FABRY DISEASE: STUDIES ON DIAGNOSIS, SCREENING AND PATIENTS' PERSPECTIVES Machtelt G. Bouwman

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CONTENTS

11

PATIENTS' AND PROFESSIONALS' OPINIONS ON NEWBORN SCREENING FOR FABRY DISEASE: A FOCUS GROUP STUDY

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Submitted

ABSTRACT

Decision policies on the advisability of including a condition in newborn screening (NBS) programs, are complex and require a careful weighing of potential benefits and harms. The aim of this study was to provide an overview of the different opinions of various involved parties regarding the inclusion of Fabry disease (FD) in NBS programs.

We conducted focus group discussions with representatives of three groups: FD experts, FD patients and ethicists. Firstly, focus group discussions were held with the three separate groups. This was followed by focus group discussions with three groups in which the participants were randomly mixed. All discussions were recorded, transcribed and analyzed, resulting in an overview of the most important arguments shared by the focus group participants.

All participants recognized the importance of early FD diagnosis, especially in symptomatic patients; however, the general opinion in all of the focus groups was that at this moment, it is too early to include FD in NBS programs due to a lack of knowledge of several crucial issues. All of the participants emphasized that the current inability to predict the severity and course of the disease in asymptomatic patients, in combination with a lack of knowledge regarding the optimal timing of treatment and the efficacy of treatment, strongly argue against inclusion of FD in NBS programs.

Although the aim of this study was not to reach a consensus, all participants showed significant agreement. Arguments considered to be crucial for the discussion on the inclusion of FD in NBS programs were identified. The key issues that were identified in this study require further study in order to allow a careful weighing of the potential benefits and harms of NBS programs for FD in the future.

INTRODUCTION

Newborn population screening (NBS) was implemented in the late 1960's to identify infants who appear healthy at birth, but have diseases that may cause severe morbidity or even death if left untreated. Phenylketonuria was the first disorder to be implemented in NBS and, to date, is a primary example of a successful screening program because early dietary intervention prevents severe cognitive impairment in children suffering from this condition[1]. Technological and therapeutic progress has resulted in rapid expansion of screening programs over the course of the last decade. Wilson and Jungners' screening criteria have long been used to determine which diseases should be implemented in NBS programs [2]; however there is currently an intense debate regarding the inclusion of diseases for which disease modifying treatment is less effective or even absent, such as cystic fibrosis and Duchenne muscular dystrophy [3-6].

In recent decades, the prognosis of patients with several lysosomal storage disorders (LSDs) have significantly improved due to advances in supportive care and the availability of disease-specific treatment by enzyme replacement therapy (ERT). Treatment appears to be more effective when initiated before organ damage has evolved; however the recognition of early signs and symptoms can be difficult. This issue has directed studies into the feasibility and advisability of including these LSDs in NBS programs.

Fabry disease (FD), which is an X-linked LSD, is caused by a deficiency of alpha-galactosidase A [7]. FD males usually develop symptoms during childhood or adolescence, and, in adulthood, disease progression is associated with renal, cardiac and neurological morbidity. Disease modifying treatment has become available since 2001 with the development of ERT[8;9]. Unfortunately, in many patients, disease progression is observed despite therapy [10-12].This might be due to limitations of the treatment itself, but some studies have shown that organ damage present before the initiation of treatment may also be an important factor[13;14]. Therefore, it is suggested that treatment should be initiated early and at least before the development of irreversible pathology. Unfortunately, the rarity of the disease in addition to the insidious onset of the disease with nonspecific symptoms often preclude the early diagnosis of FD [15]; hence, NBS for FD may be of great benefit by allowing pre-symptomatic diagnosis. Moreover, three pilot-studies, two in Taiwan and one in Italy [16-18], have addressed the feasibility of this approach. A remarkable high prevalence of up to 1 in 1250 screened newborn males with a low enzyme activity was detected. In all three studies, subsequent mutation analysis revealed mutations that were presumably associated with a later onset disease.

Determining whether a condition can be recommended for inclusion in NBS programs, is a complex process that requires a careful weighing of potential benefits and harms. The aim of this study was to provide an overview of the different opinions of several participating parties, with the intent to enrich the

ethical discussion of whether FD should be included in NBS programs. Therefore, we conducted focus group discussions with representatives of the three most important groups of stakeholders in this matter: FD experts, FD patients and ethicists.

METHODS

We used a qualitative focus group discussions study design to explore the various opinions of NBS for FD. Focus group discussions were used as we expected that group interaction would lead to a more consistent identification of all of the pertinent arguments.

Focus group participants

Three groups of participants were invited: (i) international FD experts (n=6), (ii) international specialists in the field of health policy, law and ethics (n=6) and (iii) Dutch FD patients (n=6) (see Table 1). Participants were approached by three authors of this study (GL, FW, MZ) and were selected through their network. FD experts consisted of pediatricians, clinical geneticists, an internist and a biochemist, and all participants had a broad experience with FD. Because the number of FD experts worldwide is small due to the rarity of the disease, one co-author (FW) also participated in the FD expert group; however, to prevent a conflict of interest, he was not involved in the analysis of the data presented here. The second group, specialists in law and ethicists consisted of individuals with special expertise and interest in the field of NBS. In the patient group, two members of the Dutch Fabry patient organization participated (Fabry Support en Informatie Groep Nederland, FSIGN). The other patients were selected based on their ability to reflect on the subject and to discuss in English. Participation was voluntary and no honoraria were provided. International participants received travel

Table 1. Participant characteristics.

Fabry experts (n=6)	n
Gender	
Male	4
Female	2
Nationality	
Dutch	3
Non-Dutch	3
Specialty	
Internist	1
Pediatrician	2
Clinical Geneticist	2
Biochemist	1
Ethicists (n=6)	N
Gender	
Male	3
Female	3
Nationality	
Dutch	4
Non-Dutch	2
Specialty	
Health law	1
Community genetics	1
Ethics	2
Ethics of communication	1
Ethical aspects of genetics	1
Fabry patients (n=6)	N
Gender	
Male	2
Female	4
Nationality	
Dutch	6
Non-Dutch	0

and accommodation expenses. All participants received one review article on FD and one article on the screening of high risk populations, as an introduction to the discussion [19;20].

Focus group discussions

Six focus group discussions were conducted on a single day (May 13th 2011) at the Academic Medical Center (AMC) in Amsterdam. Each discussion session was facilitated by one moderator (MvZ, ethicist/qualitative researcher; GEL, internist-endocrinologist/FD expert, and MGB, physician/ FD researcher, respectively). The task of the moderator was to encourage all of the participants to engage in the discussion and to share their views. One observer per group took notes during the discussions and assisted the moderator if necessary.

Figure 1 depicts an overview of the proceedings of the day. During a plenary meeting the aims of the focus group meeting were once again explained and additional background information on FD was provided, including information on the prevalence, clinical manifestations and results from pilot studies on NBS. It was emphasized that the aim of the meeting was not to reach consensus on NBS for FD, but rather to explore different opinions. Participants consented to

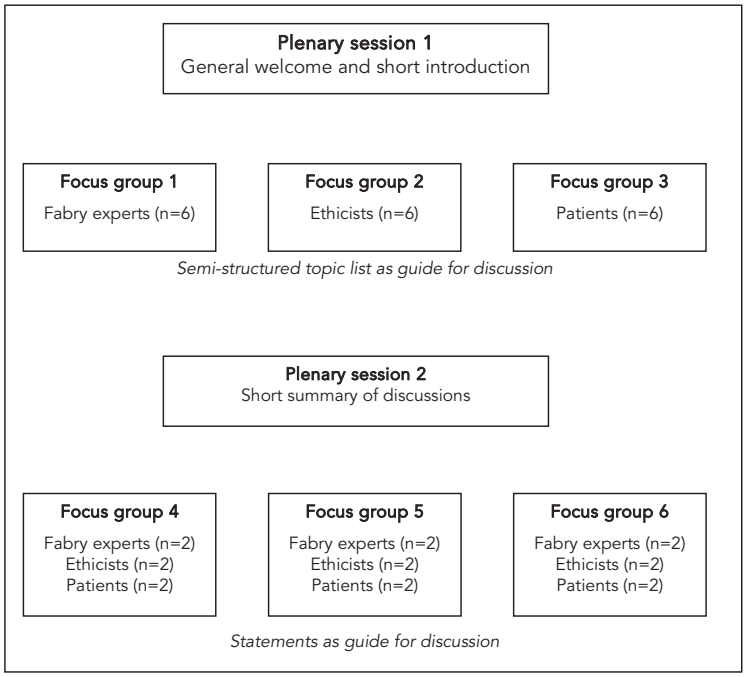

Figure 1. Overview of the program.

audio-recording of the discussions . Subsequently, three focus group discussions were conducted with the three groups of experts separately (FD experts, ethicists and FD patients). Discussions lasted approximately two hours. In a second plenary meeting the three observers briefly shared with the entire group what was discussed in the separate focus groups. This was followed by three focus group sessions, now in new, mixed settings. Each group then included two FD experts, two ethicists and two patients. These focus group discussions lasted approximately 1.5 hours. Apart from the focus group discussions in the morning with (Dutch) patients, all discussions were held in English.

A semi-structured topic-list was used during the discussions in the morning (Table 2). For the afternoon program, moderators and observers formulated five statements, based on what was discussed in the morning, as input for the mixed focus group discussions (Table 3).

Table 2. Topic list for focus group discussions.

Introduction
Introduction round
Approval audiorecording of meeting
Confidentiality
Check on knowledge on neonatal screening (patient group)
Open ended questions
General attitude towards neonatal screening Fabry disease
Expected advantages of screening for Fabry disease
Delay in diagnosis
Psychological impact delay diagnosis
Early treatment
Prevention/delay of complications
Reproductive choices
Expected disadvantages of neonatal screening Fabry disease
Pre-symptomatic diagnosis
Detection patients with a mild phenotype
Efficacy of treatment
Invasive treatment
Stigmatisation
False positives
Missing 1/3th of female patients

Table 3. Statements used as input for the mixed focus group discussions.

1) Increasing awareness of FD amongst physicians makes NBS unnecessary.
2) NBS should be performed to prevent a psychological impact of the delayed diagnosis.
3) NBS makes healthy individuals feel sick.
4) NBS should not be performed because the disease is very heterogeneous and prediction of phenotype is difficult.
5) Current treatment with ERT is efficacious enough to qualify as a treatable disease.

Data analysis

All recordings were transcribed verbatim. Summaries of the discussions were sent to all participants to determine the accuracy and completeness. The transcripts were uploaded in a software program for analysis of qualitative research (MAXqda10). All transcripts of the morning focus group sessions were openly coded by one researcher (MGB) and analysis was performed as described by Boeije *et al* [21]. All arguments in favor and against screening and the most frequently mentioned arguments were identified. These steps in the analysis were discussed with GEL and MvZ. The transcripts of the mixed focus group discussions were specifically analyzed to see whether new arguments were mentioned or other new insights were given.

Ethical considerations

The Medical Ethical Committee of our hospital declared that under Dutch law no approval was needed for this study. This study is part of the research project T6-208 'Sustainable Orphan Drug Development through Registries and Monitoring' at Top Institute Pharma in the Netherlands. None of the partners of this collaboration had any influence in the design of the study, analysis of the data or preparation of the manuscript.

RESULTS

In total the discussions generated 12 hours of recording. The quality of all of the recordings was adequate for analysis. In general, discussions were lively and all participants shared their views during the sessions. In all of the groups arguments both in favor of and against screening were expressed. All arguments that came forward in the three groups are listed in table 4. Overall, there was a clear consensus in the Fabry expert group as well as in the ethicist group that there are still insufficient data to justify NBS for FD. In general, in the Fabry expert group, pediatricians were more in favor of screening than the other medical specialists. In the focus group with only patients, there was less consensus. Besides FD-specific discussions, the general concerns of NBS, e.g., informed consent, the definition

Table 4. Arguments in favor and against NBS for FD.

Arguments in favour of NBS for FD	Arguments against NBS for FD
Fabry experts	
Importance of having a diagnosis when symptomatic	Difficulty predicting the phenotype *
Initiation of treatment before irreversible damage	Overdiagnosing and diagnosing late onset disease *
	Lack of evidence efficacy early treatment *
	Psychological medicalization
	Anxiety
	Cost treatment#
	Invasiveness treatment#
Ethicists	
Prevention of irreversible damage	Overdiagnosing and diagnosing late onset disease *
Prevention delay in diagnosis	Costs and invasiveness treatment
	Lack of evidence efficacy early treatment
	No good test with predictive value
	Little knowledge on natural history of mild phenotype
Fabry patients	
Being able to anticipate future problems *	Burden of a pre-symptomatic diagnosis *
Prevention delay in diagnosis *	Overdiagnosing and diagnosing late onset disease *
Prevention irreversible organ damage	Invasiveness treatment
Reproductive choices	Costs
	Stigmatisation (mortgages, insurances)

* Arguments most often expressed, # specifically considered a minor argument in the discussion.

of treatability and shifting of criteria for inclusion in NBS programs were discussed in all of the groups. These discussions are not further described.

We identified seven important themes from the qualitative analysis of the first three discussions: (1) difficulty of predicting the phenotype, (2) overdiagnosis and diagnosing late onset disease, (3) burden of a presymptomatic diagnosis, (4) importance of diagnosis in symptomatic patients, (5) lack of evidence regarding the efficacy of early treatment, (6) costs and invasiveness of treatment and (7) alternatives to NBS. These themes will be further described. In addition, the outcome of the mixed focus group discussions (focus groups 4-6) will be described.

1. Difficulty of predicting the phenotype

Both FD experts and ethicists mentioned that NBS would detect patients with new mutations with unclear clinical relevance. There was consensus in the Fabry expert group that the current difficulty in phenotype prediction is an important argument against NBS for FD. The need to be able to predict which patients would benefit from treatment, and preventing unnecessary burdensome treatment to others, was considered as very important.

> *"For me, that's one of the reasons why I would be very hesitant to say 'yes' to including Fabry disease at this moment. Because we are really bad at predicting the course of the disease in infants."* (focusgroup (FG) 1, paediatrician #1)

> *"So, as far as I am concerned, I would say: 'at least at this time it would be too early.' Because we need to know better whether the people detected, are actually the ones who are going to develop symptoms, as the group that is detected at birth is so much larger than the group that you know has symptoms and that have Fabry disease."* (FG 2, ethicist #1)

> *"It comes down to the fact that you cannot predict at an early stage who is going to be very sick, and if a treatment intervention is needed."* (FG 1, internist #1)

> *"One of the criteria, of course, is that it needs to be clear who needs to be treated when. If you would be able to tell quite specifically who, with what mutation, would have symptoms say before 10 years of age and who would need treatment also before 10 years or 5 years of age, then you might want to have 2 steps. First go to the enzyme and then go to the DNA and then tell exactly which children will have the severe form and then start treatment in those and then for the other ones maybe you wouldn't even want to report it initially. It's probably not that black and white."* (FG 2, ethicist # 2)

Some argued that detecting patients with unclear mutations is a common problem in NBS and is thus not specific for FD.

> *"But it is not rare in newborn screening to detect patients with new genotypes and unknown phenotypes. PKU was introduced in the early seventies and I think 30% of PKU patients have what we call hyperphenylalaninemia, which is generally not really a disease. They are just followed up and sometimes given very mild diets; essentially we really don't know what to do with them."* (FG 1, paediatrician #1)

Most FD experts agreed that if good predictors and biomarkers would be available, their opinion regarding the inclusion of FD in NBS could change favorably.

> *"In the ideal world, you could choose to have a crystal ball, when you are newborn, that says exactly what you are going to get in your life. But the problem today is that the crystal ball makes mistakes in 9 of 10 cases. (…) I mean if you have a perfect screen, that really could predict that this person is going to have Fabry disease and that it will really be Fabry disease, then it's okay."* (FG 1, clinical geneticist #2)

2. Overdiagnosis and diagnosing late onset disease

It was discussed in all of the groups that NBS may result in the diagnosis of patients with late onset disease and even in the identification of individuals who may never develop disease. Participants referred to the results of pilot screening studies on FD, where a high prevalence of presumed late onset disease was found [16-18].

> *"Also a question I have is, if previously we thought 1 in 40,000 was affected and now it's 1 in 3000, what does that mean exactly, because who comes out of the screening? Does it mean that a large group of people never develop symptoms? That could be the case and so you never see that they actually suffer from, well, have Fabry disease."* (FG 2, ethicist, #5)

> *"If it's clear that it prevents a lot of the symptoms from curing, then of course you have to do that, but if a large amount of people that you find by screening are actually not going to develop these symptoms or the symptoms are not very serious, then……."* (FG 2, ethicist #1)

A biochemist wondered whether an early diagnosis of an adult onset disease would really be beneficial to the patient.

> *"A patient, who develops an adult disease, is it really in the interest of the patient to know at day zero they will develop an adult disease. If you look at the wider spectrum he may not perhaps develop a disease at all."* (FG 1, biochemist #1)

Furthermore, the burden of the identification of individuals who will remain asymptomatic was considered to outweigh the burden of missing some patients that will end up with irreversible disease. In addition, this was weighed against the benefits of being able to make reproductive advantages.

> *"Selective high-risk screening is I think much more logical than neonatal screening, and to prevent a few patients from coming at a late and irreversible stage to your clinic, then you need to screen all patients and pick up all asymptomatic patients. That burden, in*

my view, doesn't outweigh the burden, how sad it is for the couple of patients that you miss and that end up with irreversible disease." (FG 1, internist # 1)

"*What you have to weigh is the possible disadvantage of the child knowing something that has no consequences, but that they weren't able to decide whether they wanted to know, against the reproductive advantages. That's a very complicated balance.*" (FG 2, ethicist # 4)

3. Burden of a presymptomatic diagnosis

The disadvantages of having a presymtomatic diagnosis were expressed, especially by FD experts and patients. Patients reflected on their own experience. The knowledge of having the disease while being asymptomatic was considered to be a burden by some of the participating patients.

"*I'm also concerned about my daughter, who is a carrier of the disease. It's always with you, even though she's a completely healthy girl, but you're always aware of it. When does she need to be treated, is she ill, is it related to Fabry – it's a double-edged sword. I'm not sure that it's a good thing to know what could, potentially, be coming.*" (FG 3, patient #1)

"*What affects me is that my mother was symptom free until the age of 70 and it was probably a good thing she didn't know better, because then we would have had that to worry about. When you screen and you suddenly detect 1 in 3,000 patients (…) and that may possibly be the group that never gets sick – a very, very large group – and yet they will have this hanging over their heads, as in, maybe they'll become ill. I find it creates quite a burden, also when I look at my two daughters, with everything you wonder, could it be Fabry? So I do find it creates a certain burden to be aware of it.*" (FG 3, patient #2)

FD experts mentioned that a presymptomatic diagnosis, if not guided correctly, may lead to medicalization and to increased anxiety and may result in falsely attributing symptoms to the diagnosis.

"*Knowing that there is a disease, even at the moment that there are no complaints, may result, if not guided correctly, in a lot of medicalization.*" (FG 1, pediatrician #1)

"*It creates a lot of anxiety and it may create explanations for all kinds of problems that they may have in life.*" (FG 1, clinical geneticist #1)

4. Importance of diagnosing symptomatic patients

In contrast to the burden of a presymptomatic diagnosis, the importance of a diagnosis for symptomatic patients was emphasized in both the FD expert- and patient group.

> *"And at the moment that symptoms present themselves it would have been nice if it had been diagnosed earlier because, well, especially the boys, at least for the first part of their youth, their puberty, they really missed out on that, due to being bedridden by the pain, by not being able to do anything, not being able to join in. That was really distressing."* (FG3, patient #5)

In relation to this, it was discussed that treatment with ERT is less effective when there is already irreversible damage.

> *"The main issue with these drugs is that, when started too late, it actually doesn't work properly and we are spending huge amounts of money on a drug that is not terribly effective in these patients. The incentive of diagnosing early and wanting to start early is actually in the best interest of the patient, because the idea is that you are trying to prevent an irreversible disease from progressing."* (FG1, pediatrician #2)

> *"Yes, well look, I'm an advocate for screening because I think, well, the sooner you know, the sooner it gives you some form of security. And if I relate that to my story and also what I've heard from other patients, um, yeah, the sooner you start the process and not wait for the consequences, the chances of leading a better life become increasingly greater than waiting for potential damage to happen."* (FG 3, patient #4)

5. Lack of evidence regarding efficacy of early treatment

There was agreement that treatment with ERT is less effective when irreversible damage is present. FD experts also agreed on the fact that currently there is not enough evidence to support early treatment preventing the occurrence of irreversible organ damage. FD experts concluded that there is currently insufficient evidence to justify pre-symptomatic treatment of FD patients. Although this was not one of the main themes in the ethicists group, it was mentioned that it is not clear yet at when treatment should be started.

> *"That point is always made when we talk about lysosomal storage disease: that we should identify the patients early. But in Fabry disease we really don't know if early diagnosis and early treatment will help prevent the complications later on in the disease."* (FG 1, biochemist #1)

"There is no convincing evidence at the moment yet, that if we start treatment presymptomatic we can really prevent disease, but there is circumstantial evidence from several countries that, if you can start earlier, you can delay the progression of the disease." (FG 1, internist #1)

"The treatment should also be needed then at an early stage and that's also the question: we don't know that either. So, also, there should be relevant treatment available. We may have that, but we don't know at what stage you would have to start." (FG 2, ethicist # 1)

6. Costs and invasiveness of treatment

The costs of ERT were mentioned as an issue in the discussion on NBS in all three groups. Ethicists and FD experts agreed that costs should be taken into consideration; however, FD experts explicitly mentioned that this is not a primary issue.

"It will be an issue, but it's not a primary issue for deciding on 'does this disease qualify for inclusion in newborn screening'." (FG 1, pediatrician #1)

Ethicists perceived the invasiveness of treatment as an important issue to be considered. FD experts agreed on this; however, they felt it does not weigh heavily on the discussion and in relation to the other topics, and, therefore, was considered to be a minor point.

"But even if it's not part of the criteria, it seems to be quite important, because giving treatments to people that is quite heavy on their lives; it's medicalising their lives." (FG 1, ethicist #1)

They felt that the overall experience is that patients get used to the treatment. Some patients agreed; however, others did express that it would be much easier, especially for children, if treatment would be in the form of an oral drug.

"The initial start is a burden, but after a while you get used to it." (FG 1, clinical geneticist #2)

"My feelings are torn, I must say. Look, when I look at my eldest son, I'll say I'm still happy that I know now and that we can treat him. But if I look at my own situation, I've just had relatively few symptoms, as did my relatives, and I do find the treatment to be an enormous burden. For children especially." (FG3, patient #1)

7. Alternatives to NBS

Interestingly, during the discussions several alternatives to NBS were suggested by the participants, despite the fact that this issue was not included in the topic list. These included increasing awareness for FD, family screening, cascade screening, selective high risk screening and population screening at older age.

> *"Of course it would help a great deal if the disease was at the top of the minds of doctors and specialists so that they would be able to deal with it; that if they can recognize the symptoms they can supervise you in a certain way (…) Of course it would be an enormous help if Fabry receives enough attention to shorten the diagnostic delay."* (FG3, patient #4)

> *"Could there be other kinds of models where you identify the people at the moment they need treatment and not 20 years in advance. If it would be feasible just to do a very good cascade screening and pick up all patients that way, then you don't need a newborn screening. And it could be feasible to have a prevention consultation for everybody every 5 years and pick up the patients with early kidney problems, early hypertrophic cardiomyopathy, early, without complications, all those things and then start treatment in an effective way."* (FG2, ethicist #5)

> *"If you know all the objections against newborn screening, then cascade screening might be a good alternative for newborn screening I think."* (FG2, ethicist #4)

Additional outcomes of mixed group discussions

During the mixed focus group discussions (FG 4-6), FD experts and ethicists verified some of their beliefs and opinions on FD in their interaction and discussion with FD patients. In addition, alternatives to NBS were further emphasized.

> *"In general I would say: currently, yes, increasing awareness is preferred. (…) With the current problems that we are facing with implementing NBS, I think the way to go would be to try to improve awareness, pedigree analysis and all that and look for the very early symptomatic patients to avoid non-diagnostic delays, but again, with the problems that we are facing with newborn screening."* (FG 4, internist #1)

However, the feasibility of increasing awareness was also doubted, especially for general practitioners.

> *"Whether it's feasible to increase awareness amongst all physicians, that's something I really wonder. (…)Because I think it's not feasible for all physicians to achieve awareness of Fabry in time, only small groups that see quite a lot of these patients. They might become more aware, but lots of people go to GP's with these kinds of complaints and they are rather non-specific."* (FG 4, ethicist #2)

> *"Aches, simply one symptom, that was my only symptom at that time. And it could also be e.g. a tick bite. This can probably also cause the same pains. I think it's really hard to diagnose, this disease. It's a really rare disease among all more common diseases."* (FG4, patient #3)

To overcome this difficulty, participants suggested the implementation of specific tools for general practitioners, e.g. databases on rare diseases and the inclusion of rare diseases in current protocols.

Most participants of the mixed group discussions agreed the most on statement number 4: NBS should not be performed because the disease is very heterogeneous and phenotype prediction is difficult.

> *"The problem with NBS then would be that you not only diagnose the patients early who would have severe complaints and who might have advantages of not delaying diagnosis, but you would also identify many people who have a low enzyme activity, but who will never develop disease. So, the problem is that we do not have a test that shows exactly who will have clinical symptoms and who will profit from early treatment, apart from those that only have an abnormal metabolism but who will never develop complaints."* (FG 4, ethicist #2)

DISCUSSION

In this study, we identified several arguments that are relevant to the discussion of whether or not to include FD in NBS programs by performing focus group discussions with different stakeholders. Although the aim of this study was to explore the opinions and attitudes of the topic and not necessarily reach a consensus, there was significant agreement during all of the discussions. Although it was agreed that the early diagnosis and treatment of FD is important, especially in symptomatic patients, the general opinion in the different focus groups was that it would be too early to include FD in NBS programs. It was concluded that screening might detect children who may never become symptomatic or may develop only late onset disease, with limited severity. The inability to predict the phenotype was considered to be one of the most important barriers for inclusion

of FD in NBS. Furthermore the lack of evidence of early treatment efficacy was believed to be an important barrier for NBS of FD.

There was a considerable overlap in the experiences and opinions that were expressed during the FD patient focus group (Table 4) and the experiences were expressed in a qualitative interview study by 30 FD patients regarding the timing of their diagnosis recently conducted by our group (*submitted for publication)*, especially concerning reproductive planning, medicalization, anticipating the future, and preventing disease progression with treatment. This overlap suggests that the considerations that were brought forward by the six patients involved in this focus group discussion are representative of that of the Dutch Fabry population.

Our study results indicate that before the implementation of FD in NBS programs should be seriously considered, some issues need to be fully elucidated. This study emphasizes the need for studies on genotype- phenotype correlation, phenotype predictors and early FD treatment efficacy. Interestingly, during the discussions, many alternatives to NBS were suggested that would facilitate the early diagnosis of FD patients. One suggestion was to increase awareness among physicians. Indeed, due to the rarity of the disease, many physicians are poor at recognizing Fabry manifestations, as shown in a recent survey among a large group of international rheumatologists, one of the specialists Fabry patients may consult [22]. It is known that in the absence of family members with FD, a delay in diagnosis is common and may be up to 14 years in males, as described in 194 index patients in the Fabry Outcome survey [23]. Although the feasibility of increasing awareness may be debatable, it may be important to provide specific tools for physicians to be able to diagnose rare diseases, e.g. through websites or by including rare diseases in currently applied diagnostic protocols. Improving family screening was another suggested approach. Indeed, one study revealed that, on average, five additional patients with FD may be diagnosed in a family pedigree following the identification of one proband or index case [24]. At present, at our center, index patients are provided with oral and written explanation of the hereditary nature of the disorder. They are given general advice to inform potentially affected family members and are encouraged to that they seek genetic counseling. A more active approach that uses a system of cascade screening to intensify the search for family members at risk and subsequent counseling and diagnostic studies might result in a much higher yield. Such cascade family screening approaches are currently applied in the Netherlands to patients with familial hypercholesterolemia[25].

To our knowledge, this is the first study using focus group discussions in order to explore opinions on NBS for a LSD. In our selection of the participants, we made sure to include participants with different backgrounds and nationalities. To increase the reliability of the results, different researchers were involved in both the data collection (moderators and observers) and data analysis (MG, MZ and GL). We anticipated and observed a significant interaction among all of the participants during the focus group discussions, which allowed a consistent identification of different arguments. This study is unique in the fact that FD

experts, ethicists and FD patients discussed this issue together, in an open setting and atmosphere, with no other interests aside from sharing opinions, which differs from e.g. consensus meetings. The unanimous positive reactions that we received from the participants confirmed our idea that this method of research could be of value for other complex and ethical discussions concerning other LSDs.

In summary, this study gives profound insight into the arguments that are relevant to the discussion of including FD in NBS programs and demonstrates that there is insufficient knowledge regarding associated crucial issues. All of the participants, emphasized that the lack of a clear phenotype prediction and uncertainty of the efficacy of early treatment should be fully elucidated before NBS for FD can be considered. These key issues should be further studied, to facilitate a careful weighing of potential benefits and harms of NBS programs for FD.

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REFERENCES

1. Bickel H, Gerrard J, Hickmans EM. Influence of phenylalanine intake on phenylketonuria. Lancet 1953;265:812-813.
2. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. Bol. Oficina Sanit.Panam. 1968;65:281-393.
3. Grob R. Is my sick child healthy? Is my healthy child sick?: changing parental experiences of cystic fibrosis in the age of expanded newborn screening. Soc.Sci. Med. 2008;67:1056-1064.
4. Kharrazi M, Kharrazi LD. Delayed diagnosis of cystic fibrosis and the family perspective. J.Pediatr. 2005;147:S21-S25.
5. Parsons EP, Clarke AJ, Hood K, Lycett E, Bradley DM. Newborn screening for Duchenne muscular dystrophy: a psychosocial study. Arch.Dis.Child Fetal Neonatal Ed 2002;86:F91-F95.
6. Ross LF. Screening for conditions that do not meet the Wilson and Jungner criteria: the case of Duchenne muscular dystrophy. Am.J.Med.Genet.A 2006;140:914-922.
7. Kint JA. Fabry's disease: alpha-galactosidase deficiency. Science 1970;167:1268-1269.
8. Eng CM, Guffon N, Wilcox WR et al. Safety and efficacy of recombinant human alpha-galactosidase A--replacement therapy in Fabry's disease. N.Engl.J.Med. 2001;345:9-16.
9. Schiffmann R, Kopp JB, Austin HA, III et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001;285:2743-2749.
10. Banikazemi M, Bultas J, Waldek S et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann. Intern.Med. 2007;146:77-86.
11. Warnock DG, Ortiz A, Mauer M et al. Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. Nephrol. Dial.Transplant. 2011
12. Weidemann F, Niemann M, Breunig F et al. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation 2009;119:524-529.

13. Banikazemi M, Bultas J, Waldek S et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann. Intern.Med. 2007;146:77-86.
14. Weidemann F, Niemann M, Breunig F et al. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation 2009;119:524-529.
15. Mehta A, Ricci R, Widmer U et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur.J.Clin.Invest 2004;34:236-242.
16. Hwu WL, Chien YH, Lee NC et al. Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A (IVS4+919G>A). Hum.Mutat. 2009;30:1397-1405.
17. Lin HY, Chong KW, Hsu JH et al. High incidence of the cardiac variant of Fabry disease revealed by newborn screening in the Taiwan Chinese population. Circ. Cardiovasc.Genet. 2009;2:450-456.
18. Spada M, Pagliardini S, Yasuda M et al. High incidence of later-onset fabry disease revealed by newborn screening. Am.J.Hum.Genet. 2006;79:31-40.
19. Schiffmann R. Fabry disease. Pharmacol. Ther. 2009;122:65-77.
20. Linthorst GE, Bouwman MG, Wijburg FA et al. Screening for Fabry disease in high-risk populations: a systematic review. J.Med. Genet. 2010;47:217-222.
21. Boeije H. Analysis in qualitative research. 2009. Sage, London.
22. Cimaz R, Guillaume S, Hilz MJ et al. Awareness of Fabry disease among rheumatologists--current status and perspectives. Clin.Rheumatol. 2011;30:467-475.
23. Hopkin RJ, Bissler J, Banikazemi M et al. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. Pediatr.Res. 2008;64:550-555.
24. Laney DA, Fernhoff PM. Diagnosis of Fabry disease via analysis of family history. J.Genet.Couns. 2008;17:79-83.
25. Ned RM, Sijbrands EJ. Cascade Screening for Familial Hypercholesterolemia (FH). PLoS.Curr. 2011;3:RRN1238.