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ORIGINAL ARTICLE

Parents' experience with positive newborn screening results for cystic fibrosis

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Abstract

In Germany, screening for cystic fibrosis (CF) is part of the newborn screening since September 2016. The risk of psychological harm due to false-positive screening results is a longstanding concern. We investigated the parents' perception of the CF screening process in Bavaria and the communication after positive screening results with a questionnaire. Until August 2018, 192 children went through a final diagnostic testing after a positive CF screening result, and 105 (54.7%) families completed the questionnaire. Of these, only 30 parents obtained information about the newborn screening by a physician, despite this being mandatory in Germany. Parents being informed by a CF specialist (28.6%) about the positive screening result were more satisfied with the given information (80.0 versus 50% informed by the maternity ward), and the delay until the final diagnostic testing was shorter. More than 3 days between the information about the screening result and the diagnostic testing was too long for 77.7% of the families.

Conclusion: Performing final diagnostic testing with only short delays and receiving satisfactory information is important. Therefore, parents should be informed directly by a CF center about positive screening results and only when sweat testing is possible within the next days.

What is Known:
- *The risk of psychological harm due to false-positive screening results is a longstanding concern.*
- *Satisfactory information about the positive CF screening result seem to reduce the parental stress.*

What is New:
- *Parents being informed directly by a CF specialist were more satisfied with the given information and the delay until the final diagnostic testing was shorter.*
- *Our data support the concept that parents should better be informed directly by a CF specialist about positive screening results and only when sweat testing is possible within the next days to reduce parental stress.*

Keywords Cystic fibrosis · Positive screening results · Newborn screening · Parental stress

Abbreviations

CF	Cystic fibrosis
CFSPID	CF screening positive, inconclusive diagnosis
CFTR	Cystic fibrosis transmembrane conductance regulator gene
IRT	Immunoreactive trypsinogen
LGL	Bavarian Health and Food safety authority
NBS	Newborn screening
PAP	Pancreatitis-associated protein
PPV	Positive predictive value

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Introduction

Cystic fibrosis (CF) is one of the most common life-threatening autosomal recessive disorders with an estimated incidence of one out of 3300–4500 newborns in Germany [6, 21]. From 1980 onwards, screening for CF was established in

many European countries [24] with different screening algorithms. It is part of the newborn screening (NBS) in Germany since September 2016 [17]. There are many different screening protocols worldwide, all relying on immunoreactive trypsin (IRT) as the primary test and on sweat testing to confirm or exclude the diagnosis of CF [7]. Intermediate steps are required to achieve an acceptable combination of sensitivity and specificity. These steps may consist of pancreatitis-associated protein (PAP) or CFTR mutation analysis with the first blood spot, a second IRT testing with another blood spot collected later on, or various combinations of these [2]. In Germany, a three-step screening protocol is used (IRT/PAP/screening for 31 CFTR mutations + fail-safe). With this algorithm, the rate of false-positive CF screening results is relatively high. The risk of psychological harm in families of newborns with false-positive results is a longstanding concern [8]. Several studies have shown that the distress is lower if parents are properly informed and if the period of time between receiving the positive screening result and the confirmatory diagnostics is short [10, 19]. Therefore, this study aims to investigate the CF screening process in Bavaria with focus on (1) the screening information for parents provided orally and by brochure, (2) their experience with the communication of positive screening results, (3) the parents' opinion about the given information, and (4) the process after receiving a positive CF screening result. The results of this evaluation may help to improve the screening process in Bavaria.

Methods

Newborn screening for CF in Germany

Since September 2016, screening for CF is part of the NBS in Germany. The CF screening protocol is part of the Pediatrics Directive of the Federal Joint Committee [17]. Parents have to give their written consent to the NBS. A physician must inform the parents about the CF screening procedure, and they receive a brochure about the NBS, including a section on CF and a declaration of consent. The screening center in the Bavarian Health and Food safety authority (LGL) receives the Bavarian screening data from the laboratory if parents have given their consent.

In Germany a three-step screening protocol is used for the CF screening: Normally, nurses take the heel-prick blood sample for the screening on the third or fourth day of life and send it to one of two screening laboratories in Bavaria where, as a first step, IRT is measured. PAP is measured when IRT is ≥ 99th and < 99.9th IRT percentile, followed by a screening for the 31 most common CFTR mutations in Germany if PAP ≥ 87.5th PAP percentile. An IRT-dependent (≥ 99.9th percentile) fail-safe is included. According to the protocol, the screening is positive if one or two CFTR mutations are found or the IRT is ≥ 99.9th IRT percentile. Parents do not receive information about a possible carrier status of their child. In case of a positive screening result, one of the two Bavarian screening laboratories will inform the physician—normally of the maternity ward—who ordered the NBS. This physician then has to call the parents to inform them that they should get in contact with a CF center for a sweat test appointment. In Bavaria, one of five certified CF centers and six CF centers that fulfill the quality criteria for diagnostic testing according to the international guideline [4] by a self-evaluation questionnaire should carry out the sweat test. Parents can give their consent to be informed directly by a specialist in case of a positive screening result. Before introducing the CF screening in Bavaria, all involved CF centers decided in a conference that if parents gave their consent to be informed directly, normally, the nearest CF center should get in contact with the parents. After the diagnostic evaluation, CF physicians write test results into a form and send the data to the screening center with parental consent.

Parental questionnaire

Since February 2018, a questionnaire, written in German, was sent to all parents by mail after the diagnostic evaluation. Parents answered the questions anonymously. This questionnaire was adapted from the Suisse questionnaire [19]. The questionnaire contains questions about the information parents received concerning the NBS in general, the screening brochure, and their satisfaction with the received information. Other questions were about parents' feelings during the screening procedure and their overall opinion on the NBS and sociodemographic data.

Statistical analysis

We entered and analyzed all data in an SPSS database (IBM SPSS Statistics for Windows, Version 23.0.; IBM Corp., Armonk, NY, USA). Information received by the parents and their satisfaction with this information, parents' feeling about the screening process and general approval was analyzed descriptively. For associations between variables, we used chi-square tests.

Results

Study population

A total of 238,117 children were screened for CF between 1 September 2016 and 31 July 2018 in Bavaria. Of these, 206 newborns had a positive CF screening result, 159 through an IRT ≥ 99.9th percentile (fail-safe), and 47 had one or two

mutations in the CFTR gene. One child had a negative screening but a meconium ileus. In the following sweat test, 44 children were diagnosed with CF or CFSPID (CF screening positive, inconclusive diagnosis) (positive predictive value (PPV) = 21.8%). Until today, we have sent the questionnaire to 192 families after the final diagnostic testing and 105 returned it (response rate 54.7%). Out of these, for 72 (68.8%) children, CF could be excluded; 27 (25.7%) were diagnosed with CF; and 6 (5.7%) with CFSPID. Further details of the study population are described in Table 1.

Information about the screening process

Out of all the parents who responded ($n = 105$), 39% received general information about the NBS process before birth, 72.4% after birth, and 9.5% could not remember getting any information. Mainly nurses or midwives informed the families (61.7%). The information was satisfactory for 71.4% of the parents that remembered it.

Families could remember receiving the screening brochure including the form for the necessary written consent before birth in 21.9% of the cases and after birth in 74.3%; 11.4% could not remember the brochure at all. The screening brochure was satisfactory for 67.4% of the families but too short for 9.5% and too long for 11.6% of the parents. Sociodemographic factors did not influence the opinion about the flyer, but parents with first-borns were less satisfied with the flyer ($p = 0.011$).

Out of all the responders, only 28.5% could remember receiving general screening information or the brochure from a physician, even though being informed by a physician before giving the written consent is mandatory in Germany.

Table 1 Study population ($N = 105$)

		Percent
Sex ($n = 104$)	Male	42.3
	Female	57.7
Place of birth ($n = 105$)	Hospital	94.3
	Others	5.7
Year of birth ($n = 102$)	2016	27.5
	2017	51
	2018	21.6
First-born child ($n = 104$)	Yes	55.8
	No	44.2
Educational level mother ($n = 101$)	Low	11.9
	Middle	37.6
	High	50.5
Place of origin mother ($n = 103$)	Germany	83.5
	Other country	16.5
Result of the diagnostic testing ($n = 105$)	CF excluded	68.8
	CFSPID	5.7
	CF	25.7
Questionnaire answered by ($n = 102$)	Mother	62.7
	Father	7.8
	Both	29.4

Information about the positive CF screening result

Parents received the information about the positive CF screening results from the maternity ward (43.8%), the children's hospital (13.3%), the CF center (28.6%), a pediatrician (11.45), or others (2.9%); 78.1% over the telephone (one family only by mailbox) and 23.8% personally. The information given about the positive screening result was satisfactory for 65.7% of the responders. If a physician informed the family about the screening or handed them the flyer, instead of nurses or midwives doing so, the given information about the positive screening result was more often satisfactory ($p = 0.016$). The mother's origin or education did not influence the outcome. The obtained information from a CF center was satisfactory for 80.0% of the parents, but if the maternity ward provided the information, only 50% of the parents were satisfied ($p = 0.036$) (Fig. 1). Parents were missing exact information about what to do next and especially about the fact, that the diagnostic testing confirms the positive screening result only in every fifth child. Accordingly, they complained about time (Friday afternoon) or manner (very unfriendly, in bad German, not sympathetic) of the telephone call.

Diagnostic testing

A CF center performed the diagnostic sweat test in 60.6% of the newborns, a children's hospital for 39.4% of the children with positive screening results. The time between receiving the information about positive screening results, and the sweat test was less than 1 day for 35% of the parents, 1–3 days for 30.1%, 4–6 days for 13.6%, and more than 6 days for 21.4% of the families. If a CF center informed the family about the positive screening, 83.5% of the families had an appointment for the sweat test within the next 3 days. If the information came from a maternity ward, only 52.2% were able to get an appointment with such a short waiting period ($p = 0.042$) (Fig. 2).

Out of all the families with an appointment within 3 days after receiving the information, 88.1% thought this time was acceptable. Families with an appointment after more than 3 days found this time too long in 77.8% of the cases ($p = 0.000$). The information given about the diagnostic testing and CF was satisfactory for 77.1% of the parents; the origin or education level of the mother had no influence in our data. All families with a child with CF were satisfied with the given information, but only 50% of the parents with a child with

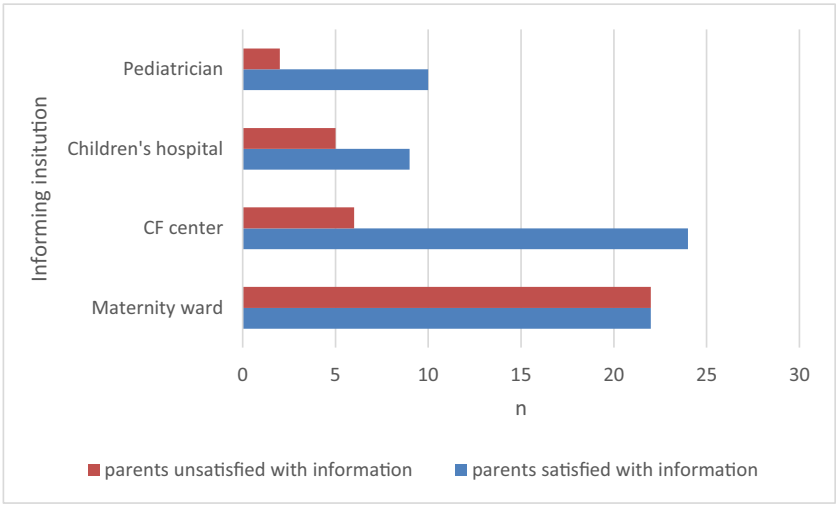

Fig. 1 Parents' opinion on the given information about the positive CF screening result from different institutions

CFSPID and 72.2% with a healthy child felt that the information was satisfactory ($p = 0.003$).

Feelings of parents during the screening process

After receiving the information about the positive screening results, most parents were deeply concerned or worried (86.4%). Whether or not the NBS information was given by a physician, the mother's education, the informing institution, the satisfaction with the given information, and whether or not the questionnaire was answered by father or mother had no influence on how much the parents worried. However, parents with a first-born ($p = 0.021$) and mothers not born in Germany ($p = 0.061$) were more worried. After the diagnostic testing, still 15.9% of the parents with a healthy child, 69.2% with a child with CF, and 83.3% with children with a CFSPID diagnosis ($p = 0.000$) were concerned or sad. While mothers with a higher education level were still more worried after the diagnostic testing (43.8%) than mothers with less education (23.4%; $p = 0.077$), the origin of the mother had no influence on the feelings after the diagnostic test.

General opinion about the screening

Out of all the 103 responders of this question, 83.5% said that altogether they were happy that their child was screened, 9.5% were not sure about it, and 6.8% were unhappy about it. The mother's origin, the education level, or the place of the diagnostic testing did not influence this opinion. Out of all the families with a child with CF, 92.3% were happy that their child was screened, mostly because the child could be treated early now, but only 50% of the parents with a child with CFSPID appreciated the screening. Out of all the parents with a healthy child, 83.1% were happy about the screening and 11.3% were not sure about their opinion ($p = 0.000$).

Discussion

CF screening is well established in many countries. Still, there is a lot of effort to improve the screening procedure. The aims are a low recall rate with few false-positive screening results and not missing children with CF. Therefore, we evaluated parents' experiences with the screening process and a positive

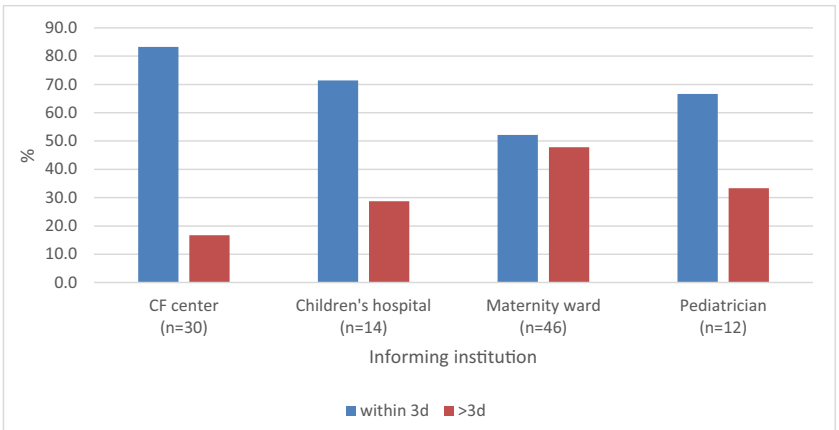

Fig. 2 Time between information about the positive CF screening result from different institutions and diagnostic testing

CF screening result to improve the screening procedure in Bavaria.

Our survey data consisting of 105 families indicate that only 28.6% of the parents were informed by a physician about the screening, despite this being mandatory in Germany. The information about the positive CF screening result, provided by a maternity hospital, was not satisfactory for 50% of the parents. If a CF center informed the parents about the positive screening result, 80.0% of the parents were satisfied with the given information and the delay between calling and diagnostic testing was less than 3 days for 83.5% of the families.

Throughout the world, different CF screening protocols are used due to the fact that no single algorithm is perfect. The goal is to find a balance between sensitivity, specificity, and the rate of false-positive screening results indicated by the positive predictive value (PPV). Sommerburg et al. gave an overview [21] that the PPV might be as low as 7.8% in the originally used protocol in the Czech Republic (IRT/PAP), is at around 25% in Australia (IRT/12 CFTR mutations), and can reach 87.5% in the Netherlands (IRT/PAP/36 CFTR mutations/sequencing). Other papers describe a PPV of 20% (Colorado, IRT/IRT//41–48 CFTR mutations + fail-safe [23]), 35.7% (Switzerland, IRT/7CFTR mutations [18]), and 43%, (Norway, IRT/71 CFTR mutations [14]). For the German screening protocol (IRT/PAP/31 CFTR mutations +fail-safe), a sensitivity of 96% and a PPV of 20.2% is estimated [22], which is in accordance with the calculated PPV from our data of 21.8%. An advantage of the German algorithm is that no carriers are identified, as the screening can be positive only because of an IRT ≥ 99.9th IRT percentile (fail-safe). This fail-safe was also included to identify children with CF who have other mutations than the 31 screened for, which might be the case especially for children with non-Caucasian ethnicity [26]. Additionally, only one single specimen is needed for the complete screening algorithm. On the other hand, high IRT values alone are associated with multiple causes and the fail-safe protocol increases the number of sweat test referrals and reduces the PPV remarkably [5]. In the German algorithm, 70% of the positive screening results are due to an IRT ≥ 99.9th IRT percentile (fail-safe) and only one out of five children with a positive CF screening is diagnosed with CF. Therefore, the planned evaluation of the CF screening protocol after 3 years is very important to decide if the screening algorithm should eventually be altered. As at present the rate of false-positive results is rather high, it is very significant to reduce the stress for families with positive screening results as far as possible.

The effect on families after a positive screening result is a longstanding concern [8, 11]. Our data show that almost 90% of the families are deeply concerned or worried when receiving the positive screening result. Beucher et al. observed that 96.5% of the families with false-positive screening results felt significantly stressed at the time of the sweat test, but after 3 months, only a few were still worried [1]. In our data, the only influencing factors on the stress level that we could find were that parents of first-borns and mothers not born in Germany were more worried. Some studies indicate that competent information is very important to the parents [10, 13, 20]. The negative effects of false-positive screening results might be mitigated through improved parental education [9] since well-informed parents showed less feelings of anxiety and depression [27]. Chudleigh et al. described that parents receiving the NBS result from a non-CF specialist found this resulted in a negative experience [3]. This is concurrent to our data where parents found the given information provided by a CF center more satisfactory. In addition, most families had a sweat test appointment within 3 days only if a CF center informed the parents about the positive NBS. An appointment within 3 days was acceptable for 88% of the families. A short delay between receiving the information about the positive screening results and the diagnostic testing seems to be important to reduce the stress for the families [10, 27].

Our data support the positive impact for the families if a CF center informs them about the positive NBS as these families were more satisfied with the given information and more often had a sweat test appointment within 3 days. This is only possible since an agreement was found in Bavaria specifying that the nearest CF center is the one contacting the family. However, this is only the case when parents gave their special consent to be informed directly by a specialist. Normally, in Germany, the families have to be contacted by the physician of the maternity ward who ordered the NBS and are provided with a list of all CF centers to make an appointment for the diagnostic testing by themselves. It would be helpful to implement structures in the German screening process that allow specialists to always inform the parents directly as it is done, e.g., in Switzerland [19].

Even after the diagnostic sweat test has confirmed the health of the child, some parents are still worried and some studies describe long-term negative effects, including alterations in the perception of their infant's health [13]. Other studies, however, indicated no long-term negative effects due to a false-positive screening result [1]. In our survey, 16% of the parents with a healthy child were still concerned or sad after the diagnostic testing. Since we asked the parents about this only once and only shortly after the diagnostic testing, we were not able to evaluate long-term effects so far.

Altogether, 84% of the parents in our survey were happy about the CF screening of their child. All parents of children with a confirmed CF appreciated the screening, and many were thankful that the child could be treated early now. These data are similar to the results of a survey in Switzerland, where 88% of the parents were glad about the screening of their child. [19]. Overall, many studies indicate that parents support a CF NBS despite false-positive screening results [25]. Nevertheless, 5.6% of the families with a healthy

child would have preferred no CF screening and 11.3% were not sure about it; for parents with the diagnosis of CFSPID, even 50% saw no benefit in the screening. Especially these families show various manifestations of health-related uncertainty and subtle distress [12] and need support [15]. It seems to be important, even with the obvious benefits of a screening, to keep the potential harm in mind that can be caused by false-positive or inconclusive results. Considering this, it is important to find the optimal screening algorithms and suitable screening targets [5, 16].

7This study has some limitations. First, the number of 105 questionnaires is still quite low and a larger sample would have increased the power of the data. Nevertheless, the response rate of almost 55% is acceptable. A limitation is that due to the anonymity of the survey, we could not remind families that did not answer the questionnaire to do so or ask about obviously implausible or missing answers. As we started our survey in February 2018, there might also be a recall bias for the older children, resulting in the possibility that especially parents with long-lasting memories answered the questionnaire. Accordingly, our study attracted a well-educated cohort of mothers so that the results may not be generalized to all families. A strength of the study is the very good cooperation with the Bavarian CF centers and the two screening laboratories so the lost-to-follow-up rate of only 3 out of 206 (1.5%) of children after a positive CF screening result is very low.

Conclusion

To reduce the potential harm by the communication of preliminary positive screening results, short delays until final diagnostic testing and satisfactory information are important. Therefore, parents should be informed directly by a CF center about positive CF screening results when sweat testing is possible within the next days. In the future, we would like to evaluate the long-term effects resulting from the communication of false-positive CF screening results in a non-anonymous survey over a longer period.

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Authors' contributions Both authors made substantial contributions to conception and design, acquisition, analysis and interpretation of data, drafted the article, and reviewed it critically for important intellectual content and have given final approval of the version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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