Carrier screening in preconception consultation in primary care

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Abstract Discussing carrier screening during preconception consultation in primary care has a number of advantages in terms of promoting autonomy and enabling the greatest range of reproductive choices. For those with a family history of an inherited condition, this ought to be a routine discussion; however, this can be expanded to include the wider population, especially for those conditions for which carrier frequencies are considered relatively common. There is published literature from around the world regarding experiences with carrier screening in primary care for cystic fibrosis, haemoglobinopathies, fragile X syndrome, Tay–Sachs disease and spinal muscular atrophy, although many of these have tended to focus on consultations during rather than before pregnancy. Overall, these studies reveal that population carrier screening is well received by the participants with apparent minimal psychosocial harms; however, challenges exist in terms of approaches to ensure couples receive adequate information to make personally relevant decisions and for ongoing health professional engagement.

Keywords Carrier screening · Preconception · Pregnancy · Cystic fibrosis · Haemoglobinopathies · Fragile X syndrome · Tay–Sachs disease · Spinal muscular atrophy

Introduction

Carrier screening for genetic conditions causing serious disease has been explored for many years, commencing with Tay–Sachs disease in 1969 in neighbourhood health centres (Kaback 2001) and later in high schools (Mitchell et al. 1996); many other formal programs of population carrier screening have since followed in a variety of countries.

The focus of this article is to provide an overview of the worldwide experience of carrier screening for reproductive risk within preconception consultations in primary care, principally with general practitioners/family physicians and, in some countries, with midwives. It is, therefore, confined to autosomal recessive and X-linked recessive conditions. Furthermore, since carrier screening often occurs in practice during pregnancy, this article will also include such studies in which obstetricians are considered primary care providers depending on the model of care in the specific country.

When carrier couples at risk of having an affected child are identified during pregnancy, the couple may choose to accept the risk of having an affected child and not undertake any other procedures or opt for prenatal diagnosis to test for the same mutation(s) that they carry. For an unaffected pregnancy, this can be reassuring information (although there may still be a residual risk). Conversely, if the pregnancy is affected, the couple may use this information to prepare themselves clinically and emotionally for the birth or may choose to terminate the pregnancy. While carrier testing during pregnancy is probably the most pragmatic time as many women will visit their general practitioner (GP) or obstetrician at a reasonably early stage in pregnancy, identifying such couples *before* they are pregnant allows greater time for decision-making. Hence, this timing is most compatible

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with notions of individual autonomy, and clearly broadens couples' reproductive choices. These include refraining from having children, adoption, utilising pre-implantation genetic diagnosis (PGD), donor gametes or donor embryo. Nevertheless, such procedures involving IVF are not straightforward, with no guarantee of success, are usually expensive and require extensive counselling. Carrier screening in a preconception consultation can focus on offering a couple choices for a future pregnancy, and ideally, would be discussed routinely when there is a family history of a genetic condition (see Bennett, in this issue). However, for many autosomal recessive conditions and some X-linked conditions, there may be no obvious family history unless couples are from populations in which the practice of consanguinity is more typical (see Hamamy, in this issue).

In the absence of a family history, the discussion around screening for carriers may occur less commonly and is often ad hoc. Studies exploring carrier screening in primary care have often examined uptake of testing as the main outcome while others have assessed psychosocial parameters including knowledge and attitudes of the couples themselves as well as health practitioners. These studies have centred around genetic conditions found at higher frequencies in particular populations and, therefore, deemed to be appropriate for carrier screening (Godard et al. 2003; Delatycki 2008), namely: cystic fibrosis in those of Northern European descent; haemoglobinopathies in a wide range of populations including Southern European, Middle Eastern, African, Indian, Asian and South East Asian descent; Tay–Sachs disease and others in those with Ashkenazi Jewish descent. Carrier screening for fragile X syndrome and, more recently, spinal muscular atrophy have also been performed on unselected populations.

Carrier screening for cystic fibrosis

Cystic fibrosis (CF) has a birth prevalence of approximately 1 in 3,500 in Caucasians (Southern et al. 2007) and is the most common autosomal recessive condition severely affecting children in this population. Carrier frequency for individuals of Northern European ancestry is around 1 in 25–30 (Williamson 1993). CF affects respiratory, gastrointestinal/digestive, reproductive as well as other systems and, although there is yet no cure, a range of treatments, especially those aimed at reducing the malnutrition (Southern et al. 2009), have resulted in increased life expectancies (Dodge et al. 2007; O'Sullivan and Freedman 2009). Identification of the *CFTR* gene associated with CF in 1989 (Kerem et al. 1989; Rommens et al. 1989; Riordan et al. 1989) led to the introduction of newborn screening in a number of countries. It also prompted debate about the value

of offering population carrier screening for this condition (with views that primary care is an appropriate clinical setting (Modell 1993)), vs. cascade screening in families (Wilfond and Fost 1990; Williamson 1993). Despite the identification of carriers of CF through newborn screening and cascade testing of at-risk relatives, a recent study from Australia, an early adopter of newborn screening for CF, showed that only 12% of relatives (other than parents) undertook carrier testing (McClaren et al. 2010). Over the years, several professional organisations have produced recommendations and guidelines for CF carrier screening at the population level, prenatally and preconceptionally as well as in families, (Grody et al. 2001; American College of Obstetricians and Gynecologists 2005; American College of Obstetricians and Gynecologists 2011; Human Genetics Society of Australasia 2010). The guidelines also discuss using panels of relevant (i.e., most frequent) mutations in specific populations, generally containing between 12 and 23 of the 1,700 known mutations in the *CFTR* gene accounting for up to 85% of mutations. Recently, the USA panel of 23 mutations has been shown to be performing as predicted, suggesting there is no added value in increasing the number of mutations in the panel (Strom et al. 2011).

There is substantial literature examining attitudes (with or without offering testing), test uptake and psychosocial outcomes. Although screening has occurred in high school settings and in antenatal hospital settings, only findings from studies in primary care for preconception and prenatal screening will be summarised here.

Attitudes about population CF carrier screening

Overall, individuals with CF, their parents and other relatives are supportive of population CF carrier screening being made available (Watson et al. 1991a; Myers et al. 1994; Henneman et al. 2001a; Poppelaars et al. 2003a; McClaren et al. 2008; Maxwell et al. 2011) as are many members of the general public in studies in which screening was not offered: in the UK (Watson et al. 1991a), Belgium (Decruyenaere et al. 1992; Welkenhuysen et al. 1996), USA (Botkin and Alemagno 1992; Myers et al. 1994), Canada (Melancon and De Braekeleer 1996), the Netherlands (Poppelaars et al. 2003a, 2003b; Poppelaars et al. 2004a) and Australia (McClaren et al. 2008). Nevertheless, barriers to implementing screening were often acknowledged, in particular, around the lack of prior awareness of CF and perceptions of relevance for those without a family history. Indeed, health practitioners, while still supportive, often had more mixed views, and there were concerns around potential for psychosocial harms as well as the feasibility of offering screening, especially in the preconception setting (Watson et al. 1991a; Boulton et al. 1996; Faden et al. 1994; Mennie et al. 1998; Poppelaars et al. 2003a, 2003b;

Poppelaars et al. 2004b; Baars et al. 2004; McClaren et al. 2008).

Preconception carrier screening for CF in primary care

Initial studies were carried out in the early 1990s, mostly offering testing for p.508del (delta F508), the single most common mutation in these populations, typically performed on buccal/mouthwash samples. The active opportunistic offer of CF carrier screening in the UK was associated with greater uptake of testing when sample collection occurred immediately (i.e., without needing to return on another occasion) in general practice clinics (66%) or family planning clinics (87%), compared with only 10% tested in those who were offered a screening appointment by letter (Watson et al. 1991b). Uptake was higher in family planning clinics “because a higher proportion of those attending were young and had not yet had children and, therefore, perceived the test as particularly relevant to them” and the authors also felt that those who attended the clinics to see their doctor because they were unwell were less likely to participate (Watson et al. 1991b). Similar trends of lower uptake following an offer by letter, rather than directly by a clinician/researcher, were also seen in other UK (Bekker et al. 1993; Payne et al. 1997), USA (Tambor et al. 1994; Clayton et al. 1996), and the Netherlands (Henneman et al. 2001b; Henneman et al. 2003; Lakeman et al. 2009) studies. In Australia, the passive (i.e., without pre-test discussion) opportunistic offer of testing at GP and family planning clinics resulted in 43.5% uptake of testing. Patients received a pamphlet describing CF and could discuss with the doctor if they wished, but how many did so was not reported. For such a passive approach, the uptake of testing is relatively high and the authors commented that those attending family planning clinics tended to be younger and/or planning a family, possibly contributing to this rate of uptake (Honnor et al. 2000). In all of these studies, testing was offered free of charge to the research participants, and some also assessed knowledge and anxiety, typically finding that knowledge, while variable, was adequate though often decreased over time (Bekker et al. 1993; Bekker et al. 1994; Bernhardt et al. 1996; Henneman et al. 2002; Honnor et al. 2000; Gordon et al. 2003). Anxiety, while often higher in test-positive couples, also decreased over time (Bekker et al. 1993; Bekker et al. 1994).

Prenatal carrier screening for CF in primary care

As previously suggested, health professionals generally considered that screening during pregnancy was more feasible than screening preconceptionally. Consequently, there have been several studies whereby CF carrier

screening was offered only to pregnant women in primary care. There have been various approaches to testing the partner, either testing both partners simultaneously (the one-step or pair wise process) or testing the woman first followed by the partner if she were found to have a mutation (the two-step or sequential process). Harris et al. in the UK implemented a pilot project in 1991 that offered testing free of charge to women at their first diagnosis of pregnancy in general practice, and GPs themselves conducted the counselling as well as providing a leaflet (Harris et al. 1992; Harris et al. 1996). All but one woman accepted screening (75/76), only one regretted being tested and the acceptability of the pilot led to it being rolled out to further practices (Harris et al. 1993) with a reported overall uptake of 84.9%, although uptake ranged from 11 to 99% in the eight practices (Hartley et al. 1997). After receiving their result, 97% felt they had made the right decision, while generally full disclosure of results to couples was associated with lower anxiety compared with the two-step method, although 29% of non-carriers believed they had no residual risk (Hartley et al. 1997). Another UK study in primary care revealed somewhat lower uptake of 62% (Cuckle et al. 1996).

No other studies have reported offering CF prenatal screening by GPs only; instead some studies have included obstetricians, considered primary care providers in the USA. In one such USA study, free carrier screening was offered to both pregnant and non-pregnant women by family physicians and obstetricians (37 providers at 10 practices), with eight practices relying mostly on a brochure to provide the information. Decision to be tested was required immediately, with an estimated uptake of 57%, although only 6.2% identified their physician's recommendation as the main reason for accepting testing (Loader et al. 1996). Non-pregnant women represented just 10% of those offered testing. Follow-up 1 year later suggested that “most of the adverse outcomes observed in this trial could have been avoided by more effective patient education by the primary care provider” (Levenkron et al. 1997). In Victoria, Australia, CF carrier screening is offered as a fee-for-service (AUD\$200 per person) to women planning pregnancies and those in early pregnancy. Initially (2006) offered through obstetricians in private practice, i.e., requiring referrals in Australia, it was later expanded to GPs in 2007 (Massie et al. 2009). Pre-test information is provided by the physician, together with written information about CF and screening. Although an uptake rate of testing has not been reported, the program has been evaluated with a small sample of carrier and non-carrier participants (Ioannou et al. 2010). The main reasons for choosing screening were the perception of the severity of CF and a doctor's recommendation. Similar to other studies, those found to be carriers remembered their result better

than those with a test-negative result while 22% incorrectly recalled their residual risk, although there was no difference in anxiety levels (Ioannou et al. 2010).

A systematic review by Chen and Goodson has assessed factors influencing decisions on whether or not to be tested in CF carrier screening studies published up to 2006, and the authors comment on the difficulties of drawing inferences due to the very varied nature of reporting of the studies (Chen and Goodson 2007).

Carrier screening for haemoglobinopathies

Disorders of haemoglobin, comprising the alpha and beta thalassaemias, sickle cell disease (SCD) and other variants, are autosomal recessively inherited anaemias present globally with at least 4.5% of the world's population estimated to be carriers (Angastiniotis et al. 1995; Angastiniotis and Modell 1998). Carriers of haemoglobinopathies were originally confined to tropical/sub-tropical regions in which malaria is endemic; however, high carrier frequency is now seen in many countries around the world as a result of migration (Angastiniotis et al. 1995). Although there are more carriers of thalassaemias globally, SCD represents about 70% of haemoglobinopathies worldwide because the carrier frequency is so high in certain regions leading to a high birth rate of affected homozygotes (Angastiniotis et al. 1995). The frequency of healthy carriers of haemoglobinopathies may be as high as 1 in 4 in some populations, increasing to 40% in some Southeast Asian countries (WHO 2006). Without treatment, many children will die from anaemia or infections early in life. Treatment of thalassaemia involves regular blood transfusions together with iron chelation therapy to remove otherwise potentially fatal levels of accumulated iron. In high income countries where this treatment is available and safe, life expectancy has increased dramatically, although is still not without its problems relating to compliance (WHO 2006). The decrease in birth prevalence of haemoglobinopathies is based on identifying individuals at risk through carrier screening programs or family history and providing adequate information on risk and possibilities to reduce that risk. Typically, screening for carriers of beta-thalassaemia commences with findings of reduced red blood cell indices in full blood examinations, prompting analysis of haemoglobin, but haemoglobin analysis is often required as a starting point for alpha-thalassaemia and sickle cell carriers and those who might be double heterozygotes, and many different testing procedures are used (Cao et al. 2002). In some countries, population-based carrier screening programs have long been established resulting in decrease in levels of birth prevalence ranging between 80 and 100% (Angastiniotis and Modell 1998), whereas in other

countries difficulties arise either with accessing immigrant at-risk populations within the country or because resources in developing countries are inadequate for a variety of reasons (Angastiniotis and Modell 1998).

A recent review of international practice of beta-thalassaemia carrier screening described a wide variety of programs in different countries that might be mandatory or voluntary, preconceptional or prenatal, and involve a broad range of education and counselling practices (Cousens et al. 2010). Typically, preconceptional carrier screening is voluntary when it occurs in high schools and more often mandatory when applying for a marriage license (described as pre-marital screening) (Cousens et al. 2010). These seem to be acceptable to the communities in which these approaches exist such as in Bahrain (Al Arrayed and Al Hajeri 2010) or in Malaysia where these might be implemented (Wong et al. 2011a, 2011b). However, in the Netherlands where a screening program is not offered, there appeared to be a reluctance by GPs and midwives to facilitate the testing of at-risk ethnic groups, which could be a barrier to implementation (Weinreich et al. 2009). The majority of worldwide experiences of free voluntary programs for beta-thalassaemia carrier screening in primary care have predominantly been with pregnant women, see Cousens et al. (2010), and sickle cell disease (Heredero-Baute 2004); also see Angastiniotis et al. (1995).

There are very few published studies reporting experiences or opportunities for *voluntary preconceptional* carrier screening as part of consultations in primary care. Early successful haemoglobinopathy (mostly beta-thalassaemia) screening programs commenced in the 1970s in Greece, Sardinia, continental Italy and Cyprus (although here the program has since become quasi-mandatory) (Cao et al. 2002). All programs utilised intensive public awareness and education media campaigns, training for a range of health professionals, and was targeted to adults of child-bearing age: premarital, preconceptional and prenatal. Although, initially, these programs relied heavily on the mass media, in Sardinia 33% of couples were informed through GPs and 23% through obstetricians, which increased over time such that by 2002 more than 70% of the population were given information by physicians (Cao et al. 2002). In Sardinia and Cyprus school-based screening has also been introduced (Cao et al. 2002).

In Israel, carrier screening for beta-thalassaemia is offered free through a public health system along with carrier screening for Tay–Sachs disease and a number of other conditions (which are typically covered through a national health insurance scheme) more prevalent in the various resident ethnic groups (Zlotogora et al. 2009). Screening of non-pregnant women occurs in local family clinics, but the majority of screening typically occurs early in pregnancy in ‘maternal and child health clinics’, and has

resulted in almost two-thirds reduction of babies born with thalassaemia per year since the late 1980s. Parents who had affected children knew their carrier status and elected not to have prenatal diagnosis and/or termination (Zlotogora et al. 2009).

In a report from the UK, Modell et al. described a randomised controlled trial of preconception screening for haemoglobinopathies in primary care, which involved a multidisciplinary team and a nurse to promote the service in the intervention arm general practices (Modell et al. 1998). The setting was in a region of London in which 29% of residents and 43% of births are in high risk ethnic groups. The primary care teams in the intervention practices were trained and provided with educational material and leaflets for discussion with their patients. The number of requests in the study year for intervention practices (adjusted for baseline requests) was 3.2 times higher (95% confidence interval 2.9 to 3.4) than for control practices (Modell et al. 1998). There was considerable variation in the extent to which some GPs in the intervention arm engaged with the process and the authors felt that prenatal screening through maternity services should be available as well (Modell et al. 1998).

Indeed, in the UK, a universal prenatal screening program for haemoglobinopathies has recently been developed, and is offered to all pregnant women including in primary care (NHS, accessed July 2011). Some issues have been raised around the apparent ‘voluntary’ nature of the program, with some carriers surprised and shocked to learn their results (Locock and Kai 2008). These authors have also reported that many would prefer to be tested for haemoglobinopathy carrier status before conception (Locock and Kai 2008). In the USA (Ormond et al. 2007) and Australia (Cousens et al. 2010), prenatal carrier screening for haemoglobinopathies occurs ad hoc, yet there are similar findings regarding the lack of awareness of screening. In practice, screening of the population for haemoglobinopathy carrier status may occur incidentally in primary care as a result of blood being taken for other reasons. In such cases, some women believe they would have preferred to have been told that the blood results may reveal a carrier status, even if they did not necessarily feel they needed to consent to the test (Locock and Kai 2008; Ahmed et al. 2005). In the absence of community education programs that raise the public's awareness, taking the opportunity to discuss the possibility of haemoglobinopathy screening in primary care seems to have merit.

Carrier screening for fragile X syndrome

Fragile X syndrome (FXS), an X-linked genetic condition, is the leading cause of inherited intellectual and develop-

mental disability. FXS is a complex condition: the range of severity is broad and varies from person to person, the inheritance is complicated and carriers have both reproductive and personal health risks. Clinical features include anxiety, attention deficit hyperactivity disorder, aggressive outbursts, autism spectrum features and various physical and medical features (Hagerman and Hagerman 2002). As an X-linked condition, affected females generally have a less severe phenotype than males. The prevalence of the full mutation in the general population has been reported recently as 1:3,335 overall (Hantash et al. 2011). Although FXS is not curable, specific treatment strategies can improve some of the physical and behavioural symptoms.

Unlike the previous conditions, the mutation primarily responsible for FXS is a triplet repeat (CCG) that, when increased in repeat number size and hypermethylated, leads to silencing of the gene. The number of repeats causing FXS is ≥ 200 (full mutation), while the ‘normal’ range is 6–44 repeats, and 55–200 repeats is the premutation range (i.e., carrier of FXS) (Fu et al. 1991; Snow et al. 1993). The length of the CGG repeat is unstable over a certain size such that a premutation can expand to a full mutation when passed onto offspring through female, but not male, carriers (Fu et al. 1991; Berkenstadt et al. 2007; Nolin et al. 1996). Therefore, carrier screening in primary care for reproductive risk in women is more relevant as male carriers are not at risk of having children affected with FXS. A repeat range of 45–54 (the ‘grey zone’ or intermediate allele) can increase to a premutation allele when transmitted through females such that a grandchild could be affected with FXS (Nolin et al. 2003). Notably, premutation carriers themselves have an increased risk of mild learning/emotional difficulties and are at a risk of developing a late-onset neurodegenerative condition (fragile X associated tremor/ataxia syndrome; FXTAS) (Hagerman et al. 2001; Jacquemont et al. 2003). Female carriers also have a 20% risk of developing primary ovarian insufficiency (Hagerman and Hagerman 2002). Therefore, a medical or family history of FXS, developmental delay, tremor or ataxia would also warrant testing in males as well as a history of infertility or primary ovarian insufficiency in females.

Some large-scale screening studies have found that the premutation frequency in females is 1 in 549 in Canada (Lévesque et al. 2009), 1 in 158 in Israel (Berkenstadt et al. 2007) and 1:179 in USA on non-selected individuals (Hantash et al. 2011). Carrier frequency may be different again in other population groups, with no carriers found in 370 women screened in a Japanese study (Otsuka et al. 2010) and 1,002 women from Taiwan (Huang et al. 2003), although these were much smaller sample sizes. The feasibility, cost-effectiveness and cost-benefit of population-based carrier screening for FXS have been widely discussed, with arguments generally in favour (Wildhagen et al. 1998;

Toledano-Alhadeef et al. 2001; Song et al. 2003; Palomaki 1994; Finucane 1996; Meadows and Sherman 1996; Musci 2005). However, guidelines from the American College of Medical Geneticists state that population carrier screening for FXS is not recommended except within well-defined clinical research protocols (Sherman et al. 2005) because of the difficulties around counselling and education regarding the meaning and interpretation of results (McConkie-Rosell et al. 2005). Nevertheless, carrier screening for FXS does occur in clinical practice, predominantly during pregnancy, especially in Israel (Berkenstadt et al. 2007; Geva et al. 2000) and parts of the USA (Cronister et al. 2005).

A systematic review of the literature regarding carrier (as well as newborn) screening for FXS has been published recently (Hill et al. 2010), noting several reports in which carrier screening for FXS has been offered in clinical settings to women from the general population, but with pre-test counselling occurring at genetics referral centres. The majority were with pregnant women (Berkenstadt et al. 2007; Cronister et al. 2005; Fanos et al. 2006; Huang et al. 2003; Pessoa et al. 2000; Spence et al. 1996; Ryyanen et al. 1999; Toledano-Alhadeef et al. 2001; Kallinen et al. 2001), while some included relatively smaller numbers of non-pregnant women (Pessoa et al. 2000; Spence et al. 1996; Toledano-Alhadeef et al. 2001; Berkenstadt et al. 2007; Geva et al. 2000). Most studies essentially focused on the uptake of testing, with rates varying between 7.9% (Cronister et al. 2005) and 21% (Spence et al. 1996) in the USA, 80% in Israel (Pessoa et al. 2000), and 85% (Ryyanen et al. 1999) and 92% respectively in two Finnish studies (Kallinen et al. 2001). Notably, those with higher uptake rates were those in which testing was free, see Hill et al. (2010).

Only one study, developed as a pilot model, has examined offering carrier testing to 338 non-pregnant women in a primary care family planning clinic; however, pre-test counselling together with the use of a purpose-designed brochure was carried out by genetic counselors rather than physicians (Metcalf et al. 2008). Uptake of testing was 20%, possibly reflecting the Human Research Ethics Committee's requirement for women to return to the clinic at a later date to give the blood sample (Metcalf et al. 2008). Although this was a likely barrier to uptake it should not, however, be considered a negative aspect of how testing was offered as follow-up interviews with a sub-group of women revealed that women had more time to weigh their decision and, therefore, this barrier may have, in fact, supported informed decision-making (Archibald et al. 2009).

Awareness of FXS is considered low in the general community (Anido et al. 2005; Anido et al. 2007; Archibald et al. 2009; Fanos et al. 2006; Metcalf et al. 2008). There have been only two reports measuring women's knowledge of FXS who were offered testing. This was measured

1 month after testing in 20 pregnant women (10 with a family history of FXS and 10 without), which showed their understanding was limited (Fanos et al. 2006). In the study by Metcalf et al., women completed a questionnaire measuring knowledge, attitudes and anxiety levels at the time of being offered testing and 1 month after, and included women who declined testing (Metcalf et al. 2008). While prior awareness of FXS was low, women generally answered the knowledge questions well following pre-test counselling and 1 month later. Follow-up interviews with a sub-group of women from this study revealed, however, that women had trouble relating to the clinical information about FXS and wanted to know more about families' experiences of FXS (Archibald et al. 2009). No harms to psychological well-being have been demonstrated to date, although only three studies have specifically investigated the impact of offering screening on psychological factors such as anxiety (Ryyanen et al. 1999; Fanos et al. 2006; Metcalf et al. 2008).

Overall, studies examining attitudes to carrier screening for FXS have shown that the community and health professionals are supportive, and it would appear that women value being offered carrier screening preconceptionally even though they may not choose to take up the testing at that time for a variety of reasons, see Hill et al. (2010). McConkie-Rosell et al. (2007) have highlighted the need to develop information materials such as targeted brochures and fact sheets to increase women's understanding of risks and benefits at the time of offering screening that should be based on appropriate pre-test and post-test counselling guidelines (Archibald et al. 2009).

Carrier screening for other conditions

Carrier screening for Tay–Sachs disease (TSD), a fatal neurodegenerative condition in children, has been established for around 40 years in populations with higher carrier frequency such as those of Ashkenazi Jewish ancestry. TSD carrier screening is often conducted within high school programs in Canada (Mitchell et al. 1996) and Australia (Gason et al. 2003), with seven other conditions now included (Delatycki 2008; Gross et al. 2008) but is also offered within the voluntary program in Israel described above (Zlotogora et al. 2009). Since 2002, this program now includes targeted carrier screening primarily aimed at non-Ashkenazi Jewish communities in which severe genetic diseases are present with a frequency higher than 1/1,000 live births, performed through local clinics preconceptionally and prenatally (Zlotogora et al. 2009). Increasingly carrier screening for TSD and other conditions is offered as part of ethnicity-based screening prenatally by primary care providers in the USA (Musci and Caughey 2005; Scott et al. 2010).

There is currently a debate (Prior 2008; American College of Obstetricians and Gynecologists 2009; Muralidharan et al. 2011) about population carrier screening for spinal muscular atrophy (SMA), a neuromuscular autosomal recessive condition with variable clinical severity but which is often fatal in the first year of life, with a carrier frequency of 1 in 23 to 1 in 66 (Prior 2010). Several pilot studies have been performed: in Israel with 168 pregnant and non-pregnant women (Basel-Vanagaite et al. 2008); in Taiwan with 107,611 pregnant women from 383 primary clinics (Su et al. 2011); and with 500 pregnant and non-pregnant women in the USA (Prior et al. 2010). In the first two studies, no uptake rate was reported, whereas in the latter 60% accepted testing.

Conclusions

Primary care consultations can provide opportunities to discuss both family history and carrier screening for conditions that are known to be more prevalent in that population, even in the absence of an inherited condition in the family. Use of printed and reputable online information, ideally produced with the input of consumers (Myers et al. 1994; Metcalfe et al. 2008), is a valuable adjunct to the discussion, which should explore the patient's understanding of the conditions in question and the potential benefits and concerns they might have about finding out that they are a carrier including implications for insurance and potential for discrimination. Where appropriate, this discussion should also include the partner. The findings from the variety of literature around population carrier screening would indicate that even though the patient/couple might decide not to be tested at that time, raising their awareness is useful in itself, as the effectiveness of screening should not be measured by test uptake alone (Godard et al. 2003). Ideally, this consultation process would occur before the couple becomes pregnant and, if testing is declined at that time, the repeat offer of testing during pregnancy would act as a 'safety net' but, of course, with potential for reduced reproductive options of test-positive couples who would then benefit from discussions with genetics specialists regarding their reproductive choices including prenatal diagnosis.

The technological capability for multiplex carrier genetic screening continues to expand (Srinivasan et al. 2010), and the potential to harness next-generation sequencing for carrier screening of more than a thousand severe recessive childhood conditions is becoming a reality as costs continue to decrease (Bell et al. 2011). With the advent of direct-to-consumer genetic testing and the ability to perform these tests at home, it is increasingly important that decisions couples make about the utility of carrier genetic testing are

supported by informed but non-directive health professionals who can provide medical follow-up, if necessary (Borry et al. 2011). Obviously, challenges still exist in terms of the need for a well-educated work force and inevitable time constraints (Metcalfe et al. 2002; Qureshi et al. 2006), issues around whether cost of testing should be fee-for-service or reimbursed through public healthcare as well as identifying the best opportunities to initiate a discussion about carrier screening, e.g., consultations on preparing for pregnancy, Pap smears or even contraception. It may also be appropriate to consider other models of how genetics can be implemented into primary care that best meets the needs of patients and health professionals. However, if preconception carrier screening is considered preferable to prenatal in terms of promoting greater autonomous choices, the primary care consultation would seem to provide an ideal setting.

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