

Genetic screening for cystic fibrosis: An overview of the science and the economics

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Abstract

The aim of this paper is to provide an overview of the current scientific and economic thinking on the use of genetic technologies for cystic fibrosis (CF) screening. The paper takes a public health genetics viewpoint and gives an overview of the genetics behind CF, then describes current practices in screening for the disease. We then discuss the current literature on the economic evaluations of screening for CF. As the “wet” science improves, there are direct implications for health service. Therefore, it is important to keep examining both clinical practice and economics behind the technologies.

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1. Introduction

The purpose of this paper is to provide an overview of the current scientific and economic thinking on the use of genetic technologies for cystic fibrosis (CF) screening. CF, a life-threatening disease that progressively worsens over time, most commonly occurs in people of Caucasian extraction. It causes

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severe respiratory problems and inadequate pancreatic function due to the production of excess sticky mucus; most males affected by CF are also sterile. Disease severity varies between affected individuals. Death usually results from respiratory failure, although improvements in treatment in recent years have increased average life expectancy to over 30 years. At least half of individuals born with CF since 1990 are now expected to live beyond 40, but there remains no known cure for the disease.

The paper takes a public health genetics viewpoint and will first give an overview of the genetics behind CF, then lay out current practices in screening for the disease. The remainder of the paper will be a discussion of the economic evaluations carried out in the area of screening for CF.

2. Genetics and CF

Cystic fibrosis is caused by deleterious mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), which regulates the transport of chloride ions across epithelial cell membranes in the lungs, gut, pancreas and certain other organs. Inadequate or absent chloride transport in individuals with CF leads to the accumulation of mucus, which can cause blockages and makes infections more likely. Excessive chloride output in the sweat increases the probability of dehydration and mineral imbalances. These features of the disease typically result in poor nutrition and growth, frequent respiratory infections and lung damage, although there are many other associated complications.

The CFTR gene on human chromosome 7 was identified in 1989. Cystic fibrosis is an autosomal recessive genetic disorder; heterozygous carriers of CF mutations (about 4% of the population) do not show symptoms of the disease. In order to be affected, a child must inherit a CF mutation from both of its parents. The chances of two carrier parents conceiving an affected (homozygous) child are 1 in 4 for each pregnancy.

The prevalence of CF in populations of northern European origin is around 1 in 2500 [1]. In the UK, a much lower incidence of 1 in 12,000 births has been estimated for groups of Asian origin, and this figure is likely to be lower still among populations of Afro-Caribbean and Oriental origin [1]. In the US, incidences among Asian-Americans, African-Americans and Hispanics have been estimated at around one per 31,000, 15,000 and 9500 births, respectively [2]. Cystic fibrosis also affects South American populations.

So far, well over 1000 different mutations have been reported in the CFTR gene, but most are very rare. The most common CF mutation is $\Delta F508$ (also called Delta F508, F508del or $\Delta F508$) a small deletion in the gene; this mutation accounts for about 70–75% of CF cases in the UK, though there is some regional variation. The frequency of different mutations also varies in different ethnic groups; for example, $\Delta F508$ is present in fewer than half of Jewish, Afro-Caribbean and Asian individuals with the disease, whereas the W1282X mutation is present in around half of all Ashkenazi Jewish CF carriers but is rare in other populations [1]. W1282X is also

common in Israel, most Mediterranean countries and north Africa; overall, more than fifty mutations are common (with a frequency in excess of 1%) in one or more European countries or regions [3]. However, some mutations are so rare that they are only known to exist in individual families.

The correlation between genotype and phenotype in cystic fibrosis is variable, with a subgroup of patients experiencing milder and later-onset symptoms and improved survival rates. Certain mutations are associated with less severe forms of the disease, notably less serious mutations that permit partial function of the CFTR gene. However, genotype is a poor predictor of lung function, which varies considerably between patients sharing the same mutation (such as the $\Delta F508$ mutation). Environmental factors such as smoking or malnutrition may also influence the severity of lung disease.

One report has proposed that a functional classification of patients according to their CF genotype could be of value in predicting likely clinical outcome, despite a substantial degree of phenotypic variability among patients with similar or identical mutations [4]. A commonly occurring CFTR genetic variant present in around 1 in 10 of the general population has been linked to a milder cystic fibrosis phenotype when present in conjunction with a severe CFTR mutation; the length of an adjacent region of TG repeats has been found to influence disease severity and has been advanced as a potential predictor of outcome [4–6]. There is also evidence to suggest that other secondary genetic factors (besides the CFTR gene itself) may influence the extent of lung disease in cystic fibrosis patients. Candidate ‘modifier’ genes include inflammatory and anti-inflammatory mediators, molecules involved in CFTR trafficking and mediators of airway reactivity.

3. Implications of current knowledge of the genetics of cystic fibrosis

3.1. Genetic testing

Genetic testing for CF in the UK detects $\Delta F508$ plus up to 20 other mutations, together accounting for 90% of CF mutations in people of northern European origin, so that the probability of detecting a mutation in both members of a Caucasian CF-carrier couple is about 80%. In pregnancy, if a couple are both known CF carriers, they can be offered antenatal fetal genetic testing (via amniocentesis or chorionic villus sampling, procedures with an associated miscarriage risk of around 1%) to determine whether the fetus is affected. This genetic test is virtually 100% accurate, although it cannot predict the severity of disease. Alternative non-invasive techniques for the analysis of fetal cells for cystic fibrosis mutations are currently in development.

If a CF carrier is discovered in a family, cascade testing of other family members can also be offered, generally to close family members of child-bearing age, for whom the information available may influence reproductive decisions, although there may be ethical and economic issues associated with this approach.

4. Genetic screening

Pilot programmes of various forms of population-screening have been investigated; these include:

4.1. Antenatal and pre-conception carrier screening

Pregnant couples or those planning a pregnancy are offered genetic testing for CF carrier status; if both parents are found to be carriers they are offered antenatal genetic testing. In couple screening, samples are taken from both parents and the test is reported as positive only if both parents are found to be carriers; the ethical issues associated with non-disclosure of carrier status if only one parent is a carrier are contentious. In sequential screening, a sample is first taken from the woman and a sample from her partner is requested only if the woman is found to be a carrier.

A nationwide programme of antenatal or pre-conceptional carrier screening for CF mutations is available in the US, where a screening panel of 25 common mutations (recommended by the American College of Medical Genetics) is routinely offered to all couples who are Caucasian or have a family history of CF, and is also available to couples of different lower risk ethnic groups on request. Concerns have been raised about the degree of compliance with guidelines to ensure that screening should remain an informed and personal choice for parents. There have been reports that in rare cases invasive testing and even abortions may have been performed unnecessarily, due to the misinterpretation of test results [7–9]. It has also been suggested that screening is sometimes presented as a routine or recommended procedure, rather than an optional choice.

There are plans for pilot schemes to precede a national antenatal or pre-conceptional genetic screening programme to be introduced in the UK. One publication [4] proposes that the most appropriate form of prenatal screening is couple screening, being safe, reliable and non-invasive and allowing a 72% detection rate for a 0.1% false-positive rate, but the level of priority for introducing this programme would depend on cost-effectiveness which was not analysed by Wald and colleagues. Another issue of potential concern in carrier screening for CF is the situation of couples where one partner is identified as a carrier; ten Kate [10] proposed that the risk for a couple after testing for carrier status should not be greater than before testing, but this would require a test sensitivity in excess of 96%, which is not generally achievable.

4.2. Population-based screening

In practice there appears to be little demand for population screening, as people only become interested in their carrier status when considering having children. Widening uptake by targeting specific groups such as school children would raise problems of informed consent. There is also evidence that information about carrier status and risk are not well retained in the long term, and that some people who discover they are carriers begin to have a poorer perception of their health.

4.3. Neonatal screening

Neonatal screening for CF typically uses an initial biochemical test for immunoreactive trypsin (IRT) in plasma, followed by genetic testing in infants with raised IRT. If a CF mutation is detected, a definitive diagnostic test for CF is given, such as the sweat test for raised levels of secreted chloride. The overall sensitivity of neonatal screening is about 85–90%. The introduction of DNA-based testing means that unaffected heterozygous carriers of CF are detected, with a consequent need for genetic counselling of the parents.

The rationale for neonatal screening is that very early detection and treatment may improve outcomes for children with CF; it may also be important to inform future reproductive decision making by the parents. Whether early detection actually does improve outcomes – particularly in countries with good health care systems, where the majority of CF cases are diagnosed in infancy – has been the subject of some debate. Reviews of some early studies failed to find conclusive evidence of benefit [1,11] but more recent data have suggested a possible decrease in mortality with screening [12–14] and there is increasing evidence to support a link between screening and improved nutritional status resulting in better growth and lower morbidity [12,15]. Possible harms resulting from pre-symptomatic diagnosis by neonatal screening include overly aggressive treatment and earlier lung infection with *Pseudomonas* due to mixing with infected, older CF patients; these are indirect harms linked to modifiable healthcare practices [16]. It has been suggested that neonatal CF screening programmes require very careful design in order to achieve a favourable balance between the potential risks and benefits [17].

Psychosocial issues associated with neonatal screening show a range of potential risks and benefits. Early identification and diagnosis of children with CF spares parents the anxiety typically experienced in the time between the onset of symptoms and diagnosis (which may be a period of years), and may also prevent a second affected pregnancy if parents become aware of their carrier status before conceiving another child. However, adverse psychosocial effects have been reported for the families of children identified as carriers of the CF mutation, a much larger group than those with the disease. Farrell and Farrell [16] note that the key to ensuring that neonatal screening achieves ‘more good than harm’ is excellence in implementation, including effective communication of information and counselling for affected families. Indeed, the provision of easily comprehensible information and genetic counselling to interpret the true meaning of positive results are essential components of all forms of genetic testing and screening for CF.

In the UK, neonatal screening for CF in Northern Ireland, Wales, and parts of England (East Anglia, Leeds, Northampton, the West Midlands and the Trent region) has been running since the nineteen eighties. It was introduced throughout Scotland at the start of February 2003, and in 2004 it was announced that universal screening would be introduced throughout England by April 2007. There have been reports

that the CFTR mutation analysis used for neonatal genetic tests in the UK should detect 96% of affected (homozygous) babies [18] but the 1999 HTA review [1] suggests that a lower overall detection rate of 86% is realistic, based on a population prevalence of 1 in 2400. It has been questioned whether this rate could be achieved for ethnic groups other than Caucasians, where the prevalence of CF is lower. Australia has a comprehensive neonatal screening programme for cystic fibrosis, as does France, but provision in much of the rest of Europe and in the US is patchy.

4.4. International genetic testing and screening for CF

The emergence of cystic fibrosis as a ‘pan-ethnic’ disease poses new problems specifically associated with genetic testing and screening, in addition to the scarcity of healthcare resources in developing countries [19]. Even within predominantly northern Caucasian populations such as that of the UK, the efficacy of genetic testing for CF is reduced among population subgroups of different ethnic origins due to the different types and frequency of common CF mutations in such groups. In other countries, this heterogeneity of common mutations between different subpopulations can be even more marked, making the choice of the most appropriate mutation panel for screening programmes more difficult. Understanding of regional variations in CF mutation frequencies to inform the creation of suitable mutation panels is a prerequisite for delivery of high sensitivity prenatal and neonatal screening programmes and to avoid discrimination against population subgroups [20]. One potential problem with the use of alternative mutation panels for ethnic minority groups is that self-reported ethnicity is not necessarily an accurate reflection of genetic ancestry [21]. Another possibility would be the use of much larger, pan-ethnic mutation panels that could detect the presence of many more mutations [20] an option that may be facilitated by current developments in array-based DNA diagnostics.

5. Economic implications of screening for CF

It is often thought that screening for a disease is cost-effective simply because it would mean that cases could be either prevented and/or found earlier. However, this is not always the case. The literature on CF does not necessarily agree on the costs or benefits of screening (newborn or otherwise). Detection of carriers and the number of prevented affected fetuses are the main measures of benefits in most economic evaluations of CF screening programmes.

The following is an overview of published literature found when carrying out a critical review of economic evaluation and genetics literature [22], as well as additional CF specific searches using PubMed. There were limits on language (English only) and time (1983–2006). All costs are reported in 2006 US dollars. However, it must be noted that the studies used different methods of collecting and reporting cost data,

Table 1
Summary of economic evaluations of screening for cystic fibrosis

Source	Country/year	Target population	Screening alternatives	Type of study/ perspective	Results/unit/outcome measure
Baumann et al. [23]	Germany/2002	Pediatric cases	N/A	Costing/German health insurance	€23,989 per annum per patient
Robson et al. [24]	Britain/1991	Adult CF patients in the Northwest	N/A	Costing/health service	£8241/annum per patient
Wildhagen et al. [25]	Netherlands/ 1998	Couples	Carrier screening vs. no screening	CEA/health service	Favourable/Cases detected
Lieu et al. [26]	USA/1993	CF patients	N/A	Costing/health service	US\$13,300/annum per patient; US\$314 million per year.
Cuckle et al. [27]	Britain/1994	Pediatric population	Antenatal screening vs. no screening	CEA/health service	Between £40,000–£90,000 per case detected
Vintzileos et al. [28]	USA/1997	Couples	Prenatal carrier screening vs. no screening	CEA/Insurer	Net savings per prenatally diagnosed case \$58,369–382,369
Rowley et al. [29]	USA/1997	Pregnant women	Prenatal screening programme vs. no screening	CEA and CUA/Health Care	US\$1,322,376 per CF birth averted. Assuming replacement child, cost per QALY \$8,290
Van den Akker-van Marie et al. [30]	Netherlands-2006	Hypothetical pediatric cohort	Antenatal screening (comparing IRT and DNA screening)	CEA/health service	€24,800/Life-year gained for IRT screening; Could save €1.8 million annually
Asch et al. [31]	USA/1996	Couples	15 carrier screening techniques to no screening	CEA/Insurer	US\$367,000–930,000 per CF birth avoided.
Neilsen and Gyrd-Hansen [32]	Denmark/2002	Couples	Carrier screening vs. no screening	CEA/health service	€282,692–592,307 per birth averted

therefore comparability is limited. A summary is listed in Table 1.

Because of the variation between genotype and phenotype in CF patients, and therefore different clinical pathways, it is somewhat difficult to estimate the burden of illness on a local (or national) economy. However, several studies [23–26] have attempted to show the burden of the disease on their respective centres. For example, Baumann et al. [23] found that from a health insurance perspective in Germany, total annual expenditure per CF patient amounted to €23,989 and that costs rose with age and doubled in the first 18 years. They also found that patients with chronic lung infection were more than three times more expensive than those with no chronic lung infection, illustrating that differing clinical pathways have different associated costs of care. In the US, Lieu et al. [26] found that the annual cost of medical care averaged \$13,300 but ranged from \$6200 for patients with mild disease to \$43,300 for patients with severe disease. When the authors used observed costs (from the Cystic Fibrosis Foundation computerised cost database) to extrapolate the costs for the entire population of CF patients in the US, they estimated the costs to be \$314 million per year in 1996.

Screening for CF may help alleviate the burden of illness (mostly by preventing affected foetuses and identifying carriers). However, the evidence below shows a wide variation in terms of costs and effectiveness. Almost all of the studies found that the cost-effectiveness was strongly tied to the couple's reproductive plans and the cost of the tests.

In the UK, Murray and colleagues [1] carried out a Health Technology Assessment (HTA) of screening programmes for CF. Within the review of the health economic literature they found that a number of researchers [26–28], both in the UK and US, have found that a combination of prenatal and antenatal screening was the most cost-effective way to screen for CF. Effectiveness of antenatal programmes in these evaluations was usually measured as number of affected pregnancies avoided (aborted), or number of carriers detected.

Rowley et al. [29] compared a prenatal screening programme to not screening for CF. The authors found that when prenatal screening is offered to 100,000 pregnant women, the cost of screening per CF birth voluntarily averted is \$1,322,376 without a replacement child and \$1,396,038 when there is a replacement child. When costs of direct and indirect care are deducted from these figures (discounted at 3% per annum), the costs fall to \$294,078 and \$367,740, respectively. The authors also found that assuming a replacement child is born, cost per QALY gained of offering a test is \$8290. The authors suggest that the cost per QALY estimate seems to compare favourably with that of other preventative measures carried out in the US. However, the authors noted that the results were very sensitive to the cost of the test, life expectancy of a CF child, and the probability of the termination of an affected fetus.

More recently, van den Akker-van Marle et al. [30] used a hypothetical cohort of pediatric cases in the Netherlands to compare four different screening techniques. Using life years

gained as an outcome measure, the authors found that IRT+IRT had the most favourable cost-effectiveness ratio of €24800 per life-year gained. However, the incremental costs per life-year gained of the IRT+DNA+denaturing gradient gel electrophoresis strategy compared with the biochemical screening only strategy were €130700, whereas the incremental costs of the IRT+DNA strategy compared with the IRT+DNA+denaturing gradient gel electrophoresis strategy were €2154300. The authors also looked at the effects of screening on future reproductive decisions and found that depending on which screening strategy was used, the health system could save up to €1.8 million annually.

Asch and colleagues [31] carried out a cost-effectiveness analysis that compared 15 different carrier screening strategies to no screening. The authors used CF births avoided as an outcome measure. They found the cost-effectiveness ratio ranged from \$367,000 to \$930,000 per CF birth avoided depending on which strategy was adopted (sequential carrier screening and couple screening respectively) compared to no screening. The authors found that the cost-effectiveness was greatly dependent on the couples' reproductive plans.

Cuckle and colleagues [27] analysed two different antenatal screening strategies for CF: sequential carrier testing (mother, then partner) and couple carrier testing (mother and partner). The outcome measure used for the analysis was the number of affected pregnancies detected. The authors found that the cost to the health care system of sequential screening was estimated to be £46,000 per affected pregnancy detected. The cost of couple screening was estimated to be £53,000 per affected pregnancy detected. The authors found that the screening programme's cost-effectiveness was sensitive to the cost of the test and the proportion of carriers it can detect.

The cost-effectiveness of screening programmes seems to be very sensitive to changes in assumptions on the birth of 'replacement' children, costs of the DNA test and whether the study takes into account screening past the initial fetus (for subsequent pregnancies). These conclusions are also supported in Asch et al. [31]. However, in Denmark, Nielsen and Gyrd-Hansen [32] carried out a cost-effectiveness analysis which found that introducing a prenatal screening programme could be net cost saving from both a societal and health service perspective, whether or not a replacement child is born. In their analysis, costs per CF patient ranged from €296,154 over their lifetime, whereas estimated benefits for avoiding a case of CF ranged from €282,692 to 592,307. Such cost-effectiveness analyses do not take account of the intangible quality and value and length of life questions for parents and health workers that accompany decisions to opt for screening tests, and/or for termination of pregnancy.

6. Discussion

Similar to other health areas, the CF literature uses various health economics techniques to describe costs and benefits and are therefore difficult to compare with any accuracy. Doran and

Vos [33] discuss the use of cost-effectiveness analysis in CF and mention that given the increasing pressure on resources, it is important for studies to be carried out in a methodologically comparable manner. The authors site two of the most commonly used recommendations [34,35]. Both try to give checklists and guidelines on how to prepare a quality economic evaluation. Another excellent resource for preparing economic evaluations is the National Health Service Economic Evaluation Database (NHSEED) which can be found on the York University Web site (<http://www.york.ac.uk/inst/crd/index.htm>). Many studies used decision tree and other types of modelling techniques were used by many of the authors. In addition to the economic evaluation guidelines, authors may also find the guidelines produced by the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) helpful [36]. We would also encourage future authors to use all these guidelines before attempting to do an economic analysis.

It is often the case with genetic technologies (not just within CF) that outcome measures are difficult to quantify. It is apparent in the literature that relatively simple outcome measures of birth(s) avoided or case detected is common. However, increasingly economists are using the QALY in order to capture health outcomes and quality of life. However, it can (and is) argued that neither of these measures is adequate to value the outcome of a genetic test or screening programme. Future authors may want to investigate techniques such as willingness-to-pay and/or discrete choice experiments in order to incorporate both health and non-health benefits of a genetic screening programme (see [37–39] for a description of these techniques). There is disagreement among economists over what the “best” outcome measure is for economic evaluations of screening programmes. As Doran and Vos [33] point out, “the perspective adopted for an economic evaluation needs to reflect the purpose of the research.” The same is true for the outcome measures as well as costs.

Work in the area of CF screening is progressing. The more information gathered from the human genome on the interactions of genes and environment will no doubt add much to the techniques used to screen for CF and the treatment paths for patients suffering from the disease. It is important to note that while we are constantly making advances in the ‘wet’ science, the ability to implement them in a health setting may be limited. It is therefore important to keep examining both clinical practice and the economics behind the technologies.

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