# CYSTIC FIBROSIS

Both antenatal and neonatal screening for CF have been considered. *Antenatal* screening aims to identify fetuses affected by CF so that parents can be offered an informed choice as to whether they wish for termination of pregnancy. This account concentrates mainly on neonatal screening with a brief resume of antenatal screening, which is the remit of the antenatal subgroup.

***The condition:***

1. **The condition should be an important health problem. YES.**

Cystic fibrosis is an inherited disorder affecting the lungs & the digestion of food, leading to frequent chest infections, and under-nutrition. It is inherited as an autosomal recessive condition, so that parents are healthy, but if both parents are carriers of the cystic fibrosis gene they have a one in four risk of having an affected child. It is one of the most common recessively inherited paediatric disorders in Northern Europe, affecting one in every 2500 children of Northern European origin. It is much less common in children from other ethnic groups.

2. **The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker and a latent period or early symptomatic stage. YES.**

*Neonatal* screening aims to identify cases before they present clinically with symptoms. The rationale for this is that this may reduce the risk of permanent lung damage by avoiding malnutrition and repeated chest infections. While there have been striking improvements in outlook for cystic fibrosis, with more than half of affected children now surviving to adult life, most still die prematurely and of the respiratory complications of the condition. For this reason preservation of respiratory function is an important therapeutic goal. A secondary benefit of screening is to avoid the lengthy delays and frequent admissions that sometimes characterise the early history of these infants prior to diagnosis. This is an important cause of parental dissatisfaction. However screening the whole population represents only one strategy to achieve earlier diagnosis of clinically presenting cases. In Canada a national campaign to increase health professionals' awareness of cystic fibrosis reduced delays in diagnosis - and data from the Canadian patient registry suggests that nutrition and survival among children with cystic fibrosis have improved.

3. **All the cost-effective primary prevention interventions should have been implemented as far as practicable. NOT APPLICABLE**

There are no primary prevention measures except that pre-conceptional counselling might avoid conceptions of CF fetuses. Antenatal screening identifies affected fetuses so that termination can be offered, but strictly speaking this is secondary prevention.

***The test***

4. **There should be a simple, safe, precise and validated screening test. NO AGREEMENT ON WHICH IS BEST TEST TO USE.**

*Newborn infants* can be screened at the same time as the phenylketonuria test, and here the aim is to identify the condition as early as possible. CF screening is available to about 18% of UK infants. The neonatal blood spots are tested, initially for IRT (immunoreactive trypsin). If positive, there are several options – six protocols are listed in the HTA review (Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

Screening for cystic fibrosis. *Health Technology Assessment* 1999;3(8).). A second IRT test may be done. Some of the most common gene mutations may be checked for. Infants who screen positive on any of these protocols will need to be seen for diagnostic testing by a specialist experienced in cystic fibrosis. This usually involves a sweat test to measure the amount of chloride in the sweat. Quality assurance mechanisms must be in place and are not currently defined. There is currently considerable variation between UK laboratories in the test protocols used and the test kit used.

5. **The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. PROBABLY**

The sensitivity (proportion of true cases identified) of *neonatal screening* is 90-97% depending on the protocol used, but these figures may be over-optimistic as there may be under-ascertainment of missed milder cases. The HTA review suggests an overall detection rate of 86% is realistic.
Specificity (labelling correctly someone as not having the condition, i.e. false positive rate or 1- specificity) is more difficult to assess because the protocols differ significantly in their approach. The three stage protocol will identify 7.2 per 1000 infants tested as positive on first screening and an overall false positive rate of 0.6 per 1000, i.e. out of about 3000 neonates tested, 2 will be labelled as having the disease when they don't and one will be correctly labelled as having the condition.

6. **The test should be acceptable to the population.**

The test uses a blood specimen already obtained so it involves no added distress to the baby. However whether the genetic testing is acceptable to families is not known and in many ways the use of DNA based testing procedures in the child raises similar issues to that of DNA based testing procedures antenatally. Currently there is no formal consent to testing obtained from parents when the blood specimen is obtained but this is likely to change.

7. **There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals. NO**

Using the IRT method as the starting point, there are six different protocols for the process to be followed when the first screen is positive. Some differences are rational e.g. differences in the type of DNA probes used reflect differing prevalence of genotypes in the population, but the diversity in procedure is generally confusing and difficult to justify. Management of classic cases is not controversial but there is insufficient agreement on how to diagnose and manage children with atypical diagnostic features (see below) who are detected through screening programmes but whose clinical outlook is uncertain. The information that should be given to parents of carrier infants is not currently well defined.

***The treatment***

8. **There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment. THIS IS DEBATABLE AND IS THE MAIN ITEM FOR FURTHER STUDY.**

There are between 250 and 300 births per year in the UK of infants with CF. Of these, around 15% are diagnosed at birth because of meconium ileus. Some, perhaps 20%, are second children in a known at-risk family. Some cases are mild and may benefit relatively little from early diagnosis; some are severe and present early, even

before the result of the screen is known. There are no hard data but these figures suggest that perhaps only 1 in 6 or 1 in 8 CF children may gain any major benefit from being identified before they present clinically. This amounts to between 30 and 50 children each year in UK.

Some children have unusual genotypes, with mild symptoms. The sodium concentration in sweat, for long considered the gold standard of diagnosis, can be close to normal in the mild cases. The advice to be given and the follow-up needed for mild cases are still controversial.
Early diagnosis allows the maintenance of optimal nutrition which may improve the long-term prognosis. RCTs still in progress suggest benefits from screening in terms of nutritional status but benefits in terms of lung function need longer follow up and have not yet been reported. There is indirect evidence that continuous antibiotic treatment may be of benefit. Parents and clinicians are strongly supportive of neonatal screening.

There is a lack of robust evidence that early diagnosis by screening really makes a significant difference to the outcome. The conclusion on current data is that there is some modest benefit. Further research, especially with respect to cohorts currently being followed, may throw more light on this, but the long life expectancy and good health status of the current cohort suggest that a different result is unlikely.

9. **There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered. YES, IN MOST CASES.**

Yes, for classic cases, but lack of consensus on how to manage cases with minimal symptoms and signs associated with some of the less common mutations.

10. **Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme. YES, IN MOST CASES.**

In general, yes: >70% of CF children cared for by teams with a special interest, quality of care for remainder probably satisfactory.

***The screening programme***

11. **There must be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. NOT CLEAR YET**

RCTs to date suggest modest benefits especially in terms of nutritional status, but no data yet for lung function. There are few data on other benefits of screening such as avoiding long delays before diagnosis or multiple admissions to hospital.

12. **Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened. NOT APPLICABLE**

However the introduction of an antenatal screening programme might change the balance of benefits and hazards.

13. **There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public. SEE 6 ABOVE.**

14. **The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).**
    **NOT DIRECTLY KNOWN BUT PROBABLY YES**: but only for programmes run to a high standard, since neither the screening protocol nor the judgements that have to be made when unusual mutations are found are simple and straightforward.

15. **The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).**
    Neonatal cost data suggest that a UK programme would cost around £0.7 to 1 million, for the screening test (it does not include the cost of subsequent diagnosis) with the lower figure associated with economies of scale and rationalisation of laboratories. Economic analyses of the true cost of neonatal screening are of uncertain reliability but both cost and quality would probably benefit from rationalising laboratory services.

16. **There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.**

Individual laboratories run quality control systems, but each programme has its own protocols and methods. A standardised programme would have to be developed and implemented.

17. **Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme.**

Around 18% of UK children are screened at present. New investment would be needed to extend the programme.

18. **All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.**
    Evidence from Canada suggests that increased professional awareness reduced delays in diagnosis. At the same time nutrition and survival of Canadian children with cystic fibrosis have improved.

19. **Evidence based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.**
    Parents could be informed about the screen via the Personal Child Health Record, if it were given out soon after birth. This could ensure some uniformity of information. Failing this, a leaflet could be given to mother soon after delivery. This could encompass all screening tests performed on the baby. Currently there is a lack of uniform approach to information about newborn testing and no formal consent procedure.

**20. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public. NOT APPLICABLE**

**Other aspects of CF screening**

*Antenatal screening* is offered in some centres, but this is still on a small-scale and there is as yet no experience of mass population screening. It was reviewed by the antenatal sub-group.

Screening for cystic fibrosis can also be provided as part of an *assisted conception programme*. This is best regarded as good clinical practice and is recommended in the HTA review on CF screening.

When an infant is diagnosed with cystic fibrosis, a referral to *genetics service* is advisable so that when appropriate other members of the extended family can be advised of their risk status.

**Summary – state of the art, recommendations**

- The evidence was reviewed by the *antenatal sub-group* and they concluded that the evidence does not currently support introduction of countrywide *antenatal* screening.
- The case for "screening" in cases of assisted conception is well presented in the HTA review and is supported.
- *Neonatal screening* is already offered for 18% of UK infants. The probability is that any further trials would confirm that screening has only modest benefits. Definitive evidence may not be forthcoming for several years. This is a programme in which the ratio of potential benefit to harm, in terms of wasted resources, false positives and false negatives, is finely balanced.

The CSG did not wish to recommend neonatal screening at present. As one fifth of babies are already being screened in the UK, considerations of equity cannot be ignored. This decision should be reviewed in the light of further research in which the following issues would need to be addressed:

1. Re-analysis of current trial data and further follow-up of trial subjects especially in respect of lung function.
2. The cost is kept to a minimum and the quality of the process is assured by automation, concentrating services in a small number of labs, ensuring that uncertain results are interpreted by an experienced person, developing protocols for referral to expert paediatric services and investing in follow-up advice, for instance by a specialist nurse.
3. The protocol for screening, obtaining second samples and informing parents is agreed between centres, or if there is genuine justifiable disagreement, a trial is designed to settle the issues.
4. There is a consensus, or failing that an agreed trial design, on the management of mild, borderline and atypical cases; on the management of cases who turn out to be false positives or carriers; and on the nature of quality monitoring and control mechanisms for the laboratory service, the information flows to parents and the clinical care provided for infants diagnosed with CF.
5. Quality control and management. This will follow the model proposed at the start of this report.

**Quality of evidence**
For care of CF in general: many strands – rising life expectancy, trials on individual treatment issues (overall II-2).
For screening: RCTs but the interpretation is difficult because of design problems. In UK there is strong clinician support. (overall II-1)

**Strength of recommendation**
The evidence for and against screening is finely balanced. Purely on NSC criteria, the neonatal programme should be rejected at present, because of uncertainty about long term benefits for respiratory function, lack of agreement on screening protocols, lack of consensus on care of mild cases, and lack of a quality management structure beyond local level. However, it may be questioned whether further trials will do other than again show modest benefits. The other issues could be addressed if there is the professional will to do so

**Research and development issues.**
See above.

**Sources of information**
Screening for cystic fibrosis was considered in two systematic reviews on biochemical screening in the newborn ((Seymour C A, Thomason M J, Chalmers R A, et al. Newborn screening for inborn errors of metabolism: a systematic review. *Health Technology Assessment* 1997;1(11) and Pollitt R J, Green A, McCabe C J, Booth A, Cooper N J, Leonard J V, et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. *Health Technology Assessment* 1997;1(7).) and has been the subject of a further systematic review (Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J. Screening for cystic fibrosis. *Health Technology Assessment* 1999;3(8)).. In addition, a number of recently published papers have provided further information, in particular an economic analysis undertaken by a Dutch group.

**Status of the recommendations**
The issue has been considered at a joint seminar held by members of the antenatal and the children's subgroups of the National Screening Committee and the recommendations set out above were considered at a full meeting of the National Screening Committee.