Newborn screening for cystic fibrosis: the practical implications

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Depending on their place of birth, an infant in the UK currently has about a 1 in 4 chance of being screened for cystic fibrosis (CF). This paper will consider the evidence for newborn CF screening, reflect on the methods currently in place and discuss the practical implications of future developments towards a national programme for CF newborn screening in the UK.

WHY SCREEN FOR CF?

There are many protocols to screen for CF in the newborn period and, generally, they fulfil the criteria laid down by the World Health Organization (WHO) with respect to sensitivity and specificity (i.e. they identify most cases and miss only a few).[1] These protocols are relatively economical and, if run efficiently, should not cause harm to the infant. However, there is no robust evidence that CF screening fulfils the final WHO criterion that a newborn programme should result in significant improvement in outcome for the child. Data are available from two randomized controlled trials examining clinical outcomes following newborn screening.[2,3] The first study, based in the UK, demonstrated reduced admissions in the first year of life but no other benefit from being identified early.[4] The second study, based in Wisconsin, demonstrated evidence of early improved nutritional outcomes in screened children compared with those diagnosed conventionally. Subsequently the nutritional condition of the screened and non-screened groups has converged and the most recent published data from the group demonstrates that the screened children now have more evidence of CF lung disease on their chest radiographs (related to earlier chronic *Pseudomonas aeruginosa* chest infection).[5]

These studies have focused on clinical outcomes and have not assessed the psychological outcome of distress associated with a delayed diagnosis,[6] nor the consideration that newborn screening gives parents the opportunity to terminate future affected pregnancies. A report from France confirmed this to be a factor in a significant number of families.[7]

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SCREENING PROTOCOLS FOR CF

All current screening programmes employ measurement of immunoreactive trypsinogen (IRT) on a sample of blood in the first week of life as the initial screening test.[1] This is a sensitive test and very few infants with CF will be missed. However, a significant number of infants without CF will be included and a further step is required to improve the specificity of the screening programme. One method is to simply repeat the IRT test at about 28 days of life in these infants, at which point the test becomes much more specific. Infants with a persistently raised IRT are referred for assessment and sweat test.[8] A number of countries/centres still employ this protocol: however, studies have demonstrated that a significant number of CF infants are missed with repeat IRT at 28 days and this has prompted laboratories to explore alternative methods to increase the sensitivity of the programme. Identification of the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene in 1989 provided such a method. ΔF508 is by far the commonest mutation of the *CFTR* gene that causes CF and advances in molecular genetics have made rapid identification of this mutation straightforward.[9]

It is possible, therefore, to employ DNA analysis on a raised first IRT sample. A significant number of infants with two ΔF508 mutations will be identified as having CF at this stage; however, over 1000 mutations of the *CFTR* gene have been identified and some infants with CF will be missed. Infants with one ΔF508 mutation will either be carriers (studies suggest that carriers have higher IRT levels so the screening programme is more likely to recognize carriers than would be expected by chance[10]) or will be affected infants with a different mutation on their other *CFTR* gene. The sensitivity of the test can be improved by examining for other commonly occurring mutations. However, this is associated with a 'law of diminishing returns', in that after a certain point increasing the number of mutations on the DNA panel by say 10 or 20 will result in the recognition of fewer and fewer additional cases but will increase the number of carriers identified.[10] Although recognition of carrier status may be of some benefit (particularly to family members through cascade screening[11]) the potential harm to families needs also to be considered, particularly concerning the issue of non-paternity (i.e. ΔF508 not recognized in either parent following a positive ΔF508

result on their infant). If an infant is recognized to have one *CFTR* mutation, a raised second IRT test at 28 days is almost always associated with a positive diagnosis. Some programmes have incorporated this into the screening protocol in an attempt to reduce the number of infants requiring a sweat test. However, as many as 1 in 10 infants with one *CFTR* mutation recognized and a low IRT at 28 days will still have CF, so it is important that families are provided with clear and precise information if such a programme is to be employed.

THE CURRENT SITUATION IN THE UK

Northern Ireland, Wales and Scotland all run newborn screening programmes for CF. Northern Ireland employs an IRT–IRT programme. Wales undertakes DNA analysis on raised IRT samples and organizes a sweat test on all infants with one or two CF-causing mutations. Scotland has the most recent programme and has incorporated measurement of IRT at 28 days on those infants with one *CFTR* mutation in order to reduce sweat tests. The four programmes in England employ a variety of methods (East Anglia and Northampton have employed IRT–IRT; Trent IRT–DNA–IRT; and the City of Leeds undertakes IRT–IRT but also DNA analysis on all samples).

The proposed national screening programme

A multidisciplinary group, chaired by Dr George Rylance, Newcastle, has been formed to aid implementation of a national UK screening programme, provisionally targeted to begin in April 2004. The group has decided to employ a protocol that includes DNA analysis of an initial raised IRT and a second IRT on samples when only one *CFTR* mutation is recognized (similar to the Trent and Scottish programmes). The successful running of such a programme will depend on clear links between laboratories and CF centres and primary and secondary health care professionals (Figure 1). Particular attention needs to be paid to the initial contact with the family.

Processing a positive result

A positive result will be channelled through the Regional CF Centre to the local designated CF team. The local team will liaise with primary care and arrange for a visit to the family home. This may be undertaken by the Health Visitor or the general practitioner, depending on circumstances, and the primary care team may opt to make this visit with the CF Nurse Specialist. The first visit should be made early in the week and in the latter part of the day (afternoon or early evening). The family should not be overloaded with information at this point, but informed that 'the screening test suggests a possible diagnosis of cystic fibrosis and further assessment is required by the specialist CF team'.

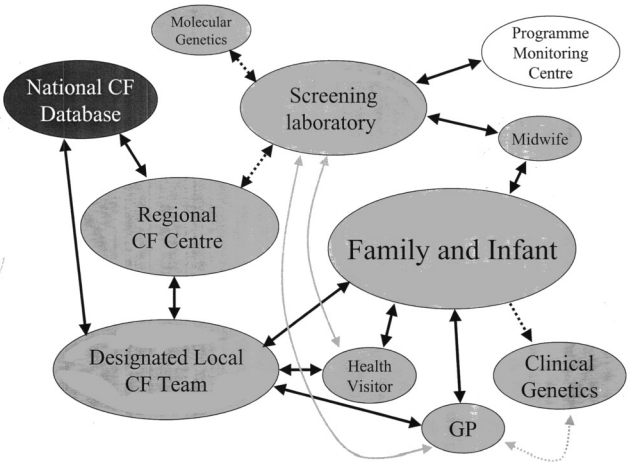

Figure 1 **Diagram demonstrating the multidisciplinary links required to run a successful newborn screening programme for CF** (bold arrows, established links; dashed arrows, not established; light arrows, recognition of a carrier)

Arrangements should be made for the family to be seen the following morning. In the meantime, clear information and links to reputable web sites may be left with the family. It is important that the primary care professionals feel supported by the CF team, but it is inappropriate for them to be giving the family a lot of information at this first visit, even though the family may seek it. The Regional Centre will be able to provide support if staff are unavailable from the local CF team (for example during periods of annual leave). Local implementation groups are being established to clarify these pathways. It is important that positive results are processed rapidly; however, this process should not be rushed and preparation is needed for each case.

Recognition of carrier status

Any newborn screening programme that employs DNA analysis will result in the recognition of carriers and the number of CF carriers recognized by this programme may be more than one would expect by chance for the reasons highlighted above. Infants with one recognized mutation and a raised second IRT will require assessment by a CF team as described above, with a prompt sweat test forming part of that assessment (a lower threshold is used for a positive sweat test at this age[12]). When one *CFTR* mutation is identified and the second IRT is below the threshold the result will be 'CF not suspected'. However, a small number of these infants will have CF (approximately 1 in 10), albeit sometimes not a 'classical' form of the condition. The general practitioner and family will be informed of this result. It is important that the family has information at this point that is clear and easily understood. They need to know that (1) a diagnosis of CF has not completely been excluded in this infant, (2) as a couple, they are still at risk

of having a child with CF in the future, and (3) the screened infant is a carrier of one CF-causing mutation. CF carrier status will have implications for the infant in later life and may have current implications for relatives. The family will be advised to seek advice from a clinical geneticist. In some cases the family may not wish to initiate cascade screening for personal reasons. As the programme develops this will need to be reviewed.

Potential benefits and caveats

Despite the lack of robust evidence to support a national newborn screening programme for CF, there are potential benefits:

- to provide each family with a CF infant the opportunity of specialist centre care (through an established shared care system)
- a reduction in the distress associated with delayed diagnosis
- the potential for full acquisition of cases onto the National CF Database
- the opportunity to establish large multicentre randomized controlled trials examining therapeutic interventions.

However, we need to be aware of certain caveats if this programme is to be successful:

- there is no perfect screen for CF in newborns (cases will be missed and paediatricians and adult physicians will need to remain vigilant to the possible diagnosis)
- the identification of carrier status is not necessarily a positive experience and may result in distress, particularly in the situation of non-paternity
- there is still the potential to cause distress to families if the result of the screen is not given in a thoughtful and empathetic manner
- parents of 'well' children with CF will still find the situation stressful (in some ways it is more difficult to be living with the anticipation of future deterioration in condition).

The way forward

Issues of funding to cover laboratory costs, training, production of information materials and administration are being addressed, although presently there are no 'top sliced' funds available for this programme. If a national programme is to commence in April 2004 this will require some considerable commitment from CF carers around the country and the concerted efforts of a number of disciplines. With a coordinated effort the potential benefits to families and children in this country will be significant.

REFERENCES

1 Southern KW, Littlewood JM. Newborn screening programmes for cystic fibrosis. *Paediatr Respir Rev* 2003;**4**:299–305

2 Chatfield S, Owen G, Ryley HC, *et al*. Neonatal screening for cystic fibrosis in Wales and the West Midlands: clinical assessments after five years of screening. *Arch Dis Child* 1991;**66**:29–33

3 Farrell PM, Kosorok MR, Laxova A, *et al*. Nutritional benefits of neonatal screening for cystic fibrosis. *N Engl J Med* 1997;**337**:963–9

4 Doull IJ, Ryley HC, Weller P, Goodchild MC. Cystic fibrosis-related deaths in infancy and the effect of newborn screening. *Pediatr Pulmonol* 2001;**31**:363–6

5 Farrell PM, Li Z, Kosorok MR, *et al*. Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. *Am J Respir Crit Care Med* 2003;**168**:1100–8

6 Merelle ME, Huisman J, Alderden-van der Vecht A, Taat F, *et al*. Early versus late diagnosis: psychological impact on parents of children with cystic fibrosis. *Pediatrics* 2003;**111**:346–50

7 Scotet V, De Braekeleer M, Roussey M, *et al*. Neonatal screening for cystic fibrosis in Brittany, France: assessment of 10 years' experience and impact on prenatal diagnosis. *Lancet* 2000;**356**:789–94

8 Crossley JR, Elliott RB, Smith PA. Dried blood spot screening for cystic fibrosis in the newborn. *Lancet* 1979;**i**:472–4

9 Bobadilla JL, Farrell MH, Farrell PM. Applying CFTR molecular genetics to facilitate the diagnosis of cystic fibrosis through screening. *Adv Pediatr* 2002;**49**:131–90

10 Pollitt RJ, Dalton A, Evans S, Hughes HN, Curtis D. Neonatal screening for cystic fibrosis in the Trent region (UK): two-stage immunoreactive trypsin screening compared with a three-stage protocol with DNA analysis as an intermediate step. *J Med Screen* 1997;**4**:23–28

11 Super M. Cystic fibrosis newborn screening and detection of carriers. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F448–9

12 Massie J, Gaskin K, Van Asperen P, Wilcken B. Sweat testing following newborn screening for cystic fibrosis. *Pediatr Pulmonol* 2000;**29**:452–6