

## ANNOTATION

## Community-wide screening for cystic fibrosis carriers could replace newborn screening for the diagnosis of cystic fibrosis

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**Abstract:** Most babies with cystic fibrosis (CF) are born to parents who did not know they were carriers until their baby was diagnosed with CF, usually by newborn screening. It is only after the birth of their first child with CF that couples are offered genetic counselling and reproductive choices. Most use this information for prenatal testing of subsequent pregnancies. With the high uptake of first trimester screening for Down syndrome (80% in Victoria) most couples have had screening during the CF affected pregnancy. Yet screening for CF carrier status is available, costs are similar to that for Down syndrome screening and CF carrier screening only ever needs to be done once. Waiting for couples to have a baby with CF before they are identified as carriers denies them choice. A national policy on CF carrier screening in Australia, and determination to equitably fund such a programme, is required.

**Key words:** carrier screening; choice; cystic fibrosis; newborn screening.

Newborn screening for cystic fibrosis (CF) was an innovation in paediatric care, first developed in New Zealand in 1979 and first applied in New South Wales in 1981.<sup>1,2</sup> It is now universal in Australasia, the only region in the world that can claim that fact. Making the diagnosis of CF early and getting the infants into care came with strong intuitive logic, but not on an evidence base that would be acceptable today. However, with further research, evidence has been built, initially in case control and cohort studies, and now by the ultimate arbiter, randomised controlled trial.<sup>3</sup> Infants screened in the newborn period have better nutrition and cognitive function, and perhaps better lung function. How this will impact on survival is yet to be determined but expectations are high. Regardless of the impact on the infants with CF, newborn screening comes with the additional benefit of identification of the affected infant's parents as carriers. In Australia and New Zealand this has been

considered a benefit, as it allows parents to be offered genetic counselling and reproductive choices for subsequent pregnancies. Most parents of babies detected by newborn screening in Australia avail themselves of this opportunity.<sup>4</sup> However, the gene mutation analysis that is part of the newborn screening protocol could be used to determine whether the parents were both carriers *before* their first baby with CF was born. In essence, failure to offer carrier testing to all prospective parents denies them choice regarding the birth of their first baby with CF.

CF is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Chronic suppurative lung disease and pancreatic exocrine insufficiency are the most common serious clinical manifestations. The incidence is 1:2500, and 1:25 in our community are CFTR mutation carriers.<sup>5</sup> CF remains a serious, life-shortening condition. The daily therapies are rigorous and there is still no cure. The median survival has increased to the late 30 s (data recently released from the US CF Foundation, <http://www.cff.org>) although the inclusion of patients with mild CFTR gene mutations and polymorphisms may skew the data. Furthermore, this means that half of patients do not reach even this age, and does not take into account that there are many years of ill health prior to death. Lung transplantation does not offer complete cure, and median survival post transplantation is 5 years.

While the carrier frequency of CFTR gene mutations is 1:25 (4%), carriers are completely healthy and most are unaware of their carrier status. There are about 70 babies with CF born each year in Australia, most (>90%) to parents with no family history.<sup>5</sup> This means that there is virtually no opportunity to identify carriers if we rely on extended (so-called 'cascade') family testing of affected individuals.

### Key Points

- 1 Most babies with cystic fibrosis (CF) are born to parents who do not know they are carriers.
- 2 Genetic testing can reliably detect most carrier couples before they have their first baby with CF.
- 3 A national policy, and equitable funding, for CF carrier screening in Australia is urgently required.

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Most babies with CF in Australia and New Zealand are diagnosed by newborn screening. This is part of a more extended programme that now includes up to 20 metabolic conditions, most of which are inherited as autosomal recessive conditions. From the newborn heel prick, taken at 48–72 h, serum levels of trypsinogen are measured by immunoreactive assay as the primary screen for CF. Babies with a value above the 99th percentile have CFTR gene mutation analysis from the same blood spot. The number of mutations included in the screen varies between the states of Australia and in New Zealand, depending on the frequency of those mutations in the community being tested. Babies with CF are identified by 3–6 weeks of age and referred to specialised CF centres. Genetic counselling is provided as part of the introduction to CF for the parents, and is available anytime subsequently. Identification of the causative mutations in the affected baby allow the parents' mutation to be identified and their families to benefit from testing (if they desire) by 'cascade' family testing. However, this process is passive and has not resulted in a dramatic reduction in the birth incidence of CF.<sup>6</sup> Active cascade family screening through genetic counsellors attending family gatherings has been reported from overseas, but privacy legislation in Australia means that practitioners cannot approach at risk family members directly.<sup>7</sup>

Most (70%) parents who have a child with CF elect to determine whether subsequent pregnancies are affected by using prenatal testing (chorionic villous sampling) or preimplantation genetic diagnosis.<sup>4</sup> This is despite most having infants or children with CF who are apparently well. Many had prenatal investigations for chromosomal abnormalities (such as Down syndrome) during the CF affected pregnancy. Currently, 80% of all pregnancies in Victoria are screened for chromosomal abnormalities which suggests that prospective parents are willing to make choices about termination of pregnancy if the foetus is affected by a severe condition. There is no reason why Australian couples who would choose to use reproductive technologies should not be offered carrier testing for CF before or during their first pregnancy.

There are a number of models of population-based CF carrier screening that have been examined: prenatal carrier testing (either individual or couple screening),<sup>8</sup> preconception carrier detection in primary practice<sup>9</sup> or group adolescent testing in high school.<sup>10</sup> The most successful programme has been in Edinburgh, where couple testing is offered in the prenatal period (in this model the couple do not receive individual results, but are informed of a 1:4 risk for each pregnancy if both are carriers and a low-risk if one or neither are carriers). This has resulted in a halving of the incidence of CF in this community.<sup>11</sup> However, despite this success, which was largely driven by a locally influential obstetrician, similar programmes have not been established elsewhere. Making change to established health-care practices is difficult. Preparing this annotation is part of a broader attempt by our group to inform health-care providers about the possibility of CF carrier screening and call for a national policy and funding. It is the recommendation of the National Institutes of Health in the USA, the American College of Obstetricians and Gynaecologists and the American College of Medical Genetics, that all couples planning a pregnancy or in the early phases of pregnancy be offered carrier testing

for CF.<sup>12,13</sup> Following these recommendations, screening for CF carriers is considered standard of care in the USA, although without government funding uptake is not universal and there is no 'programme' to monitor outcomes. There is no such policy from the equivalent medical groups in Australia.

In Australia, CFTR mutation testing is not Medicare rebateable so only those with a family history of CF are offered free testing through state funded genetic counselling services. All others have to pay for the test. Some genetic services offer carrier screening, but only if asked. One Australian *in vitro* fertilisation centre offers carrier screening for 30 mutations on a fee-for-service basis. A pilot programme commenced in Victoria in January 2006, offering testing for 12 mutations by cheek swab to couples planning a pregnancy or  $\leq 14$  weeks gestation. So far 1600 people have been tested and five carrier couples identified.

Uptake of a screening programme is a key measure of its success. The Edinburgh model had an 80% uptake of CF carrier screening<sup>8</sup> and a similar uptake was reported from a Dutch study.<sup>14</sup> In Victoria, 70% of couples who had a child with CF used prenatal testing for subsequent pregnancies.<sup>4</sup> Similar figures are reported from overseas showing that most relatives of individuals affected with CF would utilise carrier testing or prenatal diagnosis (93% and 70%, respectively).<sup>15</sup> In a British survey of parents with children with CF, 92% supported the introduction of population screening and 74% said that they would choose prenatal testing if they became pregnant.<sup>16</sup>

The testing for CFTR gene mutations is reliable and relatively inexpensive. In Australia, about 83% of possible mutations can be detected by a 12 mutation panel, although this figure is higher in some ethnic groups such as Ashkenazi Jews (95%). A programme offering carrier screening needs to include genetic counselling for carrier couples, individual carriers and relatives of carriers who may also wish to be tested. Unlike Down syndrome screening which is necessary for each pregnancy, CF carrier screening is needed just once for the woman and her partner in their reproductive life.

One of the risks of CF carrier screening is the potential for ongoing anxiety among carriers, even if their partner is not a carrier. However, this has not been shown to be the case<sup>17</sup> and longer follow-up studies do not support long-term anxiety as a result of the test.<sup>14</sup> High-quality pretest information and good counselling for identified carriers has been shown to be the key to reducing the psychological impact of a positive result. Importantly, women in a Danish study did not alter their reproductive plans as a result of the test.<sup>14</sup>

Community-based carrier screening appears to offer benefits from a health economic perspective. Modelling the cost-effectiveness of prenatal CF screening suggests the cost per case prevented is favourably balanced against the life-time cost of care for a patient with CF.<sup>18</sup> These studies do not take into account other considerations such as lost productivity by parents and social costs related to the care of an individual with CF, but do suggest that cost considerations should be no obstacle for prenatal testing.

Carrier screening for CF fits most models of screening: CF is a life-threatening disease with no cure, carrier frequency is common and a reliable test exists. Counselling, information and

support is available for carriers when they are identified. Carrier screening will not be chosen by everyone, but it is about choice. In our society, families should have the right to be offered a choice before having their first baby with CF.

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