

CYSTIC FIBROSIS

Ethical issues at two extremes

Emma Farrar and Jemma Smith worked as medical students with consultant paediatrician Clare Peckham at a time when services for cystic fibrosis were undergoing a transformation. Clare herself is leading the local service development. Neonatal screening for cystic fibrosis started in the North West on 1 October 2007.

The right of a child to be involved in decision making concerning his or her future has recently been affirmed by the General Medical Council. These events provide the backdrop to two timely articles on the ethical issues involved in the management of a difficult illness.

NEWBORN SCREENING

What are the issues?

Emma Farrar

Cystic fibrosis (CF) is the United Kingdom's (UK) most common life threatening inherited disease, affecting over 7,500 people. Over two million people are carriers of the faulty gene causing the condition, which represents approximately 1 in 25 of the population.⁽¹⁾

CF is an autosomal recessive inherited disorder which results in a gene mutation on chromosome 7. This causes a defect in a transmembrane regulator protein (known as the cystic fibrosis transmembrane conductance regulator) which transports chloride across epithelial cell membranes. This results in increased viscosity and tenacity of secretions in the airways, pancreas, gastrointestinal and genital tracts.

CF patients usually present either at birth with meconium ileus, or later on with symptoms of malabsorption, such as failure to thrive and frequent loose stools, or respiratory symptoms such as cough and recurrent chest infections. Diagnostic tests include sweat testing, which identifies increased levels of chloride in the patient's sweat, or DNA analysis. Most cystic fibrosis sufferers are managed using a multidisciplinary healthcare approach and are treated with replacement pancreatic enzymes, vitamin supplements, antibiotics and physiotherapy. The average life expectancy for a person with CF is 31 years, although this is likely to increase given recent improvements in treatment.⁽¹⁾

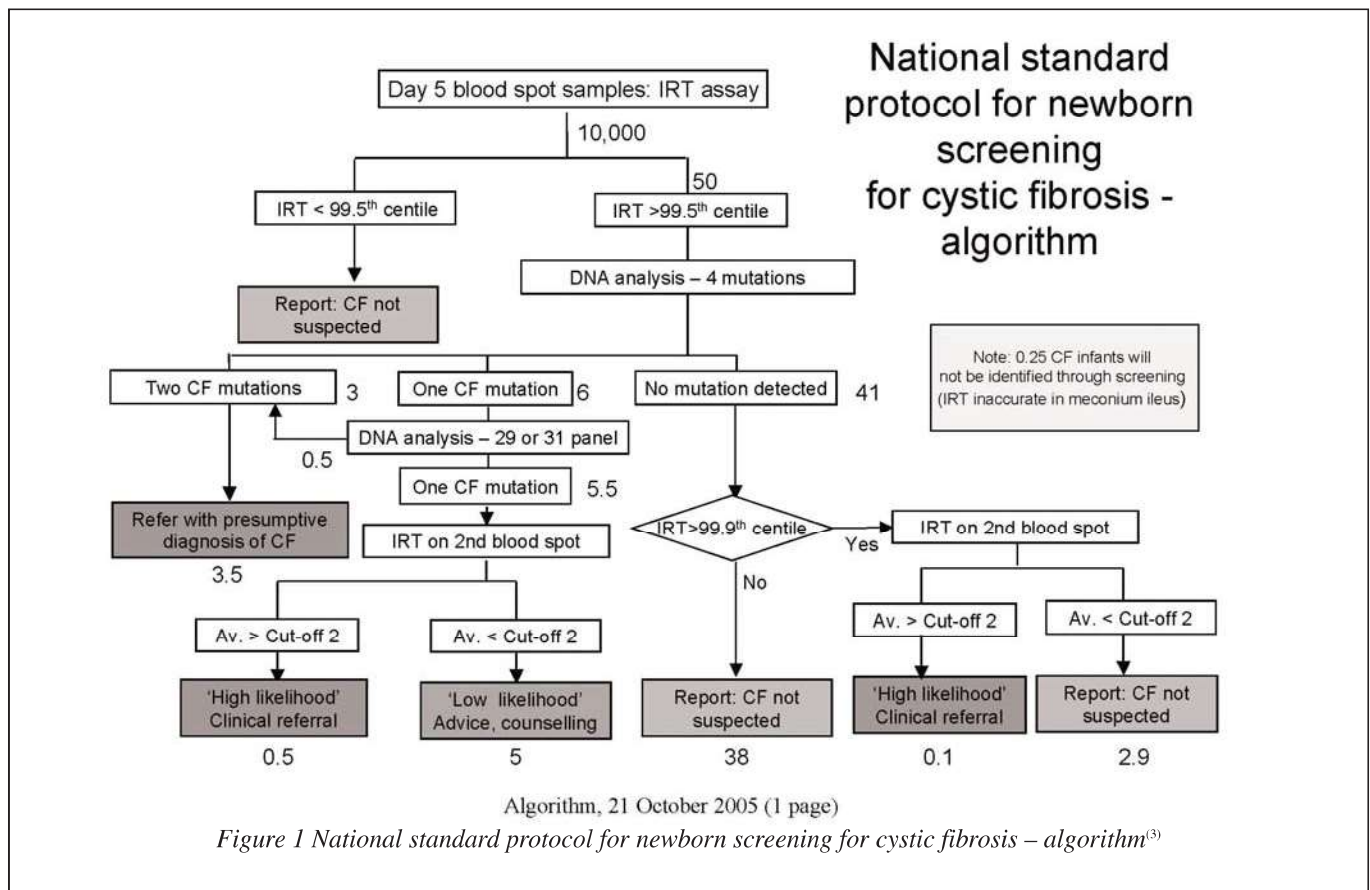
In the UK, newborns are routinely screened for a variety of conditions as part of the newborn bloodspot screening programme. These conditions have traditionally included phenylketonuria, congenital hypothyroidism, sickle cell disorders and others specific to certain regions. Since the 1980s, cystic fibrosis has become part of the programme, but only in a few areas. It wasn't until 2004 that plans to extend this to the whole of the UK began to be implemented and it was estimated that all newborn babies would be routinely screened for CF by April 2007.⁽²⁾ Due to funding issues in the North West, newborn CF screening has actually only just been implemented this month.

THE SCREENING PROCESS

So how is screening for cystic fibrosis carried out? With parental consent, a blood sample is taken from the baby as part of the usual heel prick test and is tested for levels of an enzyme called immunoreactive trypsin (IRT). If the levels are low then it is reported as 'CF not suspected'. However, if the levels are high then the blood goes for DNA analysis. After DNA analysis, if two CF mutations are detected then a diagnosis of cystic fibrosis is suspected and a clinical referral is made for further diagnostic tests including the gold standard, the sweat test. If one CF mutation is detected then a further blood sample is taken and sent for repeat, more sensitive IRT levels. Results from this test can either be 'CF suspected' or 'CF carrier'. If no CF mutation is detected after DNA analysis and the initial IRT levels were raised, then the second IRT test is carried out. Results in this instance can be 'CF suspected' or 'CF not suspected'. The national standard protocol for newborn screening for CF can be viewed in figure 1.⁽³⁾

Regardless of the condition, newborn screening is, on the whole, seen to be advantageous as it allows early detection of pre-symptomatic babies who have serious and potentially life-threatening conditions if not treated. It can also ensure that early treatment is given to improve health in the long term. Screening for cystic fibrosis is evidently a complicated process and it can only raise a suspicion of CF not a confirmed diagnosis. Also, not all gene mutations that cause CF can be tested for '*as there are over 1200 identified alterations and screening, at present, only aims to identify 29-31 of these.*'⁽⁴⁾ There is also debate as to whether it is ethically just to inform parents of a child's CF carrier status, as this could cause just as much distress as an actual diagnosis.

With the amount of controversy surrounding incorporating CF testing as part of newborn screening the aim of this project was to discover, from an ethical point of view, whether the advantages outweigh the disadvantages, and also to relate these to ethical principles using relevant literature where appropriate.



The ethical principle of autonomy

The ethical principle of autonomy is 'the capacity to think, decide, and act on the basis of such thought and decision, freely and independently'.⁽⁵⁾ Health professionals respect patient autonomy by enabling patients to come to their own decisions about their care and by respecting and following these decisions.

With regards to CF newborn screening, it can be seen that, to an extent, parental autonomy is being respected. Parents can make an autonomous decision as to whether they want their child to be screened and this may serve to avoid professional paternalism. On the other hand, however, it should be highlighted that, even though the child is not old enough to consent (or even speak), it does not show respect for the child's autonomy. It could, however, be argued that even if the child was to be tested at a later date, a decision about whether to test or not would most likely be made by the parents anyway.

Another element of screening that respects parental autonomy is the fact that parents can be alerted to the risks of having other CF-affected children. This enables them to then go on to make informed decisions about future fertility. Despite this, however, some research suggests that having a child with CF detected at neonatal screening does not necessarily influence future reproductive decision making. A study in 1998 found that 70% of their study population who had CF diagnosed in their first child conceived more children.⁽⁶⁾ Prenatal diagnosis was only used by 26% with CF being detected in three pregnancies, all of which were carried to term. Despite the study sample being small, the authors concluded that neonatal CF screening does not have a significant impact on the future fertility of most families and were surprised how underutilised prenatal diagnosis was.

A 2006 study showed contrasting results.⁽⁷⁾ In a similar-sized study sample, 60% of parents used prenatal screening and CF was detected in five pregnancies. All of these pregnancies were terminated. It was thus concluded that families with a child diagnosed with CF at birth do in fact actively use reproductive technologies, and they maintain the right to do so.

Neonatal CF screening not only detects children with a suspected diagnosis of CF but also those who carry the mutation and are unaffected. Little literature exists in relation to attitudes of children who were detected as carriers at birth. This is most likely due to the fact that neonatal CF screening has only recently been introduced and these children have yet to reach adulthood. In some respects, knowing about carrier status will allow autonomous decision making about future fertility and may warrant carrier testing of a reproductive partner. It also gives the person time to come to terms with the possibility of having a CF-affected child and what this involves. On the other hand, they may resent knowing about their carrier status and the fact that they had no part in making an informed decision about this. Knowing one is a carrier for a disease may prove more detrimental and harder to accept than having a confirmed diagnosis.

The ethical principle of beneficence

Carrier status identification can also be related to the ethical principle of beneficence. This principle places importance on doing good to others and in a medical context means doing the best for our patients.⁽⁵⁾ The question of who decides what is best for the patient is subject to some debate. In relation to newborn CF screening, doctors and the parents may feel that screening a newborn for CF is what is best for the patient, thus promoting beneficence. As mentioned before, a person may experience a certain amount of distress knowing their carrier status which goes against this.

Identifying CF at birth rather than later on in life may also encourage beneficence. Both the sufferer and their parents may show better psychosocial adjustment through knowing about the diagnosis from the beginning. There is also some evidence that suggests that an earlier diagnosis may prevent worse illness in later life. This is, however, better related to the principle of non-maleficence.

The ethical principle of non-maleficence

'Non-maleficence is the other side of the coin to the principle of beneficence as it states that we should not harm patients.'⁽⁵⁾ By screening patients at birth for cystic fibrosis it could be said that we are acting with non-maleficence by attempting to prevent worse outcomes in later life. This is a topic that has been widely researched and it was found that a lot of the evidence was conflicting.

A 2003 study compared early versus late diagnosis of cystic fibrosis using outcomes of bronchopulmonary disease 10 years later.⁽⁸⁾ It was found that, initially, the newborn screened group showed fewer chest X-ray abnormalities, but after the ten-year period had worse X-rays as a result of earlier *Pseudomonas aeruginosa* colonisation. Interestingly, later research provided support for these findings as it also discovered mean times from CF diagnosis to initial infection with *Pseudomonas* to be shorter in the screened group.⁽⁹⁾

A similar study two years later found similar results with regards to chest disease.⁽¹⁰⁾ This study, however, included more outcome measures and provided convincing support for the benefits of newborn CF screening. It was found that those diagnosed through screening at birth had better heights, weights and head circumferences and generally showed better growth than the later-diagnosed group. These findings were supported by results of a similar study in 2007.⁽¹¹⁾ Both studies concluded that it is possible that newborn CF screening serves to prevent malnutrition and growth failure which could prevent disease progression.

Further studies that provide support for CF screening at birth include one which found that patients who had CF detected at birth required less treatment compared with age and genotype matched cystic fibrosis affected controls.⁽¹²⁾ If this is the case, it would be interesting to discover if costs incurred by newborn screening could be counteracted by the reduction in future treatment costs of CF patients. It will always be important to discover if newborn screening prevents not only a reduction in future morbidity, but also mortality. Research relating to this is quite sparse. A study in 2006, however, did detect a modest difference between groups concluding that newborn CF screening may result in improved child survival.⁽¹³⁾

Related anxieties

Further issues with regards to newborn CF screening can be related to the ethical principles of beneficence and non-maleficence. It could be argued that screening eliminates parental anxiety about why their child is ill when the disease manifests itself in later life. The screening process does, however, go against beneficence and non-maleficence with the related anxieties it itself can initiate.

Despite the provision of support and genetic counselling along the way, parents are likely to experience significant amounts of stress and worry at many of the different stages of the screening process. They may experience anxiety after being told their child requires a further blood spot as well as after being told that a diagnosis of CF is highly likely. Indeed, a

2005 study found that parents waiting for sweat test appointments to confirm diagnosis scored highly on measures of emotional distress and depressive symptoms.⁽¹⁴⁾ These did, however, vary depending on their perceptions of the likelihood of CF being detected. Parents may also feel guilty about having their children screened and going through the process, irrespective of the result, may cause harm to relationships and family dynamics.

Further limitations of screening

Before concluding, it is necessary to mention some further limitations of newborn CF screening that cannot as easily be related to ethical principles. As mentioned before, screening cannot pick up all mutations and tests are also not 100% sensitive and specific. Only around 90% of cases of CF will be accurately picked up through neonatal screening. *'Screening doesn't identify those babies with CF who have meconium ileus. These babies will need treatment in the neonatal period for this condition and so will be diagnosed anyway.'*⁽¹⁴⁾ Finally, it is also difficult to differentiate between those that are healthy carriers (those with only one alteration) and those who actually have CF (who have a second unidentified alteration). It is estimated that as many as 6% of carriers identified could actually have CF as they actually have another unidentified genetic alteration.

CONCLUSION

It is clear that the subject of newborn cystic fibrosis has generated much interest and discussion as well as varying amounts of praise and criticism. It should be mentioned that many of the studies referred to in this piece do have their limitations. It is very difficult to compare disease progression in CF patients as the disease manifests itself differently in different individuals. It may simply have been that those who had worse illness later on were simply worse-affected individuals, not because CF was detected any earlier or later. Many of the study samples were also small, making results less generalisable to larger populations. It may actually be far more appropriate to regard CF as a spectrum of diseases rather than one specific disease. This makes it quite difficult to apply the general principles of screening to CF.

On the whole, however, much of the research reviewed as part of this piece provided support for newborn CF screening. From an ethical standing, it also appeared favourable.

Newborn CF screening is still developing, although its benefits are evident given that it is soon to become part of the heel prick test in all centres in the UK. In Europe, approximately 1,600,000 newborns are already being screened for CF with over 400 affected infants being recognised.⁽¹⁵⁾ Given this, maybe we should now shift the focus of whether it is appropriate to screen for CF onto how we can optimise both the medical and psychosocial outcomes of screening.

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LUNG TRANSPLANTATION

What are the issues?

Jemma Smith

INTRODUCTION

Since the 1960s, when the first-ever heart transplant was carried out, organ transplants have become one of the great medical advances of the 20th century.⁽¹⁾ Organ transplantations now provide real opportunity for improved quality of life and survival, and cystic fibrosis (CF) is a perfect example of this. There is no effective therapy of end-stage pulmonary disease in CF other than lung transplantation.⁽²⁾ Lung transplantation has been used as a treatment for end-stage lung disease since the 1980s, and by 1999 almost 1,000 children had received lung or heart/lung transplantations worldwide.⁽³⁾ The majority have been children with CF.

CF patients tend to have better survival rates after lung transplantation, compared to other indications for this

procedure. The survival rate of patients one year after lung transplantation is 75-85%.^(4,1) Five-year survival is estimated to be somewhere between 45-65%.^(4,5) However, this assumes that the patient receives the transplant; unfortunately, 40% of patients will die whilst on the waiting list.⁽¹⁾

Children with CF, especially females, have a higher two-year mortality rate than their adult or male counterparts.⁽⁶⁾ Young female patients are even highlighted in the referral guidelines because they have a poorer prognosis,⁽⁷⁾ and need early referral.⁽⁴⁾ This means that a lot of the transplants occurring in CF patients are in children, which introduces many more issues into the scenario, both medical and ethical. This article aims to look at several pertinent ethical issues surrounding the decision for lung transplantation in children with CF.