Choosing not to undergo predictive genetic testing for hereditary colorectal cancer syndromes: Expanding our understanding of decliners and declining.

Choosing not to undergo predictive genetic testing for Lynch Syndrome: expanding our understanding of decliners and declining.

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ABSTRACT

While medical research continues to investigate the genetic basis of cancer, and personalised prevention gains momentum, little research has been conducted with the individuals who decline predictive genetic testing for cancer. We recruited individuals who had been offered genetic testing for Lynch syndrome or bi-allelic *MUTYH* mutations due to their participation in a large, population-based, Australia-wide colorectal cancer study. Thirty-three individuals in mutation-carrying families, unaffected by cancer, who had actively or passively declined testing at one of four decision-making points, took part in a qualitative interview about their decision. Data analysis revealed a typology of 'decliners': (1) uninformed about genetic testing; (2) a weak intention to undergo genetic testing; (3) conditionally declining; and (4) unconditionally declining testing. In this population we found substantial barriers to achieving the benefits promised by predictive genetic testing; a lack of knowledge of the availability of genetic testing; a lack of trust in genetic test information; a desire to see a stronger benefit from genetic testing before proceeding; and a sense that there may be more negative than positive outcomes from genetic testing. These discourses must be addressed if medical research on the genetic basis of cancer continues to be funded, and personalised prevention of cancer continues to be recommended by experts.

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INTRODUCTION

Most sociological and psychological research on genetic testing for cancer pre-disposition has been conducted with the self-selected individuals who attend familial cancer clinics or their relatives (McAllister 2002; Claes, Denayer et al. 2004; Collins, Meiser et al. 2005;

Featherstone, Atkinson et al. 2006; Domanska, Nilbert et al. 2007; Arribas-Ayllon, Sarangi et al. 2013), or those diagnosed with cancer and receiving treatment-focused testing (Hallowell, Foster et al. 2004; Esplen, Madlensky et al. 2007). Psychological research on these groups has confirmed that; genetic counseling and testing causes little psychological distress (Claes, Denayer et al. 2004; Collins, Meiser et al. 2007); genetic counselling increases knowledge about hereditary conditions and improves accuracy of risk perception (Domanska, Nilbert et al. 2007; Smerecnik, Mesters et al. 2009; Linnenbringer, Roberts et al. 2010); and limited research indicates that adherence to screening guidelines can be achieved for tested individuals (Hadley, Jenkins et al. 2004; Claes, Denayer et al. 2005; Collins, Meiser et al. 2007). Sociological research has contributed to our understanding of the experience and consequences of genetic testing; the impact of genetic information on self-identity and family practices (Featherstone, Atkinson et al. 2006); the gendered nature of genetic screening programs and genetic responsibility (Steinberg 1996; Hallowell, Arden-Jones et al. 2006; Reed 2009); and the intensification of blame and responsibility for ill-health that can arise from genetic testing (Arribas-Ayllon, Sarangi et al. 2013). In contrast, however, little is known about those who decline genetic testing, who are likely to be positioned differently in relation to genetic information to those who are taking part in genetic counseling and testing consultations. We have studied this population in the context of hereditary colorectal cancer syndromes, ~~a genetic predisposition to cancer~~, in order to understand; the reasons offered for declining genetic testing; individual's position in relation to information about genetic testing; and the prevalent discourses about genetic information and tailored screening for colorectal cancer for those declining an offer of testing.

Lynch syndrome is one of the most common inherited cancer syndromes, and accounts for approximately 1-3% of all colorectal malignancies (Lynch and Smyrk 1996). Cases of Lynch syndrome are attributable to mutations in four DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2). Colorectal cancer is also increased for carriers of a mutation in another DNA

repair gene, MutYH. Persons inheriting a mutation in a mismatch gene from one parent are at risk of Lynch syndrome and with Lynch syndrome have an increased risk of colorectal cancer (CRC) with a lifetime risk estimated between 50% and 80%, and are at a substantially higher risk of developing endometrial cancer (30% to 70%), ovarian cancer (3 to 13%), gastric cancers (3% to 13%) and other extra-colonic malignancies, including hepatobiliary tract, urinary tract, brain and skin (Umar, Boland et al. 2004; Senter, Clendenning et al. 2008; Dowty, Win et al. 2013). Persons with a mutation in MutYH inherited from both parents have a 75% lifetime risk of colorectal cancer (Win, Dowty et al. 2014). For unaffected mutation-carrying individuals, colonoscopy enables detection of CRC at an early stage, at which point all premalignant polyps and lesions can be removed. Regular screening of the colon and rectum of unaffected carriers of Lynch syndrome reduces risk of CRC by 56% and death by 65% (Järvinen, Aarnio et al. 2000). Genetic testing for both Lynch syndrome and bi-allelic *MUTYH*, if followed by appropriate colorectal cancer screening, has the potential to reduce CRC morbidity and mortality.

In Australia, genetic testing is offered only in conjunction with expert counselling and advice (Clinical Oncologist Society of Australia and Australian Cancer Network 1999; American Society of Clinical Oncology 2003). There are over 20 Family Cancer Clinics (FCCs) in Australia, providing this counseling and advice, including informing clients of the benefits and limitations of genetic testing, providing risk information, and helping with psychological and behavioural adjustment to the information provided (Hallowell, Murton et al. 1997). Individuals at increased risk of familial cancer can be referred to a FCC by their general practitioner and for those who are determined to be eligible for testing, the testing is free-of-charge. Once tested, guidelines recommend the most appropriate screening modality and interval and the implementation of these guidelines is managed by either a GP or specialist. Life insurance companies are free to use genetic information to assess applicants for a new life insurance policy or for renewal of a policy in Australia, however are not able to compel

an individual to have genetic testing (Financial Services Council 2005). Individuals are usually informed about the possibility of becoming ineligible for new or renewed life insurance cover during genetic counseling, prior to testing (reference).

Significant cost savings to the health system and a reduction in the burden of colorectal cancer have been modeled in an Australian population by routine screening for Lynch syndrome (Breheny, Geelhoed et al. 2006; Collins, Meiser et al. 2007), and US guidelines recommend routine screening for Lynch Syndrome for Colorectal cancer patients (Berg, Armstrong et al. 2009). In the Australian state of Victoria however, only 22% of patients with colorectal cancer eligible for referral to a family cancer clinic were referred (Wong, Gibbs et al. 2008). From our research into the uptake of genetic testing by over 800 research participants in Australia, we also know that of those who were offered testing, only half pursued it (reference). We argue that even if both the scientific evidence and the health economic analysis indicate the benefits of a program like population screening for Lynch Syndrome, research on how eligible individuals might respond to an offer of predictive testing must also form part of the evidence base informing implementation. Without an understanding of how end-users of a program are likely to respond, there is a high chance of unintended consequences and/or reduced uptake.

In contrast to this public health perspective, sociologists have criticised the assumptions that underpin the promotion of predictive genetic testing as a way to prevent disease. Konrad suggests that the hope of predictive testing and personalised pharmaceuticals rests on a flawed assumption, of the 'active information-seeking subject' on whose decisions the health of the population rests. (Konrad 2005, p.10) Sociologists have also criticised the focus on individual behavior imagined to be free of social context (Bunton and Petersen 2005; Konrad 2005). Yet much research on health behavior still treats decision-making as an individual choice, ~~disconnected from the reality of day-to-day life~~, and underpinning much medical research is

the assumption that knowledge of genetics will be beneficial to the health of individuals (Konrad 2005; Timmermans and Shostak 2016). For example, decision-making regarding health behaviours is often interpreted through the lens of informed consent based on both knowledge and values (Michie *et al* 2003), or as a response to a range of potential motivations and deterrents (e.g. Esplen *et al* 2007), or as a logical flow of steps from unaware, through to aware, informed and then finally making and sustaining a decision (Prochaska and Diclemente 1983). Extensive research on genetic testing has revealed that clarifying cancer risk for self and family members is a motivator, as is determining appropriate risk reduction strategies (Hadley, Jenkins et al. 2003; Keller, Jost et al. 2004; Esplen, Madlensky et al. 2007; Tilburt, James et al. 2011). Deterrents include insurance discrimination and the perceived negative impact of a positive result (reference).

~~The theoretical models commonly applied to behavior change, often draw solely on psychological theory, and thereby focus on individual choice and emphasise the role of knowledge and education (Cockerham 2005). For example, the Transtheoretical Model of Change (Prochaska and Diclemente 1983) describes a three-step process for behavioural change; firstly individuals move from being unaware or unwilling to do anything about a behaviour (pre-contemplation); to considering the possibility of change (contemplation); then taking action (action); and finally, sustaining or maintaining that change over time (maintenance). Some researchers have suggested that decision-making about genetic testing can be understood in terms of such a stage model despite such testing being a one-time decision, rather than an ongoing behaviour (Jacobsen, Valdimarsdottir et al. 1997; Houlihan 1999; Taylor 2005). However, many questions remain: can this model account for people who choose not to pursue genetic testing? Can the theory of health lifestyles and sociological insights into predictive genetic testing be integrated with a stage-of-change model to enhance and contextualise our understanding of genetic testing decision-making?~~

Our research uses a qualitative research design and aims to develop a typology of decliners incorporating both known psychological factors and sociological critiques with new data generated from a population-based sample. We use thematic analysis to explore in-depth the experience of declining genetic testing. We move beyond the clinic and beyond individualistic explanations to understand the context of individuals choosing not to receive information and advice about genetic testing, despite being eligible. It is likely that the experience, knowledge, perceptions and motivations of this group are different to clinic attenders and their family members. Understanding this group of decliners may lead to more informed medical and scientific research that takes into account not only the science and economics of health care, but also the social experience and possible unintended consequences of health technology. By illuminating the specific concerns associated with declining genetic testing, we aim to explore and explain the interface between genetic technologies and those resistant to them.

METHOD

Setting

The setting of this research is a population-based research study in which participants are given the opportunity to receive clinically relevant genetic test results generated through the study. Participants are asked at the outset of the study if they wish to receive clinically relevant genetic information from the research. If genetic information is found, participants are informed about the availability of genetic test results in writing, including providing information about insurance (see Box 1) and if they choose to receive their results, clinical grade test results are provided in one of the 20 government-funded Familial Cancer Clinics in Australia according to standard clinical protocols.

Participants in this study were recruited from the XXXXX, a large cohort which is part of the XXXX, an international consortium funded by the XXX. The participants were part of a study looking at risk perception and genetic test decision-making (reference). In 1997, the XXXXX

started recruiting family members via population-based cancer cases (recently diagnosed with CRC) from the XXX (Australia), and via clinic-based cancer cases from multiple-case families referred to family cancer genetics clinics in Australia (Melbourne, Adelaide, Perth, Brisbane, Sydney) and New Zealand (Auckland) (reference). Population-based cancer cases with tumours exhibiting signs of loss of mismatch repair function were tested for germline mutations in *MLH1*, *MSH2*, *MSH6* and *PMS2* (reference). All clinic-based cancer cases with a prior diagnosis of colorectal cancer were tested for germline mutations in *MLH1*, *MSH2*, *MSH6* and *PMS2*. All population-based cancer cases were also tested for bi-allelic germline mutations in the DNA repair gene MutYH. If a mutation was found in a cancer case, all family members who had given a blood sample were also tested. We have described elsewhere the process by which these individual genetic results were returned to research participants (reference) and have reported that 56% of participants offered genetic information chose to receive results (reference) (outline of process illustrated in Figure 1). In brief, participants were told at the time of joining the study, that if clinically relevant genetic information were to be found by researchers, participants could choose to be informed. At the consent stage participants indicated whether they wished to receive personal genetic information in the case that something was found. If a mutation was identified in a family, all members of that family were sent either: 1) an 'opt back in' letter if they had not consented to receiving results, asking if they still did not want to receive results, or 2) if they had consented, a 'notification' letter offering the participant referral to a FCC to have genetic testing, to find out their genetic test result in a suitably resourced setting. For 1), if they chose to opt back in, a notification letter was then sent. All those who ticked 'yes' to wanting further information about their personal genetic information were referred to their closest Familial Cancer Clinic for genetic counseling where a clinically accredited genetic test would be performed. The XXXXX kept a record of who attended and received their results, and who did not.

Sampling and recruitment

From the XXXXX dataset, inclusion criteria were designed to capture those in the sample who had been offered genetic information, had declined, and who would be likely to benefit from predictive genetic test results;

- Participants who were members of a family found by the XXXXX to carry mutations in MMR or MutYH
- No previous diagnosis of cancer
- Under 70 years of age at the time of recruitment to this study
- Declined an offer of genetic test results, either actively (i.e. indicated refusal on response to letters) or passively (i.e. did not reply to letters or agreed to referral but did not attend)
- The offer of genetic information was more than 12 months ago but not more than 10 years ago, to allow time for the participant to make a decision, and to allow sufficient recall of decision.

Participants meeting these criteria were then grouped according to the point in the process at which they declined genetic testing: at the time of consenting to the XXXXX study, at the time of notification, or after referral to a FCC. In order to ensure the sample included all points at which participants could decline genetic testing, we purposively sampled until all groups were represented. We also aimed to represent the diverse demographics of the decliner sample in the XXXXX (age, gender and rural vs city location), so purposively sampled these groups. Participants in the XXXXX were contacted by a member of the XXXXX study team and invited to participate in this sub-study. Only once they agreed to have their details released were any identifying details provided to the qualitative study team. The qualitative study team then posted a participant information sheet and consent form and followed up by phone to determine whether participants wished to take part. If so, a mutually convenient time and place for the interview was organised.

Data collection

A semi-structured qualitative interview on risk perception, decision-making about genetic testing and cancer screening was used for data collection. XX and XX conducted in-person or phone interviews, if in-person was not possible. Before consenting to the study, participants were informed that they had been invited to participate because they had declined an offer of genetic testing. It was made clear to participants that we were interested in their view of genetic testing and how they had made their decision. Interviews proceeded by asking about their family history and experience of cancer, how they understood and managed their own risk of cancer, including their cancer screening practices, their understanding and current decision-making about genetic testing as well as future intentions. Preliminary analysis was conducted alongside interviewing and an early version of the typology presented in this paper was used to assess saturation. After 28 interviews it was possible to classify all new participants into the existing typology, and at 33 interviews we assessed that we had reached saturation, and recruitment ceased. Interviews were digitally recorded, transcribed verbatim, and audio files were checked against the transcript by the interviewer. Participants were given a pseudonym, and all identifying details were removed from the transcript.

Data analysis

Transcripts were entered into NVivo software to manage the data (QSR International Pty Ltd 2010). Through reading and re-reading of all transcripts by XX, XX and XX, key themes were identified. A coding framework was developed and data were double-coded initially to ensure high reliability of coding. Once over 90% reliability was consistently achieved, transcripts were single-coded by either XX or XX. Thematic analysis continued in an iterative manner after coding, to ensure the variability in each code could be fully explained. This paper details the analysis developed from the codes related to genetic testing decision-making; the participants' stated reasons for declining, whether they were aware of the purpose

of the genetic test, if they had consulted a health professional or had discussed it with other family members, and plans for the future with regard to genetic testing. Elsewhere we have reported on a quantitative measure of risk perception collected during the interviews with the participants from mismatch repair mutation carrying families (reference). Relevant findings regarding these measures are also discussed below.

Ethical considerations

We addressed several ethical issues in the conduct of this study and received ethical approval from the XXX. The XXXXX had collected a large amount of personal information about the participants we interviewed, for example, mutation status, cancer family history, and self-reported data on screening and other health behaviours. We chose not to be informed of this data prior to interviewing participants, and were only aware that an offer of genetic information had been made, as well as the point in the process and date at which they had actively or passively declined. This allowed interviewers to be unaware of participants' mutation status, and to know no more about the participant's health status than the participants themselves knew. The interview process revealed that some participants had misunderstood the offer of genetic testing being made to them by the XXXXX study, including what the genetic test results meant. Where relevant, information was provided after the interview, and we clarified that as researchers, and not clinicians, we could only provide generic information. In addition, all participants were provided with information leaflets about Familial Cancer Clinics, and we indicated that it was possible to receive general information and advice about familial cancer risks from clinics, even if they did not wish to pursue testing. We are not aware of the impact that either this information or the interview itself had on their decision to seek further information about genetic testing or even potentially decide to pursue genetic testing.

FINDINGS

Sixty individuals who fit the inclusion criteria were invited to join this study before recruitment ceased. Of the 60 decliners invited, 14 refused the invitation to participate, and upon being contacted, a further 6 refused to take part. Data saturation was reached by interview 33, so no further interviews were conducted. Overall, the refusal rate was 33% and a total of 33 interviews were conducted in 2011 and 2012; 19 females (58%), a mean age of 43 (26-68). Participants lived in four Australian states (23 in Victoria, seven in South Australia, two in New South Wales, and one in Queensland) with 21 participants from metropolitan areas (64%), and 12 from regional or rural areas. Nineteen of the 33 participants were parents. Participants had been offered testing more than one year prior to being interviewed and less than ten years, with an average time since offer of 2.9 years.

Participants had actively or passively 'declined' genetic information at one of four decision points (see Figure 1), which we call 'points of declining'; eleven had not consented to receiving personal genetic information, referred to as 'declining consent', nine had declined referral to a clinic when notified that information was available, called ' declining notification', eleven agreed to referral, but had not attended a clinic, called ' declining after referral', and two had attended a clinic but declined testing or test results, called 'declining after attending clinic'.

The assumption that all participants were 'decliners' was found to be erroneous once a detailed picture of the different stages of decision-making and patterns of genetic test declining emerged from the analysis. We found that, in fact, some participants had not yet made a decision to decline despite the average time since offer of 2.9 years. A number of factors were key to the decision participants had made (or not made): their level of knowledge about genetic testing, their attitude towards genetic testing, and their perception of what would need to change for them to proceed with genetic testing. These factors were interrelated

and taking all the features of decision making together, we were able to categorise participant's experiences into a framework of four types of 'decliners.' A summary of the main features of each type of decliner is shown in Table 1.

Uninformed (n = 4)

Four participants were not aware that it was possible to have genetic testing for bowel cancer, (we describe this as 'poor' knowledge in Table 1). This is despite receiving letters from the XXXXX explaining that genetic information was available. Three participants had declined to consent to receiving results, and one had declined a notification letter. For these participants, a decision to accept or decline the offer of genetic testing had not been made. When the test was explained to them, all expressed a positive attitude and an interest in having genetic testing and receiving their test results. The characteristics of the participants in this group are summarized in Table 2.

Clare, 30, when asked whether anyone has discussed genetic testing with her, said, *'No, no-one's really brought it up, but obviously if it can be tested and you can find out before it's too late, well yeah it'd be great.'*

Similarly, Fiona, 32, also described herself as '*not having made a decision'*. Her and her family decided that her mother's cancer was more likely to be due to lifestyle factors and not genetics. She described the perceived causes of her mother's cancer as *'stress in her lifestyle and how hard she was working and just, a lot of things you know, she was a smoker.'* She felt that if a test were available she would like to know more about it.

The least informed participant, Henry (29 years), had received a notification letter about genetic information in his family, but was uncertain about the nature of the test, describing it as a '*general health test*'. He felt that it was not an appropriate test for someone in his

twenties. When asked about the role of Family Cancer Clinics, through which testing would be offered, he said, '*Yeah, I'd only be guessing. I wouldn't have a clue really. I'm not too sure.*'

Once the test was explained to them by the interviewer, all four participants expressed potential interest in receiving genetic information. However, ~~despite their involvement in a study of bowel cancer, and having received an offer of information about their own genetic predisposition,~~ they displayed little prior knowledge of the availability of genetic testing. This group highlight the large disconnect between the expert discourse about the promise of personalised prevention of cancer through genetic information (for e.g. Speicher et al. (2010)), and the discourse among some members of the community who are eligible for testing, that this technology is still exists only as a future possibility. ~~This group add support to the findings of Featherstone et al. (Featherstone, Atkinson et al. 2006) who, in their study of families with a genetic condition in South Wales, did not find 'wholesale changes in self-identity as a consequence of genetic medicine.' (p143) They found instead, that genetic information was incorporated into a 'stable idea of self'~~. The uninformed group expressed more comfort with the traditional public health explanations for cancer risk (stress, smoking and lifestyle factors) than with genetic testing for understanding of their own cancer risk.

Weak intention (n =9)

Nine participants displayed a weak intention to undergo genetic testing for bowel cancer. Six of the nine participants in this group had been referred to a FCC to receive their genetic test results following notification, while two had not consented to receiving genetic results, and one had declined notification. While this group was aware that a genetic test for bowel cancer existed, there was variation in how well they understood the purpose and benefits of the genetic test. Some were aware of the purpose only (i.e. to determine whether an individual is at increased or population risk) which we deemed to be 'partial' knowledge (in Table 1),

while others were aware that screening recommendations would change depending on their result, which we considered to be 'complete' knowledge (in Table 1).

None of the participants in this 'weak intention' group were screening at the level required for mutation carriers, so any of those found to be positive for a hereditary colorectal cancer syndrome would be recommended to increase their screening frequency. All nine participants planned to receive genetic test results at some point, and did not describe themselves as 'decliners'. Instead, they described their reasons for delaying genetic testing. The most common reason, stated by six of the nine participants, was that genetic testing was not a priority. Emma, 42, describes the reason she has not pursued genetic testing as mainly because she '*has not got around to it.*'

> *I knew it was available to me, and my brother has the test done as well. So I've been considering it for the last eighteen months – two years but it's really, to tell you the honest truth, it's just something I haven't got around to more than anything else.*

A further two felt that it wouldn't alter anything, and one was delaying solely because of insurance concerns. These participants all described what would need to change in order for them to attend a clinic to obtain their results. Ben, 32, was initially positive about receiving his genetic information, but when he thought that there might be health insurance implications, he was put off, until he could find out more information.

> *I've been putting it off until I look into getting health insurance policy and getting that first and then finding out the results of the study.*

David, 47, says, '*it's just my slackness that [I] haven't had it done.*' He intended to have the genetic test, but due to the inconvenience, in his words, '*it just didn't work out*.' He exhibits a weak intention to receive his genetic test results. Reflecting on his decision, he says, '*probably should have, but yeah.*'

Caroline describes her intention to return the letter to indicate her intention to receive her results;

Interviewer *Okay. So you'll get the – you are planning on getting that information?*

Caroline *Yeah but I don't think it will change. Whatever the result is it won't change the way I run my life.*

This weak intention group expressed that it would probably be better to know their genetic test results, but they do not prioritise this activity. Both the inconvenience and the added barrier of potential 'health insurance' implications are enough to generate inactivity. They speak of the test as benign, that whilst it may provide some useful information, as Caroline says, *'it won't change the way I run my life'*. This group does not describe major negative implications of genetic test results, instead they are passive or unsure in their approach to finding out their genetic test results. Like the uninformed group, the majority is young, with five of the nine participants under 40 and four of these young people not yet having colonoscopies. Once again, these data show the discrepancy between the expert discourse about predictive genetic testing and the distinct lack of value placed on this test result from some eligible individuals. Unlike the uninformed group, it is not due to a lack of awareness of the availability of genetic testing, instead it is due to a perception that genetic testing is not of significant value, and is given a low priority compared to other activities in life. ~~For some, added to the low value, is a fear of potential negative outcomes (e.g. health or life insurance implications).~~

Conditional Decliners (n=9)

Conditional decliners were the first group to describe themselves as declining genetic testing, differentiating them from the previous two groups. However, this group talked about the possibility of deciding to receive results in the future if things were to change. Their reasons

for declining were based on factors that were subject to change: it won't alter anything (n=6), results will cause anxiety (n=3), and insurance concerns (n=1). Other characteristics of this group are summarised in Table 2. Again they expressed a range of levels of knowledge from partial to complete. Andrea, 40, seemed to have only partial understanding of the value of the test, and explained that she declined genetic testing because there were not clear benefits.

> *I didn't feel like it was going to make that much difference to me or my life so that's why I thought I don't really need to…I think if I felt there was some really good benefits of knowing then I'd go ahead with it, but I didn't really think that there were.*

Lorraine, 38, also seemed to have little knowledge of the benefits of the test. She felt the benefits or implications of the test results were not compelling enough to go forward with testing at this stage.

Interviewer *So if the test could tell you something, what would it need to tell you for you to be interested in finding out the result?*

Lorraine *[pause] oh, I don't really know. I just, I think maybe, maybe a likelihood or, you know, okay yes you've got a, a strong chance, you know, a really, really strong chance and you know, really something you should do or um, and, you know, we'll need to step up what have you … So, yeah, I, I probably, you know, I think it would just have to be the really 'oh my God, it's just full on now, that's it, you need to have this done' sort of.*

And she says later,

> *I mean, I could, may change my mind down the track but for the moment it's not something I'm worried about doing.*

Others were better informed, for example, Lauren had discussed genetic testing with her consultant

Lauren *.... I mean the consultant said you know it'd make his life a bit easier.... If we knew whether or not I had the gene then I probably wouldn't need such regular colonoscopies... So that would be a positive. So and I think just knowing that you don't have it would be nice. But then I think if I found out that I did have it I'd – yeah. So there's pros and cons for both so I think I'd rather just stay in the middle. There's definitely pros though for knowing.*

Interviewer *Okay. And do you think you might change your mind in the future?*

Lauren *Yeah I mean there's a chance I might decide to have it, so it's not set in concrete by any means.*

This group displayed varying levels of knowledge, ~~from poor knowledge to having received substantive medical advice. They~~ and could all describe the things that would need to happen in order for them to change their mind; for the test to offer clear benefits (n=5), for insurance concerns to be removed (n=1), if their children wanted the results (n=1), or if there were signs of cancer (n=2). This group were older, and having colonoscopies more regularly than the previous two groups, although still at a level lower than recommended for mutation carriers in most cases.

~~Five of the nine conditional decliners described feeling that if there seemed to be 'clearer benefits' from receiving their genetic test results, they would probably go ahead. Two others felt that if there were signs of cancer that it might indicate a reason to go ahead with testing; one felt that she would go ahead if her children wanted the information; and another if insurance concerns could be removed.~~ While ~~becoming~~ more strident in their decision, and less open to changing their mind, this group show a similar passivity and a range from disinterest to distrust of genetic information that was displayed by the two previous groups.

Unconditional Decliners (n=11)

The final group, 'unconditional decliners,' stated that they did not want to receive their genetic results and that they would be very unlikely to change their mind in the future. Unlike previous groups, they were confident in their decision, and were able to rule out genetic testing for themselves. Reasons for declining in this group were stated clearly and in strong terms: insurance concerns (n=5); anxiety causing (n=4); it won't alter anything (n=2); and fear of decreased screening (n=1).

Loretta (53), like Graham (58) who thought his son's future retirement funds may be affected, was concerned about insurance implications for her children, and expressed strong concern about potential negative implications of knowing her result.

> *I just worry in the future, insurance companies are gonna get a little bit more cut-throat and if they find out you've got some definite gene they may not want to insure you and I think health's gonna get more and more expensive as we're an aging population so I'm just concerned for them. And I think you know it's a pretty strong gene, I think you've just gotta assume that you've got that gene. I think that's the best way to go in this family, just assume you've got it.*

Sally (30), Roy (31), Cassie (42) and Rachel (54) were all interested in avoiding the anxiety that would be associated with a positive result. For example, Sally describes the fear she has about finding out she is positive for a hereditary colorectal cancer syndrome.

> *I prefer not to know than to know. It's still fifty-fifty. I wouldn't want to know if I had it because I suppose, based on the family history and you know, seeing other people go through it and their family, I wouldn't wanna live with a thought in the back of my mind of, 'Oh when, when might this show its head?'...I guess that's my thinking. And having it constantly there and constantly playing on your mind, I'd prefer to live my*

life where I can obviously, you know with screening and things like that, be proactive. But like, what's gonna happen will happen is my thinking, yeah so that's why I don't really wish to know.

Tony, 28, felt that 'it wouldn't alter anything' because he and his family were undertaking the screening they thought appropriate for mutation carriers. He and his family also wanted to avoid the potential insurance discrimination associated with receiving a positive result, and the risk of becoming 'lazy with check-ups' if they received a negative result. They appear to be using uncertainty about their genetic status as a motivator for screening.

We decided as a family that my brother and I and my dad would continue to have regular colonoscopies and endoscopies no matter what the result was going to be – so we sort of felt that if the result came back and it said we didn't have the gene then that would perhaps lead us to be a bit lazy with our check-ups. So if it was unknown then we'd just assume that we do have it and continually get regular check-ups as though we are at high risk of getting cancer…I'm happy to just keep going along the way things are.

Participants in this group, ranging from 28-58 years of age, tended to have made informed, considered decisions about their choice not to receive genetic test results. They were confident in describing their reasons, and did not think they would change their mind in the future. They mostly expressed a sense that the risk of cancer for themselves and their families was high, but also that screening was the best response to this risk, rather than genetic testing.

~~Unconditional decliners were confident in their decision not to receive their genetic test result for a range of reasons. The most common reason was because of insurance concerns, and this encompassed a range of issues, from private health insurance, retirement funds, and life insurance, death and disability entitlements and children's access to these policies. The belief~~

~~that genetic testing would not alter anything was also strong in this group, along with the idea that living with a positive result would provoke anxiety, or that a negative result might reduce motivation to screen, or access to screening.~~ While the reasons for declining genetic testing did not differ greatly from previous groups, this group displayed the strongest opposition to genetic testing, and the most confidence in their decision. In most cases, participants were choosing to undergo screening as though they had the hereditary colorectal cancer syndrome, while not having to live with the potential downsides of knowing their mutation status, indicating they had made an informed decision, in line with their values.

DISCUSSION

The data present a range of levels of negotiation and engagement with the idea of genetic information and raise a number of discourses likely to impact on any future population screening program. All the individuals who participated in this study are potentially carriers of a hereditary colorectal cancer syndrome who, by way of a letter from a research study, were offered the chance to learn genetic information by attending a familial cancer for counseling and clinical genetic testing. There is no reason to assume these participants are different from those who would be identified through a population screening program, except their participation in a genetic study may have increased their awareness of genetic testing for hereditary cancer syndromes.

The results offered would remove uncertainty about their status by either confirming carrier status or identifying that they are 'true' non-carriers. This information would have implications for screening recommendations and for their future health, and yet all had declined the offer of this information. In this population factors that contributed to delaying or declining were; a lack of knowledge of the availability of genetic testing; or only partial knowledge of the benefits of the test; a lack of trust in genetic test information; a desire to see a stronger benefit from genetic testing before proceeding; and a sense that there may be more

negative than positive outcomes from genetic testing; greater trust in screening than genetic testing. We have identified a group not represented in the literature so far, those who make an informed decision to unconditionally decline genetic testing with adequate knowledge of the benefits of testing.

We initially classed all participants as 'decliners' of genetic testing, as they had either actively or passively declined an offer made to them by the XXXXX to refer them to a FCC for testing. It is clear however, that not all participants considered themselves decliners. Instead we found a typology of delayers and decliners; four were uninformed and had therefore not made a decision, nine had a weak intention to undergo genetic testing but had not yet done so, nine were conditionally declining and eleven were unconditionally declining testing. ~~Groups varied by how well they understood the test, their attitude towards the test, the reasons for their decision and what would need to change for them to proceed with testing. The genetic testing discourses they engaged with and the position of genetic knowledge in relation to other health and lifestyle factors all influenced their final decisions.~~

The difference between the expert discourse about genetic testing and the lay discourse expressed by these delayers and decliners is stark. They described genetic test results as not having clear benefits and potentially having negative consequences. In addition, there was a trend towards the better informed participants being more strongly opposed to genetic testing, indicating that there is likely to be a group who remain opposed to predictive testing despite adequate information. ~~There is some evidence from these data that genetic testing decision-making may involve a number of stages of decision-making. The uninformed group could be considered in the stage of 'pre-contemplation', and those expressing a weak intention could be in the 'contemplation' stage and therefore not necessarily decliners. However, the conditional and unconditional decliners have not undertaken the action of genetic testing, despite a significant period of 'contemplation'.~~ The first three groups however, expressed in various ways the notion that the test was not likely to provide enough value. Most people in

these groups would consider testing if they understood that there were clear benefits to themselves or their children, it was convenient, and/or concerns about insurance could be removed. ~~These delayers and decliners expressed varying levels of openness to the idea that the benefits of testing may outweigh potential harms or costs or effort involved, but none were convinced that this was currently the case for them. At a practical level, the decision involved weighing up a number of related factors, and unless the balance tipped in favour of testing, participants remained in a state of either delaying or declining.~~ In contrast, those who unconditionally declined testing perceived genetic test results as likely to produce a negative outcome in the form of either causing anxiety, insurance discrimination, or reduced motivation and screening availability. ~~These unconditional decliners were reasonably well informed about genetic testing and yet remained in little doubt that the harms or costs of testing outweighed any benefits for them, and did not express openness to changing their mind.~~ In this group, genetic testing was either seen as providing information of doubtful benefit to health, or alternatively, as leading to a more sinister outcome likely to result in poorer overall health. These participants concurrently expressed faith in surveillance as a reliable way to reduce one's risk of cancer.

Using a quantitative measure of risk perception with the subgroup of participants offered genetic information about Lynch Syndrome, we have previously reported that these participants indicated a substantially higher risk perception than their risk as calculated using software program MMRpro, independent of age and sex and reported colonoscopy screening (reference). The possibility that increased risk perception is driving the declining requires further research and exploration.

~~This discourse of genetic information as unreliable (and potentially sinister) information, and less trusted as part of cancer prevention than a colonoscopy, must be addressed if expensive medical research on the genetic basis disease continues to be funded, and population-based~~

~~genetic testing schemes continue to be recommended by experts. The lack of interest in genetic information is in stark contrast to the rhetoric of the promise of genetics, and provides evidence that information about the value of genetic testing has so far failed to overturn strongly held positions and norms.~~

The factors influencing delayers and decliners are not just health factors, as the distance travelled for testing, the time taken, insurance implications or the emotional fallout of a test for patients and family members are all considered important factors by participants. These findings confirm sociologists argument that improved knowledge alone is unlikely to lead to appropriate decision-making and that everyday understandings and positions are not easily changed (Featherstone, Atkinson et al. 2006).

~~Eight in total had discussed testing with a medical practitioner and two of the 33 participants had attended a FCC for comprehensive pre-test counseling. These two intended to have genetic testing, but when the possibility of insurance discrimination was explained to them at the clinic, decided not to go ahead with testing.~~ We have previously reported the potential of insurance discrimination to deter people from genetic testing (reference), and these results confirm it as a significant factor, with seven of 33 participants naming it as a key reason for not proceeding. ~~It is important to understand and address these structural barriers to genetic testing.~~ Worryingly, those declining because of insurance concerns were much more likely to be unconditional decliners (five of the seven), meaning they were less open to reconsidering their position. While some of the issues raised by participants as reasons for not having testing can be addressed by further education or better explanations of the benefits of testing, the issue of insurance discrimination will require regulatory change. Current regulations in Australia do not protect people from genetic discrimination in the area of life insurance (reference). However, misunderstanding about the implications for health insurance and

funding in retirement could be addressed, as there are regulations protecting individuals suffering genetic discrimination in these areas.

CONCLUSIONS

We were provided a rare opportunity to consider genetic testing decision-making for healthy study participants who decline genetic testing, and are therefore outside the usual clinical samples seen in genetic testing decision research. Our study is part of a large population- and clinic-based registry in which participants are informed from the outset that they will be offered the opportunity to learn of clinically significant genetic information through clinical services. Consequently our sample was diverse in terms of geographic location, socio-economic status, age, family history and exposure to advice and support about genetic testing. This sample may thus represent the "naïve" group who will be offered genetic testing if population screening for Lynch syndrome were enacted (Bellcross, Bedrosian et al. 2012). While we continued data collection until saturation had been reached, it is possible that there is a type of decliner who chose not to participate in this study, or who was not part of our sampling frame and is therefore not represented here. However we believe these findings provide novel and important information to guide efforts to address concerns and misconceptions about genetic testing for hereditary colorectal cancer syndromes, and to provide information for those considering the role of genetic testing in the health system. In health care systems designed primarily to deliver care to the sick, it is a challenge to find an effective means by which to support fully informed decision making by healthy people who are not independently motivated to attend a health service. Mechanisms to support access to information, advice and support for this group may assist informed decision-making for predictive genetic testing. We have shown that efforts to optimise predictive genetic testing uptake are likely to need a multifaceted approach that address a range of barriers, some that may be addressed by changing the local discourses about the irrelevance or potential danger

of genetic testing, others that may require systemic changes, or medical research that is better informed and embedded in the perceptions of patients and their experience.

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Table 1: Summary of types of 'decliners'

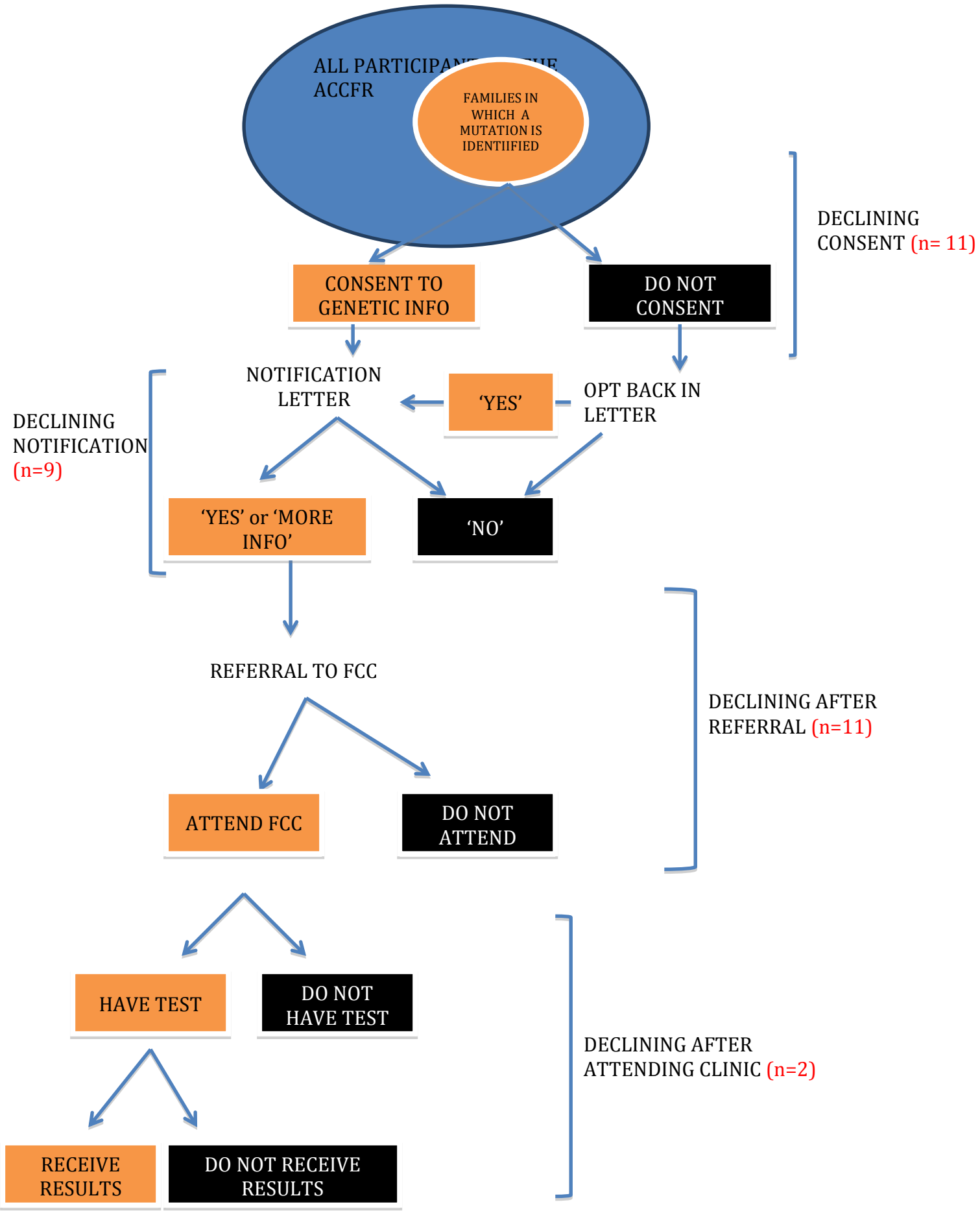
	Knowledge	**Attitude**	**What would need to change to proceed with testing?**
Uninformed (n=4):			
Were not informed enough about genetic testing to be able to make a decision	Poor	Positive	Provide information about availability of genetic testing and benefits
Weak intention (n=9):			
Intended to undergo genetic testing, but had not yet done so	Partial to complete	Ambivalent to negative	Increase motivation, provide information about benefits of testing, remove barriers
Conditional Decliner (n=9)			
Declined at time of interview, but did not rule out genetic testing at some future point	Partial	Negative	Provide information about benefits of testing, remove barriers
Unconditional decliner (n=11)			
Strongly opposed to genetic testing both now and into the future	Partial to complete	Very negative	Did not think they would change their position

Table 2: Characteristics of decliner types

	Uninformed	Weak intention	Conditional decliner	Unconditional decliner
No. of participants (female)	4 (2)	9 (5)	9 (6)	11 (6)
Mean age (range)	35.2 (29-50)	39.7 (26-65)	49 (29-68)	45 (28-58)
Colonoscopy at least once (%)	2 (50)	5 (56)	8 (89)	8 (73)
No. of FDR with CRC (%)				
0 FDR	-	3 (33)	3 (33)	3 (27)
1 FDR	4 (100)	5 (56)	4 (44)	6 (55)
2 FDR	-	1 (11)	1 (11)	1 (9)
≥ 3 FDR	-	-	1 (11)	1 (9)
Stage of declining				
Consent	3	2	1	5
Notification	1	1	4	3
Referral	-	6	3	2
Clinic	-	-	1	1
Reason for delay/declining*				
Insurance concerns	-	1	1	5
Anxiety causing	-	-	3	4
Fear of decreased screening	-	-	-	1
Won't alter anything	-	2	6	2
Not a priority	-	6	-	-
What would need to change to proceed with testing?*				
Information about availability of testing	4	-	-	-
Clearer benefits	-	2	5	-
More convenient	-	5	-	-
Remove insurance concerns	-	3	1	-
Signs of cancer	-	-	2	-
For children	-	-	1	-

*more than one response could be given

Figure 1: Diagrammatic representation of the process of notifying participants in the ACCFR of genetic results and the 'points of declining'


ALL PARTICIPANTS
ACCFR
FAMILIES IN WHICH A MUTATION IS IDENTIIFIED
CONSENT TO GENETIC INFO
DO NOT CONSENT
DECLINING CONSENT (n= 11)
NOTIFICATION LETTER
'YES'
OPT BACK IN LETTER
DECLINING NOTIFICATION (n=9)
'YES' or 'MORE INFO'
'NO'
REFERRAL TO FCC
DECLINING AFTER REFERRAL (n=11)
ATTEND FCC
DO NOT ATTEND
HAVE TEST
DO NOT HAVE TEST
DECLINING AFTER ATTENDING CLINIC (n=2)
RECEIVE RESULTS
DO NOT RECEIVE RESULTS

Box 1. Insurance information offered to participants

Information about life insurance implication of genetic testing provided to participants
• If we inform you that we have found genetic information relevant to you or your family, you will have to inform your insurance company if you apply for a ***new*** life, trauma or disability insurance policy or ***renew*** your trauma and disability insurance in the future and this might affect your policy. (See Health and Life Insurance Section.) • The genetic research in this study will have no implications if you apply for a ***new*** life, trauma or disability insurance policy or ***renew*** your trauma and disability policy in the future.