will be interesting to see how the reformed NHS deals with this question. This is yet another reason for our erring on the side of financial caution.

Conclusion

We have to ask ourselves whether or not we are really enhancing patient choice and using money to the best effect. What is absolutely certain is that we are spending a lot of management and clinical time making

decisions on a relatively small number of patients. This time may not be used to its best advantage. There are benefits from NHS reforms, but billing may not be one of them. There are other methods by which provider units could have been recompensed or sanctioned for better or worse than average performance. True, we gain a lot of information about patient care within the service and we have been stimulated to find out what is available, but patient choice could easily be progressively restricted in future.

Screening for carriers of cystic fibrosis through primary health care services

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Abstract

Objective—To evaluate the uptake of cystic fibrosis carrier testing offered through primary health care services.

Design—Carrier testing for cystic fibrosis was offered to patients of reproductive age through primary health care services.

Setting—Three general practice surgeries and four family planning clinics in South West Hertfordshire District Health Authority.

Subjects—Over 1000 patients aged 16-44 attending two general practices and four family planning clinics and a stratified random sample of patients aged 16-44 from one general practice's age-sex register.

Results—When screening was offered opportunistically the uptake was 66% in general practice and 87% in family planning clinics. Ten per cent of those offered a screening appointment by letter took up the invitation. Of the screened population, 76% had previously heard of cystic fibrosis, 35% realised it is inherited, and 18% realised that carriers need not have any family history. If they found themselves in an "at risk" partnership 39% would consider not having children and 26% would consider terminating an affected pregnancy, but in each case most people were unsure how they would react.

Conclusions—Most people offered a cystic fibrosis test opportunistically wish to be tested, and the responses of those tested indicate that knowledge of carrier state would be considered in future reproductive decisions.

Introduction

Cystic fibrosis is a severe, autosomal recessive disease affecting one in 2500 live births in the British population. The clinical expression of cystic fibrosis is variable, although most patients show progressive pulmonary disease and pancreatic insufficiency with malabsorption. The average life expectancy for people with cystic fibrosis who were listed on the British Paediatric Association's register between 1977 and 1985 was 20 years, but these data relate to patients who were first treated more than 20 years ago and there have been considerable advances in treatment since then.¹ The carrier frequency in the British population is approximately one in 25; as for all autosomal recessive disorders, most infants with cystic fibrosis are born into families with no previous history of the disorder. A sizable reduction in the number of new cases of cystic fibrosis can only come from a programme of early identification of heterozygotes followed by prenatal diagnosis and selective termination if requested.

The gene mutated in cystic fibrosis has been shown to code for the cystic fibrosis transmembrane regulator.^{2,4} A three base pair deletion at position 508 of the protein accounts for about 78% of cystic fibrosis mutations in the British population.⁵ Two point mutations, G551D and R553X,⁶ account for a further 4% of cystic fibrosis mutations (unpublished data from this laboratory). These three mutations can be detected simultaneously by using the polymerase chain reaction, which will identify approximately 82% of carriers in our population. A simple mouthwash test serves as a reliable method of obtaining DNA for such an analysis.

Not all mutations within the cystic fibrosis gene have yet been identified, and many occur in only a few people. It may not be economically possible to achieve a much higher rate of carrier detection on a large scale. About two thirds of "at risk" couples can already be identified by using the simple test described above, so we carried out a pilot study of one approach to population screening for carrier state.

There are several approaches to carrier screening in the community, each with advantages and disadvantages (table 1).⁷ As cystic fibrosis carrier state has no known harmful effect on the personal health of the carrier it could be argued that screening should be offered to couples planning a pregnancy rather than to individuals. We chose to study pre-pregnancy carrier testing offered through community health services (general practitioners and family planning clinics). It is difficult to envisage how testing could be offered either opportunistically or by letter to "couples" through these services and we therefore elected to offer screening to any person of reproductive age who requested testing after they had been provided with an information leaflet and had a short discussion with a counsellor. We thought that by offering screening to people of reproductive age the carriers could be counselled at length, would have time to learn about cystic fibrosis and carrier state, and would retain a full range of reproductive options. The approach we have adopted is one of two recommended for pilot studies by the Cystic Fibrosis Research Trust (United Kingdom). It is important that such pilot studies are carried out in advance of widescale testing, whether by public bodies or commercial bodies, as such testing is not assessed for effectiveness or impact on those tested and counselled. We report the results of tests on 1000 people offered screening in three ways through primary health care facilities in south west Hertfordshire.

Methods

Subjects were recruited for screening from four health service family planning clinics and three general

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TABLE 1—Advantages and disadvantages of screening strategies

Strategy	Advantages	Disadvantages
Neonatal screening	Early identification of affected children Easily integrated into existing services (for example, screening for phenylketonuria)	Inefficient at reducing incidence of cystic fibrosis Delay until information is useful
Screening in schools	Captive population Majority pre-pregnancy Educational opportunity	No informed consent Stigmatisation of carriers Delay until information is useful
Screening in primary care	Majority offered test pre-pregnancy Autonomy and maximum choice	Miss non-attenders Education difficult to systematise
Antenatal screening	Relevant group Motivated Counselling integrated into general antenatal care	4% Identified as carriers at a sensitive time, of whom only 1 in 25 is at risk of having an affected child Late booking at antenatal clinic restricts diagnosis in first trimester Cystic fibrosis screening becomes a women's issue rather than a community issue
Testing of couples through antenatal clinic and notifying as positive only those who are carriers	As for antenatal group Only couples at risk notified, thereby minimising anxiety and costs in counselling Tests couples as a reproductive unit rather than individuals as carriers	As for antenatal group Must be tested again if partner changes Danger of misinterpreting a negative result as meaning both partners are negative

practices within South West Hertfordshire District Health Authority. Patients aged 16-44 were approached through one of two recruitment procedures. In all of the family planning clinics and in two general practices screening was offered opportunistically by one of two researchers (EW and KH) to each person attending during a given session. Although not medically qualified, both researchers have a detailed knowledge of the genetics, severity, and prognosis of cystic fibrosis and have met many people with cystic fibrosis and their families. At the other general practice screening was offered by invitation letter to a stratified, random sample of the target population obtained from the practice's age-sex register. The invitation letter was signed by a general practitioner and included an explanatory leaflet.

Each person offered testing was given (or sent) a leaflet outlining the nature of cystic fibrosis, the significance of the test, and how the sample is collected (mouthwash). Before testing the researcher spoke to the subject, describing cystic fibrosis as a serious and potentially life threatening disorder. Care was taken to mention the variation in severity of cystic fibrosis and that an increasing number of sufferers now live into adulthood and can lead a relatively normal life. The counsellor emphasised the voluntary nature of the test, that the health of carriers is not affected, that both parents must be carriers to be at risk of having an affected child, and the false negative rate of the test due to unidentified cystic fibrosis mutations.

All participants were asked to fill in a questionnaire, which investigated prior knowledge of cystic fibrosis and the possible effect knowledge of carrier state would have on future reproductive plans.

Buccal samples were collected according to a procedure modified from Lench *et al.*⁸ Subjects were asked to rinse their mouths with 10 ml of 0.9% sterile saline. The sample was collected in a Sterilin universal container and buccal cells were pelleted by centrifugation at 4K for five minutes. The cell pellet was resuspended in 500 µl 50mM sodium hydroxide and boiled for 15-30 minutes. Samples were neutralised with 100 µl 1M TRIS (pH 7.5) and 5 µl was taken for analysis.

Genomic DNA samples were amplified by the polymerase chain reaction. Each sample was coamplified with primers for $\Delta F508$, G551D, and R553X. The $\Delta F508$ mutation was detected directly on a 13% polyacrylamide gel. G551D and R553X were detected on the same gel after digestion of the polymerase chain reaction product with 0.5 U *HincII* (Gibco BRL) (figure).

Subjects were notified of their results by post. For those screening negative it was emphasised this result

Lanes 1 - 5, 7 - 11: buccal samples coamplified with ex10 and ex11 primers
Lane 6: known $\Delta F508$ /G551D heterozygote coamplified as above
Coamplification of buccal samples to detect $\Delta F508$, G551D, and R553X mutations

did not completely rule out the risk of being a carrier but lowered the risk from one in 25 to one in 130. Those identified as carriers were sent a more detailed explanatory leaflet with their result and given an appointment for genetic counselling. Counselling in each case was provided by the researcher with previous experience of genetic counselling for cystic fibrosis (EW). At the counselling session more detailed explanations of both the clinical and genetic aspects of cystic fibrosis were provided and testing was offered for partners or spouses and other family members. All carriers were given a follow up questionnaire (with stamped addressed envelope) at the counselling appointment to post back within two weeks. Those who did not attend counselling were posted a questionnaire.

Results

The uptake for opportunistic screening in the family planning clinics was 87% (374/431); in the general practice surgeries the uptake was 66% (340/513). In the general practice population the difference in uptake between men and women was not significant ($\chi^2=0.15$, $p=0.7$) (tables II and III). Forty five people requested a test themselves after seeing leaflets in the participating clinics or hearing about the test from friends.

In the screening by invitation letter, 852 patients from one general practice aged 16-44 were invited for screening; a total of 87 (10%) attended. There were no significant differences in uptake between men and women ($\chi^2=0.9$, $p=0.343$) (table IV). These data were

TABLE II—Uptake for opportunistic screening in two general practices

	Practice 1	Practice 2	Total
Men	53% (37/70)	78% (50/64)	65% (87/134)
Women	61% (123/201)	73% (130/178)	67% (253/379)
Total	59% (160/271)	74% (180/242)	66% (340/513)

TABLE III—Uptake for opportunistic screening in family planning clinics

Clinic	Uptake		
	Women	Men	Total
1	92% (47/51)	50% (1/2)	91% (48/53)
2	89% (182/204)	79% (11/14)	88% (193/218)
3	97% (69/71)	100% (2/2)	97% (71/73)
4	71% (62/87)		71% (62/87)
Total	87% (360/413)	78% (14/18)	87% (374/431)

TABLE IV—Uptake for screening by invitation letter

Age of target group	Men	Women	Total
16-20	4% (3/72)	18% (15/82)	12% (18/153)
21-25	19% (15/78)	10% (7/72)	15% (22/150)
26-30	8% (6/77)	8% (5/66)	8% (11/143)
31-35	11% (9/80)	18% (11/62)	14% (20/142)
36-44	5% (6/117)	7% (10/147)	6% (16/264)
Total	9% (39/424)	11% (48/429)	10% (87/852)

not corrected for inaccuracies in the age-sex register.

Before testing 77% of participants had heard of cystic fibrosis and 35% were aware that it is an inherited condition. In all, 44% knew that at present there is no cure for the condition, but only 18% knew that carriers need to have no previous family history of cystic fibrosis. There was no significant difference between men and women with respect to knowledge of cystic fibrosis.

Participants were asked how they thought their future reproductive plans might be affected if both they and their partner were found to be carriers. The responses are summarised in table V. The sample was divided into those with no direct experience of cystic fibrosis (877) and those who had a relative or knew someone with cystic fibrosis (123); in these groups 38% and 45% respectively felt that they might choose not to have children whereas 78% and 82% would request prenatal diagnosis for a high risk pregnancy, and 16% and 20% would not consider terminating an affected pregnancy. In the group with no direct experience of cystic fibrosis 25% would consider a termination but most (59%) were unsure what course of action they would take. A higher proportion (33% *v* 25%, $\chi^2=3.38$, $p=0.07$) of those with experience of cystic fibrosis would consider a termination, although again the largest group (47%) were unsure how they would react.

Of the first 1000 people who have been tested, 884 were non-Jewish, white British with no family history

TABLE V—Effect of knowledge of carrier state on future reproductive plans. Participants were asked what they would do if their pregnancy carried a one in four risk

Option	No previous experience of cystic fibrosis (n=877)	Relative or friend has cystic fibrosis (n=123)	Total (n=1000)
Would consider not having children:			
Yes	38% (274/717)	45% (44/98)	39% (318/815)
No	12% (84/717)	7% (7/98)	11% (91/815)
Don't know	50% (359/717)	48% (47/98)	50% (406/815)
Would request prenatal diagnosis:			
Yes	78% (660/839)	82% (98/120)	79% (758/959)
No	5% (40/839)	6% (8/120)	5% (48/959)
Don't know	17% (139/839)	12% (14/120)	16% (153/959)
Would consider terminating an affected pregnancy:			
Yes	25% (211/840)	33% (39/118)	26% (250/958)
No	16% (135/840)	20% (24/118)	17% (159/958)
Don't know	59% (494/840)	47% (55/118)	57% (549/958)

of cystic fibrosis. Other races, and those of Jewish ancestry, are excluded from this calculation because the frequency of the major mutation, $\Delta F508$, is much lower in these populations.⁹ Twenty nine carriers were identified, giving a population carrier frequency of one in 30 (884/29). As we detected only 82% of the cystic fibrosis mutations in the London population with our procedure (those for $\Delta F508$, G551D, and R553X) this is equivalent to a carrier frequency of one in 25.

Follow up studies of those found to be carriers are not yet complete, but we have formed preliminary conclusions. Of the 29 identified carriers, 25 to date have attended the counselling appointment arranged and four chose not to attend. Twenty five follow up questionnaires have been received. Three people have not returned the questionnaire despite a reminder. Initial reactions to the communication of carrier state varied from "surprised" (13) to "slightly anxious" (five) to "worried" (five) or "depressed" (one). Two to three weeks later (after counselling, or after notification of result when counselling was declined) 11 people were "less worried," eight were "not worried," and four remained "surprised." Two reported they were still worried. The wife of one of these two was pregnant at the time of testing and subsequently elected to be tested; she tested negative and the husband no longer felt worried. The second of these two was worried about the risk of his young children having cystic fibrosis. His anxiety was considerably lessened when his wife tested negative. Further counselling was available for anyone who requested it. Those counselled all felt it to be helpful (with the exception of one who was not sure) and either felt less worried or not worried after the appointment. Twenty of 25 found the information leaflet helpful and 20/25 were glad that they now knew their carrier state; five were not sure, and three of this group were those who chose not to attend for counselling. No carrier couples have yet been identified. In the study protocol they would be offered further specialist counselling to discuss the reproductive options open to them.

Discussion

We have shown that the uptake of cystic fibrosis carrier testing in the community is high when it is offered opportunistically in a primary care setting, whether through general practices (66%) or family planning clinics (87%). We believe that uptake was higher in the family planning clinics because a higher proportion of those attending were young and had not yet had children and therefore perceived the test as particularly relevant to them. In addition, those patients attending the general practitioner who felt unwell or depressed were, in our experience, unlikely to welcome any additional concerns.

Screening by invitation letter achieves a much lower uptake (10%). This is in line with findings from other screening programmes.¹⁰ These data conform to the predictions of the health belief model¹¹ in that screening is welcomed by most of those approached in a favourable setting, and particularly in the context of planned reproduction, but that most people are not sufficiently motivated to make an extra effort to be tested.

We have shown a high uptake for screening when it is offered opportunistically by committed researchers who have extensive experience with cystic fibrosis. If community screening on a large scale is introduced in a primary health care setting it is essential that the written information provided can be backed up by health workers who have a clear understanding of cystic fibrosis. If appropriate training courses were implemented health workers could easily acquire sufficient knowledge of cystic fibrosis and of genetics to

offer pretest information and counselling for those identified as carriers.

We have offered carrier testing to all those of reproductive age whether in a stable partnership or not, because this offers the maximum amount of reproductive choice; if testing is offered to couples it will often only be taken advantage of at the time of pregnancy, leaving only the choice of whether or not to opt for prenatal diagnosis and to terminate the pregnancy if the fetus is affected. Parallel pilot studies will determine whether testing of couples is equally, or more, acceptable to the community.

Knowledge of cystic fibrosis in the community is limited, as our previous studies have shown.¹²⁻¹³ Good educational material on genetics in general and cystic fibrosis in particular is lacking, and although genetic concepts are now recommended for inclusion in the British school curriculum, most of those tested would have received no genetic education at school.

The main aim of cystic fibrosis screening is to allow couples to make fully informed reproductive choices. These could include choice of partner, whether or not to have children, egg or sperm donation, adoption, antenatal diagnosis with or without termination of affected pregnancies, or choosing to have children without using the information. Participants in this study were asked to consider the possible effect on future reproductive plans if both they and their partner were found to be cystic fibrosis carriers.

In our sample about 40% of couples thought that they may opt not to have children. Almost 80% felt that they would want a prenatal test to determine whether or not the fetus was affected, although the possible risks to a pregnancy of prenatal testing were not discussed. Seventeen per cent of couples would not consider terminating an affected pregnancy, 26% would, and 57% were unsure how they would react. The difficulty of answering such complex questions, particularly for someone who may just have learnt of cystic fibrosis, should be taken into account when considering these responses.

The cost of laboratory items alone for cystic fibrosis carrier screening is about £1.75 per sample. Other costs that need to be assessed are capital costs of running the laboratory, collecting samples, and counselling needs. The costs of a total screening service are therefore likely to be measured in tens of pounds per sample, with a cost per carrier discovered measured in hundreds and the cost per case identified in the order of £50 000.

The average cost of treating someone with cystic fibrosis was estimated to be £10 000 a year in 1988¹⁴; the total cost for an affected person with a life expectancy of 20 years is thus £200 000, which is greater than the cost of testing and counselling through primary care practices. In these terms carrier screening for cystic fibrosis may prove to be cost effective for the NHS, but until it becomes clear what proportion of identified carrier couples modify their reproductive plans it is difficult to attempt a formal cost-benefit analysis. We must also consider opportunity costs, whether the cost of treatment for babies born with cystic fibrosis will rise, and the social and ethical considerations

involved in introducing carrier testing throughout the community.

Screening programmes have the potential to do more harm than good if those who test positive either do not receive adequate counselling or remain anxious or distressed.¹⁵⁻¹⁶ We are continuing to monitor the effect of screening on those identified as carriers in terms of possible anxiety caused, level of knowledge retained, and whether other family members have opted for testing. To date we have found that the reaction of most newly identified carriers is one of surprise, with a smaller proportion initially anxious or worried. Counselling was found to be helpful, and the great majority were glad they had been tested. Three of the five people who reported more negative feelings about knowing their carrier state had not attended the counselling session arranged. Therefore, though there are no technical problems associated with the introduction of the test and though most of those found to be carriers welcome testing, there is a small proportion of carriers whose needs are not met by the combination of education and counselling offered at present.

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