicates the relevance of this criterion in deciding if NBS is desirable for a certain condition [40]. In contrast, even in the absence of treatment, Hayes et al., demonstrated that the majority of parents were in favor of NBS for MPS [30] and a majority of expectant parents from the Netherlands were in favor of screening childhood-onset disorders, regardless of the disease's treatability [41]. Although in our study, treatment opportunities and the prevention of complications emerged as important arguments in favor of an early diagnosis, patients also reported uncertainty about treatment efficacy. In addition, patients weighed the benefits of treatment against the invasiveness of receiving intravenous medication every other week.

For this study, the patients were randomly selected based on planned visits at the clinic. Although we ensured that the included patients represented the entire spectrum of the disease, we cannot be certain that the results covered all the experiences of FD patients. However, because only two patients declined participation, the likelihood of bias in the selection of participants seems negligible.

### 4. Conclusion

This is the first study to examine the experiences and reflections of FD patients in relation to the timing of their diagnosis. Important, divergent themes were identified, reflecting both the phenotypic heterogeneity of the disease and the substantial differences in experiences between patients with and without FD symptoms before diagnosis and among the patients within each group. These results are highly relevant to the current discussion about NBS programs, because they present considerable nuances that must be incorporated into the debate about whether FD should be included in NBS programs.

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