Reproductive Genetic Screening

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Abstract

Aim

The aims of this thesis were to explore the characteristics of individuals who accepted, declined or were not offered cystic fibrosis (CF) carrier screening and the outcomes of reproductive genetic screening through the evaluation of two separate carrier screening programs in Victoria, Australia.

Research Projects

Multi-disease carrier screening program in Jewish high schools

Background/Aim: A screening program for Tay Sachs disease (TSD) carrier status was introduced in high schools in Victoria in 1997, and was expanded to screen for six other genetic conditions common in the Ashkenazi Jewish population in 2008. The aim of this questionnaire-based study was to evaluate the current program and compare it with an evaluation of the program when screening was offered for TSD alone.

Methods: All students, in the second last year of high school, who were offered multi-condition carrier screening were invited to participate in the study.

Results/Conclusion: This study found that knowledge levels were decreased and predictive negative feelings if found to be a carrier increased, compared to the previous study when only TSD screening was offered.

Carrier couples identified through the Genetic Health Services Victoria CF carrier screening program

Background/Aim: In 2006 a population-based CF carrier screening program was implemented in Victoria by Genetic Health Services Victoria (GHSV). Screening is offered to pregnant women and couples planning a pregnancy by private obstetricians and general practitioners for a cost of $220 for each test. The aim of this study was to explore the experiences of couples who were both identified as carriers of CF.

Methods: Between January 2006 and December 2010, 10 carrier couples were identified, and all were invited to participate in the study. A total of nine interviews were conducted, seven couple interviews and two individual interviews, and 12 completed questionnaires were received.

Results/Conclusions: The results of the interview-based study indicated that couples were shocked and were unprepared for a positive carrier couple result. All couples changed their reproductive behaviour as a result of their carrier couple status and informed family members of their increased risk. The results of the questionnaire-based study were compared to a previous evaluation of the program exploring the attitudes and outcomes of CF screening for carriers and non-carriers. It was found that carrier couples have a high knowledge of CF and screening and there is no difference in knowledge between carrier couples and carriers, however both groups have a significantly higher knowledge than non-carriers. No carrier couples regretted having screening, with all saying that if they had their time again they would still have CF carrier screening.

Pregnant women who declined CF carrier screening

Background/Aim: CF carrier screening is currently offered to women during the early stages of pregnancy and couples planning a pregnancy by private obstetricians and general practitioners. The aim of this study was to assess the attitudes of women declining an offer of screening and to compare these to the attitudes of individuals who accepted an offer of screening.

Methods: Pregnant women who were offered CF carrier screening through the GHSV program and declined the offer were recruited at ultrasound and obstetric clinics and invited to participate in this questionnaire-based study.

Results/Conclusion: There was no difference in demographics between those who declined and those who accepted an offer of screening. However, knowledge levels were significantly lower in those who declined screening compared to those who accepted it (carrier couples, carriers and non-carriers). The main reason for declining an offer of screening was lack of family history of CF.

Pregnant women who were not offered CF carrier screening

Background/Aim: Carrier screening for CF is currently only offered in the private health system in Victoria. The aim of this study was to determine the attitudes of pregnant women who did not receive an offer of CF carrier screening, towards carrier screening for CF and compare it to those who were offered screening.

Methods: Participants were recruited at antenatal clinics at two public hospitals and were invited to participate in this questionnaire-based study.

Results/Conclusion: Those who were not offered screening were significantly younger, had a lower level of education and lower income compared to those who

were offered screening. Knowledge of CF and screening was significantly lower in those who were not offered screening compared to those who were. Family history is potentially the most influencing factor in the decision whether to have screening. While only half of the participants would have liked to receive an offer of screening during their current pregnancy, the majority believe CF carrier screening should be available to those who wish to have it.

Conclusions

As programs expand to screen for more diseases, truly informed consent may not be possible, with the more diseases screened resulting in a decrease in knowledge. Pre-test information should provide basic information on the genetics of recessive conditions which can be applied to all of the diseases screened for, while detailed information should be targeted towards carriers during post-test counselling.

As the main reason for declining an offer of CF carrier screening is lack of family history of the disease, pre-test information needs to make clear that most children with recessive conditions have no family history of the condition.

The current CF screening program is inequitable as screening is only offered in the private health sector. In order to ensure equity of access, screening needs to be offered in the public health sector with no out-of-pocket expenses, and educational resources and programs need to be developed and targeted towards potential participants.

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Abbreviations

TSD: Tay Sachs disease
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
GHSV: Genetics Health Services Victoria
NIH: National Institutes of Health
ACOG: American College of Obstetricians and Gynaecologists
ACMG: American College of Medical Genetics
HGSA: Human Genetic Society of Australasia
WHO: World Health Organisation
HBM: Health Belief Model

List of Publications

The following is a list of publications written in part or in full by myself during my candidature.

1. Massie, J., Petrou, V., Forbes, R., Curnow, L., **Ioannou, L.**, DuSart, D., Bankier, A., Delatycki, M.B. (2009). Population-based carrier screening for cystic fibrosis in Victoria: The first three years experience. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 49: 484-489.
2. **Ioannou, L.**, Massie, J., Lewis, S., Petrou, V., Gason, A., Metcalfe, S., Aitken, M., Bankier, A., Delatycki, M.B. (2010). Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools. *Clinical Genetics*, 78: 21-31.
3. **Ioannou, L.**, Massie, J., Lewis, S., McClaren, B., Collins, V., Delatycki, M. (2013). 'No thanks'-reasons why pregnant women declined an offer of cystic fibrosis carrier screening. *Journal of Community Genetics*, In Press.
4. Stark, Z., Massie, J., **Ioannou, L.**, Cousens, N., McClaren, B., Lewis, S., Metcalfe, S., Delatycki, M.B. (2012). Current practice and attitudes of Australian Obstetricians towards population-based carrier screening for inherited conditions. *Twin Research and Human Genetics,* In Press.
5. **Ioannou, L**.,* McClaren, B.,* Massie, J., Lewis, S., Forrest, L., Metcalfe, S., Delatycki, M.B. (2013).Population-based carrier screening for cystic fibrosis: A systematic review of 23 years of research. *Genetics In Medicine,* Accepted.
6. **Ioannou, L.**, Massie, J., Lewis, S., McClaren, B., Collins, V., Delatycki, M.B. (2013). Attitudes and opinions of pregnant women who are not offered cystic fibrosis carrier screening. *European Journal of Human Genetics*, Under Review.
7. **Ioannou, L.**, Delatycki, M.B., Massie, J., Hodgson, J., Lewis, S. (2013). Experiences of couples both identified as carriers of cystic fibrosis identified through a population-based carrier screening program. *Journal of Genetic Counselling*, Submitted.

List of Presentations

Poster Discussion

1. **Ioannou, L.**, Massie, J., Lewis, S., McClaren, B., Collins, V., Delatycki, M.B. (2011). 'No thanks'- why pregnant women choose not to have cystic fibrosis carrier screening. Paper discussed at the 9th Australasian Cystic Fibrosis Conference, Melbourne, Australia.

Poster Presentations

1. **Ioannou, L.**, Massie, J., Lewis, S., Petrou, V., Gason, A., Metcalfe, S., Aitken, M., Bankier, A., Delatycki, M.B. (2010). Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools. Poster presented at the Human Genetics Society of Australasia 34th Annual Scientific Meeting, Melbourne, Australia.
2. **Ioannou, L.**, Massie, J., Lewis, S., McClaren, B., Collins, V., Delatycki, M.B. (2010). 'No thanks'- why pregnant women choose not to have cystic fibrosis carrier screening. Poster presented at the Human Genetics Society of Australasia 34th Annual Scientific Meeting, Canberra, Australia.
3. **Ioannou, L.**, Massie, J., Lewis, S., Petrou, V., Gason, A., Metcalfe, S., Aitken, M., Bankier, A., Delatycki, M.B. (2011). Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools. Poster presented at the 9th Australasian Cystic Fibrosis Conference, Melbourne, Australia.
4. **Ioannou, L.**, Massie, J., Lewis, S., McClaren, B., Collins, V., Delatycki, M.B. (2011). 'No thanks'- why pregnant women choose not to have cystic fibrosis carrier screening. Poster presented at the 9th Australasian Cystic Fibrosis Conference, Melbourne, Australia.
5. **Ioannou, L.**, Massie, J., Lewis, S., McClaren, B., Collins, V., Delatycki, M.B. (2011). 'No thanks'- why pregnant women choose not to have cystic fibrosis carrier screening. Poster presented at the 12th International Congress of Human Genetics Conference, Montreal, Canada.
6. **Ioannou, L.**, Massie, J., Lewis, S., McClaren, B., Collins, V., Delatycki, M.B. (2012). 'No thanks'- why pregnant women choose not to have cystic fibrosis carrier screening. Poster presented at the Human Genetics Society of Australasia 36th Annual Scientific Meeting, Canberra, Australia.

General Declaration

Monash University

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 1 original paper published in a peer reviewed journal and 4 unpublished publications. The core theme of the thesis is Reproductive genetic screening. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Medicine under the supervision of Prof Martin Delatycki.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 4-8 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
4	Population-based carrier screening for cystic fibrosis: A systematic review of 23 years of research	*Accepted*: Genetics In Medicine	Literature search; inclusion and exclusion of studies; data extraction; data analysis and interpretation; writing of manuscript
5	Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools	*Published*: Clinical Genetics	Conception and design of study; attainment of ethics approval and on-going reporting requirements; questionnaire development; participant requirement; data collection, analysis and interpretation; writing of manuscript
6	Experiences of couples both identified as carriers of cystic fibrosis (CF) identified through a population-based CF carrier screening program	*Submitted*: Journal of Genetic Counselling	Conception and design of study; attainment of ethics approval and on-going reporting requirements; interview schedule development; participant requirement; interviews; transcription of interviews; data analysis and interpretation; writing of manuscript
7	'No thanks'- reasons why pregnant women declined an offer of cystic fibrosis carrier screening	*In Press*: Journal of Community Genetics	Conception and design of study; attainment of ethics approval and on-going reporting requirements; questionnaire development; participant requirement; data collection, analysis and interpretation; writing of manuscript
8	Attitudes and opinions of pregnant women who are not offered cystic fibrosis	*Under Review*: European Journal of Human	Conception and design of study; attainment of ethics approval and on-going reporting requirements;

	carrier screening	Genetics	questionnaire development; participant requirement; data collection, analysis and interpretation; writing of manuscript

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: ....

20th February 2013

Date: .....

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To my sister Elissa whom I love dearly, she is my greatest friend and also my greatest rival. She has become an incredibly strong, independent, smart, beautiful and successful young woman. I am extremely proud of her. She inspires me and pushes me to be the best that I can be, and to achieve the most that I can out of life. I admire her greatly and I hope that in some way I resemble her and who she has become.

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This thesis is dedicated to my beloved grandfather

Spíros Doubaras

It was through him that I learnt the meaning of unconditional love, the importance of family, and the significance of knowledge.

'Thank you for your eternal love and support. You are my inspiration. I hope I have made you proud.'

Chapter 1

General Overview

1.1 Background

This Chapter presents a brief overview of reproductive genetic screening in order to set the context for the rationale of the PhD. A more detailed background on reproductive genetic screening is provided in later chapters. This is then followed by the aims of the PhD and the overview and structure of the Thesis.

1.1.1 Genetic screening

Genetic screening is a test performed for the early detection or exclusion of a heredity disease, or to determine a predisposition to the disease in a population or sub-population with or without any family history of the disease.[1, 2] Reproductive genetic screening is the screening of individuals or couples to determine if they are carriers of a genetic disease that will not put them at risk of developing the disease but may result in disease in their offspring.[2] This is also referred to as carrier screening. A carrier is an individual who has a heterozygous mutation for an autosomal or X-linked recessive genetic condition. This thesis will focus on carrier screening for autosomal recessive genetic conditions.

The term 'carrier couples' refers to couples where both individuals are identified as carriers of an autosomal recessive condition and they have a one in four risk of having a child with the genetic disease with each pregnancy. Population-based carrier screening identifies carriers and carrier couples by offering testing to as many individuals as possible, regardless of whether or not they have a family history of the genetic disease.[3] Carrier couples can then be informed about available reproductive options.

In order to provide population-based carrier screening a condition must generally satisfy the World Health Organisation (WHO) guidelines that justify population screening. Namely, the disease needs to be an important health problem, mutation analysis can be performed to determine carrier status with known test sensitivity and reproductive options are available to prevent the birth of a child with this disease.[4] Two autosomal recessive conditions that meet these criteria are: Tay Sachs disease and cystic fibrosis.

1.1.2 Tay Sachs disease

Tay Sachs disease (TSD) is a severe, autosomal recessive condition most common among Ashkenazi Jews, with a birth prevalence of approximately 1 in 3,100 live births and a carrier frequency of approximately 1 in 28.[5] There is currently no cure for TSD and, in the infantile-onset form, has a life expectancy of less than 5 years.

TSD is the result of mutations in the *HEXA* gene causing a severe reduction of enzyme β-hexosaminidase A activity. Screening for carriers of TSD, in those of Ashkenazi Jewish descent, can be conducted by either enzyme or mutation testing. Enzyme testing involves detecting the level of enzyme in the blood, with carriers generally having lower levels than non-carriers.[6] Mutation testing involves screening a DNA sample, taken from blood or non-invasive methods such as cheekbrush, for the three most common HEXA mutations, accounting for approximately 99% of mutations in the Ashkenazi Jewish population.[7]

Carrier screening for Tay Sachs disease was first introduced in 1970 in the United States, with Israel and other countries with a high population of Ashkenazi Jews following suit.[8] Since the implementation of TSD carrier screening programs there has been a greater than 90% reduction in the incidence of TSD, the number of children affected with TSD, in these countries.[8]

TSD carrier screening programs have been implemented in Jewish high schools in both Canada and Australia. Screening in a high-school setting has many advantages including increased awareness and uptake, opportunity to educate students and the timely receipt of results for future reproductive decision making.[9] In 1997, a TSD carrier screening program was implemented by Genetic Health Services Victoria (GHSV) in Jewish high schools in Melbourne, Australia. The program provides education, testing and counselling to students in the second last year of high school. An evaluation of the program showed high uptake, high knowledge and a positive attitude towards carrier screening for TSD.[5]

1.1.3 Cystic fibrosis

Cystic fibrosis (CF) is the most common severe, recessive, autosomal condition in Northern Europeans, with a prevalence of 1 in 2500-3500 live births and a carrier frequency of 1 in 25.[10] Although treatments have improved life expectancy to a median of about 37 years, there is currently no cure for CF.[11]

In 1989 the gene responsible for CF was discovered making carrier screening for CF possible.[12] CF is the result of mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Since the discovery of the gene more than 1,900 *CFTR* alterations have been identified, with p.F508del accounting for approximately 70% of all mutations present in the Northern European population.[13]

In 1989, screening for CF in newborns was added to the tests performed in Victoria on a heel-prick blood-spot, obtained from babies in the first few days

of life.[14] The diagnosis of CF through newborn screening also identifies the parents as carrier couples, providing the couple with reproductive options for future pregnancies.

Carrier couples may also be identified by cascade testing, which aims to identify carriers of CF who are at increased risk because they are relatives of individuals either diagnosed with CF or identified as CF carriers. While cascade testing is highly accurate and sensitive, as the familial mutations are usually known, only about 11% of relatives for every proband take up cascade testing.[15, 16]

The total number of carriers identified in a population is far higher in population-based carrier screening compared to cascade testing[17] as more than 95% of carriers have no family history of CF.[18, 19] The implementation of population-based carrier screening for CF has resulted in a reduction of the incidence of CF, with significant decrease in the number of infants with CF being identified through newborn screening in areas where population screening has been implemented.[20]

1.2 Rationale

1.2.1 Multi-disease carrier screening in the Ashkenazi Jewish population

In Australia, there are approximately 90,000 Jews, with the majority being of Ashkenazi descent.[21] Carrier screening for reproductive risk is widely accepted in this population due to the high frequency of a number of autosomal-recessive genetic conditions. Ashkenazi Jews are at increased risk for certain genetic diseases due to endogamy, the practice of marrying within a specific community, and genetic drift.[22] Therefore, there are a number of autosomal recessive diseases that satisfy the criteria justifying carrier screening in this population. In the USA, the American College of Obstetrics and Gynecology (ACOG) released a statement recommending that individuals and couples of Ashkenazi Jewish descent be offered screening for TSD, cystic fibrosis, Canavan disease and Familial dysautonomia.[23]

This led to the expansion of the GHSV TSD Jewish high school carrier screening program. In 2008, the program was expanded to screen for an additional six diseases, including cystic fibrosis, Canavan disease, familial dysautonomia, Fanconi anaemia type C, Bloom syndrome and Niemann Pick disease type A. However, little is known about the effects of multi-disease carrier screening, particularly with regard to knowledge and psychological factors.

1.2.2 Population-based carrier screening for CF

In the USA, guidelines recommend that CF carrier screening be offered to all pregnant women and couples planning a pregnancy (ACOG).[24] In Australia there have been similar recommendations with the Human Genetic Society of Australasia (HGSA) stating that all pregnant women and couples planning a pregnancy be made aware of the availability of CF carrier screening.[25] Also, various pilot programs in New South Wales, Western Australia and Victoria all showed that the general population supports the routine offer of CF carrier screening.[26-28] However, despite these recommendations, CF carrier screening is not routinely offered in Australia.

A population-based carrier screening program, aimed at identifying CF carriers was implemented in Victoria in 2006, by Genetic Health Services Victoria. The program offers screening to individuals or couples before or during the early stages of pregnancy via obstetricians and general practitioners. Carrier screening for CF is currently only offered in the private health system for a cost of AUD$220 with no rebate from the national health fund, Medicare or private insurance.

1.2.3 Carrier screening in the future

The future of carrier screening is set to expand as screening becomes increasingly affordable, available for more conditions and new high throughput technologies are developed. Screening for a panel of over 400 severe recessive childhood conditions has been developed using next generation sequencing.[112] As consumers become increasingly interested in screening there will be a great deal of pressure on the general healthcare setting to provide it. This will have implications for healthcare professionals with regard to providing pre- and post-test information and counselling.

1.3 Aims of this PhD

In order to routinely offer screening for CF carrier status to the whole population and expand the program to screen for additional conditions, a great deal can be learnt from the evaluation of the current programs. Little is known about the characteristics of individuals who accept, decline and are not offered CF carrier screening as well as the effects of screening for multiple conditions in Australia. An increased understanding of these characteristics and outcomes will assist with the development of educational resources, increase uptake of screening and inform the provision of support and counselling.

The aims of this PhD project were to:

1. To determine the effects of screening for multiple diseases on knowledge and psychological factors of high school students
2. To identify the factors that influence the decision to accept or decline an offer of CF carrier screening
3. To assess the impact of screening for CF carrier status amongst carrier couples
4. To evaluate knowledge of CF and screening for women and couples in obstetric services
5. To determine the attitudes of women and couples in obstetric services towards the offer of CF carrier screening

Findings from this thesis will assist with the expansion of the current CF carrier screening program:

1. To offer screening for multiple diseases
2. To offer screening to all pregnant women and couples planning a pregnancy
3. To inform and assist with the development and implementation of other similar population-based carrier screening programs.

1.4 Thesis overview/structure

The structure of this thesis is as follows: Chapter 2 provides a detailed overview of reproductive genetic screening, the principles of genetic screening including the guidelines of screening as well as the legal, social and ethical implications of genetic carrier screening. Chapter 2 also includes an overview of the current reproductive screening practices in Victoria, Australia, as well as an overview of the Australian Healthcare System.

Chapter 3 presents a detailed overview of TSD including its genetics, clinical manifestations, current treatments and diagnosis as well as the various screening strategies for TSD carrier status in the Ashkenazi Jewish population. Chapter 3 also includes a detailed description of the TSD and related conditions Ashkenazi Jewish high school carrier screening program currently implemented in Victoria, to provide additional background information for studies in this thesis.

Chapter 4, the first research chapter, presents a published study that explored multi-condition carrier screening in Jewish high schools. It examines the reasons for accepting screening and the effects of screening for multiple conditions on knowledge and predicted negative feelings if found to be a carrier.

Chapter 5 provides a detailed overview of CF including its genetics, clinical manifestations, current treatments and diagnosis as well as the various screening strategies for CF carrier status. To set the context for studies in this thesis, Chapter 4 also includes a detailed description of the CF carrier screening program currently implemented in Victoria as well as a comprehensive review of the literature on population-based carrier screening for CF.

Chapters 6-8 present three separate research studies designed primarily to explore various aspects of carrier screening for CF. Chapter 6 is a qualitative study exploring the experiences of couples that were both identified as carriers of CF through the GHSV CF carrier screening program.

Chapter 7 explores the reasons why pregnant women choose to decline an offer of CF carrier screening. The results of this study were compared to those of the previous study where the offer of CF carrier screening was accepted.

The final research chapter, Chapter 8, focuses on the attitudes and opinions of pregnant women who were not offered CF carrier screening. Again the results of this study were compared to those of the studies presented in Chapter 5 and 6, where CF carrier screening was offered.

In total there are four research chapters (Figure 1). Each research chapter is preceded by a preamble to set the context for the subsequent paper. This thesis is presented in line with the Monash University guidelines as a "Thesis by publication" and as such the research chapters all consist of a published paper, a paper in press or a paper under review. Thus, due to the nature of the format of this thesis and the requirements of Monash University there will be some unavoidable repetition in the experimental chapters.

Given each experimental chapter has an individual discussion, the final chapter, Chapter 9, provides an overall discussion of the findings, limitations of the study, future directions and conclusion.

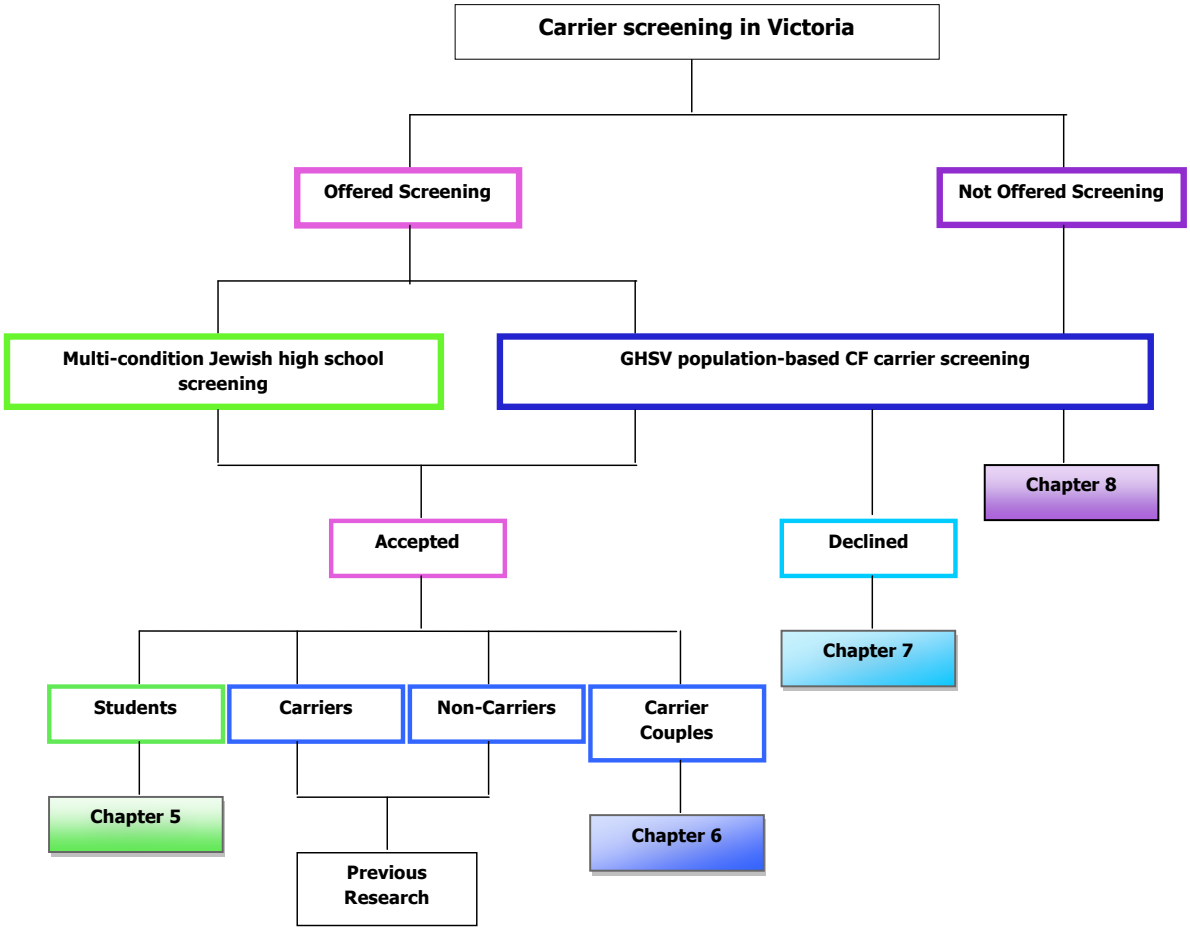

Figure 1. Flow chart of Thesis Structure for Research Chapters

Chapter 2

Overview of Cystic Fibrosis

This chapter provides a detailed background on reproductive genetic screening, including: the principles of screening; current screening programs in Victoria, Australia; the legal, ethical and social implications of carrier screening; as well as an overview of the Australian health care system.

2.1 Overview of genetic screening

Genetic screening is becoming more common in modern medicine. Many genes associated with disease have been identified enabling genetic screening for these conditions. With the completion of the sequencing of the Human genome in 2003, continued advances in technology, the linking of genes with disease and the decreasing costs of DNA sequencing, genetic screening is continuing to be a growing area with companies now offering genetic screening for over 100 genetic diseases.[29]

2.1.1 Types of screening

Screening is the process of identifying apparently healthy individuals who might be at increased risk of a disease. *Genetic* screening is the testing of individuals to determine if they possess a certain genotype that is associated with disease in themselves and/or may cause disease in descendants.

Reproductive genetic screening is the screening of individuals or couples to determine if they are carriers of a disease-causing mutation that will not put them at risk of developing the disease but may cause disease in their offspring.[2] The goal of reproductive genetic screening is to inform individuals and couples at risk of having children with genetic disorders of their reproductive options.

Genetic screening also has implications for the wider family unit, with family members of those identified having a higher risk of possessing the same genotype.

2.2 The principles of screening

Although genetic screening is becoming a regular part of medical care opinions still vary widely as to the value of screening. Some of the potential benefits of screening include: early detection and intervention leading to improved prognosis; reduced morbidity and mortality; and savings in medical and health care resources.[30] Some of the potential disadvantages include: no change to prognosis regardless of early diagnosis or intervention; increased anxiety and fear; and psychological harm from false-positive and false negative screening

results.[30]

To ensure screening programs are beneficial they must be assessed to ensure the disease being screened for meets the appropriate criteria, to determine the potential barriers and facilitators, and to confirm appropriate education and counselling is provided.

2.2.1 Guidelines for screening

Wilson and Jungner developed the principals and practice of screening for disease in 1968 for the World Health Organisation (WHO) (Figure 1).[4] Since then, the WHO principles have been adapted to form the guidelines for screening for genetic diseases.[31]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognised disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

Figure 1. Wilson and Jungner WHO disease screening criteria (1968)

In 1997 the WHO guidelines were expanded to include additional guidelines on genetic screening and testing.[32] The additional guidelines stated that screening should: be voluntary, be preceded by adequate information and genetic counselling should be provided following a positive test result.

In 2008 the guidelines were revisited with additional criteria included based on screening knowledge over the years that had elapsed since the guidelines were implemented. Further inclusions were: programs should be evaluated to determine effectiveness; programs should combine education, counselling and clinical services; programs should promote equity of access to screening and the overall benefits of screening should outweigh the harms.[33]

The European Society of Human Genetics (ESHG) and the American Society of Human Genetics (ASHG) have also formulated guidelines with regard to

population genetic screening.[34, 35] In Australia, the National Health and Medical Research Council have recommended similar guidelines.[36] They state that: screening should be voluntary, have defined health goals, distinct target population, laboratory controls, maintain confidentiality and ensure provision of information. The ESHG also stated that pilot programs should precede the implementation of programs within the population to assess: test validity and acceptability; uptake rates; the impact of screening results on reproductive decision making; psychological consequences and costs.[34]

2.2.2 Facilitators and barriers to screening

It is important to explore the factors that influence whether an individual will take part in a screening program to determine uptake in the population. Factors that influence whether an individual will have screening are based on the Health Belief Model (HBM), which was developed to predict health-related behaviour.[37] The Health Belief Model consists of four constructs: perceived susceptibility, perceived severity, perceived benefits and perceived barriers.[37]

Perceived susceptibility refers to an individual's perception of whether they are likely to be affected by/be a carrier of the disease, while *perceived severity* is an individual's perception concerning the seriousness of the disease, including medical, financial and social consequences of the disease. High perceived susceptibility and severity are believed to elicit a health-related behaviour, however they may not define the course of action that is likely to be taken.[37]

The course of action, whether to accept or decline an offer of screening, may be determined based on the *perceived benefits* of the action. The perceived benefits of screening can be reduced anxiety, knowledge and availability of reproductive options to avoid the birth of a child with the disease. However, the *perceived barriers* of a particular action may prevent an individual from undertaking that course of action.[37] Perceived barriers of screening can be cost, lack of time and/or being against reproductive intervention such as prenatal diagnosis and pregnancy termination.

Modifying factors that influence health-related behaviour were later added to the HBM including: demographics; sociological and psychological variables such as socio economic status and personality; perceived efficacy or the individual's ability to adopt the desired behaviour; motivation to commit to the desired health goal; perceived self-control; and external factors such as knowledge/education, the media, health professionals and personal experience.[38] Demographic factors that can influence the decision to have screening include: gender, age, ethnicity, education, income and parity. Older women who have a

high level of education, high income and low parity are most likely to have screening.[27, 39, 40] Ethnicity is an important factor in choosing which diseases to screen, with certain diseases being more common amongst certain ethnicities.

A review exploring the factors associated with accepting or declining an offer of CF carrier screening found that the four most frequently reported factors associated with accepting an offer of screening were: perceived benefits of CF carrier screening, low perception of barriers to CF carrier screening, low parity or desire to have children and research-related factors.[113] The four most frequently reported factors associated with declining an offer of CF carrier screening were: perceived barriers to having CF carrier screening, low perception of benefits related to CF carrier screening, higher parity and lack of knowledge.[113]

2.2.3 Education and counselling

Educating and informing healthcare professionals as well as potential participants is essential to ensure the screening program is effective. In Australia, many healthcare professionals are not familiar with genetics and require appropriate education and information in order to best offer screening to their patients.[28, 41]

Education and counselling can be provided to potential participants both prior to screening (pre-test) and after receiving a screening result (post-test). *Pre-test* information and education is necessary to ensure potential participants make an informed decision in regards to having screening. This is particularly important as it has been shown that perceived severity of the disease and perceived susceptibility are influencing factors in the decision to have screening.[40, 42, 28]

Post-test information and genetic counselling are an essential component of a screening program to ensure participants have an adequate understanding of their carrier status. This is particularly relevant for carriers and carrier couples, as they require information in regards to reproductive options and support throughout the process. Where test sensitivity is less than 100%, education and counselling should focus on informing non-carriers of their residual risk.

2.3 Screening programs in Victoria, Australia

2.3.1 Maternal serum screening

Prenatal screening is used to identify pregnancies at increased risk of chromosomal abnormalities such as Down syndrome (Trisomy 21), Edward's syndrome (Trisomy 18) and structural abnormalities such as neural tube defects.

The Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG) produced guidelines recommending that all pregnant women be informed of the availability of prenatal screening.[43]

In Victoria, screening is available to pregnant women during either the first or second trimester although the vast majority who have screening have first trimester screening. The first trimester combined screen, involves a combination of maternal serum screening (blood test) and ultrasound measurement, while the second trimester screening involves maternal serum screening (blood test) only.[44]

Screening for Trisomy 21 identifies pregnancies that are at increased risk of being affected but it is not a diagnostic test. Women with an increased risk screening result can choose to have prenatal diagnosis to determine whether their pregnancy is affected. Prenatal diagnosis is conducted using either chorionic villus sampling or amniocentesis. Women or couples with an affected pregnancy may choose to continue with or terminate the pregnancy.

2.3.2 Newborn screening

Newborn screening (NBS) is a public health program that is designed to screen for a number of serious conditions, using a heel-prick blood test taken from newborns during the first few days of life (48-72hrs).[45] NBS is conducted worldwide, although the number and type of conditions tested for varies between countries. The criterion for inclusion in the NBS panel is that early diagnosis can lead to interventions that can improve the health outcomes of affected newborns.

In Victoria, NBS was first introduced in 1966 with the first condition being screened for being phenylketonuria (PKU).[46] In 1976 the panel was extended to screen for congenital hypothyroidism, followed by cystic fibrosis in 1989.[46] In 2001, tandem mass spectrometry was introduced allowing for the identification of many more conditions.[47] In Victoria, there are currently 25 conditions that are screened for as part of the NBS program.[48]

More than 99% of newborns have a normal screening result. Those with an abnormal result usually require further testing before a diagnosis is made.[48]

2.3.3 Carrier screening

Carrier screening, for the purposes of this thesis, will be considered as the identification of heterozygotes for an autosomal or X-linked recessive disease. A heterozygote, or a carrier, is an individual who possess one copy of a disease-causing mutation such that they are not at risk of developing the disease themselves, but are at increased risk of having a child with the disease. If two

carriers of an autosomal recessive disease reproduce there is a 25% chance of disease in their offspring.

The aim of carrier screening is to identify carriers and carrier couples through screening and inform them of their carrier status and the availability of reproductive options. Reproductive options that are available to carrier couples include: continuing with previous reproductive plans, having no children, adoption, using prenatal diagnosis with termination of an affected foetus or preimplantation genetic diagnosis.

Carrier screening can be aimed at a target population who are at increased risk of the disease, due to family history (cascade testing) or ethnicity, or towards the general population. In Victoria, there are both targeted and population-based screening programs for various genetic diseases.

2.3.3.1 Targeted screening

i. Cascade testing

Cascade testing is the carrier testing of family members of an affected individual or carrier. Family members of an affected individual are more likely to be carriers of the disease than the general population. Therefore, it is generally highly accurate and more sensitive than population carrier screening, as the familial mutations are usually known.[15]

One of the limitations to cascade testing is the necessity of identifying a carrier or affected individual in order to determine family members who are increased risk. Another potential limitation to the efficacy of cascade testing is the reliance on communication of genetic information to extended family members by carriers, individuals diagnosed or their parents.[15]

The Human Genetic Society of Australasia (HGSA) recommends offering cascade testing to family members for genetic diseases. Health professionals and genetic services provide cascade testing to family members of affected individuals or carriers, with the majority of genetic testing being subsidised by State Governments.

ii. Jewish community

There are approximately 13 million Jewish people worldwide, with the majority residing in the US and Israel.[49] The Jewish population in Australia is approximately 90,000 with the majority being of Ashkenazi descent due to a large migration of this group to Australia from the late nineteenth to the mid twentieth centuries.[21]

Due to endogamy, the practice of marrying within a specific community, and genetic drift, random sampling that alters the frequency of an allele in the population, Ashkenazi Jews are at increased risk of a number of autosomal recessive genetic conditions.[22] These include: Tay-Sachs disease (TSD); cystic fibrosis (CF); Bloom syndrome; Canavan disease; Niemann-Pick disease Type A; Fanconi anaemia. Individuals of Ashkenazi Jewish decent have a one in four chance of being a carrier for at least one identifiable recessive condition.[22] Due to the high prevalence of recessive conditions in the Ashkenazi Jewish population, carrier screening for reproductive risk is widely accepted.

In Victoria, a carrier screening program is operational in Jewish high schools, offering screening for seven of the most common genetic diseases to students in the second last year of school. This program is described in further detail in Chapter 3.

2.3.3.2 Population screening

i. Thalassaemia

β-thalassaemia is an autosomal recessive disease most common in individuals of Mediterranean descent.[50] β-thalassaemia is characterised by blood transfusion-dependant anaemia in those affected, and reduced mean corpuscular haemoglobin levels in carriers.[51] Screening for carriers of β-thalassaemia can be conducted using a standard full blood examination. The blood examination is not a diagnostic test, with those who are screen positive requiring further confirmatory tests.

In Australia, screening for β-thalassaemia carrier screening is not organised, however screening is conducted in early pregnancy in most women with the request of a full blood examination (FBE) during antenatal care. It has been shown that most women do not make a decision with regard to having β-thalassaemia carrier screening, with the majority of carriers not being informed about screening prior to receiving their carrier result.[52] Most women identified as a possible carrier by FBE are informed of their increased risk of being a carrier and referred for further testing in order to confirm their carrier status.

ii. Cystic fibrosis, spinal muscular atrophy and fragile X syndrome

Multi-disease carrier screening is becoming more common as technology advances and screening costs decrease. In Victoria, Genetic Health Services Victoria (GHSV) implemented a cystic fibrosis carrier screening program in 2006 (discussed further in Chapter 4). Through the program screening is offered to women and couples before or during the early stages of pregnancy in the private

health sector by private obstetricians and general practitioners. The test is offered on a user pays cost recovery basis, with each test costing AUD$220 and no Medicare rebate.

In 2012 the program was extended to screen for an additional two diseases, spinal muscular atrophy (SMA) and fragile X syndrome. The extended panel of tests costs AUD$350. The program is currently in the pilot phase with only a select few obstetricians offering the extended screening panel.

2.4 Legal, ethical and social implications of carrier screening

2.4.1 Legal considerations

There is currently no national policy statement for population genetic screening within Australia. However, laws governing both medical and genetic testing in general are applicable due to the collection, storage, usage and disclosure of health information by screening programs.[53]

2.4.2 Ethical considerations

The ethical considerations in relation to genetic screening include autonomy, beneficence and non-maleficence, and equity.

Autonomy refers to the protection of an individual's right to make informed, un-coerced decisions. To ensure that autonomy is protected, informed consent needs to be obtained prior to participating in a screening program. Legally, informed consent is only valid if the following three criteria are met: the individual is competent, consent is given voluntarily and the individual is adequately informed.[54] In the context of population screening there are concerns that it may be difficult to obtain informed consent on a large scale.[53]

Another concern is the difficulty of protecting individual autonomy due to the familial nature of genetic diseases. The information obtained from screening may provide unwanted information to other individuals within the family who did not wish to participate in testing. Conversely an individual may not be provided with genetic information that is relevant to them. Genetic screening could also result in the identification of non-paternity.

Beneficence and non-maleficence refers to maximising the benefits and minimising the harms associated with genetic screening. The implementation of genetic screening programs maximises the benefits although there will always be some harm associated. To minimise this aspect of screening the potential harms associated with screening should be explained.

Equity refers to ensuring all individuals in the population are provided equal access to testing. One major concern that may lead to inequity is the cost of genetic screening to the individual. Providing genetic screening to the population is extremely expensive, and without government funding screening is offered on a user pays basis with the cost being unaffordable for some.

Other ethical considerations relating specifically to reproductive genetic screening include: pregnancy termination, time of offering screening, potential reduced societal value of those with genetic disease and screening based on ethnicity. Many concerns have been raised with regard to the information provided to couples prior to a *termination of pregnancy,* with pregnant women and their partners not completely understanding the implications of having a child with the disease.[27] Relating to termination of pregnancy, is the issue of when life begins with some individuals believing that life begins at conception and that it is unethical to end life at any stage. While at the other extreme some individuals believe that life does not begin until birth. Preimplantation genetic diagnosis is considered to be ethical by many, however there are groups of people who believe that discarding unwanted/affected embryos through the use of preimplantation genetic diagnosis is unethical, as once the embryo is formed it has the same ethical standing as an embryo in the uterus.[27]

Time of offering screening has raised a few concerns, with offering screening prenatally resulting in limited reproductive choices for at-risk couples. Offering screening preconceptionally has been proposed as the best time, however there are barriers associated with offering screening preconceptionally including lack of preconception health care setting and lack of interest at that life stage.[55] High school carrier screening has been implemented in various countries, starting with TSD carrier screening in Montreal in the 1970's.[56] Carrier screening in high school provides a setting in which to educate and test a large proportion of the population or sub-population, however there have been many concerns with regard to the ability of young people to make informed decisions and the usefulness of this information at this life stage.[27]

There are also concerns that the implementation of reproductive genetic screening programs have led to the *reduced societal value of those with genetic disease*, with parents who choose not to utilise screening and those who have a child with a preventable disease receiving negative reactions from health professionals and society.[27]

The main issue surrounding *screening based on ethnicity* is potential discrimination, with individuals of a particular ethnicity who are offered screening

and/or those who are not offered screening based on ethnicity possibly reporting feelings of discrimination.

2.4.3 Social implications

The majority of the social implications are interconnected with the ethical implications. One that has not yet been mentioned is the consideration of cultural and religious attitudes. A person's culture and religion may impact on their attitude towards health, reproduction, pregnancy, childbirth, disability and in particular genetic diseases. It is essential to consider these cultural and religious issues when developing a screening program in order to ensure the program is accepted. This will minimise the potential for discrimination and adverse psychosocial outcomes as a result of screening.

2.5 Australian health care system

2.5.1 Medicare

Medicare is a government funded health care system that provides affordable primary health care to Australian citizens and permanent residents. Individuals with a valid Medicare card have access to subsidised health care from health professionals with a Medicare provider number and free health care in public hospitals.[57]

Under the Medicare system, cardholders are reimbursed some of the medical fees with the remaining costs being out of pocket expenses.[57] Not all medical expenses are covered, as Medicare only covers primary health care. Some things that are not covered by Medicare include; private hospital costs, some genetic testing, dental services, ambulance services, cosmetic surgery and medical services that are not clinically necessary to name some.[57]

Medicare provides a private health insurance rebate, which subsidises approximately 30% of their premium, to encourage those who can afford it to obtain insurance even though they have access to free or affordable health care in the public health system.[57] Currently 54.5% of Australian citizens and permanent residents have private health insurance.[58]

2.5.2 Prenatal care

In Australia, there is a choice between private and public prenatal care. In the public health system prenatal care is usually provided in a public hospital by a combination of general practitioners, midwifes and obstetricians. Public hospital care is funded by state Government, covering the majority of costs in the public

health system including the bulk of ultrasound costs.[59] However, 1st trimester combined screening is not fully covered by Government funding.

In the private health system, private health insurance is used to cover the costs of prenatal care in combination with Medicare and individual finances. In the private health system prenatal care is provided by GPs, obstetricians and in ultrasound clinics, with individuals having their choice of health professionals.

Chapter 3

Carrier screening in the Jewish community

3.1 Tay Sachs disease

Tay Sachs disease (TSD) is a severe, autosomal recessive condition most common among Ashkenazi Jews, with a birth prevalence of approximately 1 in 3,100 live births and a carrier frequency of approximately 1 in 28.[5]

3.1.1 Genetics

The Hexosaminidase A (alpha polypeptide) (*HEXA*) gene was discovered in 1985.[60] The *HEXA* gene encodes the alpha subunit of an enzyme called β-hexosaminidase A; the alpha subunit produced by the *HEXA* gene combines with the beta subunit produced by the *HEXB* gene to form the enzyme.[61] β-hexosaminidase A plays a critical role in central nervous system. The enzyme is found in lysosomes, which are cellular organelles that act to break down toxic substances, and forms part of a complex that breaks down a fatty substance called GM2 gangliosides.[62]

TSD is the result of mutations in the *HEXA* gene causing a loss of enzyme β-hexosaminidase A activity. The absence/reduction of enzyme activity prevents the breakdown of GM2 gangliosides, resulting in a toxic accumulation of the fatty substance in the nerve cells of the brain and spinal cord.[63] The build up of GM2 ganglioside causes progressive damage and the destruction of nerve cells.[64]

Enzyme deficiency can be detected in the blood of carriers, making carrier screening for TSD possible.[6] The test is simple, inexpensive and highly sensitive although initial methods resulted in false positive results when testing women who were pregnant or taking oral contraception.[65] The enzyme assays were further developed to minimise the risk of the results being affected by pregnancy or hormones.[66]

More than 120 mutations have been discovered since the identification of the gene.[67] Three mutations are the most common, accounting for approximately 96% of mutations in the Ashkenazi Jewish population.[7] The three mutations identified are: c.1275_1278dupTATC, c.1421+1G>C and p.G269S.[7] The identification of these mutations and the high sensitivity in Ashkenazi Jews increased the accuracy of carrier screening for TSD in this population. In individuals who are not of Ashkenazi Jewish background, carrier testing by HEXA measurement is still the method of choice. For those of Ashkenazi Jewish background, enzyme testing and mutation testing have similar sensitivity and specificity. Mutation detection has the advantage that it can be done from non-invasive samples such as cheekbrush whereas enzyme testing requires a blood sample.

3.1.2 Clinical manifestation

During the 1880's a British ophthalmologist and an American neurologist, Warren Tay and Bernard Sachs respectively, separately described cases that later became known as TSD.[68-70] The clinical features of infantile-onset TSD are generally displayed from six months of age and include: developmental regression, progressive deafness and visual impairment.[70] By approximately one year of age symptom include: loss or voluntary movement or spasticity, enlarged head and loss of peripheral vision.[70]

As the disease progresses affected infants may experience blindness, impaired breathing and swallowing, paralysis and seizures.[70] Deterioration increases until the affected infant is in an unresponsive, vegetative state. Lifespan is markedly reduced with an average life expectancy of less than 5 years. TSD can be present in other forms including juvenile-onset and adult-onset. However, these forms will not be discussed in further detail.

3.1.3 Diagnosis

Diagnosis can be confirmed with a blood test to determine the presence and quantity of β-hexosaminidase A.[6] An eye test can also assist with the diagnosis of TSD, with a red spot on the retina being characteristic, although not diagnostic of TSD.

3.1.4 Treatment

There is no treatment or cure for Tay Sachs disease, with symptomatic treatment being the only available therapeutic intervention.[5]

3.2 Carrier screening in Jewish community

Carrier screening for Tay Sachs disease was first initiated in 1970 in the US, with Israel and other countries (with a high population of Ashkenazi Jews) following suit.[8] TSD carrier screening is widely supported and promoted by Jewish leaders providing awareness and education to the whole community.

Screening for TSD is offered to inform individuals and couples of their carrier status allowing them to make informed reproductive decisions. Since the implementation of TSD carrier screening programs there has been a greater than 90% reduction in the incidence of TSD in the Ashkenazi Jewish population.[8]

Initially the ultra orthodox Ashkenazi Jewish community did not participate in these programs due to their strong religious beliefs in regards to prenatal

diagnosis and termination.[71] This changed with the introduction of the Dor Yeshorim Program

3.2.2 Dor Yeshorim program

In 1983 a unique not-for-profit organisation, Dor Yeshorim, was established in the ultra orthodox Ashkenazi Jewish community.[7] Rabbi Joseph Ekstein founded the organisation to ensure the preservation of both religion and community after losing four of his own children to TSD.[22] The Dor Yeshorim Program provides anonymous and confidential pre-marital screening for nine recessive conditions to ultra-orthodox couples during the match-making process. Blood samples are taken from students at ultra orthodox high schools and each student is given an individual code.[22] When they reach a marriageable age and a potential match is found, the match maker contacts Dor Yeshorim and upon providing the codes the couple are told whether they are carriers of the same condition by receiving a result of either 'match advisable' or 'match not advisable'.[22] No individual results are provided eliminating the fear of stigma in the community. More than 95% of ultra orthodox Ashkenazi Jews participate in the Dor Yeshorim program and since its implementation there have been no children born with a common recessive genetic disease to ultra-orthodox couples in Israel.[72]

3.2.3 High school carrier screening

Due to the advantages of preconception carrier screening and the acceptability of screening in the Jewish population, high school carrier screening is a favourable option. Screening in a high-school setting achieves maximum awareness in the target population and provides an opportunity to educate students in order for them to make an informed decision in regards to screening.[9]

High school carrier screening for Tay Sachs disease has been associated with higher uptake than that of adult-based programs and students have been shown to have a high knowledge of general genetics and specific conditions of higher prevalence in the Jewish community.[56, 73, 74] While there are advantages to high-school screening, there have been concerns as to the relevance of this information at this stage of life and the potential psychological harm.

Studies have shown that carriers identified in high-school programs recall their carrier status and use this information in reproductive decision-making later in life.[75, 76] Informed consent is obtained from students over 16 years of age in some programs, with psychological research showing no difference between the competency of adults and adolescents towards decision-making.[76] Having

freedom and the capability to make independent decisions that comes from being autonomous, has been shown to have various psychological benefits including an increase sense of efficacy in adolescents.[77]

The lack of psychological harm displayed by students participating in these programs may be due to high knowledge, with knowledge having an influence on attitudes.[78] Overall students have a positive attitude towards screening for TSD with a large number requesting screening.[79]

Tay Sachs disease high school carrier screening programs have been implemented in both Canada and Australia. High school carrier screening programs for TSD have existed in Montreal, Canada, for more than 30 years.[76] A 20-year analysis found that the program is effective with a 90-95% reduction in the incidence of TSD with the majority of cases of TSD being born to couples outside the target community or to non-screened couples.[76]

In 1995 a TSD carrier screening program was implemented in four Jewish high schools in metropolitan Sydney, Australia, by the Australasian Community Genetics Programme (ACGP).[21] Before the implementation of this program screening for TSD was only offered through a medical consultation service.[21] The program provides compulsory education sessions and voluntary testing to students between the ages of 15-17 years. Testing was done via a blood test but in 1998 cheek swabs were used in replace of blood tests and the program was extended to include screening for cystic fibrosis.

3.3 GHSV TSD and related conditions carrier screening program

In Melbourne, Australia, a TSD carrier screening program was established in Jewish high schools in 1997. The aims of the program are: education and awareness, carrier screening and prevention of TSD. Carrier screening is offered to high school students aged between 15 and 18 years and University students attending Monash University and the University of Melbourne. The program also conducts two community education screening days each year.

Testing was initially performed using a blood sample and incurred a cost of AUD $40.[5] Testing has been offered free of charge, to both high school and University students, since 1999, with the introduction of cheek brush sampling in 2003.[78]

In 2008, the program was extended to screen for another six genetic conditions, with carrier frequencies that range from 1 in 25 to 1 in 100.[73] These conditions are: (i) cystic fibrosis (CF), (ii) Fanconi anaemia type C, (iii) Bloom

syndrome (BS), (iv) Canavan disease (CD), (v) Niemann Pick disease type A, and (vi) familial dysautonomia.

An education session is provided in the form of a PowerPoint presentation. The presentation outlines: the conditions screened for, inheritance of recessive conditions, the importance of ancestry, testing procedure, what it means to be a carrier and future options for carriers. Students are also given an information brochure, a leaflet on the specific conditions screened for, and, a consent form. Informed consent is required in order to have testing. If students are less than 16 years of age written parental consent is also required.

This program offers individual testing. Students have the choice whether or not to have screening and the results of the test are provided directly back to them. Testing is conducted approximately one week after the education session. All students have a one-on-one counselling session in order to discuss the consent form and ask any further questions. The consent form covers family history, conditions for which they wish to be screened for and explains the various aspects of testing. Students need to complete and sign the consent form following counselling. Testing is by cheekbrush sampling. DNA extracted from the sample is tested for the most common mutations that underlie the seven recessive conditions.

If an individual is found to be a carrier they are contacted by a genetic counsellor via telephone and offered further counselling. A letter and copy of results also follow the phone call. Parents are also informed of the results.

Table 1. Autosomal recessive conditions screened for in the GHSV TSD and related conditions Ashkenazi Jewish high school carrier screening program

	Life expectancy	**Gene**	**Carrier Frequency**
Tay Sachs Disease (TSD)	Childhood 2 to 3 yrs	*HEXA*	1 in 28
Cystic Fibrosis (CF)	Early Adulthood 30-40 yrs	*CFTR*	1 in 25
Canavan Disease (CD)	Childhood 3 yrs	*ASPA*	1 in 40
Niemann Pick Disease Type A (NP)	Childhood <3 yrs	*SMPD1*	1 in 70
Familial Dysautonomia (FD)	Early Adulthood	*IKBKAP*	1 in 30
Bloom Syndrome (BS)	Early Adulthood	*BLM*	1 in 100
Fanconi Anaemia Type C (FA)	Early Adulthood	*FANCC*	1 in 90

Chapter 4

Multi-disease carrier screening in Ashkenazi Jewish high schools

4.1 Declaration

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Conception and design of study; attainment of ethics approval and on going reporting requirements; questionnaire development; participant requirement; data collection, analysis and interpretation; writing of manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**
A/Prof John Massie	Contributed to design of study; assisted with development of questionnaire; interpretation of data; discussion of ideas expressed in and critical revision of manuscript
Dr Sharon Lewis	Contributed to design of study; assisted with development of questionnaire; assisted with data analysis; interpretation of data; discussion of ideas expressed in and critical revision of manuscript
Dr Alexandra Gason	Previous study
Dr Vicki Petrou	Previous study
Prof Sylvia Metcalfe	Previous study
A/Prof MaryAnne Aitken	Previous study
Prof Agnes Bankier	Previous study
Prof Martin Delatycki	Contributed to design of study; assisted with development of questionnaire; interpretation of data; discussion of ideas expressed in and critical revision of manuscript

Candidate's Signature	[redacted]	**Date** 20/02/13

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Murdoch Childrens Research Institute

Signature 1	[redacted]	1/3/13
Signature 2		1/3/13
Signature 3		19/3/13
Signature 4		20/3/13
Signature 5		4/3/13

Signature 6	[redacted]	4/3/13
Signature 7		13/3/13
Signature 8		1/3/13

4.2 Paper preamble

This chapter explores the outcomes of a multi-disease carrier screening program and compares it to the outcomes of a single-disease carrier screening program, in Jewish high schools. This project was conducted at the outset of my candidature and published in Clinical Genetics, in 2010. The participant information sheet and questionnaire used in the study are displayed in the Appendices (Appendix A and B respectively). Additional concluding statements follow the paper.

4.3 Paper: 'Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools'

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Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools

Ioannou L, Massie J, Lewis S, Petrou V, Gason A, Metcalfe S, Aitken MA, Bankier A, Delatycki MB. Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools.
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A screening programme for Tay Sachs disease (TSD) carrier status was introduced in high schools in Victoria, Australia in 1997, and was expanded to screen for six other genetic conditions common in the Ashkenazi Jewish population in 2008. The aim of this study was to evaluate the current programme and compare it with an evaluation of the programme when screening was offered for TSD alone. All students from Jewish high schools in Melbourne who offered the programme in 2009 were invited to participate in the study. A purpose-designed questionnaire explored the following domains: knowledge (disease and genetics), reasons for screening, anxiety, and predicted negative feelings if found to be a carrier. Two hundred and seventy-three students were offered screening, and 272 (99.6%) completed the questionnaire. Only two students chose not to have screening. Two hundred and seventy-one students were in the penultimate year of high school (99.6%) and 222 were of Ashkenazi Jewish descent (82.5%). The main reasons for choosing screening were the desire to know carrier status and convenience. Knowledge level decreased and negative feelings increased in the current cohort compared to that when screening was offered for TSD alone. We conclude that the current programme is efficient, although increasing the number of conditions resulted in a decrease in knowledge and increase in predicted negative feelings if found to be a carrier of one of the conditions. This has implications for multi-disease screening programmes that will increase in frequency as more conditions can be screened for and costs diminish.

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Key words: carrier screening – cystic fibrosis – education – high school – Jewish – multi-disease screening – Tay Sachs disease

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Carrier screening for inherited diseases provides information regarding reproductive risks by detecting whether an individual carries a gene mutation that may cause disease in their offspring (1). Carrier screening programmes may be directed at the whole population or targeted towards a subgroup at increased risk, with the aim to test and counsel as many individuals as possible regardless

of whether or not they have a family history of the genetic disorder (2).

In the Ashkenazi Jewish community, carrier screening for reproductive risk is widely accepted due to the high frequency of a number of autosomal-recessive genetic conditions. There are approximately 30 million Jewish people in the world of whom more than 90% are of Ashkenazi descent (3). Ashkenazi Jews are at increased risk for certain genetic diseases due to endogamy, the practice of marrying within a specific community, and genetic drift (4).

Tay Sachs disease (TSD) is a severe, life-shortening, autosomal-recessive disease most common among Ashkenazi Jews, with a prevalence of about 1 in 3100 live births and a carrier frequency of approximately 1 in 28 in that community (5). TSD carrier screening was first introduced in the United States in 1971 and similar programmes were later implemented in other countries where there are large populations of Ashkenazi Jews (6). TSD carrier screening programmes have been associated with relatively high uptake in Ashkenazi Jewish populations all over the world and have resulted in a more than 90% reduction in children affected with TSD in countries where screening is widely offered (7).

Ultra-orthodox Jews do not participate in the screening programmes due to their strong religious beliefs in regard to prenatal diagnosis and pregnancy termination (8).

A not-for-profit organization, Dor Yeshorim, was established in 1983, which provides premarital carrier screening of ultra-orthodox couples for nine conditions, currently, during the matchmaking process (4,9). Screening is anonymous and confidential with the couple receiving a result of either 'match advisable' or 'match not advisable' (4). This programme has high uptake with more than 95% of the ultra-orthodox Jewish community participating in the programme (4).

TSD carrier screening programmes have been implemented in Jewish high schools in Canada and Australia (6). Screening high school students provides an opportunity to educate and the timely use of results for reproductive planning and behaviour (10). The screening programme for TSD carried out in Montreal high schools showed high uptake, high knowledge levels and positive attitudes towards screening with the vast majority of carriers recalling their carrier status and having their partners screened (11). High school carrier screening carried out in the Jewish community is associated with higher uptake than the state-funded screening programmes targeted towards adults (10). Although some have argued that the results of screening are not relevant at this life stage, students do not consider high school screening to be too early (11).

In Australia, the Jewish population is approximately 90,000 with the majority being of Ashkenazi Jewish descent (6). In 1995, a TSD carrier screening programme was implemented in Jewish high schools in Sydney, Australia. The programme provided a compulsory educational session for all students aged 15 years and above and voluntary testing (6). High uptake of testing (94%) was observed as well as high knowledge retention, low concern if found to be a carrier and high intention to use results (6).

In Melbourne, Australia, a TSD carrier screening programme was established in Jewish high schools in 1997. The programme provided education, counselling and testing to students aged between 15 and 18 years (5). An evaluation of the programme was conducted from 1998 to 2001 (5). During this period, testing was performed using a blood sample, and testing incurred a cost of AUD $40 for those tested in 1998, but free testing was offered thereafter (5). An uptake rate of 67% was observed during this period, with students displaying high knowledge levels and a positive attitude towards screening (5). The uptake increased to 96% with the introduction of cheek brush sampling in 2003 (12).

In 2008, the programme was extended to screen for another six genetic conditions, with carrier frequencies that range from 1 in 25 to 1 in 110 (13). These conditions are: (i) cystic fibrosis (CF), (ii) Fanconi anaemia type C, (iii) Bloom syndrome (BS), (iv) Canavan disease (CD), (v) Niemann Pick disease type A, and (vi) familial dysautonomia. Here we report an evaluation of educational and attitudinal outcomes of this programme and compare it with an evaluation of the programme when only TSD screening was offered (5). The aims of this study were to assess reasons for undergoing screening and the effect of screening for multiple diseases compared to screening for TSD alone, on knowledge and predicted feelings if found to be a carrier.

Materials and methods

Ashkenazi Jewish carrier screening programme

The carrier screening programme is conducted by Genetic Health Services Victoria (GHSV) (5). TSD carrier screening is offered to students in the second last year of high school at six Jewish high schools in Victoria. In 2008 the programme expanded to include six other genetic conditions

that are prevalent in the Jewish community. Testing is currently free of charge with funding from a number of philanthropic organizations. Results of the test are mailed to all non-carrier students. All carriers receive a telephone call from a genetic counsellor who discloses the results and provides genetic counselling by telephone with the offer of face-to-face genetic counselling. Carriers then received the results and a letter summarizing the genetic counselling given. In addition, carriers also received a letter that they could pass on to other family members to facilitate cascade testing within the family.

Testing

Testing is by cheek swab and a DNA lysate is prepared from this and subsequently analysed for the most common mutations in the Ashkenazi Jewish population for each disease (Table 1). The range of mutations for each condition accounts for more than 95% of all mutations in this population (14).

Pre-test education

Pre-test information is supplied in the form of a 40-min Power Point presentation followed by a short DVD. Students are given brochures on TSD and an information sheet that describes each of the conditions that is offered in the screening programme. In addition, a website (www.taysachs.net) is provided for further information. Students have a one-on-one interview with a member of the screening team before testing to ensure that questions are answered and to gain informed consent prior to testing. Students can decline testing at this point.

Table 1. The mutation panel used for the screening programme

Disease	Gene	Mutations
TSD	HEXA	p.G269S
		c.1275_1278dupTATC
		c.1421+1G>C
CD	ASPA	p.Y231X
		p.E285A
FA	FAC	c.IVS4+4A>T
FD	IKBKAP	c.2507+6T>C
		p.R696P
NP	SMPD1	p.L302P
		c.990delC
		p.R496L
BS	BLM	c.2281delATCTGAinsTAGATTC
CF	CFTR	c.489+1G>T
		c.1585−1G>A
		p.F508del
		p.1507del
		p.V520F
		p.G542X
		p.G551D
		p.R553X
		p.R560T
		p.W1282X
		p.N1303K
		c.3718-2477C>T

BS, Bloom syndrome; CD, Canavan disease; FA, Fanconi anaemia type C; FD, familial dysautonomia; NP, Niemann Pick disease type A.

Subjects

All students in the second last year of high school at four Jewish high schools were invited to participate in this study. Two other schools were excluded from this evaluation study as they are strict orthodox schools where most of the students choose to be screened via the Dor Yeshorim programme.

Questionnaire

A questionnaire was purpose-designed to address the following domains: demographic variables, knowledge of genetics and specific conditions screened for, anxiety levels at the time of completing the questionnaire, reasons for participating in screening, family history of the conditions and testing, and predicted feelings if found to be a carrier of one of the conditions. The knowledge questions, reasons for screening and predicted feeling scales were adapted from a validated survey evaluating the school-based TSD genetic screening programme in 2003, for the purpose of comparison (5,12). The anxiety scale used in the questionnaire was the short version of the State Trait Anxiety Inventory (STAI) (15). Scores range from 20 to 80 and a higher score indicates greater anxiety. The questionnaire was anonymous and completed immediately after screening. The questionnaire can be found at www.mcri.edu.au/Downloads/Questionnaire/AJHS Questionnaire.pdf.

Scales

Students were asked to answer 10 questions regarding their knowledge of the different diseases and carrier screening. They were asked to select one of three options: true, false or unsure. Knowledge questions were scored as correct (1) or incorrect (0). The total knowledge score for each student was calculated.

Factors influencing the decision to have screening were measured on a five-point Likert scale. For

analysis, points '1' and '2' were combined to form the category 'did not influence', the middle point '3' remained neutral, while points '4' and '5' were combined to form the category 'influenced'.

Predicted feelings if found to be a carrier were also measured on a five-point Likert scale. For analysis, points '1' and '2' were combined to form the category 'not likely', the middle point '3' remained neutral, while points '4' and '5' were combined to form the category 'likely'.

Data analysis

Data analysis was conducted using SPSS (Windows, version 16.0; SPSS Inc., Chicago, IL, USA). Preliminary descriptive analysis generated frequency data to elicit the description of respondents.

Statistical significance of between-group comparisons was assessed using Chi-square tests of association for categorical variables. In the case of variables having more than two categories, degrees of freedom are given with the chi-square statistic.

Comparisons were made between the data from the current study and data from a previous study evaluating high school carrier screening for TSD alone (5). Statistical significance was determined using Chi-square tests of association.

Results

Response

Questionnaires were given to all students ($n = 273$) present on the day of screening. Two hundred and seventy-two students completed the questionnaire representing a 99.6% response rate.

Demographic variables

All students were 15–17 years of age with the vast majority (271/272) in the second last year of high school. Of the 272 students, 267 (98.2%) had Jewish ancestry with 222 (81.6%) reporting being solely of Ashkenazi Jewish ancestry (Table 2).

Reasons for having screening

Two hundred and seventy-one out of 273 (99.3%) students had undergone screening. The most influential factor for undergoing screening (Fig. 1) was the desire to know their carrier status (82.4%) followed by convenience (74.1%). Parents' opinion towards carrier screening was influential for 118 participants (44.2%), while 87 participants (32.7%) indicated the fact that their friends having undergone the test influenced their decision.

Knowledge

There were six knowledge questions, which were answered correctly by less than 50% of the students (Fig. 2). These were: (i) CF affects the brain (F), (ii) BS predisposes to cancer (T), (iii) CD usually causes a person to die in childhood (T), (iv) if the test shows you are not a carrier you cannot have a child with that condition (F), (v) this programme screens for five different genetic conditions (F), and (vi) all people have some altered genes (T). There was no difference in knowledge among the four schools.

Information

Two hundred and twenty-nine students (87.1%) felt that they had enough information to make a decision in regard to having screening, while 69 students (26.2%) sought further information. The most common source of further information was family (21.0%), followed by a doctor (4.0%) (data not shown).

Family history

One hundred and twelve students (42.6%) had a relative who had been tested for at least one of the seven genetic conditions in the screening programme, with the majority of those screened

Table 2. Demographics of students participating in the multi-disease carrier screening programme[a]

Demographics	Categories	Number of participants
School ($n = 272$)	School A	49 (18.0%)
	School B	68 (25.0%)
	School C	59 (21.7%)
	School D	96 (35.3%)
Gender ($n = 272$)	Male	154 (56.6%)
	Female	118 (43.4%)
Age (in years) ($n = 271$)	15	8 (3.0%)
	16	193 (71.2%)
	17	70 (25.8%)
Jewish ancestry ($n = 272$)	Yes	267 (98.2%)
	No	2 (0.7%)
	Unsure	3 (1.1%)
Type of Jewish ancestry ($n = 269$)	Ashkenazi	222 (82.5%)
	Sephardi	1 (0.4%)
	Mixed	35 (13%)
	Not sure	11 (4.1%)
Currently studying biology ($n = 272$)	Yes	44 (16.2%)
	No	228 (83.8%)

[a]Note that the denominator is less than 272 for some of the categories, as not all students answered all questions.

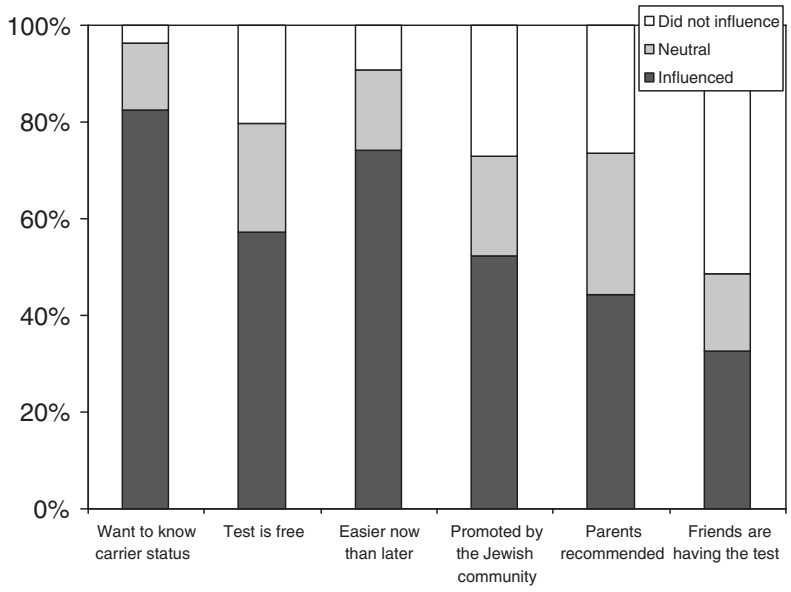

Fig. 1. Influence of various factors in the decision to participate in the multi-disease carrier screening programme.

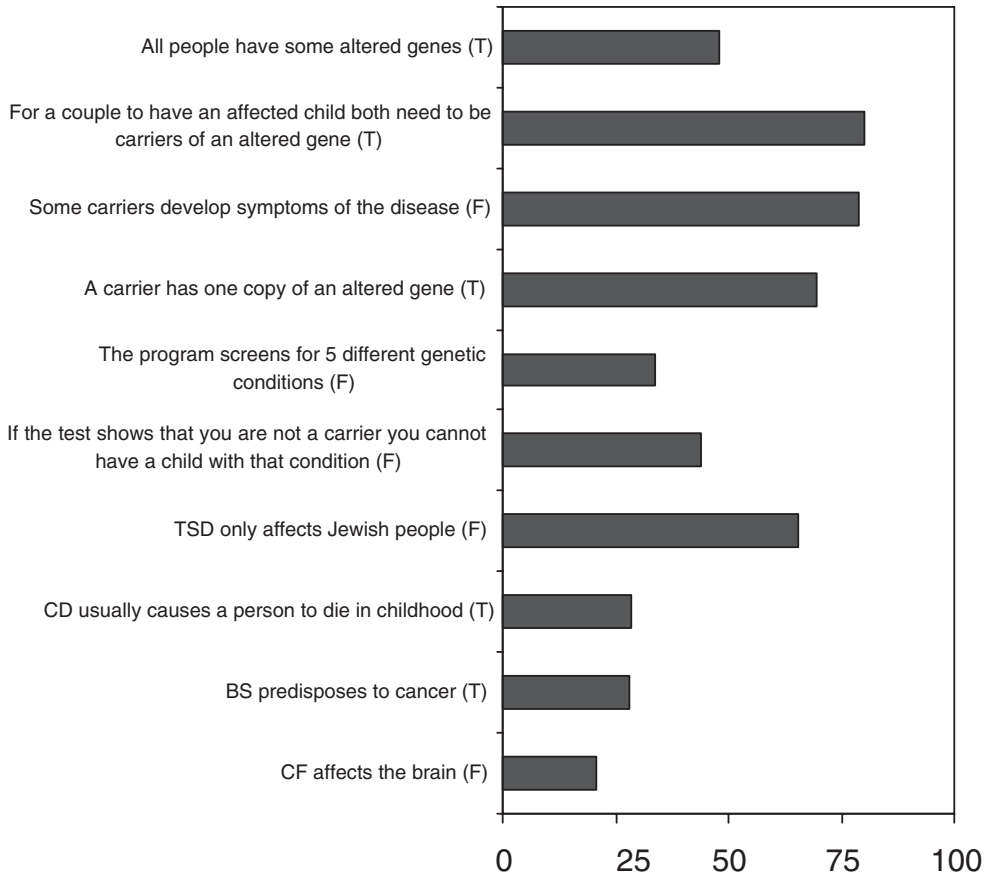

Fig. 2. Percentage of students who correctly answered each knowledge question in the multi-disease carrier screening programme.

being siblings (25.0%) and parents (19.5%). Two hundred and forty students (91.6%) had no family history or were unsure of a family history, while 22 students (8.4%) stated that one or more family members are carriers of one of the conditions (data not shown).

Anxiety

The STAI scores ranged from 20 to 80, with a median of 27 (data not shown). There was no significant difference in the anxiety scores between males and females.

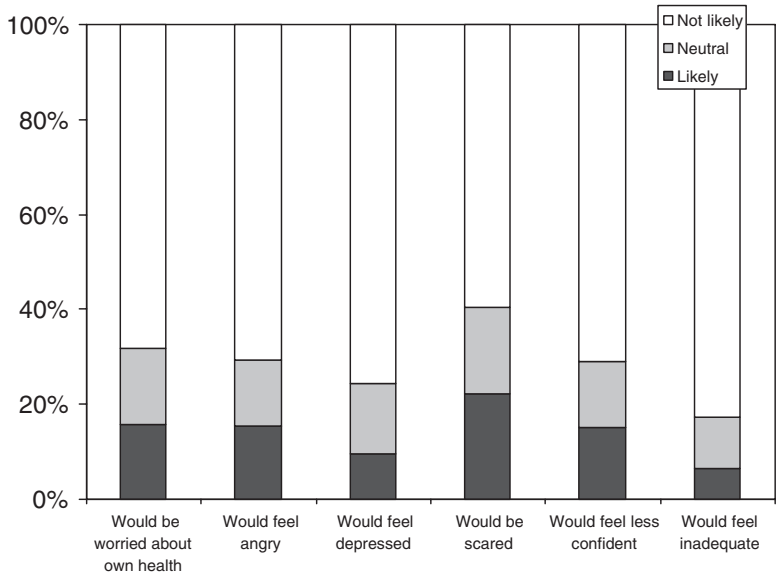

Fig. 3. Predicted negative feelings if found to be a carrier of any of the genetic diseases screened for in the multi-disease carrier screening programme.

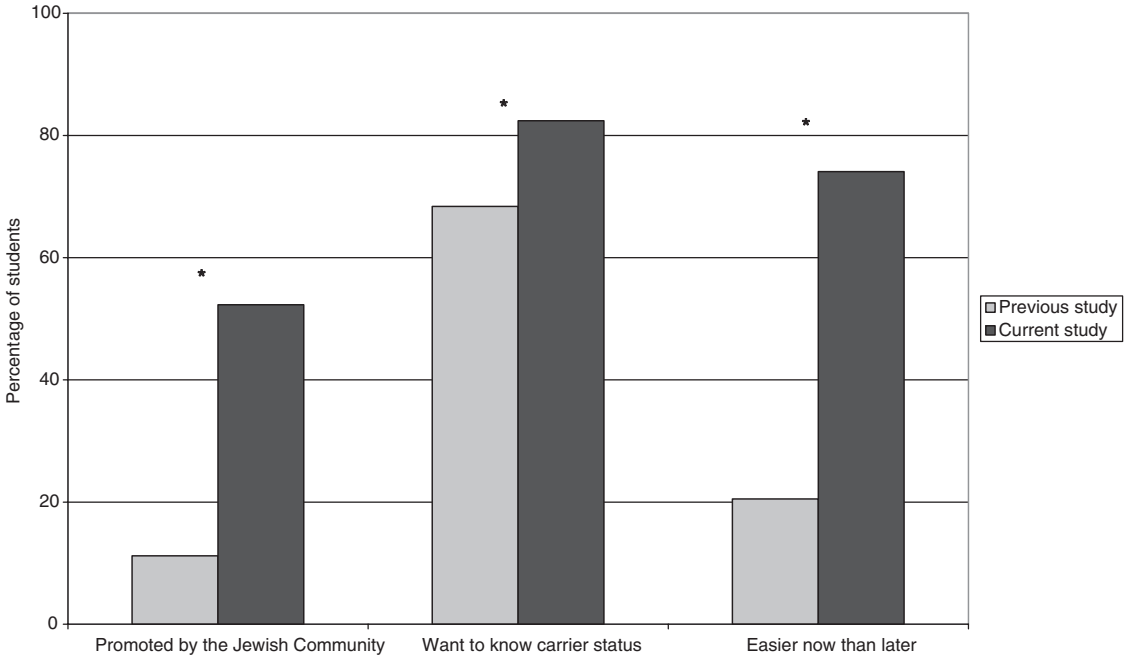

Fig. 4. Comparison of factors that influenced the decision to have screening in the previous and current study. *$p < 0.05$ for comparison of percentage influenced in current *vs* previous study using χ^2 test.

Predicted feelings

The most common predicted feeling in regard to being detected as a carrier was fear, with 58 students (22.3%) stating that they would be extremely scared if they found out that they were a carrier of one of the genetic diseases screened for (Fig. 3).

Comparison with single-disease carrier screening programme

Test uptake increased from 67.0%, with blood tests, to 96.0% with cheek brush sampling, when screening was offered for TSD only. In the current programme, test uptake was 99.6%. The main reason for having screening remains the same, with 68.4% of students offered TSD screening only and 82.4% of students offered multi-disease screening, stating that they wanted to know their carrier status (Fig. 4). Compared to the first study, students from the current study were significantly more influenced by promotion of carrier screening by the Jewish community ($\chi^2 = 38.95$, $p < 0.01$), wanting to know carrier status ($\chi^2 = 5.23$, $p = 0.02$) and their perception that it was easier to have the test now than later ($\chi^2 = 56.32$, $p < 0.01$).

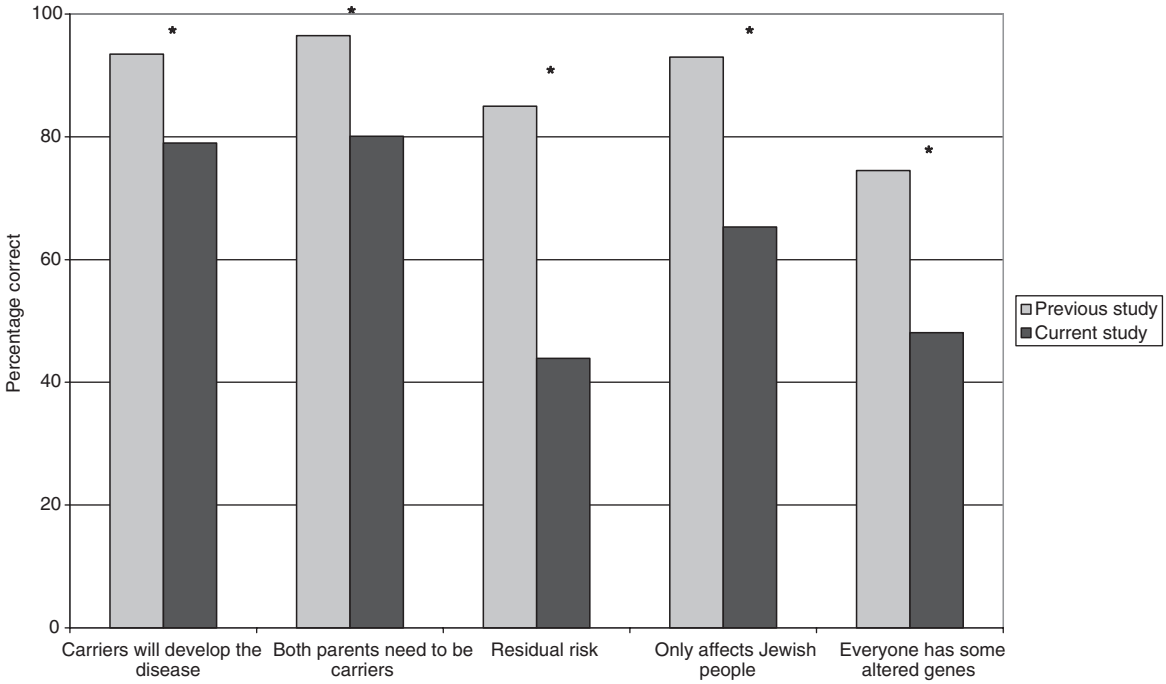

Fig. 5. Comparison of general genetics knowledge of students in the previous and current study. *$p < 0.05$ for comparison of percentage correct in current *vs* previous study using χ^2 test.

Five of the knowledge questions in each study were the same and could be directly compared (Fig. 5). All of these five knowledge questions were answered correctly significantly more frequently by students who were only offered TSD screening compared to students who were offered multi-disease screening. These were: (i) carriers will develop the disease (F) ($\chi^2 = 44.2$, $p < 0.01$), (ii) both parents need to be carriers to have an affected child (T) ($\chi^2 = 71.3$, $p < 0.01$), (iii) if test is negative you cannot be a carrier (F) ($\chi^2 = 169.5$, $p < 0.01$), (iv) only Jewish people are affected (F) ($\chi^2 = 119.7$, $p < 0.01$), and (v) everyone has some altered genes (T) ($\chi^2 = 61.0$, $p < 0.01$).

Whether or not the student studied biology did not influence the level of knowledge in the previous study ($\chi^2 = 0.7$, $p = 0.4$), while the current study showed that those studying biology did significantly better on the knowledge questions than those not studying this subject ($\chi^2 = 7.0$, $p = 0.01$). The previous study found that knowledge level was significantly higher in females compared to males ($\chi^2 = 6.7$, $p = 0.01$) and that predicted negative feelings if found to be a carrier were lower in students who had a high knowledge level ($\chi^2_{2df} = 21.6$, $p < 0.01$). The current study showed no such associations between knowledge level and gender or predicted negative feelings [($\chi^2 = 3.2$, $p = 0.07$) ($\chi^2_{2df} = 3.2$, $p = 0.2$) respectively].

The most frequently reported predicted feeling if found to be a carrier was fear, with 17.1% of students from the previous study and 22.3% of students from the current study stating that they would be scared if they found out they were carriers (Fig. 6). Students from the current study were significantly more concerned than students from the previous study for three out of the six predicted feelings. They were: (i) worried about their own health ($\chi^2 = 9.16$, $p < 0.01$), (ii) would feel angry ($\chi^2 = 6.6$, $p = 0.01$), and (iii) would feel less confident ($\chi^2 = 16.0$, $p < 0.01$). There was no difference in predicted feelings between males and females in the previous ($\chi^2_{2df} = 1.4$, $p = 0.5$) or the current study ($\chi^2_{2df} = 3.5$, $p = 0.2$).

Discussion

This is the first study to evaluate a seven-condition carrier screening programme performed in Ashkenazi Jewish high schools and to compare the effects of multi-disease screening to single-disease screening. The majority of students participating in this study was in the second last year of high school and of Ashkenazi Jewish decent. Students stated that the desire to know their carrier status was the most influential factor in the decision to have screening. The expansion of the programme to screen for an additional six conditions

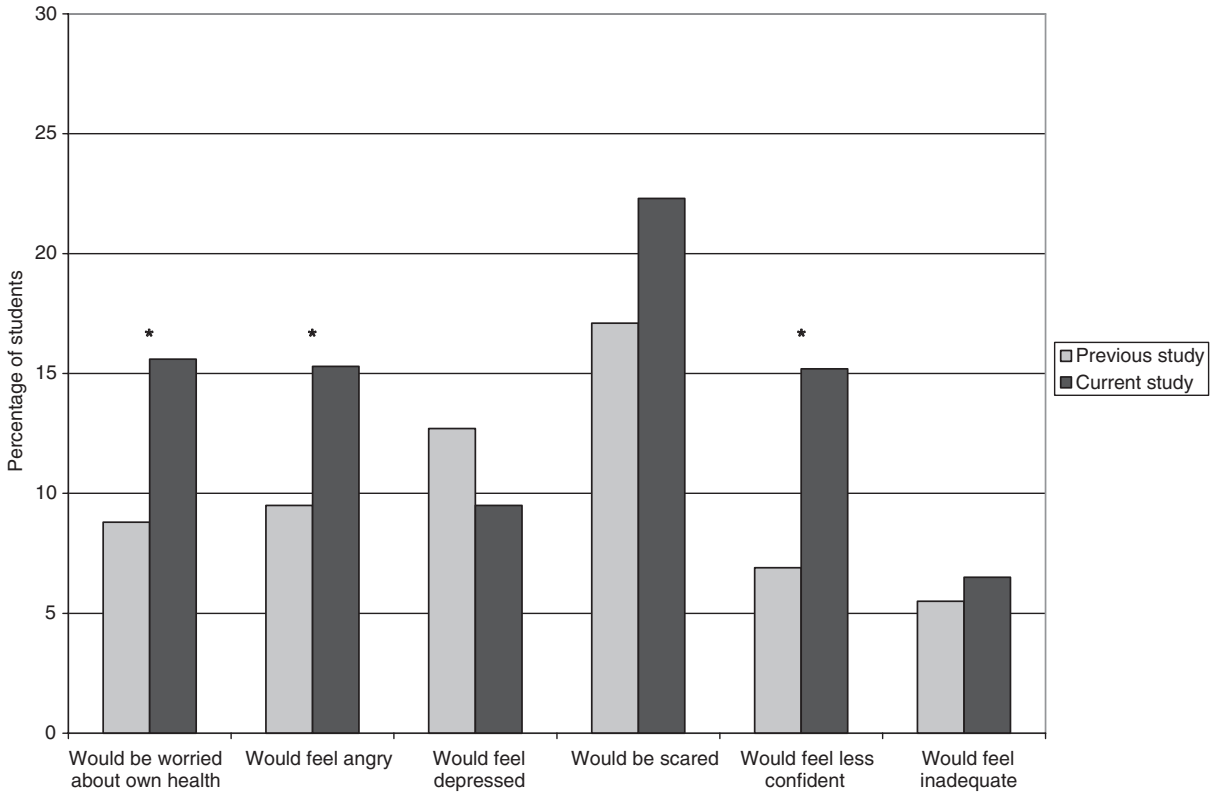

Fig. 6. Comparison of students' predicted negative feelings if found to be a carrier in the previous and current study. *$p < 0.05$ for comparison of predicted feelings in current *vs* previous study using χ^2 test.

has resulted in a decrease in knowledge levels and an increase in predicted negative feelings.

The current programme experienced high uptake, with only two students declining the offer of screening. The uptake has greatly increased in the current study (99%) compared to the previous study (67%) (5). This is largely due to the introduction of cheek brush swabs to collect DNA sample compared to blood tests. In the previous study, the students' main reason for declining screening was the fear of needles, with 41% of decliners stating that they would have had screening if a cheek brush test was offered (5). When comparing the impact of sampling on test uptake it was shown that 96% of students had testing when a cheek brush test was offered compared to 85% who were offered blood tests (12). Higher uptake and lower anxiety were shown with the use of cheek brush sampling compared to blood tests (12).

In 1973, an evaluation of a population-based carrier screening programme for TSD in Montreal revealed that high school students had the highest uptake followed by University students and then couples in the community (10). High school screening for TSD has been offered in Montreal for over 20 years with higher participation rates than among adults (16,17).

The level of knowledge in the current study was relatively low, with only 4 out of the 10 questions being answered correctly by more than 50% of students. Knowledge in regard to the specific conditions screened for, excluding TSD, was lowest. This is most likely due to the fact that the education session only briefly introduced the various conditions, focussing mainly on TSD as a model for carrier screening. Knowledge of general genetic concepts, including recessive inheritance and residual risk, decreased compared with that when screening was offered for TSD only. The information provided in the education session in the current programme is almost the same as what was presented when only TSD screening was offered, with the difference being the addition of five extra slides and an A4 flyer on the six other conditions that screening is now offered. Students who participated in the current study may have a lower level of general genetic knowledge due to the increase in information provided on the specific conditions.

There have been few studies comparing knowledge level with the number of diseases screened. A prenatal carrier screening programme in a medical

genetics referral centre in New York which offered triple disease screening for TSD, Gaucher disease and CF showed high knowledge retention after education session (18). In the TSD carrier screening programme conducted in Sydney high schools, the knowledge levels remained high after the addition of CF to the test panel in 1998 (6).

Although there were no differences in anxiety as measured by the STAI measure between those offered screening for TSD alone and those offered screening for seven conditions, predicted negative feelings if found to be a carrier for one or more of the conditions screened increased compared with when screening was only offered for TSD. More students in the current study predicted feelings of anger, reduced confidence and worry in regard to their own health if they were found to be a carrier. This increase in predicted negative feelings may be due to the increased number of conditions screened, as it increases the chance of being a carrier for one of the conditions, or may be due to the lower level of knowledge among students in the current study.

Knowledge level was a significant factor in predicted negative feelings in the Sydney-based programme, with students having a lower level of knowledge predicting increased negative feelings compared to those with a higher knowledge level (6). In another study, approximately half of the students identified as carriers expressed feelings of worry and depression (19).

The main reasons students had screening were: the desire to know their carrier status, the test is easier to be done now rather than later, and the test is currently free. Knowledge of carrier status was also the most influencing factor for having screening when it was offered for TSD only. In contrast, students in the original study who were only offered TSD carrier screening did not find 'easier now than later' as an influencing factor on the decision to have screening (5). This is most likely due to the use of blood tests to collect DNA samples, as the previous study that offered testing via cheek swab reported that the main reasons for screening were knowledge of carrier status followed by convenience, with blood testing being reported as a deterrent (12).

The fact that having screening is promoted as 'a good thing to do by the Jewish community' was likely to be a more influencing factor in the current study, than that when only TSD screening was offered. The operation of this screening programme over the last 10 years has increased education and awareness in the Jewish high school community, resulting in carrier screening being widely accepted (20). One of the concerns of screening in the high school setting is the influence of peer pressure on the decision to have screening (10). In the current study 32.7% of students stated that their friends having undergone the test influenced their decision to undergo screening. This is high compared to students in a high school haemochromatosis carrier screening programme, with only 0.8% of students reporting that their principal reason for having the test was because all there friends were (21). An important difference between these studies is that in the haemochromatosis study, only one answer could be given, whereas in the current study, the student could provide more than one answer to this question.

The programme is effectively reaching its target population with the majority of students in the study being of Ashkenazi Jewish descent, although Ashkenazi Jewish students at non-Jewish high schools will not receive an offer of screening. Screening in high school is the only setting in which the majority of the target population can be offered screening (22). All students in Jewish high schools in Victoria are offered screening through the Ashkenazi Jewish carrier screening programme.

The majority of students stated that they had enough information to make a decision in regard to having testing, with only 13 students seeking further information before making their decision. Although students felt they had enough information, their knowledge of genetics and the conditions for which they are screened indicated that for many students, knowledge was inadequate to make a truly informed decision. This is an interesting paradox. It may be that students perceived the overall notion of screening as worthwhile and did not believe that the level of knowledge assessed by the questions was necessary for them to make a decision about whether or not to have screening.

One of the major criticisms of screening in high schools is the ability of high school students to provide informed consent (23). Although studies have shown that students of this age are capable of making educated decisions, the students in this study were not well informed in regard to basic genetic concepts and the conditions for which they are being screened. It is notable that studies of screening programmes in adults such as mammography and cervical cancer screening have demonstrated poorer knowledge to that of the students in the current study (24,25). As noted below, although proper informed consent is an ideal that should be aimed for, it may not be possible as the number of conditions screened for increases.

In conclusion the current programme is effective with high uptake, low predicted negative feelings and high knowledge level as compared to adult screening programmes. However, increasing the number of conditions for which they are screened resulted in a decrease in knowledge and an increase in predicted negative feelings if found to be a carrier. As carrier screening becomes available for more conditions and becomes more affordable, it is likely that multi-disease screening programmes will become much more common. Notably, a company in the United States recently released a direct-to-consumer test that screens for 100 genetic conditions at a cost of $349 per test (26). It is likely that truly informed consent may not be possible for many potential participants and that the focus of education and counselling will need to be directed to carriers identified.

Further study into effective educational tools for multi-disease screening would be useful to ensure students are making informed decisions in regard to screening in the current programme. A follow-up study of students identified as carriers through this screening programme conducted in Jewish high schools is underway to ascertain their views on the programme, knowledge of the condition, recollection and understanding of carrier status and the influence the test result had on entering relationships and reproductive decisions.

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Conflict of interest

There is no conflict of interest for any of the authors on this paper.

Ethics approval

This study was approved by The Royal Children's Hospital Human Research Ethics Committee, Victoria, Australia (HREC CA29037).

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4.4 Further Conclusions

As carrier screening has become available for more diseases and is growing increasingly more affordable, it is important to determine the effects of screening for multiple diseases.

This research is timely as the GHSV population-based CF carrier screening program is expanding in 2013, to include carrier screening for fragile X syndrome and spinal muscular atrophy. Also an American company, Counsyl, has recently released a direct to consumer test that screens for more than 100 genetic conditions, including the diseases common amongst Ashkenazi Jews.[29]

While offering direct to consumer testing for multiple conditions increases accessibility and may reduce the incidence of these conditions, potential consumers may not be making informed decisions in regards to testing. This has been shown in the current research with knowledge decreasing as the number of conditions screened for increases. Therefore, truly informed consent may not be possible and post-test information to carriers will become the point at which specific information is provided.

Chapter 5

Population-based carrier screening for cystic fibrosis

Addendum

p 55 para 5: Comment: studies were not excluded if they offered CF carrier screening in addition to other genetic conditions. However, studies were excluded if screening was offered to targeted populations such as the Jewish community.

p 56 para 4: Comment: The term preconception carrier screening, for the purpose of this review, refers to screening outside of pregnancy.

p 73: Table 3: Insert the following into the Table to provide relevant data for the Netherlands.

Country	Setting	Uptake (%)	References
The Netherlands	Prenatal	89-91%	[52]
	Preconception	2-25%	[32, 33, 34, 89]

5.1 Declaration

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Literature search; inclusion and exclusion of studies; data extraction; data analysis and interpretation; writing of manuscript	50%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**
Dr Belinda McClaren	Development of search strategy; literature search; assistance with inclusion and exclusion of studies; data extraction; discussion of ideas expressed in and critical revision of manuscript
A/Prof John Massie	Discussion of ideas expressed in and critical revision of manuscript
Dr Sharon Lewis	Discussion of ideas expressed in and critical revision of manuscript
Dr Laura Forrest	Discussion of ideas expressed in and critical revision of manuscript
Dr Sylvia Metcalfe	Discussion of ideas expressed in and critical revision of manuscript
Prof Martin Delatycki	Discussion of ideas expressed in and critical revision of manuscript

Candidate's Signature	[redacted]	**Date** 20/02/13

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Murdoch Childrens Research Institute

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]	1/3/13
Signature 2		1/3/13
Signature 3		1/3/13
Signature 4		16/3/13
Signature 5		4/3/13
Signature 6		1/3/13

5.2 Cystic fibrosis

Cystic fibrosis (CF) is the most common, severe, autosomal recessive condition among individuals of Northern European decent, with a birth prevalence of approximately 1 in 2,500-3,500 live births and a carrier frequency of approximately 1 in 25.[10]

5.2.1 Genetics

The cystic fibrosis transmembrance conductance regulator (*CFTR*) gene was discovered in 1989.[12] The *CFTR* gene encodes a chloride channel that is largely expressed in the epithelial cells of various organs including the lung, pancreas, liver, sweat ducts, male reproductive tract and digestive tract.[80] The CFTR protein maintains ion and water homeostasis in the apical membrane of the epithelial cells.[81]

CF is the result of mutations in the *CFTR* gene causing loss or impairment of chloride channel function. The absence of channel activity results in altered homeostatic ion and water regulation at epithelial surfaces and altered macromolecular secretions, such as mucins.[80, 81] The effects are most severe in the ducts of the pancreas and airways of the lungs.[81]

More than 1,900 gene alterations have been identified since the gene was discovered.[13] Mutation frequency is dependent on ethnic population, with different mutations being more common in different ethnic groups. The most frequently occurring mutation in the Northern European population is a single codon deletion p.F508del, which accounts for approximately 66% of all mutations found.[13]

The discovery of the *CFTR* gene made carrier screening for CF possible. Screening with a panel of the 23 most frequently occurring mutations identifies approximately 88% of carriers in the Northern European population.[82] Test sensitivity depends on ethnicity and the mutation panel used.

5.2.2 Clinical manifestation

Due in part to allelic heterogeneity the clinical features of CF vary, with some described as typical and others as atypical. The typical features of CF, seen in the majority of affected individuals, are chronic suppurative lung disease, pancreatic exocrine insufficiency and elevated sweat electrolytes.

In the respiratory system the accumulation of mucus in the airway leads to bronchial obstruction and microorganism colonisation. This evolves into progressive suppurative lung disease and deterioration of lung function.[81] Chronic

suppurative lung disease affects nearly all people with CF, is progressive and is the major cause of mortality.[80]

Gastrointestinal symptoms may present earlier than respiratory symptoms with intestinal obstruction in-utero called meconium ileus. This occurs in 15-20% of newborns. Most people with CF also have lifelong issues with recurrent constipation and abdominal pain and some develop distal intestinal obstruction syndrome. The other key clinical issue is failure to thrive due to pancreatic exocrine insufficiency. The pancreatic excocrine insufficiency is due to mucus build-up in the pancreatic ducts compromising the release of digestive enzymes and resulting in autolysis of the pancreatic acinar tissue. This affects 85-90% of people with CF.[80] In addition to the impact on growth and weight gain there are secondary complications such as malabsorption of fat soluble vitamins. With disease progression there is loss of pancreatic islet cells with reduced insulin production, and increased insulin resistance that manifests as CF related diabetes. This affects approximately 40% of adults with CF. Another gastrointestinal feature of CF is biliary cirrhosis that in some cases can cause liver failure.[83]

Other clinical systems of CF involve the reproductive system. Infertility is a typical feature of CF in affected males due congenital bilateral absence of the vas deferens.[84] While most affected males have normal sexual function, the sperm cannot travel from the testes through the vas deferens resulting in infertility.[85]

The progression of CF is not uniform amongst affected individuals with environment, ethnicity, gender and age of diagnosis all playing a role. Due to the variable clinical progression the survival of people with CF is usually expressed as a median and is currently 37 years.[11]

5.2.3 Diagnosis

The sweat test is the standard tool to diagnose CF. Impaired chloride channel function in the sweat ducts causes impaired reabsorption of chloride and sodium leading to an elevated concentration of chloride and sodium in sweat.[83] The test stimulates sweat production and measures the level of chloride and sodium present. Elevated levels of chloride >60 mmol/L are diagnostic of CF.[85, 14]

Historically the diagnosis of CF, by use of a sweat test, was made in response to clinical symptoms. However, in 1979 newborn screening (NBS) for CF was developed making the diagnosis of CF possible prior to the development of clinical symptoms.[86, 45] The benefits of NBS for CF include improved nutrition as well as improved cognitive, respiratory and gastrointestinal function.[87] It is also

thought to be associated with improved life expectancy although this is not yet proven.[45]

NBS for CF involves the measurement of immunoreactive trypsinogen (IRT), with an elevated level of IRT (>99th percentile) leading to further testing. There are a number of different screening paradigms, but most centres that have CF NBS use *CFTR* mutation analysis, using a panel of the most frequently occurring mutations in the population tested.[14] A diagnosis of CF is made if two mutations are identified, although generally confirmed by sweat test or identification of characteristic clinical features. If only one mutation is identified a sweat test is performed. Those infants with a positive result have CF (and have a second, unidentified CFTR mutation) and those with a negative test are healthy carriers. Infants with an elevated IRT but no mutations have a low risk of having CF and are considered NBS negative. The diagnosis of CF is usually made by 3-6 weeks of age.[45]

Parents of an affected newborn identified by NBS are a high risk carrier couple. These couples receive genetic counselling and they have a number of reproductive options for future pregnancies including: no further children, adoption, prenatal diagnosis or donor gamete and preimplantation genetic diagnosis. The parents of carrier infants should also receive genetic counselling as some may be carrier couples, and their wider family may benefit from cascade testing.[88]

NBS for CF is now routine in many countries, including the United States, the United Kingdom, Australia and New Zealand and in many parts of Europe.[87] More countries are expected to follow this trend and include CF in their NBS programs.

5.2.4 Treatment

There is currently no cure for CF however current treatments delay the progression of serious complications. Daily treatments are rigorous. They involve: chest physiotherapy, by percussion and use of various breathing devices, to clear the airways of the lungs; antibiotics and anti-inflammatory drugs to treat respiratory infections; and pancreatic enzymes and a controlled diet to maintain growth and nutrition.[85]

Regular hospital admissions are often required to provide intensive physiotherapy, intravenous antibiotic treatment and nutritional support.[89] Lung transplantation is a possibility for some affected individuals with end stage lung disease. The outcomes of lung transplant in individuals with CF are continually improving, however the six year survival post transplantation is still only 50%.[85]

Treatment has significantly advanced over the last 20 years with the development of CF specific medications, improved infection control measures, new devices to clear airways and improved nutritional support.[90] These advances in treatment together with early diagnosis have lead to an improved median survival rate of 37 years, with the prediction that this will be increased for newborns recently diagnosed.[11]

5.3 Carrier screening

5.3.1 Cascade testing

Testing directed towards individuals who are at increased risk of being carriers because they are relatives of individuals either diagnosed with CF or identified as CF carriers is known as cascade testing. Cascade screening is widely recommended by leading genetic and screening groups world-wide recommending that CF carrier screening be made available to those who have a family history of CF.[91, 24]

Cascade testing is highly accurate and more sensitive than population carrier screening as the familial mutations are known.[15] However, the efficacy, which is defined as the total number of carriers identified in a population, is much lower in cascade screening than in population screening for CF.[17] This is due to the fact that more than 95% of carrier couples identified through newborn screening have no family history of CF.[18, 19]

Cascade testing relies on the communication of genetic information. Most often the communication to extended family and relatives who are at increased risk is by carriers, individuals diagnosed or their parents.[15] It has been shown that cascade testing is associated with low uptake, with only 12% of relatives per proband being tested.[16]

5.3.2 Population screening

Population-based carrier screening aims to offer testing to as many individuals as possible regardless of family history so that these individuals can make an informed choice about whether or not to have screening.. Carrier screening for CF satisfies the WHO requirements that justify population screening.[4] In the USA and Australia, guidelines have been released recommending that all pregnant women and couples planning a pregnancy be offered, or made aware of the availability, of CF carrier screening.[24, 25]

The following paper is a systematic review of 23 years of research on population-based carrier screening for CF.

Population-based carrier screening for cystic fibrosis: A systematic review of 23 years of research

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Preface

Cystic fibrosis (CF) is the most common, severe, autosomal recessive disease with a prevalence of 1 in 2,500-3,500 live births and a carrier frequency of 1 in 25 amongst Northern Europeans. CF population-based carrier screening has been possible since *CFTR*, the disease-causing gene, was identified in 1989. This review provides a systematic evaluation of the literature on population-based CF carrier screening from the last 23 years focussing on: uptake of testing; how to offer screening; attitudes, opinions and knowledge; factors influencing decision-making; and follow-up after screening. Recommendations are given for the implementation and evaluation of future carrier screening programs.

Introduction

It has been 23 years since the discovery of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene in 1989, which made possible carrier screening for cystic fibrosis (CF).[1] CF is the most common, severe, autosomal recessive condition in those of Northern European ancestry, with a prevalence of 1 in 2,500-3,500 live births and a carrier frequency of 1 in 25.[2] Mutations in the *CFTR* gene result in reduced or absent CFTR channel function in epithelial cells of the lung, pancreas, liver, sweat duct, male reproductive tract and digestive tract.[2] More than 1,900 gene alterations have been identified, with p.F508del the most frequently occurring mutation in the Northern European population accounting for approximately 70% of all mutations present.[2]

Chronic suppurative lung disease is the most severe feature of CF and is largely responsible for reduced life expectancy. There is currently no cure for CF and the median survival is 37 years.[3] Treatment involves daily chest physiotherapy, regular antibiotics, pancreatic enzyme replacement, vitamin and salt replacement and a controlled diet.[4] Lung transplantation is possible, although the six year survival post transplantation is 50%.[2] Diagnosis of CF by newborn screening (NBS) is routine in many European countries, as well as the United States, Australia and New Zealand.[5] Parents of children diagnosed with CF through NBS are identified as carrier couples and many of these have no further children or use prenatal diagnosis for subsequent pregnancies. [6]

Carrier couples may also be identified through population-based carrier screening, the aim of which is to offer testing to as many individuals as possible regardless of family history. In the USA, guidelines recommend that CF carrier screening be offered to all pregnant women and couples planning a pregnancy.[7] In Australia there have been similar recommendations.[8] In the UK, Canada and France population-based carrier screening for CF is not currently recommended, and is generally only offered to those who have a family history of CF and to partners of individuals with CF. The UK National Screening Committee is currently reviewing their policy on screening for CF carrier status during pregnancy.[9]

Some major issues with regard to implementing routine CF carrier screening in the general population include: accessibility; how best to provide education and counselling; perceived relevance in the absence of a family history; carrier detection rate; and the psychological impact of being found to be a carrier.

Therefore, it is timely to review the available evidence on population-based CF carrier screening. This review provides a systematic evaluation of the literature from the last 23 years.

Methodology

Search Strategy

The following electronic databases were searched (latest search date: 31 October 2012): Medline (1950-present), Embase (1980-present), CINAHL, PsychINFO, The Cochrane Library. A detailed search strategy for each database is available upon request from the authors.

Search terms were keywords and relevant medical subject headings (MeSH) for cystic fibrosis, genetic carrier testing or screening. Search terms, combined with the term 'cystic fibrosis', were: carrier testing, heterozygote detection, screening, genetic research, medical genetics, population genetics, pregnancy, prenatal diagnosis, preconception care, behaviour, psychological processes, attitude to health, genetic counselling and genetic risk. Reference lists of identified papers were examined, and citations were tracked for any potentially relevant additional studies.

The search outputs were managed using Endnote (version X).

Criteria for inclusion

The focus of this article is peer-reviewed original research in which participants were either offered CF carrier screening, were asked to consider a hypothetical offer of screening or their views were sought in regard to CF carrier screening.

The areas reviewed are:

1. Attitudes to screening: studies assessing attitudes of participants/potential participants, formally or informally, towards population-based screening for CF.

2. How to offer screening: studies exploring the method of offering CF carrier screening.

3. Uptake of screening: studies measuring the number of individuals/couples who accepted or declined an offer of CF carrier screening.

4. Factors influencing decisions about screening: studies determining barriers and facilitators in regard to having CF carrier screening.

5. Knowledge: studies reporting knowledge of CF and genetic screening at any point prior to, during, or after the screening process.

6. Outcomes and follow-up of screening for cystic fibrosis carrier status: studies reporting outcomes of screening in terms of recalling/understanding carrier status, screening of partner, current/future reproductive behaviour and dissemination of information to family members.

7. Psychological factors: studies exploring psychological effects on participants involved in screening for CF carrier status.

Key findings of the studies and experiences are described in this review.

Criteria for exclusion from review

Non-English language articles and studies not generating any original research data, such as editorials, opinions, commentaries, and reviews, were excluded from the review. Studies in which diagnostic testing such as NBS, as opposed to carrier testing, was conducted and studies focusing on laboratory aspects of screening, rather than clinical aspects, were also excluded.

Assessment for potential inclusion of studies

Three reviewers (BM, LI and LF) independently assessed the studies based on title and abstracts for inclusion or exclusion according to the criteria outlined above. Another reviewer (SM) was available to resolve any potential differences.

Data extraction

Data collected from the papers included: first author name, year, title, country, aim/hypothesis of study, participant characteristics, study design, sample size, measures used, key results and conclusions.

Data analysis

Analysis of categorical variables was undertaken using χ^2 analyses. A p-value <0.05 was considered statistically significant. Meta-analysis was not possible due to heterogeneity of studies.

Results

The search yielded 15,982 references and after duplicates were removed, 14,761 remained. A total of 85 references met the inclusion criteria for data extraction (Figure 1) (see Supplementary information S1 (Table 1)).

All the papers were published after 1989: 31 (37%) from the UK, 21 (25%) from the USA and 8 (9%) from Australia. Sixty-four (75%) papers involved actually offering CF screening, with 34 (40%) focusing on prenatal screening and 26 (31%) on preconception screening. The remaining 25 (29%) either did not specify between the two settings or provided screening in both. For the purposes of the review we have referred to participants in the latter studies as general population (Table 1).

During data extraction the papers were coded into the seven areas of interest, with some covering multiple areas (Table 2). The number of papers was relatively evenly spread across these areas. The highest number of papers (n=40) reported 'uptake' (47%) and the least number of papers (n=17) evaluated 'how to offer' of screening (20%). In this review, the descriptions of the areas of interest are organised according to the way screening is usually offered (Figure 2).

When comparing studies that offered screening and those in which screening was hypothetical, studies in which screening was offered were more likely to measure: knowledge ($\chi^2=24.79$, $p<0.01$); outcomes and follow-up of screening ($\chi^2=15.77$, $p<0.01$); and psychological factors associated with screening ($\chi^2=10.35$, $p<0.01$).

Attitudes towards carrier screening for cystic fibrosis

Assessing attitudes of the target population towards population-based carrier screening for CF can inform likely interest in and uptake of screening. In the general population, 60-100% believed screening for CF carrier status should be made available[10-16] and 80-96% felt it should be routinely offered.[17-19] There were, however, some reservations reported about the widespread offer of screening, and its perceived systematic implementation by governments.[10, 14] The best time to offer screening was believed to be to individuals of reproductive age, prior to pregnancy or when planning a pregnancy.[10-12, 20] The general population believed results of screening would influence their reproductive decisions.[10, 21, 22] Interest in screening was high: 54%-80% of the general population were interested[19, 22-24] although interest differed depending on life stage with those of reproductive age showing more interest than those who had finished or are yet to start their family[19, 24, 25].

Population-based carrier screening for CF can be implemented at various life stages including: neonate, school age, reproductive age, when planning a family or during the early stages of pregnancy. The majority of studies in which attitudes were measured showed that individuals of school age had positive attitudes towards screening for CF[19, 26-28] with 86%-96% believing such screening should be available[19, 28, 29] and 40%-59% stated that the best time to offer screening is before pregnancy.[27, 28] However, most studies showed that the majority of those questioned did not want to have screening while at school.[19, 24, 27]

Non-pregnant women and couples planning a pregnancy had positive attitudes,[30-34] with 69%-89% believing that CF carrier screening should be routinely offered to all couples planning a pregnancy.[30, 32-34] Pregnant women had similar attitudes towards screening.[35-39] Ninety-eight percent of pregnant women believed the best time to offer screening is prior to pregnancy,[23] while 69% indicated they would accept an offer of screening during pregnancy and 67% would utilise prenatal diagnosis.[23] Attitudes of pregnant women towards screening have been shown to be influenced by perceived susceptibility as well as barriers to and benefits of screening, with barriers having the most negative impact on attitudes.[40]

How to offer of cystic fibrosis carrier screening

Determining the most effective approach to provision of information and the offer of screening is essential to ensure maximum opportunity for participation and informed decision-making.

Between 50%-94% of the target population preferred to receive an offer of CF carrier screening, pre-test information and counselling from a general practitioner (GP).[12, 15, 24, 37, 41] A consultation with a GP resulted in higher uptake of screening: 25% uptake in couples planning a pregnancy compared with only 9-12% uptake when invited to attend a dedicated group information session.[33, 34]

When exploring the method of offering testing, 39%-70% of the target population preferred to be offered testing in person rather than receiving the offer via a letter or brochure.[42, 43] How information is provided has been explored, with 77%-96% reporting brochures/information leaflets as useful.[14, 21, 41, 44, 45] The main source of information potential participants wanted to receive was information about CF and screening, in particular risk of being a carrier and having a child with CF.[46]

Written and audio-visual information were found to be equally effective.[47] There was no difference in knowledge for those who received pre-test information from an interactive computer program compared to a genetic counselling session.[48] However, one study showed presenting a videotape in addition to a leaflet resulted in significantly higher knowledge than when only a leaflet was provided.[39]

Uptake of cystic fibrosis carrier screening

Uptake was reported in the included studies as the percentage of individuals/ couples who accepted an offer of CF carrier screening of the total number of individuals /couples offered. Uptake ranged from 46-99.8% in the prenatal setting, 2-96% in the preconception setting and 8-17% in the general population (Table 3).

Uptake was higher for females compared to males,[49, 50] and the screening approach, whether couples were screened as a unit (couple screening) or individually (stepwise screening), did not influence uptake.[51, 52]

Factors influencing decisions in regard to cystic fibrosis carrier screening

Factors that influence the decision to accept or decline an offer of CF carrier screening have been explored in various studies. Gender, ethnicity, parity, future reproductive plans, income and level of education were all factors that influenced the decisions regarding CF carrier screening. Affluent, Caucasian women with high education who had no children and were planning future pregnancies were most likely to accept an offer of screening.[43, 66, 69, 70] Life stage was also shown to be important in decisions about screening, with studies showing lower interest from individuals preconceptionally compared to those already pregnant.[14, 15] Although a study exploring the decision-making of pregnant women regarding an offer of screening concluded that pregnancy is not the best time for informed decision-making, pregnancy had a powerful influence on the decision-making process.[71]

The main factors that arose when exploring the reasons for accepting and declining an offer of screening are shown in Table 4. Other factors that influenced the decision to accept screening were: ease of test procedure; individuals feeling they could not refuse the offer; would regret not having screening; perceived importance of test; perceived positive consequences; perceived fewer barriers; and perceived less difficulty informing relatives.[30, 53, 72] Other factors that influenced the decision to decline an offer of screening were: concern about test sensitivity; not wishing to be tested during pregnancy; not wanting to know; insurability; limited knowledge; the requirement of a blood test; and religious beliefs.[15, 31, 73]

Knowledge of cystic fibrosis and genetic screening

Evaluating knowledge of CF and CF carrier screening can assess individuals'/couples' informed decision-making in regard to accepting or declining such an offer. Knowledge has been tested at various points during the screening process: prior to receiving information, after receiving information and after receiving test results. Testing knowledge prior to receiving information is indicative of the general knowledge held by the population. Many studies have shown that initial knowledge of CF and CF carrier screening is low,[10, 12, 21, 22, 24, 28, 29, 60, 79] with gender and education significantly influencing knowledge level:[12, 47, 80] well educated women had higher knowledge scores. Secondary and tertiary students tended to have a higher level of knowledge compared to those in the general population.[27-29, 68] In general, the studies showed that participants were unaware that CF is an inherited condition,[12, 21, 24, 53] did not know CF affected the lungs,[10, 12, 79] were unaware that the majority of carriers do not have a family history of CF[16, 21, 79] and thought carriers had symptoms of the disease.[79] Knowledge levels increased after receiving information on CF and screening.[28, 29, 60, 72, 80] One study found that those who declined screening had a lower level of knowledge than those who accepted.[32]

Evaluating knowledge after receiving the test result has shown that carriers of CF had a higher level of knowledge compared to non-carriers.[20, 42, 72, 81] Knowledge decreased

with the time elapsed since the test,[81] although this may only be the case for non-carriers with no decrease in knowledge observed for carriers three months after testing.[72]

The majority of those screened did not understand the concept of residual risk for future pregnancies believing that a negative test result meant they had no chance of having a child with CF.[48, 68, 81-85] The residual risk is due to the fact that screening is less than 100% sensitive.[68, 81-85] While the majority of non-carriers understood the meaning of their carrier status, some believed that they were definitely not a carrier,[20, 42, 47, 50, 52-54, 58, 65-67, 86, 87] and some carriers believed they had no risk of having a child with CF due to their partner's negative test result.[72, 87] The confusion in regard to residual risk may have implications for the carrier if they are to change partners in the future.

Outcomes and follow-up of screening for cystic fibrosis carrier status

Studies involving the follow-up of CF carrier screening were undertaken at various time points ranging from two weeks to three years after testing and explored recollection and understanding of carrier status, testing of partner, impact on current and future reproductive plans, as well as the dissemination of information to other family members. The majority of carriers and non-carriers correctly recalled their carrier status,[47, 52, 65, 81, 87, 88] with carriers more frequently recalling their carrier status compared to non-carriers.[20, 66, 84, 86, 89] Nevertheless, some carriers believed they were only *likely* to be carriers of CF.[42, 50, 66, 81, 86]

Individual carrier status did not affect reproductive intentions or behaviours, with carriers not altering their reproductive plans after receiving a positive test result.[59, 61, 65, 82-84, 86, 89] Screening of partners of carriers to determine risk of having a child with CF had an uptake of 61%-100%,[20, 36, 52, 56, 61, 64, 87, 90-92] with reasons for partners not being tested stated as: anxiety about result; would be tested when planning to start a family; would not alter reproductive plans; and had no further reproductive plans.[61, 87] When participants were asked to consider their reproductive intention if they were found to be a carrier couple the majority stated that they: would not have (more) children,[10, 65] would utilise prenatal diagnosis in future pregnancies,[10, 52, 65] were unsure or would not terminate an affected fetus.[23, 52, 53] In actuality, 80-100% of carrier couples identified utilised prenatal diagnosis[38, 39, 41, 51, 56, 57, 60-62, 64, 83, 88, 91] and the majority terminated an affected fetus.[38, 51, 56, 57, 60, 64, 83, 88, 91] Only one study reported the continuation of an affected pregnancy, with the carrier couple having twins who were both identified as affected.[39]

The dissemination of information from carriers to other family members about increased risk is often evaluated when exploring the outcomes of screening. The majority of carriers reported informing relatives of their carrier status,[20, 68, 72, 82, 84, 87, 90] most frequently to parents and siblings.[87, 90, 93] While level of dissemination was high, little is known about testing rates of family members following population-based carrier screening.

Psychological factors associated with screening for cystic fibrosis carrier status

Concerns have been raised over the potential psychological harm of population screening for CF carrier status. While there was an increase in anxiety upon receiving a positive test result[42, 50, 56, 84, 87, 92] this dissipated once partners were tested and found to be negative,[56, 82, 92] following genetic counselling,[61, 65] or after a period of 3 months or

more.[42, 50, 61, 65, 82, 87] While anxiety appeared to be transient amongst carriers, 15-24% stated they were still worried or anxious about their test result 3-6 months after testing.[65, 89] There was no significant difference in anxiety between carriers and non-carriers[37, 39, 57, 61, 86] and between those who were screened and those not screened.[62]

Upon receiving test results, the majority of those screened were reassured while some were slightly apprehensive.[45] Most carriers expressed feelings of surprise, shock and worry upon receiving their positive test result,[53, 65, 90] while some expressed negative feelings and troubling thoughts.[94] All individuals screened attributed negative feelings about being a carrier, while carriers attributed positive feelings about themselves but negative feelings about other carriers.[81] A study involving secondary school students showed a marked increase in uncertainty regarding feelings of concern and self-esteem, after receipt of test results.[28] Some studies showed that carriers perceived their current health to be poorer than non-carriers[86, 89] although other studies showed no difference between carriers and non-carriers for past, present and future perception of health.[57, 84] Despite these reports, 83%-97% of those screened, including carriers, felt that they made the right decision and would make the same decision again[20, 34, 54, 61] with only 2%-12% stating that they were unsure or regretted their decision to have screening.[61, 83]

Discussion

The available studies of population-based screening for CF carrier status have positive implications for the routine offer of screening to pregnant couples, couples planning a pregnancy and individuals wishing to know their carrier status. The review demonstrates for the majority of studies: positive attitudes towards the routine offer of CF carrier screening; high uptake of screening in a prenatal setting; correct recall and understanding of carrier status; high rate of testing of carrier's partners; willingness to inform family members and relatives of increased risk if found to be a carrier; and no long term psychological harm. Understanding residual risk was poor in many of the studies evaluated in this review.

These studies are heterogeneous in a number of ways, including: the setting in which screening was offered; populations who were offered screening; the cost of the test; how testing was offered; pre-test counselling; pre-test information; disclosure of test results; and post-test counselling. In addition, a number of the studies involved hypothetical screening, therefore while the results are still important in determining predicted attitudes and behaviours towards screening these might change upon receipt of an actual offer of screening. While there is some difficulty in comparing these studies a great deal can still be learnt.

The discovery of the *CFTR* gene in 1989, enabling carrier screening for CF to take place, sparked a rise in research with the majority of studies included in the review published in the 1990s. Most were conducted in the USA, in line with recommendations for the routine offer of CF carrier screening there. However, since its implementation there has been limited evaluation. A smaller number of studies were based in the UK, which is currently reviewing their advice to not recommend routine screening. These UK studies

often reported psychological factors in response to a policy recommendation to gather further data on the psychological consequences of carrier detection.[95]

Uptake rates are an important evaluation tool of screening programs. However, in a number of the studies included in this review uptake rate could not be reported because the overall number of individuals or couples who were offered screening was not recorded. Generally, uptake of CF carrier screening was higher in those who were pregnant at the time of offer compared to those who were not pregnant or the general population. Screening was perceived as more relevant during pregnancy, with some non-pregnant individuals of reproductive age stating that they would not accept screening at this life stage.[14, 15, 27]

When determining attitudes and opinions towards the offer of screening, most studies showed that potential participants would like to receive an offer of screening as well as pre-test information and counselling from their GP, and would prefer a direct offer rather than a passive offer. An information leaflet or brochure on CF carrier screening was perceived to be useful in addition to the face-to-face information. While this review did not report on the attitudes of health professionals towards CF carrier screening, studies have shown that they perceived various practical barriers to the offer of screening. A recent study by Stark et al. (2012) showed that barriers identified by Australian obstetricians in regard to routinely offering genetic (not just CF) carrier screening were: time constraints, costs, and availability of supporting services.[96] Health professionals are often the gatekeepers of screening and their attitudes, opinions and knowledge regarding screening are significant in the effectiveness of offering population-based screening for CF carrier status. This is borne out by a number of studies that have shown that doctor's recommendation is an influencing factor in accepting screening.[14, 20, 62, 70]

Potential participants believed the best time to have CF carrier screening is prior to pregnancy, as identification of carrier couples preconceptionally provides the most reproductive options as well as giving couples more time to make reproductive decisions compared to prenatal screening. While this may be the most advantageous time to screen, preconception screening was associated with lower uptake than prenatal screening due to: lack of interest at this life stage; lack of preconception health care setting in which to offer screening; and a large number of unplanned pregnancies.[18] Offering carrier screening for CF in high school has been proposed as it can reach a large proportion of the population. High uptake has been associated with screening in Jewish high schools with 98% of Jewish high school students accepting an offer of carrier screening for a number of conditions including CF.[97] The delay in the use of information obtained from CF carrier screening in high school is the main criticism of this approach and the American College of Medical Genetics stated that carrier screening should 'not be offered to adolescents as the information is only relevant for reproductive planning'.[98] Nonetheless, the adolescents studied recalled their positive carrier status, had their partner tested and used this information to make future reproductive decisions.[99] Despite concerns that adolescents identified as carriers of CF would face stigmatisation and discrimination from peers,

adolescent carriers had few negative psychological effects as a result of knowing their carrier status.[99]

The majority of studies reported that willingness to accept an offer of screening was associated with: wanting to know carrier status, high perceived susceptibility and avoiding having a child with CF. The main factors associated with declining an offer of screening were: low perceived susceptibility, would not terminate a pregnancy and lack of family history of CF. More than half of the studies in this review exploring these influencing factors did not involve an actual offer of screening. Therefore the majority of factors mentioned are perceived to influence the decision for hypothetical screening but may or may not actually influence decisions when faced with an offer of screening. Increasing acceptance of CF carrier screening could be achieved by increasing knowledge, as perceived susceptibility and perceived severity appeared to be the main themes amongst the influencing factors. For example, absence of a family history of CF as a reason for declining screening highlights a lack of knowledge because the carrier rate is 1 in 25 and most children with CF are born to couples who do not have a family history.[100]

Henneman et al. (2001) found that those who declined screening had lower knowledge than those who accepted screening.[32] Knowledge of CF and screening has been shown to be low prior to screening, but improves after screening. A potential reason for this increase may be the perceived relevance of that information, particularly if found to be a carrier. Provision of post-test counselling is likely to also improve knowledge, with carriers usually receiving more follow-up than non-carriers.[20]

Lack of knowledge and understanding of residual risk has been one of the major issues to arise from this review. While carrier screening for most diseases has a test sensitivity of close to 100%, CF carrier screening has a test sensitivity of approximately 80% among Northern Europeans when screening for 23 *CFTR* mutations each with a frequency equal or greater than 0.1% in the CF population.[2] Individuals who obtain a negative result for CF carrier screening therefore still have a residual risk of being a carrier and having an affected child. This has led to confusion amongst non-carriers, and carriers with a non-carrier partner, with some of these individuals believing they have no risk of having a child for CF.

Studies have shown that approximately 70% of the target population in UK, USA and the Netherlands stated that the results of screening for CF carrier status would influence their reproductive behaviour.[15, 22, 33] However, the review showed that the majority of carriers would not change their reproductive behaviour as a result of their carrier status unless their partner was also found to be a carrier.

An outcome of population-based carrier screening is the reduction of CF in the population through the provision of reproductive choices to individuals and couples identified as carriers. This is borne out by the majority of carrier couples utilising prenatal diagnosis and terminating an affected fetus. NBS also identifies parents as carrier couples and provides reproductive options for future pregnancies. In Australia, 67% of parents identified as carriers through NBS chose to use prenatal diagnosis if having more children.[6]

As judged by the number of infants with CF identified by NBS, the incidence of CF has decreased since the implementation of CF carrier screening in Massachusetts.[101]

The dissemination of information by carriers to family members is important as they are at increased risk of being carriers of CF. This is particularly relevant if they are planning a pregnancy, but less so if they are not of reproductive age, do not have a partner or have finished reproducing.[20] While it is evident that most carriers stated that they informed family members of their carrier status, a study by McClaren et al. (2010) evaluating cascade testing after a child is diagnosed with CF through NBS showed that identifying an individual as a carrier of CF usually results in an average of only 11% of family members being tested.[102]

Psychological harm as a result of screening has been proposed as a barrier to the implementation of population-based CF carrier screening. While there have been various studies reporting anxiety and feelings of poorer health in carriers, anxiety was generally transient and perception of poor health reflected a lack of knowledge. The majority of studies reported no long term psychological harm, with the provision of counselling. This is supported by Henneman et al. (2002) who reported that the potential psychological harms associated with population carrier screening for CF are insufficient to warrant the refusal to offer carrier screening to the general population in the Netherlands.[103]

Conclusion

In conclusion, this review demonstrates that population carrier screening for CF is generally associated with relatively high uptake, positive attitudes, correct recall and understanding of carrier status as well as no long-term psychological harm. While barriers to implementing CF carrier screening routinely in the population exist, they are not insurmountable. There would appear to be no psychosocial reasons why population-based carrier screening for CF should not become part of regular healthcare.

Despite the considerable heterogeneity between the included studies, there is now a substantial body of evidence collected to inform programs. What is needed now are large scale studies of 'routine' screening to evaluate in a real-world setting the perceived benefits, harms, barriers and motivators, and behaviours that have been identified in the literature so far.

Abbreviations

CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator gene
NBS	Newborn screening

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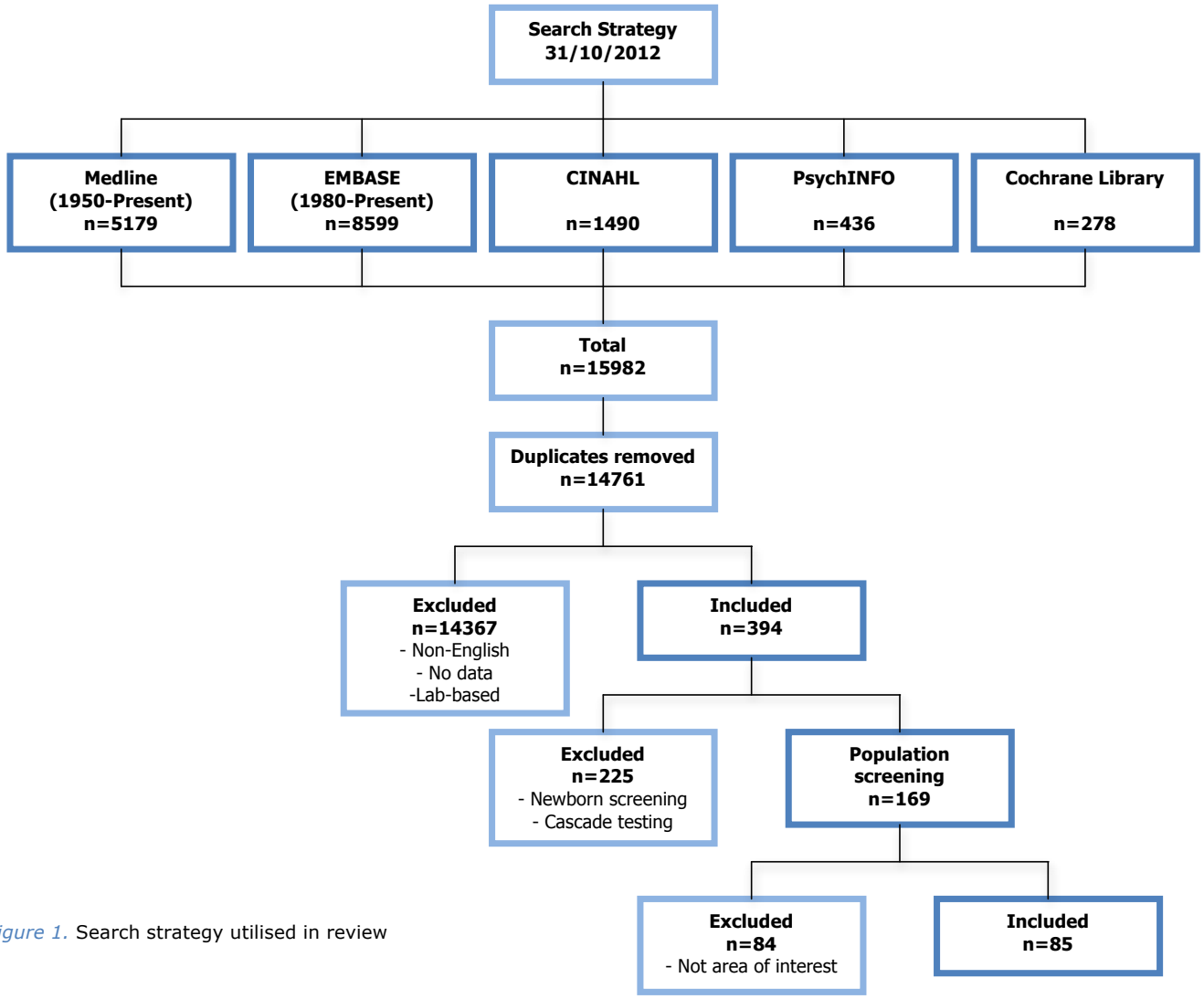

Figure 1. Search strategy utilised in review

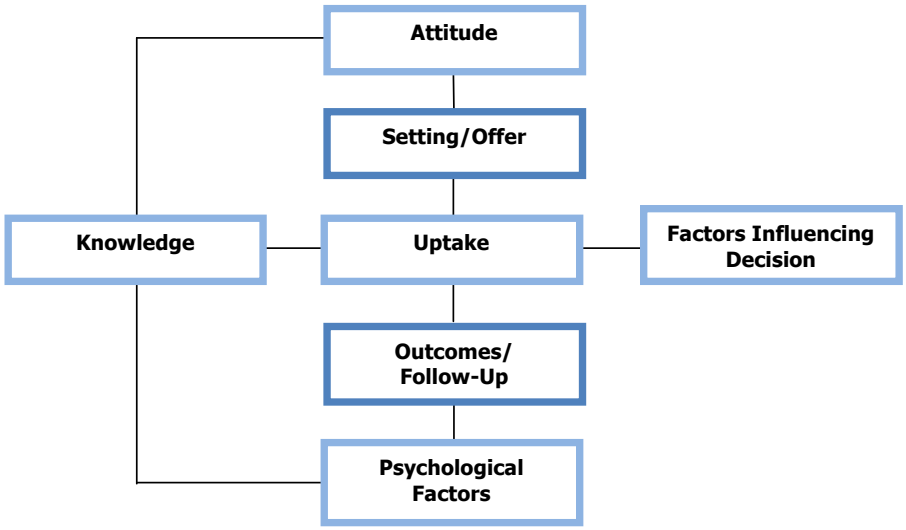

Figure 2. Relationship between areas of interest

Table 1. Demographic characteristics of articles included in review

Demographic	Category	N	%
Year	1989	2	2.4
n=85	1990-99	59	69.4
	2000-09	20	23.5
	2010-2012	4	4.7
Country	UK	31	36.5
n=85	USA	21	24.7
	Netherlands	10	11.8
	Australia	8	9.4
	Other	15	17.6
Screening	Offered	64	75.3
n=85	Not offered	21	24.7
Setting	Prenatal	34	40.0
n=85	Preconception	26	30.6
	General pop.	25	29.4
Method of data	Quantitative	59	70.2
collection	Qualitative	7	8.3
n=84*	Mixed	13	15.5
	Evaluation	5	6.0

*Note: One study did not specify the method utilised

Table 2. Percentage and description of articles in each of the seven areas of interest

Category	No. of articles n (%)	Reference
Attitudes	31 (36.5)	10-40
How to offer	17 (20.0)	12, 14, 15, 21, 24, 33, 34, 37, 39, 41-48
Uptake	40 (47.1)	21, 31-36, 39, 41, 42, 51-55, 57-63, 65, 66, 69, 72, 75, 80, 83, 84
Influencing factors	37 (43.5)	14-16, 20, 27, 30-36, 53, 55, 58, 61-63, 65, 66, 69-72, 74-78
Knowledge	25 (29.4)	16, 20, 21, 27, 32, 42, 48, 53, 60, 72, 79-85
Outcomes/follow-up of screening	40 (47.1)	20, 23, 36, 39, 41, 42, 51-54, 57-62, 65, 66, 72, 81-86, 88-91, 93
Psychological factors	23 (27.1)	20, 34, 39, 42, 53, 54, 57, 61, 62, 65, 81-83, 89, 90, 94

Table 3. Uptake of screening for CF carrier status according to country and setting

Country	Setting	Uptake (%)	References
UK	Prenatal	62-99%	36, 44, 51, 53-57
	Preconception	20-31%	49, 58
	General population	~17%	42, 50
USA	Prenatal	46-78%	39, 59-62
	Preconception	<2%	31, 63
Germany	Prenatal	99.8%	38
Denmark	Prenatal	89%	64
Canada	Preconception*	40%	67, 68
Australia	Preconception*	42-75%	65, 66
	General population	4-8%	65, 66

Note: * High school setting

Table 4. Factors influencing the decision to accept or decline an offer of CF carrier screening

Decision	Factors influencing decision	Prenatal	Preconception	General population
Accept	Perceived severity of disease			20, 74, 76
	Avoid having an affected child	35, 36, 44, 45, 61, 62, 72, 75	11, 33	
	Want to know carrier status	35, 45, 53, 72	11, 32, 65	24, 77
	Doctor's recommendation	62		14, 20, 70
	High perceived susceptibility	35, 62		20, 74
	To be prepared	35, 75		
	Reassurance	35, 36, 61, 72, 75		
	Willingness to have all tests offered	36, 53		
Decline	Low perceived susceptibility	35, 36, 61, 62, 73		
	Lack of family history	16, 55, 78		14, 58, 77
	Would not terminate a pregnancy	36, 44, 56, 61, 62, 73		
	Opposed to prenatal diagnosis	38, 78		
	No further reproductive plans			58, 77
	Lack of time		32-34	58
	Partner's opinion	36, 73		
	Anxiety	35, 62	27	
	Cost of test	35, 78	15, 63	
	Lack of interest at this life stage		15	

Note: For **Supplementary Information** see Appendix C

5.4 GHSV CF carrier screening program

A CF carrier screening program was implemented in Victoria, in 2006, by GHSV. Screening is offered in the private health sector for a cost of $220 per test. There is currently no Australian government (Medicare) rebate. Individuals or couples before or during the early stages of pregnancy are offered screening by obstetricians and general practitioners. Potential providers throughout Victoria were informed of the program through information disseminated by specialty colleges, seminars given by staff associated with the program, posters, brochures and direct contact.

Potential consumers are informed about the program by their health professional and those that are interested in screening are provided with a screening pack. The screening pack contains: a brochure on carrier testing for CF; a cheek brush; a three-step guide on how to collect a cheek brush sample; an invoice for the cost of the CF carrier screening test; a pathology request form which must be signed by a medical practitioner; and a return pre-paid envelope (Figure 1). A website is also available to provide detailed information to both potential consumers and providers (www.cfscreening.com.au).

Figure 1. CF carrier screening pack provided by GHSV

The brochure (see Appendix D) outlines the clinical features of CF and the risk of an individual from the general population being a carrier, and having a baby with CF. It explains that there is a test to determine carrier status, and when is the most beneficial time to have carrier screening. It also provides details on the interpretation of results including residual risk (meaning those with a negative result do not carry one of the common *CFTR* mutations tested, and their risk of being a carrier is greatly reduced but not eliminated) as well as the

implications of being identified as a carrier couple. Screening packs can also be sent out to individuals who contact Genetic Health Services Victoria (GHSV) directly.

The cheek brush is simple, painless and can be performed by the individual at home. Buccal cells for DNA analysis are obtained by wiping the brush against the inside of both cheeks for approximately ten seconds each side. The sample collected using the cheek brush is then returned to GHSV by post where it is screened for 12 of the most common *CFTR* mutations. These mutations are: p.F508del; p.G542X; p.W1282X; p.N1303K; p.I507del; p.G551D; c.489+1G>T; p.R560T; p.V520F; p.R553X; c.3718-2477C>T; and c.1585-1G>A. The results of the test are available within five to seven working days from the receipt of the cheekbrush sample at the laboratory and are sent directly to the referring doctor.

If an individual is found to be a carrier of a *CFTR* mutation, they are offered free counselling and testing to determine their partner's carrier status. If both individuals in the couple are found to be carriers, genetic counselling is provided to discuss all available options and an appointment with a CF specialist is offered to educate couples about CF. Cascade testing is available to family members and relatives. A summary of the program outcomes from January 2006 to July 2012 is shown in Table 1.

Table 2. Statistics of the GHSV CF carrier screening from Jan 2006- Jul 2012

Outcomes of screening			**n (frequency)**
Total screened			8872
	Carriers		251 (1/35)
	Carrier Couples		12 (1/739)
		Pregnant at time	10
		Prenatal diagnosis	10
		Affected Pregnancies	3
		Termination	3

Chapter 6

Accepted CF Carrier Screening

Addendum

p 83 para 5: Replace superscript 7 at the end of the first sentence with (Massie et al. 2009).

p 84 para 2: Insert reference (Murray et al. 1999) at the end of first sentence.

p 100 para 1: Comment: One way of reducing anxiety during the screening process is to utilise double sampling instead of sequential testing. Double sampling allows testing both individuals in the couple sequentially without having to inform the couple that the first tested individual is a carrier, which eliminates the anxiety in the individual who is first identified as a carrier while waiting for their partner's test result.

p 106: Add reference to reference list:
Murray, J., Cuckle, H., Taylor, G., Littlewood, J., & Hewison, J. Executive summary: Screening for cystic fibrosis. *Health Technology Assessment* 3 (1999)

6.1 Declaration

Declaration by candidate

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Conception and design of study; attainment of ethics approval and on-going reporting requirements; interview schedule development; participant requirement; interviews; transcription of interviews; data analysis and interpretation; writing of manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**
Prof Martin Delatycki	Conception and design of study; assisted with development of interview schedule; discussion of ideas expressed in and critical revision of manuscript
A/Prof John Massie	Conception and design of study; discussion of ideas expressed in and critical revision of manuscript
Dr Jan Hodgson	Assistance with data analysis and interpretation; discussion of ideas expressed in and critical revision of manuscript
Dr Sharon Lewis	Conception and design of study; assisted with development of interview schedule; assistance with data analysis and interpretation; discussion of ideas expressed in and critical revision of manuscript

Candidate's Signature		**Date** 20/02/13

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Murdoch Childrens Research Institute

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]		1/3/13
Signature 2			1/3/13
Signature 3			21/3/13
Signature 4			1/3/13

6.2 Paper preamble

This chapter reports the outcome of interviews of carrier couples identified by the GHSV program. It commences with a brief summary on previous research evaluating the attitudes and outcomes of carriers and non-carriers identified by the GHSV program, where the carrier's partner was found not to have any of the CFTR mutations tested for.[92]

This is then followed by a manuscript reporting the outcomes of a qualitative research project exploring the experiences of couples that are both identified as carriers of CF through the GHSV program. This paper is then followed by further research outcomes that were not included in the paper. This research was conducted throughout my candidature, to ensure enough time had elapsed between carrier identification and participation in the project, and was submitted to the American Journal of Medical Genetics in March 2013.

6.3 Previous research

In 2008, I completed my Honours research project exploring the characteristics of individuals who chose to have CF carrier screening, and their attitudes towards carrier screening (Appendix E). One hundred and twelve individuals participated in the study, 47 carriers and 65 non-carriers. There were several major findings to come out of this study.[92] Individuals who participated in this screening program were more likely to be well educated, affluent women between the ages of 35 and 39. The main reasons for choosing screening were the perception of CF as a severe condition and a doctor's recommendation. All carriers correctly recalled their carrier status and the risk of having a child with CF; while three non-carriers (4.7%) were unsure of their carrier status and 12 (22%) incorrectly recalled their residual risk. Carriers answered the knowledge questions correctly more often than non-carriers. There was no difference in anxiety between carriers and non-carriers. The majority of carriers informed relatives of their increased risk of being a carrier. Individuals screened were generally satisfied with the program.

6.4 Paper: 'Experiences of couples who are both identified as carriers of cystic fibrosis'

Experiences of Couples both Identified as Carriers of Cystic Fibrosis Identified through a Population-based Carrier Screening Program

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Abstract

Background/Aims

Cystic fibrosis (CF) is the most common severe, autosomal recessive disease amongst Caucasians. A population-based CF carrier screening program was implemented in Victoria, Australia in 2006. The aim of this study was explore the experiences of couples that were both identified as carriers of CF through this program.

Methods

Between January 2006 and December 2010, 10 carrier couples were identified. All couples were invited to participate in this qualitative study by a genetic counselor associated with the program. Interviews were semi-structured and analyzed using inductive content analysis.

Results

A total of nine interviews were conducted, seven couple interviews and two individual interviews. The main reasons for having screening were high perceived severity of CF, high perceived susceptibility and to avoid having a child with CF. All couples experienced shock on learning their carrier couple result. Six of the nine couples were pregnant at the time of screening and all had prenatal diagnosis. Two of the pregnancies were affected with participants reporting grief upon receiving the prenatal diagnosis result. Both couples elected termination of the affected foetus. Three of the nine couples had no further children since being identified as a carrier couple. Of the remaining six couples, four utilized prenatal diagnosis and two utilized preimplantation genetic diagnosis for subsequent pregnancies. All participants informed at least one family member of their carrier status.

Conclusions

Couples were unprepared for a positive carrier couple result. However, all the couples changed their reproductive behaviour as a result of their carrier status and informed family members of their increased risk.

Keywords: genetic screening, cystic fibrosis, cystic fibrosis carrier screening, attitudes

Introduction

Reproductive genetic screening is the screening of individuals or couples to determine if they are carriers of a disease-causing mutation that may result in disease in their offspring. The goal of reproductive genetic screening is to provide individuals or couples with reproductive options to avoid the birth of a child with the disease. Reproductive options for carrier couples include: no further children, adoption, donor gametes, prenatal diagnosis to prepare for the birth of an affected child or to terminate an affected pregnancy, and, preimplantation genetic diagnosis.

Cystic fibrosis is the most common, severe, autosomal recessive condition in those of Northern European descent, with a prevalence of 1 in 2,500-3,500 live births and a carrier frequency of 1 in 25 (Southern et al. 2007). Chronic suppurative lung disease is largely responsible for reduced life expectancy, which is currently a median of 37 years (Dodge et al. 2007). Other clinical manifestations of CF include pancreatic exocrine insufficiency, cirrhosis, elevated sweat electrolytes and male infertility. Although there is no cure for CF, treatment has improved outcome over the last 30 years. Treatments include daily chest physiotherapy, inhaled mucolytic agents, hospital admissions, antibiotics, pancreatic enzyme replacement and a controlled diet. Lung transplantation is available for some patients, but does not cure CF (Rowe et al. 2005).

In the USA, the National Institute of Health, the American College of Medical Genetics and the American College of Obstetricians and Gynaecologists have recommended that CF carrier screening be offered to all pregnant women and couples planning a pregnancy (ACOG 2005; Watson et al. 2004). Similar recommendations were made in Australia by the Human Genetic Society of Australasia (HGSA 2010).

In the state of Victoria, Australia, a population-based CF carrier screening program was implemented by Genetic Health Services Victoria (GHSV) in 2006. The program offers screening to women and couples before or during the early stages of pregnancy via private obstetricians and general practitioners. It is currently a fee-for-service program with each test costing AUD$220.

During the first three years of the program (2006-2008) 3,200 individuals were screened, 106 carriers were identified, all partners of carriers were screened and nine carrier couples were found.[7] Of the nine carrier couples, six were pregnant at the time of screening, all utilised prenatal diagnosis and two affected pregnancies were identified and terminated (Massie et al. 2009). Therefore, the carrier couples identified through the program used the information obtained from screening to make reproductive decisions. This is supported by the findings from other studies, showing that approximately 70% of the target population in UK, USA and the Netherlands stated

that the results of screening for CF carrier status would influence their reproductive behaviour (Poppelaars et al. 2003; Watson et al. 1991; Henneman et al. 2003).

The reproductive decisions and experiences of CF carrier couples have been well documented for those identified by the birth of an affected child, newborn screening and/or cascade testing (Sawyer et al. 2006; Myring et al. 2011; Wertz et al. 1991; Mischler et al. 1998; De Braekeleer et al. 2000; De Braekeleer et al. 2004; Evers-Kiebooms et al. 1988; Boue et al. 1991; Dudding et al. 2000; Henneman et al. 2001a; Henneman et al. 2002). These studies have shown that most couples changed their reproductive plans as a result of their carrier status, with the majority opting to have no further children or utilize prenatal diagnosis in subsequent pregnancies. However, little is known about the reproductive decisions and experiences of couples that are identified as carriers of CF through population-based screening programs.

The dissemination of information from carriers to other family members about increased risk is often evaluated when exploring the outcomes of population-based screening, with a number of studies showing that the majority of carriers inform family members of their carrier status (Ioannou et al. 2010; Delvaux et al. 2001; Watson et al. 1992; Boulton et al. 1996). While dissemination of information regarding CF carrier status is high, little is known about the testing rates of family members following receipt of this information.

In 2010 we conducted a study to evaluate the GHSV population-based CF carrier screening program and to assess the attitudes and outcomes of screening among carriers and non-carriers. The program was found to meet the needs of those undertaking screening with provision of pre and post-test information rated satisfactory, the process of testing considered simple, with relatively high knowledge retention and recall of carrier status (Ioannou et al. 2010). However, carrier couples were excluded from the study. Therefore, the aims of this current study were to explore the views and experiences of couples that were both identified as carriers of CF with regard to the process of screening and reproductive decision-making.

Materials and Methods

GHSV Population-based CF Carrier Screening Program

Pre-test information about CF and screening is provided by the offering doctor, information brochure and the program website (www.cfscreening.com.au). Those interested in screening are provided with a screening pack containing: a brochure on carrier testing for CF; a cheekbrush; a three-step guide on how to collect a cheekbrush sample; an invoice for payment for the test; a

pathology request form which must be signed by a medical practitioner; and a return pre-paid envelope.

Sequential testing is generally used, with one partner being tested first and, if found to be a carrier, their partner is tested. The sample collected using the cheek brush is returned to VCGS by post where it is screened for 12 of the most common *CFTR* mutations. The results of the test, available within five to seven working days from the receipt of the cheekbrush sample at the laboratory, are sent directly to the referring doctor. Individuals are informed of their carrier status via a telephone call from either a genetic counselor associated with the program and/or their obstetrician.

If an individual is found to be a carrier of a *CFTR* mutation, they are offered free counseling and testing to determine their partner's carrier status. If both partners are found to be carriers, genetic counseling is provided to discuss all available options and an appointment with a CF specialist is offered to educate couples about CF. Carriers are informed of the importance of informing family members and relatives of their carrier status and are provided with an anonymous letter which can be sent to family members and relatives informing them of their increased risk of being a carrier of CF.

Participants

From the implementation of the program in January 2006 to December 2012, 8,872 individuals had been screened through the program, with 251 carriers and 12 carrier couples identified. Carrier couples identified after 2010 were not included in the current study as it was thought that not enough time had perhaps elapsed since screening to allow them to come to terms with the potential outcomes or to have made decisions about future pregnancies.

Methodology

Qualitative methods were chosen to enable an exploration of the experiences of couples when they were both identified as carriers of CF. Open-ended questions, informed by the literature and process of screening, were used in the semi-structured interview schedule (Appendix). This methodology provided participants with the opportunity to freely take the discussion in any direction while keeping some focus on the topics under investigation.

Interviews

All interviews were conducted over a 12-month period beginning in June 2011. All interviews were conducted by the same author (LI). Interviews discussed the following: offer of screening; reasons for having screening; testing process; outcomes of testing; evaluation of program;

reproductive outcomes as a result of screening; and cascade testing. Interviews were digitally recorded and transcribed verbatim with each participant assigned a pseudonym.

Analysis

Transcripts were analyzed by inductive content analysis using NVivo 10 (QSR International Pty Ltd, Melbourne, Australia) (Elo & Kyngas 2008). This process involved coding and categorization of similarities and differences independently by LI and SL. Comparisons for coding reliability was a process of discussion and deliberation of themes and connections between themes.

Ethics Committee Approval

This study was approved by the Human Research Ethics Committee of the Department of Human Services, Victoria, Australia (HREC 15/05).

Results

Response

One of the ten carrier couples that had carrier screening declined to participate due to the recent termination of an affected pregnancy. Two couples were divorced and both of the male partners from these couples declined to participate in the study. Therefore, a total of nine interviews were conducted, seven couple interviews and two individual interviews, resulting in 16 participants in the study (Table 1).

Six of the nine couples had been pregnant at the time of receiving an offer of screening, and one pregnancy occurred as the result of IVF. The remaining three couples were not pregnant when screened, and one couple had recently miscarried a pregnancy.

The results presented in this paper outline the major themes that emerged from the interview discussions about offer of testing, the testing process itself and outcomes after testing (Figure 1). The major themes are illustrated using quotes from transcripts as evidence. In some examples, quotes were truncated by the use of … for clarity, without changing the meaning.

1. Offer of screening

Participants were asked to discuss the offer and acceptance of screening.

Receiving offer of screening

When participants talked about how they found out about CF carrier screening or who offered them the test, seven of the nine couples stated that they were offered screening by their obstetrician. One other couple was offered screening by a genetic counselor following the

birth of her first child who was diagnosed with a chromosomal abnormality. The remaining couple was offered screening by a gynecologist from whom they sought pre-pregnancy advice.

Health professional's explanation with regard to screening

Participants were asked if they were satisfied with their doctor's explanation with regard to CF and CF screening. The majority of participants stated that they were satisfied with the explanation and information provided by their doctor.

> *Absolutely. She sort of outlined the main concerns, the health issues* (Delta).

However, some participants reported that they did not receive much, if any, information on CF or screening.

> *Nope it was just here's cystic fibrosis you go and do your own research and work it out so there was very little* (Blake).

> *He just said 'look this is nothing to worry about but just something you can do at home, it is just to take a precaution and test for cystic fibrosis and that sort of thing but not much information was told by the doctor* (Felicity).

Health professional's recommendation towards screening

When describing how testing was offered, several participants felt that their health professional had recommended screening.

> *He just sort of said that it was an important thing he thought.* (Isobel).

> *'The bottom line is if you are pregnant and you were to find out this child has cystic fibrosis based on the medical facts she told me of what's involved in taking care of a child with that condition would you still have it?' and I said no. And she said 'then you should probably take the test.'* (Delta).

Other participants, however, reported that their doctor's approach in offering the test was more casual.

> *He just basically explained it and gave me the mouth swab and said if we want to do it just sort of fill in the form and send it off.* (Addison).

> *It was here's the pack go and look at it.* (Blake).

Lack of knowledge of CF prior to screening

None of the participants had a family history of CF. Before having the test, most participants (n=12) had never heard of CF, or had heard of it but did not know anything

about it. Some participants reported having heard about it due to fundraising events in the community, while others reported having known that it was genetic but not much else.

> *I knew of it, and I think that I knew it was a genetic disease but I don't think I would have known any more than that.* (Callan).

> *I had heard the name but I didn't know what it was.* (Daniel).

Four individuals had been involved or had prior experience with CF. Two of these had known someone who had CF while the remaining two had worked with individuals who had CF, one as a registered nurse and the other for an organisation that worked in collaboration with CF Victoria.

Motivations for having screening

Many different reasons for deciding to have screening were evident.

One couple, of Ashkenazi Jewish descent, stated that they were aware of the increased risk of being a carrier for particular genetic diseases due to their ethnicity. That together with the fact that one of them had known someone with CF was the main reason that they accepted the offer of screening.

A female participant wished to avoid the birth of a child with CF, stating that she perceived the disease as severe.

> *Well no I don't want to have a child who has got that illness that is so serious and so then I took [the test].* (Delta).

One participant, Garrett, also considered the disease to be severe and perceived that he and his partner had a higher risk of having a child with CF due to their age.

> *I knew enough about it that I knew it was really serious but I thought it was because we were both 38, 39 and older sort of parents so I thought it was really good to just have it if you could rule out a serious illness.* (Garrett).

Two females reported that their main reason for wanting to have screening was due to prior genetic issues or concerns, with one participant having given birth to a child with a chromosomal abnormality and the other having miscarried her first pregnancy.

> *At that point we had had such bad luck that I thought that I needed to know for the sake of being thorough.* (Helena).

I was pregnant and I miscarried and they just decided to try just eliminate why could a baby miscarry and then this test came up and we did it… (Eva).

One participant stated that her reason for having screening was to assist with the piloting of the then 'new' carrier screening program.

…it would help to go with the research and promoting it and having it Government backed and what not so I was happy to have a go and be part of it. (Isobel).

One female also described having recently travelled prior to receiving the offer of screening and visiting her great grandmother's grave, which was surrounded by three baby graves. This event raised for her the possibility that cystic fibrosis could have been present in her family's background without her being aware of it.

Influence of cost on the decision to have screening

Participants were asked if they recalled the cost associated with screening and if it was an influencing factor in their decision to have screening. Two of the participants stated that the cost of the test was an issue for them and/or their partner in terms of accepting the offer of screening.

The cost is an obstacle 'cos we very much considered not getting it. (Helena).

Originally [partner Blake] didn't feel comfortable about being tested just thought that it was such an expense associate with the entire process. (Bella).

The other participants (n=14) did not find the cost an influencing factor in the decision to have screening.

Not 200. I mean even now at 220 dollars I mean if it is a lifetime of being in and out of hospital and most of them don't live past 30. You pay more for a pair of jeans. (Isobel).

However, some stated they could see how it could be a potential barrier to other couples.

I did think it was a bit expensive but you know I guess you can't put a price on it really. (Addison).

I can imagine people would find it a lot. (Chanel).

Satisfaction with the information provided

All participants were asked if they were satisfied with the information provided and the ease of collecting and returning the cheekbrush sample included in the screening pack. Some

couples reported that they could not recall the screening pack in its entirety due to the time elapsed since screening. Nevertheless, all couples found the process of collecting and returning the cheekbrush sample straightforward, and the cheekbrush easy to use. Two participants remembered the brochure that was provided, and both found it informative.

2. Testing for CF carrier status

Participants were asked to discuss their experiences of being tested. The female partner was tested first in all but one couple, with that couple electing to test the male partner first stating that they perceived the female partner to be less likely to be a carrier of CF due to her Asian ethnicity.

The test results were generally received between one to three weeks later. Participants reported that they were not very anxious while waiting for their results and this period was perceived as fairly fast.

Shock at finding out test result

Participants who were tested first stated that they were surprised to learn of their carrier status but they were not overly concerned, as they perceived the risk of their partner also being a carrier as low.

> *I came back positive which was a bit of a shock but you know still not that severe…* (Helena).
>
> *I just assumed I wouldn't be because I had no family history. So I don't remember being at all worried about it until we got the results.* (Callan).

Therefore, the shock was even greater after learning of their partner's result and their carrier couple status.

> *It was a bit like gosh how much more, like how many more genetic problems can one family have, but it was a much bigger shock when then my ex-husband was tested and back positive. That was very significant.* (Helena).
>
> *It was all, you know, it will be rare that you both have it, that is what we were told pretty much all along, so when I got it I was like oh that's strange but it will be fine because [he] won't have it cause it's so rare. Then he got it and it's like ok so unlucky.* (Eva).

Understanding the meaning of being a carrier couple

Upon receiving their carrier couple test result most couples immediately understood the significance of their result. Some mentioned the genetic risk of having a child with CF due to being a carrier couple.

> *There was a high possibility or a one in four chance that the baby I was carrying was positive or had cystic fibrosis. That was difficult because I never thought I would have a problem.* (Isobel).

Others described the severity of the situation they were in.

> *It was absolutely terrifying at that point yep. Cause then we knew that this was the real deal.* (Delta).

All participants mentioned that they were informed of the possible outcomes and implications of screening by the genetic counselor when they received their first carrier result. When participants were contacted regarding their partner's result, the information was reiterated with an invitation for a face-to-face counseling session.

One couple reported that they did not instantly understand the meaning of being a carrier couple and accredited the Internet and various health professionals for their increased understanding.

> *We found out over the phone and we probably then jumped on the Internet to find out more and then we had these very, you know, helpful meetings with the counselor and physician, but I don't think I instantly understood what it meant.* (Callan).

Role of genetic counseling

As part of the VCGS CF carrier screening program, carrier couples are offered face-to-face genetic counseling and an appointment with a CF specialist. Of the nine couples, only one, not pregnant at the time of screening, declined the offer of a counseling session. Another couple declined an appointment with the CF specialist, as the female of the couple is a registered nurse.

The majority of participants were satisfied with the counseling session and information provided. One male, Callan, reported that the counseling session together with the meeting with the CF specialist gave him and his partner an understanding of cystic fibrosis and clearly outlined their reproductive options.

> *I think after we had come out of the (Hospital) visit we had a much more probably realistic attitude to what life would be like living with a child with cystic fibrosis, but out of those two visits together I think we developed a view, we had understood our options and understood how strongly we were being recommended that we not just go out and get pregnant. Which that was the most shocking confronting bit for me.* (Callan).

Another participant, Delta, added that the information gave them a realistic view of what life would be like with a child who has cystic fibrosis.

> *I got to say they handled it quiet well because we were sort of at this point going blind really… It was very clearly explained, the care that is involved and because at that point we really needed to hear that because all we were thinking is maybe we can handle it because of course, you know, we were questioning, we didn't want to let go of this pregnancy.* (Delta).

In addition, one female, Gabrielle, noted that the counselor was helpful in aiding them in making an informed decision.

> *They really stepped us through it, where of course you kind of want to rush over all the details when they're explaining when you're both carriers it's this and this is how it all works and you kind of just want to rush to the bit where you say ok what decision will we make but she was very good in holding us back and making us really understand it.* (Gabrielle).

Two participants expressed dissatisfaction with the information that was provided during the counseling session and the meeting with the CF specialist. One participant, Helena, felt that the information provided encouraged families to make a decision with regard to terminating an affected pregnancy. She said:

> *I think the information given to us was that it was a very severe condition, it was life threatening, it was a terrible ordeal to live with, all of which now in hindsight I think now was quite overstated and I've since seen doctors that are CF experts who have had a much more positive approach. So I think the genetic counseling process is quite biased towards encouraging families to terminate and I think simplifying the decision or simplifying the information to encourage it to be a very simple decision.* (Helena).

The other participant, Blake, felt that the information provided could have been more direct with regard to the impact CF has on the parents, the family unit and society.

> *We were quite happy with it whatever the outcome was I am sure and we went away just more convinced that we were going down a certain path and what the risks were. They probably weren't harsh enough actually. I think it was probably afterwards when we started to look at CF more I think they could have been a little bit more clinical and actually sort of said look this is actually the impact and this is what is going on. I don't think I got, we got presented probably the, I call it the burden on society or the burden on the parents about what the actual impact is and how it will completely change, potentially completely change your life.* (Blake).

Decision making about prenatal diagnosis

Of the nine couples, six (n=10) were pregnant at the time of screening, and accepted an offer of prenatal diagnosis to determine whether their fetus had cystic fibrosis. When talking about prenatal diagnosis (PND) most of the couples described the decision to have prenatal diagnosis as not being difficult, but rather the next step in the screening process. One female, Addison, explained:

Oh it would have been the next step, that wasn't difficult to have [PND], it would have been more difficult to determine the next step [termination of pregnancy] (Addison).

Another participant, Gabrielle, stated that the decision was not difficult as both her and her partner had already agreed on the outcomes of screening.

I guess we were both testing for the same purpose, we weren't going to continue the pregnancy if it was a positive result, so we kind of knew the outcome. We weren't heading for something where there was going to be this great level of indecision so it was just that we are going to do this and so it was hard but easy in a way. (Gabrielle).

However, one female, Isobel, described her difficulty in making a decision with regard to prenatal diagnosis due to the risk of miscarriage associated with the test.

Oh well I suppose the next step was that I chose to have the amnio done, which was difficult because you don't know if it is going to terminate it or what's going to happen… because I wanted to know either way and I knew it would affect my marriage, it would affect the other children and everyone's lives, so I at least needed to be sure before I made a decision beyond that. (Isobel).

Another couple reported that they went into the prenatal test appointment uninformed; therefore they did not make the decision to have prenatal diagnosis until they were at their appointment.

We went in to actually get the test done and the doctor sort of said 'you know why you are here?' and we sort of said well we are here cause we were told to turn up, and she actually spent an hour going through it all. We were going down a path already so it wasn't a major issue. (Blake).

All participants received their prenatal diagnostic test results between one to two weeks after testing. All were informed of their results via a telephone call from either a genetic counselor associated with the program or their obstetrician. Most participants were anxious or worried while waiting for their results and this period was perceived as very long.

I was freaking out… (Isobel).

It was obviously a horrendous wait... (Addison).

That two weeks was horrible. (Edward).

…It felt like a long time (Gabrielle).

Grief upon learning prenatal diagnosis result

Of the six couples that underwent prenatal diagnosis, two of the pregnancies were affected with cystic fibrosis. These couples described their feelings of devastation and grief upon receiving their test result.

> *Oh absolutely devastated. It's probably, you know, one of the most terrible, you know, results we've got.* (Helena).
>
> *…we were left with absolute grief.* (Delta).

The remaining four couples that received an unaffected test result expressed feelings of fortune and relief.

> *Lucky…* (Isobel).
>
> *Unbelievable relief.* (Eva).
>
> *Like crying. Yeah that was fantastic.* (Felicity).

Decision making about termination of an affected pregnancy

The two participants that received a positive test result decided to terminate their affected pregnancy. Both participants expressed the difficulty and uncertainty they felt with regard to making this decision.

> *I think that if I'd slowed time down we made a very very rushed decision because I couldn't handle having an alive, kicking around, sucking it's thumb baby in my, you know, growing inside of me… I very much got that I killed a baby… it was quite a sort of shocking process to go through.* (Helena).
>
> *Critical. It was tormenting, absolutely tormenting. We basically went through you know maybe we shouldn't maybe we should you know. My husband was actually one of the ones who said how bad can it be? We can handle it; maybe it might not have a very severe case of it. You know, as much of the medical facts that we had we were still questioning whether it was, whether aborting it or terminating it was really necessary.* (Delta).

Two participants, who terminated an affected pregnancy, raised concerns with regard to the genetic counseling they received when deciding whether or not to terminate the pregnancy.

> *It is certainly not a neutral process. I mean though they don't in particular encourage you to terminate, cause I understand that… there would be ethical or moral reasons for them to directly say that, it is indirectly implied in everything that is said across the board. From nearly, from every specialist, every genetic counselor, the language that is used, the way the condition is*

described, the impact on the families, and it is constructed as being something that you would very much want to terminate and I think that really, yeah it does then influence the way people behave in terms of terminating or not and it certainly influenced me. (Helena).

The only thing I would have said that was a little disturbing I'll say was, I know that they were trying to be quite clear about the facts of the statistics and where we fitted in at that point, and so they had this picture of a baby… it was literally just like a drawing… they showed you know this is what two healthy ones look like and then the carrier one and then I think it showed the statistic of cystic fibrosis and I remember the picture being like like this, it sounds terrible…it was like black like it was almost… looks like a burnt child or something. I would say that the probably the illustrations that went along with the counseling were a little concerning and probably a little unnecessary. I think maybe just outlining the statistics on paper in numbers would have been sufficient. (Delta).

3. Future outcomes of screening

The participants were asked about the outcomes of screening, with regard to future reproductive plans as well as informing family members of their increased risk of being a carrier of CF.

Subsequent/Future pregnancies

All participants were asked if they had any further children since having screening, and if so what reproductive decisions they made. Of the nine couples, three (n=5) have had no further children since being identified as a carrier couple. Of the remaining couples, four (n=7) utilized prenatal diagnosis for their subsequent pregnancies. Six pregnancies have occurred since screening, with one pregnancy affected, which was terminated. The participant who had the affected pregnancy regretted her decision to terminate, stating that the experience had been very traumatic for her.

We rushed the abortion through at a private clinic but I think if I had slowed down time I actually would have kept the baby. So I actually then experienced a lot of grief over that decision… it was incredibly traumatic. (Helena).

Therefore, upon conceiving her second [subsequent] child she sought further information from a CF specialist, and decided to keep the pregnancy regardless of the prenatal test result.

I think the day I got a positive pregnancy test result I saw a specialist at the (Hospital), a cystic fibrosis specialist, and I said 'I am pregnant. I think this baby could very much have cystic fibrosis. I want to keep the pregnancy. Can you tell me about cystic fibrosis?' (Helena).

One of the participants who had previously terminated an affected fetus, expressed the difficulties she faced utilizing prenatal diagnosis for her subsequent pregnancy.

> *The first pregnancy of course you're pregnant and everything is going well but the second pregnancy though, you know that things might end in twelve weeks time. So it was very hard.* (Gabrielle).

Three couples stated that they contemplated the use of pre-implantation genetic diagnosis (PGD) for future pregnancies, however one couple became pregnant naturally while the remaining two couples utilized PGD for subsequent pregnancies. One of these couples had already had an IVF pregnancy due to fertility issues, so prenatal diagnosis was not a valid reproductive option for them. The couple that elected to use PGD reported that after discussing the various options this appeared to be the best option for them.

> *We went through the options of adopting, you know, that was one option for us. There was the option of getting pregnant and doing an amnio at 4 months and then aborting, and then there was the option of IVF, which just came out as such an obvious direction for us to go.* (Chanel).

However, they expressed a number of concerns and difficulties with the PGD process, namely the cost and time associated with the process. The couple reflected that the information provided during genetic counselling did not prepare them for these issues.

Communicating genetic information to family members

When talking about the dissemination of genetic information to family members, all of the participants mentioned that they had informed at least one family member of their carrier status.

> *…we've told everyone with, like, there is a side of my family that we are sort of estranged we don't really see them, but I made the effort to get in touch with them and tell them that cause it is relevant health information for them* (Callan).

Some participants raised issues with regard to informing family members and relatives. Lack of knowledge held by family members appeared to be a barrier, with some participants stating that their family members believed they would not be carriers.

> *I think that there is a lot of misconception with them sort of saying 'oh it couldn't possibly be me.'* (Blake).

> *I think I found when I was talking to relatives they get confused because they would say but no one's had cystic fibrosis and they get confused with the carrier bit and having it…* (Felicity).

Another issue that was raised by participants in terms of family communication was the relevance of life stage of family members, with some participant's not informing family members who had finished or were not having children.

Look most of our brother's and sister's had already had kids, had sort of finished having kids so it wasn't so important to them. (Addison).

One couple had found it difficult to decide whether to inform their siblings, who were both pregnant and too far along for testing.

It was hard for us because we had… we had siblings in literally the worst position because they were pregnant and it was too late to do anything about it. So that was particularly difficult in terms of being the bearer of bad news. (Callan).

4. Concerns with regard to CF carrier screening program

All participants were asked to add any comments about the program or the offering of screening for CF carrier status.

Lack of awareness of CF

The main concern mentioned by the participants was lack of awareness of CF and CF carrier screening in the population.

No one's aware and even to this day if I speak to people about it… I've got a girlfriend at the moment that's trying to fall pregnant, I said make sure you do the CF… no one knows. Even in the private sector they don't. She is through IVF and they haven't spoken about it once. (Isobel).

No I think it just really needs to be put in people's faces. In their face, absolute confrontation, you know pamphlets, pictures, it has to go in there with the leaflets of you know, don't eat brie when you're pregnant, you know what I mean. It has to be in there alongside it. (Delta).

Accessibility to program

One participant voiced concerns about the accessibility of the current program. Particularly concerning couples not being offered screening and later being identified as carriers after the birth of a child with CF.

So I'd hate to sort of think that the families that the first time they know about this is when you get the results back say 'oh look we found this and by the way we had a service that can be offered which you didn't get access to.' You would be furious. (Blake).

Utility of screening information for reproductive planning and decision-making

Another participant discussed the willingness of carrier couples to use the information obtained from screening to make reproductive decisions.

I do think I think testing being more universal, more widely available, preferably universally available, but testing has to be coupled, for it to be useful, testing has to be coupled with action.

> *In terms of what people will do with that information because unless people are prepared to not have kids as a result of it then in fact there is no point in having the testing, you know. It has got to be coupled with a willingness to act on the results of the test.* (Callan).

Discussion

This qualitative study is the first to explore the experiences of couples who are both identified as carriers of CF through population screening. This study provides valuable information that can be used to assist with implementation and development of CF carrier screening programs, specifically with regard to the provision of counseling and support.

Couples were most commonly offered screening by their obstetrician, with the majority being pregnant at the time of receiving the offer. It is generally agreed that the best time to offer screening is before pregnancy, as it provides the couple with the most reproductive options (Ioannou et al. 2010; Decruyenaere et al. 1992; Green 1992; Magnay et al. 1992). However, preconception carrier screening has been associated with various barriers including the absence of a preconception health care setting and lack of interest of individuals and/or couples at this life stage (Poppelaars et al. 2003; Henneman et al. 2003; McClaren et al. 2008). The three couples in our study who were offered screening preconceptionally perceived that they were at increased risk due to ethnicity and genetic concerns relating to miscarriage and chromosomal abnormalities.

While some participants were satisfied with their doctor's explanation with regard to CF and CF screening, the majority of participants reported that their doctor provided them with little if any information about the nature of the condition or the screening process prior to screening. Health professional lack of knowledge and experience with regard to CF and genetic screening has previously been identified as a barrier in CF carrier screening programs, with many reporting that they did not have confidence in their ability to provide screening to their patients (Qureshi et al. 2006; Morgan et al. 2004a; Morgan et al. 2004b; Rowley et al. 1993). Mennie and colleagues also found a gap in the knowledge of health professionals, with only a small number of GPs believing CF carrier screening should be offered to those without a family history (1998).

Prior knowledge of CF was relatively poor amongst the study participants. Four of the participants had prior knowledge of CF, due to knowing someone with the condition or working in an area related to CF, but the remaining participants had no knowledge of CF other than having previously heard the name of the condition and knowing that it is inherited. Knowledge of CF and screening has been shown to be low prior to screening, when making the decision in regards to having screening, but improves once having been screened (Durfy et al. 1994; Grody et al. 1997;

Cobb et al. 1991). A potential reason for the increase in knowledge, from before to after screening, may be the perceived relevance of that information, particularly if found to be a carrier. Provision of post-test counseling is likely to also improve knowledge, with carriers usually receiving more follow-up than non-carriers (Ioannou et al. 2010). Knowledge of CF and CF screening has been shown to be an important factor in the decision about whether to have screening, with those who decline screening having lower knowledge than those who accept screening (Henneman et al. 2001b; Ioannou et al. 2012).

Factors that influenced the couple's decisions to accept an offer of screening included a desire to avoid the birth of a child with CF, high perceived severity of the disease and/or a high-perceived susceptibility due to ethnicity and age. This resonates with findings from other studies that have shown the main factors associated with accepting an offer of screening are: high perceived severity of disease, high perceived susceptibility and to avoid having a child with CF (Henneman et al. 2003; Ioannou et al. 2010; Delvaux et al. 2001; Henneman et al. 2001b). Participants also mentioned a doctor's recommendation as a factor that influenced their decision to have screening and this is supported by a number of other studies (Ioannou et al. 2010; McClaren et al. 2008; Loader et al. 1996; Hall et al. 2006). While all of the couples accepted the offer of screening despite the cost of the test, two couples described the cost as a significant issue in their decision to have screening and the remaining couples felt the cost could be a barrier to other couples. Previously, studies involving the GHSV CF carrier screening program have shown that cost was not an influencing factor in the decision to accept or decline the offer (Ioannou et al. 2010) [Ioannou et al. 2012 Submitted]. However, reports from other screening programs suggest that the cost of screening is a significant factor in the decision whether to have screening (Barlow-Stewart et al. 2003; Durfy et al. 1994). This discrepancy may reflect the private health setting in which the screening was offered in the GHSV program, where individuals tend to be better educated and have a higher household income than those in the public health system (data not shown).

Population-based screening tests involve individuals and/or couples who are not at increased risk of being a carrier due to a family history of the condition, and therefore may not expect to receive a positive test result. All participants described their feeling of shock and concern, first upon learning their own carrier status, and secondly when the second member of the couple was found to be a carrier, as many had not believed their partner would also be found to be a carrier. Henneman and colleagues had similar findings with couples reporting that they were shocked as

they did not expect to both be identified as carriers of CF (2002). This has also been shown in studies exploring the feelings of women who receive a high risk ultrasound screening result for chromosomal abnormalities, with the majority of women perceiving the scan as a social, non-medical event and are unprepared for a positive result (Baillie et al. 2000).

Prenatal diagnosis was considered to be the 'next step' for the majority of couples with only one stating that the decision was difficult. Six couples were pregnant at the time of screening and all had decided to have prenatal diagnosis. Two women were found to have a fetus affected by CF and expressed feelings of devastation and grief. Studies have shown that the majority of carrier couples identified through population-based carrier screening for CF utilize prenatal diagnosis and terminate an affected fetus (Massie et al. 2009; Clausen et al. 1996; Schwartz et al. 1993; Brock et al. 1996).

Reproductive behaviour of carrier couples identified through newborn screening have shown that the majority of carrier couples either had no further children or used prenatal diagnosis for future pregnancies (Sawyer et al. 2006; Dudding et al. 2000). This was supported in the current study, with three of the couples deciding to have no further children, four utilizing prenatal diagnosis and two undergoing preimplantation genetic diagnosis, for subsequent pregnancies. Of the two couples that utilized preimplantation genetic diagnosis, one of the couples had infertility problems and could not conceive naturally. One of the participants in the current study who utilized prenatal diagnosis for two subsequent pregnancies, changed her mind with regard to pregnancy termination after her first pregnancy stating she regretted terminating her affected pregnancy.

Genetic counselling is a neutral non-directive process that facilitates reproductive decision making taking into account personal, moral, social, religious and ethical considerations (Resta et al. 2006). Participants raised several issues in regard to the genetic counseling process. Two couples who had terminated an affected pregnancy felt that the genetic counseling process subtly encouraged termination of an affected fetus through language and illustrations. A study of carrier couples, identified as a result of a family history of CF or having had an affected child, found that a majority of couples perceived genetic counseling to leave them with no other option than to refrain from having children (Frets et al. 1991).

One couple expressed surprise at their perception that the genetic counseling process actually discouraged them from continuing with their reproductive plans. An inevitable outcome of population screening for CF is a reduced incidence of the condition due to the majority of carrier

couples utilizing prenatal diagnosis and terminating affected fetuses. This has been shown in Massachusetts, USA, where the number of infants with CF identified by newborn screening decreased since the implementation of population CF carrier screening (Hale et al. 2008).

Cascade testing as a result of dissemination of information from carriers to family members is an important outcome of screening. The majority of carrier couples informed family members of their increased risk, with parents and siblings being the most likely to be informed. The main reason for not informing family members were if they were not having (further) children. There were some issues with regard to the dissemination of information to family members including lack of knowledge about CF of family members and pregnancy gestation. Studies have shown that dissemination is high with the most frequently informed being parents and siblings (Ioannou et al. 2010; Delvaux et al. 2001; Watson et al. 1992; Boulton et al. 1996). A recent study showed that only about 11% of close relatives of individuals with CF have carrier screening (McClaren et al. 2010).

A lack of awareness by the general population with regard to CF and screening was a common concern for these study participants. Participants commonly mentioned the lack of awareness held by the population with regard to CF and screening. In order to increase informed decision making in the community in relation to CF carrier screening, people need to be informed about cystic fibrosis and made aware of the availability of screening. Many participants compared the importance of screening for CF carrier status to Down syndrome screening and believe that CF carrier screening should be implemented into routine practice to ensure all couples are offered testing.

The current program is inequitable, with pregnant women and couples in the public health system not receiving an offer of screening. This was raised as a concern by one of the participants, as newborn screening for CF is performed on all newborns identifying couples as carriers after the birth of a child with the disease and thus preventing them from utilizing the reproductive options that would have been available had they been offered screening pre-pregnancy. In order to ensure equity of access, CF carrier screening needs to be offered to all pregnant women and couples planning a pregnancy, in both the public and private health systems. In an ideal situation, this would also be free of charge.

Since the implementation of the GHSV CF carrier screening program in 2006, only a small percentage of the population has been screened due to screening only being offered in the private health system and not all health professionals offering screening to their patients. The limited

number of individuals who have been screened has resulted in only a small number of carrier couples being identified. Therefore a limitation of the study was the small sample size restricting the generalizability of these findings. In addition, the former male partner's of both couples that divorced since screening declined to participate in the study, preventing their experiences from being heard.

In conclusion, carrier couples were generally satisfied with program and service provided, changed their reproductive behaviour as a result of their carrier status and informed family members of their increased risk. Nevertheless, improvements to the program should include better pre-test information and very clear advice to carrier couples identified during pregnancy that not having prenatal diagnosis and not terminating an affected fetus are valid options.

Abbreviations:

CF: Cystic fibrosis

GHSV: Genetic Health Services Victoria

PND: Prenatal diagnosis

TOP: Termination of pregnancy

PGD: Preimplantation genetic diagnosis

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Supplementary Information:

Appendix F: Interview schedule

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Table 1. Summary of screening outcomes for carrier couples identified through the GHSV program 2006-2010

Carrier Couple	Year Tested	Year Interviewed	Previous children	Preg. Status	PND?	PND Result	TOP	Future Outcomes
1. Helena	2007	2011	2	N	N/A		N/A	**PND**: Affected - TOP; Unaffected - no TOP
2. Isobel	2006	2011	2	Y	CVS	Carrier	N	**No further children**
3. Aaron and Addison	2006	2012	1	Y	CVS	Carrier	N	**No further children**
4. Blake and Bella	2007	2012	-	Y	CVS	Non-Carrier	N	**PND**: Unaffected - no TOP
5. Callan and Chanel	2008	2011	-	N	N/A		N/A	**PGD**: Currently in the process of PGD for second child
6. Daniel and Delta	2008	2011	-	Y-IVF	CVS	Affected	Y	**PGD**: One child
7. Edward and Eva	2008	2012	-	N	N/A		N/A	**PND**: 2 Unaffected - no TOP - carrier and non-carrier
8. Fynn and Felicity	2009	2011	1	Y	CVS	Non-Carrier	N	**No further children**
9. Garrett and Gabrielle	2009	2012	-	Y	CVS	Affected	Y	**PND**: Unaffected - no TOP

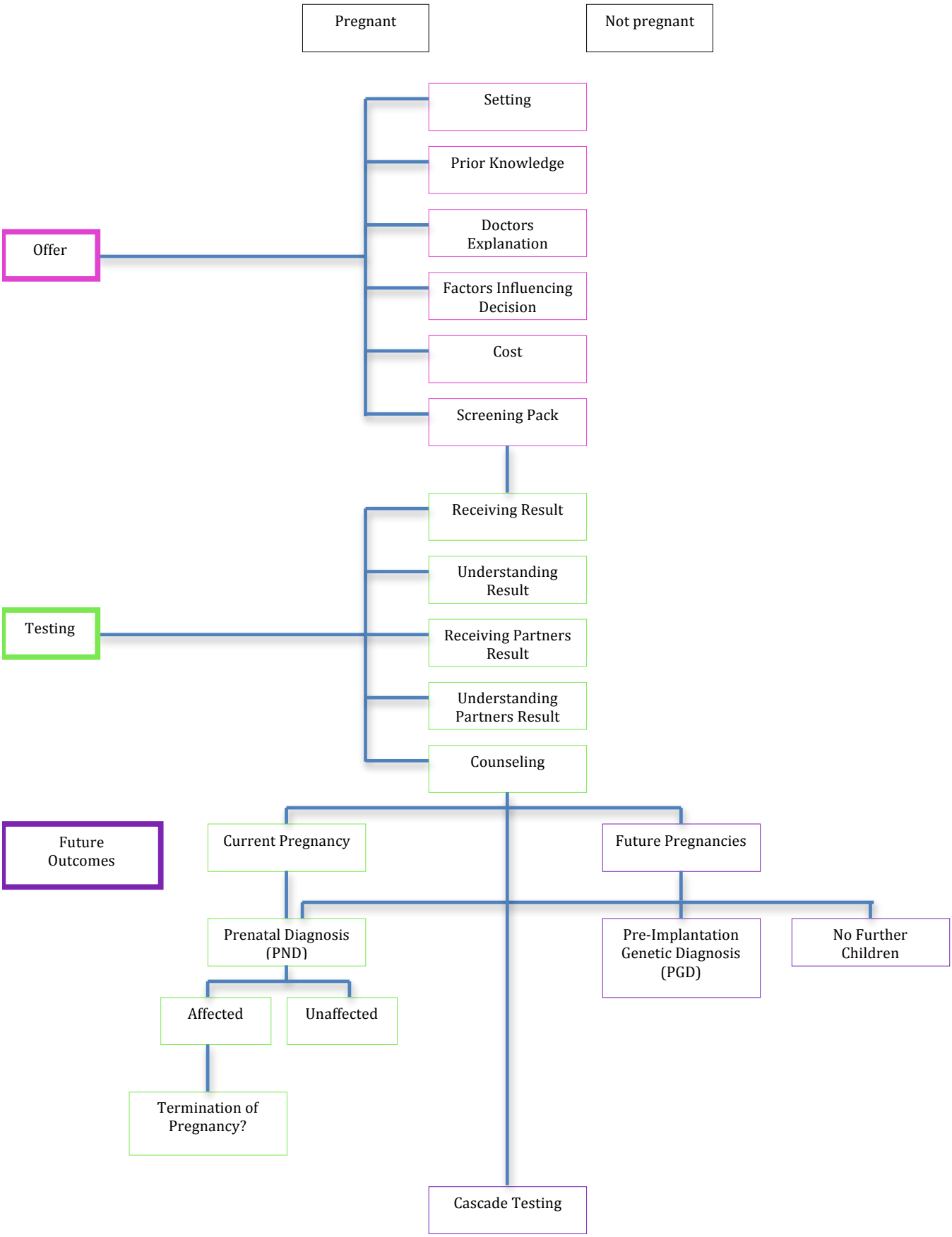


Figure 1. Flow chart of themes arising from interviews with CF carrier couples

6.5 Questionnaire-based study

The aims of this study were to explore the attitudes and outcomes of screening for carriers whose partners were also identified as carriers (carrier couples), and compare them to the attitudes and outcomes of screening for carriers whose partners were not identified as carriers (carriers) and those who were not identified as carriers (non-carriers).

6.5.1 Methodology

Participants

All 10 carrier couples identified through the program, from 2006-2010, were invited to participate in the study. Couples were given a participant information sheet (Appendix A) and questionnaire (Appendix B) at the time of their interview. They were asked to complete the same questionnaire as that in the previous study of carriers and non-carriers so that direct comparison could be made.[92] Two couples were divorced and both male partners declined to participate in an interview. These male partners were invited to complete the questionnaire via post. A reminder letter was sent approximately two weeks after receipt of the questionnaire.

Questionnaire

The questionnaire explored the following domains: demographic variables, knowledge of CF, anxiety levels at the time of completing the questionnaire, reasons for participating in screening, recollection of carrier test result and meaning of carrier status.

There were 15 statements regarding knowledge about CF and carrier screening requiring one of three responses; true, false or unsure. Answers were scored as being correct or incorrect, with unsure being scored as incorrect. The total knowledge score for each participant was calculated as the sum of correct responses. The anxiety scale used in the questionnaire was the validated, short version of the State Trait Anxiety Inventory (STAI).[93]

The questionnaire was returned in a reply-paid envelope. A study number was used to identify questionnaires allowing reminder letters to be sent to non-respondents. If the questionnaire was not returned after one reminder no further contact was made.

Comparison group

The results of the current study of carrier couples were compared the

previous study of people accepting an offer of screening, undertaken in my Honour's year, as described earlier. This study included 47 carriers and 65 non-carriers.[1]

Data analysis

Data analysis of questionnaires was conducted using SPSS (Windows, version 17.0; SPSS Inc., Chicago, IL). Preliminary descriptive analysis generated frequency data to elicit a description of participants.

Potential factors influencing the decision to have screening were measured on 5-point Likert scales. For analysis, points '1' and '2' were combined to form the category "did not influence", the middle point '3' remained neutral, while points '4' and '5' were combined to form the category "influenced".

The data from the current study of carrier couples were compared with data from the previous study evaluating the attitudes and outcomes for carriers and non-carriers.[1] Analysis of categorical variables was undertaken using χ^2 analyses and, for continuous variables, differences in means between groups were assessed using t-tests. A p-value <0.05 was considered statistically significant.

Ethics committee approval

This study was approved by the Human Research Ethics Committee of the Department of Human Services, Victoria, Australia (HREC 15/05).

6.5.2 Results

Response rate

Of the 10 carrier couples identified (20 individuals), one couple (two individuals) and two male partners declined to participate in the study while the remainder were sent questionnaires to be completed. Of the 16 questionnaires distributed a total of 12 completed questionnaires were received, resulting in a 75% response rate.

Demographics

All 12 participants were over the age of 35 years, with six (50%) having a university degree and eight (66.7%) earning household income of more than $100,000 per annum (Table 3). There were no significant differences between carrier couples, carriers and non-carriers with regard to demographics, with the exception of gender where there were a higher number of males (50%) in the carrier couples compared to carriers (6.4%) and non-carriers (0%).

Table 3. Demographics of participants who were offered screening through the GHSV CF carrier screening program.

Demographic	Categories	No. of Participants (%)			
		Carrier Couples n=12	Carriers n=47	Non-Carriers n=65	Significance (χ^2)
Gender	Male	6 (50.0)	3 (6.4)	0 (0.0)	10.69
	Female	6 (50.0)	44 (93.6)	65 (100.0)	*p<0.01
Age (in years)	25-29	0 (0.0)	2 (4.3)	7 (11.3)	5.23 (df=3)
	30-34	0 (0.0)	17 (36.2)	15 (24.2)	p=0.16
	35-39	6 (50.0)	21 (44.7)	33 (53.2)	
	40+	6 (50.0)	7 (14.9)	7 (11.3)	
Highest completed level of education	Secondary/Trade/Apprenticeship	4 (33.4)	3 (6.5)	7 (11.5)	1.29 (df=3)
	College certificate or diploma	1 (8.3)	11 (23.9)	9 (14.8)	p=0.73
	University degree	6 (50.0)	31 (67.4)	44 (72.1)	
	Other	1 (8.3)	1 (2.2)	1 (1.6)	
Occupation	Managerial	6 (50.0)	16 (34.8)	14 (23.0)	6.93 (df=4)
	Professional	3 (25.0)	16 (34.8)	30 (49.2)	p=0.14
	Office Duties	0 (0.0)	4 (8.7)	9 (14.8)	
	Skilled/Trades	2 (16.7)	9 (19.6)	7 (11.5)	
	Unskilled	1 (8.3)	0 (0.0)	1 (1.6)	
Household Income (in AUD$1000s)	<60	0 (0.0)	4 (8.7)	14 (23.7)	6.07 (df=3)
	61-80	2 (16.7)	3 (6.5)	7 (11.8)	p=0.11
	81-100	2 (16.7)	7 (15.2)	7 (11.8)	
	>100	8 (66.7)	33 (71.7)	37 (62.7)	
Ethnicity	Australian	4 (33.4)	29 (61.7)	33 (53.2)	5.33 (df=3)
	North European	2 (16.7)	14 (29.8)	14 (22.6)	P=0.26
	South European	2 (16.7)	2 (4.3)	11 (17.7)	
	West European	2 (16.7)	0 (0.0)	0 (0.0)	
	Other	2 (16.7)	2 (4.2)	4 (6.5)	
Affinity with a Religion	Yes	6 (50.0)	14 (30.4)	31 (50.0)	2.95
	No	6 (50.0)	32 (69.6)	31 (50.0)	p=0.09
Partner at time of testing	Yes	12 (100.0)	46 (97.9)	61 (98.4)	0.00
	No	0 (0.0)	1 (2.1)	1 (1.6)	p=0.97
Pregnant at time of testing	Yes	10 (83.3)	38 (80.9)	52 (83.9)	0.13
	No	2 (16.7)	9 (19.1)	10 (16.1)	p=0.72
Number of children at time of testing	0	4 (33.3)	14(29.8)	17 (27.9)	1.61 (df=3)
	1	8 (66.7)	23 (48.9)	28 (45.9)	p=0.66
	2	0 (0.0)	8 (17.0)	12 (19.7)	
	3 or more	0 (0.0)	2 (4.3)	4 (1.6)	

Note: for comparison purposes carrier couple group and carrier group were combined.

Note: * p<0.05 for comparison of proportions in carriers versus non-carriers using χ^2 test.

Factors influencing the decision to have CF screening

The main reasons stated by carrier couples for having screening were perceived severity of CF and doctor's recommendation, while lack of a family history of CF or other genetic conditions was not an influencing factor for any of the couples (Figure 4). There is no significant difference between the three groups for factors that influenced the decision to accept screening.

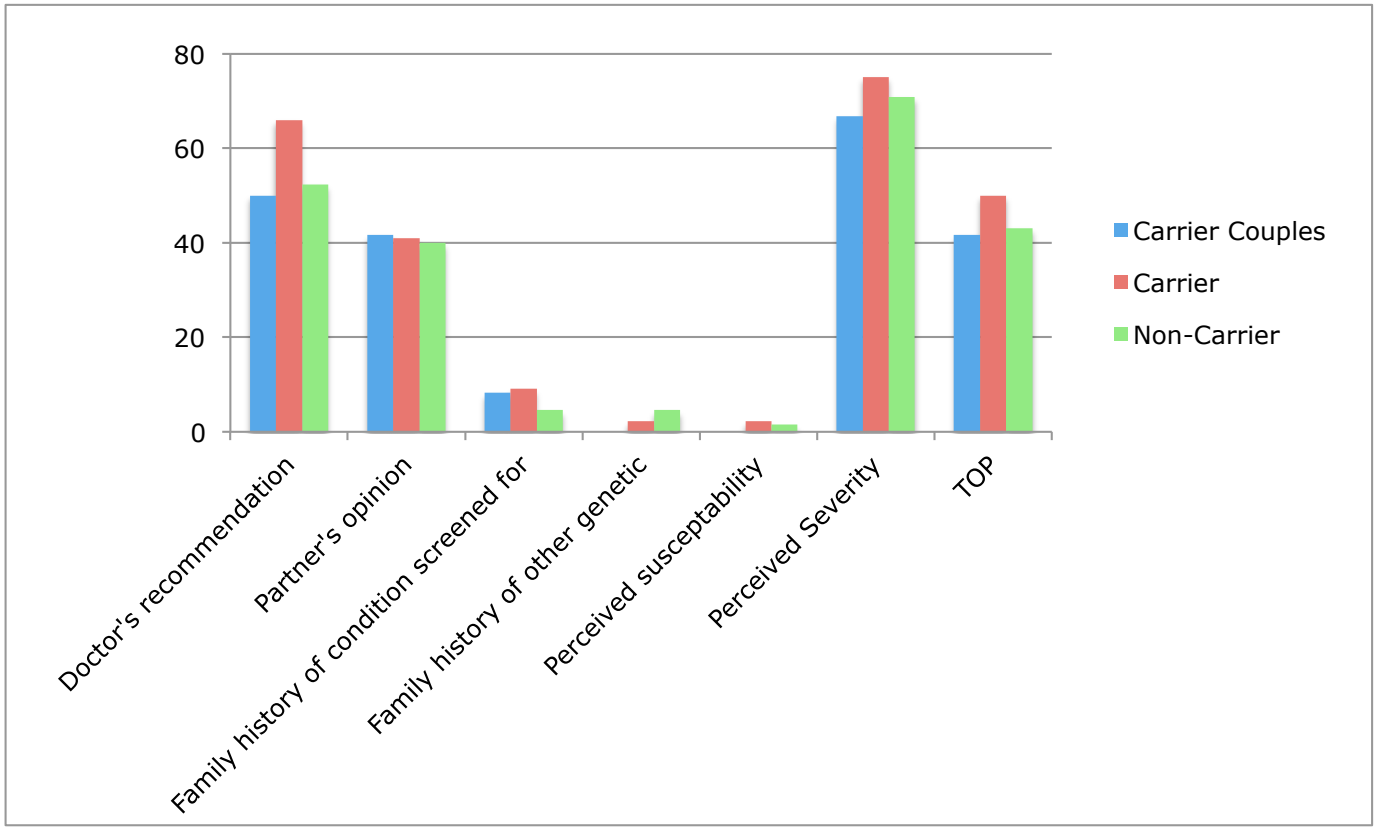


Figure 4. Comparison of factors that influenced the decision to have CF carrier screening between those who were identified as carrier couples and those who were identified as carriers and non-carriers

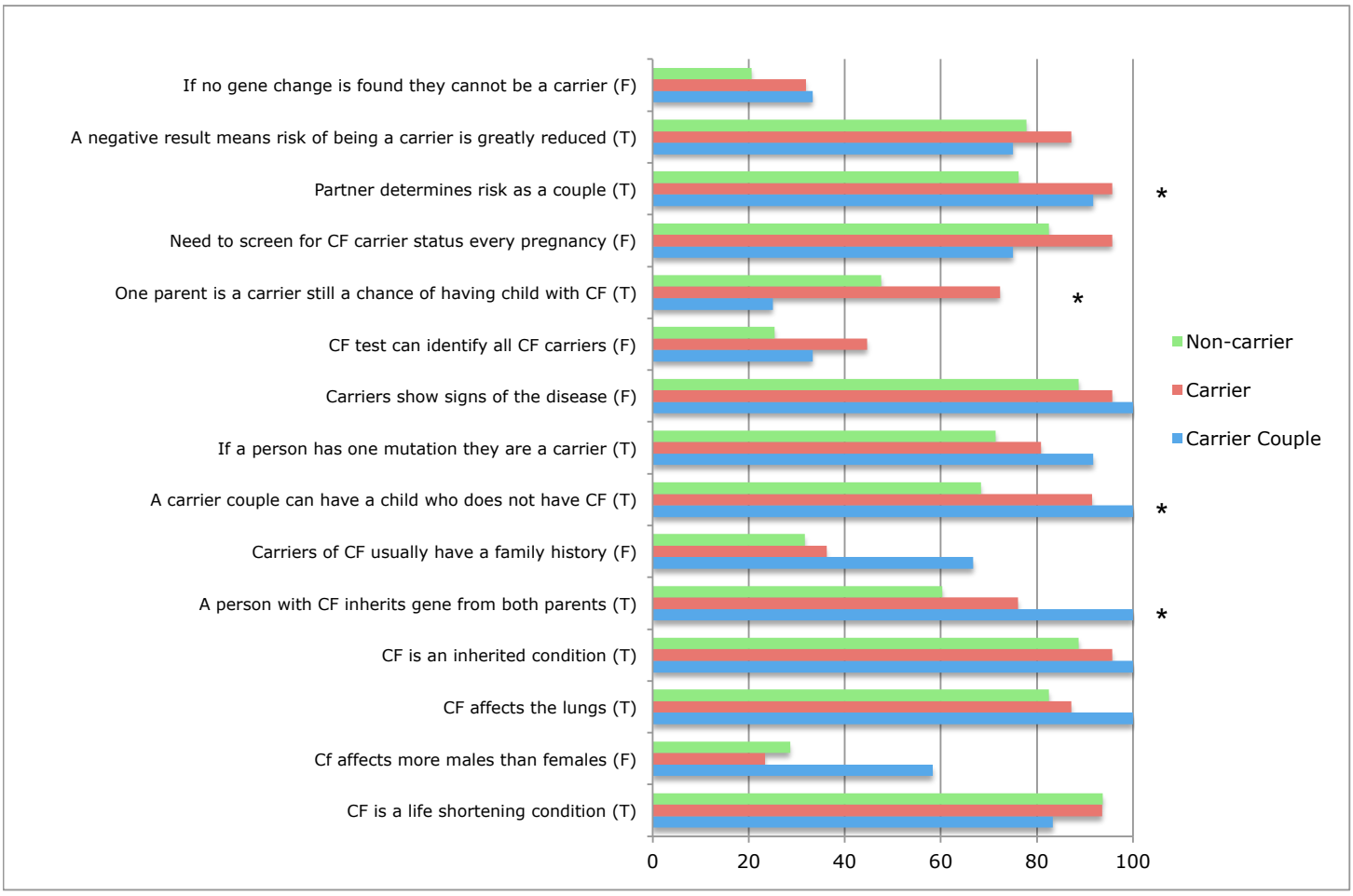
Knowledge of CF and screening

Participants were asked to select true/false/unsure as a response to 15 knowledge statements regarding CF and carrier screening. Nine of the participants (75%) answered between 11 to 15 of the 15 knowledge statements correctly.

When comparing knowledge between carrier couples, carriers and non-carriers, there was a significant difference in the number of correct responses for four of the 15 knowledge questions (Figure 5). Two of these were answered correctly more often by carriers: partner determines risk as a couple ($\chi^2 = 8.81$, $p<0.01$) and if one parent is a carrier there is still a chance of having a child with

CF (χ^2 = 12.46, p<0.01). The other two by contrast were answered correctly more often by carrier couples: a carrier couple can have a child who does not have CF (χ^2 = 11.46, p<0.01) and a person with CF inherits the gene from both parents (χ^2 = 8.81, p<0.01).

An independent samples t-test was conducted and it was found that there was no difference in total knowledge scores between carriers and carrier couples (t=0.36, p=0.72).



Note: *p<0.01 for comparison of proportions in current versus previous study using χ^2 test

Figure 5. Comparison of knowledge of those who were identified as carrier couples and those who were identified as carriers and non-carriers

Knowledge of carrier status

All 12 individuals correctly recalled their carrier screening result as well as their partner's. Participants were asked in an open-ended question to explain their CF carrier screening test result with respect to their risk of having a child with CF. Six (50%) individuals responded that their risk of having a child with CF was 1 in 4, while 4 (33%) stated that they had an increased or high risk of having

a child with the CF. The remaining individual stated that their risk of having a child with CF was dependent on their partner's test result.

Anxiety

There was no significant difference for anxiety scores in carrier couples compared to carriers or non-carriers (Median STAI scores were 33, 33 and 30 respectively).

Attitudes towards CF screening

The attitudes of carrier couples towards screening are displayed in Table 4. All carrier couples would still have CF carrier screening if they had their time again and believe that the best time to offer screening is before pregnancy. Eleven (91.7%) individuals recommended CF carrier screening to others.

All groups; carrier couples (100%), carriers (98%), and non-carriers (87%), believed that the best time to offer screening for CF carrier status was before pregnancy. More carrier couples (92%) and carriers (94%) recommended CF carrier screening to others compared to non-carriers (41%). The majority of carrier couples (100%), carriers (96%) and non-carriers (97%) would still have CF carrier screening if they had their time again.

Table 4. Attitudes of carrier couples, carriers and non-carriers towards CF carrier screening

	Categories	No. of Participants (%)		
		Carrier Couples n=12	**Carriers n=47**	**Non-Carriers n=65**
Best time to offer	Before pregnancy	12 (100.0)	46 (98.0)	53 (87.0)
	During pregnancy	0 (0.0)	0 (0.0)	4 (6.5)
	Unsure	0 (0.0)	4 (6.5)	4 (6.5)
Recommend to others	Yes	11 (91.7)	44 (94.0)	26 (41.0)
	No	1 (8.3)	3 (6.0)	37 (58.0)
	Unsure	0 (0.0)	0 (0.0)	1 (1.0)
If had time again would do again	Yes	12 (100.0)	45 (96.0)	61 (97.0)
	No	0 (0.0)	1 (2.0)	1 (1.5)
	Unsure	0 (0.0)	1 (2.0)	1 (1.5)

Note: n = Number of actual responses provided, as not all questions were answered by all participants

Cascade testing

Eleven (91.7%) individuals informed family members of their result, with 10 (83.3%) recommending their family members have screening. Six individuals (50%) reported that they had family members who have been tested, while three (25%) were unsure.

6.5.3 Conclusion

The difference in gender between carrier couples, carriers and non-carriers is due to the stepwise process of testing where one partner in the couple, most commonly female, is tested first and if found to be a carrier then their partner is tested. Carrier couples have high knowledge of CF and screening. While there is no difference in knowledge between carriers and carrier couples, both groups had a significantly higher knowledge level than non-carriers. This is most likely due to the post-test counselling received by carriers.

The main reasons for accepting an offer of CF screening were perceived severity of CF and doctor's recommendation. All carrier couples correctly recalled and understood the meaning of their carrier status as well as their partner's result. There was no difference in anxiety between carrier couples, carriers and non-carriers at the time of completing the questionnaire. Therefore, if anxiety was present in carrier couples and/or carriers it appears to be transient.

It is important to note that this study is underpowered in terms of identifying significant differences between the carrier couple group and the carrier and non-carrier group, since the number in the carrier couple group is small with only a maximum of 20 members of carrier couples to survey.

In conclusion, carrier couples undertaking screening through the GHSV program have a good level of knowledge and don't appear to have any residual anxiety. Those who accept an offer of screening generally are well educated and from a high-income group, which may influence knowledge acquisition and retention. Carrier couples have a positive attitude toward screening as evidenced by their recommendations to family members and others. This has important implications for a more widespread offer of carrier screening in the population.

Chapter 7

Declined CF Carrier Screening

7.1 Declaration

Declaration by candidate

In the case of Chapter 7, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Conception and design of study; attainment of ethics approval and on going reporting requirements; questionnaire development; participant requirement; data collection, analysis and interpretation; writing of manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**
A/Prof John Massie	Contributed to design of study; assisted with development of questionnaire; interpretation of data; discussion of ideas expressed in and critical revision of manuscript
Dr Sharon Lewis	Contributed to design of study; assisted with development of questionnaire; assisted with data analysis; interpretation of data; discussion of ideas expressed in and critical revision of manuscript
Dr Belinda McClaren	Previous study; critical revision of manuscript
Dr Veronica Collins	Previous study; critical revision of manuscript
Prof Martin Delatycki	Contributed to design of study; assisted with development of questionnaire; interpretation of data; discussion of ideas expressed in and critical revision of manuscript

Candidate's Signature		**Date** 20/02/13

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Murdoch Childrens Research Institute

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]		1/3/13
Signature 2			1/3/13
Signature 3			1/3/13
Signature 4			3/3/13
Signature 5			1/3/13

7.2 Paper preamble

This Chapter explores the opinions and attitudes of pregnant women in the private health system that declined an offer of cystic fibrosis carrier screening. The paper is currently under review at the Journal of Community Genetics. The paper is preceded by an expansion of the methodology, to include further detail on recruitment.

In the previous study the outcomes of screening were explored for carrier couples as well as carriers and non-carriers (previous study). As stated in Chapter 6 it was evident that the main reason for accepting screening was the perception that CF is a severe disease, that carrier couples and carriers had a higher knowledge of CF and CF screening compared to non-carriers, high recollection of carrier status and low anxiety. In order to evaluate the program it was considered necessary to explore the views of those who had been offered screening and declined it, and to compare them to those who accepted the offer.

7.3 Expanded methodology

Between December 2009 and October 2010, pregnant women under 16 weeks gestation were recruited at two private ultrasound clinics in Melbourne. Women were approached in the waiting room and invited to participate in the study if they had declined a direct offer of cystic fibrosis carrier screening. Participation in the study involved the completion of questionnaire (Appendix B), which was given to participants with a participation information sheet (Appendix A), while they waited for their appointment. Participants could either complete the questionnaire in the waiting room and return it to the researcher or return it via a reply-paid envelope.

During this recruitment phase, field notes were recorded for all women approached, which included; age, parity, name of obstetrician, recruitment status and reason for non-recruitment. The majority of women approached were between the ages of 30-39 and were either in their first (41%) or second (45%) pregnancy (Table 5). The uptake of CF screening and questionnaire response rate of the women approached is displayed in Figure 6.

Table 5. Demographic characteristics of women approached in the waiting rooms of ultrasound clinics

Demographic	Category	% Approached
Age (in years)	<29	17.5
n=307*	30-39	79.2
	40+	2.9
Parity	0	40.6
n=308	1	44.8
	2	12.0
	3+	2.6

Note: *Data missing as one women declined to state her age.

Of the 308 women approached only 22% had been offered screening for CF. This made recruitment at these sites difficult, with the majority of women approached not eligible to participate in the study. Therefore, two obstetricians who offer CF carrier screening to their patients through the GHSV program, assisted with recruitment in the study. Between July 2010 and May 2011 they invited patients to participate in the study upon declining a direct offer of screening. As they did not record the number of women who they invited to participate in the study no response rate could be calculated. Twenty-five questionnaires were received via this method, giving a total of 54 completed questionnaires.

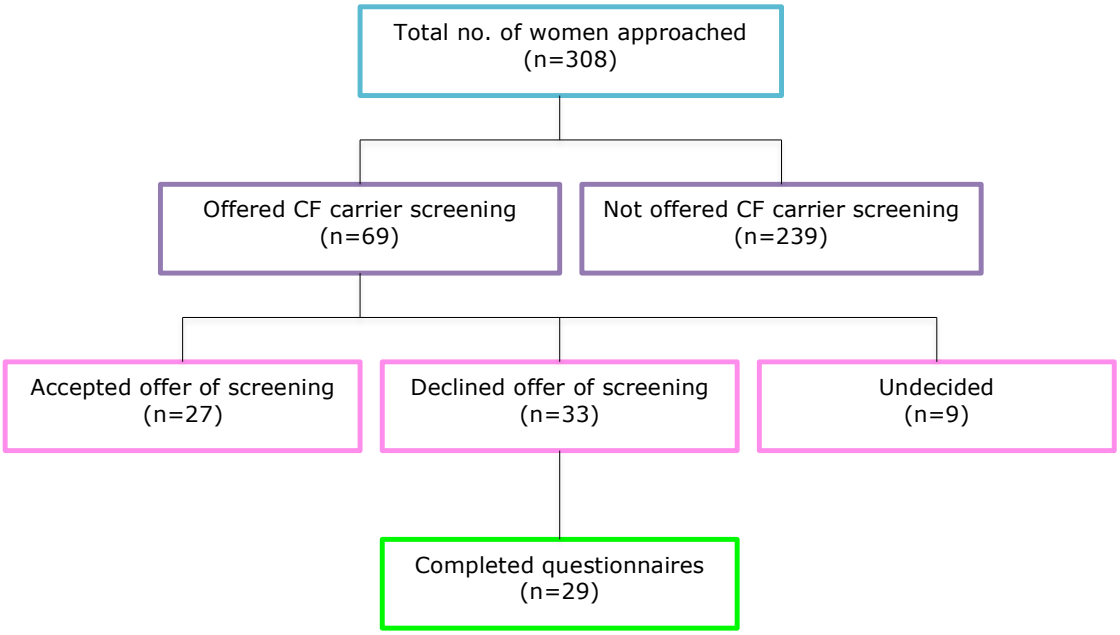


Figure 6. Uptake of CF carrier screening and questionnaire response rate amongst pregnant women recruited in the waiting room at two obstetric ultrasound clinics in Melbourne

7.4 Paper: ''No thanks'- reasons why pregnant women declined an offer of cystic fibrosis carrier screening'

'No thanks' - Why pregnant women choose not to have cystic fibrosis carrier screening

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Running title: Why people decline cystic fibrosis carrier screening

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Abstract

Aim

To assess attitudes and opinions of women declining the offer of cystic fibrosis (CF) carrier screening through a population-based program in Victoria, Australia.

Methods

Between December 2009 and May 2011, women declining an offer of CF carrier screening were invited to participate in a questionnaire-based study. Recruitment was at two private obstetric ultrasound clinics and two private obstetric practices in Melbourne.

Results

Of the participants (n=54), the majority were well educated (76%), aged 30-34 years (54%), with a household income of >AUD$100,000 (76%). Compared to those who accepted screening (reported in a previous study) (Ioannou et al. 2010), knowledge levels were significantly lower in participants declining screening ($t=3.32$, $p<0.01$). The main reasons for declining screening were: having no family history of CF (58%); and not considering a termination of pregnancy for CF (53%).

Conclusion

The community should be informed that most children born with autosomal-recessive conditions such as CF have no family history of the condition.

Keywords: cystic fibrosis, carrier screening, population screening, attitudes

Introduction

Cystic fibrosis (CF) is the most common, severe autosomal recessive disease in Caucasians, with about 1 in 2,500 live births affected and a carrier frequency of 1 in 25 (Southern et al. 2007). CF is characterised by chronic suppurative lung disease and pancreatic exocrine insufficiency, with a life expectancy of 30 to 40 years (Rowe et al. 2005). There is currently no cure for CF. Treatment involves time-consuming daily therapies including: chest physiotherapy, antibiotics, pancreatic enzymes, a controlled diet and lung transplantation for some (O'Sullivan & Freedman 2009).

CF results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. To date, more than 1,800 alterations have been identified with the most common mutation being p.F508del, which accounts for approximately 70% of all mutations in individuals from Northern Europe (CFTR Mutation Database 2008). Since the discovery of the gene in 1989, screening for carriers of CF has been possible.

CF carrier screening involves testing healthy, unaffected individuals or couples to determine if they are heterozygous carriers of specific *CFTR* mutations which could be inherited by their children. Screening offers couples, where both partners are carriers, reproductive choices regarding the birth of a child with CF. There are two approaches to carrier identification; cascade testing and population screening. Cascade testing is the testing of individuals who have a family history of CF and are therefore at increased risk of being a carrier. This method of testing is widely accepted and utilized worldwide. However, it has been shown that more than 95% of carriers have no family history of CF (Boulton et al. 1996). Population screening aims to educate and test as many individuals as possible regardless of whether or not they have a family history of the disease.

In 1999 the National Institutes of Health (NIH) recommended that CF carrier screening should be offered to all couples planning a pregnancy and seeking prenatal care (Grody et al. 2001). Subsequently the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) released statements supporting the availability of population carrier screening for CF, recommending that all pregnant women and couples planning a pregnancy should be offered CF screening (Grody et al. 2001). In Australia, similar recommendations were made with the Human Genetics Society of Australasia (HGSA) stating that

all pregnant couples and couples planning a pregnancy should be made aware of the availability of carrier screening for CF (Human Genetics Society of Australasia 2011).

In the state of Victoria, Australia, a population-based CF carrier screening program was implemented in 2006. The program offers screening to women and couples before or during the early stages of pregnancy via private obstetricians and general practitioners. It is currently a fee-for-service program with each test costing AUD$220. During the first three years of the program (2006-2008) 3,200 individuals were screened, all partners of carriers were screened and carrier couples used the information received to make reproductive decisions (Massie et al. 2009). In 2008 we conducted a study exploring the attitudes and outcomes of individuals who accepted CF carrier screening, excluding carrier couples, through this program (Ioannou et al. 2010). The program was found to be adequate with relatively high knowledge retention and recall of carrier status. There was no difference in the level of anxiety between carriers and non-carriers and many carriers passed on information about the risk of carrier status to other family members (Ioannou et al. 2010).

The aim of this study was to explore the attitudes of pregnant women who declined an offer of CF carrier screening and compare these to the attitudes of individuals who accepted CF carrier screening from our previous study (Ioannou et al. 2010).

Materials and Methods

The CF carrier screening program

The CF carrier screening program in Victoria, Australia, is conducted by Genetic Health Services Victoria (GHSV) and screening is offered to women and couples before or during the early stages of pregnancy by private obstetricians and general practitioners. The test screens for 12 of the most common *CFTR* mutations and is conducted using a check brush swab at a cost of AUD$220, with no government or health insurance rebate.

Participants

Participants were recruited using two different methods:

1. Women were approached in the waiting room of two private obstetric ultrasound clinics in Melbourne, Victoria. Those who had received an offer of CF carrier screening and declined the offer were invited to participate in the study.

2. Two obstetricians who have private practices and offered CF carrier screening to their patients through the GHSV program, invited patients to participate in the study upon declining a direct offer of screening.

Questionnaire

The purpose-designed questionnaire assessed the following domains: demographic variables; knowledge of CF and CF carrier screening; reasons for declining screening; satisfaction with the decision to decline screening; evaluation of carrier screening information provided; and attitude towards CF carrier screening. The knowledge questions and factors influencing the decision to decline screening were sourced from the questionnaire used in the previous study of people who accepted the offer of carrier screening, to allow for comparison (Ioannou et al. 2010). The questionnaire can be viewed at http://www.mcri.edu.au/cfscreening.

The questionnaires were completed anonymously, either in the waiting room and handed to the researcher or returned via a reply paid envelope. As details of the people who were given questionnaires to return by post were not recorded, further contact was not possible if the questionnaire was not returned.

There were 15 statements regarding knowledge about CF and carrier screening requiring one of three responses; true, false or unsure. Answers were scored as being correct or incorrect, with unsure being scored as incorrect. The total knowledge score for each participant was calculated as the sum of correct responses.

The decisional scale used in the questionnaire was the validated Decision Regret Scale (Brehaut et al. 2003).

Comparison Group

The results of the current study were compared to a previous study involving 47 carriers and 65 non-carriers, exploring the characteristics of individuals who chose to have CF carrier screening, and their attitudes towards carrier screening (Ioannou et al. 2010).

Analysis

Data analysis was conducted using SPSS (Windows, version 17.0; SPSS Inc., Chicago, IL). Preliminary descriptive analysis generated frequency data to elicit the description of participants.

Factors influencing the decision to decline screening were measured on 5-point Likert scales. For analysis, points '1' and '2' were combined to form the category "did not influence", the middle point '3' remained neutral, while points '4' and '5' were combined to form the category

"influenced". Satisfaction with the decision to decline screening was assessed according to the level of agreement with five statements (listed in Figure 4), using 5-point Likert scale responses. For analysis, points '1' and '2' were combined to form the category "agree", the middle point '3' remained neutral, while points '4' and '5' were combined to form the category "disagree".

The data from the current study of participants who declined screening were compared with data from the previous study evaluating the attitudes and outcomes for individuals who had accepted screening (Ioannou et al. 2010). Analysis of categorical variables was undertaken using χ^2 analysis and, for continuous variables, differences in means between groups were assessed using t-tests. A p-value <0.05 was considered statistically significant.

Ethics Committee Approval

This study was approved by the Human Research Ethics Committee of the Department of Human Services, Victoria, Australia (HREC 15/05).

Results

Response

Between December 2009 and May 2011, a total of 308 women were approached in the waiting room of two private obstetric ultrasound clinics, of whom only 69 (22%) had been offered CF carrier screening. Of these women 33 declined the offer of screening and were invited to participate in the study. Twenty nine completed questionnaires were received, giving a response rate of 88%.

In addition, 25 completed questionnaires were received, over a period of five months, recruited by the participating obstetricians. No response rate was able to be recorded for this method of recruiting as the number of women provided with the questionnaire was not reported. Overall, 54 completed questionnaires were received and used in the analysis.

Demographic variables

The demographic features of those who declined screening and those who accepted screening are presented in Table 1. All participants were female with 29 (54%) aged between 30 and 34 years, 41 (76%) having a university degree and 40 (76%) having an annual household income of more than AUD$100,000 per annum. All participants had a partner and were pregnant at the time of receiving the offer of CF carrier screening.

Those who declined the offer of screening were significantly younger in age, with the majority in the 30-34 age group, compared to those who accepted the offer of screening, where the majority were in the 35+ age group (χ^2=12, p<0.01, df=3).

Knowledge about cystic fibrosis and screening

Participants were asked to select a response to 15 knowledge statements regarding CF and carrier screening. Twenty five (47%) of the participants selected the correct response to 10 or more of these knowledge statements. There were five knowledge statements for which less than 50% of participants selected the correct response. These were: (i) CF affects more males than females (false); (ii) couples who have a child with CF usually have a family history of this condition (false); (iii) CF genetic test can identify all CF carriers (false); (iv) if only one partner is identified as a carrier, there is still a small chance of having a child with CF (true); and (v) if no gene change is found the person cannot be a carrier of CF (false). With the exception of knowledge statement (iv), less than 50% of participants who accepted screening selected the correct response for these statements as well (Ioannou et al. 2010).

Knowledge of CF and CF carrier screening was significantly lower in those who declined screening compared to those who accepted screening (t=3.32, p<0.01) (Figure 1).

Factors influencing the decision to decline screening

Participants were asked to rate factors that might have influenced their decision to decline CF carrier screening on a Likert scale. The factors most commonly rated as influencing the decision to decline screening were having no family history of CF and having no family history of other genetic conditions, chosen by 31 (58%) and 29 (54%) participants respectively. Believing that they would not consider a termination of pregnancy for CF was identified as an influential factor for 24 (45%) participants. Thirty-three (61%) and 46 (84%) participants, respectively, stated that their doctor's recommendation or lack of time did not influence their decision to decline screening (Figure 2).

Three factors were considered to be influential in the decision by a significantly greater proportion of those who declined screening than those who accepted screening. These were: (i) family history of CF (χ^2=83, p<0.01, df=2); (ii) family history of other genetic conditions (χ^2=79, p<0.01, df=2); and (iii) perceived susceptibility of being a carrier of CF (χ^2=43, p<0.01, df=2). Doctor's recommendation was an influencing factor more often amongst those who had screening than those who declined screening (χ^2=18, p<0.01, df=2) (Figure 3).

Twenty (37%) participants who declined screening believed that a reasonable price to pay for CF carrier testing is between AUD$50 and AUD$100 and 17 (32%) thought the test should be free. Only nine (16.7%) participants indicated that over AUD$100 is a reasonable price to pay.

Satisfaction with decision to decline screening

Participants were asked to rate their feelings in regards to their decision not to have CF carrier screening (Figure 4). Thirty-eight (72%) participants felt they had made the right decision, 30 (58%) felt their decision was a wise one and 38 (72%) stated they would make the same choice if they had to do it over again. However, seven (14%) participants felt that their decision did them a lot of harm and five (9%) regretted the choice that they made.

Pre-test Information

Forty one (76%) participants believed they had enough information to make the decision to decline screening, with 32 (60%) stating that they received the bulk of their information from their doctor. Forty (80%) participants were satisfied with the information provided with only 11 (20%) seeking further information – the main source of further information was family and friends (55%) followed by their doctor (36%). None of the participants viewed the GHSV CF carrier screening program website.

Attitude towards CF carrier screening

Thirteen (24%) participants wished to be offered testing at another time – of these, 72% stated that they would have liked to be offered testing before pregnancy. Fifty one (95%) participants believe that CF carrier screening should be available to those who wish to have it, with two participants being unsure and one stating that it should not be.

Discussion

This study explored the reasons why pregnant women chose to decline an offer of population-based CF carrier screening, and compares these to the factors that influenced women to accept screening as determined in a previous study (Ioannou et al. 2010). All participants in this study were women who were pregnant and had a partner at the time of receiving an offer for CF carrier screening. The most common reason for declining screening was a lack of family history of CF or other genetic conditions. Most participants were satisfied with the information provided, however 24% of participants wished that they had been offered screening at another

time and 95% of participants believe CF carrier screening should be available to those who wish to have it.

The majority of participants were well educated with higher than average income, reflecting the private health setting in which screening is currently offered in Victoria, Australia. Women who declined screening were significantly younger than those who accepted screening (Ioannou et al. 2010). Other studies have found that women who have had previous healthy children are less likely to accept the offer of screening (Fries et al. 2005). A study conducted in Western Australia found that individuals without children were 50% more likely to have screening than those with children (Honor et al. 2000). In our study we found no difference in the number of children between those who declined screening and those who accepted it, although having previous healthy children was chosen as an influencing factor by a significantly greater proportion of participants who declined screening than of those who accepted it.

Participants who declined screening had significantly less knowledge in relation to CF and CF screening than acceptors. Lack of knowledge appears to be a significant factor in the decision to decline screening, with the main reason for declining screening being the lack of a family history of CF or family history of other genetic conditions. However, the majority of carriers of CF and children born with CF in fact have no known family history of the condition (Boulton et al. 1996). A study from Canada had similar findings, with participants who declined screening stating that the main reason for declining screening was having no family history of CF (O'Conner & Cappelli 1999).

The current program is inequitable with the test only being offered in the private health system to those willing to pay. Reports from other screening programs suggest that the cost of screening is a significant factor in the decision whether to have screening yet this did not appear to be a major factor in our study (Durfy et al. 1994; Barlow-Stewart et al. 2003). Although the majority of participants felt that a reasonable price to pay for the test would be between AUD$50-100, the cost of the test was not stated as an influencing factor in the decision to have screening by two thirds of participants. This is most likely due to the setting in which screening is currently offered, with women in the private health system, on average, having a significantly higher household income than those in the public health system (Australian Bureau of Statistics 2012). Nevertheless it could be reasonably anticipated that if screening were free then uptake would be higher.

While education about CF and carrier status and equity of access are important factors likely to increase the uptake of CF carrier screening, many pregnant women will still choose not to have screening even if they are well informed and the test is free, as many would not consider a termination of pregnancy in the event of a CF diagnosis. While there was no significant difference in affiliation with religion between acceptors and decliners, not considering a termination of pregnancy for CF was an influencing factor in the decision to decline screening for a large proportion of participants. Similarly, another study found that non-pregnant women often cited that abortion and religious beliefs are important factors in the decision whether or not to have screening (Clayton et al. 1996). In a number of studies that explored the reasons for declining CF carrier screening, all found that a main reason for declining screening was not intending to terminate a pregnancy (Cuckle et al. 1996; Levenkron et al. 1997; Livingstone et al. 1993; Loader et al. 1996; Mennie et al. 1992).

There are a few limitations to this study. The screening program is currently only offered in the private health sector and not every obstetrician informs their patients of the availability of CF carrier screening. Participants were all sourced from relatively few obstetricians, with approximately half of the participants being recruited from a single obstetric clinic. This has implications for the results, as there would be limited variability in the way information about the test was provided to participants. The response rate for recruitment at the ultrasound clinics was 88% which is very high for this type of study, and is likely to be representative of the women who declined screening in this program, as the majority of private obstetricians offering CF carrier screening refer their patients to these clinics.

In conclusion, the main factor affecting uptake of CF screening is lack of knowledge regarding the inheritance patterns of recessive genetic conditions. In order to increase uptake of CF carrier screening and facilitate informed decision making, the program needs to focus more on informing and educating both providers and consumers and ensuring equity of access by offering the test in the public as well as the private health sector, at a lower cost.

Abbreviations

CF: Cystic Fibrosis

CFTR: Cystic fibrosis transmembrane conductance regulator

NIH: National Institute of Health

ACOG: American College of Obstetricians and Gynecologists

ACMG: American College of Medical Genetics

HGSA: Human Genetics Society of Australasia

GHSV: Genetic Health Services Victoria

Acknowledgements

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We thank Drs Andrew Ngu, Lionel Steinberg and Chester Yeoh for assistance with subject recruitment.

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Table 1. Demographics of participants who were offered screening through the GHSV CF carrier screening program.

Demographic	Categories	No. of Participants (%)		Significance
		Accepted n=112	Declined n=54	(X^2)
Gender	Male	3 (2.7)	0 (0.0)	1.47
	Female	109 (97.3)	54 (100.0)	p=0.22
Age (in years)	25-29	9 (8.2)	5 (9.3)	12.16 (df=3)
	30-34	32 (29.1)	29 (53.7)	*p=0.01
	35-39	54 (49.1)	19 (35.2)	
	40+	14 (12.7)	1 (1.9)	
Highest completed level of education	Secondary/Trade/Apprenticeship	10 (9.3)	3 (5.7)	0.89 (df=3)
	College certificate or diploma	20 (18.7)	9 (16.7)	p=0.83
	University degree	75 (70.1)	41 (75.9)	
	Other	2 (1.9)	1 (1.9)	
Occupation	Managerial	30 (28.3)	17 (32.1)	2.43 (df=4)
	Professional	46 (43.4)	22 (41.5)	p=0.66
	Office Duties	13 (12.3)	4 (7.5)	
	Skilled/Trades	16 (15.1)	8 (15.1)	
	Unskilled	1 (0.9)	2 (3.8)	
Household Income (in AUD$1000s)	<60	7 (9.6)	1 (1.9)	2.14 (df=3)
	61-80	10 (9.6)	4 (7.5)	p=0.54
	81-100	14 (13.5)	8 (15.1)	
	>100	70 (67.3)	40 (75.5)	
Ethnicity	Australian	62 (56.9)	23 (43.4)	7.37 (df=3)
	North European	28 (25.7)	11 (20.8)	P=0.06
	South European	13 (11.9)	15 (28.3)	
	Other	6 (5.5)	4 (7.5)	
Affinity with a Religion	Yes	45 (41.3)	28 (51.9)	1.51
	No	63 (58.7)	26 (48.1)	p=0.22
Partner at time of testing	Yes	107 (98.2)	54 (100.0)	1.00
	No	2 (1.8)	0 (0.0)	p=0.32
Pregnant at time of testing	Yes	90 (82.6)	54 (100.0)	10.65
	No	19 (17.4)	0 (0.0)	*p=0.00
Number of children at time of testing	0	31 (29.0)	16 (29.6)	0.28 (df=3)
	1	50 (46.7)	26 (48.1)	p=0.96
	2	20 (18.7)	10 (18.5)	
	3 or more	6 (5.6)	2 (3.7)	

Note: * $p<0.05$ for comparison of proportions in current versus previous study using χ^2 test.

Figure 1. Comparison of CF and CF screening knowledge of participants who declined and accepted screening. * $p<0.05$ for comparison of percent correct in current versus previous study using χ^2 test.

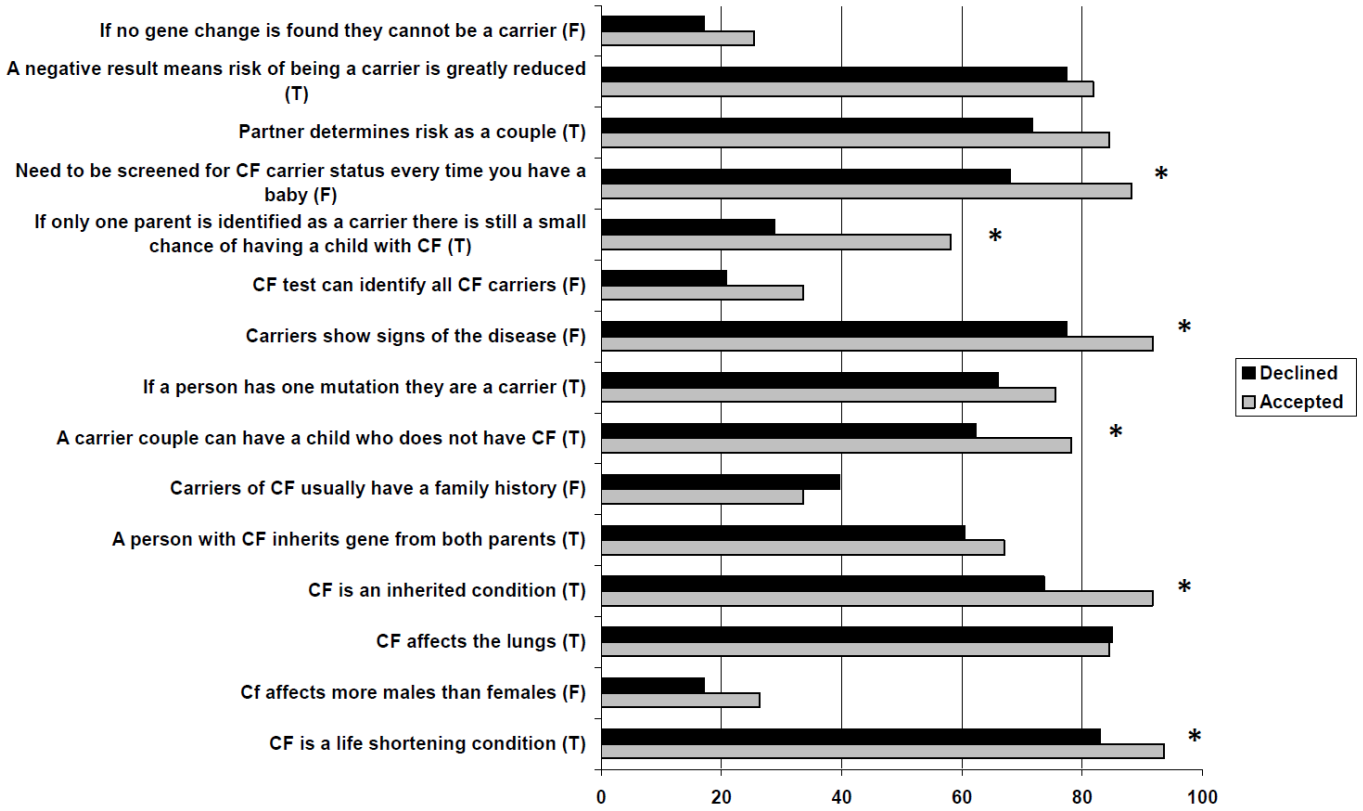


Figure 2. Influence of various factors in the decision to decline CF carrier screening

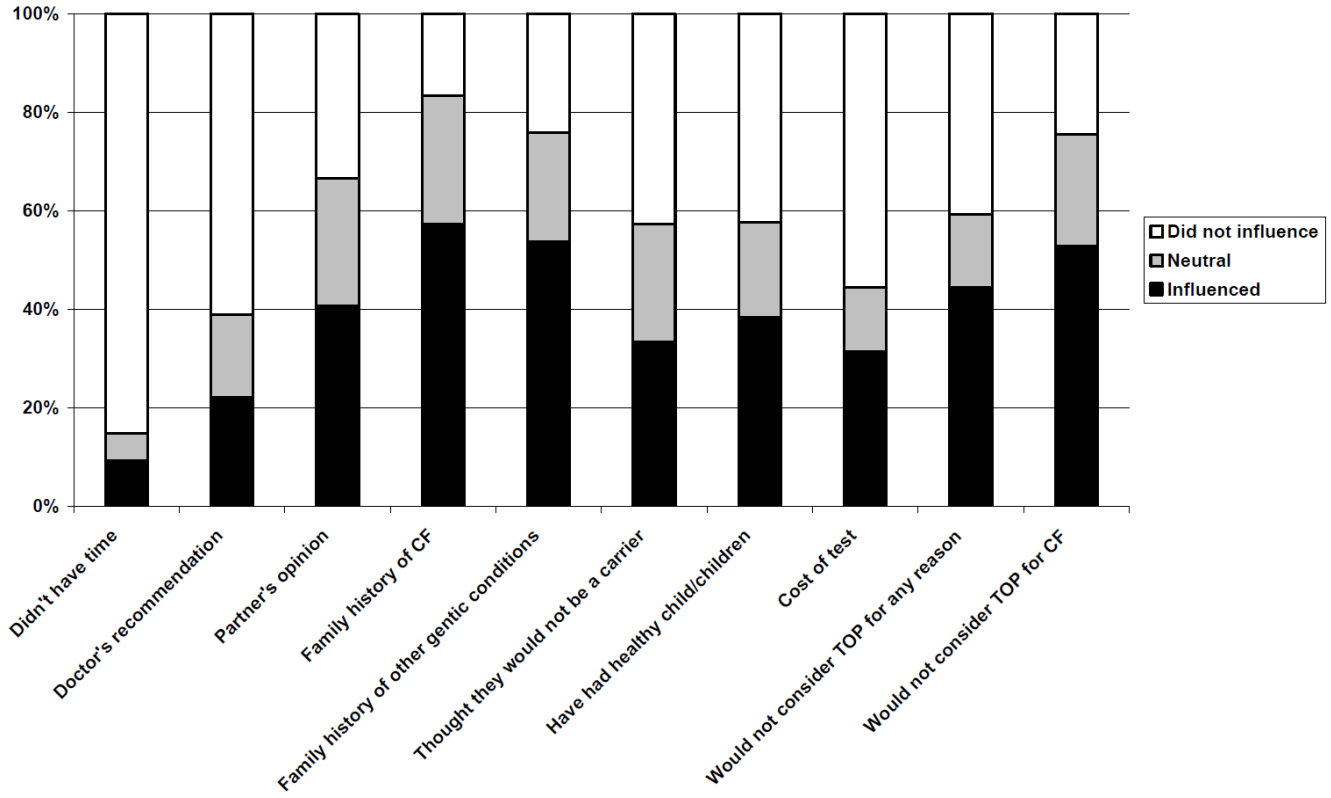


Figure 3. Comparison of factors that influenced the decision to decline or accept CF carrier screening. * $p<0.05$ for comparison of proportions in current versus previous study using χ^2 test.

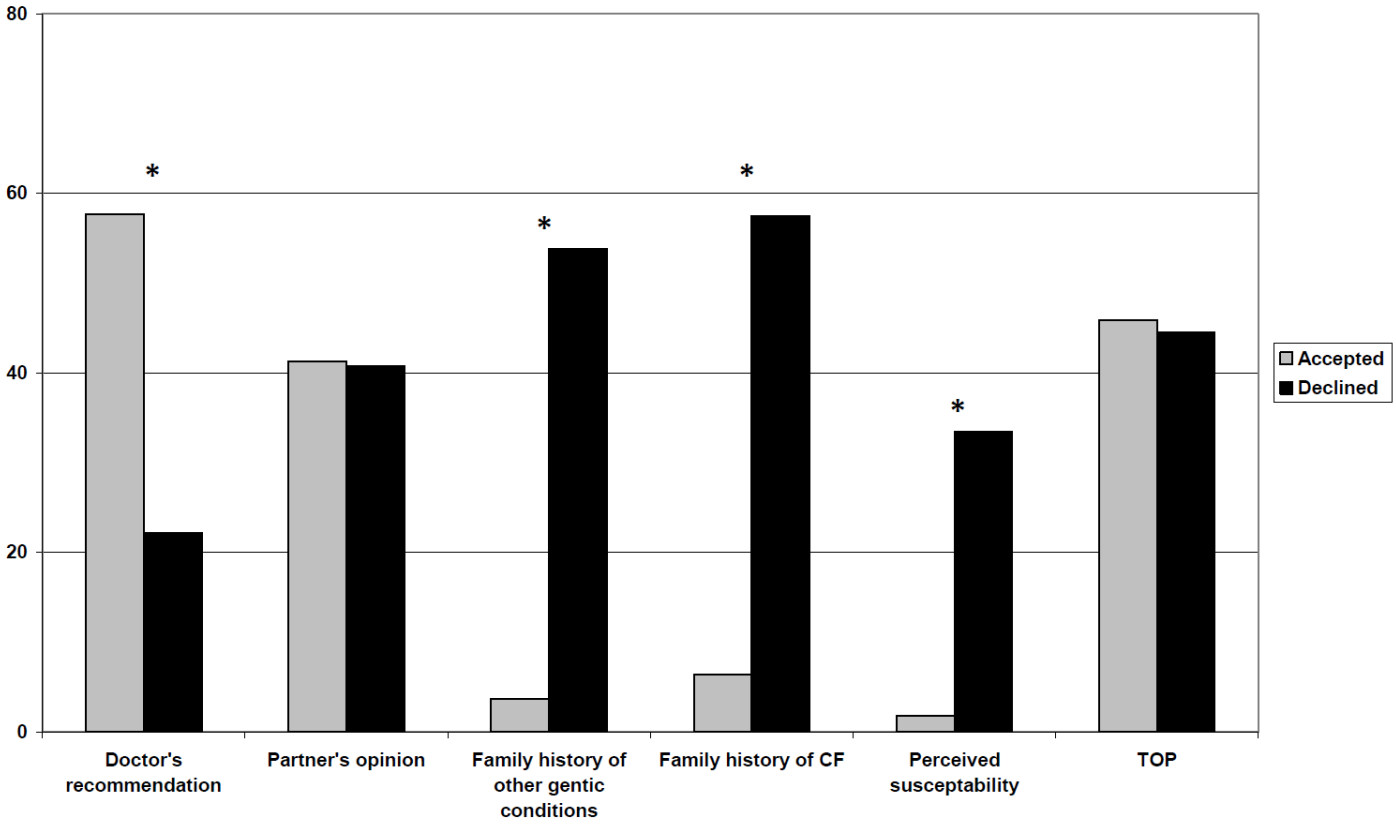
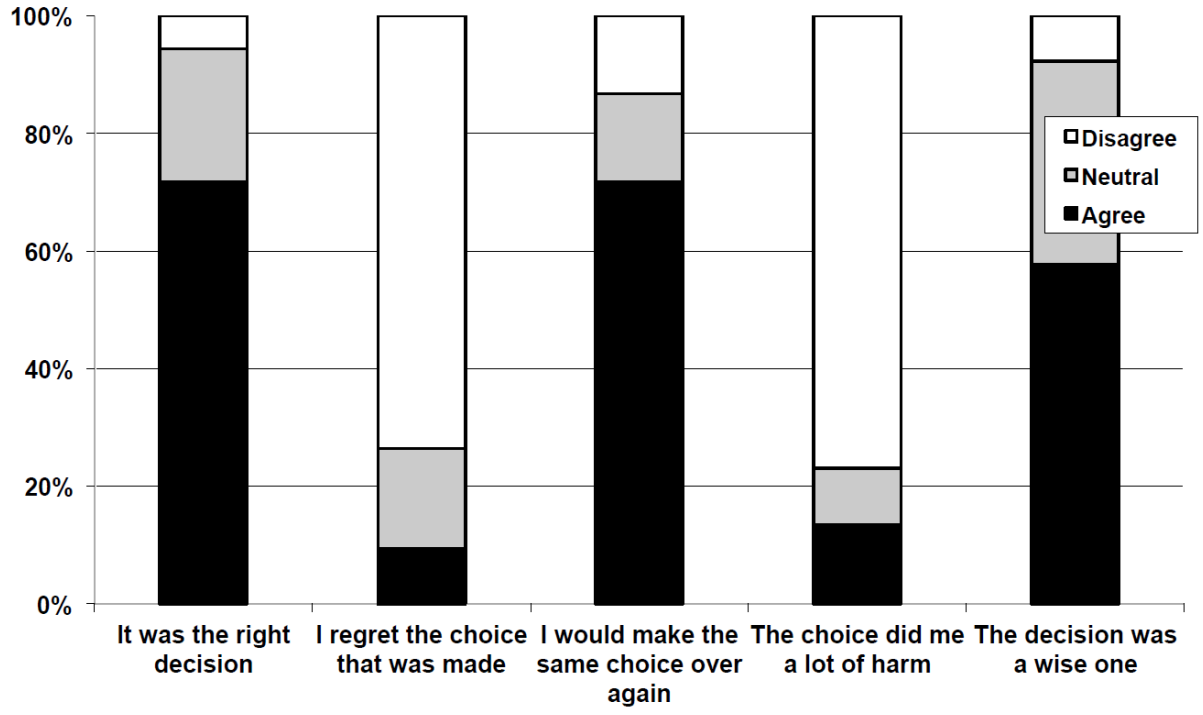


Figure 4. Satisfaction with decision to decline CF carrier screening



Chapter 8

Not Offered CF Carrier Screening

Addendum

p 151 para 2: Comment: One of the barriers identified in the study was offering carrier screening for CF to an ethnically diverse population. One solution could be to develop a decisional instrument to determine whether pregnant women and/or couples should be offered carrier screening for CF based on their ancestry. [114]

8.1 Declaration

Declaration by candidate

In the case of Chapter 8, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Conception and design of study; attainment of ethics approval and on-going reporting requirements; questionnaire development; participant requirement; data collection, analysis and interpretation; writing of manuscript	70%

The following co-authors contributed to the work:

Name	**Nature of contribution**
A/Prof John Massie	Contributed to design of study; assisted with development of questionnaire; interpretation of data; discussion of ideas expressed in and critical revision of manuscript
Dr Sharon Lewis	Contributed to design of study; assisted with development of questionnaire; assisted with data analysis; interpretation of data; discussion of ideas expressed in and critical revision of manuscript
Dr Belinda McClaren	Contributed to development of questionnaire used for comparison; interpretation of data; discussion of ideas expressed in and critical revision of manuscript
Dr Veronica Collins	Contributed to development of questionnaire used for comparison; interpretation of data; discussion of ideas expressed in and critical revision of manuscript
Prof Martin Delatycki	Contributed to design of study; assisted with development of questionnaire; interpretation of data; discussion of ideas expressed in and critical revision of manuscript

Candidate's Signature	[redacted]	**Date** 20/02/13

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Murdoch Childrens Research Institute

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]		1/3/13
Signature 2			1/3/13
Signature 3			1/3/13
Signature 4			3/3/13
Signature 5			1/3/13

8.2 Paper preamble

This chapter explores the attitudes and opinions of pregnant women in the public health system that did not receive an offer of CF carrier screening. This paper is preceded by an expansion of methodology, with regards to the development of the questionnaire. The paper was submitted to the European Journal of Human Genetics in February 2013.

The previous research chapters explored the attitudes and opinions of individuals who were offered CF carrier screening. In order to expand the GHSV CF carrier screening program into the public health system, ensuring equity of access, the views of potential consumers need to be explored.

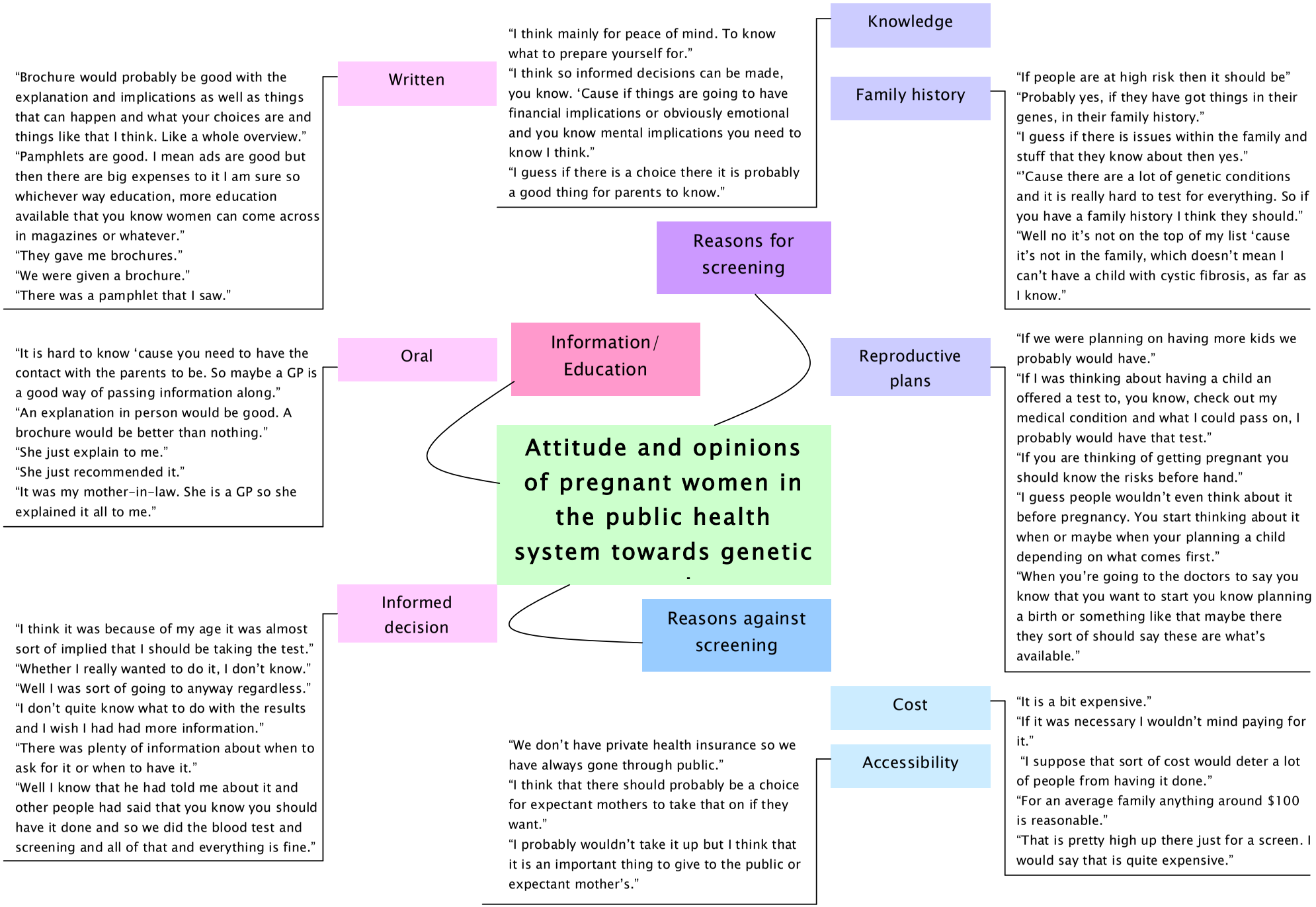
8.3 Extended methodology

Interviews were conducted to assist with the development of the questionnaire used in this study. Pregnant women (<16 weeks gestation) were recruited in the waiting rooms of antenatal clinics at two public hospitals in Melbourne, Victoria. Women who were unable to read or write English or required an interpreter were excluded from the study.

Interviews were semi-structured, approximately 10 minutes in duration and were conducted in the waiting room of the clinic. The interview schedule is included in Appendix F. Interviews were recorded and transcribed. Content analysis was used to analyse the data.

Between January and June 2011, nine interviews were conducted. The main themes to arise were: reasons for screening, reasons against screening and information/education. A flow chart of the themes is shown in Figure 7. The participant information sheet and questionnaire that was developed are included in Appendix A and B.

Figure 7. Flow chart of the themes arising from semi-structured interviews with women in the public health system regarding CF carrier screening



8.4 Paper: 'Attitudes and opinions of pregnant women who are not offered cystic fibrosis carrier screening'

Attitudes and opinions of pregnant women who are not offered cystic fibrosis carrier screening

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Running title: Views of women not offered cystic fibrosis screening

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Abstract

Background/Aims

Cystic fibrosis is the most common severe, autosomal recessive disease amongst Caucasians. A population-based cystic fibrosis carrier screening program was implemented in Victoria, Australia, in 2006. Carrier screening for cystic fibrosis is currently only offered in the private health system. The aim of this study was to determine the attitudes and opinions of pregnant women in the public health system, towards screening for cystic fibrosis.

Methods

Pregnant women were recruited in the antenatal clinics of two public hospitals. Results of this study were compared to previous studies where screening for cystic fibrosis carrier status was offered.

Results

The majority of the 158 participants were aged 25-34 years old (66.1%) and the largest ethnic group was Caucasians (45.8%). Compared to those who were offered screening participants in the current study were younger, had a lower level of education and a lower income. Knowledge was significantly lower in those who were not offered screening compared to those who were offered screening ($t= 3.32$, $p<0.01$). The majority of participants believe cystic fibrosis carrier screening should be offered in the public health system (80.5%) and almost half would have liked to receive an offer of screening during their current pregnancy (49.7%).

Conclusions

In order for the program to be equitable, screening for CF carrier status needs to be offered in both the public and private health system and ideally should be at no cost to the user.

Keywords: genetic screening, cystic fibrosis, cystic fibrosis carrier screening, attitudes

Introduction

Genetic screening is a test performed for early detection of a hereditary disease, predisposition to a hereditary disease or to determine whether a healthy individual carries a predisposition that may cause disease in offspring.[1] A carrier is an individual who has a heterozygous mutation for an autosomal or X-linked recessive genetic condition, such that they are not at risk of the condition themselves, but are at higher risk of having a child with the condition. Carrier screening can identify couples in which both individuals are carriers of an autosomal recessive disorder, and therefore have a high risk of having a child with the condition tested for. The couple can then be informed about available reproductive options.

Population-based genetic carrier screening is directed towards the whole population with the aim being to counsel and test as many individuals as possible for genetic risk regardless of whether or not they have a family history of the genetic disorder. In order to justify population-based screening for particular diseases, the World Health Organisation (WHO) proposed certain criteria that should be met. These include that the condition is an important health problem, testing can be performed to determine carrier status with known test sensitivity and reproductive options are available to prevent the birth of a child with the disease.[2]

Cystic fibrosis (CF) is an example of a genetic disease that satisfies the WHO requirements for population-based screening. It is the most common, severe, autosomal recessive disease in Caucasians, with a birth frequency of about 1 in 2,500 and a carrier frequency of 1 in 25.[3] CF is the result of mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and since the discovery of the gene in 1989 more than 1,900 alterations have been identified. The most frequently occurring mutation in the Caucasian population is p.F508del, accounting for approximately 70% of all mutations present.[4]

The main clinical features of CF are suppurative lung disease, pancreatic exocrine insufficiency and elevated sweat electrolytes. There is currently no cure for CF but various therapies have markedly improved lifespan. Treatment involves daily therapies including chest physiotherapy, antibiotics, pancreatic enzymes and a high calorie diet.[5] The suppurative lung disease is progressive and largely responsible for the reduced life expectancy.[6] The median life expectancy is 37 years.[7] Lung transplantation is possible in some patients and although the outcomes are continually improving, the five-year survival post transplantation is still only 50%.[8]

Cascade testing is highly accurate and more sensitive than population carrier screening for CF, as the familial mutations are usually known .[9] However, it has been shown that cascade testing is only taken up by 2-3 relatives per proband.[10] Also the efficacy, which is defined as the total number of carriers identified in a population, is much lower in cascade testing than in population screening for CF[11] due to the fact that more than 95% of carriers have no family history of CF.[12, 13]

In 1999 the National Institute of Health (NIH) recommended that CF carrier screening be offered to all pregnant women and couples planning a pregnancy. The American

College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynaecologists (ACOG) subsequently released similar recommendations.[14, 15] The Human Genetic Society of Australasia (HGSA) position paper states that "all pregnant women and couples planning a pregnancy should be made aware of the availability of carrier screening for CF".[16]

In Victoria, Australia, a population-based CF carrier screening program was implemented by the Victorian Clinical Genetics Services (VCGS) in 2006. The program offers screening to women or couples before or during the early stages of pregnancy via obstetricians and general practitioners in the private health sector. It is currently a fee-for-service program with each test costing AUD$220. During the first three years of the program (2006-2008) 3,200 individuals were screened, all partners of carriers were tested and carrier couples used the information received to make reproductive decisions.[17]

We have studied a number of aspects of this program, including the attitudes and outcomes of individuals who accepted CF carrier screening[18] and compared their responses with those of individuals who declined CF carrier screening.[19] These studies reflected the attitudes of people offered screening in the private obstetric sector and were biased towards women of higher education and family income than the general population. There are limited data about attitudes toward CF carrier screening from women attending public obstetric services.

The aim of this study was to explore the attitudes and opinions of pregnant women in the public health system who were not offered CF carrier screening and compare these to the attitudes and opinions of individuals who were offered CF carrier screening from our previous studies.[18, 19]

Materials and Methods

Participants

Pregnant women (<16 weeks gestation) were recruited in the waiting rooms of antenatal clinics at two public hospitals in Melbourne, Victoria. Women who were unable to read or write English or required an interpreter were excluded from the study.

Questionnaire Development

Interviews were conducted, with nine pregnant women in the public health system, to assist with the development of the questionnaire. Interviews were semi-structured, approximately 10 minutes in duration and were conducted in the waiting room of the clinic. The interview schedule is included in supplementary material (S1). Interviews were recorded and transcribed. A combination of content and thematic analysis was used to analyse the data for themes to be included in the questionnaire.

Questionnaire

The purpose-designed questionnaire assessed the following domains: demographic characteristics; screening history; knowledge of CF and CF carrier screening; factors that may influence a decision to have screening; attitude towards screening for genetic conditions; attitude towards CF carrier screening. The knowledge questions and factors

influencing the decision to have screening were sourced from the questionnaires used in the previous studies of individuals who were offered CF carrier screening, to allow for comparison.[18, 19] The questionnaire can be viewed at http://www.mcri.edu.au/notofferedcfscreening/.

Analysis

Data analysis of questionnaires was conducted using SPSS (Windows, version 17.0; SPSS Inc., Chicago, IL). Preliminary descriptive analysis generated frequency data to elicit a description of participants.

The 'knowledge score' was calculated by giving one point for a correct response to each knowledge question and adding correct responses together. A response of 'unsure' was considered as an incorrect response.

The importance of various factors that might potentially influence a decision to have screening were measured on 5-point Likert scales. For analysis, points '1' and '2' were combined to form the category "would not influence", the middle point '3' remained neutral, while points '4' and '5' were combined to form the category "would influence".

The data from the current study of participants who were not offered CF carrier screening were compared with data from the previous studies evaluating the attitudes and outcomes for individuals who had accepted[18] or declined an offer of screening.[19] Analysis of categorical variables was undertaken using χ^2 analyses and, for continuous variables, differences in means between groups were assessed using t-tests. A p-value <0.05 was considered statistically significant.

Ethics Committee Approval

This study was approved by the Southern Health Human Research Ethics Committee, Victoria, Australia (HREC#10084B).

Results

Response rate

Between July 2011 and August 2012, a total of 187 eligible pregnant women were approached in the waiting room at two antenatal clinics. Of the 187 women approached, two directly declined to participate while the rest were provided questionnaires to complete in the waiting room. Of the 187 women approached, 158 returned completed questionnaires, giving a response of 84.5%.

Demographics of respondents

The demographics of participants are presented in Table 1. Those who were not offered screening were significantly younger in age (χ^2= 97.65, $p<0.01$, df=5), had a lower level of education (χ^2=62.64, $p<0.01$, df=5), were less likely to have managerial or professional occupations (χ^2=84.82, $p<0.01$, df=8), and had lower household incomes (χ^2= 113.67, $p<0.01$, df=4) compared to those who were offered screening. There was also a significant difference in ethnicity between the two groups, with a higher proportion of individuals of Asian descent and lower proportion of individuals of European descent among those not offered screening (χ^2= 97.91, $p<0.01$, df=5) (Table 1).

Knowledge of CF and Screening

Participants were asked to select true, false or unsure as a response to 15 knowledge statements regarding CF and carrier screening. The majority of participants (53.5%) answered between one and five of the knowledge statements correctly. All fifteen knowledge statements were answered correctly by less than 50% of participants. Thirteen of the 15 knowledge questions were answered correctly significantly more often by those who were offered screening (accepted and declined combined) compared to those who weren't offered screening. Mean total scores for knowledge of CF and carrier screening was significantly lower in those who weren't offered screening compared to those who were offered screening ($t=3.32$, $p<0.01$) (Figure 1).

More than 50% of participants who were not offered screening selected unsure as a response to all fifteen knowledge statements. Those who were not offered screening selected unsure as a response to knowledge statements more often than those who were offered screening for all of the fifteen knowledge questions (Figure 2).

Potential Factors Influencing the Decision to have Genetic Screening

Participants not offered screening were asked to rate factors that might influence their decision to have carrier screening for genetic conditions on a Likert scale. The factors most commonly rated as potentially influencing a decision to have screening were partner's opinion, n=88 (59.5%), and lack of family history, n=68 (46.3%). Believing that they would not consider a termination of pregnancy for CF was identified as a potential influential factor for 55 (38.7%) participants. Fifty-five (36.9%) and 89 (61.4%) participants, respectively, considered that their doctor's recommendation and cost of the test would not influence their decision to have screening (Figure 3).

Three factors were found to be influential in the decision about whether or not to have testing by a significantly greater proportion of those who were not offered screening or those who declined screening compared with those who accepted screening. These were: (i) family history of condition screened for ($\chi^2=59.80$, $p<0.01$, $df=2$); (ii) family history of other genetic conditions ($\chi^2=63.20$, $p<0.01$, $df=2$); and (iii) perceived susceptibility of being a carrier of CF ($\chi^2=54.09$, $p<0.01$, $df=2$). Doctor's recommendation was an influencing factor more often amongst those who had screening than those who declined or were not offered screening ($\chi^2=39.78$, $p<0.01$, $df=2$) (Figure 4).

Screening history

Eighty-one (52.6%) participants sought medical advice prior to pregnancy, with 26 (32.1%) of these having discussed genetic issues. In their current pregnancy, 124 (81%) stated that they had screening for trisomy 21, and 26 (16.5%) had been offered testing for other genetic conditions. Fourteen (53.8%) of the latter group stated they were offered screening for thalassaemia and 10 were tested.

Attitude towards screening for genetic conditions

One hundred and fifteen (75.7%) participants believe screening for genetic conditions should be available regardless of having a family history. Of these, 50 (48.1%) stated that before pregnancy would be the best time to offer screening and 79 (68.7%)

wished they had been offered screening for genetic conditions during their current pregnancy.

Attitude towards carrier screening for CF

Fifty-four percent of participants had heard of CF prior to completing the questionnaire. Eighty-one percent of participants believe screening for CF should be offered in the public health system, with only two percent of participants stating it should not be offered, and the remaining 17% being unsure.

Fifty-seven percent of participants believe that CF carrier screening should be less than AUD$50, with 37% of these believing it should be free of charge. When asked if they would have liked to have received an offer of CF carrier screening during their current pregnancy 50% stated they would and 83% of these women stated they would have accepted the offer. Seventeen percent stated that they would not like to have been offered CF carrier screening during their current pregnancy, but 60% of these would have accepted the offer prior to pregnancy. The remaining 33% were unsure if they would have liked to have been offered screening for CF.

Discussion

The majority of pregnant women in the Australian public hospital system in this study believe that CF carrier screening should be offered in the public hospital system or by family doctors. Most believe screening should be offered before pregnancy, but many would have taken up an offer of screening in the current pregnancy. The cost of screening was an important factor, and it was thought that it should be available for less than AUD$50 per test. Knowledge of CF and screening was significantly lower in those who were not offered screening compared to those who were offered screening. This indicates that receiving an offer of screening is likely to increase knowledge although the difference in educational levels between the groups is also likely to be playing a role. Factors seen as most likely to influence a decision to accept an offer of screening were partner's opinion, family history and perceived susceptibility. These factors were different to those indicated by the group who accepted an offer of screening where doctor's recommendation was the major influence.[18, 19]

The differences in the demographic factors between those offered and those not offered CF screening reflects the private and public health settings in which participants were recruited. Compared to our previous studies, participants from the present study were recruited in the public health system and were younger, had a lower level of education, lower household income and the more than 40% were of Asian descent. These findings suggest possible barriers to the implementation of a population-wide CF carrier screening program. Previously we have shown that uptake of CF carrier screening is associated with maternal age, with those who declined screening being significantly younger than those who accepted it.[19] A higher level of education has also been associated with higher uptake of screening.[20, 21] Knowledge of CF and screening is also higher in those with a higher level of education.[22] Low income could also be a potential barrier with evidence showing that uptake is associated with high income.[21] The current cost of the test in Victoria is AUD$220. Together with out of

pocket costs for screening for trisomy 21 and other pregnancy-related tests, CF carrier screening may not be affordable to many couples in the public hospital system with an average household income of AUD$20-40,000.

The fact that over 40% of the participants identified as having Asian origins has important implications for a population CF carrier screening program. As the participants in the study were required to read and write English it excluded a number of women from non-English speaking backgrounds and therefore our study population is likely to under-represent the ethnic mix attending public obstetric services. In addition to the issues of education and income discussed above, CF is less common in non-Caucasian populations so that baseline awareness of the condition is likely to be lower. Furthermore the ethnic diversity in this population will affect the sensitivity of the screening test with the mutations tested for in the current screening panel being the most common mutations in the Caucasian population.[23] This complicates pre-test information about relevance of CF screening to certain ethnic populations and affects residual risk calculations. However, identification of ethnic background can be difficult and not offering carrier screening on the basis of race has ethical implications. For this reason the pre-test information in our CF carrier screening program includes data on the incidence of CF in different populations and the associated residual risk estimates.

Participants were asked to rate factors that may influence a hypothetical decision to accept or decline an offer of genetic carrier screening, however these factors may change upon receiving an actual offer of screening. The main factors that might influence their decision with regards to having screening were partner's opinion, family history of the specific condition or other genetic conditions, and perceived susceptibility. These influencing factors, with the exception of partner's opinion, were found to be important in the decision to decline CF carrier screening.[19] Therefore, if offered CF carrier screening, our data suggest that the majority of women in the public hospital system would decline the offer based on a lack of family history and low perceived susceptibility.[24]

One of the other interesting outcomes of this study was the relatively high proportion of women who saw health professionals prior to pregnancy. Preconception carrier screening, while being the preferred time to screen, has previously been associated with low uptake due to a lack of preconception health care settings in which to offer screening.[25] However, the results show that almost half of the participants in this study sought medical advice prior to pregnancy, from their GP or obstetrician. This was also shown in another Australian study with a higher uptake of CF screening at a family planning clinic compared to general practice.[26]

The majority of participants indicated that they would prefer to receive an offer of CF carrier screening and pre-test information from their GP. Therefore, health professionals are key stakeholders in CF carrier screening, as they are the gatekeepers of screening and their attitudes, opinions and knowledge in regards to CF carrier screening are significant in the effectiveness of offering population-based screening. There is also evidence that doctor's

opinion and recommendation is an influencing factor in the decision to accept an offer of screening.[18, 21, 24, 27]

There are barriers to offering CF carrier screening from the health care provider's perspective, including costs, time constraints and availability of supporting services. Another barrier is a lack of knowledge and experience with CF or genetic screening, resulting in a lack of confidence in their ability to provide screening.[28-31] Health professionals have also been found to lack knowledge in regards to the carrier frequency of CF in the general population with only a small number of GPs believing CF carrier screening should be offered to those without a family history of the condition.[32]

In conclusion, the majority of participants who are currently not offered screening stated that CF carrier screening should be available in the public health system. A major barrier to accepting an offer of screening appears to be lack of knowledge with potential participants citing lack of family history as a significant factor in their decision to decline screening. Health professionals offering CF carrier screening need education to provide accurate pre-test information in order for women and couples of all ethnic backgrounds to make an informed decision. Cost is a significant barrier that could be overcome with government funding which would address the current inequity of access to CF carrier screening in Australia.

Supplementary information is available at the European Journal of Human Genetics' website.

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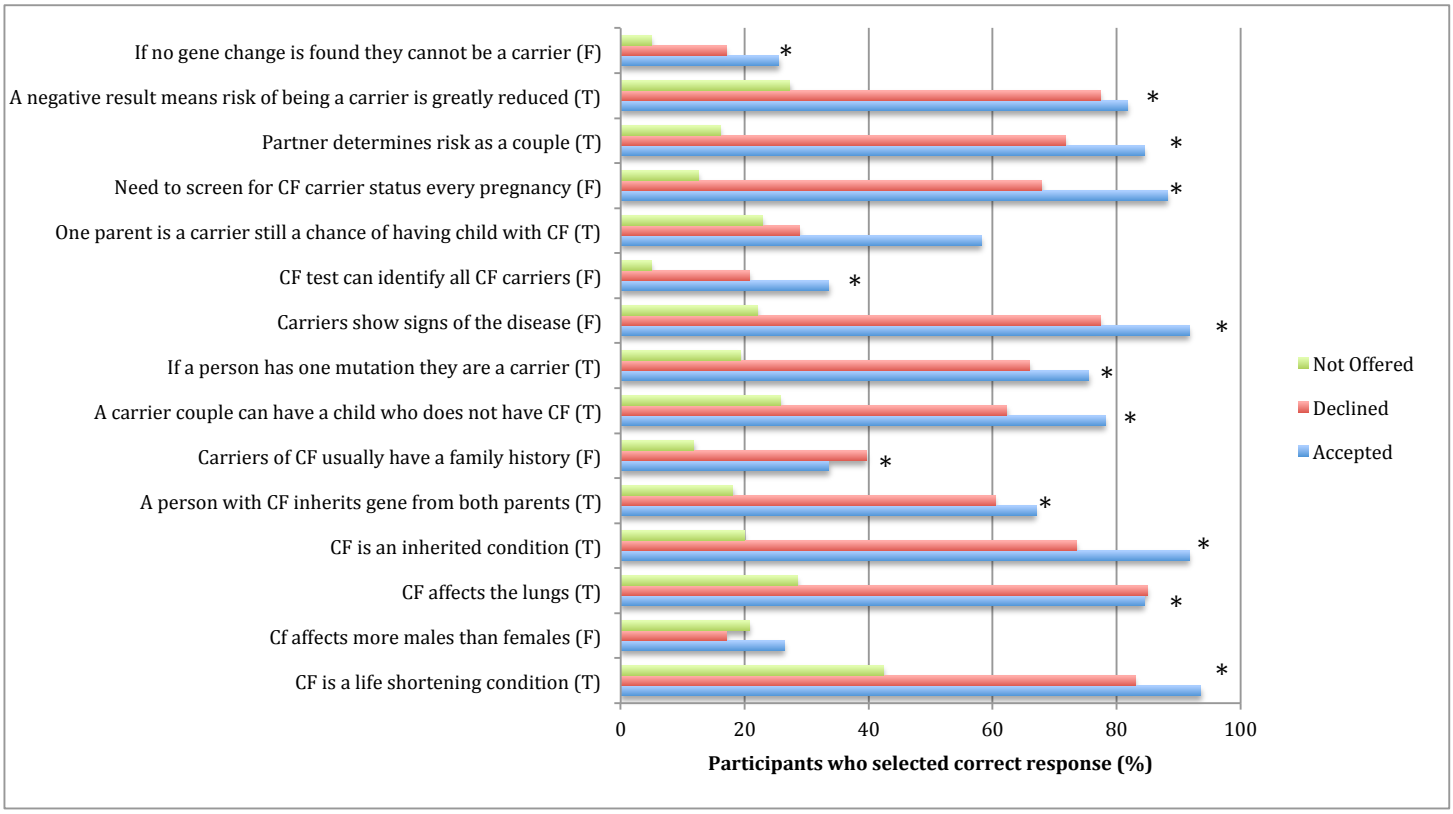
Table 1. Comparison of demographic characteristics of those who were offered screening and those who were not offered screening for CF carrier status

Demographic	Categories	No. of Participants (%) Offered** n=166	No. of Participants (%) Not offered n=158	Chi square statistic (degrees of freedom) and p-value (χ^2)
Gender	Male	3 (1.8)	0 (0.0)	2.88
	Female	163 (98.2)	158 (100.0)	p=0.09
Age (in years)	<20	0 (0.0)	5 (3.2)	97.65 (df=5)
	20-24	0 (0.0)	28 (17.9)	*p<0.01
	25-29	14 (8.6)	50 (32.1)	
	30-34	61 (37.4)	53 (34.0)	
	35-39	73 (44.8)	19 (12.2)	
	40+	15 (9.2)	1 (0.6)	
Highest completed level of education	Year 11 or less	3 (1.9)	24 (15.4)	62.64 (df=5)
	Finished secondary school	8 (5.0)	36 (23.1)	*p<0.01
	Trade/Apprenticeship	2 (1.2)	3 (1.9)	
	College certificate or diploma	29 (18.0)	41 (26.3)	
	University degree	116 (72.0)	51 (32.6)	
	Other	3 (1.9)	1 (0.6)	
Occupation	Managers	37 (23.3)	10 (6.9)	84.82(df=8)
	Professionals	61 (38.4)	12 (8.3)	*p<0.01
	Technician & Trade	11 (6.9)	6 (4.2)	
	Community & Personal Service	30 (18.9)	45 (31.3)	
	Clerical/Administration	13 (8.2)	28 (19.4)	
	Sales	4 (2.5)	14 (9.7)	
	Machinery Operators & Drivers	0 (0.0)	3 (2.1)	
	Labourers	0 (0.0)	4 (2.8)	
	Unskilled	3 (1.9)	22 (15.3)	
Household Income (in AUD$1000s)	20-40	3 (1.9)	43 (29.7)	113.67 (df=4)
	41-60	8 (5.1)	38 (26.2)	*p<0.01
	61-80	14 (8.9)	25 (17.2)	
	81-100	22 (14.0)	15 (10.3)	
	>100	110 (70.1)	24 (16.6)	
Ethnicity	Australia	100 (61.7)	33 (22.9)	97.91 (df=5)
	America	1 (0.6)	5 (3.5)	*p<0.01
	Europe	52 (32.1)	28 (19.4)	
	Asian	6 (3.7)	59 (41.0)	
	New Zealand/Islander	3 (1.9)	17 (11.8)	
	Africa	0 (0.0)	2 (1.4)	

Affinity with a Religion	Yes	73 (45.1)	74 (47.1)	0.35
	No	89 (54.9)	79 (50.3)	p=0.56
Partner at time of testing/participation	Yes	161 (98.8)	141 (90.4)	11.12
	No	2 (1.2)	15 (9.6)	*p<0.01
Pregnant at time of testing/participation	Yes	144 (88.3)	158 (100.0)	19.58
	No	19 (11.7)	0 (0.0)	*p<0.01
Number of children at time of testing	0	47 (29.2)	77 (50.0)	14.76 (df=3)
	1	76 (47.2)	55 (35.7)	*p<0.01
	2	30 (18.6)	17 (11.0)	
	3 or more	8 (5.0)	5 (3.2)	

Note: * p<0.01 for comparison of proportions in current versus previous study using χ^2 test.
Note: ** Data from previous studies[18, 19]

Figure 1. Comparison of knowledge of those who were offered screening (accepted and declined) and those who were not offered screening for CF carrier status



Note: * p<0.05 for comparison of proportions in current versus previous study using χ^2 test.

Figure 2. Comparison of participants who selected 'unsure' as a response to knowledge statements between those who were offered screening (accepted and declined) and those who were not offered screening for CF carrier status

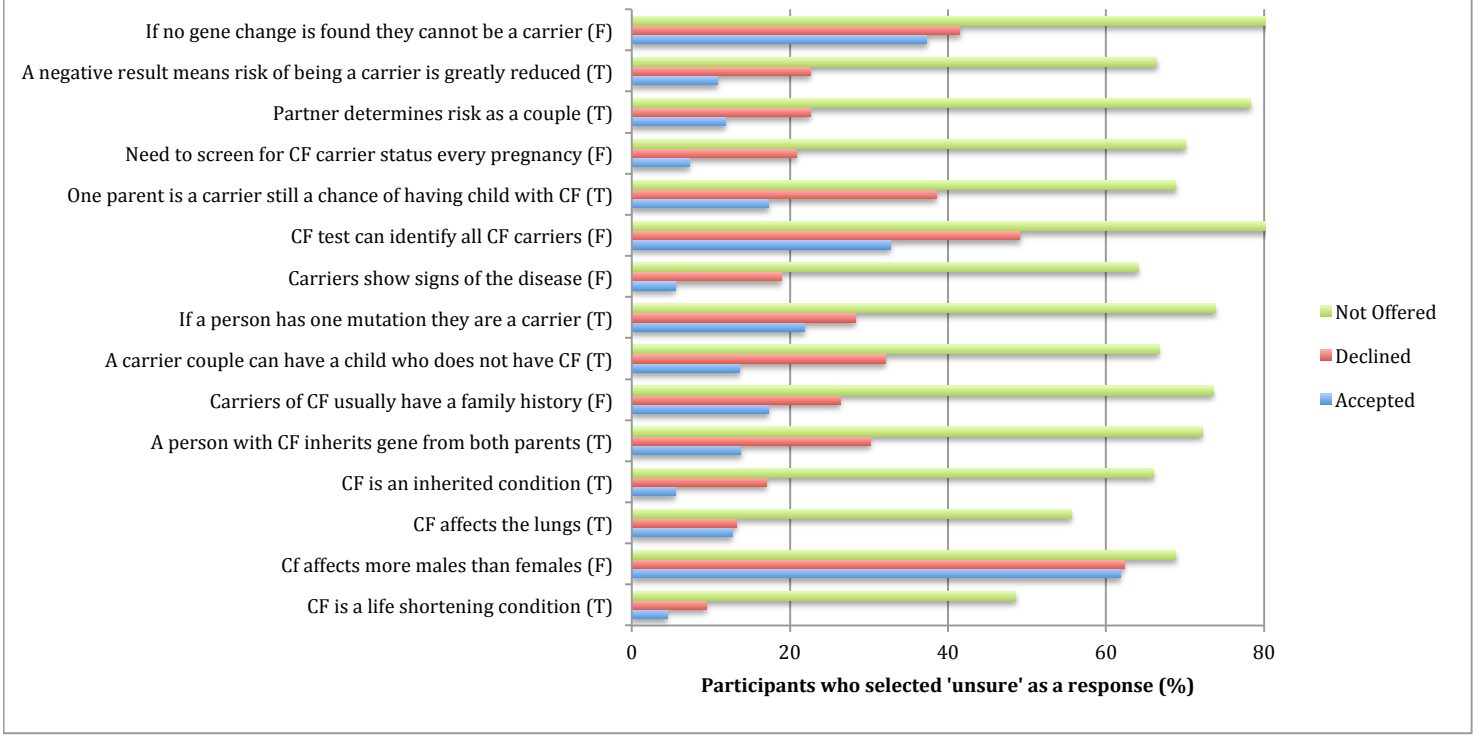
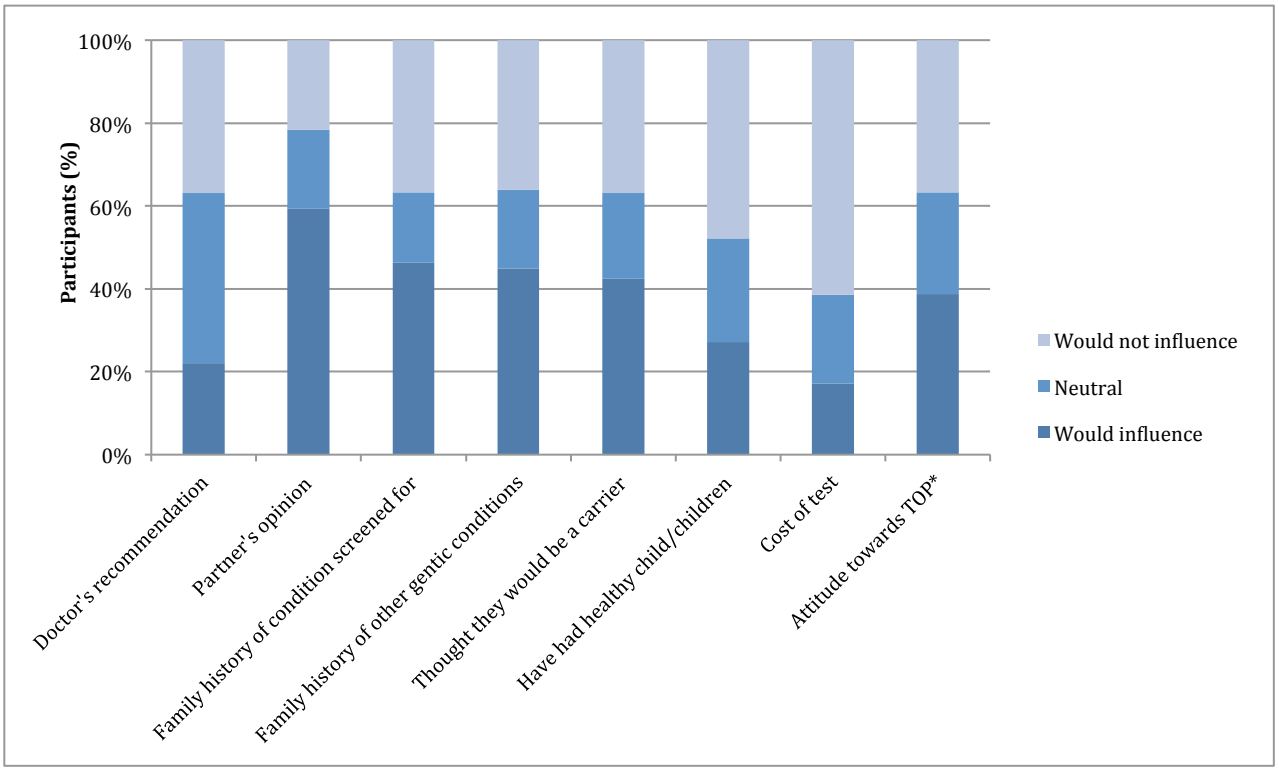
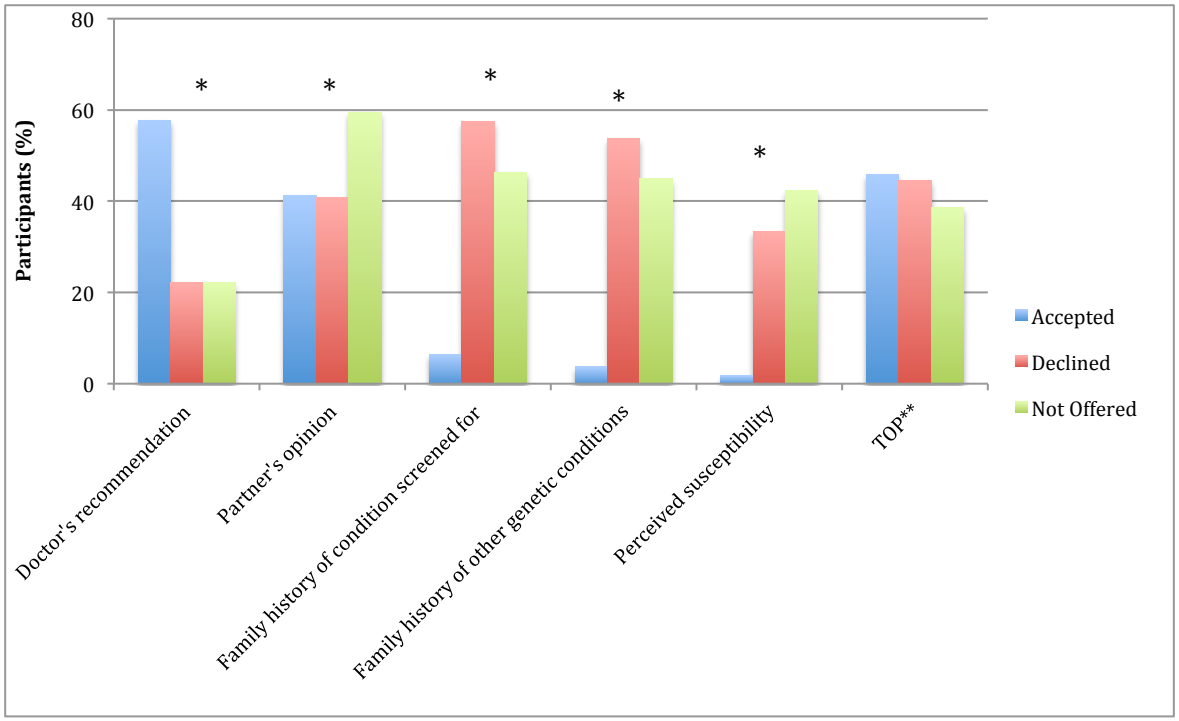


Figure 3. Potential factors that may influence the decision whether or not woman would accept an offer of CF carrier screening (not offered screening group)



Note: * TOP= Termination of Pregnancy

Figure 4. Comparison of factors that influenced the decision to have CF carrier screening, or potential factors that may influence the decision to have CF carrier screening, respectively, between those who were offered screening (accepted and declined) and those who were not offered screening for CF carrier status



Note: * $p<0.05$ for comparison of proportions in current versus previous study using χ^2 test.
Note: ** TOP= Termination of Pregnancy.

Chapter 9

General Discussion

The aims of this thesis were to explore the characteristics of individuals who accepted, declined or were not offered CF carrier screening and the effects of multi-disease carrier screening through two separate carrier screening programs in Victoria.

This final chapter summarises the findings of the studies and provides an overall discussion. Limitations of this thesis as well as directions for future research are also discussed, with the final section presenting concluding remarks.

9.1 Overview of findings

The findings of this thesis enhance our knowledge of population-based reproductive genetic screening for autosomal recessive diseases in several ways.

9.1.1 Characteristics

Accepted screening

Previous research conducted in my Honour's year explored the attitudes and outcomes of screening retrospectively for carriers (excluding carrier couples) and non-carriers of CF. It showed that: individuals who participated in this screening program were more likely to be well educated, affluent women between the ages of 35-39. There was no difference between carrier couples, carriers and non-carriers with regard to demographic characteristics.

Declined screening

When evaluating the attitudes and opinions of pregnant women who declined an offer of CF carrier screening it was found that there was no difference in demographic characteristics between those who declined an offer of screening and those who accepted, with the exception of age. Pregnant women who declined an offer of CF carrier screening were significantly younger than those who accepted an offer of screening, with majority being between the ages of 30-34. This most likely represents the private health setting in which screening is offered.

Not offered screening

An exploration of the attitudes and opinions of pregnant women in the public health system, who were not offered screening, showed that they were younger, had a lower level of education, lower income and were more ethnically diverse compared to those who were offered screening in the private health system.

9.1.2 Knowledge

Knowledge of CF and screening was highest in those who accepted an offer of screening. While there was no difference in knowledge level between carrier couples and carriers, non-carriers however had a significantly lower level of knowledge.

Pregnant women in the public health system, who were not offered screening, had low knowledge with regard to CF and screening with more than half of the participants being unsure of the correct response for all the knowledge questions. Knowledge level was significantly lower in those who were not offered screening compared to those that were offered screening, both accepted and declined.

9.1.3 Factors influencing decisions

Accepted screening

The main reasons for accepting an offer of screening were the perception of CF as a severe disease and doctor's recommendation. There was no difference between carrier couples, carriers and non-carriers with regard to factors influencing the decision to have screening.

Declined screening

The main reason for declining an offer of screening was having no family history of CF or no family history of other genetic conditions. Family history of CF or other genetic conditions as well as perceived susceptibility of being a carrier of CF were significantly more influential in the decision to decline screening than to accept it.

Not offered screening

The main factors that would potentially influence the decision of pregnant women in the public health system towards CF carrier screening were: partner's opinion and family history of the disease. There was no significant difference between those who were not offered screening and those who declined screening with regard to factors influencing the decision whether to have screening. Therefore, the findings suggest that if offered CF carrier screening the majority of women in the public hospital system would decline the offer based on a lack of family history.

9.1.4 Effects of screening for multiple diseases

There is limited previous research on carrier screening for multiple conditions. This is becoming an increasing area of interest as carrier screening becomes available for more diseases and the cost of screening becomes more

affordable. An evaluation of a carrier screening program implemented in Jewish high schools in Melbourne, Victoria, offering screening for seven of the most common genetic diseases in the Ashkenazi Jewish population has shown that the program is associated with high uptake of screening, high knowledge compared to adult screening programs and low predicted negative feelings if found to be a carrier.

However, the addition of a further six genetic diseases to the screening panel resulted in decreased knowledge and increased predicted negative feelings if found to be a carrier compared to when single-disease (TSD only) carrier screening was offered. The decrease in knowledge shown by participants, particularly regarding the specific diseases screened for, raises questions about informed consent with participants not fully aware of the diseases they are being screened for. Furthermore, truly informed consent may not be possible as the number of diseases screened for increases. Therefore education and counselling will need to be directed towards carriers identified to ensure they understand the disease for which they are a carrier and the meaning of their carrier status.

9.1.5 Outcomes of screening

An exploration of the experiences of couples that were both identified as carriers of CF found that all couples were generally satisfied with the program and service provided; did not expect and were unprepared for a positive result; changed their reproductive behaviour as a result of their carrier status; and communicated genetic information to family members.

Together with the findings of my Honour's study, these results provide a comprehensive evaluation of the current program, showing that the program effectively offers CF carrier screening to pregnant women and couples planning a pregnancy, supporting the implementation of the routine offer of CF carrier screening.

9.1.6 Attitudes towards screening

Best time to offer screening

The majority of participants who accepted an offer of CF carrier screening, carrier couples, carriers and non-carriers, believe that the best time to offer CF carrier screening is before pregnancy. The majority of pregnant women who declined an offer of CF carrier screening and wished to be offered testing at another time, would have liked to be offered testing prior to pregnancy. Pregnant women in the public health system had a similar attitude, with almost half of the

participants seeking medical advice prior to pregnancy and the majority believing that that is the best time to offer genetic screening.

Routine offer of screening

Nearly all of the participants who declined an offer of CF carrier screening stated that screening should be available to those who wish to have it. Furthermore, the majority of participants who were not offered CF carrier screening believe that CF carrier screening should be offered in the public health system.

9.2 Implications

9.2.1 Knowledge

Provision of information is essential to ensure potential participants make an informed decision with regard to accepting or declining an offer of CF carrier screening. Knowledge of CF and CF screening is evaluated at various points during the screening process: prior to receiving information, after receiving information and after receiving test result. Studies have shown that the knowledge of the general population, when making the decision whether or not to have screening, is low but increases once having been screened.[94-96] A potential reason for the increase in knowledge, from before to after screening, may be the perceived relevance of that information, particularly if found to be a carrier.

Our studies have shown that carrier couples and carriers have a higher knowledge of CF and CF screening than non-carriers.[92] The greater knowledge shown by carrier couples and carriers is likely to be due to the provision of post-test counselling, with carriers usually receiving more follow-up than non-carriers. It is also likely that carriers would be more motivated to retain any knowledge learned through the program, as it is more relevant to them.

Knowledge of CF and CF screening has been shown to be an important factor in the decision whether to have screening, with those who decline screening having lower knowledge than those who accept screening.[97] Studies have shown that some of the main reasons for accepting an offer of screening are perceived severity of the disease being screened for and perceived susceptibility to that disease.[92, 98] Individuals who lack knowledge with regard to CF and CF screening may form a perception of the severity of the disease and their risk of being a carrier or having a child with disease based on incorrect information leading them to decline an offer of screening.

Furthermore, our studies have shown that the main reason for declining an offer of CF carrier screening is due to a lack of family history of CF. However,

more than 95% of carriers identified through screening have no known family history of the disease.[18] A study from Canada had similar findings; with participants who declined screening stating that the main reason for declining screening was having no family history of CF.[99]

Receiving an offer of screening is likely to increase knowledge of CF and CF screening, with our study showing that knowledge was significantly lower in those who were not offered CF carrier screening compared to those who were offered screening. However, the difference in educational levels between the two groups is also likely to be playing a role in this finding. Other studies have shown that individuals who have a higher level of education have higher knowledge than those who have a lower level of education.[100-102]

Our research has also shown that increasing the number of diseases screened for results in a decrease of knowledge and an increase in predicted negative feelings if found to be a carrier. It could be implied that predicted negative feelings if found to be a carrier increased due to a lack of knowledge, with individuals having poorer understanding of the meaning of being a carrier. This has implications for future programs which will screen for more diseases as such testing becomes technically more feasible and more affordable.

Therefore, provision of information is important to ensure informed decision making, reduce the likelihood that people will make the decision to decline screening based on a lack of understanding of autosomal recessive conditions and to reduce anxiety as a result of not understanding the meaning of being a carrier. Post-test information and counselling should be targeted towards individuals who are identified as carriers.

9.2.2 Factors influencing decisions

It is important to determine and understand the factors that influence an individual or couples decision whether to accept or decline an offer of CF carrier screening in order to develop appropriate education programs and increase uptake in the population. The majority of the factors identified in our research that influenced the decision whether to accept an offer of screening were Health Belief Model (HBM) constructs. These were: perceived severity, perceived susceptibility, lack of knowledge and opinion of healthcare professionals.

Perceived susceptibility and perceived severity are two of the four main constructs of the HBM that predict health-related behaviour. Lack of knowledge and opinion of healthcare professionals were later added to the HBM as modifying factors that can predict health-related behaviour. Our findings are similar to those reported in a review by Chen and Goodson who identified lack of knowledge as

one of the most influential factors in deciding to decline an offer of CF carrier screening.[113]

Age is also a modifying factor that was added to the HBM. Our results show that those who declined an offer of screening were significantly younger than those who accepted screening. This was expected as it has been shown that older women who have a high level of education, high income and low parity are most likely to accept an offer of screening.[27, 39, 40] However, there was no difference in education, income or parity between those who accepting screening and those who declined screening in our study.

Those who were not offered CF carrier screening were significantly younger than those who were offered screening, had a lower level of education, lower income and higher ethnic diversity, all of which are modifying HBM factors that are associated with declining an offer of screening.

The main factors influencing the decision whether to have screening, perceived susceptibility, perceived severity, lack of knowledge and opinion of healthcare professionals, can be altered through the provision of information and education. Therefore, health education aimed at the general population relating to CF and CF carrier screening could increase uptake of CF carrier screening in the population.

9.2.3 Equity of access

Equity of access refers to ensuring all individuals in the population have equal access to screening for CF carrier status regardless of their demographic characteristic including age, ethnicity, socio-economic status and health care insurance cover. The GHSV CF carrier screening program is currently only offered in the private health system rendering it inequitable. In order to ensure equity of access the program needs to be expanded to the public health system, however there are several barriers to the offer of screening in the public health system that need to be overcome before screening can be implemented. These include: cost, diversity of ethnicity and provision of information.

Cost of testing

CF carrier screening is offered through the GHSV program for a cost of AUD$220 for each test. Offering screening in the public health system for this price would be inequitable, as our studies have shown that individuals in the public health system have a significantly lower annual household income, AUD$20-40,000, compared to those in the private health system, AUD$100,000+. In addition, if offered during pregnancy couples will already be paying out of pocket costs for screening for trisomy 21 and other pregnancy-

related tests. Therefore, CF carrier screening may not be affordable to many couples in the public hospital system.

Our study showed that less than one third of pregnant women in public health system thought that cost of testing would influence their decision to have genetic screening. However, the majority of participants believe screening for CF carrier status should be offered for less than AUD$50. Furthermore, reports from other screening programs show that the cost of screening is a significant factor in the decision whether to have screening.[94, 21]

In order to offer screening in the public health system, and ensure equity of access, screening for CF carrier status needs to be offered free of charge through a Government funded program.

Ethnic diversity

Screening for CF carrier status does not detect all carriers of CF, as more than 1,900 *CFTR* alterations have been identified to date.[13] The GHSV CF carrier screening provides screening for 12 of the most common *CFTR* mutations in those of Northern European descent, as it is the most common, severe, autosomal recessive disease in this ethnicity. Offering screening for these 12 mutations in those of Northern European descent has a test sensitivity of approximately 83%.[13]

Test sensitivity would be lower for many people who might be offered screening for CF carrier status in the public health system due to the high ethnic diversity in this population. For example, less than 50% of Asian CF carriers will be identified by the 23 *CFTR* mutation panel recommended by ACMG/ACOG albeit that the *a priori* risk of being a carrier is much lower in this population compared to for Northern Europeans.[13]

Offering screening in the public health system will not only decrease test sensitivity, reducing the number of carriers identified, it will also complicate pre-test information and residual risk calculations. In addition, as previously mentioned, not offering carrier screening based on ethnicity has ethical implications. In order to offer screening in the public health system pre-test information needs to include data on the incidence of CF in different ethnic populations and the associated residual risk estimates.

Provision of information

Women in the public health system have a lower level of general knowledge with regard to CF and CF carrier screening compared to those in the private health system. As previously mentioned, this may be linked to education level, with women in the public health system having a lower level of education

than those in the private health system. In addition, there are a higher number of women who do not speak English and women from non-English speaking backgrounds in the public health system compared to the private health system, making provision of information with regard to screening for CF carrier status more difficult. The information in relation to screening would need to be available in multiple languages.

Lack of knowledge has implications with regard to both informed consent and uptake of screening. It is important to provide enough information to ensure participants can make an educated decision with regard to having screening, particularly as our studies have shown that the majority of participants decline an offer of screening based on misinformation on recessive diseases and the misconception that the majority of carriers of CF have a family history of the disease.

In order to effectively offer screening for CF carrier status in the public health system, education resources and programs need to developed and targeted towards potential participants as well as health professionals, including obstetricians, general practitioners and midwives, who will be offering screening to their patients.

9.2.4 Setting

Gatekeepers of screening

CF carrier screening is mainly offered by health professionals, to pregnant women and/or couples planning a pregnancy. Our study shows that the majority of women who did not receive an offer of screening would prefer to receive an offer of screening and pre-test information from their doctor. Doctor's recommendation with regard to screening has also been shown to be an influencing factor in the decision to accept an offer of screening.[28, 40, 42] Therefore, health professionals are key stakeholders in CF carrier screening, as they are the gatekeepers of screening and their attitudes, opinions and knowledge in regards to CF carrier screening is significant in the effectiveness of offering population-based screening.

Various studies have shown that health professionals perceive various practical barriers to the offering of screening for CF carrier status. A recent study by Stark and colleagues showed that barriers identified by health professionals in regards to the routine offering of genetic carrier screening were: time constraints, costs and availability of supporting services.[41] A lack of knowledge and experience in regards to CF and genetic screening has also been indicated as a barrier to the offer of screening for CF carrier status, with health professionals not having

confidence in their ability to provide screening to their patients.[103-106] Mennie and colleagues also found a gap in the knowledge of health professionals, with only a small number of GPs thinking CF carrier screening should be offered to those without a family history.[107]

During the recruitment phase of our study exploring the attitudes of women who declined an offer of CF carrier screening, we discovered through field notes that obstetricians were not routinely offering screening to all their patients. This may be due to some of the barriers previously mentioned or the fact that health professionals offer screening to patients based on certain criteria. The proposed selection criteria used by health professionals for offering screening may include: perceived susceptibility, maternal age, ethnicity, perceived interest and parity.

Therefore, while health care has been determined as the preferred setting in which to offer screening, in order for health professionals to routinely offer CF carrier screening effectively several barriers still need to be overcome.

Best time to offer screening

All of our studies have shown that participants believe the best time to offer CF carrier screening is prior to pregnancy as identification of carrier couples preconceptionally provides the most reproductive options as well as giving couples more time to make reproductive decisions. However preconception screening is associated with lower uptake than prenatal screening due to barriers including: lack of interest at this life stage, lack of preconception health care setting in which to offer screening and the fact that a large number of pregnancies are unplanned.[55]

The findings of our study exploring the opinions of pregnant women who did not receive an offer of CF carrier screening, showed that almost half of the participants saw health professionals prior to pregnancy. This was also shown in another Australian study with a higher uptake of CF screening at a family planning clinic compared to general practice.[27] While it has been proposed that preconception carrier screening is associated with low uptake due to a lack of preconception healthcare setting in which to offer screening, our results indicate that screening can be offered to women and couples seeking medical advice prior to pregnancy from their obstetrician or general practitioner.

Offering screening for CF carrier status in high school has been proposed as it can reach a large proportion of the population. High uptake has been associated with screening in Jewish high schools and screening can be offered in an educational environment, facilitating voluntary and informed decisions.[21, 9] Our

study had similar findings with 98% of Jewish high school students accepting an offer of screening.

The main criticism of offering CF carrier screening in a high school setting is the delay in the use of information obtained, with the American College of Medical Genetics (ACMG) stating that carrier screening should not be offered to adolescents as the information is only relevant for reproductive planning.[79] However, research indicates that adolescents not only recall their positive carrier status but also have their partner tested and use this information to make future reproductive decisions.[76, 108] Other concerns were that adolescents identified as carriers of CF would face stigmatisation and discrimination from peers. Yet research has shown that adolescent carriers have few negative psychological effects as a result of knowing their carrier status.[108]

9.3 Limitations

Since the implementation of the GHSV CF carrier screening program in 1996, only a small percentage of the population has been screened due to screening only being offered in the private health system and not all health professionals offer screening to their patients in that setting. The limited number of individuals who have been screened has resulted in only a small number of carrier couples being identified. Therefore a limitation of the study presented in Chapter 6 which reported the outcome of interviews with carrier couples, was the small sample size restricting the generalisability of these findings. In addition, the former male partners of both couples that divorced since screening declined to participate in the study, preventing their experiences from being heard.

Furthermore, in the case of Chapter 7, which reported the study of those who declined screening, participants were recruited from a small number of obstetric clinics, with approximately half of the participants being recruited from a single obstetrician. This is due, as previously mentioned, to the fact that screening is only offered in the private health system with only a limited number of obstetricians and obstetric clinics associated with the program. This results in limited variability in the sample, particularly with regard to provision of information, and may not be truly representative of the population of pregnant women in the private health system that declined an offer of CF carrier screening.

The public health system is ethnically diverse. Participants in the study, reported in Chapter 8, were required to read and write English in order for them to complete the questionnaire. The exclusion of women from non-English speaking backgrounds resulted in the under-representation of certain ethnic

groups in our sample. Therefore, the ethnicity of our sample is limited in variability and may not be truly representative of the population of pregnant women in the public health system.

9.4 Concluding statements

In order to increase uptake of CF carrier screening, pre-test information needs to be targeted towards potential participants to inform them about the genetic nature of autosomal recessive diseases as the main reason for declining an offer of CF carrier screening was lack of family history of the disease.

The current program is inequitable as screening is only offered in the private health sector. In order to ensure equity of access screening needs to be offered in the public health sector with no out-of-pocket expenses, and educational resources and programs need to be developed and targeted towards potential participants.

As programs expand to screen for more diseases truly informed consent may not be possible, with the more diseases screened for likely to result in less knowledge. Pre-test information should provide basic information on the genetics of recessive conditions which can be applied to all of the diseases screened for, while detailed information should be targeted towards carriers during post-test counselling.

9.5 Future directions

To date research has been conducted to ascertain the views of the majority of key stakeholders with regard to the offer of population-based CF carrier screening in Victoria, Australia. We have sought of the views of individuals who accepted an offer of CF carrier screening (carrier couples, carriers and non-carriers), pregnant women who declined an offer of CF carrier screening and pregnant women in the public health system that were not offered CF carrier screening.

The attitudes and opinions of individuals who have been diagnosed with CF have been explored with regard to offering CF carrier screening.[109] In addition, the views of family members of individuals diagnosed with CF and individuals with a family history of CF have been sought.[28]

Various studies have explored the attitudes of health professionals towards offering CF carrier screening to the general population.[28, 41, 110] However, they

were not in-depth studies and none have evaluated the offer of screening by health professionals associated with program.

Future studies should assess the attitudes of other key stakeholders to inform the Governments regarding population CF carrier screening.

1. Pregnant women in the private health system who were not offered CF carrier screening. While screening is offered in the private health system, not all obstetricians offer screening for CF carrier status or offer screening to all their patients. It would be interesting to explore the attitudes of such women towards and knowledge of CF and CF carrier screening and seek their views on whether they would like to have been offered screening.
2. Exploration of the attitudes, knowledge, facilitators and barriers of health professionals who have been involved in the current program (particularly obstetricians and general practitioners), as well as their experience with offering CF carrier screening, particularly with regard to the criteria for offering screening to their patients. It is important to obtain the views of this group as they are the gatekeepers of screening.
3. A study of health professionals in the public health system (obstetricians, general practitioners and midwives) who do not currently offer CF carrier screening exploring their attitudes towards and knowledge of CF and CF carrier screening as well as potential facilitators and barriers to offering CF carrier screening in the public health system. It will be of great interest to assess the views of those who do not currently offer CF carrier screening to help to determine how the program can be expanded to the public health system.
4. The views of policy makers, including State and Federal politicians and bureaucrats involved in health policy, in particular their views in relation to the introduction of a government funded population-wide CF carrier screening program.

An evaluation of the outcomes of multi-disease carrier screening in Ashkenazi Jewish high schools has been conducted. This was important to determine the effects of screening on carriers for single and/or multi-diseases.[111] In addition, it will be important to evaluate the outcomes of screening for direct-to-consumer multi-disease screening tests. The release of a direct-to-consumer test by United States company Counsyl, which screens for more than 100 autosomal and X-linked recessive diseases, provides an opportunity to evaluate

the test and assess the attitudes and outcomes of screening for both carriers and non-carriers.

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Appendix A

Participant Information Sheet

This appendix contains copies of the participant information sheets used in the evaluation of both the Multi-disease carrier screening program in Ashkenazi Jewish high schools and the GHSV population-based CF carrier screening program.

1. Carrier couples identified through the GHSV CF carrier screening program
2. Pregnant women in private health system who declined an offer of CF carrier screening
3. Pregnant women in the public health system who were not offered CF carrier screening (Interview)
4. Pregnant women in the public health system who were not offered CF carrier screening (Questionnaire)

GENETICHEALTH
Victorian Clinical Genetics Services

Dear Sir and Madam,

Research Project: Attitudes and outcomes of population genetic screening for cystic fibrosis

We are currently conducting a research project exploring the attitudes and outcomes of cystic fibrosis carrier screening. We are writing to you because you have had carrier screening for cystic fibrosis through Genetic Health Services Victoria, which was offered through your obstetrician or General Practitioner.

What is the purpose of this research?
We are seeking your views on cystic fibrosis carrier screening to find out why people do or do not choose to have carrier screening and to see how well our program is meeting the needs of people being offered screening. We will use the information from the study to improve the cystic fibrosis carrier screening program. We also intend to publish the results of the research so that others who are setting up carrier screening programs may benefit from the information.

Where did we find out your contact details?
Some time ago you had a carrier screening test for cystic fibrosis. Genetic Health Services Victoria run the screening program and your contact details were obtained from the cystic fibrosis carrier screening program database. As a clinical geneticist employed by Genetic Health Services Victoria I am coordinator of the screening program and I am sending this letter to you on behalf of the researchers from Murdoch Childrens Research Institute, who are named at the end of this letter. Please be assured that your details are only available to those involved in the screening program and the researchers will not be given details about your identity.

How can you be involved?
Participation in this project will involve a face-to-face interview, which will be audio-taped, and the completion of a questionnaire. You do not need to write your name on the questionnaire and your responses to the questionnaire and interview will be kept confidential. The information we obtain from you and others who respond will only be used for the purposes of this project. The data you contribute to the study will be kept for a period of seven years after publication. Any publication will not reveal information about you as an individual. We will not disclose any information you give us to any other organisation.
To participate in the interview please complete the enclosed consent form and questionnaire and return it in the reply-paid envelope provided. Once we have received your consent form will contact you to organize a suitable time and location for the interview. If you do not wish to participate in the interview you can still participate in this project by completing the questionnaire. The questionnaire should take less than 15 minutes to complete. Please return it in the reply-paid envelope to the Murdoch Childrens Research Institute.

Are there possible benefits or risks from taking part in this research?
We cannot guarantee or promise that you will receive any benefit from participating in this study. The results of the study will contribute to the future development of the cystic fibrosis screening program.

There is not likely to be any harm arising from completing the questionnaire. If any concerns are raised by participating in this study please contact one of the researchers who can arrange for you to see a genetic counsellor from Genetic Health Services Victoria.

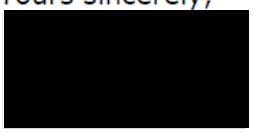
Do you have to take part in this research project?
Participation in this research project is voluntary. Your decision whether to take part or not to take part will not affect your relationship with the researchers or the care you receive from your doctor. By completing and returning the consent form and questionnaire you are consenting to participate in the research project. Participants can withdraw from research projects. However, please note that once you return this questionnaire we can not withdraw your data as the questionnaire is anonymous.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of the Department of Human Services. This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Who can you contact?
If you have any questions about the study or would like to know anything about the information you provide us, please contact Liane Ioannou or any of the other researchers on the numbers given below.

If you have any complaints about any aspects of the project or any questions about being a research participant in general, then you may contact Ms Vicki Xafis, Executive Officer, DHS Human Research Ethics Committee on (03) 9096 5239.

Yours sincerely,



Prof Martin Delatycki
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Clinical Geneticist, Genetic Health Services Victoria
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The researchers involved in this study are:

A/Prof John Massie
Respiratory Physician
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(03) 8341 6370

Liane Ioannou
PhD Student
Bruce Lefroy Centre for Genetic Health Research
Murdoch Childrens Research institute
0422118614

Research Project: Attitudes and outcomes of population genetic screening for cystic fibrosis

We are currently conducting a research project exploring the attitudes and outcomes of cystic fibrosis carrier screening. You can participate in this study because you have been offered cystic fibrosis carrier screening through your obstetrician or General Practitioner.

What is the purpose of this research?
We are seeking your views on cystic fibrosis carrier screening to find out why people do or do not choose to have carrier screening. We will use the information from the study to improve the cystic fibrosis carrier screening program. We also intend to publish the results of the research so that others who are setting up carrier screening programs may benefit from the information.

How can you be involved?
Participation in this project will involve completing the questionnaire and either returning it to Liane Ioannou in the waiting room or you can return it in the reply-paid envelope provided to the Murdoch Childrens Research Institute. You do not need to write your name on the questionnaire and your responses to the questionnaire will be kept confidential. The information we obtain from you and others who respond will only be used for the purposes of this project. The data you contribute to the study will be kept for a period of seven years after publication. Any publication will not reveal information about you as an individual. We will not disclose any information you give us to any other organisation. The questionnaire should take less than 15 minutes to complete.

Are there possible benefits or risks from taking part in this research?
We cannot guarantee or promise that you will receive any benefit from participating in this study. The results of the study will contribute to the future development of the cystic fibrosis carrier screening program.

There is not likely to be any harm arising from completing the questionnaire. If any concerns are raised by participating in this study please contact one of the researchers who can arrange for you to see a genetic counsellor from Genetic Health Services Victoria.

Do you have to take part in this research project?
Participation in this research project is voluntary. Your decision whether to take part or not to take part will not affect your relationship with the researchers or the care you receive from your doctor. By completing and returning the questionnaire you are consenting to participate in the research project. Participants can withdraw from research projects. However, please note that once you return this questionnaire we can not withdraw your data as the questionnaire is anonymous.
The ethical aspects of this research project have been approved by the Human Research Ethics Committee of the Department of Human Services. This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Who can you contact?
If you have any questions about the study or would like to know anything about the information you provide us, please contact Liane Ioannou or any of the other researches on the numbers given below.

If you have any complaints about any aspects of the project or any questions about being a research participant in general, then you may contact Ms Vicki Xafis, Executive Officer, DHS Human Research Ethics Committee on (03) 9096 5239.

The researchers involved in this study are:

Prof Martin Delatycki
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THE CYSTIC FIBROSIS CARRIER SCREENING STUDY

What is the study about?
The purpose of this project is to explore women's opinions about a genetic carrier test for cystic fibrosis.

Who is eligible to participate?
Women over the age of 18, who speak, read and write English and who are less than 20 weeks pregnant.

What is involved if I participate?
Participation in this project will involve an interview, which will take approximately 5-10 minutes and will be audio-taped.

How do I participate?
If you wish to participate in the project please see the student researcher, Liane Ioannou, in the waiting room. She will conduct the interview while you are waiting for your appointment and answer any questions you may have about the study. Participation will not delay your clinic appointment.

Participation in this research project is voluntary. Your decision whether to take part or not to take part will not affect your relationship with the researchers or the care you receive from your doctor.

If you do not have time today but would like to participate in the study via a telephone interview, please provide us with your name, telephone number and the most convenient time to contact you.

Name: _____

Contact No.: _____

Please **circle** the most convenient day/s and time/s in which to contact you:

Monday:	Morning	Afternoon	Evening
Tuesday:	Morning	Afternoon	Evening
Wednesday:	Morning	Afternoon	Evening
Thursday:	Morning	Afternoon	Evening
Friday:	Morning	Afternoon	Evening

GENETICHEALTH
Victorian Clinical Genetics Services

Research Project: The opinions and attitudes of women in the public health system towards the offer of cystic fibrosis carrier screening

We are currently conducting a research project exploring the attitudes and outcomes of cystic fibrosis carrier screening. You can participate in this study because you have not been offered cystic fibrosis carrier screening.

What is the purpose of this research?
We are seeking your views on cystic fibrosis carrier screening to find out whether people would like to be offered cystic fibrosis carrier screening. We will use the information from the study to improve the cystic fibrosis carrier screening program. We also intend to publish the results of the research so that others who are setting up carrier screening programs may benefit from the information.

How can you be involved?
Participation in this project will involve completing the questionnaire and either returning it to Liane Ioannou in the waiting room or you can return it in the reply-paid envelope provided to the Murdoch Childrens Research Institute. You do not need to write your name on the questionnaire and your responses to the questionnaire will be kept confidential. The information we obtain from you and others who respond will only be used for the purposes of this project. The data you contribute to the study will be kept for a period of seven years after publication. Any publication will not reveal information about you as an individual. We will not disclose any information you give us to any other organisation. The questionnaire should take less than 15 minutes to complete.

Are there possible benefits or risks from taking part in this research?
We cannot guarantee or promise that you will receive any benefit from participating in this study. The results of the study will contribute to the future development of the cystic fibrosis carrier screening program.

There is not likely to be any harm arising from completing the questionnaire. If any concerns are raised by participating in this study please contact one of the researchers who can arrange for you to see a genetic counsellor from Genetic Health Services Victoria.

Do you have to take part in this research project?
Participation in this research project is voluntary. Your decision whether to take part or not to take part will not affect your relationship with the researchers or the care you receive from your doctor. By completing and returning the questionnaire you are consenting to participate in the research project. Participants can withdraw from research projects. However, please note that once you return this questionnaire we can not withdraw your data as the questionnaire is anonymous.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of the Department of Human Services. This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Who can you contact?

If you have any questions about the study or would like to know anything about the information you provide us, please contact Liane Ioannou or any of the other researches on the numbers given below.

If you have any complaints about any aspects of the project or any questions about being a research participant in general, then you may contact Julie Gephart, Research Directorate, Southern Health Human Research Ethics Committee on (03)9594 4611.

The researchers involved in this study are:

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Appendix B

Questionnaire-based surveys

This appendix contains copies of the questionnaires used in the evaluation of both the Multi-disease carrier screening program in Ashkenazi Jewish high schools and the GHSV population-based CF carrier screening program.

1. Students offered multi-disease carrier screening at Ashkenazi Jewish high schools
2. Carrier couples identified through the GHSV CF carrier screening program
3. Pregnant women in private health system who declined an offer of CF carrier screening
4. Pregnant women in the public health system who were not offered CF carrier screening

High School Screening Program Questionnaire

GENETICHEALTH Victorian Clinical Genetics Services

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

MONASH University

About you

1 Gender

- ☐ Male
- ☐ Female

2 Age

- ☐ 14
- ☐ 15
- ☐ 16
- ☐ 17
- ☐ 18

3 Year level

- ☐ 10
- ☐ 11
- ☐ 12

4 Do you have Jewish Ancestry?
Tick one box only

- ☐ Yes
- ☐ No
- ☐ Unsure

If yes, what type?
Tick one box only

- ☐ Ashkenazi (Eastern European)
- ☐ Sephardi (Middle Eastern)
- ☐ Mixed
- ☐ Not sure

5 Are you studying Biology?

- ☐ Yes
- ☐ No

Your knowledge

Please answer the following questions
Tick one box only

6 Cystic fibrosis affects the brain

- ☐ True
- ☐ False
- ☐ Unsure

7 Bloom syndrome predisposes to cancer

- ☐ True
- ☐ False
- ☐ Unsure

8 Canavan disease usually causes a person to die in childhood

- ☐ True
- ☐ False
- ☐ Unsure

9 Tay Sachs disease only affects Jewish people

- ☐ True
- ☐ False
- ☐ Unsure

10 If the test shows you are not a carrier you cannot have a child with that condition

- ☐ True
- ☐ False
- ☐ Unsure

11 This program screens for 5 different genetic conditions

- ☐ True
- ☐ False
- ☐ Unsure

12 **A carrier has one copy of an altered gene**

- ☐ True
- ☐ False
- ☐ Unsure

13 **Some carriers develop symptoms of the disease**

- ☐ True
- ☐ False
- ☐ Unsure

14 **For a couple to have a child with one of the diseases being tested for, both need to be carriers of an altered gene**

- ☐ True
- ☐ False
- ☐ Unsure

15 **All people have some altered genes**

- ☐ True
- ☐ False
- ☐ Unsure

Your decision

16 **Are you going to have the genetic test today**

Tick one box only

☐ **Yes**

If you are having the genetic test today, how much did each of the following factors influence your decision on having screening?

Please circle a number on EACH of the following scales

	Not at all				Extremely
1. Want to know if I am a carrier	1	2	3	4	5
2. The test is free now	1	2	3	4	5
3. It is easier to have the test now than later	1	2	3	4	5
4. It is promoted as a good thing to do by the Jewish community	1	2	3	4	5
5. My parents want me to have the test	1	2	3	4	5
6. My friends are having the test	1	2	3	4	5

☐ **No**

If you are not having the genetic test today, how much did each of the following factors influence your decision on having screening.

Please circle a number on EACH of the following scales

	Not at all				Extremely
1. I never want to know if I am a carrier or not	1	2	3	4	5
2. I do not want to know if I am a carrier at this time in my life	1	2	3	4	5
3. My risk of being a carrier is low	1	2	3	4	5
4. My parents do not want me to have the test	1	2	3	4	5
5. I want more time to think/ discuss it	1	2	3	4	5
6. I want more information	1	2	3	4	5

17 **Do you feel you know enough to make a decision about having the genetic test?**
Tick one box only

- ☐ Yes
- ☐ No
- ☐ Unsure

If no, what else would you like to know? .....
.....

18 **Have you discussed with someone or sought any further information about the genetic diseases or the screening program since the education session?**

- ☐ Yes
- ☐ No

If yes, from where or with whom?

- ☐ Internet
- ☐ Family
- ☐ Doctor
- ☐ Friends
- ☐ Library
- ☐ Genetic Counsellor
- ☐ Rabbi or other religious leader
- ☐ Other

If Other, please specify.....
.....

19 **Have any of your relatives been tested for any of the genetic diseases being screened for?**
Tick one box only

- ☐ Yes
- ☐ No
- ☐ Don't know

If yes, who?

- ☐ Parent
- ☐ Brother/Sister
- ☐ Grandparent
- ☐ Aunt/Uncle
- ☐ Cousin

20 **Do you have a family history or have a relative who is a carrier of any of the diseases being screened for?**

- ☐ Yes
- ☐ No
- ☐ Don't know

Your feelings

21 **A number of statements which people have used to describe themselves are given below. Circle a number for each statement to indicate how you feel right now at this moment...**

	Not at all	Somewhat	Moderately	Very Much
1. I feel calm	1	2	3	4
2. I feel tense	1	2	3	4
3. I am upset	1	2	3	4
4. I feel relaxed	1	2	3	4
5. I feel content	1	2	3	4
6. I am worried	1	2	3	4

22 **How do you think you would feel if you found out that you are a carrier of a genetic disease?**
Please circle a number on EACH of the following scales

	Not at all				Extremely
1. I would be worried about my own health	1	2	3	4	5
2. I would feel angry	1	2	3	4	5
3. I would feel depressed	1	2	3	4	5
4. I would be scared	1	2	3	4	5
5. I would feel less confident	1	2	3	4	5
6. I would feel inadequate	1	2	3	4	5

Carrier screening for cystic fibrosis

Questionnaire

Thank you for completing this questionnaire. This is for a research project exploring the attitudes and outcomes of cystic fibrosis carrier screening. You can participate in this study because you have been offered cystic fibrosis carrier screening through your Obstetrician or General Practitioner and accepted it.

For further information please contact:

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Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

GENETICHEALTH
Victorian Clinical Genetics Services

MONASH University

Section 1:

All Participants

Below is a list of questions about you that will help us with analysing the responses from this survey.

1. Gender: ☐ Male ☐ Female

2. Age: ____

3. Education Level (highest level achieved):

   ☐ Year 11 or less ☐ Finished secondary school ☐ Trade/apprenticeship

   ☐ College certificate/ diploma ☐ University qualification ☐ Other: _____

4. In the main job you currently hold, what is your occupation? (give full title)
   (*If no longer working due to parenthood, please state your previous occupation*)

   _____

5. Household Income (per annum):

   ☐ $20-40,000 ☐ $41-60,000 ☐ $61-80,000

   ☐ $81-100,000 ☐ $100,000+

6. Which culture/ancestry/ethnicity do you most identify with?
   (*please list as many as apply to you, for example: Australian-Chinese*)

   _____

7. Do you have an affinity with any religion or church?

   ☐ Yes ☐ No ☐ Unsure

   a. **If yes, which** religion or church do you have an affinity with?

   _____

   b. **If yes, how much** do your religious beliefs influence the decisions you make in your life?

   ☐ Not at all ☐ Very little ☐ Neutral ☐ Very much ☐ Completely

8. **At the time** of the offer of screening:

   a. Did you have a **partner**? ☐ Yes ☐ No

   b. Were you **pregnant**? ☐ Yes ☐ No

      I. If you were pregnant, would you have preferred to have been offered testing **before pregnancy**?

      ☐ Yes ☐ No ☐ Unsure

   c. How many **children** did you have? ___

9. **Knowledge** of cystic fibrosis

INSTRUCTIONS:
Below is a list of questions about your knowledge of cystic fibrosis. Please read each one carefully, and tick the box that best describes your knowledge, views or feelings. Tick only one box for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.

	True	False	Unsure
a. Cystic fibrosis is a life shortening condition.	☐	☐	☐
b. Cystic fibrosis affects more males than females.	☐	☐	☐
c. Cystic fibrosis is a condition that affects the lungs.	☐	☐	☐
d. Cystic fibrosis is an inherited condition.	☐	☐	☐
e. A child with cystic fibrosis inherits the gene change (mutation) from both parents.	☐	☐	☐
f. Couples who have a child with cystic fibrosis usually have a family history of this condition.	☐	☐	☐
g. If both parents are carriers of the cystic fibrosis gene change (mutation) they can have a child who does not have cystic fibrosis.	☐	☐	☐
h. If a person has one copy of the cystic fibrosis gene change (mutation), they are a carrier.	☐	☐	☐
i. Carriers of cystic fibrosis show signs of the disease.	☐	☐	☐
j. The cystic fibrosis genetic test can identify all cystic fibrosis carriers in a group that is tested.	☐	☐	☐
k. If only one partner of a couple is a carrier of the cystic fibrosis gene change (mutation), there is still a small chance of having a child with cystic fibrosis.	☐	☐	☐
l. A couple needs to be tested to determine their risk as a couple of having a child with CF every time they have a baby.	☐	☐	☐
m. If you are a carrier of cystic fibrosis your partner's test result will determine your risk as a couple of having a child with CF.	☐	☐	☐
n. If your test result indicates that you are a non-carrier your risk of being a carrier is greatly reduced.	☐	☐	☐
o. If no gene change is found the person can not be a carrier of cystic fibrosis.	☐	☐	☐

Section 2:

Reasons for accepting cystic fibrosis carrier screening

INSTRUCTIONS:
Below is a list of factors that may have influenced your decision to have a cystic fibrosis carrier screening test. Please read each one carefully, and state whether the factor influenced your decision to have screening by **circling the appropriate number**.
1 represents 'did not influence decision in the least' and 5 represents 'strongly influenced decision.' *Circle only one number for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.*

	Did Not Influence				Strongly Influenced
1. My doctor's recommendation about whether I should have the test	1	2	3	4	5
2. My partner's opinion about whether I should have the test	1	2	3	4	5
3. I have a family history of cystic fibrosis	1	2	3	4	5
4. I have a family history of other genetic conditions	1	2	3	4	5
5. I think that cystic fibrosis is a severe disease	1	2	3	4	5

	Did Not Influence				Strongly Influenced
6. I thought I would probably be a carrier of the gene change (mutation)	1	2	3	4	5
7. I could consider a termination of pregnancy in certain circumstances	1	2	3	4	5

If there was **another reason that is not listed above**, please write it in the space below and indicate how influential it was in you making the decision to have cystic fibrosis carrier screening.

8. Other (please specify): _____	1	2	3	4	5

Section 3:

Feelings

INSTRUCTIONS:
A number of statements which people use to describe themselves are given below. Read each statement and then circle the most appropriate number to indicate how you *feel **right at this moment***. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which best describes your ***current feelings***. *Please make sure you circle one number for each option*

	Not at all	Somewhat	Moderately	Very much
a. I feel calm	1	2	3	4
b. I feel tense	1	2	3	4
c. I am upset	1	2	3	4
d. I feel relaxed	1	2	3	4
e. I feel content	1	2	3	4
f. I am worried	1	2	3	4

Section 4:

Cystic fibrosis carrier screening process

INSTRUCTIONS:
Some time ago, you had a carrier screening test for cystic fibrosis. Below is a list of questions in regards to your feelings towards the cystic fibrosis carrier screening process. Please read each one carefully, and provide an appropriate answer that best describes your view and feelings. *Tick only one box for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.*

1. Who offered you carrier screening for cystic fibrosis?

☐ My Obstetrician ☐ My General Practitioner ☐ I asker for screening ☐ Other

If Other, please specify: _____

2. How long has it been since you had cystic fibrosis carrier screening?

☐ <6 months ☐ 6-12 months ☐ Over 12 months

3. Were you **satisfied** with the information provided before you had cystic fibrosis carrier screening?

a. Doctor's explanation ☐ Yes ☐ No ☐ Don't remember

b. Brochure ☐ Yes ☐ No ☐ Don't remember

4. Did you seek more information?

☐ Yes ☐ No ☐ Don't remember

a. If **yes**, where did you obtain more information?

☐ Internet
☐ Healthcare Professional
☐ Library
☐ Other (please specify):
_____

5. Did you discuss your decision to have a carrier screening test for cystic fibrosis with any of the following people? (*tick as many as apply*)

☐ Parent/s ☐ Partner ☐ Friend/s
☐ Brother/Sister ☐ Grandparent/s ☐ Aunt/Uncle
☐ Healthcare Professional ☐ Other relative ☐ Not anyone

6. At the time of being offered carrier screening you were given a "screening pack" by your doctor to take home with you. We are very interested to hear your thoughts about the contents of the pack and how helpful it was to you. Please indicate whether the following aspects of the cystic fibrosis carrier screening pack met your needs. (*If you do not remember receiving a screening pack please proceed to Question 7*)

a. **Information** provided about cystic fibrosis and cystic fibrosis carrier screening
☐ Yes ☐ No ☐ Unsure

b. **Instructions** relating to the process of cystic fibrosis carrier screening
☐ Yes ☐ No ☐ Unsure

c. **Ease of returning** the cheek brush swab
☐ Yes ☐ No ☐ Unsure

d. Do you have any comments on how the screening pack could be **improved**?

7. Where did you do your cheek brush test?

☐ Home ☐ Doctor's office ☐ Other (please specify): _____

8. Would you have preferred a blood test instead of a cheek brush swab?

☐ Yes ☐ No ☐ Unsure

9. What was the **best feature** of the cystic fibrosis carrier screening program?

10. What was the **worst feature** of the cystic fibrosis carrier screening program?

11. What were the **results** of your cystic fibrosis carrier screening test?

☐ Carrier ☐ Non-carrier ☐ Unsure

12. What does this result mean with respect to your risk of having a child with cystic fibrosis?

13. Has your **partner** had cystic fibrosis carrier screening?

☐ Yes ☐ No ☐ Don't Remember

a. If yes, what were the **results** of their cystic fibrosis carrier screening test?

☐ Carrier ☐ Non-carrier ☐ Unsure

14. Have you **recommended** cystic fibrosis carrier screening to other family members and friends?

☐ Yes ☐ No ☐ Unsure

15. If you had your time again, would you have the carrier test for cystic fibrosis?

☐ Yes ☐ No ☐ Unsure

16. When would be the **best time** to be offered cystic fibrosis carrier screening?

☐ Before pregnancy ☐ During pregnancy ☐ Unsure

Section 4:

Cascade testing

INSTRUCTIONS:
Below is a list of questions in regards to your actions after participating in cystic fibrosis carrier screening. Please read each one carefully, and tick the box that best describes your knowledge, views or feelings. *Tick only one box for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.*

1. Have you **informed** other family members of their increased risk of being carriers?

☐ Yes ☐ No ☐ Don't remember

a. If yes, who?

☐ My mother and/or father ☐ My cousin ☐ My Grandparent/s

☐ My brother or sister ☐ My Aunt/Uncle ☐ Other relative (please specify):

_____

b. Why did you **inform** the specific relative/relatives above?

_____

_____

_____

_____

2. Have you **recommended** cystic fibrosis carrier screening to other family members?

☐ Yes ☐ No ☐ Don't remember

a. If yes, who?

☐ My Mother and/or father ☐ My cousin ☐ My Grandparent/s

☐ My brother or sister ☐ My Aunt/Uncle ☐ Other relative (please specify):

_____

b. Why did you **recommend** screening to the specific relative/relatives above?

_____

_____

_____

_____

3. Has anyone in your immediate or extended **family had testing** for cystic fibrosis since you participated in the cystic fibrosis carrier screening program?

☐ Yes ☐ No ☐ Unsure

a. If yes, who?

☐ My mother and/or father ☐ My cousin ☐ My Grandparent/s

☐ My brother or sister ☐ My Aunt/Uncle ☐ Other relative (please specify):

_____

Thank-you for completing this survey.

Your participation is greatly appreciated.

Carrier screening for cystic fibrosis
Questionnaire

Thank you for completing this questionnaire. This is for a research project exploring the attitudes and outcomes of cystic fibrosis carrier screening. You can participate in this study because you have been offered cystic fibrosis carrier screening through your Obstetrician or General Practitioner and declined it.

For further information please contact:

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Healthier Kids. Healthier Future.

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Victorian Clinical Genetics Services

MONASH University

Section 1:

All Participants

Below is a list of questions about you that will help us with analysing the responses from this survey.

1. Gender: ☐ Male ☐ Female

2. Age: ____

3. Education Level (highest level achieved):

   ☐ Year 11 or less ☐ Finished secondary school ☐ Trade/apprenticeship

   ☐ College certificate/ diploma ☐ University qualification ☐ Other: _____

4. In the main job you currently hold, what is your occupation? (give full title)
   (*If no longer working due to parenthood, please state your previous occupation*)

   _____

5. Household Income (per annum):

   ☐ $20-40,000 ☐ $41-60,000 ☐ $61-80,000

   ☐ $81-100,000 ☐ $100,000+

6. Which culture/ancestry/ethnicity do you most identify with?
   (*please list as many as apply to you, for example: Australian-Chinese*)

   _____

7. Do you have an affinity with any religion or church?

   ☐ Yes ☐ No ☐ Unsure

   a. **If yes, which** religion or church do you have an affinity with?

   _____

   b. **If yes, how much** do your religious beliefs influence the decisions you make in your life?

   ☐ Not at all ☐ Very little ☐ Neutral ☐ Very much ☐ Completely

8. **At the time** of the offer of screening:

   a. Did you have a **partner**? ☐ Yes ☐ No

   b. Were you **pregnant**? ☐ Yes ☐ No

      I. If you were pregnant, would you have preferred to have been offered testing **before pregnancy**?

      ☐ Yes ☐ No ☐ Unsure

      II. If you were pregnant, did you have **Down syndrome** screening/testing?

      ☐ Yes ☐ No ☐ Unsure

   c. How many **children** did you have? ___

9. **Knowledge** of cystic fibrosis

INSTRUCTIONS:
Below is a list of questions about your knowledge of cystic fibrosis. Please read each one carefully, and tick the box that best describes your knowledge, views or feelings. Tick only one box for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.

	True	False	Unsure
a. Cystic fibrosis is a life shortening condition.	☐	☐	☐
b. Cystic fibrosis affects more males than females.	☐	☐	☐
c. Cystic fibrosis is a condition that affects the lungs.	☐	☐	☐
d. Cystic fibrosis is an inherited condition.	☐	☐	☐
e. A child with cystic fibrosis inherits the gene change (mutation) from both parents.	☐	☐	☐
f. Couples who have a child with cystic fibrosis usually have a family history of this condition.	☐	☐	☐
g. If both parents are carriers of the cystic fibrosis gene change (mutation) they can have a child who does not have cystic fibrosis.	☐	☐	☐
h. If a person has one copy of the cystic fibrosis gene change (mutation), they are a carrier.	☐	☐	☐
i. Carriers of cystic fibrosis show signs of the disease.	☐	☐	☐
j. The cystic fibrosis genetic test can identify all cystic fibrosis carriers in a group that is tested.	☐	☐	☐
k. If only one partner of a couple is a carrier of the cystic fibrosis gene change (mutation), there is still a small chance of having a child with cystic fibrosis.	☐	☐	☐
l. A couple needs to be tested to determine their risk as a couple of having a child with CF every time they have a baby.	☐	☐	☐
m. If you are a carrier of cystic fibrosis your partner's test result will determine your risk as a couple of having a child with CF.	☐	☐	☐
n. If your test result indicates that you are a non-carrier your risk of being a carrier is greatly reduced.	☐	☐	☐
o. If no gene change is found the person can not be a carrier of cystic fibrosis.	☐	☐	☐

Section 2:

Reasons for declining cystic fibrosis carrier screening

INSTRUCTIONS:
Below is a list of factors that may have influenced your decision not to have a cystic fibrosis carrier screening test. Please read each one carefully, and state whether the factor influenced your decision to have screening by **circling the appropriate number**.
1 represents 'did not influence decision in the least' and 5 represents 'strongly influenced decision.' *Circle only one number for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.*

	Did Not Influence				Strongly Influenced
1. I didn't have time	1	2	3	4	5
2. My doctor's recommendation about whether I should have the test	1	2	3	4	5
3. My partner's opinion about whether I should have the test	1	2	3	4	5
4. I don't have a family history of cystic fibrosis	1	2	3	4	5
5. I don't have a family history of other genetic conditions	1	2	3	4	5
6. I thought that I would not be a carrier of the gene change (mutation)	1	2	3	4	5

	Did Not Influence				Strongly Influenced
7. I have previously had healthy child/ children	1	2	3	4	5
8. The cost of the cystic fibrosis carrier screening test	1	2	3	4	5
9. I would not consider a termination of pregnancy for any reason	1	2	3	4	5
10. I would not consider a termination of pregnancy for cystic fibrosis	1	2	3	4	5

If there was **another reason that is not listed above**, please write it in the space below and indicate how influential it was in you making the decision to not have cystic fibrosis carrier screening.

11. Other (please specify): _____ _____ _____ _____	1	2	3	4	5

12. What do you think is a **reasonable price to pay** for a cystic fibrosis carrier test?

☐ Free ☐ Less than $50 ☐ $50-100

☐ $100-200 ☐ $200-300 ☐ $300-500

☐ $500+

Section 3:

Decision Making

INSTRUCTIONS:
Please **circle the number** which represents the words that best show how you feel about the decision you made. *Circle only one number for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.*

	Strongly Agree				Strongly Disagree
a. It was the right decision	1	2	3	4	5
b. I regret the choice that was made	1	2	3	4	5
c. I would make the same choice if I had to do it over again	1	2	3	4	5
d. The choice did me a lot of harm	1	2	3	4	5
e. The decision was a wise one	1	2	3	4	5

Section 4:

Information and Education

1. Did you feel you had enough **information** to make a decision about having cystic fibrosis carrier screening?

   ☐ Yes ☐ No ☐ Unsure

   a. If **no**, what else would you have liked to know?

   .....

   .....

2. Where did you receive the **majority of your information** about cystic fibrosis and cystic fibrosis carrier screening?

   ☐ Doctor ☐ Brochure ☐ Website ☐ Other

   If Other, please specify: _____

3. Were you **satisfied** with the information provided in the brochure?

   ☐ Yes ☐ No ☐ Unsure

4. Did you look at the Genetic Health Services Victoria cystic fibrosis carrier screening program **website**?

   ☐ Yes ☐ No ☐ Unsure

5. Did you discuss with someone or seek any **further information** about cystic fibrosis or cystic fibrosis carrier screening before making your decision?

   ☐ Yes ☐ No

   a. If **yes**, from where or with whom?

   ☐ Internet
   ☐ Doctor
   ☐ Family/Friends
   ☐ Genetic Counsellor
   ☐ Other (please specify):
   _____

6. Would you like to be offered the opportunity to be **tested at another time**?

   ☐ Yes ☐ No ☐ Unsure

   a. If **yes**, when do you think would be the best time?

   ☐ Before Pregnancy ☐ During pregnancy ☐ Unsure

7. Do you think cystic fibrosis carrier screening **should be available** for those who would like it?

   ☐ Yes ☐ No ☐ Unsure

Thank-you for completing this survey.

Your participation is greatly appreciated.

Genetic Screening
Questionnaire

Thank you for completing this questionnaire. This questionnaire explores your attitudes and opinions towards screening for inherited conditions. These are genetic conditions that can be inherited from healthy parents for which options are available if they wish to prevent the birth of a child with the condition.

For further information please contact:

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Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

GENETICHEALTH
Victorian Clinical Genetics Services

MONASH University

Section 1:

Demographics

Below is a list of questions about you that will help us with analysing the responses from this survey.

1. Gender: ☐ Male ☐ Female

2. Age: ____

3. Education Level (highest level achieved):

   ☐ Year 11 or less ☐ Finished secondary school ☐ Trade/apprenticeship

   ☐ College certificate/ diploma ☐ University qualification ☐ Post Graduate qualification

   ☐ Other: _____

4. In the main job you currently hold, what is your occupation? (give full title)
   (*If no longer working due to parenthood, please state your previous occupation*)
   _____

5. Household Income (per annum):

   ☐ $20-40,000 ☐ $41-60,000 ☐ $61-80,000

   ☐ $81-100,000 ☐ $100,000+

6. Which culture/ancestry/ethnicity do you most identify with?
   (*please list as many as apply to you, for example: Australian-Chinese*)
   _____

7. Do you have an affinity with any religion or church?

   ☐ Yes ☐ No ☐ Unsure

   a. **If Yes, which** religion or church do you have an affinity with?
   _____

   b. **If Yes, how much** do your religious beliefs influence the decisions you make in your life?

   ☐ Not at all ☐ Very little ☐ Neutral ☐ Very much ☐ Completely

8. **At the time** of completing the questionnaire:

   a. Do you have a **partner**? ☐ Yes ☐ No

   b. How many **children** do you have? (not including this pregnancy) ___

   c. Are you **pregnant**? ☐ Yes ☐ No

Please continue over page

9. Did you see a doctor prior to pregnancy to discuss health issues relating to pregnancy?

☐ Yes ☐ No ☐ Unsure

If No, please continue on to Section 2.

a. If Yes, who did you discuss pre-pregnancy health issues with?

☐ Family Doctor / GP ☐ Obstetrician ☐ Midwife ☐ Other

If Other, please specify: _____

b. If Yes, were any genetic issues discussed?

☐ Yes ☐ No ☐ Can't Remember

Please continue over page

Section 2:

Genetic Screening during Pregnancy

1. Where you provided with any information in regards to screening **for Down syndrome**?

☐ Yes ☐ No ☐ Unsure

a. If yes, how was the information provided? (please tick as many as apply)

☐ Doctor's Explanation ☐ Brochure ☐ Website ☐ Other

If Other, please specify: _____

2. If you are currently pregnant, did you have or are you planning to have screening/testing **for Down syndrome**?

☐ Yes ☐ No ☐ Unsure

3. Who offered you screening for **Down syndrome**?

☐ Doctor ☐ Obstetrician ☐ Midwife

☐ Wasn't offered ☐ Other

If Other, please specify: _____

4. Below are some inherited conditions that can be screened for during pregnancy.

a. Where you offered testing for any of these conditions?
(*please tick as many as apply*)

☐ Thalassemia ☐ Tay Sachs disease ☐ Spinal Muscular Atrophy

☐ Cystic fibrosis ☐ Fragile X Syndrome ☐ Other: _____

b. Were you tested for any of these conditions?
(*please tick as many as apply*)

☐ Thalassemia ☐ Tay Sachs disease ☐ Spinal Muscular Atrophy

☐ Cystic fibrosis ☐ Fragile X Syndrome ☐ Other: _____

Please continue over page

5. Factors that may influence your decision to have genetic screening

INSTRUCTIONS:
Below is a list of factors that may influence your decision to have genetic screening for inherited conditions. Please read each one carefully, and state whether the factor would influence your decision to have screening by **circling the appropriate number**.
1 represents 'would not influence decision in the least' and 5 represents 'would strongly influence decision.' *Circle only one number for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.*

	Not Influence				Strongly Influence
1. Doctor's recommendation about whether I should have the test	1	2	3	4	5
2. Partner's opinion about whether I should have the test	1	2	3	4	5
3. Family history of the condition being screened for	1	2	3	4	5
4. Family history of other genetic conditions	1	2	3	4	5
5. If I thought that I would be a carrier of the gene change (mutation)	1	2	3	4	5
6. I already have healthy children	1	2	3	4	5
7. Cost of the test	1	2	3	4	5
8. My attitude towards termination of an affected pregnancy	1	2	3	4	5

If there was **another reason that is not listed above**, please write it in the space below and indicate how influential it was in you making the decision to not have cystic fibrosis carrier screening.

	Not Influence				Strongly Influence
11. Other (please specify): _____	1	2	3	4	5

6. Do you think that genetic screening for inherited conditions should be offered to everyone even if there is no family history of these conditions?

☐ Yes ☐ No ☐ Unsure

If No, please continue on to Section 3.

a. If Yes, when do you think would be the best time to offer screening?

☐ Before Pregnancy ☐ During Pregnancy ☐ High School ☐ Anytime

b. If Yes, would you want to have been offered screening in this pregnancy?

☐ Yes ☐ No ☐ Unsure

Please continue over page

Section 3:

Cystic fibrosis carrier screening

1. Have you heard of **cystic fibrosis**?

☐ Yes ☐ No ☐ Unsure

2. **Knowledge** of cystic fibrosis

INSTRUCTIONS:
Below is a list of questions about your knowledge of cystic fibrosis. Please read each one carefully, and tick the box that best describes your knowledge, views or feelings. Tick only one box for each question and do not skip any questions. If you change your mind, cross out your first mark clearly.

	True	False	Unsure
a. Cystic fibrosis is a life shortening condition.	☐	☐	☐
b. Cystic fibrosis affects more males than females.	☐	☐	☐
c. Cystic fibrosis is a condition that affects the lungs.	☐	☐	☐
d. Cystic fibrosis is an inherited condition.	☐	☐	☐
e. A child with cystic fibrosis inherits the gene change (mutation) from both parents.	☐	☐	☐
f. Couples who have a child with cystic fibrosis usually have a family history of this condition.	☐	☐	☐
g. If both parents are carriers of the cystic fibrosis gene change (mutation) they can have a child who does not have cystic fibrosis.	☐	☐	☐

	True	False	Unsure
h. If a person has one copy of the cystic fibrosis gene change (mutation), they are a carrier.	☐	☐	☐
i. Carriers of cystic fibrosis show signs of the disease.	☐	☐	☐
j. The cystic fibrosis genetic test can identify all cystic fibrosis carriers in a group that is tested.	☐	☐	☐
k. If only one partner of a couple is a carrier of the cystic fibrosis gene change (mutation), there is still a small chance of having a child with cystic fibrosis.	☐	☐	☐
l. A couple needs to be tested to determine their risk as a couple of having a child with CF every time they have a baby.	☐	☐	☐
m. If you are a carrier of cystic fibrosis your partner's test result will determine your risk as a couple of having a child with CF.	☐	☐	☐
n. If your test result indicates that you are a non-carrier your risk of being a carrier is greatly reduced.	☐	☐	☐
o. If no gene change is found the person can not be a carrier of cystic fibrosis.	☐	☐	☐

Cystic fibrosis carrier screening is currently only offered on a fee-for-service basis at a cost of $220 a test. Individuals can be tested before or during pregnancy to determine whether they are a carrier of cystic fibrosis. If both individuals in a couple are carriers they are at risk of having a child with the condition and there are options available if they wish to prevent the birth of a child with that condition.

3. Do you think **cystic fibrosis** carrier screening should be offered in the public health system?

☐ Yes ☐ No ☐ Unsure

4. Who do you think should offer **cystic fibrosis** carrier screening?

☐ Family Doctor / GP ☐ Obstetrician ☐ Midwife ☐ Other

If Other, please specify: _____

5. How would you like to receive information about **cystic fibrosis** carrier screening?

☐ Doctor's Explanation ☐ Brochure ☐ Website ☐ Other

If Other, please specify: _____

6. How much do you think would be a reasonable price to pay for a **cystic fibrosis** carrier screening?

☐ Free ☐ Less than $50 ☐ $50-100 ☐ $100-200

☐ $200-300 ☐ $300-500 ☐ $500+

7. Would you like to have been offered carrier screening for **cystic fibrosis in this pregnancy?**

☐ Yes ☐ No ☐ Unsure

a. If Yes, would you have accepted the offer?

☐ Yes ☐ No ☐ Unsure

b. If No, would you have accepted the offer before you became pregnant?

☐ Yes ☐ No ☐ Unsure

Thank-you for completing this survey.
Your participation is greatly appreciated.

If you wish to find out more about cystic fibrosis carrier screening please contact:

Genetic Health Services Victoria
(03) 8341 6201

Or visit the website:

www.cfscreening.com

Appendix C

Supplementary material

This appendix contains supplementary information for the publication 'Population-based carrier screening for cystic fibrosis: A systematic review of 23 years of research.'

First Author	Year	Country	Setting	Method	Testing	Uptake
Axworthy et al.	1996	UK	General Pop.	Quant	Offered	
Bekker et al.	1994	UK	General Pop.	Mixed	Offered	17.3%
Bekker et al.	1993	UK	General Pop.	Quant	Offered	17.0%
Bernhardt et al.	1996	USA	General Pop.	Quant	Offered	23.5%
Botkin & Alemagno	1992	USA	Prenatal	Quant	Attitude	
Boulton et al.	1996	UK	General Pop.	Mixed	Offered	
Brandt et al.	1996	Denmark	General Pop.	Quant	Offered	
Brock et al.	1996	UK	Prenatal	Program Evaluation	Offered	69.0 - 71.0%
Castellani et al.	2011	Italy	Preconception	Quant	Offered	
Clausen et al.	1996	Denmark	Prenatal	Quant	Offered	89.0%
Clausen et al.	1996	Denmark	Prenatal	Quant	Offered	80.0 - 98.0%
Clayton et al.	1995	USA	Preconception	Quant	Offered	
Clayton et al.	1996	USA	Preconception	Quant	Offered	<1.0%
Cobb et al.	1991	UK	Preconception	Quant	Attitude	
Coiana et al.	2011	Italy	General Pop.	Quant	Offered	
Cuckle et al.	1996	UK	Prenatal	Quant	Offered	62.0%
Dacus et al.	2006	USA	Prenatal	Program Evaluation	Offered	46.0%
Decruyenaere et al.	1992	Belgium	General Pop.	Quant	Attitude	
Delvaux et al.	2001	Belgium	Prenatal	Quant	Offered	27.0%
Doherty et al.	1996	USA	Prenatal	Mixed	Offered	
Donaldson et al.	1995	UK	Prenatal	Quant	Offered	89.0 - 91.0%
Durfy et al.	1994	Canada	Preconception	Quant	Offered	84.2%
Fang et al.	1997	USA	Prenatal	Quant	Offered	
Flinter et al.	1992	UK	General Pop.	Program Evaluation	Offered	20.0%
Fries et al.	2005	USA	Prenatal	Quant	Offered	58.2%
Gordon et al.	2003	Australia	Preconception	Quant	Offered	
Green et al.	1992	UK	General Pop.	Quant	Attitude	
Grody et al.	1997	USA	Prenatal	Quant	Offered	67.0%
Hall et al.	2006	Australia	General Pop.	Mixed	Attitude	
Harris et al.	1993	UK	Prenatal	Mixed	Offered	95.7%
Harris et al.	1996	UK	Prenatal	Mixed	Offered	98.7%
Harris et al.	1992	UK	Prenatal	Mixed	Offered	
Hartley et al.	1997	UK	Preconception	Mixed	Offered	84.9%
Henneman et al.	2001	Netherlands	Preconception	Quant	Offered	2.0%
Henneman et al.	2002	Netherlands	Preconception	Quant	Offered	
Henneman et al.	2003	Netherlands	Preconception	Quant	Offered	5.2 - 15.0%
Henneman et al.	2004	Netherlands	Preconception	Quant	Offered	9.0 - 25.0%
Hill et al.	1995	UK	General Pop.	Quant	Attitude	
Honnor et al.	2000	Australia	Preconception	Quant	Offered	43.5%
Ioannou et al.	2010	Australia	General Pop.	Quant	Offered	
Ioannou et al.	2010	Australia	Prenatal	Quant	Offered	
Jung et al.	1994	Germany	Prenatal	Qual	Offered	99.8%
Kaplan et al.	1991	Canada	Preconception	Mixed	Offered	40.7%
Levenkron et al.	1997	USA	Prenatal	Quant	Offered	
Livingstone et al.	1994	UK	Prenatal	Quant	Offered	75.7%
Livingstone et al.	1993	UK	Prenatal	Quant	Offered	65.2%
Loader et al.	1996	USA	Prenatal	Quant	Offered	57.0%
Magnay et al.	1992	UK	General Pop.	Quant	Attitude	
Marteau et al.	1997	UK	General Pop.	Quant	Offered	

First Author	Year	Country	Setting	Method	Testing	Uptake
Marteau et al.	1999	UK	Prenatal	Quant	Offered	
Massie et al.	2009	Australia	General Pop.	Program Evaluation	Offered	
McClaren et al.	2008	Australia	General Pop.	Qual	Attitude	
Melancon & De Braekeleer	1996	Canada	Preconception	Quant	Attitude	
Mennie et al.	1993	UK	Prenatal	Quant	Offered	
Mennie et al.	1993	UK	Prenatal	Quant	Offered	
Mennie et al.	1992	UK	Prenatal	Quant	Offered	72.8%
Mennie et al.	1993	UK	Prenatal	Quant	Offered	
Mennie et al.	1992	UK	Prenatal	Quant	Offered	
Miedzybrodzka et al.	1995	Netherlands	Prenatal	Quant	Offered	89.0 - 91.0%
Mitchell et al.	1993	Canada	Preconception	Quant	Offered	42.0%
Myers et al.	1994	USA	General Pop.	Qual	Attitude	
Neiger et al.	1992	USA	Preconception	Quant	Attitude	
O'Conner & Cappelli	1999	Canada	General Pop.	Quant	Attitude	
Ormond et al.	2003	USA	General Pop.	Quant	Offered	
Payne et al.	1997	UK	Preconception	Quant	Offered	31.0%
Poppelaars et al.	2003	Netherlands	Preconception	Quant	Attitude	
Poppelaars et al.	2004	Netherlands	Preconception	Quant	Attitude	
Poppelaars et al.	2003	Netherlands	Preconception	Qual	Attitude	
Schwartz et al.	1993	Denmark	Prenatal	Program Evaluation	Offered	89.2%
Slostad et al.	2007	USA	Preconception	Program Evaluation	Offered	2.2%
Sparbel et al.	2007	USA	Prenatal	Qual	Offered	
Sparbel & Williams	2009	USA	Prenatal	Qual	Offered	
Strum & Ormond	2004	USA	Prenatal	Qual	Offered	43.0%
Tambor et al.	1994	USA	General Pop.	Quant	Offered	13.6 - 39.2%
Ten Kate & Tijmstra	1989	Netherlands	General Pop.	Quant	Attitude	
Ten Kate & Tijmstra	1990	Netherlands	General Pop.	Quant	Attitude	
Twal et al.	1998	USA	General Pop.	Mixed	Attitude	
Wake et al.	1996	Australia	Preconception	Quant	Offered	8.0%
Wald et al.	1995	UK	Prenatal	Quant	Offered	67.0%
Watson et al.	1991	UK	Preconception	Quant	Offered	66.0 - 87.0%
Watson et al.	1992	UK	Preconception	Quant	Offered	
Watson et al.	1991	UK	Preconception	Quant	Attitude	
Welkenhuysen et al.	1996	Belgium	Preconception	Mixed	Attitude	
Williamson et al.	1989	UK	General Pop.	Mixed	Attitude	
Witt et al.	1996	USA	Prenatal	Mixed	Offered	78.0%

Appendix D

GHSV CF information brochure

This appendix contains the information brochure on CF and CF screening that is provided to individuals who wish to have screening in the GHSC CF carrier screening pack.

Frequently Asked Questions

1. Do I need to be tested every time I have a baby?
   NO. If you are not a carrier, you remain at very low risk of having a child with CF. If you are a carrier and you have a new partner, your partner will need to be tested.

2. If no gene change is found, could I still be a carrier?
   YES. The current carrier test is only 85% accurate, and cannot detect every gene change that causes CF. If no gene change is found, you are not a carrier of the most common gene changes, but there is still a small risk that you may be a carrier.

3. If I am a carrier, can I develop CF?
   NO. If you are a carrier, you have a gene change in one of your two CF genes. The other copy of the gene works properly and there is no effect on your own health.

4. What if I have a relative who is a carrier or has CF?
   YOUR CHANCE of being a carrier of CF is greater than most people and you and your partner should consider testing.

5. If I have no family history of CF can I have a child with CF?
   YES. Most families where a child is born with CF have no family history of this condition.

6. Does this guarantee our baby will be healthy?
   NO, this test is only for CF.

Contact Details

For Testing and Genetic Counselling
Contact:
Genetic Health Services Victoria
10th Floor
Royal Children's Hospital
Flemington Road
Parkville VIC 3052
Ph: (03) 8341 6201
http://www.geneticheathvic.net.au/

GENETICHEALTH
Victorian Clinical Genetics Services

For Information on Cystic Fibrosis
Contact:
Cystic Fibrosis Victoria Inc.
80 Dodds Street
Southbank Victoria 3006
Open Monday to Friday 9am - 5pm
Ph: (03) 9686 1811
FreeCall: 1800 633 685
http://www.cfv.org.au/

Cystic Fibrosis

carrier testing for

Cystic Fibrosis

carrier testing for Cystic Fibrosis

What is Cystic Fibrosis?

Cystic fibrosis (CF) is an inherited disease that affects breathing and digestion in infants, children and young adults. It causes mucus to thicken, trapping bacteria, resulting in recurrent infections that damage the lungs. Thick mucus in the gut also makes digestion of food difficult.

Infants and children with CF require daily chest physiotherapy to clear mucus from their lungs, frequent courses of antibiotics and must take medication to assist digestion.

Until recently, many children with CF died in early childhood, but now many live to be 30, 40 or more. There is no cure for CF but better treatments are constantly under research and development.

Is our baby at risk?

Babies inherit one copy of each gene from each parent. Genes can have changes, known as mutations, which affect their function. About 1 million Australians 'carry' a gene change for cystic fibrosis as well as a healthy copy. **Carriers are completely healthy.**

A baby will have CF only if they inherit a gene change for cystic fibrosis from **both** parents. This is only possible if **both** parents are carriers of a gene change for CF.

If you are...	Then your risk of being a carrier is:
Caucasian	1 in 25 (4%)
Ashkenazi Jewish	1 in 25 (4%)
Asian	1 in 90 (1.1%)

(For individuals with no family history of CF.)

How can we find out our risk of having a child with CF?

A couple is only at risk of having a child with CF if BOTH the father and mother are carriers. We cannot test every gene change for CF, but we can test for the 10 most common gene changes and identify about 85% of carriers. Testing both you and your partner will give an accurate risk assessment as a couple having a child with CF.

If neither of you carry a gene change for CF, your risk of having a child with CF goes down from about 1 in 2500 to about 1 in 70,000.

The carrier test involves gently wiping your inner cheek with a soft swab that is similar to a large cotton bud, this is a painless procedure. In the laboratory, DNA from the cheek cells on the swab will be removed and tested.

When should we have carrier testing?

It is up to you whether you choose to be tested. To ensure there is time to make decisions it is best to test either before pregnancy, or early in pregnancy.

We recommend testing before 14 weeks of pregnancy. Then you have the maximum time to decide what to do if you are among the small number of couples who are both carriers.

How do we get tested?

Speak to your Obstetrician or Midwife. As yet there is no Medicare rebate for this test and there will be a charge.

What do the results mean?

There are two possible results from the test; carrier or non-carrier

Carrier

If your test shows that you have one copy of the gene change, you are a carrier. Your partner's results will determine your risk as a couple of having a child with CF.

Non-Carrier

This means that you do not have one of the common gene changes and so your risk of being a carrier is greatly reduced. However this test can not absolutely rule out the possibility that you may have a gene change.

Couple Results	Risk of having a child with CF
Both non-carrier	Less than 1/70,000
1 non-carrier, 1 not tested	Less than 1/13,000
1 carrier, 1 non-carrier	Less than 1/500
1 carrier, 1 not tested	Approx. 1/100
Both carriers	1/4

What if we are both carriers?

Two people who are carriers have a 1 in 4 (25%) chance of having a child with CF in each pregnancy. If you are both carriers you will be provided with genetic counselling. Following counselling you may choose to have tests to identify whether your baby has CF. If the tests diagnose CF you have a choice about whether to continue or terminate the pregnancy.

Appendix E

Additional publications

Original Paper

Public Health Genomics

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Population-Based Genetic Screening for Cystic Fibrosis: Attitudes and Outcomes

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Key Words
Attitudes · Carrier screening · Cystic fibrosis · Outcomes · Population screening

Abstract
A population-based cystic fibrosis (CF) carrier screening program was introduced in Victoria, Australia in 2006, and was offered to couples planning a pregnancy or in early pregnancy for a fee. Individuals received pre-test advice from their doctor and through a brochure. Carriers identified received genetic counseling. The aim of this study was to assess the attitudes of people undertaking screening. Between January 2006 and June 2008 all carriers (n = 79) and a randomly selected cohort of non-carriers (n = 162) were invited to participate. A purpose-designed questionnaire explored the following domains: knowledge, recollection and meaning of carrier status, reasons for having screening, anxiety and communication of results to family members. Forty-seven carriers (62%) and 65 non-carriers (41%) returned the questionnaire. Most participants were female (97%) aged 35–39 (46%). The main reasons for choosing screening were the perception of CF as a severe condition and a doctor's recommendation. All carriers correctly recalled their carrier status and the risk of having a child with CF, while 3 non-carriers (4.7%) were unsure of their carrier status and 12 (22%) incorrectly recalled their residual risk. Carriers answered the knowledge questions correctly more often than non-carriers. There was no difference in anxiety between carriers and non-carriers. The majority of carriers informed relatives of their increased risk of being a carrier. We conclude that participants' attitude towards carrier screening for CF was generally very positive. Our model of screening could be applied on a larger scale.

Cystic fibrosis (CF) is the most common severe autosomal recessive disease in childhood among Caucasians, with a birth prevalence of about 1 in 2,500 live births and a carrier frequency of approximately 1 in 25 [1]. In the state of Victoria, Australia, which has a population of about 5 million, there are approximately 200,000 heterozygous carriers of CF and 20 children with CF born each year [2]. The main clinical features are chronic suppurative lung disease and pancreatic exocrine insufficiency [3]. Although treatments have prolonged life expectancy to the mid thirties, there is no cure for CF. Quality of life,

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particularly for individuals with end stage disease, is poor [4].

Carrier screening for CF offers couples who are both carriers reproductive choices regarding the birth of a child with CF and reassurance of the low risk of having an affected child if they are not carriers. The current situation in Australia is that relatives of people with CF or known carriers are offered carrier testing for the known gene mutation in their relative. However, the reality is that more than 95% of CF carriers have no family history of the condition [5]. Population carrier screening refers to the screening of individuals who have no family history of the condition [6]. Remembering that 4% of the Australian population are carriers, population-based carrier screening makes sense [7].

Following the U.S. National Institutes of Health and the American College of Obstetricians and Gynaecologists and the American College of Medical Genetics recommending CF carrier screening [6], a fee-for-service CF carrier screening program was introduced in Victoria, Australia in 2006. However, there has been little exploration of the characteristics of individuals who might choose to have CF carrier screening in Australia. Honnor et al. [8], seeking to gauge test acceptance in the community, offered CF carrier screening in a primary care setting in Western Australia. A similar study was conducted in a variety of different settings in New South Wales including hospitals, workplaces and high schools with good community test acceptance [9].

Here we report the results of a study determining the attitudes towards genetic screening for CF in Victoria, Australia. The aims of this study were to explore reasons for having screening, knowledge of CF, recollection, understanding and impact of carrier status and communication of results to family members.

Subjects and Methods

Carrier Screening Program

A population-based CF carrier screening program was implemented in 2006 by Genetic Health Services Victoria (GHSV). CF carrier screening was offered to couples planning a pregnancy or during the early stages of pregnancy by obstetricians and general practitioners [7]. Pre-test information was supplied in the form of a brochure (available at www.cfscreening.com.au).Testing was by cheek swab with the swab posted to the DNA laboratory at GHSV and tested for 12 *CFTR* gene mutations. Both partners were encouraged to undertake testing together, although generally one partner was tested and the other partner was tested only if the first tested individual was identified as a carrier. All carriers underwent free genetic counseling including free cascade testing for partners and family members. Non-carriers were not offered formal genetic counseling through the program although they could contact the service to discuss their result. Very few did this. Carriers were informed of their carrier result by telephone and either had genetic counseling over the telephone at the time of receiving their result or had face-to-face counseling. The test cost AUD 200 and there is no government or health insurance rebate for the test.

Subjects

All individuals identified as carriers (n = 79) and a random sample of non-carriers (n = 162) were sent an invitation to participate. Subjects had been screened between January 2006 and June 2008. The non-carriers were randomly selected by choosing every 15th non-carrier in the files to result in a sample of 2 non-carriers for every carrier [10]. Carrier couples were excluded from the study.

Questionnaire

The questionnaire was designed to address the following domains: demographic variables, knowledge of CF, anxiety levels at the time of completing the questionnaire, reasons for participating in screening, recollection of carrier test result and meaning of carrier status. The knowledge questions were sourced from validated surveys assessing the impact of cascade testing on families affected with CF and evaluating school-based Tay Sachs disease genetic screening programs [11]. The anxiety scale used in the questionnaire was the validated, short version of the State Trait Anxiety Inventory (STAI) [12].

The questionnaire was returned in a reply-paid envelope. The questionnaires were identified by a study number allowing reminder letters to be sent to non-responders 3 weeks after the first mail-out. If the questionnaire was not sent back after one reminder no further contact was made.

Analysis

Data analysis was conducted using SPSS Version 16.0. Preliminary descriptive analysis generated frequency data to elicit the description and attitudes of respondents. This was followed by comparisons between groups defined by carrier status. Statistical significance of between-group comparisons were assessed using χ^2 tests of association for categorical variables. Where variables had more than 2 categories, degrees of freedom are given with the χ^2 statistic. As anxiety scores were not normally distributed, box plots of scores are presented for each group, and between-group comparisons were assessed for statistical significance using the Mann-Whitney U test.

This study was approved by the Human Research Ethics Committee of the Department of Human Services, Victoria, Australia (HREC 15/05).

Results

Response

Questionnaires were sent to 241 eligible individuals, 79 carriers and 162 non-carriers. A total of 112 completed questionnaires were received, 47 from carriers, with a re-

Table 1. Demographic characteristics of participants

Demographic	Categories	Participants
Gender n = 112	Male Female	3 (3%) 109 (97%)
Age (years) n = 109	25–29 30–34 35–39 >39	9 (8%) 32 (29%) 54 (50%) 14 (13%)
Carrier status n = 112	Non-carrier Carrier	65 (58%) 47 (42%)
Highest completed level of education n = 107	Secondary school only Trade/apprenticeship College certificate or diploma University degree	9 (8%) 1 (1%) 20 (19%) 77 (72%)
Current occupation n = 106	Managerial Professional Office duties Skilled/trades Unskilled	30 (28%) 46 (44%) 13 (12%) 16 (15%) 1 (1%)
Household income, AUD $\times 10^3$ n = 104	<60 61–80 81–100 >100	10 (10%) 10 (10%) 14 (13%) 70 (67%)
Partner at time of testing n = 109	Yes No	107 (98%) 2 (2%)
Pregnant at time of testing n = 109	Yes No	90 (83%) 19 (17%)
Number of children at time of testing n = 107	0 1 2 3 or more	31 (29%) 50 (47%) 20 (19%) 6 (5%)

n = Number of actual responses provided, as not all questions were answered by all participants.

sponse rate of 62%, and 65 from non-carriers, with a response rate of 41%.

Demographic Variables

Demographic features of the cohort are presented in table 1. Most respondents were female (97%) with only 3 males (3%) participating in the study. Of the 112 participants, 98% had a partner and 83% were pregnant at the time of being offered CF carrier screening.

Reasons for Having Screening

Participants were asked to rate factors that influenced their decision to participate in CF carrier screening on a 5-point Likert scale, 1 being 'did not influence' and 5 being 'strongly influenced'. For analysis, points 1 and 2 were combined to form the category 'did not influence', the middle point 3 was neutral and points 4 and 5 were combined to form the category 'influenced' (fig. 1).

The most influential factor for participating in CF carrier screening was the perception that CF is a severe disease (72%) followed by their doctor's recommendation (58%). Partner's opinion towards CF carrier screening was influential for 45 participants (41%) while 44 participants (40%) indicated their partner's opinion did not influence their decision. The majority of participants (87%) stated that their perception of being a carrier of CF was not an influencing factor in participating in screening.

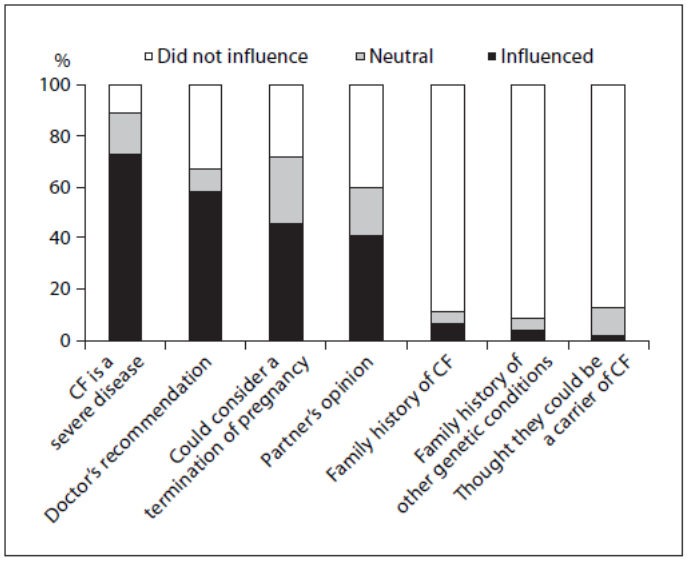

Fig. 1. Level of influence of various factors in the decision to participate in CF carrier screening.

Table 2. Meaning of results with respect to risk of having a child with CF

	n	%
Carriers		
Dependent on partner's result	17	41.5
Increased or high risk	9	21.9
1 in 500	8	19.5
Low risk	5	12.2
Child could be a carrier	2	4.9
Non-carriers		
Low risk	33	60.0
No risk	12	21.8
At ease	6	11.0
Don't know	2	3.6
1 in 500	1	1.8
Child could be a carrier	1	1.8

n = Number of actual responses provided, as not all questions were answered by all participants.

Knowledge of Carrier Status

All 47 carriers (100%) correctly recalled their carrier screening result while 3 (5%) non-carriers were unsure of their carrier screening result. Participants were asked in an open-ended question to explain their CF carrier screening test result with respect to their risk of having a child with CF (table 2). Seventeen carriers (42%) responded that their risk of having a child with CF was dependent on their partner's result, while 9 (22%) carriers stated that they had an increased or high risk of having a child with CF. Thirty-three non-carriers (60%) responded that their risk of having a child with CF was low, while 12 (22%) stated that they have no risk of having a child with CF.

Knowledge of CF

Participants were asked to answer 15 questions regarding CF and carrier screening (fig. 2). They were required to select 1 of 3 options: true, false, unsure. There were 4 knowledge questions in which less than 50% of both carriers and non-carriers were correct. These were: (a) if no gene change is found they cannot be a carrier; (b) CF test can identify all carriers; (c) carriers usually have a family history; (d) affects more males than females.

Five of the fifteen questions were answered correctly significantly more frequently by carriers compared with non-carriers. These were: (a) a carrier couple can have a child who does not have CF ($\chi^2 = 8.52$, $p < 0.01$); (b) CF test can identify all CF carriers ($\chi^2 = 4.48$, $p = 0.03$); (c) if only one parent is identified as a carrier there is still a small chance of having a child with CF ($\chi^2 = 6.76$, $p = 0.01$); (d) need to be screened for CF carrier status every time you have a baby ($\chi^2 = 4.50$, $p = 0.03$); (e) partner determines risk as couple ($\chi^2 = 7.88$, $p = 0.01$). No questions were answered correctly more often by non-carriers than carriers.

Anxiety

The STAI scores for carriers ranged from 20 to 60, with a median of 33, while the STAI scores for non-carriers ranged from 20 to 70, with a median of 30. There was no significant difference for anxiety scores in carriers compared to non-carriers ($p = 0.56$).

Attitudes towards Screening

The attitudes towards screening are presented in table 3. Most carriers (98%) and non-carriers (87%) believe the best time to offer CF carrier screening is before pregnancy. Significantly more carriers (94%) than non-carriers (41%) recommended carrier screening to others ($\chi^2 = 31.88$, $p < 0.01$). The vast majority of both carriers (96%) and non-carriers (97%) stated that if they had their time again they would still have CF carrier screening.

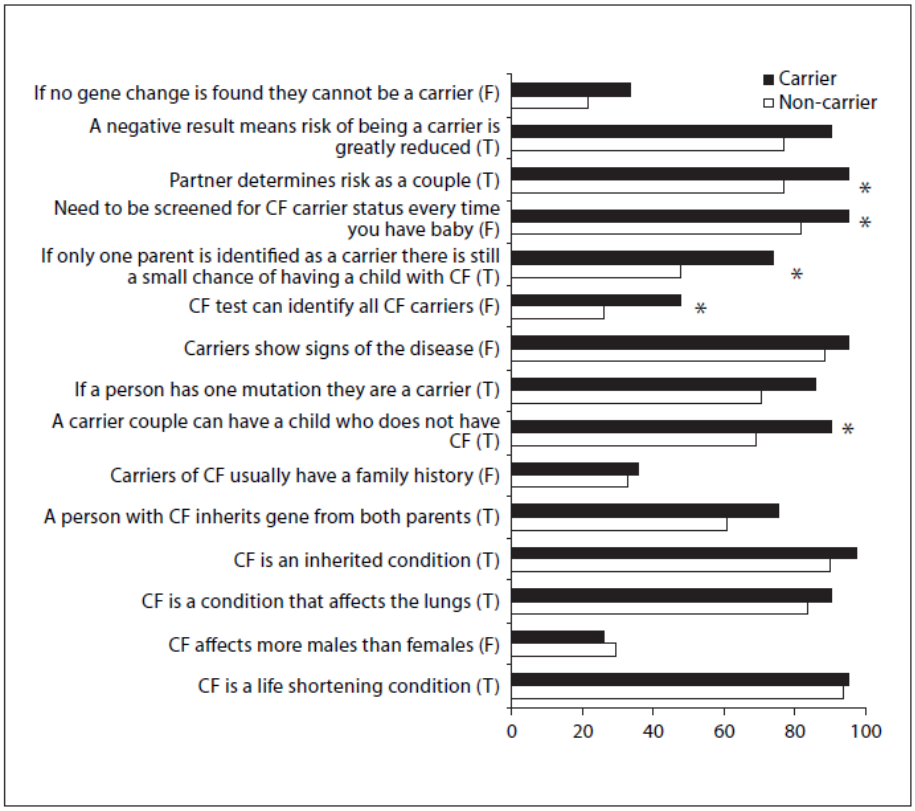

Fig. 2. Percentage of participants who correctly answered each CF knowledge question according to carrier status. * $p < 0.05$ for comparison of percent correct in carriers versus non-carriers using χ^2 tests. The correct answer is provided in parentheses (T = true, F = false).

Table 3. Attitudes towards screening according to carrier status

	Categories	Carrier n (%)	Non-carrier n (%)
Best time to offer	Before pregnancy	46 (98%)	53 (87%)
n = 108	During pregnancy	0 (0%)	4 (6.5%)
	Unsure	1 (2%)	4 (6.5%)
Recommended to others	Yes	44 (94%)	26 (41%)
n = 111	No	3 (6%)	37 (58%)
	Unsure	0 (0%)	1 (1%)
If had time again would do again	Yes	45 (96%)	61 (97%)
n = 110	No	1 (2%)	1 (1.5%)
	Unsure	1 (2%)	1 (1.5%)

n = Number of actual responses provided, as not all questions were answered by all participants

Attitudes of Carriers to Family Communication and Testing

Forty-five (96%) of the carriers informed 95 family members of their result (table 4). Sixteen carriers (34%) reported that they had relatives who had been tested.

Discussion

This is the first study to evaluate participants in a population-based CF carrier screening program in Australia. Most participants were women and already pregnant

Table 4. Communication of increased risk of carrier status to family

	Categories	n (%)
Informed family	Yes	45 (96%)
n = 47	No	2 (4%)
Informed who*	Parent/s	34 (76%)
n = 45	Sibling/s	41 (91%)
	Aunt/uncle	7 (16%)
	Cousin/s	13 (29%)
Informed why	Childbearing age/ planning pregnancy	22 (50%)
n = 44	Awareness/interest	7 (16%)
	At risk	6 (14%)
	Implications for next generation	4 (9%)
	Support/advice	3 (7%)
	Other	2 (4%)
Family tested	Yes	16 (34%)
n = 47	No	27 (58%)
	Unsure	4 (8%)
Tested*	Parent/s	5 (31%)
n = 16	Sibling/s	11 (69%)
	Aunt/uncle	0 (0%)
	Cousin/s	1 (6%)
	Other	2 (13%)

n = Number of actual responses provided by carriers, as not all questions were answered by all carriers. * Carriers could select more than one response.

at the time of screening. They generally chose to be screened because of a perception that CF is a serious disease and because of a recommendation by their doctor. Carriers recalled their result and its implications better than non-carriers, probably due to their result being more significant and because of the additional genetic counseling received. Carriers were not more anxious as a result of the screening test than non-carriers. Most carriers informed members of their family of their increased risk of being a CF carrier, and many relatives followed through with cascade family testing. Despite most being pregnant at the time of testing, participants recommended carrier screening should be undertaken prior to conception.

The majority of participants in this study were well educated, affluent women between 30 and 40 years of age. The demographics of our participants reflect the setting in which screening is offered, mainly through private obstetricians and some shared care general practitioners. This may have implications for generalizability of our results to the Australian population. The cost of AUD 200 is likely to have been a barrier to some. Similarly, the lack of government support may be an indication to some people that CF carrier screening is not necessary. Most people tested were women, reflecting attendance at prenatal medical visits and a sense of responsibility for testing. Most participants had no children or only one child at the time of screening. This is in keeping with evidence that women without children are more likely to have screening than those with children [8]. This may be due to women with children without CF believing that they are not at risk.

The main reason participants stated they had CF carrier screening was the perception that CF is a severe disease. It is unclear whether many knew about CF prior to the offer of screening and it is likely the severity was judged from the pre-test information brochure. The attitude of the treating doctor was also an important factor in the decision to screen. Higher uptake of screening is associated with an active offer of screening from the treating doctor, which includes providing the CF information pack and discussing screening, while lower uptake is associated with a passive offer of screening, which involves including information on CF screening with the other information pamphlets provided [13]. This was cited as a key factor by McClaren et al. [14] who interviewed pregnant women and their partners regarding factors that may influence their decision to have CF carrier screening. In a study exploring the attitudes of non-pregnant couples towards the offer of free CF carrier screening, Clayton et al. [13] found that the most influential factors in participating in screening were the opinions of both doctor and partner. However, less than half of participants in our study stated that their partner's opinion influenced their decision to have screening. The findings of our study may reflect the fact that women often attend obstetrician appointments unaccompanied by their partner. This was noted by Wald et al. [15] who found that 46% of women in their study attended obstetrician appointments alone.

We hypothesized that the perception that individuals were likely to be carriers of CF would be an important factor in choosing to be screened based on the findings of Fang et al. [16]. However, this was not the case. Henneman et al. [17] presented similar findings from a study of preconception carrier couple screening. Interestingly the uptake of cascade family testing for CF carriers following the diagnosis of CF by newborn screening for CF has

been poor even though relatives are at high risk of being carriers [18]. The consideration of pregnancy termination in certain circumstances was an influential factor for nearly half of the participants in this study. Similarly, Levenkron et al. [19] found that pregnant women who had CF carrier testing had an accepting attitude towards pregnancy termination.

The recollection of carrier status was high for both carriers and non-carriers despite a time lag between testing and questioning of over 12 months in many instances. Carriers had better knowledge of CF and screening than non-carriers. The most important point was the lack of understanding about residual risk by non-carriers. Residual risk is covered in the pre-test brochure but also may not be easily understood by those being screened. Carriers received genetic counseling whereas non-carriers did not and this is the most likely reason for the better knowledge of the former group.

We showed that there was no difference in anxiety levels between carriers and non-carriers at the time of completing the questionnaire. This is an important finding as an argument against population-based carrier screening is the detection of carriers who may consider they have the disease or who may remain anxious about the result. The low level of anxiety shown by carriers is likely to be a reflection of the genetic counseling they received. Levenkron et al. [19] found that the anxiety levels after receiving a positive test result (carrier) was significantly reduced following genetic counseling.

We found that having been through screening, most participants felt that the best time to offer CF carrier screening is before pregnancy. This is a common finding from other studies [19–21], however, preconception carrier screening is difficult to achieve. This is because of the low attendance at general practice of healthy young women (and men) with most people attending for pregnancy advice when already pregnant. Furthermore, while intention to participate in screening has been shown to be high it has been associated with low uptake rates [21]. In an exploration of attitudes to carrier screening in Australia, McClaren et al. [14] found that unless already pregnant, testing for CF was not considered relevant to many.

The majority of carriers in the present study reported that they had recommended carrier screening to others. Although the positive endorsement of our program was less by non-carriers, only one carrier and one non-carrier regretted their decision to participate in CF carrier screening. It is likely that carriers, who received additional genetic counseling, recognized the importance of screening. The low numbers regretting involvement with screening is a positive reflection of the pre-test information and informed decision to participate and deal with the consequences of the result. In a similar study concerned with test acceptance and follow-up one year after screening, Levenkron et al. [19] studied 124 carriers and showed that while the majority of carriers would recommend CF screening to others, 12% regretted their decision to participate in the program due to anxiety and stress while waiting for their partner's result. By contrast, Henneman et al. [22] reported that all carriers identified in their study would make the same decision to participate in screening.

Most carriers identified in our population-based program informed family members of their increased risk of being a CF carrier. The main reason for passing information to at risk relatives was the age of the relative and their reproductive plans, with relatives of childbearing age or those planning a pregnancy being the most likely to have been informed. Ormond et al. [23] found the main reason for disclosure of genetic information is a close bond with the relative and is dependent on the relationship status, with the main reason for non-disclosure being that the relative is not in a significant relationship. Despite many carriers telling at-risk family members about CF screening, only 16 carriers reported that family members had undergone testing. This is likely to be the lowest estimate of tested relatives as participants may have been unaware of their relatives' testing status. Ormond et al. [23] also found that while the passing of information or recommendation by carriers to at-risk relatives is high, the screening of these relatives as a result of this information or recommendation is low. This is similar to the low rate of cascade family testing after newborn screening for CF in Australia [18].

There are a few limitations of this study. Our program is based on fee-for-service testing and not every obstetrician or shared care general practitioner informs their patients of the availability of CF carrier testing. As such, the target population for this study is not likely to be representative of the Australian population. The overall response rate was just under 50%. Although this is generally considered a satisfactory response rate for this type of study, where individuals are approached by mail without prior knowledge of the study, it was not possible to determine how representative the responders were of the total tested population. There is very limited information available on non-responders.

Our program of population-based carrier screening for CF can safely identify carriers without inducing un-

necessary anxiety and enable them to pass this information on to relatives. We would recommend pre-conception carrier screening where possible. With government funding, this model of screening could be applied on a larger scale enabling equity of access.

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Current Practice and Attitudes of Australian Obstetricians Toward Population-Based Carrier Screening for Inherited Conditions

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An anonymous survey of Australian Fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists was conducted with the aim of understanding current practice and attitudes toward population-based carrier screening for inherited conditions in the setting of routine pregnancy care. Of 1,121 Fellows invited to complete the online questionnaire by e-mail, 237 (21%) responded, and of these 156 were practicing obstetricians and completed the whole survey. Of the respondents, 83% expressed support for population-based carrier screening for at least some conditions, with 97% supporting carrier screening for β-thalassaemia, and 83% supporting carrier screening for cystic fibrosis (CF). A small proportion of obstetricians reported offering carrier screening as part of routine pregnancy care (20% for β-thalassaemia, 8% for CF, 5% for fragile X syndrome, and 2% for spinal muscular atrophy). The main practical barriers identified for screening were cost, time constraints, and availability of supporting services. Addressing these issues is crucial for the successful implementation of population-based carrier screening programs in Australia and internationally.

■ **Keywords:** carrier screening, cystic fibrosis, thalassaemia, screening programs

The purpose of population-based carrier screening is to identify asymptomatic carriers of autosomal and X-linked recessive conditions and give prospective parents reproductive options to prevent the birth of an affected child. Screening programs began formally in the 1970s with screening for Tay–Sachs disease carrier status in the Ashkenazi Jewish community (Kaback, 1997). Subsequent programs have targeted cystic fibrosis (CF) in the United States and parts of Italy (Castellani et al., 2009; Hale et al., 2008), thalassaemia in Mediterranean at-risk populations (Cao et al., 1984, 1997; Modell & Mouzouras, 1982), fragile X syndrome in Israel (Berkenstadt et al., 2007), and most recently, spinal muscular atrophy (SMA) in the United States and Taiwan (Su et al., 2011; Sugarman et al., 2012). Several of these programs have reported reductions in the incidence of affected infants born with the conditions tested. Developments in genetic technology mean that it is now possible to simultaneously screen for an individual's carrier status for hundreds of inherited conditions using a single sample (Levenson, 2010), and such panel-based testing is likely to replace testing for individual conditions in the future.

In Australia, healthcare is available through the government-funded public health system, as well as through a user-pays private health system. The availability of carrier screening varies for different conditions and in different settings. Screening for β-thalassaemia carrier status is publically funded and generally triggered by abnormal results on full blood examination (FBE), which is performed as part of routine pregnancy care (Cousens

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et al., 2010). There are several well-established, non-government funded, community-based programs offering carrier screening to people of Ashkenazi (Eastern European) Jewish ancestry for conditions such as Tay–Sachs disease (Ioannou et al., 2010). A fee-for-service CF population carrier screening program has been in existence in the state of Victoria, Australia since 2006 (Massie et al., 2009). In its first three years of operation, the program screened 3,200 individuals, detecting 106 carriers, and 9 carrier couples. All the couples identified through the program altered their reproductive decisions, to avoid having a child with CF. Screening for other relatively common genetic conditions, such as SMA and fragile X syndrome carrier status, are less frequently offered in Australia (Metcalfe et al., 2008).

The uptake of carrier screening is generally higher when offered in pregnancy than when offered to the non-pregnant population (Harris et al., 1996; Mennie et al., 1992; Wald et al., 1993). The reasons may be that the first contact with a health professional does not occur until the woman is pregnant or that screening does not become a priority until this time. In addition, couples may not believe they need to consider screening until pregnant (Delatycki, 2008). There is little known about the attitudes of Australian obstetricians toward carrier screening for inherited conditions. Knowledge in relation to these attitudes is of great importance as the frequency with which obstetricians and other pregnancy healthcare providers offer tests to patients is a major determinant of the success of population-based carrier screening programs.

The aim of this study was to gather information about the current practice and attitudes of Australian obstetricians toward carrier screening for genetic conditions as part of routine pregnancy care.

Methods

Participants

Australian Fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) were invited by e-mail to complete an anonymous online survey between January 27 and March 3, 2011. Only Fellows actively practicing obstetrics were requested to complete the whole survey. A reminder was sent three weeks after the initial invitation to participate, inviting those who had not completed the survey to do so.

Measurement Tool

The survey was developed by a panel of clinicians and researchers with expertise in carrier screening programs and was informed by previous international studies (Morgan et al., 2004, 2005; Wilkins-Haug et al., 1999). The survey was reviewed by the RANZCOG Continuing Professional Development committee, and the content was modified in response to their feedback. The survey was divided into four parts: demographic information, current practice and attitudes toward screening for β-thalassaemia, current practice and attitudes toward screening for CF, and attitudes toward population-based genetic carrier screening in general. Respondents were asked to rate certain aspects of β-thalassaemia and CF screening tests on a 5-point scale, where 1 was *very poor*, 2 *poor*, 3 *satisfactory*, 4 *good*, and 5 *excellent*. They were also asked to rate their level of concern regarding general aspects of population-based screening for genetic conditions using a 4-point scale, where 1 was *no concern*, 2 *minor concern*, 3 *moderate concern*, and 4 *major concern*. Respondents were provided with two, free text boxes at the end of the survey and asked for any additional comments about specific barriers to screening or general comments. Responses to the questionnaire were anonymous.

Data Analysis

LimeSurvey software was used to generate the electronic version of the survey, and to store and analyze the responses. Using content analysis, open-ended responses were categorized independently by Zornitza Stark, Belinda McClaren, and Sylvia Metcalfe based on similarity and differences. Numbers of responses in categories are reported.

Ethics Committee Approval

The study was approved by the Royal Children's Hospital, Victoria, Australia Human Research Ethics Committee (HREC 30068).

Results

Demographic Details

A total of 1,206 e-mails were sent to practicing Australian Fellows of the RANZCOG who had supplied the College with an e-mail address. Eighty-five e-mails were returned as undeliverable, leaving 1,121 potential respondents. From those, 237 responses were received (response rate minimum of 21.1%) with representative proportion of responses received from each state/territory; 55 respondents identified themselves as not practicing obstetrics, and 26 did not complete the survey sufficiently for their responses to be included in the analysis. One hundred and fifty-six eligible Fellows completed the full survey. Demographic information and type of practice of the respondents is shown in Table 1.

Current Practice and Attitudes Toward Carrier Testing for β-Thalassaemia and Cystic Fibrosis

One hundred and fifty-two obstetricians (97%) supported carrier testing for β-thalassaemia in pregnancy, and 130 (83%) supported carrier screening for CF. Self-reported current practice patterns with respect to these two conditions are summarized in Table 2. The opinion of obstetricians regarding certain aspects of β-thalassaemia and CF carrier screening are presented in Table 3.

TABLE 1

Demographic Information and Type of Practice of the 156 Survey Participants

Respondent characteristics	*N* (%)
Gender	
Male	82 (53%)
Female	74 (47%)
State/territory of main practice	
Australian Capital Territory	3 (2%)
New South Wales	39 (25%)
Northern Territory	2 (1%)
Queensland	37 (24%)
South Australia	17 (11%)
Tasmania	7 (5%)
Victoria	41 (26%)
Western Australia	10 (6%)
Years of obstetric experience	
<5	1 (0.6%)
6–10	26 (16.7%)
11–15	36 (23.0%)
>16	93 (59.7%)
Size of obstetric practice (deliveries/year)	
1–20	18 (11%)
20–100	32 (21%)
100–200	38 (25%)
>200	68 (43%)
Location of practice	
Metropolitan	115 (74%)
Rural/regional	41 (26%)
Type of practice	
Mostly private	80 (51%)
Mostly public, tertiary center	40 (26%)
Mostly public, other	36 (23%)
University appointment	
Yes	60 (39%)
No	96 (61%)

TABLE 2

Self-Reported Current Practice Regarding Offering Carrier Screening for β-Thalassaemia and CF in Routine Pregnancy Care (Total Number of Respondents: 156)

Current practice pattern	β-thalassaemia *N* (%)	Cystic fibrosis *N* (%)
Offer screening to all patients	32 (20%)	12* (8%)
Offer screening to some patients	113 (72%)	128 (82%)
Personal or family history	109 (70%)	123 (79%)
Higher risk ethnic group	85 (55%)	28 (18%)
Patient request	75 (48%)	88 (56%)
Private patients	0	9 (6%)
Screening not offered to any patients	11 (7%)	16 (10%)

Note: *All 12 practiced in states where there are established fee-for-service CF carrier testing programs (Victoria and New South Wales).

Current Practice and Attitudes Toward Carrier Testing for Other Inherited Conditions

One hundred and thirty obstetricians (83%) supported population-based carrier screening for at least some inherited conditions. However, only 9 (6%) felt this should take place during pregnancy, with 90 respondents (58%) stating it should ideally take place in adulthood before pregnancy, 33 (21%) at birth and 24 (15%) in high school. A very low number of obstetricians reported routinely offering carrier tests for any other conditions: 7 (5%) for Tay–Sachs disease, 8 (5%) for fragile X syndrome, and 3 (2%) for SMA.

TABLE 3

Respondents' Mean Rating on Scale of 1–5 of Practical Aspects of β-thalassaemia and Cystic Fibrosis Carrier Screening

	β-thalassaemia	Cystic fibrosis
Ease of access to test	4.0	3.7
Cost of test	3.4	2.9
Sensitivity and specificity of the test	3.7	3.6
Availability of laboratory and counseling support to help with the interpretation and follow-up of abnormal results	3.6	3.6
Availability of educational materials to help counseling patients	2.8	3.3
Community awareness of condition	2.3	2.5

The participants were asked to rate their level of concern regarding various aspects of population-based carrier screening and their responses are presented in Figure 1. Ninety-three (60%) of survey participants stated they would like more training in this area.

Additional Comments

Forty-six participants provided further comments in the open-ended questions. Five of these commented on survey design only and these are not reported. The responses of the remaining 41 participants were categorized based on similarity of content. Some participants' responses covered more than one topic and their comments were coded into more than one category. Forty-nine comments addressed topics raised in Tables 2 and 3 and Figure 1. There were eight new topics raised in 25 comments that were not already covered in the survey. These were: concern about equity of access and distributive justice, from the perspective of reaching disadvantaged or multicultural populations, or limiting testing to high genetic risk populations, or targeting populations such as preconception/pregnant couples ($n = 14$), potential for causing harm through creating a perception of eugenics in society ($n = 1$), potential for stigmatization ($n = 1$), or raising questions regarding paternity ($n = 1$), impacting on life insurance ($n = 2$), the lack of evidence of cost-benefit ($n = 3$), and the need for screening to be policy driven ($n = 1$). Two respondents commented on their personal view that screening has eugenic undertones.

Discussion

This is the first study to examine current practice and attitudes of Australian obstetricians toward population-based carrier screening for genetic conditions in routine pregnancy care. The majority of obstetricians expressed support for population-based carrier screening for at least some conditions, with 97% supporting carrier screening for β-thalassaemia, and 83% supporting carrier screening for CF.

The largely positive attitudes toward universal carrier screening among Australian obstetricians are not translated into practice, with only 20% reporting they routinely offer

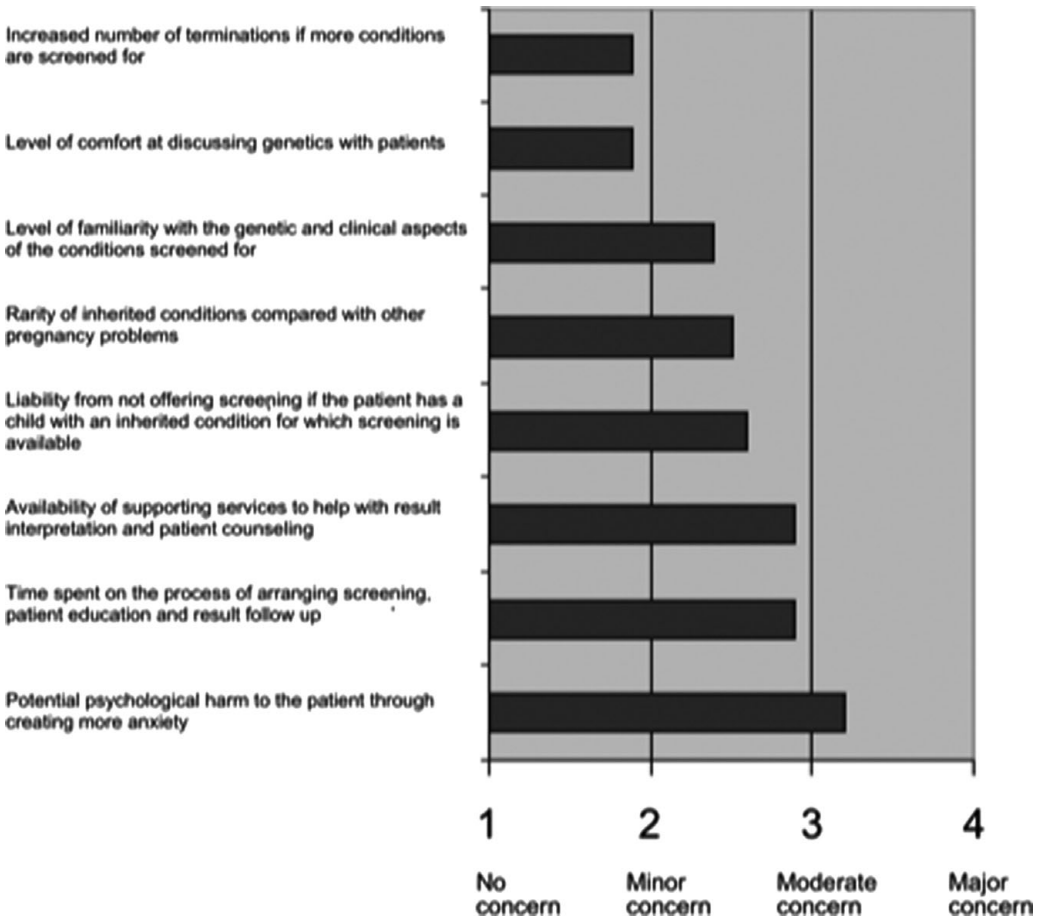

FIGURE 1

Responses to survey questions asking participants to rate their level of concern regarding general aspects of population-based carrier screening for genetic conditions on a scale of 1–4.

β-thalassaemia screening to all their patients, 8% offering carrier screening for CF, 5% for fragile X syndrome, and 2% for SMA. This contrasts with self-reported practice among obstetricians in the United States, where a similar survey found that 65.8% of respondents offered CF carrier screening to all prenatal patients (Morgan et al., 2004). The low number of Australian obstetricians reporting offering β-thalassaemia screening to all patients, when in practice the majority of pregnant women have a FBE performed, most likely reflects the indirect nature of β-thalassaemia screening, with FBE testing not being perceived by obstetricians as a screening test for β-thalassaemia. This finding is consistent with patients found to be carriers for β-thalassaemia typically reporting that they were unaware that screening had taken place (Locock & Kai, 2008).

Most Australian obstetricians report offering carrier testing in specific circumstances, most commonly in the presence of a personal or family history of a genetic condition. However, the majority of babies with CF are born to families with no family history of CF (McClaren et al., 2011), and even when a family history of CF is known, only a small proportion of relatives undertake carrier testing (McClaren et al., 2010). This is not unique to CF, but applies to all recessively inherited conditions. Therefore, the family history-based approach (so-called 'cascade testing') is likely to identify only a small proportion of couples who are at risk of having a child affected by an autosomal recessive condition.

In 2001, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) issued joint guidelines recommending healthcare providers to offer CF carrier screening to all couples planning a pregnancy or seeking prenatal testing (ACOG/ACMG, 2001), and a similar position statement has been issued by the Human Genetics Society of Australasia (HGSA, 2009). The RANZCOG specifically recommends β-thalassaemia screening in routine pregnancy care (RANZCOG, 2009), and with regard to other conditions suggests that 'counselling should address availability of carrier status screening for genetic conditions of perceived high prevalence or consequence' (RANZCOG, 2010).

A number of practical issues were raised by the obstetricians in this survey as barriers to offering universal carrier

screening. Chief among these was financial cost, both to individual patients and to the health system as a whole. As a guide, one Australian laboratory charges A$220 for CF carrier screening, A$250 for fragile X screening, and A$350 for SMA screening. With the exception of the FBE and hemoglobin electrophoresis that can diagnose carrier status for β-thalassaemia, the cost of population-based genetic carrier screening tests is not currently covered by government funding or private health insurance. By contrast, several health insurance providers in the United States cover the cost of such testing. It should be noted that some of the cost of the first trimester trisomy 21 screen is similarly not covered by government funding or private health insurance in Australia. This is commonly offered as part of routine pregnancy care, and the majority of pregnant women choose to pay between A$200–300 to include maternal serum screening and a nuchal translucency measurement by ultrasound. Carrier testing has the advantage that it only needs to occur once in each individual's lifetime rather than in each pregnancy, provided partners remain unchanged. Nevertheless, cost is an important barrier to universal carrier screening. The current arrangement in Australia creates inequity in healthcare, with only those that can afford it being in a position to take up carrier screening.

Patient education is an integral part of informed consent. Time constraints, language and cultural barriers, uncertainty in interpreting results, and lack of supporting services were all identified as important barriers to offering screening. With the number of available screening tests set to increase, it may be that detailed counseling will need to be reserved for those couples found to be at increased risk of specific conditions. Of note, the majority of obstetricians offering CF carrier screening routinely to all patients practiced in the states where there are existing fee-for-service carrier screening programs. Having a dedicated program facilitates screening through the provision of practitioner education, a clear pathway for testing, and support with interpretation and follow-up of results.

Creating psychological harm was the most significant concern that Australian obstetricians had with regards to offering population-based carrier screening programs. In addition, some survey participants commented that those found to be carriers may be stigmatized and subject to insurance restrictions. Carriers for recessive genetic conditions are generally asymptomatic, and each person is estimated to be a carrier for several recessive conditions. The evaluation of existing carrier screening programs has shown that carriers are often initially anxious about their positive test results (Ioannou et al., 2010; Scriver et al., 1984). However, this anxiety subsides, and the long-term follow-up of individuals who have taken part in carrier screening programs has shown that the majority have enduring positive feelings about the experience of being screened (Locock & Kai, 2008; Zeesman et al., 1984). Although commonly cited in professional circles and in the mass media, the concern regarding life insurance implications for those found to be carriers is unfounded (Delatycki et al., 2002).

Australian obstetricians expressed only moderate levels of concern regarding liability arising from not offering carrier screening for genetic conditions in pregnancy. This contrasts with studies of American obstetricians, who cited liability from not offering screening as their most significant concern (Morgan et al., 2004) and there are reports of 'wrongful birth' legal action being taken in the United States over failure to provide CF carrier screening (Hausen, 2012). We are not aware of successful legal action being taken for failure to offer such screening in Australia, but if this were to occur, it is likely that the level of concern would increase considerably.

One of the most notable findings of this survey was that only 6% of surveyed obstetricians felt that pregnancy is the ideal time to offer carrier screening, with most favoring preconceptual screening in adulthood. The ethical considerations in choosing a model for universal carrier screening have recently been reviewed, with CF as an example (Modra et al., 2010). It has been argued that preconceptual carrier screening done outside of the medical context (e.g., in schools or workplaces) is ethically superior as it promotes greater autonomy and maximizes the number of reproductive options open to people identified to be carriers. This model works well for conditions that are limited to certain ethic groups, with attendant high degree of community support and education (e.g., Tay–Sachs disease screening programs in Ashkenazi Jews). However, whether it can be translated to the wider community remains to be seen, and in the absence of such programs, offering carrier testing in pregnancy remains important.

This electronic survey elicited responses from only 21% of those successfully e-mailed. It is likely that the distribution list included many Fellows who do not practice obstetrics, and therefore the true response rate of practicing obstetricians is considerably higher. Nevertheless, a relatively low response rate may be indicative of this issue not being perceived as relevant by Australian obstetricians, which in itself would constitute a major barrier to the development of screening programs. Fertility specialists comprise another group of RANZCOG Fellows who are well placed to perform preconceptional carrier screening and ascertaining their views, as well as the views of general practitioners who deliver a substantial part of pregnancy care, will be equally important.

The field of carrier screening for genetic conditions evokes unique ethical, legal, psychosocial, and privacy concerns. Advances in genetic technology mean that the ability to simultaneously screen for an individual's carrier status for hundreds of inherited conditions using a single sample is already a reality (Levenson, 2010) and the cost of such screening will continue to decline. We have identified specific practical barriers and ethical concerns among Australian obstetricians regarding the implementation of

population-based carrier screening programs. Addressing some of these concerns may increase support for screening and the findings of this survey have important implications for the future planning of screening programs and genetic services in Australia and internationally.

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Original Article

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

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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

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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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Appendix F

Interview Schedules

This appendix contains copies of the interview schedules used in the evaluation of the GHSV population-based CF carrier screening program.

1. Carrier couples identified through the GHSV CF carrier screening program
2. Pregnant women in the public health system who were not offered CF carrier screening

Thank you very much for taking the time to talk to me. I thought I'd start off with giving you a quick run down on the study; why I want to have a chat with you and how the interview will work:

- **About the study**

The reason I asked a genetic counsellor to contact you on my behalf was because I wanted to speak to some individuals or couples about their experiences when they were identified as carriers of cystic fibrosis.

We are doing this study to improve the program and make changes to improve the service to help make the experiences better for new couples, when they first find out they are both carriers.

- **About the interview**

I will ask some quite general questions, and they are very open. I am happy to hear your views if you think I have left anything out that might be important. I also want you to feel as comfortable as possible and to know there are no right or wrong answers. I am just interested in your thoughts and experiences.

- **Stop me if you want**

Also, if at any time I am asking anything that is upsetting to you or if I am broaching subjects you don't want to discuss with me that's fine and please let me know.

- **Taping the interview**

I would like to tape our interview so that I don't have to write everything down while we are talking. The tape will be used to transcribe our entire conversation onto paper and then it will be deleted. But if you'd like me to turn the tape off during our conversation, please let me know.

- **Confidentiality**

Once our conversation is on paper it won't have your name on it any more and no-one will be able to identify your responses. Whatever you say here today will not be relayed to anybody else. I also want to say that whatever we talk about today will definitely not affect your relationship with the researchers or the care you receive from your doctor.

- **Wrapping-up**

Does this all sound ok?

Would you like to ask anything before we start?

Interview Schedule

Carrier screening process:

1. Offered screening
    - Obstetrician or GP?
    - Pregnant or not pregnant? First pregnancy?
    - Doctor's explanation/advice
    - Had they heard of CF prior to the offer of screening
    - Decision making
        - Info (seek further info)
        - time
        - reasons/factors that influenced decision
2. Screening pack
    - Process (swab, post?)
    - Information
    - Cost
3. Results
    - Time?
    - Understand meaning of results
    - How did you feel?
    - Counselling?
    - Partner tested?
4. Partners results
    - Time?
    - Understand meaning of results
    - How did you feel?
    - Counselling
5. Support/Info
    - GC
    - Respiratory physician
    - Satisfied with info and options provided
    - Satisfied with support provided
6. Prenatal diagnosis (if applicable)
    - How did you feel about having PND? Difficult decision?
    - Time?
    - Understand meaning of results
    - How did you feel?
    - Decision TOP?
    - Support?
    - Looking back are you happy with your decision to have screening in the first place?
7. Future reproductive plans
    - Did anyone discuss your future reproductive options?
    - Any other pregnancies since test result?
    - PGD?
    - PND?
    - Termination?
8. Cascade testing
    - Have you told any family members that you are a carrier?
    - What did you tell them?
    - Have any family members had testing?
    - Do you feel that genetic information should or should not be disclosed to family members?

9. Overall
    - Do you feel you were given enough information/support/advice?
    - What do you feel needs to be changed?
10. Individual interview (optional)
    - Is there anything else you would like to discuss about your individual experience?
11. Closing
    - Is there anything else you would like to tell me?
    - What was it like talking about all this?
    - Do you feel that you would like to speak to anyone else?

Thank you for your time

Introduction

Approach in waiting room:

Hi my name is Liane Ioannou and I am doing my PhD at Murdoch Childrens Research Institute on cystic fibrosis carrier screening. I was wondering if I could ask you a few questions while you are waiting for your appointment, to get your opinion on genetic screening. It should only take about 5-10 minutes. The receptionist will know where you are so you will not lose your place in line.

Private room:

I would like to tape our interview so that I don't have to write everything down while we are talking. The recording is used to ensure that I don't get anything wrong after the interview as I may not remember exactly how something was said. The tape will be used to transcribe our entire conversation onto paper and then it will be deleted. If you'd like me to turn the tape off at anytime during our conversation, please let me know.

Section 1: Personal Information

I would like to begin by asking you some questions about yourself. This is to ensure that I get a sample of people that is representative of the women attending this clinic.

1. What is your age?
2. Is this your first pregnancy?
3. How many weeks pregnant are you?
4. Is this your first appointment?
5. How has your pregnancy been so far?
6. Have you experienced any pregnancy losses?

Section 2: Screening during pregnancy

7. Have you had or will you have Down syndrome screening/testing?

   - Blood test at 10 weeks and measurement of thickness of the back of the neck at 11-13 weeks

   OR//

   - Blood test at 15 weeks

   If YES//

   a. Who offered you Down syndrome screening?

   If NO//

   b. Have you been offered Down syndrome screening?

   Determine whether they are still deciding whether to have screening or if they have declined the offer of screening.

8. How was the information about Down syndrome screening provided?

9. Do think you had enough information to make a decision about having Down syndrome screening?

10. Were you given any information or offered any screening or tests for other genetic/inherited conditions that can be done during pregnancy?

11. Do you think women should be offered screening/testing for genetic/inherited conditions during pregnancy?

    a. Why yes or no?

Section 3: Carrier screening for cystic fibrosis

12. Have you heard of cystic fibrosis which is a genetic condition that can be screened for?

    If YES//

    a. What do you know about it?

    Provide more information if necessary

    If NO//

    Provide information about CF including: severity, treatment, recessive inheritance

13. Do you think screening should be offered for cystic fibrosis?

14. Would you like to have been offered carrier screening for cystic fibrosis?

15. Couples can be tested at anytime, if you had been offered screening for cystic fibrosis before pregnancy would you have accepted the offer?

16. Who do think should offer carrier screening for cystic fibrosis? ie. GP, Ob, midwife etc.

17. How should the information about cystic fibrosis carrier screening be provided? ie. Brochure, doctor's explanation etc.

18. Currently cystic fibrosis carrier screening is only offered in the private health system as each test costs $220. Do you think this is a reasonable price to pay?

19. How much would you be willing to pay for cystic fibrosis carrier screening?

20. Do you think that cystic fibrosis carrier screening should be offered in the public health system?

Conclusion

Do have any questions about what we have discussed. I have a brochure which contains information on cystic fibrosis carrier screening and has a contact number if you wish to speak to someone.

Thank you very much for your time.