review

Evaluation of cystic fibrosis carrier screening programs according to genetic screening criteria

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Genetic screening programs should meet certain criteria before they can be introduced into the community. The aim of this study was to discuss pilot studies for cystic fibrosis (CF) carrier screening before and during pregnancy in the light of important genetic screening criteria. Overall, CF carrier screening meets the prerequisites that justify screening. However, more specific criteria for the development of screening programs were not always taken into consideration. Most project leaders concentrated on uptake as an important outcome, and less on informed decision-making. To further investigate the long-term psychological and social effects of genetic screening, continuous monitoring of screening projects is recommended. ***Genet Med* 2002:4(4):241–249.**

Key Words: *cystic fibrosis, carrier screening program, genetic screening criteria, outcome measures*

Genetic screening programs should meet certain criteria before they can be introduced into the community. In the evaluation of a specific screening program a distinction can be made between (1) a conceptual approach to determine whether the subject of the screening would meet the criteria if introduced, and (2) a pilot phase.[1] The results of the pilot phase serve as a basis for a final decision on whether or not to proceed with the introduction of a genetic screening program, and how best to offer and implement this program. Until now, a range of pilot programs for cystic fibrosis (CF) carrier screening in the general population have been developed and completed.[2] The project leaders drew certain conclusions from these studies, but the question remains as to the extent to which these were evaluated according to the genetic screening criteria applied to these programs. The purpose of this study was (1) to determine how project leaders of pilot studies for CF carrier screening evaluated their programs, and (2) to discuss these pilot studies in the light of criteria applied to genetic screening to define how they could best be evaluated.

SELECTION OF PILOT STUDIES

This study discusses CF carrier screening, as recommended by the National Institutes of Health (NIH), that is screening for couples who are currently planning a pregnancy and for couples seeking prenatal care.[3] Screening programs aimed at individuals of reproductive age are also considered, because these programs were designed to screen before conception.

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Screening offered during pregnancy, compared with preconceptional screening, has the advantage that this target group is highly receptive to the idea of screening and easy to reach, because most women contact their general practitioner (GP) or visit an antenatal clinic. However, this method of screening leaves limited reproductive options open for a carrier couple, and there is little time for counseling and reflection before decisions about a prenatal diagnosis have to be made, in contrast to screening outside pregnancy.

Since the identification of the gene in 1989, a series of pilot studies focusing on CF carrier screening have been conducted and evaluated in the United States, Australia, and various European countries. This review is based on a literature search in the electronic reference database of MEDLINE (1990–2001) for peer-reviewed published literature describing these pilot studies. Only the results published in these articles and reported by Henneman et al. (unpublished data, 2001) are discussed. No additional information was requested from the project leaders. Furthermore, pilot studies were not included if CF carrier screening was offered in combination with screening for other diseases. In total, 13 studies on carrier screening during pregnancy and 7 studies on screening programs aimed at individuals of reproductive age or couples planning to have a pregnancy were selected (Tables 1 and 2).

SELECTION OF SCREENING CRITERIA

It is now possible to use genetic screening for an increasing number of disorders. Therefore, standards relating to the introduction and organization of genetic screening programs have been developed. In the past 10 years, various reports on genetic screening criteria have been published by different committees, such as the Nuffield Council on Bioethics in the United Kingdom,[4] the Health Council of the Netherlands,[5] the Public and Professional Policy Committee of the European Society of Human Genetics,[1] and the U.S. National Academy of Sciences.[6] In the United States, general guidelines for the

Table 1
CF carrier screening programs during pregnancy

First author	Setting	Target group	Method of approach	Pre-education	Sampling	Method of testing[a]	Report of test results[b]
Mennie[19,37,41,51]	Hospital[c]	Women $n = 4,348$	Leaflet sent home after booking	Leaflet	Women $n = 3,165$	Sequential	Full
		<18 wk pregnant	Immediate testing offered at visit	Counseling if needed			
Schwartz[59]	Hospital	Women $n = 7,400$	Leaflet sent home after booking	Leaflet	Women $n = 6,599$	Sequential	Full
		Pregnant	Immediate testing offered at visit	Questions answered			
Jung[60]	Hospital	Women $n = 638$	Immediate testing offered at visit	Leaflet	Women $n = 637$	Sequential	Full
		<16 wk pregnant		Questions answered			
Livingstone[42]	Hospital[c]	Women $n = 8,536$	Leaflet sent home after booking	Leaflet	Couples	Sequential	Combined
		<18 wk pregnant	Testing offered at visit	Counseling if needed	$n = 5,922$		
			Immediate testing or return visit				
Wald[52,61]	Hospital	Women $n = 810$	Testing offered at visit	Leaflet	Couples $n = 543$	Sequential	Combined
		<19 wk pregnant	Return partner's sample by mail				
Miedzybrodzka[43]	Hospital	Women $n = 2,002$	Testing offered at visit	Leaflet	Women $n = 1,475$	Sequential	Full and combined
		<17 wk pregnant	Immediate testing or return visit	Counseling	Couples $n = 321$		
Hartley[25]	General practice	Women $n = 623$	Testing offered at visit	Leaflet	Women $n = 267$	Sequential	Full
		<14 wk pregnant	Immediate testing or return visit	Counseling	Couples $n = 262$	Simultaneous	
Witt[29]	Primary prenatal care	Women $n = 6,617$	Immediate testing offered at routine prenatal class	Video and brochure	Women $n = 5,161$	Sequential	Full
		<17 wk pregnant					
Loader[20]	Hospital	Women	Immediate testing offered at visit	Leaflet	Women $n = 4,879$	Sequential	Full
		Pregnant (90%)		Questions answered			
				Counseling if needed			
Doherty[53]	Primary prenatal care	Women	Testing offered at visit	Leaflet	Couples	Sequential	Combined
		<18 wk pregnant	Return with partner's sample	Questions answered	$n = 1,682$		
Cuckle[26]	Hospital	Women $n = 6,071$	Leaflet sent home after booking or given on arrival	Leaflet	Women $n = 3,773$	Sequential	Full
	General practice	<18 wk pregnant	Immediate testing offered at visit or after confirmation pregnancy	Face-to-face explanation			
Grody[22]	Prenatal clinics	Women $n = 4,739$ <19 wk pregnant	Immediate testing offered at visit	Video or brochure Questions answered	Women $n = 3,192$	Sequential	Full
Delvaux[28]	Hospital	Couples $n = 1,156$	Immediate testing offered at visit	Counseling	Couples $n = 314$	Sequential	Full
		<21 wk pregnant					

[a]Sequential testing: the second partner is tested only if the first is positive. Simultaneous testing: both partners are tested at the same time.
[b]Full report: participants are fully informed about the test results. Combined report: only those couples in which both partners are found to be carriers are informed about their carrier status.
[c]In 1994, the pilot study was integrated into routine prenatal care.[58]

development of genetic tests have been issued by the NIH Task Force on Genetic Testing.[7] Recently, the American College of Medical Genetics Subcommittee on Cystic Fibrosis Screening published laboratory standards and guidelines for population-based CF carrier screening.[8]

Criteria for the evaluation of screening for diseases in the general population are not new. Famous and traditionally accepted are the criteria formulated in 1968 by Wilson and Jungner at the request of the World Health Organization (WHO).[9] However, genetic screening is distinguished from other types of medical screening by the genetic nature of the disorder. There is also a shift from the aim of treating, preventing, and alleviating disease—an important goal of any screening program—to the aim of offering the individual certain options. Therefore, these criteria are not entirely suitable for genetic screening but may have served as the basis for many of the reports on genetic screening.

To evaluate the various different pilot studies on CF carrier screening according to genetic screening guidelines, the criteria that were considered most important were selected

Table 2
CF carrier screening programs outside pregnancy

First author	Setting	Target group	Method of approach[a]	Pre-education	Sampling	Method of testing[b]	Report of test results[c]
Watson[30,36]	General practice	Individuals	Letter + leaflet	Leaflet	Individuals $n = 801$	Sequential	Full
	Family planning clinic	$n = 1{,}796$	Active-opportunistic	Counseling			
		16–44 yr	Immediate testing				
Bekker[31,46]	General practice	Individuals	Letter + leaflet	Leaflet	Individuals $n = 957$	Sequential	Full
		$n = 5{,}529$	Active-opportunistic	Counseling			
		18–45 yr	Passive-opportunistic				
			Immediate testing or return visit				
Tambor[32]	Primary care	Individuals	Letter + leaflet	Leaflet	Individuals $n = 244$	Sequential	Full
		$n = 3{,}321$	Active-opportunistic	Education session			
		18–44 yr	Immediate testing				
Clayton[21,48]	Various settings	Individuals	Posters and take-away letters Return with partner's sample	Videotape or brochure	Couples $n = 179$	Sequential	Full
Payne[24]	General practice	Individuals	Letter + leaflet	Leaflet	Individuals $n = 481$	Sequential	Full and combined
		$n = 3{,}057$	Active-opportunistic	Counseling	Couples $n = 31$		
		16–45 yr	Immediate testing or return visit				
Honnor[35]	General practice	Individuals	Passive-opportunistic	Leaflet	Individuals	Sequential	Full
	Family planning clinic	$n = 5{,}102$ 18–50 yr	Immediate testing	Counseling if needed	$n = 2{,}220$		
Henneman[33]	General practice	Individuals	Letter + leaflet	Leaflet	Couples $n = 559$	Sequential	Full
	Municipal Health Services	$n = 38{,}114$ 20–35 yr		Group session or GP consultation			

[a]Active opportunistic: testing offered personally by a health professional. Passive opportunistic: testing offered by handing out a leaflet.
[b]Sequential testing: the second partner is tested only if the first is positive (single-entry testing). Simultaneous testing: both partners are tested at the same time.
[c]Full report: participants are fully informed about the test results. Combined report: only those couples in which both partners are found to be carriers are informed about their carrier status.

(Table 3). These criteria are listed in all of the above-mentioned reports on genetic screening criteria. The cost-effectiveness of screening programs has been studied extensively,[2] however, this is not taken into consideration in this review. First, although some maintain that cost-effectiveness is an important consideration in the debate over which target groups should be offered CF carrier testing,[8,10] it is generally acknowledged that there is something problematic about cost saving through termination of affected fetuses as the primary aim of screening.[5,11] Therefore, costs considerations should only play a limited part in decisions concerning genetic screening. Second, an earlier study has

Table 3
General criteria and specific criteria to be met by genetic screening programs

General criteria

1. The disease is an important health problem
2. There is an effective intervention or a decision to be taken by the person screened
3. There is a suitable test with known predictive value

Specific criteria

4. Participation is voluntary, with time allowed for consideration and based on consent
5. The target group is provided with good quality, comprehensible, and balanced information
6. There is enough evidence that psychological harm caused by the offer and/or participation is negligible
7. There is enough evidence that social harm caused by the offer and/or participation is negligible

already indicated that cost considerations need not be an important barrier.[12] Third, the costs and available resources will differ between countries.

Genetic screening criteria can be subdivided into general criteria and specific criteria. General criteria relate to the prerequisites for starting a community-wide carrier screening for a genetic disease, as outlined by the WHO.[13] To justify screening, a screening program has to meet these general criteria, before pilot studies investigating the more specific criteria can be developed.

GENERAL CRITERIA FOR GENETIC SCREENING

In general, the authors of the published pilot studies seem to agree that CF carrier screening is justified because it meets most of the general criteria.

1. The disease is an important health problem

YES. CF is a serious, well-characterized, incurable disorder. The disease is characterized by severe, relapsing respiratory and gastrointestinal problems due to the accumulation of sticky mucus.[14] The symptoms and course of CF are variable.[3] In general, during the course of the disease the symptoms worsen. The median life expectancy for CF is now approximately 30 to 40 years, and it is projected that, in newborns, it will become more than 40 years.[15] CF is one of the most common autosomal recessive disorders found in Caucasians, with a birth prevalence of approximately 1 in 2,500 to 4,000. In populations that are of European origin, approximately 1 in 25 to 30 individuals is a healthy CF carrier. If both partners in a couple are carriers, each child they have has a 1 in 4 risk of having CF.

2. There is an effective intervention or a decision to be taken by the person screened

YES. The purpose of CF carrier screening is to enable participants to find out whether they are a carrier and to take a decision based on that information. Carrier screening during pregnancy offers carrier couples the possibility of prenatal testing and, subsequently, the termination of a pregnancy. Screening before pregnancy offers couples a greater range of reproductive options, such as deciding not to have children, adoption, prenatal testing, preimplantation genetic diagnosis, or pregnancy by means of artificial insemination with sperm from a screened donor or egg-cell donation.

3. There is a suitable test with known predictive value

YES, PROBABLY. CF is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The gene was identified in 1989[16–18] and, to date, over 900 mutations have been identified (http://www.genet.sickkids.on.ca/cftr). In some of the pilot studies, the test sensitivity was found to be 85% or less, which was considered to be less than ideal for a screening test.[19–22] Nowadays, in most screening centers, the sensitivity of the test is at least 85% to 90% in Caucasians.[3] The test specificity is approximately 100% (no false positives), if stringent quality assurance guidelines are adhered to, as specified, for example, in the report of the NIH-DOE Task Force on Genetic Testing[7] or issued by the Steering Committee of the European Concerted Action on Cystic Fibrosis.[23] Direct mutation analyses can be applied after collecting samples by buccal scraping, the mouthwash method, or blood-sampling. In general, buccal scraping and the mouthwash method, which are noninvasive and painless, are considered by the target group to be the most acceptable methods of testing.[21,22,24]

SPECIFIC CRITERIA FOR GENETIC SCREENING PROGRAMS

Outcome measures described in each CF carrier screening pilot study, relevant to this review, are listed in Tables 4 and 5. To determine whether these studies meet the specific criteria for genetic screening programs, the outcome measures are discussed according to each individual criterion for genetic screening programs.

4. Participation is voluntary, with time allowed for consideration and based on consent

Carrier screening in pregnancy has mainly been offered to women during routine visits to antenatal clinics or, alternatively, to save time, when a pregnancy is first confirmed by a GP. High uptake rates of 53% to 99% have been reported, and many project leaders, therefore, have suggested that there is considerable interest in screening in a target group that is highly receptive to the idea of screening. However, reasons for participation were not always asked, but when assessed, it was sometimes found that important reasons for women to accept screening were that they believed that all tests are important during pregnancy,[25,26] that they could not refuse,[27] that the doctor told them to participate,[20] or that the test was easy to carry out.[28] Witt et al.[29] reported that among the 259 women who had the test, almost 26% accepted the test because a blood sample had already been taken. These data suggest that carrier testing during pregnancy is sometimes accepted just because it is offered and the easy way in which it can be carried out and not because of any perceived benefits of the testing.

Carrier screening outside pregnancy in the general population has been offered through primary health care services, such as general practices, family planning clinics, and other (health-related) community centers. Several studies concluded that uptake rates were mainly determined by the method of invitation.[21,24,30–32] Uptake was approximately 10% when invitations were sent by letter, and increased to 24% to 87% with active opportunistic testing, i.e., a personal approach and immediate testing. This influence of the mode of invitation on uptake has been interpreted as a lack of motivation in an unreceptive target group to participate in the test.[24,31,32]

On the one hand, it could be argued that the high uptake rate achieved in opportunistic testing is the result of a supply push rather than a demand from the population.[31] This was demonstrated in some studies by the sizable number of

Table 4
Outcome measures mentioned in CF carrier screening programs during pregnancy

First author	Uptake rate	Reasons to accept	Reasons to decline	Time to decide	Satisfaction	Understanding	Psychological impact	Social impact
Mennie[19,37,41,51]	X	X	X	X	X	X	X	X
Schwartz[59] Clausen[27]	X	X			X	X	X	X
Jung[60]	X		X				X	
Livingstone[42]	X	X	X			X	X	
Wald[52,61]	X		X					
Miedzybrodzka[43]	X					X	X	X
Hartley[25] Harris[62]	X	X		X	X	X	X	
Witt[29]	X	X	X		X	X	X	X
Loader[20]	X	X	X		X	X	X	
Doherty[53]					X			
Cuckle[26]	X	X	X					
Grody[22]	X		X		X	X	X	X
Delvaux[28]		X			X	X	X	X

Table 5
Outcome measures mentioned in CF carrier screening programs outside pregnancy

First author	Uptake	Reasons to accept	Reasons to decline	Time to decide	Satisfaction	Understanding	Psychological impact	Social impact
Watson[30,36]	X				X	X	X	X
Bekker[31,46]	X					X	X	X
Tambor[32] Bernhardt[49]	X					X		
Clayton[21,48]		X	X			X		
Payne[24]	X		X			X	X	X
Honnor[35]	X			X		X	X	
Henneman[33]	X	X	X		X	X	X	X

individuals who decided to have the test, even though they were not planning to have (any more) children.[24,30,32] On the other hand, the low uptake rate achieved by mailed invitations might be due to other reasons, such as lack of knowledge and inconvenience of the time or location, even though the nonrespondents were interested in testing. Lack of time to attend an educational session was reported by 53% of nonpregnant couples as the main reason for not participating in a study carried out by Henneman et al.,[33] whereas half of these couples perceived high benefits of screening. Furthermore, uptake increased after a second invitation (Henneman et al., unpublished data, 2001), suggesting that some people are not prepared for the initial offer of screening and that they might attend if the subsequent offer of screening is more convenient.

Time to decide whether or not to have the test is important and necessary to prevent people from regretting their decision later on. It also gives participants the opportunity to make a decision based on the conviction that screening is to their benefit and not just because it is offered or strongly recommended, as was argued in connection with opportunistic screening programs.[34] In most studies, consent for testing was asked directly, but participants were only occasionally asked whether they were satisfied with the amount of time they were allowed to consider participation. Honnor et al.[35] showed that, when a consent form was signed immediately after testing was offered, 4.8% of participants and 15.5% of those who had not been tested felt that they would have liked to have had more time to decide.

Satisfaction was evaluated in most studies, by asking participants whether they had any regrets about their decision, whether they were satisfied with testing, and whether they would recommend testing to others. Overall, the participants were satisfied, although some studies reported that carriers were less satisfied than those who tested negative.[27,29,36,37] Remarkably, one pilot study showed that, although the participants were satisfied with the test, they did not advise others to have it.[28]

5. The target group is provided with good quality, comprehensible, and balanced information

Educating people about carrier screening is complicated, due to the limited knowledge about genetics in the general population[38] and a test sensitivity of <100%, causing a residual risk to individuals who are not found to be a carrier. The content of the written information provided in most pilot studies was evaluated in an earlier study carried out by Loeben et al.[39] It was concluded that the wide variation in the information about CF and reproductive options contained in the pamphlets did not seem to meet the recommendations for balanced information. The impact of (unbalanced) information on decisions was not investigated, but it was, however, suggested that interest in CF testing might be influenced by the nature of the information that is presented.[34,40] Furthermore, there was some evidence that uptake as part of a routine visit was based on poorer knowledge than when it required a separate visit.[32]

The effectiveness of the information provided has been measured by assessing knowledge of the clinical and genetic aspects of CF (testing), recall of test results, and understanding of the residual risk. Some studies showed that the level of knowledge increased after pretest information had been provided, thus supporting informed choice.[29,31] After testing, however, it was demonstrated that a sizable percentage of those who received a screen-negative result believed that they were definitely not carriers,[22,24,25,27,35,36,41–43] and accurate recall of risk of having a child with CF decreased after a few months.[24,31] After 3 years, a subset of 466 negative-tested individuals selected from six pilot studies showed that 81% correctly remembered the results they had received. However, 50% incorrectly believed that they were definitively not carriers.[44] Also of concern are the test-positive individuals who believed that they were only likely to be carriers.[24,31,35,36,41] Furthermore, in two studies, it was shown that some carriers believed there was a 1 in 4 risk of having a child with CF if one partner was a carrier.[24,36] Personal counseling after receiving positive test results did not necessarily increase understanding.[35]

It has been suggested that a psychological inclination to process and recall information in a way that minimizes risk underlies the inaccurate recall that has been reported in previous studies.[44] This inclination may be a useful psychological defense mechanism.[45] However, misunderstanding might also have arisen because people were not motivated to undergo testing in the first place.[46] In addition, differences in presentation, content, emphasis on information, and time spent on counseling have been suggested as possible influences on understanding of the test results.[41,47] Henneman et al. (unpublished data, 2001) showed that the predictors of a correct understanding of test results in preconceptional couples after 6 months were a positive test result, a high level of knowledge about CF, a high level of education, attending an educational session, and previously heard of CF.

Only a few studies aimed at the best way of providing the information to optimize understanding. Written materials and video recordings were shown to be equally effective methods of educating most people about carrier screening.[22,48] However, these methods were found to be less effective for those people with a low educational background.[48,49] Higher scores on a knowledge test were achieved by those who had received personal education during an educational session[50] (Henneman et al., unpublished data, 2001) compared with those educated only by printed materials, suggesting that face-to-face verbal information might be needed, in particular to inform couples with a low level of education about screening.

6. There is enough evidence that psychological harm caused by the offer and/or participation is negligible

Anxiety levels were assessed in most screening studies. In stepwise screening, in which one partner is sampled and tested first and the second only if the first partner tested positive, it was often found that women who were identified as a carrier were more anxious while waiting for the partner's result. However, these feelings of anxiety seemed to be short-lived and disappeared once their partners were tested negative.[22,27,43,51] In a study in which it was found that women experienced no anxiety while awaiting their partner's result, it was suggested that this was because of the high quality of the pretest education.[29]

Couple-based screening, in which both partners are sampled at the same time and only those couples in which both partners are found to be carriers were informed about their carrier status, whereas all others are told that they have no marked increased risk (nondisclosure of test results), was proposed by Wald[52] and evaluated in several studies.[42,43,53] One reason for the introduction of this method was avoidance of the unnecessary anxiety and need for counseling that might arise when one partner is tested positive and the other partner is asked to provide a sample. It was, indeed, shown that there was no peak in anxiety after couple-based testing, compared with stepwise testing when positive results were received.[42,43] Long-term follow-up showed no differences in anxiety between the two different methods of screening.[47] There have been many debates on the introduction of Wald's proposal of couple-based screening. Recently, it has been stated that the introduction of this couple-based screening model is not recommended, among other things because the nondisclosure of test results deprives the positive-tested partner of the positive-negative couple the opportunity to inform their family of their increased risk.[8] In addition, nondisclosure was less well accepted by the target population, as was found in a couple-screening study carried out by Henneman et al. (unpublished data, 2001).

Long-term psychological effects have been assessed, and it was found that 16% of 280 identified carriers selected from six pilot studies remained worried after 3 years of follow-up.[44] There were no differences in reproductive behaviors or intentions between carriers and those tested negative.

Three studies, all using a general health questionnaire, found no impact of screening on health perceptions at the initial time of testing or after receiving (positive) test results,[24,27,46] although in carriers, there was a small negative ef-

fect on how they perceived their current health at 3 years follow-up.[44]

7. There is enough evidence that social harm caused by the offer and/or participation is negligible

Evaluations of social harm were mainly limited to asking identified carriers whether they shared the information with their partner, family, and friends. In a study carried out by Watson et al.,[36] over 90% of the carriers discussed the results with their partner or family and brought their partner or close relatives for testing within 6 months, indicating that there is little perceived stigma associated with the diagnosis. Witt et al.[29] found that among 76 female carriers, only 3% felt that people would look at them differently if they knew they were carriers.

The misuse of information, and discrimination based on test results after disclosure to third parties such as insurers and employers was hardly ever assessed. Furthermore, the social stigmatization of a person who declines screening was not investigated.

DISCUSSION

In this review, pilot studies for CF carrier screening before and during pregnancy were discussed in the light of important genetic screening criteria, and it was investigated whether the project leaders evaluated their studies on the basis of these criteria. Conceptually, because CF carrier screening meets the general criteria, the development of genetic screening programs is justified, and this was mainly addressed in the introduction of the reviewed articles. The outcome measures used in the evaluation of pilot studies did not always comply with the specific criteria for genetic screening programs. Most project leaders concentrated on uptake in the screening as an important outcome, and less on consent-based decision-making. Knowledge of CF, understanding of test results before and after testing, and the anxiety and satisfaction of participants have been studied extensively, but less attention has been paid to the long-term psychological and social effects of screening.

Participation is voluntary

Most pilot studies focused primarily on the rate of uptake as a measure of interest in participation. The degree of interest in screening appeared to be influenced by the setting and the way in which it was offered, i.e., opportunistically or passively, and the ease with which testing can be accomplished. In genetic screening, uptake is not important, unless for economic reasons. Determining what motivates some individuals to participate in a carrier screening program, while others decline, provides greater insight into the desirability and acceptability of screening than the uptake itself.

Information is of good quality, comprehensible, and balanced

Participants' knowledge of CF before testing was measured in some pilot studies, but there was less information about the level of knowledge of those who did not participate. However, to enable informed decisions to be made, it is important to demonstrate that the individual has fully understood the options and implications of screening.[3] To present "balanced" information, it has been suggested that a relatively equal percentage of the negative as well as the positive aspects of testing should be highlighted, alongside the neutral ones.[39] Cho et al.[54] described 10 critical elements that are needed to evaluate the content of informational materials, and these might well be used in the development of educational material about CF carrier screening. By whom and how the information should be provided is a matter that needs further serious consideration, as has also been suggested by Mennuti et al.[55]

Understanding the consequences of the test results was discussed in most pilot studies. The results suggest that, on the one hand, incorrect understanding seems to be a way of coping with risk information, rather than poor understanding. On the other hand, there are factors associated with understanding, such as the method of education and counseling, and participant characteristics, such as level of education and motivation, that could be taken into account to improve the understanding of test results.

Psychological and social harm is negligible

Although the psychological and social effects of being tested received various levels of attention, research on the anxiety caused by the invitation to undergo screening was limited. More information should be gained about the psychological effects and the social stigmatization of persons who might decline an offer of screening and also on the long-term social implications for carriers such as potential discrimination and denial of insurance.[40] Additional attention should be paid to the implications for the family, because not only the individual undergoing the test is involved but also other family members who have not consented to testing.

Limitations of the study

There are some limitations in this review. First, there was no personal contact with the project leaders who carried out the pilot studies; data were gathered only by searching the electronic reference database of MEDLINE. Therefore, elements that were lacking in the studies might have been evaluated without peer-reviewed publication. Furthermore, it may be possible that the results of some studies are still being evaluated. Second, there are other screening criteria that must be met, in addition to those that were selected for this review, e.g., relating to the provision of quality assurance, and organizational aspects. However, the criteria addressed in this review were mentioned in all the reports on genetic screening criteria and therefore were considered to be the most important.

Evaluation of pilot studies in general

The pilot studies on CF carrier screening did not evaluate all aspects of the selected genetic screening criteria. One reason for this may be that some project leaders were not fully aware of the criteria that specifically apply to genetic screening. Screening has traditionally been mainly viewed as a public health

Table 6
Suggestions for outcome measures preferably measured in the evaluation of genetic screening programs

Outcome measures in genetic screening programs[a]
1. Informed decision: time to decide, motivation, informed choice[b]
2. Cognitive aspects: level of knowledge, ability to recall test results, understanding test results/information
3. Psychological aspects: anxiety, perception of health, regret about the decision, satisfaction
4. Social aspects: stigmatization, discrimination, sharing of information
5. Behavioral aspects: reproductive and life-style decisions

[a]For all outcome measures, there should be short-term and long-term evaluation.
[b]Informed choice as a combination of knowledge, behavior, and attitude.[57]

activity, aimed at reducing the prevalence of disease, and in which a high uptake is essential if the screening is to be effective. Another reason could be difficulty in evaluating specific outcomes. Some issues are relatively easy to evaluate, because certain outcome measures have been developed and validated, such as the short form of the Spielberger state-trait anxiety inventory.[56] However, few resources are available for the evaluation of other outcome measures, for example, the concept of informed decision-making and the social consequences of screening. Recently, Marteau et al.[57] developed a method to measure informed choice, which might be useful for further studies on genetic screening. On the one hand, the use of various outcome measures does not necessarily mean that a study has been well designed. On the other hand, lack of evaluation measures does not mean that the study itself is unsuitable.

The evaluation of any screening program must include an assessment of how decisions are made after the individual has received information, and appropriate outcome measures that reflect the quality of this decision-making process are needed. Such research has predominantly concentrated on patient satisfaction, psychological well being, anxiety, and distress, but it is also important to know the impact of screening results and risk interpretation on the choices participants make with regard to lifestyle and behavior. Much more is known about reproductive behavioral choices in prenatal CF carrier screening compared with screening outside pregnancy.[2,11,58] Only a very few carrier couples have been identified outside pregnancy,[2] and samples sizes are too small to warrant valid conclusions. Information on subsequent reproductive decisions is limited in both target groups, and research on long-term reproductive behavior is worthwhile.

The evaluation of pilot studies are a prerequisite to address the question of whether CF carrier screening should be implemented in the general population and how this could best be done. Until now, considerable research has been carried out, but to further investigate the outcome measures with regard to psychological and social aspects, continuous monitoring of (pilot) screening is recommended, in participants as well as in nonparticipants. Suggestions for outcome measures in the evaluation of screening programs are given in Table 6. This study provides a framework for information to support the interpretation of outcome measures in pilot studies not only investigating CF but also other genetic disorders.

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