“It gives them more options”: preferences for preconception genetic carrier screening for fragile X syndrome in primary healthcare

Alison D. Archibald^{1,2,3} · Chriselle L. Hickerton¹ · Samantha A. Wake^{1,2,3} · Alice M. Jaques¹ · Jonathan Cohen^{4,5} · Sylvia A. Metcalfe^{1,2,6}

Received: 5 October 2015 / Accepted: 17 January 2016 / Published online: 3 February 2016
© Springer-Verlag Berlin Heidelberg 2016

Abstract This study aims to explore stakeholder views about offering population-based genetic carrier screening for fragile X syndrome. A qualitative study using interviews and focus groups with stakeholders was undertaken to allow for an in-depth exploration of views and perceptions about practicalities of, and strategies for, offering carrier screening for fragile X syndrome to the general population in healthcare settings. A total of 188 stakeholders took part including healthcare providers ($n=81$), relatives of people with fragile X syndrome ($n=29$), and members of the general community ($n=78$). The importance of raising community awareness about screening and providing appropriate support for carriers was emphasized. There was a preference for preconception carrier screening and for providing people with the opportunity to make an informed decision about screening. Primary care was highlighted as a setting which would ensure screening is accessible; however, challenges of offering screening in primary care were identified including time to discuss screening, knowledge about the test and possible outcomes, and the

health professionals’ approach to offering screening. With the increasing availability of genetic carrier tests, it is essential that research now focuses on evaluating approaches for the delivery of carrier screening programs. Primary healthcare is perceived as an appropriate setting through which to access the target population, and raising awareness is essential to making genetic screening more accessible to the general community.

Keywords Population carrier screening · Fragile X syndrome · Genetic counseling · Qualitative research · Primary healthcare

Introduction

In recent years, the scope of genetic testing has broadened substantially with advances in testing technologies having the potential to lead to improvements in diagnosis and management of individuals and families impacted by genetic conditions. There is now greater ability to screen for genetic carrier status, enabling individuals and couples to use this information for their reproductive decision-making and planning. Population-based genetic carrier screening has been offered through screening programs for individual single gene disorders such as cystic fibrosis, with screening typically offered in prenatal and preconception settings (Metcalfe 2012). Due to advances in technology, expanded carrier screening is now available involving screening for carrier status of a large number of inherited conditions simultaneously (Edwards et al. 2015). The challenge facing researchers and clinicians is in determining how best to deliver genetic carrier screening services to the general population in order to maximize benefits and minimize harms.

✉ Sylvia A. Metcalfe
sylvia.metcalfe@mcri.edu.au

¹ Murdoch Childrens Research Institute, Melbourne, VIC, Australia

² Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia

³ Victorian Clinical Genetics Services, Melbourne, VIC, Australia

⁴ Fragile X Alliance Inc., Melbourne, VIC, Australia

⁵ Centre for Developmental Disability Health Victoria, Monash University, Melbourne, VIC, Australia

⁶ Genetics Education and Health Research, Murdoch Childrens Research Institute, Royal Children’s Hospital, Flemington Rd, Parkville, VIC 3052, Australia

Fragile X syndrome (FXS) is an X-linked condition and the leading cause of inherited intellectual disability. A carrier result conveys both reproductive risk and implications for the health of the individual screened. As such, FXS carrier screening, either stand-alone or as part of expanded screening, provides a useful model through which to consider carrier screening approaches because of the complexity and duality of risk information provided (Henneman et al. 2016). As outlined by Hill et al. (2010), arguments for carrier screening for FXS include a high prevalence (which may be up to 1 in 2500 in males and females (Hagerman 2008)) and high carrier frequency (recently reported to be 1 in 179 estimated for North American populations (Hantash et al. 2011)), the prevalence of premutation alleles estimated as 1:209 in females and 1:430 in males (Tassone et al. 2012), and an accurate testing method amenable to screening populations (Tassone et al. 2008) which identifies an expanded CGG repeat in the *FMRI* gene (the cause of FXS in over 99 % of cases). In addition, the condition is well understood and defined; there are a range of significant phenotypic effects associated with the full mutation ($FM \geq 200$ hypermethylated CGG repeats) including intellectual disability and cognitive, behavioral, and medical problems, which have a substantial impact on the affected individual and their family (Hagerman and Hagerman 2002). Female carriers have up to a 50 % risk of having a child with FXS. There are also health implications for carriers of the premutation (PM 55–200 CGG repeats): females are at risk of fertility problems and early menopause (Wittenberger et al. 2007), a condition referred to as fragile X-associated primary ovarian insufficiency (McConkie-Rosell et al. 2007), and males, and to a lesser extent females, may develop fragile X-associated tremor-ataxia syndrome (FXTAS), a late-onset neurodegenerative condition (Hagerman et al. 2001). Further research will assist in fully understanding the significance of intermediate alleles (45–54 CGG repeats) identified in the general population; however, any screening program would need to have strategies in place to manage these results (Archibald et al. 2013).

Testing for *FMRI* carrier status occurs predominantly when there is a family history of *FMRI*-related conditions. However, delays in diagnosis, variability in the extent to which families communicate genetic information, and the reliance on the birth and diagnosis of an individual with FXS in the family mean that many individuals who carry *FMRI* alleles expanded beyond the normal range of 6 to 44 repeats are not aware of their carrier status. A population-based carrier screening approach would enable women who receive a test-positive result to incorporate that information into reproductive decision-making and planning.

Despite research indicating that there is support for population carrier screening for FXS (Hill et al. 2010), the American College of Medical Genetics only recommends screening as part of clinical research protocols (Sherman

et al. 2005). Recommendations from the American College of Obstetricians and Gynecologists (2010) suggest that carrier screening be offered to women without a family history of FXS if it is requested. The need for appropriate education and genetic counseling has been emphasized as has the importance of research exploring psychosocial impacts of such screening (Finucane et al. 2012; Sherman et al. 2005). Research indicates that population screening for FXS is generally perceived favorably by families and healthcare providers (Acharya and Ross 2009; Archibald et al. 2013; Rynanen et al. 1999; Skinner et al. 2003) as well as individuals offered screening in research contexts (Anido et al. 2005, 2007; Archibald et al. 2009; Fanos et al. 2006; Metcalfe et al. 2008; Sherman et al. 2005), and there appears to be a preference for screening offered before pregnancy (Acharya and Ross 2009; Archibald et al. 2013; Skinner et al. 2003). As carrier screening approaches have varied, there is no clear consensus on how best to deliver population-based carrier screening for FXS.

We have explored the views of a range of stakeholders (families of individuals with FXS, healthcare providers, and the general community) regarding population-based carrier screening for FXS. We previously reported results relating to stakeholders' perceptions of the acceptability of population-based carrier screening for FXS (Archibald et al. 2013). Here, we present the views of these stakeholders regarding practicalities of, and strategies for, offering population-based carrier screening for FXS.

Materials and methods

A qualitative approach using a grounded theory framework (Charmaz 2006) was chosen to allow for an in-depth exploration of views and perspectives of stakeholders regarding population-based carrier screening for FXS in Australia, as described in detail in Archibald et al. (2013). Briefly, stakeholders invited to take part in this study included health professionals, relatives of people with FXS, and members of the general community (this included women who had been offered FXS carrier screening through a research study (Archibald et al. 2009; Metcalfe et al. 2008)). Approval to recruit members of stakeholder groups was granted by the following Human Research Ethics Committees (HREC): The University of Melbourne HREC, Family Planning Victoria (HREC), and the Royal Childrens Hospital (RCH) (Melbourne, Victoria) HREC. We purposively sampled to ensure participants were recruited who represented a wide range of backgrounds, experiences, and perspectives. To take part, all participants needed to be fluent in English and 18 years of age or older (with the exception of the high school students who were 16 and 17 years of age). Pregnant women were able to participate if they were 10 weeks gestation or less. Relatives of people with FXS

needed to have a first-, second-, or third-degree relative with FXS, and the diagnosis of FXS had to have occurred more than 1 year prior to recruitment into the study.

Participants were recruited through letters and email bulletins through hospitals and clinics, emails to school and community member contacts, and local newspaper advertisements and by being given study information by other participants (snowball sampling). Data were collected through semi-structured interviews and focus groups using questions developed by drawing on published qualitative research in this area (Anido et al. 2005, 2007) and our prior research outcomes (Metcalf et al. 2008; Metcalf and Archibald 2012). Topics included general questions about awareness of genetic conditions, genetic screening, and FXS; perceptions of factors that might influence decision-making about carrier screening, perceived benefits, and concerns about carrier screening; views on whether population-based carrier screening should be available to all women; and when and where FXS carrier screening could be offered. Interviews occurred face to face in the participant's home, at Murdoch Childrens Research Institute, by telephone, or in the participant's workplace; focus groups were conducted at Murdoch Childrens Research Institute or in a location convenient to all focus group participants. Interviews were audio-recorded and transcribed verbatim, and participants were assigned a pseudonym. NVivo 8 software (QSR International Pty, Ltd., Melbourne, Australia) was used to manage data and facilitate coding. Transcripts were analyzed using thematic analysis, an inductive approach enabling themes to emerge from the data (Charmaz 2006). Transcripts were co-coded until consensus in coding was reached.

Results

A total of 188 people took part in an interview ($n = 125$) or in one of 11 focus groups ($n = 63$). These included 81 healthcare providers, 29 relatives of people with FXS, and 78 members of the general population (see Table 1 and Archibald et al. 2013 for further detail). Six themes emerged from participants' discussions relating to aspects of development and delivery of a screening program, including assessing feasibility, raising awareness and increasing understanding, considering timing, ensuring accessibility, facilitating decision-making, and managing results.

Assessing feasibility

Participants emphasized that for a screening program to be feasible, some specific factors would need to be considered and addressed prior to implementation. These are presented in Table 2 with representative quotes and included ensuring adequate funding and allocation of resources, development of protocols and guidelines,

training of healthcare providers who would be offering the test and managing test-positive results, assessing test accuracy as well as the timeframe for testing, consulting with key stakeholders such as healthcare providers and support groups, assessing economic aspects such as conducting economic evaluations, and weighing genetic carrier screening against other important health interventions. Less commonly, participants discussed ensuring confidentiality of results. Although there was substantial similarity in perspectives across stakeholder groups, notably, the vast majority of comments about economic considerations, the feasibility of the genetic test, and resource implications of a screening program were made by medical healthcare providers.

Raising awareness and increasing understanding

With the exception of participants who had relatives with FXS and genetic and medical healthcare providers, there was a distinct lack of knowledge and awareness of FXS among participants:

Look I've heard of it but I never treated anyone with it or dealt with anyone with it specifically, no. I mean I probably have heard more about it but I can't drum it up in my memory.

Penny, health professional (physiotherapist)

Members of the general community and some allied health professionals were also generally unaware of the possibility of genetic screening and of the implications of learning about one's genetic information. Despite the lack of knowledge and awareness, participants showed an interest and enthusiasm in discussing genetic carrier screening and emphasized that any screening program would need to be accompanied by attempts to raise community awareness:

It's not very well known in the public arena and I think that before screening... there would have to be a really big educational push to get people to have, you know, a decent understanding.

Elizabeth, general population (pregnant)

Incorporating discussion, but not an offer, of screening into the high school curriculum was the most frequently proposed strategy for raising awareness. Participants felt that this would enable carrier screening to be raised in a general way, discussed, and considered from multiple perspectives:

Being informed in high school would be good as part of health and human development subjects... if there is a range of different conditions that are covered it might be

Table 1 Composition of stakeholder groups

Stakeholder group	Number of participants in sub-groups	Number of participants in stakeholder groups
Healthcare providers		81
Clinical geneticists	7	
Genetic counselors	11	
General practitioners	15	
Maternal and child health nurses	2	
Medical scientists	6	
Midwives	6	
Obstetricians/gynecologists	6	
Occupational therapists	2	
Pediatricians	5	
Physiotherapists	7	
Psychologists	4	
Speech pathologists	7	
Support workers	3	
Relatives of individuals with FXS ^a		29
Mothers	20	
Fathers	3	
Sisters	2	
Grandmothers	3	
Grandfathers	2	
Aunts	7	
Cousins	3	
Nieces	1	
General population		78
Non-pregnant women offered screening ^b	31	
Accepted screening (<i>n</i> = 13)		
Declined screening (<i>n</i> = 18)		
Pregnant women	11	
High school community	18	
Teachers (<i>n</i> = 7)		
Students (<i>n</i> = 11)		
General community	18	
Total		188

^a Some relatives had more than one family member with FXS; for example, a woman may have had a child with FXS and her sister might also have a child with FXS, in which case the participant was classified as both a mother and an aunt. Therefore, for this stakeholder group, the number of relationships to the person with FXS is greater than the total number of participants

^b This group had been offered the FXS carrier test through a population-based carrier screening pilot study (Metcalf et al. 2008)

helpful... that's when you've got a captive audience so that would be a good way to promote awareness of it...
Lisa, general population (pregnant)

Participants also raised the possibility of utilizing the media as a useful mode of raising awareness but stressed that caution would need to be taken regarding the way information about genetic screening is presented to avoid confusion or coercion.

Considering timing

Participants discussed various stages of life at which screening could be offered: adolescence; adulthood, but not planning a family in the near future; adulthood, planning a family in the near future; and pregnancy. Various considerations with respect to the timing of screening were raised (see Table 3) and included relevance of screening to an individual's stage of life,

Table 2 Factors impacting feasibility of a fragile X carrier screening program

Themes	Participant quotes	
Availability of resources	Availability of appropriately trained and qualified health care providers to offer the test	“There’s a huge education component to population screening... part of the role of the screening program is to support the people who are offering the screening, to make sure they’re educated, that they’re comfortable, that they understand the implications of what they’re offering, etcetera. And I think that’s a huge challenge.” Chelsea, health professional (genetic counselor)
	Sufficient resources for managing test-positive results	“...it would require a lot of resources because not only would you have to do the screening but you’d have to have the appropriate back up for the positive results... so there would have to be a huge system put in place [to] actually provide the resources.” Rosalind, health professional (pediatrician)
Development of protocols and guidelines		“...you would want counseling guidelines... I think [it] would have to be obviously very well resourced and set out... protocols and pathways for each outcome and how they would be managed.” Ava, health professional (genetic counselor)
Economic considerations	Weighing fragile X carrier screening against other health interventions	“...considering whether it will take up a lot of resources... there are other major issues that we could equally tackle with those kind of resources... whenever we look at a large program like this we have to ask ourselves: is this the next priority?” Chris, health professional (clinical geneticist)
	Economic evaluations	“I need to know what the benefits are and cost because we’re talking about something at an economic cost... and the health budget has a certain size... where’s the cost-benefit [analysis]?” Nadine, health professional (pediatrician)
Feasibility of the genetic test	Timeframe for testing	“...Once you include pregnant women, which I believe you have to include, then getting timely results is a major challenge.” Anthony, health professional (clinical geneticist)
Stakeholder support	Healthcare providers	“I think it needs to be supported by health professionals offering the service... if the health professional doesn’t know about it or support it, or understand it, then it won’t get up and running.” Chelsea, health professional (genetic counselor)
	Fragile X community	“I think that’s critical, absolutely critical [to speak to families of people with fragile X]... with those sorts of things [it] is so worthwhile to get their feedback on what this would mean.” Laura, general population (accepted screening)

capacity for decision-making, impact of receiving a carrier result, utility of knowledge of carrier status at each stage of life, and accessing the target population. Inherent in the debate about when to offer FXS carrier screening was a tension between the accessibility of screening and the preferred stage of life to learn one’s carrier status, with adolescence unanimously considered the least favored option. Preconception carrier screening was the preferred approach as participants emphasized there would be time for decision-making, individuals/couples could incorporate the information into future plans, and there would be a range of reproductive options available. However, participants highlighted the challenges of accessibility at this stage of life (see Table 3). Although some felt it would be fairly straightforward to offer carrier screening to pregnant women, the potential to increase anxiety at a stressful time, the

reduced time for decision-making, and the limited reproductive options were perceived as problematic and led to concern about offering carrier screening at this stage. Nevertheless, it was acknowledged that all women, regardless of reproductive stage of life, should be provided with the option of screening.

Facilitating decision-making

A common perspective, particularly among the participants in the general population group, was that individuals offered screening be provided with the opportunity to make an informed decision:

...it would be really important to fully educate them so that they know exactly what they’re dealing with... [and] all the possible implications...
Holly, general population (offered screening)

Table 3 Participants' perceptions about offering carrier screening for FXS at each stage of life

Themes	Stage of life	Adulthood	Adulthood-preconception	Pregnancy
Relevance to stage of life	Adolescence	<p>"[it] is a bit young for them to take it all in and understand, they go, 'well I'm not thinking of having kids now so how does this affect me?' ... I think they have got to be a bit older and more mature." Lilly, general population (teacher)</p>	<p>"...most people don't sit down and plan a family, sometimes it just happens. And we should try and catch the population that... haven't thought about family but have suddenly fallen pregnant or they're in a relationship and just decide ad hoc that they'd like a child." Emily, healthcare provider (clinical geneticist)</p>	<p>"For me it's relevance to my kids... if I wasn't planning to have children I couldn't care less but it's all got to do with my children... just to know for the future." Laura, accepted screening population (pregnant)</p>
Capacity for informed decision-making	Adolescence	<p>"At 16... I don't know if I would have been able to necessarily understand this... [as an adult] I'm able to go away and educate myself about it, whereas a 16 year old, I think that's quite young to make a decision." Stacey, healthcare provider (speech pathologist)</p>	<p>"...a screening program that's happening before conception allows you time to consider your options without the urgency and the pressure of an impending decision and to me that's good because if you've already conceived and you then find out you're a carrier, you have to make a decision in a short timeframe and it's not as well considered. To me that's a tougher road to travel... [having that time was] much better. Because you can consider the implications of your decision without a deadline. You can waver backwards and forwards if you need to... it's just a more considered decision." Karla, relative (aunt)</p>	<p>"I think our current ways of dealing with this... at antenatal clinic, it's too late you know... with people having to make a whole string of rapid decisions when they're [not] fully informed." Mandy, healthcare provider (obstetrician/gynecologist)</p>
Impact of carrier result on the individual	Adolescence	<p>"...at that age... I think it might be a little bit confronting for a high school student to find out that they are a carrier for it." Wendy, general population (general community)</p>	<p>"...it was very tricky: when do you tell someone? ... you know, you go out, you meet someone, do you tell them a week after going out or do you tell them three months after going out? ... So I don't know. I think ignorance is bliss a lot of the time. I would... probably say offer it when they are planning [to have a family]..." Lara, relative (aunt)</p>	<p>"...if they fall pregnant and find out their baby is... severely affected maybe they'd probably wanna know beforehand because to be put in a situation like that would just be heartbreaking for a mother." Jenny, general population (accepted screening)</p>
Utility of knowledge of carrier status	Adolescence	<p>"[it] is quite young to be making decisions about your life and certainly to be thinking about families and your future." Penny, general population (pregnant)</p>	<p>"It gives them more options because they could perhaps even choose to have PGD... [it] gives time [and] slightly more choice than during pregnancy." Ava, healthcare provider (genetic counselor)</p>	<p>"I don't think it's probably all that helpful to do it when you're in the early stages of pregnancy like I think that's probably something that you should have done before hand because it's something that can be tested beforehand... rather than going, 'oh by the way now we could have avoided this situation but now we're testing you'." Eve, general population (general community)</p>

Table 3 (continued)

Themes	Stage of life	Adult-preconception	Pregnancy
Ease of accessibility for targeted audience	Adolescence “And I suppose if you’re going to get everyone, it would have to be done at school age, on all females... before they start to drop out of school.” Rosalind, healthcare provider (pediatrician)	“...cause that group that you’re trying to get which are probably, I’m going to guess 18 to 25, don’t regularly attend [a general practice clinic], a sort of a dip in the attendance... but I don’t think they see any other health professional either...” Alison, healthcare provider (general practitioner)	Pregnancy “...the couples often hear of these conditions when they’re pregnant rather than before they’re pregnant. You know, it makes it harder for us to organize the test if they wanted the test... I mean it’s very difficult to unravel the whole scenario in one go like that.” Thomas, healthcare provider (obstetrician/gynecologist)

However, healthcare providers who currently offer screening for genetic conditions (such as screening for Down syndrome) were concerned about the test being perceived as “routine” and commented that women are not currently making informed decisions about screening for other conditions, such as Down syndrome. Consequently, they questioned the feasibility of an “informed” decision in the context of population-based genetic screening:

...[informed decision-making is] a great theory, and in practice it doesn’t happen, and Down syndrome is a classic example of that... I get women all the time who say, ‘my GP (general practitioner) told me to have this test’... they often have no concept of what the test actually is... haven’t thought through any of those issues... people will end up making uninformed choices...

Matthew, healthcare provider (obstetrician/gynecologist)

Although it was recognized that informed choices and decisions may be more challenging to achieve in population-based screening, it was emphasized that the target population should be able to access information to assist them in their decision-making:

The important thing is that people have what they want in order to make that decision. And so the information is accessible and available to them.

Annabelle, healthcare provider (genetic counselor)

Participants discussed the importance of having information delivered in various formats (i.e., in a brochure, website, and through discussions with a health professional) which would allow people to engage to varying degrees of complexity with the subject matter as needed. Furthermore, participants from the general population believed people should have access to a health professional who could facilitate the decision-making process:

...it’d be good to speak to someone that could tell you, ‘look this is a bit about it, these are the potential issues. Are you prepared to have the test? Because if you do carry this particular gene, you need to think about these other issues. Are you ready to perhaps know about that? Do you want time to think about it, or perhaps go away and discuss it with your partner, or to think about how you’ll cope with the results if they come back adverse to what you were hoping?

Natasha, general population (offered screening)

Ensuring accessibility

Accessibility appeared to underlie much of the discussion about how a population-based carrier screening program for FXS could be offered with a common perception that screening should be easy to access and provided in an equitable way. Thus, two strategies were raised by participants. The first involved offering FXS carrier screening at the same time as another relevant health intervention currently available such as contraception, vaccinations, and Pap smear tests. It was suggested that women might be receptive to learning about FXS carrier screening if it were offered alongside these health measures:

...[they're] thinking about 'my health'... And so I think you piggy-back it at a time when they're already a captive audience about good health, I think that's perfect. Whitney, healthcare provider (psychologist)

The second strategy involved introducing the FXS carrier screening test into prepregnancy counseling:

...you do the bloods and say, '...we might need to boost your rubella or boost your chickenpox or something like that. There is this other test available... if you're interested you need to get it done before you get pregnant'... I guess you could add [carrier screening for FXS] in there. Ainsley, healthcare provider (general practitioner)

Although some participants questioned how frequently women seek pregnancy-related medical advice before they become pregnant, this was perceived to be an appropriate time to introduce the notion of FXS carrier screening.

Primary healthcare was commonly suggested as a setting in which carrier screening could be offered so that it would be accessible to a large proportion of the population. Offering screening through general practitioners (GPs) (family physicians) was most frequently discussed:

...look, the first port of call for every woman is her doctor... So I think it's got to start at the GPs, you know because this is where women are going. Alex, general population (offered screening)

In addition to general practice, family planning and women's health clinics were also mentioned, as it was suggested that women planning to have children may attend these clinics for prepregnancy information and advice. There were also suggestions about which healthcare providers might offer the test, such as GPs, obstetricians/gynecologists, midwives, genetic counselors, and nurses trained to provide pretest counseling.

There was general agreement that general practice clinics were a good location from where to offer screening, but there was limited support for GPs to actually offer the screening. Rather the discussion was more focused on who could work with GPs to provide the screening service:

...it's a general practice thing, but I really don't see general practitioners doing it. Cameron, health professional (obstetrician/gynecologist)

Participants suggested that the knowledge, time availability, and approach of the health professional offering screening may have the potential to limit accessibility of screening (see Table 4). Although not commonly raised, in some cases, this led to a suggestion that genetic counselors could play a role in the offer of such screening:

I think it should be introduced as an idea by a physician but it should be counseled by a genetic counselor... before they consider having the test... Sandra, health professional (obstetrician/gynecologist)

Managing results

Participants expressed the view that test-positive results should be given by a healthcare provider with the opportunity for a genetic counseling consultation at a clinical genetics service provided as part of the screening program as soon as practicable. As it was perceived that receiving a test-positive result may be surprising and confusing, prompt access to detailed information and support was considered essential:

...you need an explanation of what the result means... I couldn't imagine the doctor would be equipped... I imagine that in this case you'd be referred to someone for counseling or further advice. Jonathan, general population (general community)

Relatives of people with FXS contributed substantially to the discussion about managing test-positive results, often reflecting on their own experiences, and stressing the need for support and counseling. Parents of individuals with FXS frequently recalled wanting to know what FXS would "mean" for them and their family. Similarly, it was common for members of the general population who had been offered carrier screening to comment that, having never met a person with FXS before, if they were to receive a test-positive result they would want to know more about what it would be like to have a child with FXS. They suggested a genetic counselor might play an important role in supporting this process:

Table 4 Perceptions of barriers to accessibility relating to the health professional who is offering FXS carrier screening

Barrier	Participant quotes
Limited knowledge	<p>“...I think it’s unrealistic to expect all GPs to offer it ‘cause it’s just too hard to keep in touch with everything that’s going on.” Olivia, health professional (general practitioner)</p> <p>“...we are still getting people who are coming with incorrect information [about maternal serum screening] and we’re still getting midwives, obstetricians and GPs having trouble explaining maternal serum screening results. And fragile X is so much more complicated than maternal serum screening... it’s going to be challenging for them to get fragile X right.” Ainsley, health professional (genetic counselor)</p>
Limited time available to provide pretest counseling	<p>“...I’d be prepared to [offer FXS carrier screening] but I guess... opening up a can of worms like this, just from experience... women will have all these questions and that doesn’t leave room for all the other things.” Lauren, health professional (midwife)</p> <p>“...it’s all too hard and too complicated! ... the list you have to discuss gets longer and longer and longer.” Ethan, health professional, (general practitioner)</p>
A selective approach to offering screening	<p>“...and then you’re going to run into various access barriers because only people who have an interest in it will bring it up and then the other people go to the other doctor that doesn’t have an interest, don’t get offered the same thing.” Sandra, health professional (obstetrician/gynecologist)</p> <p>Facilitator: “I would like to get an idea around the room, who would be prepared to discuss this [carrier screening for FXS with their patients]?”</p> <p>Drew: “Yes, it depends”</p> <p>Hannah: “Same. For some people, but not generally.”</p> <p>Aaron: “Yeah, I think I’d be selective. The women who I thought would want to know.”</p> <p>Health professionals (general practitioners)</p>

...a genetic counselor would be a complete must... someone who you know can help them plan for having children... and can point them in the right directions and give them a guiding hand on how to deal with it and where to go for, you know, particular services or help they might need.

James, general population (general community)

Participants commented that discussing future options should be done in a balanced way providing reassurance and emphasizing the range of reproductive options available. The need to refer for management of FXPOI and FXTAS was also raised. Genetic health professionals discussed the need to assist with communication of this new genetic information to other relatives as well as having strategies in place to manage changes in knowledge about *FMRI*-associated disorders.

Discussion

Population carrier screening for FXS presents challenges due to the complexity of information to be conveyed, the fact that carrier status conveys both personal health and reproductive risks, and the lack of awareness of FXS in the general

community and among health professionals. We have previously reported that stakeholders support population-based carrier screening for FXS, provided it is optional and offered in a way that promotes choice (Archibald et al. 2013). The results of this component of this large qualitative study demonstrate a strong preference for preconception genetic carrier screening. Due to an emphasis on the importance of accessibility, primary healthcare was the preferred setting for which screening would be offered. However, the results highlight some possible barriers to general practitioners offering screening and suggest that further work is needed to develop models for screening program service delivery.

When developing any genetic screening program, there are clear guidelines to assist in the assessment of the acceptability and feasibility of a screening program (Teutsch et al. 2009). Many of the criteria outlined in screening guidelines were raised by health professionals in this study, particularly those with a medical background, perhaps reflecting content included in medical training. Cost and resources were of particular concern to medically trained health professionals (pediatricians, clinical geneticists, general practitioners, and obstetricians/gynecologists). With recent rapid advances in genetic testing technology and increasing availability of carrier screening panels, it is essential that funding is directed towards

screening program development and service provision so that a comprehensive approach can be taken and health professionals offering screening feel well equipped to do so. Although funding for genetic carrier screening varies internationally, for tests in which the consumer bears the cost of the screening, genetic counseling resources should be factored into the screening fee so that genetic counseling support is accessible to those considering and undergoing screening as well as those who receive carrier results.

While much research has shown that FXS carrier screening is feasible (Hill et al. 2010), limited awareness of FXS and of the availability and implications of genetic screening was identified as a major issue which may impact the utilization of a screening program. This concern is not unique to FXS and is a potential barrier to the delivery of genetic carrier screening services. Clearly, effort needs to be directed to raising community awareness about genetic screening which will assist in increasing familiarity and improving knowledge prior to the offer of screening. This could begin in high schools through facilitated discussions about genetic carrier screening and the associated risks and benefits, creating a basic framework for contemplating screening (Frumkin and Zlotogora 2008; Poppelaars et al. 2003).

A widely accessible screening program was strongly valued, with primary healthcare the preferred setting. Providing the opportunity for choice underpinned much of the discussion, and therefore, offering FXS carrier screening to adult women before they have children was perceived to be the optimal time to ensure women who receive carrier results have access to the widest range of reproductive options, particularly given the risk of FXPOI for *FMR1* PM carriers. However, it must be acknowledged that women early in pregnancy should also be provided the opportunity to consider screening. These findings are supported by other fragile X screening research and indicate that models for service delivery should focus on preconception carrier screening in primary care (Acharya and Ross 2009; Skinner et al. 2003). This approach is also emphasized in CF carrier screening research (Henneman et al. 2001, 2002, 2003; Honnor et al. 2000; Tambor et al. 1994).

Incorporating carrier screening into preconception consultations or raising it during general practice consultations with women of childbearing age, for example, in association with their regular Pap smear, has a number of benefits in that screening would be offered at arguably the most appropriate stage of life (ideally before having their first child), and it would be offered in a very relevant healthcare setting (Metcalf 2012; Temel et al. 2015). However, it should be noted that while the timing and setting of preconception consultations may be ideal for offering carrier screening, it is important that carrier screening is perceived as separate to other health interventions currently offered (such as contraception and Pap smears) so that the introduction of carrier screening does not impact on the uptake of those other interventions.

Research indicates that approaches in which the healthcare provider actively offers the test have the potential to be more effective than group educational sessions or passive approaches (Clayton et al. 1996; Henneman et al. 2003; Poppelaars et al. 2003; Tambor et al. 1994). However, concerns regarding the need for GP training and education, limited time and resources, and a potential selective approach to who is offered screening are significant. Furthermore, it was evident in this study that providing the opportunity to make an “informed decision” was also seen as an important component of a screening program. While it might be evident that GPs could raise the option of screening and direct patients to information sources about screening, participants’ perspectives illustrate hesitancy around GPs actually providing pretest information/counseling and offering the test to patients, both because of time constraints due to their workload as well as their lack of specific knowledge about genetic testing and the conditions being screened. While GPs are considered “the first port of call” with regard to healthcare making this an appropriate setting within which to raise FXS carrier screening, strong links to genetic services would be an essential component of any genetic screening program and genetic counselors could play an important role in the delivery of the screening program. This could be through roles including coordination of the program, providing education and training to staff at primary care clinics (including practice nurses), and the option of more in-depth discussion with patients who require additional support in making a decision about screening or with regard to carrier results. Alternatively, in healthcare systems in which not everyone has a defined GP, other primary care options may include preconception clinics and/or well-organized maternity health clinics, provided adequate training of healthcare staff occurs to ensure that appropriate counseling is available.

Regardless of the pretest counseling, information, and consent, it was clear that genetic counseling follow-up for carriers is viewed as an essential component of a FXS carrier screening program. Participants were unanimous in their views that individuals with test-positive results arising from FXS carrier screening should be provided with genetic counseling which is consistent with current recommendations (Finucane et al. 2012; McConkie-Rosell et al. 2007). Research indicates that individuals identified as carriers through population screening may differ in their genetic counseling needs compared with individuals who have a personal or family history of FXS, as they may be relatively unprepared for a carrier result (Anido et al. 2005, 2007) and may have very limited knowledge and prior experience of FXS (Archibald et al. 2009). Thus, clear pathways for referral for carriers should be an integral component of any FXS screening program and genetics services should have protocols for coordinating the management of individuals identified through population screening programs and their families (Sherman et al. 2005).

In contemplating how to progress with regard to carrier screening program delivery, it is increasingly likely that carrier screening for genetic conditions will be offered through panels of tests for multiple conditions rather than as programs offering screening for a single disorder. This would be more cost-effective, but it will be essential that focus is directed to developing approaches for service delivery. In doing so, there is clearly a tension between making carrier screening as widely accessible as possible and ensuring informed decision-making is occurring.

Participants in our study discussed the importance of individuals making an informed decision about whether to undergo carrier screening for FXS; however, health professionals were more inclined to view this as difficult to achieve in any clinical setting due to constraints on time and resources faced by many health staff. As indicated by health professionals with a role in offering prenatal screening, there is substantial variability in the extent to which informed decisions are made regarding genetic/pregnancy screening presently available. The findings of a study by van Schendel et al. (2014) who investigated views of pregnant women and male partners towards non-invasive prenatal testing (NIPT) suggest there may be fewer barriers to uptake of this testing compared to invasive procedures such as amniocentesis or more indirect screening tests such as combined first trimester screening, as NIPT has less associated risks to the pregnancy than the former and provides a more accurate risk assessment for the pregnancy than the latter. The authors suggest that informed decision-making should remain paramount in screening programs that offer tests which are accurate, safe, able to be conducted early in pregnancy (where relevant), and can test for multiple disorders as people may feel there are few, if any, disadvantages to the testing (van Schendel et al. 2014). This begs the questions—how can screening be offered to ensure those offered the test do not view the tests as simply “routine,” and how can an informed decision become an achievable objective of a screening program rather than a theoretical ideal? These questions are relevant to all screening programs, whether the purpose is to offer genetic carrier testing, screening/testing of a pregnancy, or both, and has recently been discussed in the context of prenatal screening by de Jong and de Wert (2015), who suggest that to inform this debate, more research is needed into what screening tests pregnant women want to be offered (de Jong and de Wert 2015).

It is generally agreed that people offered carrier screening will vary as to the amount of information and pretest counseling they require to make a decision that they are comfortable with (Ames et al. 2015). Recently, the American College of Medical Genetics (ACMG) acknowledged a more generic consent process may be needed in the context of expanded carrier screening (Grody et al. 2013). To allay concerns that this may not provide sufficient information for all individuals, multiple methods of information delivery (i.e., information

brochures, decision aids, smart phone applications, websites, and the opportunity to speak to a genetic counselor by telephone) could be used so that additional information and support is available to those who require it (Birch 2015; McWalter et al. 2015). Research has shown that as more conditions are added to screening programs, condition-specific knowledge decreases (Ioannou et al. 2014). Therefore, information delivery may need to focus on the common aspects of the genetic conditions (Edwards et al. 2015) and screening tests, and ensure that people comprehend the general implications of a carrier result rather than retaining detailed and condition-specific information about genetics and inheritance. However, it is important to note that FXS adds a layer of complexity due to the health implications for carriers (Archibald et al. 2013). Further research will be essential in clarifying the level of information needed to make an adequate decision with regard to a genetic carrier screening panel and to determine how information about the implications of FXS carrier status is incorporated into this.

As discussed in Archibald et al. (2013), as this was a qualitative study, the findings are not generalizable as the purpose was not to quantify stakeholders’ perspectives but rather to explore the range of views regarding how a FXS carrier screening program might be developed and delivered; nevertheless, this is a relatively large sample from a wide range of stakeholders. We have previously detailed the limitations of the study in terms of the possible selection bias of participants (Archibald et al. 2013). We also note that the findings reflect an Australian healthcare system, which consists of both public and private sectors, and may not be applicable to systems in other countries that are purely public or private, although it is likely that some of the findings would have overlapping relevance. Furthermore, the focus of this study was on exploring

Table 5 Suggestions for FXS carrier screening program development and implementation based on findings of this study

- Increasing awareness and familiarity with genetic carrier screening through incorporation of discussion of genetic testing and screening into secondary school education
- Incorporation of option of FXS carrier screening into preconception or general GP/family physician consultations and raising awareness of the benefits of GP preconception consultations
- Development of a variety of information resources to which the healthcare provider raising the option of screening can direct the patient rather than providing an in-depth discussion at the time
- Implementation of a screening program that includes standard protocols for sample collection and reporting of results, coordinated by a genetic counselor working in conjunction with primary care setting staff, including nurses and GPs
- Provision of genetic counseling for all individuals identified as carriers
- Further research into how FXS carrier screening can be best incorporated into expanded carrier screening panels and the amount and type of information/discussion people want in order to make a decision about carrier screening

views on carrier screening for FXS and, at the time of the research, expanded carrier screening programs were not available. This possible scenario, although raised by some participants, was not specifically presented to participants for discussion. Further research will be essential in exploring the feasibility and acceptability of various models of delivering population-based genetic carrier screening for FXS, either as a stand-alone test or offered as part of a panel of genetic conditions.

In summary, the message communicated by participants in this study is that women without a family history of FXS should be offered the option of FXS carrier screening (Archibald et al. 2013), provided that it is offered in an accessible way, ideally in primary healthcare settings, that choice is promoted by assisting decision-making about whether to undergo screening at an appropriate stage of their life, and that genetic counseling is provided for those who receive carrier results (see Table 5). As carrier screening for many genetic conditions is available in a single test (Bell et al. 2011) and is now accessible direct-to-consumer, it is imperative that consideration is directed to how population-based carrier screening is best delivered (Edwards et al. 2015). As genetics is becoming a more integral component of personal health care, there is clearly a need for an integrated approach to the provision of genetic services that includes carrier screening for the general population. Evidence from research conducted to date provides a strong basis to argue that it is time to trial local screening program(s) incorporating the points outlined in Table 5. Findings from such trial(s) will inform decision-making about how best to implement statewide or national genetic carrier screening programs.

Acknowledgments This work was supported by the Fragile X Alliance Inc., Murdoch Childrens Research Institute, The University of Melbourne, and the Victorian Government's Operational Infrastructure Support Program. Dr. Alison Archibald was supported by an Australian Postgraduate Award scholarship. We would like to thank Yasmin Bylstra for her assistance with data collection in the early stages of this project and Dr. Jean Paul for the assistance with preparing this manuscript for submission. The authors would also like to express their appreciation to the participants for taking the time to share their views and perspectives with us. We thank Victorian Clinical Genetics Services and the Fragile X Alliance Inc. for assisting us to recruit relatives of people with FXS through their services.

Compliance with ethical standards Alison D. Archibald, Chriselle L. Hickerton, Samantha A. Wake, Alice M. Jaques, Jonathan Cohen, and Sylvia A. Metcalfe declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

References

- Acharya K, Ross LF (2009) Fragile X screening: attitudes of genetic health professionals. *Am J Med Genet A* 149A(4):626–632. doi:10.1002/ajmg.a.32725
- American College of Obstetricians and Gynecologists Committee on Genetics (2010) ACOG Committee Opinion No. 469: carrier screening for fragile X syndrome. *Obstet Gynecol* 116(4):1008–1010. doi:10.1097/AOG.0b013e3181fae884
- Ames AG, Jaques A, Ukoumunne OC, Archibald AD, Duncan RE, Emery J, Metcalfe SA (2015) Development of a fragile X syndrome (FXS) knowledge scale: towards a modified multidimensional measure of informed choice for FXS population carrier screening. *Health Expect* 18(1):69–80. doi:10.1111/hex.12009
- Anido A, Carlson LM, Sherman SL (2007) Attitudes toward fragile X mutation carrier testing from women identified in a general population survey. *J Genet Couns* 16(1):97–104. doi:10.1007/s10897-006-9049-0
- Anido A, Carlson LM, Taft L, Sherman SL (2005) Women's attitudes toward testing for fragile X carrier status: a qualitative analysis. *J Genet Couns* 14(4):295–306. doi:10.1007/s10897-005-1159-6
- Archibald AD, Hickerton CL, Jaques AM, Wake S, Cohen J, Metcalfe SA (2013) "It's about having the choice": stakeholder perceptions of population-based genetic carrier screening for fragile X syndrome. *Am J Med Genet A* 161A(1):48–58. doi:10.1002/ajmg.a.35674
- Archibald AD, Jaques AM, Wake S, Collins VR, Cohen J, Metcalfe SA (2009) "It's something I need to consider": decisions about carrier screening for fragile X syndrome in a population of non-pregnant women. *Am J Med Genet A* 149A(12):2731–2738. doi:10.1002/ajmg.a.33122
- Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, Langley RJ, Zhang L, Lee CC, Schilkey FD, Sheth V, Woodward JE, Peckham HE, Schroth GP, Kim RW, Kingsmore SF (2011) Carrier testing for severe childhood recessive diseases by next-generation sequencing. *Sci Transl Med* 3(65):65ra64. doi:10.1126/scitranslmed.3001756
- Birch PH (2015) Interactive e-counselling for genetics pre-test decisions: where are we now? *Clin Genet* 87(3):209–217. doi:10.1111/cge.12430
- Charmaz K (2006) Constructing grounded theory: a practical guide through qualitative analysis. Sage, Los Angeles
- Clayton EW, Hannig VL, Pfotenhauer JP, Parker RA, Campbell PW 3rd, Phillips JA 3rd (1996) Lack of interest by nonpregnant couples in population-based cystic fibrosis carrier screening. *Am J Hum Genet* 58(3):617–627
- de Jong A, de Wert GM (2015) Prenatal screening: an ethical agenda for the near future. *Bioethics* 29(1):46–55. doi:10.1111/bioe.12122
- Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, Schneider A, Stoll K, Wapner R, Watson MS (2015) Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstet Gynecol* 125(3):653–662. doi:10.1097/aog.0000000000000666
- Fanos JH, Spangner KA, Musci TJ (2006) Attitudes toward prenatal screening and testing for Fragile X. *Genet Med* 8(2):129–133. doi:10.1097/01.gim.0000200158.66554.7f
- Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A (2012) Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the National Society of Genetic Counselors. *J Genet Couns* 21(6):752–760. doi:10.1007/s10897-012-9524-8
- Frumkin A, Zlotogora J (2008) Genetic screening for reproductive purposes at school: is it a good strategy? *Am J Med Genet A* 146A(2):264–269. doi:10.1002/ajmg.a.32069

- Grody WW, Thompson BH, Gregg AR, Bean LH, Monaghan KG, Lebo RV (2013) ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med* 15(6):482–3. doi:[10.1038/gim.2013.47](https://doi.org/10.1038/gim.2013.47)
- Hagerman PJ (2008) The fragile X prevalence paradox. *J Med Genet* 45(8):498–499. doi:[10.1136/jmg.2008.059055](https://doi.org/10.1136/jmg.2008.059055)
- Hagerman RJ, Hagerman PJ (2002) Fragile X syndrome: diagnosis, treatment and research, 3rd edn. The Johns Hopkins University Press, Baltimore
- Hagerman RJ, Leehey M, Heinrichs W, Tassone F, Wilson R, Hills J, Grigsby J, Gage B, Hagerman PJ (2001) Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. *Neurology* 57(1):127–130. doi:[10.1212/WNL.57.1.127](https://doi.org/10.1212/WNL.57.1.127)
- Hantash FM, Goos DM, Crossley B, Anderson B, Zhang K, Sun W, Strom CM (2011) FMR1 premutation carrier frequency in patients undergoing routine population-based carrier screening: insights into the prevalence of fragile X syndrome, fragile X-associated tremor/ataxia syndrome, and fragile X-associated primary ovarian insufficiency in the United States. *Genet Med* 13(1):39–45. doi:[10.1097/GIM.0b013e3181fa9fad](https://doi.org/10.1097/GIM.0b013e3181fa9fad)
- Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, Hall A, Howard HC, Janssens S, Kayserli H, Lakeman P, Lucassen A, Metcalfe SA, Vidmar L, de Wert G, Dondorp WJ, Peterlin, B on behalf of the European Society of Human Genetics (ESHG) (2016) Responsible implementation of expanded carrier screening. Summary and recommendations of the European Society of Human Genetics. *Eur J Hum Genet*, In press.
- Henneman L, Bramsen I, van der Ploeg HM, Ader HJ, van der Horst HE, Gille JJ, ten Kate LP (2001) Participation in preconceptional carrier couple screening: characteristics, attitudes, and knowledge of both partners. *J Med Genet* 38(10):695–703. doi:[10.1136/jmg.38.10.695](https://doi.org/10.1136/jmg.38.10.695)
- Henneman L, Bramsen I, van der Ploeg HM, ten Kate LP (2002) Preconception cystic fibrosis carrier couple screening: impact, understanding, and satisfaction. *Genet Test* 6(3):195–202. doi:[10.1089/109065702761403351](https://doi.org/10.1089/109065702761403351)
- Henneman L, Bramsen I, van Kempen L, van Acker MB, Pals G, van der Horst HE, Ader HJ, van der Ploeg HM, ten Kate LP (2003) Offering preconceptional cystic fibrosis carrier couple screening in the absence of established preconceptional care services. *Community Genet* 6(1):5–13. doi:[10.1159/000069540](https://doi.org/10.1159/000069540)
- Hill MK, Archibald AD, Cohen J, Metcalfe SA (2010) A systematic review of population screening for fragile X syndrome. *Genet Med* 12(7):396–410. doi:[10.1097/GIM.0b013e3181e38fb6](https://doi.org/10.1097/GIM.0b013e3181e38fb6)
- Honnor M, Zubrick SR, Walpole I, Bower C, Goldblatt J (2000) Population screening for cystic fibrosis in Western Australia: community response. *Am J Med Genet* 93(3):198–204. doi:[10.1002/1096-8628\(20000731\)93:3<198::AID-AJMG7>3.0.CO;2-Q](https://doi.org/10.1002/1096-8628(20000731)93:3<198::AID-AJMG7>3.0.CO;2-Q)
- Ioannou L, McClaren BJ, Massie J, Lewis S, Metcalfe SA, Forrest L, Delatycki MB (2014) Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. *Genet Med* 16(3):207–216. doi:[10.1038/gim.2013.125](https://doi.org/10.1038/gim.2013.125)
- McConkie-Rosell A, Abrams L, Finucane B, Cronister A, Gane LW, Coffey SM, Sherman S, Nelson LM, Berry-Kravis E, Hessl D, Chiu S, Street N, Vatave A, Hagerman RJ (2007) Recommendations from multi-disciplinary focus groups on cascade testing and genetic counseling for fragile X-associated disorders. *J Genet Couns* 16(5):593–606. doi:[10.1007/s10897-007-9099-y](https://doi.org/10.1007/s10897-007-9099-y)
- McWalter KM, Sdano MR, Dave G, Powell KP, Callanan N (2015) Public health genetic counselors: activities, skills, and sources of learning. *J Genet Couns* 24(3):438–451. doi:[10.1007/s10897-014-9795-3](https://doi.org/10.1007/s10897-014-9795-3)
- Metcalfe SA (2012) Carrier screening in preconception consultation in primary care. *J Commun Genet* 3(3):193–203. doi:[10.1007/s12687-011-0071-z](https://doi.org/10.1007/s12687-011-0071-z)
- Metcalfe SA, Archibald AD (2012) Fragile X population carrier screening. *Genet Med* 14(3):350. doi:[10.1038/gim.2011.79](https://doi.org/10.1038/gim.2011.79), author reply 351
- Metcalfe S, Jaques A, Archibald A, Burgess T, Collins V, Henry A, McNamee K, Sheffield L, Slater H, Wake S, Cohen J (2008) A model for offering carrier screening for fragile X syndrome to non-pregnant women: results from a pilot study. *Genet Med* 10(7):525–535. doi:[10.1097/GIM.0b013e31817c036e](https://doi.org/10.1097/GIM.0b013e31817c036e)
- Poppelaars FA, Henneman L, Ader HJ, Cornel MC, Hermens RP, van der Wal G, ten Kate LP (2003) How should preconceptional cystic fibrosis carrier screening be provided? Opinions of potential providers and the target population. *Commun Genet* 6(3):157–165. doi:[10.1159/000078163](https://doi.org/10.1159/000078163)
- Ryynanen M, Heinonen S, Makkonen M, Kajanoja E, Mannermaa A, Pertti K (1999) Feasibility and acceptance of screening for fragile X mutations in low-risk pregnancies. *Eur J Hum Genet* 7(2):212–216. doi:[10.1038/sj.ejhg.5200285](https://doi.org/10.1038/sj.ejhg.5200285)
- Sherman S, Pletcher BA, Driscoll DA (2005) Fragile X syndrome: diagnostic and carrier testing. *Genet Med* 7(8):584–587. doi:[10.1097/01.GIM.0000182468.22666.dd](https://doi.org/10.1097/01.GIM.0000182468.22666.dd)
- Skinner D, Sparkman KL, Bailey DB Jr (2003) Screening for Fragile X Syndrome: parent attitudes and perspectives. *Genet Med* 5(5):378–384. doi:[10.1097/01.GIM.0000086480.69309.1E](https://doi.org/10.1097/01.GIM.0000086480.69309.1E)
- Tambor ES, Bernhardt BA, Chase GA, Faden RR, Geller G, Hofman KJ, Holtzman NA (1994) Offering cystic fibrosis carrier screening to an HMO population: factors associated with utilization. *Am J Hum Genet* 55(4):626–637
- Tassone F, Iong KP, Tong T-H, Lo J, Gane LW, Berry-Kravis E, Nguyen D, Mu LY, Laffin J, Bailey D, Hagerman RJ (2012) FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. *Genome Med* 4(12):100–100. doi:[10.1186/gm401](https://doi.org/10.1186/gm401)
- Tassone F, Pan R, Amiri K, Taylor AK, Hagerman PJ (2008) A rapid polymerase chain reaction-based screening method for identification of all expanded alleles of the fragile X (FMR1) gene in newborn and high-risk populations. *J Mol Diagn* 10(1):43–49. doi:[10.2353/jmol dx.2008.070073](https://doi.org/10.2353/jmol dx.2008.070073)
- Temel S, van Voorst SF, de Jong-Potter LC, Waelpuut AJM, Cornel MC, de Weerd SR, Denktas S, Steegers EAP (2015) The Dutch national summit on preconception care: a summary of definitions, evidence and recommendations. *J Commun Genet* 6(1):107–115. doi:[10.1007/s12687-014-0204-2](https://doi.org/10.1007/s12687-014-0204-2)
- Teutsch SM, Bradley LA, Palomaki GE, Haddow JE, Piper M, Calonge N, Dotson WD, Douglas MP, Berg AO on behalf of the EGAPP Working Group (2009) The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med* 11(1):3–14. doi:[10.1097/GIM.0b013e318184137c](https://doi.org/10.1097/GIM.0b013e318184137c)
- van Schendel RV, Kleinveld JH, Dondorp WJ, Pajkrt E, Timmermans DRM, Holtkamp KCA, Karsten M, Vliestra AL, Lachmeijer AMA, Henneman L (2014) Attitudes of pregnant women and male partners towards non-invasive prenatal testing and widening the scope of prenatal screening. *Eur J Hum Genet* 22:1345–1350. doi:[10.1038/ejhg.2014.32](https://doi.org/10.1038/ejhg.2014.32)
- Wittenberger MD, Hagerman RJ, Sherman SL, McConkie-Rosell A, Welt CK, Rebar RW, Corrigan EC, Simpson JL, Nelson LM (2007) The FMR1 premutation and reproduction. *Fertil Steril* 87(3):456–465. doi:[10.1016/j.fertnstert.2006.09.004](https://doi.org/10.1016/j.fertnstert.2006.09.004)