

Ethical considerations in choosing a model for population-based cystic fibrosis carrier screening

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Healthy individuals can undergo testing to determine whether they are carriers of a cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutation and therefore at increased risk of having a child with cystic fibrosis (CF). In Australia, CF is the most common, life-limiting genetic disease affecting children of European ancestry, with a carrier frequency of 1 in 25.¹ Prospective parents can be tested to identify their risk of having a child with CF. If both parents are carriers (a carrier couple), each pregnancy has a 1-in-4 chance of being affected by CF. The options available to carrier couples depend on whether they have been tested before pregnancy (preconception carrier screening) or in the early stages of pregnancy (prenatal carrier screening). Carrier couples identified during pregnancy may elect to have prenatal diagnosis, with the option of pregnancy termination if the fetus is affected. Carrier couples identified when the woman is not pregnant have the additional options of having no more children, adopting, or using donor ova or sperm or in-vitro fertilisation (IVF) with preimplantation genetic diagnosis.

In Australia and the United Kingdom, most babies (90%) with CF are born to parents with no family history of CF.^{1,2} Despite this, use of CF carrier testing is limited in Australia. For those with no family history of CF, the test is provided on a user-pays basis, and many prospective parents are simply unaware that the test exists. As such, there is inequality of access both to information about CF carrier testing and to the test itself.

A government-funded, nationwide CF carrier screening program would be a fairer system, ensuring equity of access to the test. Some couples may choose not to have the test, because they would not consider pregnancy termination or other reproductive technologies.² Others may choose carrier testing and prenatal genetic testing despite intending to continue any potentially affected pregnancies, in order to be better prepared for the birth of their child.² Recent Australian studies demonstrate community support for a population-based screening program,^{3,4} noting that “[p]articipants were in agreement that [CF] carrier screening should be made available to everyone”.³ Cost-benefit analyses show that CF carrier screening programs are cost-effective in ethnically diverse

ABSTRACT

- Cystic fibrosis (CF) carrier testing can be used to inform reproductive decision making, allowing carriers to avoid having a child with CF.
- A government-funded, population-based CF carrier screening program would allow greater equity of access to this test.
- The setting in which CF carrier screening is offered significantly affects the extent to which participants make well informed, voluntary decisions to accept or decline testing.
- Screening offered before pregnancy and in non-clinical environments better promotes participant autonomy than screening offered in the prenatal consultation.

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populations. Some ethnic groups within Australia's population are at relatively low risk, and the test sensitivity for these groups should be explained to potential participants before testing.^{5,6}

CF carrier testing presents potential benefits to test subjects, but also some psychosocial risks. As common test panels have a sensitivity of 84%, some participants will be falsely reassured. Others could receive information that, in hindsight, they did not want; in rare instances, even a revelation of misattributed paternity. Therefore, CF carrier testing is only ethically acceptable when individuals make well informed, voluntary decisions to accept or decline testing. By providing genetic counselling and maintaining stringent privacy standards, an ethically sound CF carrier testing program protects participants from anxiety and discrimination.

This article examines *how* CF carrier testing should be offered if Australia were to initiate a population-based CF carrier screening program. We focus on the timing (before or during pregnancy) and setting (clinical or non-clinical) of testing. These two structural features have important ethical implications, affecting the proportion of the population offered testing, the way in which information about testing is presented, and the extent to which participants freely choose to accept or decline testing.

Models of CF carrier screening

We consider three broad models of a CF carrier screening program:

- *Prenatal carrier screening*: offered to all pregnant women or couples as part of their prenatal care. Carrier couples are offered prenatal genetic testing to determine whether their pregnancy is affected by CF. If the fetus is affected, the couple has the option of pregnancy termination.
- *Preconception carrier screening*: offered by general practitioners to individuals or couples before pregnancy.
- *Carrier screening outside the clinic*: offered in non-clinical settings, such as schools and workplaces.

We compare these models, arguing that the latter two are ethically superior to a screening program that primarily targets the

Definitions

CFTR: cystic fibrosis transmembrane conductance regulator.

CF carrier screening: CFTR gene mutation analysis on people who do not have CF and do not have an increased risk of being a carrier (ie, no family history of CF or CF carriers). This can be applied on an individual or population basis.

Prenatal CF carrier screening: CF carrier screening of pregnant women and their partners.

Prenatal genetic testing: genetic testing of a fetus using chorionic villus sampling or amniocentesis.

Preconception CF carrier screening: CF carrier screening of non-pregnant women and men.

Carrier couple: both individuals in the couple are CF carriers. Carrier couples have a 1-in-4 risk of each pregnancy being affected by CF.

prenatal population. We propose that all three models should be offered concurrently to minimise the number of people who miss out on the option of testing, including those with an unplanned pregnancy. This also allows people to choose the timing of the test.

A further consideration is whether participants are screened as individuals or couples. In individual screening, an individual is tested and receives his or her carrier status. In couple screening, both members of a couple are tested simultaneously. The results of couple screening are conveyed as the couple's overall risk of having a child with CF, with or without each individual receiving their own carrier status. We recommend that individuals receive their own result as well as the risk estimate for children conceived from their relationship, because individual results may also affect reproductive decisions in any subsequent relationships. Individual results also allow for cascade screening, where an affected individual's family members are also offered carrier testing.

Prenatal carrier screening

Offering carrier testing during early pregnancy has many logistic advantages. Australia has a well established prenatal health care system, and most pregnant women attend at least one prenatal appointment.⁷ Therefore, prenatal carrier screening promotes equity of access. Australia's prenatal care system already provides trisomy 21 (Down syndrome) screening. Like prenatal CF carrier screening, this estimates fetal risk of disease and allows parents with high-risk pregnancies the option of prenatal genetic testing.

However, from an ethical standpoint, the prenatal period is not the ideal time to offer CF carrier screening. Carrier couples identified during pregnancy have fewer reproductive options than those identified before pregnancy, and less time to consider which option is most concordant with their own values. A pilot study of prenatal CF carrier screening found that some couples "would have preferred the option of a more leisurely consideration of the implications of carrier testing in the absence of ongoing pregnancy".⁸

It is particularly difficult to ensure that participants make informed decisions to accept or decline CF carrier testing when the test is offered in a prenatal consultation. During such a consultation, numerous routine tests (eg, blood group and antibodies) are recommended to identify potentially treatable conditions in the mother and/or the fetus. Offering CF carrier testing alongside these tests can obscure the fact that CF carrier screening is performed to allow the options of prenatal genetic diagnosis and selective pregnancy termination. A pilot study of prenatal CF carrier screening found that "for 16%, agreeing to be tested was based on their belief that 'all tests in pregnancy are important'".⁸ This suggests that, for these women, the distinction between prenatal genetic screening tests and other "routine" prenatal tests was lost. Understanding this distinction is crucial, as some people decline genetic screening on the grounds that they would not consider pregnancy termination or that they do not want to be faced with the choice.^{9,10}

This conflation of genetic screening with other prenatal tests occurs in trisomy 21 screening. Some participants "consent" to trisomy 21 screening without understanding its purpose or implications,¹¹ and some consent in the mistaken belief that it screens for a disease that can be treated prenatally.¹² Trisomy 21 screening is often presented as "routine" or even mandatory,^{9,13,14} and when women believe the test is routine they are less likely to make an informed choice.^{14,15} At least three studies have demonstrated that

many participants undergo trisomy 21 screening without knowing which condition the test may detect,¹⁵⁻¹⁷ while others have found that some participants were unaware that they had been tested until they received their results.^{13,18}

Preconception carrier screening

The problems with ensuring adequate informed consent in the trisomy 21 screening program can be partly attributed to time constraints in the prenatal consultation, and the difficulty of conveying the distinctive features of genetic screening in this setting. A CF carrier screening program could address this issue by offering the test before pregnancy.

The challenge for this approach is how to target the preconception population. Pilot studies show that the preconception population supports CF carrier screening in principle, but is unwilling to expend significant time or effort on being tested.^{19,20} One solution might be to offer the CF carrier test opportunistically to young men and women presenting to their GP for other reasons, and also to women presenting for health checks before pregnancy.

It may be especially difficult to convey the relevance of testing to the preconception population. CF is not a high-profile disease, and many people are unaware of its severity and heritability.^{2,3,19} While pregnant women or couples are highly motivated to receive information about genetic traits that may be passed on to their new baby,^{3,21} young adults not considering pregnancy may dismiss the option of testing before they understand its potential advantages.³

Preimplantation genetic diagnosis or use of donor gametes with IVF is prohibitively expensive for some couples, as these are costly services despite government subsidy. Some carrier couples identified through preconception screening may use prenatal genetic testing with a view to selective termination of an affected fetus, simply because it is more affordable. This would ameliorate some of the benefit of preconception screening compared with prenatal screening.

Carrier screening outside the clinic

CF carrier testing could be offered in non-clinical settings, such as schools or workplaces, by a dedicated service that provided pre-test education, administered the test and communicated the results. Carriers could then be referred to a clinical geneticist, genetic counsellor or their GP. This model has three distinct ethical advantages.

First, it promotes distributive justice by offering the test to a broad cross-section of the population, including those who rarely visit their GP.

Second, pre-test information could be provided to groups of potential participants by clinicians trained in non-directive counselling and familiar with CF, the testing process, test sensitivity and the implications of a positive result. This is a more efficient way of disseminating accurate information than including screening discussions in GP or prenatal appointments, which necessarily have a different primary focus. A dedicated screening service staffed by certified genetic counsellors could offer family history assessments for carriers, and expand to provide other carrier tests as the need arises.

Third, offering the carrier test in a non-clinical setting can actually promote autonomous decision making. In the clinical setting, many patients compliantly accept all tests, in the belief that they are "necessary" or "routine".²² One study found that 22%—

28% of pregnant women had difficulty rejecting CF carrier testing when it was offered.²³ Another study found that uptake of CF carrier screening offered in general practice clinics ranged from 11% at one practice to 99% at another,⁸ suggesting that individual doctors were significantly influencing their patients' decisions, or that the test was not specifically discussed at all. Even when a doctor offers a test in a non-directive manner, this can be understood as a tacit recommendation to accept.²⁴ Offering the test in a non-clinical setting encourages participants to exercise the type of agency they routinely use outside the medical clinic, for example, when deliberating over an interstate job offer or a substantial purchase.²⁵

Carrier screening for both Tay-Sachs disease and CF has been offered in some Australian and Canadian Jewish high schools for many years.²⁶ Widespread CF carrier screening in schools would ensure that a high proportion of the target population is offered the test before commencing child-bearing. Presenting information about the test in an educational environment promotes good understanding of the relevant issues.^{27,28} Students offered carrier screening at school correctly answer questions about the test and the condition(s) screened for at higher rates than adults offered screening in the clinical setting.^{26,29} A Tay-Sachs carrier screening program in Montreal found that individuals tested in high school effectively used their test result in family planning many years later.³⁰

Some commentators object that high school students are unable to give voluntary, informed consent to carrier screening, as they will be unduly influenced by peer pressure.^{31,32} There is little evidence to support this objection. The uptake rate in high school carrier testing programs ranges from 42% to 94%, which suggests that students are able to decline testing.^{26,28,33} Delatycki and colleagues found that an extremely small proportion of students (0.8%) claimed to have accepted haemochromatosis testing because of peer pressure.³⁴ Similarly, Barlow-Stewart and colleagues found that the most significant factor in students' decisions to accept CF carrier testing was the desire to use the information with a future partner (56%–75%), while the *least* significant factor was the influence of peer pressure (1%–9%). Adolescents rated the influence of their parents (9%–21%) and community (4%–26%) as more significant than that of their peers.²⁶ Significant life decisions are, appropriately, made in the context of various personal, family and social factors throughout life.²⁷ Finally, the proposed influence of peer pressure in high school screening must be weighed against the covert pressures to accept testing in the health care setting.

Some studies suggest that adolescents are at particular risk of anxiety or stigmatisation as a result of carrier screening.³¹ However, interventions that aim to minimise the risk of stigmatisation in school screening emphasise the universality of "genetic mutations" across all ethnic groups, and allow students to access their test results later in life rather than while they are in school.²⁶

Workplace screening largely avoids the issue of adolescent peer pressure. However, the logistics of providing screening in diverse workplaces, many with few staff and minimal physical infrastructure, would make workplace screening more time-consuming and costly than high school screening. *Haemscreen*, a workplace haemochromatosis genetic screening program in Victoria, recorded average participation rates of 5.8%, finding that many workers were unable to attend the education session because they were too busy.³⁵

Conclusion

Given the ethical advantages of offering CF carrier testing before pregnancy, we recommend a program that primarily targets the preconception population, while also offering the test during pregnancy. Establishing the screening program in a non-clinical setting serves to bring screening to the preconception population and encourages participants to deliberate over testing rather than compliantly accepting "another medical test" from their doctor. Having the test in a non-clinical setting would not suit all participants, but people not choosing this option could be referred on appropriately.

Some measures recommended to promote participant autonomy may lead to decreased uptake of testing. CF carrier screening programs that primarily target the preconception population yield lower uptakes than programs focused on the pregnant population.^{19,29} There is also preliminary evidence that providing more information about the test empowers some people to decline testing.^{19,21} However, given that the primary aim of CF carrier testing is to promote reproductive choice, ensuring that participants make well informed, voluntary decisions about testing is more important than high uptake.³⁶ Everyone should be offered testing, but not everyone will accept it.

We have not considered all the ethical issues raised by CF carrier screening, but have highlighted the broad structural features that lead to an ethically sound carrier screening program. Developing an ethically acceptable program for CF is particularly important, as it is likely to be the first of many population-based carrier screening programs in Australia.

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Competing interests

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