Screening for cystic fibrosis and its evaluation

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Cystic fibrosis (CF) is a recessively inherited disorder for which screening has been proposed. A number of different screening strategies have been suggested, including prenatal, preconceptional, school and neonatal carrier screening, as well as screening of newborns to identify affected infants. We discuss the advantages and disadvantages of these strategies, and identify gaps in knowledge relevant to decisions to introduce a screening programme for cystic fibrosis. Screening to identify carriers during the newborn period or among school age children is inadvisable, mainly on psychosocial and cost-effectiveness grounds. Although early diagnosis of CF may improve prognosis, current scientific evidence is not sufficient to support screening newborns to identify affected infants. Of the remaining two options, prenatal screening has a practical advantage because of existing facilities, while with screening before conception all reproductive options are, in principle, open to detected carrier couples. If adequate pre- and post-test counselling can be provided, both two types of screening could be introduced.

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Cystic fibrosis (CF) is a recessively inherited disorder for which screening has been proposed. There is widespread agreement that individuals with a family history of CF should be offered genetic testing as they are at increased risk of being a carrier (Table 1). Direct experience of CF in a family member may make decisions regarding carrier testing more informed and less abstract. Partners of affected individuals and of known carriers should also be offered genetic testing, as these couples are at increased risk of having a child with CF. However, the role of population-based testing of couples who are not known to be at high risk, either in early pregnancy or before conception, and of neonatal patient screening is less clear and is the subject of review in a number of countries. Recently, a consensus development panel of the US National Institutes of Health has recommended that genetic testing for CF be offered to couples currently planning a pregnancy, and to couples seeking prenatal care, in addition to adults with a positive family history of CF and to partners of people with CF. In this article, current knowledge regarding screening for CF will be reviewed and the implications for policy assessed.
Table 1 Probability of being a CF gene carrier for relatives of an affected individual

<table>
<thead>
<tr>
<th>Relative</th>
<th>Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brother/sister</td>
<td>67</td>
</tr>
<tr>
<td>Aunt/uncle</td>
<td>51</td>
</tr>
<tr>
<td>First cousin</td>
<td>26</td>
</tr>
<tr>
<td>First cousin once removed</td>
<td>14</td>
</tr>
<tr>
<td>Second cousin</td>
<td>8</td>
</tr>
</tbody>
</table>

Natural history

Cystic fibrosis (CF), first described in the medical literature in the 1930s, is characterised by recurrent lower respiratory tract infections resulting in chronic suppurative lung disease, and pancreatic insufficiency. It is associated with a shortened life span and impaired quality of life and requires lifelong medical care, as well as extensive support from relatives and friends, which may interfere with the normal daily life of both affected individuals and their relatives.

Meconium ileus occurs in 10–20% of newborns with CF and may be the earliest clinical manifestation of the condition. Most affected individuals need daily physiotherapy, repeated courses of antibiotics to treat pulmonary infections, as well as lifelong enzyme supplementation and a high energy diet. Affected adult males almost always have azoospermia, but reduced fertility also occurs in women.

There have been considerable advances in the medical care of individuals with CF, including recombinant human DNase which reduces the viscosity of purulent airway secretions, heart-lung transplantation, and home therapy. Current research in gene therapy may soon progress to the point of widespread clinical use. While these advances may improve the length and quality of life, for most affected individuals CF remains a disorder associated with reduced life expectancy. In the US, median survival is 31.1 years for men and 28.3 years for women, while in the UK, the median life expectancy of children with cystic fibrosis born in 1990, assuming continuous progress in survival in years to come, is estimated to be 40 years.

Genetics and prevalence

Cystic fibrosis is one of the most common recessively inherited disorders in Caucasian populations. Affected individuals (or homozygotes) have a CF gene mutation present on both chromosomes, but this is present on only one chromosome of carriers (or heterozygotes), who are not affected by the disorder and are healthy. Couples in which both partners
are carriers have a 1 in 4 risk with each pregnancy of having an affected child. Without screening, the existence of a carrier within the family is often only revealed following the clinical diagnosis of an affected infant. More than 80% of affected infants are born in families with no prior family history.\textsuperscript{16}

The prevalence of CF carrier status varies widely across different racial and ethnic groups, being very common among people in Northern Ireland (carrier prevalence 1 in 21 and birth prevalence 1 in 1807) and relatively rare among Hawaiian Orientals (carrier prevalence 1 in 150 and birth prevalence 1 in 90,000)\textsuperscript{17,18}. In the US and UK, the carrier prevalence is about 1 in 25, and, in The Netherlands around 1 in 30\textsuperscript{19,20}. There are suggestions that a high frequency of carriers reflects past or present genetic advantage\textsuperscript{21,22}, for example the gene may protect against typhoid fever which was a major killer in the past\textsuperscript{23}.

The gene responsible for CF was identified in 1989\textsuperscript{24–26}. This gene, called the cystic fibrosis transmembrane conductance regulator (CFTR) gene, codes for a protein that regulates a low-conductance chloride channel\textsuperscript{27}. Many, although not all, of the clinical manifestations of CF can be explained by the lack of this function. Soon after the CF gene was cloned, it was realised that screening for carriers would be possible through direct mutation detection.

Since 1989, a large number of mutations in the CFTR gene have been discovered, some of which have been detected in only one family. Currently more than 800 mutations have been identified (CF Genetic Analysis Consortium, \url{http://www.genet.sickkids.on.ca/cftr/}), the most common of which is the ΔF508 mutation, a three-base deletion in the gene. This mutation, together with a further 6–10 non-ΔF508 mutated genes, account for more than half of the population variation in CF mutations world-wide (Table 2).

\begin{table}
\centering
\caption{Most frequent mutations in the CFTR-gene}
\label{table:mutations}
\begin{tabular}{lccc}
\hline
 & Northern Europe (%) & Northern America (%) & World (%) \\
\hline
ΔF508 & 70.3 & 66.1 & 66.0 \\
G542X & 2.1 & 2.2 & 2.4 \\
G551D & 1.7 & 2.0 & 1.6 \\
N1303K & 1.0 & 1.2 & 1.3 \\
1717-1G→T & 0.8 & 0.4 & 0.6 \\
R553X & 0.8 & 0.9 & 0.7 \\
W1282X & 0.6 & 2.3 & 1.2 \\
621+1G→T & 0.5 & 1.5 & 0.7 \\
A455E & 0.2 & 0.3 & 0.1 \\
R1162X & 0.2 & 0.2 & 0.3 \\
14–16 other mutations & 2.3 & 2.7 & 2.2 \\
\textbf{Total} & \textbf{80.2} & \textbf{79.9} & \textbf{77.3} \\
\hline
\end{tabular}
\end{table}

Source: CF Genetic Analysis Consortium\textsuperscript{29}
Screening and screening tests

CFTR mutations can be detected by PCR analysis of material obtained by a mouthwash or bloodspot\(^28\). With the mouthwash procedure there is no need for medical supervision of sample collection. The mouthwash procedure has, theoretically, an almost perfect sensitivity and specificity, apart from laboratory errors\(^28\). This relatively simple detection of CFTR mutations makes it possible to consider introducing a screening programme for carriers of the cystic fibrosis gene, where the primary aim is to assess carrier status and counsel couples whose members are both carriers of a CF gene mutation\(^29,30\). These couples can then be offered prenatal diagnosis by chorion villus sampling or amniocentesis.

Because of the large number of mutations in the CFTR gene it is not feasible to test all individuals for all possible mutations. However, if individuals are tested with a panel of probes consisting of the mutations from Table 2, approximately 80\% of the carriers and 64\% (80\% of 80\%) of the carrier couples can be detected. Because of the imperfect test sensitivity, couples with one test-positive and one test-negative partner have an (increased) risk of 1 in 484 of having an affected child, compared to a 1 in 2500 baseline risk\(^31\). However, these individuals cannot be offered prenatal diagnosis.

New methods of DNA testing, for example allele specific oligonucleotide (ASO) and denaturing gradient gel electrophoresis (DGGE), use a combination of probes in one panel. These have a high sensitivity, for example over 90\% for ASO and 98\% for DGGE per individual in The Netherlands. This means that more carrier couples can be detected, but, on the other hand, the costs of the screening will increase also since these tests are rather expensive at the moment.

Screening strategies

Several screening strategies for cystic fibrosis have been suggested\(^32-35\). Of these, prenatal, preconceptional, school and neonatal screening can be considered for general population screening.

Screening couples before conception and in early pregnancy

For high risk couples, screening before conception (preconceptional screening) has several potential advantages over screening in early pregnancy (prenatal screening), including the option not to have children, time to adjust to the information presented and time to make decisions about prenatal diagnosis, with potentially less anxiety\(^36,37\).
Other reproductive options available as a consequence of preconceptional screening include the use of artificial insemination with screened donor sperm, screened egg cell donation or pre-implantation diagnosis. However, the effectiveness of preconceptional screening is uncertain, since at present there is no routinely available opportunity to screen all couples who are not yet pregnant but may intend to become so in the near future. In view of this, a preconceptional consultation centre has been proposed as a new health service provision\textsuperscript{38}. Alternatively, couples planning to become pregnant may consult their general practitioner.

Several strategies and definitions for prenatal and preconceptional carrier screening exist, and these can be distinguished with regard to the testing process and the information process\textsuperscript{31,32,39,40}. Among the strategies are stepwise screening, where one partner (usually the woman) is screened first, and only the partners of those found to be carriers will be offered screening. One disadvantage of the approach is that it generates anxiety in women identified as carriers. However, this anxiety appears to be short-lived and disappears among women whose partners test negative\textsuperscript{41}. In stepwise screening, three test outcomes are possible: both partners are test-positive (++ couples), one partner is test-positive and the other test-negative (+− couples), and one partner is test-negative and the other is not tested (−? couples).

Another strategy is couple screening, where the couple is treated as an entity. Both partners submit a sample simultaneously and, if both are identified as carriers, the couple is designated as being at high risk and reported as positive. In contrast, couples in which one partner is tested positive and one negative are designated negative although their risk of an affected infant is higher than the prior risk for the general population. One of the arguments for couple screening is that unnecessary anxiety, due to identifying couples of mixed carrier status, can be avoided by simply treating all couples not at high risk as negative. This caused concern among geneticists as it was felt that the results of all genetic testing should be made available to those tested and not withheld\textsuperscript{42}. A compromise has been to make the results available on request rather than routinely. Early experience from pilot studies in The Netherlands shows that almost all couples want both partners to be tested and to obtain individual results (L Henneman, unpublished data).

Since stepwise screening also aims at the couple, the terminology 'stepwise' and 'couple' can be confusing. For this reason, the terms single-entry two-step (SETS) couple screening and double-entry two-step (DETS) couple screening have been proposed (Fig. 1)\textsuperscript{31}. In these strategies, both partners submit a sample. In single-entry two-step screening, one partner is tested first (first step) and if he/she is identified as a carrier the second partner is tested. The first partner is tested for the AF508 and other frequent mutations, while the second partner is tested...
Screening for carriers in the neonatal period or at school age

Screening school aged children for recessive conditions is feasible, and pilot projects have been conducted to screen for thalassaemia carriers in Italy, for Tay-Sachs disease carriers in Canada, and for CF carriers in Australia and Canada. Although, from a community-genetic perspective, school screening may offer an opportunity for teaching genetics, this has been questioned. One problem is the difficulty in...
maintaining confidentiality of test results. Furthermore, there is concern that because school screening takes place in a rather unstable stage of life, this might lead to stigmatisation.\footnote{48}

Since a blood sample, stored as a dried blood spot, is obtained from all newborns and tested for phenylketonuria and congenital hypothyroidism, it would be easy to include screening for CF carriers in the existing neonatal metabolic screening programme. Identification of newborn carriers provides an opportunity to test both parents with a view to ascertaining previously unrecognised high risk couples and extend their future reproductive choices. Obviously, as the average family has less than two children, detected carrier couples can use this knowledge of being carrier only for about one child on average. However, there are several problems with this approach. It may be a disadvantage to combine routine screening for conditions for which effective treatments are available with screening for carriers of genetic conditions.

Another disadvantage of identifying carriers as newborns or school children, is that this information only becomes relevant to the carrier when they are of reproductive age, some 10–30 years later. Considerable efforts would be required to retain this information and this would be helped by a computer database or an individual health-passport. Furthermore, it is most likely that the current screening tests will be obsolete in 10–30 years as new screening methods and new insights in the disease process will have emerged.

**Cascade testing**

Specific to genetic diseases is the possibility of testing relatives and offspring of affected patients and known carriers – this is termed cascade testing. The advantage of cascade testing is that the relatives or offspring of the affected individual have a higher-than-average risk of being carriers (Table 1). In addition, as discussed earlier, contact with an affected relative and hence greater familiarity with the implications of being affected, may allow more informed choices about screening and reproduction to be made than are possible for the general population.

A disadvantage of cascade testing is that it will not identify the majority of carrier couples since more than 80% of affected infants are born in families without a prior history of the disease.\footnote{16} It cannot, therefore, be considered an effective screening strategy. Holloway and Brock\footnote{49,50} estimated that 4–13% of all carriers in Scotland would be detected by cascade testing, which would result in 8–24% of all carrier couples being detected, compared with more than 50% detection through prenatal screening.\footnote{31} Brock\footnote{50} concluded that cascade testing
Screening

should only be considered in combination with general population screening.

**Neonatal patient screening**

In 1968, Schutt and Isles reported excessive albumin in the meconium of patients with meconium ileus due to CF\(^5\). This made neonatal screening for cystic fibrosis patients a possibility\(^{52,53}\). In 1979 Crossley *et al.* reported that immunoreactive trypsin (IRT) was raised in the serum of children with cystic fibrosis\(^5\). Since newborn screening using a dried blood-spot assay for IRT has a higher sensitivity than meconium albumin and because it was widely believed that early diagnosis would improve outcome, newborn screening programmes were developed in Europe, the USA and Australia. The sensitivity of the IRT test (85.7%) and the specificity (99.8%) are improved by testing for the AF508 mutation in high-risk bloodspots (sensitivity 95.2%, specificity 99.9%), but false positives are still possible\(^5\). Therefore, the diagnosis is confirmed by a sweat test\(^5\).

The rationale for newborn screening to identify affected infants has been questioned. It has been argued that evidence is lacking that an early diagnosis will substantially improve outcome for the patient. While the findings of several studies have suggested that patients with CF who are diagnosed early, *i.e.* before the onset of clinical pulmonary involvement, have a better prognosis than those whose diagnosis was made when pulmonary symptoms developed\(^5\), all of these studies have some methodological problems.

The only randomised controlled trial, funded by the National Institutes of Health, started in 1985 in Wisconsin, USA\(^6\). A total of 650,341 newborns were recruited, and allocated to either newborn screening or no screening. Dried blood spots were tested for the 325,170 recruited newborns allocated to no screening but the results were withheld until these infants reached 4 years of age. In the screening arm of the trial, infants who screened positive received a sweat test and confirmed positives were treated according to a protocol. Age at diagnosis was lower in the screening group (median age 7 weeks) compared with the no-screening group (median age 23 weeks). Nutritional status is being evaluated by anthropometric and biochemical methods in affected children in both groups and has been reported for the first 10 years of follow-up. It was found that children in the screening group were significantly heavier than their unscreened counterparts, both at time of diagnosis and during the follow-up period. However, although remaining better in the screened infants, these
differences were less marked and of no statistical significance by 5–6 years of age. The authors concluded that ‘neonatal screening provides the opportunity to prevent malnutrition in infants with cystic fibrosis’. Respiratory outcomes have not been reported from this trial but are proposed.

In an accompanying editorial, it was concluded that ‘the results of this new study provide further evidence that the time has come for routine neonatal screening for cystic fibrosis’\(^6^7\). However, the issue of lead-time bias, a form of selection bias, has been raised in another editorial, which, it was suggested, may substantially alter the interpretation of the trial findings\(^6^8\). This arises because the probability of diagnosis in both arms of the trial is only equal after 4 years of age. Before this age, children diagnosed in the ‘screening’ group will include those with less severe disease which may not have presented clinically by this age, in contrast to those diagnosed by this age in the ‘no screening’ group, who are likely to have more severe disease\(^6^8\). Evidence for such a bias is suggested by the fact that the overall results presented in the original trial report were strongly influenced by the results in the first three years. The authors of this second editorial have proposed that further analyses comparing outcome in the screened and unscreened groups be restricted to outcomes measured after the age of four years. They concluded that ‘the present evidence is not encouraging and does not warrant any change in policy from that suggested by the National Institutes of Health consensus statement’\(^1\), which recommended that newborns should not be screened.

### Results of (pilot) carrier screening programmes

Several pilot studies of CF carrier screening have been reported and these are summarised according to screening strategy (Tables 3 and 4). Uptake is highest for prenatal screening (either stepwise or couple) with a weighted average of 75%. The average uptake of preconceptional screening is 7–9% when individuals or couples are invited for screening, 38% and 76%, respectively, for opportunistically offered screening of individuals and couples. Uptake is influenced by the method of invitation to screening (opportunistic contact or written or other invitation) as well as the setting, with rates as low as 2% reported when the invitation is sent by post\(^8^2\), compared with rates as high as 87% when screening is offered to visitors of a family clinic by committed researchers\(^8^3\) (not shown in the table). Only two studies have been performed using a school setting: uptake was 42% in the Canadian study, and 42% and 75% in two high schools in Australia\(^4^5,4^6\).
Table 3  Summary of studies reporting prenatal screening for CF carriers69-79.

<table>
<thead>
<tr>
<th>First author</th>
<th>Place</th>
<th>Population</th>
<th>Number of couples screened</th>
<th>Coverage (% of population screened)</th>
<th>Number of affected pregnancies detected</th>
<th>Number of affected pregnancies terminated</th>
<th>% of detected pregnancies terminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris⁶⁹</td>
<td>Manchester</td>
<td>NA</td>
<td>127</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Schwartz⁷⁰</td>
<td>Copenhagen</td>
<td>7,400</td>
<td>6,599</td>
<td>89%</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Jung⁷¹</td>
<td>Berlin</td>
<td>638</td>
<td>637</td>
<td>100%</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Cuckle⁷²</td>
<td>Yorkshire</td>
<td>6,071</td>
<td>3,764</td>
<td>62%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Miedzybrodzka⁷³</td>
<td>Aberdeen</td>
<td>1,629</td>
<td>1,475</td>
<td>91%</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Brock⁷⁴</td>
<td>Edinburgh</td>
<td>6,030</td>
<td>4,978</td>
<td>83%</td>
<td>2</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>Doherty⁷⁵</td>
<td>Maine</td>
<td>NA</td>
<td>1,645</td>
<td>NA</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Loader⁷⁶</td>
<td>Rochester</td>
<td>5,646</td>
<td>3,334</td>
<td>59%</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Witt⁷⁷</td>
<td>Northern California</td>
<td>6,617</td>
<td>5,161</td>
<td>78%</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Grody⁷⁸</td>
<td>Los Angeles</td>
<td>4,739</td>
<td>3,192</td>
<td>67%</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
</tbody>
</table>

All prenatal stepwise studies: 38,770 couples screened, 75% coverage, 7 detected, 6 terminated, 86% terminated.

Prenatal couple screening:

<table>
<thead>
<tr>
<th>First author</th>
<th>Place</th>
<th>Population</th>
<th>Number of couples screened</th>
<th>Coverage (% of population screened)</th>
<th>Number of affected pregnancies detected</th>
<th>Number of affected pregnancies terminated</th>
<th>% of detected pregnancies terminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris⁶⁹</td>
<td>Manchester</td>
<td>NA</td>
<td>117</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Miedzybrodzka⁷³</td>
<td>Aberdeen</td>
<td>361</td>
<td>321</td>
<td>89%</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Wald⁷⁹</td>
<td>Oxford</td>
<td>810</td>
<td>543</td>
<td>67%</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Brock⁷⁴</td>
<td>Edinburgh</td>
<td>16,571</td>
<td>12,566</td>
<td>76%</td>
<td>6</td>
<td>6</td>
<td>100%</td>
</tr>
</tbody>
</table>

All prenatal couple studies: 17,742 couples screened, 76% coverage, 6 detected, 6 terminated, 100% terminated.

NA means that data are not available; these are omitted in the calculation of totals.

The most common reason for declining CF carrier screening was unwillingness to terminate an affected pregnancy⁷⁶,⁸⁴,⁸⁵. This does not appear to be the case once a couple has consented to be screened. The results of published prenatal screening studies show that, of the 13 high risk couples with an affected fetus identified as a consequence of screening in early pregnancy, all but one chose to terminate that pregnancy. Data for preconceptional screening studies are not available.

Economic considerations

Previously, we have estimated the costs, effects and savings of prenatal, preconceptional, school and neonatal CF carrier screening for the Dutch situation where 1 in 30 persons is a carrier⁸⁶. From this, we concluded that, in The Netherlands, savings of prenatal and single-entry two-step preconceptional screening have a favourable cost-savings balance (i.e. the savings of the programme are higher than the costs), but that double-entry two-step preconceptional screening and neonatal screening will only have...
a favourable cost-savings balance if uptake of screening, prenatal diagnosis and induced abortion are high enough. The costs of school screening will be higher than the savings for all realistic assumptions.

In Table 5, we have applied the same methodology to the UK, where 1 in 25 persons is a carrier and 732,000 children were born in 1995. Assuming that all couples will have exactly two children, 366,000 couples will then be screened yearly. As expected, the conclusions of this evaluation are comparable to those reached for The Netherlands, since the assumptions made are largely similar.

In the UK, we estimate the costs per carrier couple detected (not shown) to be lowest for neonatal carrier screening because it detects most carrier couples, as parents of detected carrier newborns are also tested, and they can use the test information for further reproduction. The costs per carrier couple detected through prenatal screening are approximately 10% lower than through preconceptional screening. Because the prevalence of CF carriers is higher in the UK than in The Netherlands, even the savings of double-entry two-step preconceptional screening and of neonatal screening (not shown) are greater than the screening costs. From this estimate, there would appear to be no economic objections to prenatal, preconceptional or neonatal screening in the UK. In contrast, the costs of carrier screening of school aged children are estimated to be higher than the savings (not shown).
Table 5 Estimated costs, effects and savings of prenatal and preconceptional CF screening

<table>
<thead>
<tr>
<th></th>
<th>Prenatal</th>
<th>Preconceptional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SETS</td>
<td>DETS</td>
</tr>
<tr>
<td>Costs of screening</td>
<td>£9,951,000</td>
<td>£14,450,000</td>
</tr>
<tr>
<td>Number of detected carrier couples</td>
<td>332</td>
<td>378</td>
</tr>
<tr>
<td>Number of couples with one detected carrier</td>
<td>9,624</td>
<td>19,249</td>
</tr>
<tr>
<td>Costs per detected carrier couple</td>
<td>£30,000</td>
<td>£38,000</td>
</tr>
<tr>
<td>Number of prenatal diagnoses</td>
<td>546</td>
<td>622</td>
</tr>
<tr>
<td>Number of terminations</td>
<td>109</td>
<td>124</td>
</tr>
<tr>
<td>Number of affected pregnancies averted*</td>
<td>113</td>
<td>128</td>
</tr>
<tr>
<td>Costs per affected pregnancy averted *</td>
<td>£88,000</td>
<td>£113,000</td>
</tr>
<tr>
<td>Net economic savings (savings – costs)</td>
<td>£16,492,000</td>
<td>£15,449,000</td>
</tr>
</tbody>
</table>

* The number of avoided patients is higher than the number of induced abortions since some detected carrier couples refrain from having children.
1 Based on 366,000 couples screened. Costs and savings are converted to present values using a 3% discount rate.

most important assumption which might not hold is that the relative magnitude of the costs and savings in the UK is similar to that in The Netherlands. However, as reported in the original paper86, the conclusions hold for a wide range of decision and cost assumptions.

We have compared our estimates of the cost per carrier couple detected through prenatal screening with those published for the UK by others. Our estimates are much higher than those reported by Cuckle et al72, who calculated a cost per carrier couple detected of approximately £20,000. However, the latter analysis assumed 100% uptake of prenatal diagnosis and induced abortion and did not include costs of further diagnosis and treatment, in contrast to our study which assumed 85% uptake of prenatal diagnosis, 80% uptake of induced abortion, and included costs of further diagnosis and treatment. In contrast, the costs estimated by Morris and Oppenheimer88 were similar to our estimates, being about £36,000 per carrier couple detected.

An assessment of CF screening

In The Netherlands, the Dutch Population Screening Act requires that central government approves certain screening programmes before they are implemented. Because genetic screening has some special implications, a committee of the Health Council of The Netherlands has issued a report on genetic screening89. In this report, the committee formulated criteria for the introduction of genetic screening programmes, taking the criteria of Wilson and Jungner90 as a starting point. The committee
divided these criteria into eleven absolute criteria that have to be complied with by every screening programme and ten weighing criteria that have to be provided to the review body so that the body can make an informed deliberation of the advantages and disadvantages of screening. Screening for cystic fibrosis is assessed in relation to these criteria in Table 6, which also identifies important gaps in the evidence required to support policy decisions. Although CF screening satisfies most of the criteria, some are not completely satisfied. These are discussed below.

Criterion 3 (‘awareness of disease or carrier status’) and Criterion 5 (‘voluntary participation and informed consent’) are not met for school and neonatal screening, since minors are tested who legally cannot give informed consent.

Criterion 4 (‘practical courses of action’) is also not completely met for school and neonatal screening, since the value of the information from screening for carriers detected as newborns or school-aged children lies far in the future, by which time they may have forgotten their test results. Since preconception screening gives the carrier couple more options than prenatal screening (avoiding pregnancy, artificial insemination, pre-implantation diagnosis), preconception screening can be considered preferable with regard to this criterion.

With regard to Criterion 6 (‘accurate and comprehensible information’), there is a debate about the amount of information to be given to couples in the single-entry two-step version of carrier screening for cystic fibrosis where one partner is identified as a carrier and the other is not. Since the latter may have a mutation that is not detectable with currently available screening tests, these couples have a higher risk than the untested general population of an affected child but do not have the option of prenatal diagnosis. Understanding these and other implications of genetic testing for CF requires a high degree of genetic knowledge, including understanding of complex concepts such as test sensitivity, carrier status, patterns of inheritance, risk/probability and genotype-phenotype correlations. Given the recognised gaps in genetic knowledge among the general public, it is essential that any genetic testing programme includes written informed consent as well as adequate resources for education and counselling.

Criterion 8 (‘sufficient facilities for screening and diagnosis’) is partially met. Approximately 350 carrier couples can be expected per year in the UK with prenatal screening and 200 couples with preconceptional screening (Table 5). For these carrier couples, there would be sufficient facilities for counselling in clinical genetic centres. This may not be the case for couples where one partner is identified as a carrier and the other is not, given that, each year, 19,249 such couples may be identified through prenatal couple screening and 12,734 through...
Table 6 Criteria for assessing screening programmes proposed by the Health Council of The Netherlands, applied to CF carrier screening

<table>
<thead>
<tr>
<th>Absolute criteria</th>
<th>CF carrier screening strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preconceptual</td>
</tr>
<tr>
<td></td>
<td>or prenatal</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>The programme concerns a health problem or condition that can lead to a health problem</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>The target population is clearly defined</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>The programme enables participants to become aware of the disease or carrier status</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>+/-</td>
</tr>
<tr>
<td>Practical courses of action are open to the participants</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>Participation is voluntary and consent is based on good information</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+/-</td>
</tr>
<tr>
<td>The target group is supplied with accurate and comprehensible information</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+</td>
</tr>
<tr>
<td>A suitable test method is available</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>There are sufficient facilities for every step in screening and diagnosis</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>+</td>
</tr>
<tr>
<td>The personal privacy of the participants is protected</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>+</td>
</tr>
<tr>
<td>If scientific research is carried out, participants are properly informed about this</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>+</td>
</tr>
<tr>
<td>There is continuous quality assurance regarding tests, follow-up and participant information</td>
<td></td>
</tr>
</tbody>
</table>

Weighing criteria. There should be information about:

| 12a The prevalence of the disease or disorder | Y | Y |
| 12b The natural course of the disorder | Y | Y |
| 12c All possible target groups and the considerations which led to the selection of the target group and the time in life for testing | Y | Y |
| 12d The performance of the screening test, including the burden which testing imposes on the participants | Y | Y |
| 12e The available courses of action after a positive test result | Y | Y |
| 12f The time allowed for consideration and possible implementation of the courses of action | Y | Y |
| 12g The possible psychological, social and other repercussions of the offer, participation and non-participation to participants and other people | N | N |
| 12h The possibility and consequences of erroneous results | Y | Y |
| 12i The guarantees to prevent participants experiencing unjustified impediments from obtaining employment or private insurance cover as a result of (non-)participation in the screening and follow-up testing | Y | Y |
| 12j The costs which are linked to the screening and to the attainment of the requisite infrastructure | Y | Y |

+ the criterion is or can be satisfied;
+/- the criterion is not completely satisfied;
- the criterion is not satisfied or there are not enough data to enable a judgement;
Y there is enough knowledge with regard to this criterion; and
N there is not enough knowledge with regard to this criterion.
preconceptional couple screening. It has been suggested that these couples could be counselled by trained paramedics ('project-nurses'), who might also have a role in testing family members of detected carriers. There are likely to be adequate facilities for an estimated maximum of 622 prenatal diagnoses and 124 induced abortions each year (Table 5).

Although Criterion 11 ('continuous quality assurance') can in principle be satisfied in any CF screening programme, special attention has to be given to the quality control of CFTR typing. In a European Concerted Action on Cystic Fibrosis, Cuppens and Cassiman found that only 25 of 40 participating laboratories throughout Europe (62.5%) were able to type correctly all nine samples with various CFTR alleles, and that 4 laboratories (10%) typed three or more alleles incorrectly. However, a significantly lower error rate was observed in laboratories from the UK, which is believed to be a direct consequence of their participation in a quality control scheme. This quality control testing has been operational for more than three years since the time of the study of Cuppens and Cassiman.

Insufficient knowledge is available regarding adverse psychological, social and other repercussions (Criterion 12g). Factors such as anticipated decision regret, perception of the severity of the condition as well as perception of risk influence the decisions to accept or decline screening. The complexity of the concept of 'carrier status' and its implications for family members may also make the screening decision difficult. Possible anxiety caused by the screening result appears to be short-lived, with most of those accepting the offer of screening expressing a preference for certainty over not knowing. Furthermore, carriership could influence the self-perception and the perceptions of others who are not carriers, for example carriers view their future health with less optimism than people who are not carriers. Most CF patients and their families appear to have a positive attitude to carrier screening and termination of affected pregnancies. No adverse repercussions from a medical point of view have been reported.

Discussion

It is very important that the target group receives adequate and balanced information. It should include at least a description of the disease, inheritance patterns and relevant aspects of test performance. The offer of testing should be made to enable couples who wish to avoid the birth of a child with CF to do so, without influencing those who do not. Care should be taken to ensure that the decision to have testing is completely voluntary.
We agree with the National Institutes of Health consensus statement that CF testing be offered to couples seeking prenatal testing and couples currently planning a pregnancy, and should not be offered to other target groups. Ideally, preconceptional screening should be provided because, with this strategy, all reproductive options remain open for carrier couples. Prenatal screening can be used as an alternative or as a ‘safety net’ for pregnant couples who have not been screened before conception. Particular emphasis should be given to the implementation of a routine quality control scheme in participating laboratories.

As for many diseases, advances in medical treatment for CF are and will be made. This progress in treatment will most likely have an impact on the length and quality of a CF patient’s life. As treatment improves the quality of life of CF patients, screening for CF gene carriers may in the future be a thing of the past.

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