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Original Article

Population-based carrier screening for cystic fibrosis in Victoria: The first three years experience

John MASSIE,[1,2,3] Vicki PETROU,[2] Robyn FORBES,[2] Lisette CURNOW,[2] Liane IOANNOU,[2] Desiree DUSART,[4] Agnes BANKIER[2] and Martin DELATYCKI[2,3,5]

[1]*Department of Respiratory Medicine, Murdoch Children's Research Institute Unit, Royal Children's Hospital,* [2]*Genetic Health Services Victoria, Murdoch Children's Research Institute,* [3]*University of Melbourne,* [4]*DNA Laboratory, Genetic Health Services Victoria, Murdoch Children's Research Institute, and* [5]*Bruce Lefroy Centre for Genetic Health Research, Genetic Health Services Victoria, Murdoch Children's Research Institute, Melbourne, Victoria, Australia*

Background: Cystic fibrosis (CF) is the most common inherited, life-shortening condition affecting Australian children. The carrier frequency is one per 25 and most babies with CF are born to parents with no family history. Carrier testing is possible before a couple has an affected infant.

Aims: To report the outcomes of a carrier screening program for CF.

Method: Carrier screening was offered to women and couples planning a pregnancy, or in early pregnancy, through obstetricians and general practitioners in Victoria, Australia. Samples were collected by cheek swab and posted to the laboratory. Twelve *CFTR* gene mutations were tested. Carriers were offered genetic counselling and partner testing. Carrier couples were offered prenatal testing by chorionic villous sampling (CVS) if pregnant. The number of people tested, carriers detected and pregnancy outcomes were recorded from January 2006 to December 2008.

Results: A total of 3200 individuals were screened (3000 females). One hundred and six carriers were identified (one per 30, 95% confidence interval one per 25, one per 36). All carrier partners were screened, and nine carrier couples identified (total carriers 115). Ninety-six individuals (83%) were carriers of the p.508del mutation. Of the nine carrier couples, six were pregnant at the time of screening (five natural conception and one *in vitro* fertilisation) and all had CVS (mean gestation 12.5 weeks). Two fetuses were affected, three were carriers and one was not a carrier. Termination of pregnancy was undertaken for the affected fetuses.

Conclusion: Carrier screening for CF by obstetricians and general practitioners by cheek swab sample can be successfully undertaken prior to pregnancy or in the early stages of pregnancy.

Key words: carrier, cystic fibrosis, screening.

Background

Cystic fibrosis (CF) is the most common inherited, life-shortening condition affecting Australian children. It is caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR), an electrolyte transport protein located in the apical membrane of epithelial lined surfaces.[1] The main clinical manifestations are chronic suppurative lung disease, pancreatic exocrine insufficiency and elevated sweat electrolytes.[2] Although treatments have improved over the two decades since the *CFTR* gene was discovered there is still no cure. Most children survive to adulthood but the treatments are complex and there are many years of poor health. The median survival is reported in the mid-thirties.[3]

Genetic testing for CF has been incorporated into newborn screening programs for the early identification of affected individuals, and reproductive choices offered to parents for subsequent pregnancies.[4,5] However, it is possible to offer carrier testing before a couple has an affected infant.[6] While over 1500 *CFTR* gene mutations and polymorphisms have been described, the majority of carriers (84%) can be detected with a panel of 12 mutations.[7] The inheritance of CF is autosomal recessive and carriers are completely healthy, a situation that makes carrier testing straightforward. Carrier screening for CF was recommended in the USA in 2001 and subsequently there has been a 50% reduction in the incidence of affected infants with the most common *CFTR* gene mutations.[8,9]

In the absence of a government-supported program, we initiated a fee-for-service population-based CF carrier screening program in Victoria, Australia, in 2006. The aim

Correspondence: Associate Professor John Massie, Department of Respiratory Medicine, Royal Children's Hospital, Parkville, Vic. 3052, Australia. Email: john.massie@rch.org.au

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of this paper is to report our experience of the first three years of carrier screening for CF.

Method

Implementation of fee-for-service CF screening program

We convened a CF screening working group in 2005 which included members from the Royal Children's Hospital CF clinic (JM), Genetic Health Services Victoria (MD, AB, VP, RF, LC) and the DNA laboratory of the Victorian Clinical Genetics Service (DS). Genetic Health Services Victoria (GHSV) is the main provider of genetic testing in Victoria. The community-based CF support group, CF Victoria was consulted, and support for the program was offered. The program commenced in January 2006, initially targeting obstetricians (2006) and was later expanded to shared-care general practitioners (GP) (2007) and subsequently all GPs (2007) in the state of Victoria, Australia. Service providers were identified through their respective specialty colleges with letters of explanation, and sample screening packs were provided. A media launch was held in January 2006 to promote the program and repeated in January 2007. Information regarding progress of the program was included with health information bulletins regularly sent out by GHSV. Education regarding the screening program was provided to most metropolitan and some regional obstetric groups. Information regarding CF screening was provided on the GHSV website, and a specific CF screening website was launched in 2008 (www.cfscreening.com.au).

Subjects

Women or couples attending an obstetrician or GP prior to pregnancy or in the early stages of pregnancy (recommended to be < 14 completed weeks gestation) were eligible to be offered CF carrier screening. The program operated in Victoria, Australia, from January 2006. Pretest information was provided by the obstetrician or GP, and written information about CF and screening was provided (see www.cfscreening.com.au for website and pdf version).

CF screening

A fee-for-service test was developed costing A$200 using a cheek swab that was posted to the DNA laboratory at GHSV. Screening packs were provided to all interested service providers (see below), and these included an information brochure about CF, a screening card detailing the three-step collection procedure, a cheek swab, reply paid envelope, request slip and billing details. The following 12 mutations were screened using a polymerase chain reaction multiplex: p.508del, p.G551D, p.G542X, p.N1303K, c.1585–1G > A, p.I507del, p.R560T, p.W1282X, p.V520F, c.489+1G > T, p.R553X and c.3718–2477C > T. These mutations were chosen because they were the most frequent in our population of CF patients. This single panel of mutations gives a sensitivity of 83.5% to the general population in Victoria, but 95% to the Ashkenazi Jewish population. A single panel of mutations removed the need to gather questions about ethnicity. Our brochures included adjusted risks for Caucasian and Asian people. To optimise residual risk calculations and minimise turn-around time, it was recommended that both partners be tested at the same time. Negative results (non-carriers) were sent by facsimile to the requesting doctor. Positive results (carriers) were notified by telephone (and by facsimile) to the requesting doctor and all carriers offered genetic counselling by a trained genetic counsellor with expertise in CF (VP, RF, LC). If only one partner was tested and found to be a carrier, testing of the other partner was arranged as soon as possible, with results generally available within five working days from arrival in the DNA laboratory. Carrier couples where the woman was pregnant were offered chorionic villous sampling (CVS) to determine whether the fetus was affected. Termination of pregnancy was offered to couples with an affected fetus. If carrier couples were not already pregnant (pre-conception testing) then in addition to the option of becoming pregnant and having a CVS, pre-implantation genetic diagnosis (PGD) was discussed. Once a carrier was identified, all subsequent genetic testing was offered free of charge. This included cascade carrier testing of family members who wished to be tested.

The initial offer of screening was left to the discretion of the individual practitioner, and data about the number of patients who declined screening are not available.

Audit of CF screening program

We accessed the results of all screening tests which were kept in a password-protected computerised database (Microsoft Access). We also extracted data about genetic counselling encounters (carriers and carrier couples) from the purposed designed genetic file maintained securely in GHSV. Statistics was performed using Stata (Stata Corporation, College Station, TX, USA).

The study was approved as a clinical audit by the Ethics in Human Research Committee of the Royal Children's Hospital (CA29050).

Results

Between January 2006 and December 2008. A total of 3200 individuals were screened, 3000 women and 200 men. One hundred couples (200 individuals) were screened together at the same time. Results were available within an average of five working days (from arrival in the laboratory).

We identified 106 carriers (carrier frequency one per 30, 95% confidence interval one per 25, one per 36), and the *CFTR* gene mutation frequencies are presented in Table 1. Ninety-two carriers were women and 14 men, reflecting the ascertainment bias as who accessed testing initially. After notification of the referring physician, in all but two cases the carrier was contacted by our genetic counsellors. The

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Table 1 Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations identified in 2006–2008

CFTR gene mutation	*n*
p.508del	96
W1282X	5
c.3718–2477C > T	5
p.G551D	3
p.G542X	1
p.N1303K	1
p.507del	1
p.R560T	1
p.R553X	1
c.489+1G > T	1
p.V520F	0
c.1585–1G > A	0
Total	115

remaining two received genetic counselling from the referring physician. In the first 12 months (2006) all 37 carriers came to our centre for face-to-face genetic counselling, while in the subsequent two years (2007–2008) initial contact was made by phone ($n = 69$) and none requested face-to-face counselling despite an offer. Subsequent results (partner testing) were given by the genetic counsellors on the phone, but partners with positive results (that is carrier couples) were requested to be seen for face-to-face counselling.

The partners of all 106 CF carriers were tested, resulting in the identification of nine carrier couples. Details of the nine carrier couples are provided in Table 2.

All six pregnant carrier couples elected to have further testing with CVS. Four fetuses were unaffected (one with no mutations, three with one mutation) and two were affected with CF (both homozygous p.508del). Both couples with an affected fetus elected to terminate the pregnancy. The three other couples elected to use PGD.

To audit the efficiency of doctor's office or home collection we reviewed the samples collected over a 12-month period (October 2007 to September 2008). Samples were required to be recollected on 30 (3%) occasions.

Discussion

This is the first statewide screening program for CF in Australia. This program is different from other health screening programs because it identifies carriers who are at risk of passing on an inherited (genetic) disease. Other programs identify diseases in the individual (for example cervical cancer screening by Pap smear) or gene mutation testing of individuals at direct risk of disease in themselves (for example BCRA gene testing for breast cancer). It is also different from Down syndrome screening that identifies fetuses at risk but not parental carriers. In our program, prospective parents have been offered testing to determine if they are carriers of a gene mutation for CF and given a risk estimate of having a child with CF. So far we have tested over 3000 people, identifying 106 carriers (1/30) and nine carrier couples. None of these people were aware they were carriers and at risk of having a child with CF. All made the decision to test the fetus or use PGD.

The reason it has been possible to establish this program in Victoria has been the coordinated approach by members of the team caring for children with CF, Genetic Health Services Victoria (including geneticists, genetic counsellors and DNA laboratory) and the community support group CF Victoria. Support from the CF advocacy group may seem counter-intuitive as their role is to improve the life of people with CF; however, screening has raised the awareness of CF among the more than 3000 people screened and has been offered in the interest of choice.

There is much to learn about carrier screening for CF from our program that will be directly relevant to a population screening service. Most of the pretest information can be provided by our detailed, but succinct brochure. This is a new paradigm of care regarding genetic testing that has traditionally included formal (face-to-face) genetic counselling by a trained genetic counsellor *before* testing. There is no doubt, however, that the pretest information offered by willing obstetricians and GPs has been invaluable. Samples can be easily collected by painless cheek-brush and mailed to a central laboratory with minimal recollections needed. The turn-around time from the laboratory is fast, a relevant issue when couples are tested during a pregnancy. Our program has offered the flexibility of carrier screening in the early stages of pregnancy and pre-conception. It has been possible to relatively cheaply test for 12 *CFTR* gene mutations which gives a sensitivity of 84%. Face-to-face genetic counselling was recommended in the first year of screening but had not been needed subsequently and this will have benefits regarding cost-saving if a universal policy of offering screening were introduced. Similarly, face-to-face genetic counselling was not required before testing or for non-carriers in the population studied. We established our program with the facility to offer genetic counselling to anyone who requested it and have included free testing of relatives. In a large-scale program, counselling could be done by midwives, obstetricians or GPs as happens currently for Down syndrome screening.

There has been some resistance to the uptake of screening by both the public and the health-care providers. The principle issue relating to the public is likely to be awareness about CF. Issues relevant to obstetricians and GPs have been perceived difficulties of providing pretest information, especially citing time constraints, a lack of knowledge of CF and the carrier frequency, a perception that CF only occurs in families (in fact 95% of babies with CF are born to parents with no family history) and poor training in counselling for genetic conditions. We did not have data that allowed us to estimate uptake of screening to those it was offered. Further research to understanding the barriers to screening and reasons for declining screening is being undertaken. These factors will all be important to address as we advocate for a more widespread and equitable screening program.

Although we have promoted the uptake of CF carrier screening to both partners in the relationship it is evident

Table 2 Carrier couples detected by cystic fibrosis population screening program, Victoria 2006–2008

Subjects	Timing of CF carrier test (gestation)	Conception	Parents genotype	Counselling	Prenatal diagnosis	Status of pregnancy	Future plans
1	Pre-pregnancy	Natural	Both p.508del	Genetic counsellor and CF physician	CVS 12 weeks Affected (p.508del/p.508del)	Termination of pregnancy	2008: Second pregnancy: CVS: carrier p508del
2	10 weeks	Natural	Both p.508del	Genetic counsellor and CF physician	CVS 12 weeks Unaffected (no mutations)	Continued	
3	11 weeks	Natural	Both p.508del	Genetic counsellor	CVS 13 weeks Carrier (p.508del/-)	Continued	
4	10 weeks	Natural	Both p.508del	Genetic counsellor	CVS 13 weeks Carrier (p.508del/-)	Continued	
5	11 weeks	Natural	Both p.508del	Genetic counsellor	CVS 13 weeks Unaffected (no mutations)	Continued	
6*	9 weeks	IVF	Both p.508del	Genetic counsellor and CF physician	CVS 12 weeks Affected (p.508del/p.508del)	Termination of pregnancy	Currently undergoing IVF conception with PGD.
7	Pre-pregnancy	Not applicable	Both p.508del	Genetic counsellor and CF physician	CVS 12 weeks Carrier p.508del	Continued	Did not attend PGD, established natural pregnancy 2 months after seen by genetic counsellor and respiratory physician
8**	Pre-pregnancy	Not applicable	Both p.508del	Genetic counsellor	Not applicable	Not applicable	Likely to pursue PGD
9***	Pre-pregnancy	Not applicable	c.3718–2477C > T, p.W1282X	Genetic counsellor and CF physician	Not applicable	Not applicable	Likely to pursue PGD

*This couple had an IVF pregnancy but were not offered carrier screening until nine weeks gestation.
**This couple were part of cascade testing after a family member was found to be a carrier via our population screening program.
***Family history of CF (female partner's family), but only had screening because of information presented about population carrier screening program.
CF, cystic fibrosis; CVS, chorionic villous sampling; IVF, *in vitro* fertilisation; PGD, pre-implantation genetic diagnosis.

that usually one partner is tested first, in this study, usually the woman. This is likely to reflect attendance at antenatal health-care visits and is effectively a two-step screening model. This makes sense economically as both partners are tested for the same 12 mutations, if one is negative the result of the other becomes less relevant. The advantage of testing both together at the first visit is a more accurate estimate of residual risk, if one partner is tests negative the residual risk of having a baby with CF is one per 14 000 compared with one per 80 000 if both are negative. Furthermore, testing together can save time by not having to wait to test the partner if one is a carrier. We elected to notify individuals of their results so that cascade testing of family members was possible. Some models of CF carrier screening only test couples and give results as a unit, denying individuals their results and the possibility of cascade family screening.[6]

We did not confine the offer of screening to pregnant women or couples but included pre-conception testing. Pre-conception testing offers couples the greatest range of reproductive options and would be the preferred model of carrier screening. However, the reality of screening is that many people present for care after they are already pregnant and our screening model was able to take that into account. One couple (couple 6, Table 2) were already pregnant by *in vitro* fertilisation (IVF) when they were offered CF carrier screening. It has not been the policy of IVF units in Victoria to routinely offer CF carrier screening although clearly there would be time to do so before establishing a pregnancy giving the couple the opportunity to have PGD.

The selection of the 12 gene mutations in our screening panel was given considerable thought. The fact that 17% of subjects had a mutation other than p.508del justifies the use of an expanded panel of mutations as the primary screen. The mutation panel allows for a single test for all people, regardless of ethnicity. There are many ethnic groups in Victoria and Australia, for whom CF is extremely uncommon. Whether they should all be offered CF screening is a difficult question. Our information brochure highlights the reduced risk of carriage in Asian people, but decision to proceed with screening should be theirs. We chose the 12 most common *CFTR* gene mutations in Victoria that cause *classic* CF with severe suppurative lung disease and pancreatic insufficiency. Screening programs overseas include *CFTR* gene mutations associated with a milder phenotype and can include mutations with an uncertain phenotype. This can make counselling of carrier parents extremely difficult and decisions around termination of an affected pregnancy more stressful than when such mutations are not tested for.

We believe that the cost of the screening program has been a factor limiting its uptake. An application for a universal state-funded program was rejected in 2002 so a fee-for-service model was developed. It is reasonable to expect that economies of scale would allow a lower cost should there be greater use of CF screening. The fee for screening throws up more than just economic issues for patients. The fact that it is not free to consumers suggests it may not be approved by 'the medical system' (similar to recommended but unfunded immunisations) and health-care providers may make decisions for patients based on what they think their patients may be able (or willing) to pay. We recognise the inequality of the program we have instituted but see it as a bridge to introducing funded CF carrier screening for the entire population. Individuals can then make their own choice as to whether they wish to be screened.

So, what does the future hold? Community-based carrier screening is now well established in Victoria, Australia, and we will work towards improving knowledge about CF and CF genetics in the community and among health-care providers. We are in the process of completing a detailed health economic analysis of the cost of CF care and cost of screening on a population basis. Our systematic review of the literature supports the cost-effectiveness of CF carrier screening in other countries, but will use our own health economic data to convince state and federal governments in decisions to fund CF carrier screening.[10] Convincing obstetricians and GPs of the importance of CF carrier screening is vital, but finding ways to offer them education and support will be critical to the success of a universal program. There is currently no policy on CF carrier screening from the relevant professional bodies in Australia (Human Genetics Society of Australasia and Royal College of Obstetricians and Gynaecologists of Australia and New Zealand). CF is only one of many inherited conditions for which testing of healthy carriers is possible. Serious childhood diseases such as spinal muscular atrophy, fragile X syndrome and many metabolic diseases are candidates for screening. The processes we are establishing for CF could be built on for these other conditions in the interests of offering prospective parents choice.

We believe that carrier screening for CF in the general community is a reality, although the ultimate model on how it should be delivered more broadly is yet to be decided. Our program offers valuable insights into the creation of that model and strategies for service provision.

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