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Screening for fragile X syndrome: a literature review and modelling study

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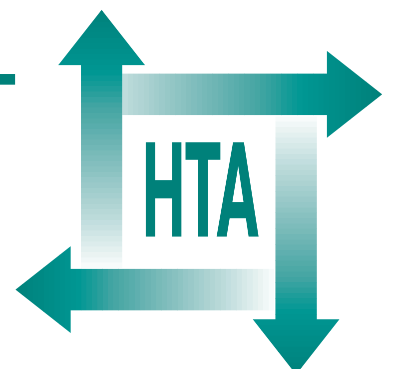

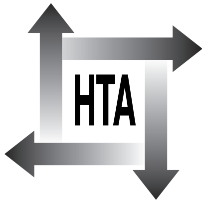

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Screening for fragile X syndrome: a literature review and modelling study

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Abstract

Screening for fragile X syndrome: a literature review and modelling study

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Objectives: To compare the effectiveness, estimate the associated costs, and summarise available evidence about the feasibility and acceptability of different screening strategies in England and Wales. Also to establish a model for estimating effectiveness and costs of these different strategies.

Data sources: Literature searches were restricted to MEDLINE and EMBASE, as well as citations in included papers. A broad search strategy was used involving all aspects of fragile X syndrome (FXS) and covered all relevant literature published between 1991 and 2001.

Review methods: An assessment was conducted of published literature and efforts focused on the development of a model that could be used to synthesise data from various sources, estimate cost-effectiveness of different strategies, and conduct sensitivity analyses according to different assumptions.

Results: The identified screening programmes were effective in detecting carriers, but a comparison of different strategies was not possible. Simulation results by the FXS Model showed that, over the first 10 years, 4% of premutation (PM) females and 70% of full mutation (FM) females could be detected by active cascade screening; it is 10% and 58%, respectively, by prenatal screening. The maximal detection rate for FM carriers by active cascade screening is higher than that by prenatal screening (91% versus 71%). However, the maximal rate of detection of female PM carriers by active cascade screening (6%) is much lower than that by prenatal screening (60%). During the first 10 years of simulation, the estimated direct cost per year to the NHS in England and Wales is £0.7–0.2 million by active cascade screening and £14.5–9.1 million by a programme of prenatal screening. The incremental cost per extra carrier detected (using current practice as the reference standard) is on average only £165 by active cascade screening and £7543 by prenatal screening. The incremental cost per FXS birth avoided is on average £8494 by active cascade screening and £284,779 by prenatal screening.

Conclusions: The empirical evidence suggests that both prenatal screening and cascade screening are feasible and acceptable. Population-based prenatal screening is more efficacious, but it will cost more than active cascade screening. The active cascade screening of affected families is more efficient, cheaper, but less effective than a population-based prenatal screening. It is suggested that both strategies be evaluated in large-scale trials, which might also help to determine whether and how the different strategies could be simultaneously or sequentially combined.

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List of abbreviations

AGG	a nucleotide triplet of adenine–guanine–guanine
CGG	a nucleotide triplet of cytosine–guanine–guanine
CI	confidence interval
CVS	chorionic villus sampling
DD	development disability
DNA	deoxyribonucleic acid
FM	full mutation (CGG repeats >200)
FMR1	gene which is mutated in fragile X syndrome
FRAXA	fragile site associated with fragile X syndrome
FMRP	protein product normally transcribed by *FMR1*
FXS	fragile X syndrome
NTM	normal transmitting male
PCR	polymerase chain reaction
PM	premutation (CGG repeats 55–200)
POF	premature ovarian failure
PUBS	peripheral umbilical cord blood sampling
RCT	randomised controlled trial

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

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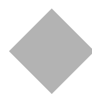

Executive summary

Background

Fragile X syndrome (FXS) is an inherited disorder that causes learning difficulty. The disorder affects an estimated one in 4000 males and one in 8000 females. Affected males are generally unable to live independently, while affected females have learning difficulty but may live independently. There is no cure for FXS. Management of affected individuals is through specific educational and psychosocial interventions and treatment of any clinical symptoms.

There are about 10,000 FXS patients in England and Wales. Since the annual cost to the NHS for managing a moderately affected adult was approximately £20,000 (1995 data), the total annual cost of managing FXS patients can be estimated to be £200 million in England and Wales.

FXS is caused by a mutation of the *FMR1* gene, which is located in the Xq27.3 region of the long arm of the X chromosome. It contains a variable trinucleotide repeat [cytosine–guanine–guanine (CGG)] which can become unstable over successive generations. The number of CGG repeats within a gene will determine whether the individual has a normal allele (<55 repeats), premutation (55–200 repeats) or a full mutation (>200 repeats). All males with full mutation (FM) and about half of females with FM are affected with learning difficulty. People with premutation (PM) are not affected in general. The PM can become unstable on maternal transmission and mothers with PM may have affected children. The risk of expansion from PM to FM depends on the number of CGG repeats in the maternal allele and other factors. The expansion risk from PM to FM is much greater in affected families than in the general population.

Options for population and targeted screening for FXS and carriers have been the focus of two previously published HTA reviews. However, the two previous HTA reports reached contrasting conclusions and recommendations for further research. The different approaches recommended by the two HTA reviews were prenatal screening of all apparently low-risk women, and cascade testing of high-risk women following systematic case finding. This review aims to bring together the findings of the two previous HTA reports.

Methods

We first conducted an assessment of published literature, to bring together and update the findings of two previous HTA reviews. Then efforts were focused on the development of a model (the FXS Model) that could be used to compare the cost-effectiveness of active cascade screening of affected families and population based prenatal screening for FXS. The assumptions about input parameters to the FXS Model were based on a comprehensive literature review and the model's test running.

Major findings

Prevalence

The overall prevalence of FXS was on average 2.3%, ranging from 0.3% to 16% in males with learning difficulty. Preselection according to family history and clinical features can increase the proportion of detected FXS cases among people with learning difficulty who were DNA tested. Using the indirect method and data from eight studies, the prevalence of FXS in the general population was estimated to be 2.3/10,000 (or 1 in 4425).

Pooling data from identified studies (16 for males and 14 for females), the prevalence of PM was 0.16% (1 in 643) among the general male population and 0.67% (1 in 149) among the general female population. These may have overestimated the prevalence of PM in the general population because of the possible founder effect and biased selection in screening programmes. The estimated prevalence of PM was sensitive to the cut-off value of CGG repeat size used to define the PM. The PM repeat sizes in the general population were generally much smaller than those in the affected families.

Risk of expansion from PM to FM

The risk of expansion from PM to FM in maternal transmission is related to the size of CGG repeats

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and the risk of expansion from PM to FM in the general population is significantly lower than that in FXS families. Based on data of 1111 maternal PM transmissions, the pooled rate of expansion from PM to FM was 63.4% [95% confidence interval (CI): 60.5 to 66.2%] in PM carriers from FXS families. According to data of 183 maternal PM transmissions, the pooled rate of expansion from PM to FM was 9.8% (95% CI: 5.5 to 14.2%) in PM carriers identified from the general population.

Feasibility and acceptability

The empirical evidence suggested that preconceptual or prenatal screening, case finding and cascade screening are feasible and acceptable by affected families and by the general population. The identified screening programmes were effective in detecting carriers, but a comparison of different strategies was not possible.

Findings of the FXS Model

Simulation results by the FXS Model showed that, over the first 10 years, 4% of PM females and 70% of FM females could be detected by active cascade screening; it is 10% and 58%, respectively, by prenatal screening. The maximal detection rate for FM carriers by active cascade screening is slightly higher than that by prenatal screening (91% versus 71%). However, the maximal rate of detection of female PM carriers by active cascade screening (6%) is much lower than that by prenatal screening (60%). During the first 10 years of simulation, the additional number of births of FXS children that can be avoided each year is estimated to be about 15 (range: 4–31) by active cascade screening, and about 39 (range: 9–76) by prenatal screening.

Due to the fact that the screening candidates need to be tested only once, the total number of women with unknown carrier status will be reduced by the screening programmes. During the first 10 years, the estimated direct cost per year to the NHS in England and Wales is £0.7–0.2 million by active cascade screening and £14.5–9.1 million by a programme of prenatal screening. The incremental cost per extra carrier detected (using current practice as the reference standard) is on average only £165 (range: £129–182) by active cascade screening and £7543 (range: £5316–14,636) by prenatal screening. The incremental cost per FXS birth avoided is on average £8494 (range: £1367–27,314) by active cascade screening and £284,779 (range: £135,510–950,572) by prenatal screening.

Considering that the lifetime care of each FXS patient will cost the NHS about £380,000, the most expensive strategy (population prenatal screening) is still cost-saving in the long term. The estimated net savings per year in England and Wales are about £10 million by active cascade screening and about £8 million by prenatal screening.

Conclusions

The empirical evidence suggested that both prenatal screening and cascade screening are feasible and acceptable. Both prenatal screening and active cascade screening can reduce the number of births of FXS children and are cost-saving in the long term. Population-based prenatal screening is more efficacious and has a greater impact on the population, but it will also cost more than active cascade screening. The active cascade screening of affected families is more efficient, cheaper, but less effective than a population-based prenatal screening.

Since both prenatal screening and active cascade screening have advantages and disadvantages, we believe that both strategies should be evaluated in large-scale trials. It may also be important to explore and evaluate whether and how the different strategies could be simultaneously or sequentially combined.

Chapter 1

Aim of the review

Options for population and targeted screening for fragile X syndrome (FXS) have been the focus of two previously published HTA reviews (Appendix 1).[1,2] However, the two HTA reports reached contrasting conclusions and recommendations for further research. The different approaches recommended by the two HTA reviews were prenatal screening of all apparently low-risk women[1] and cascade testing of high-risk women following systematic case finding.[2]

This review aims to bring together the findings of the two previous HTA reports.[1,2] The principal objectives of this review are as follows:

- to compare the effectiveness of different screening strategies (prenatal screening versus systematic case finding and cascade screening);
- to estimate the costs associated with different strategies;
- to summarise available evidence about the feasibility and acceptability of different strategies;
- to answer the above questions (i) by providing an overview and update of the existing reviews and (ii) by establishing a model for estimating effectiveness and costs of different strategies.

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Chapter 2
Background

Fragile X syndrome

FXS is an inherited disorder that causes learning difficulty. The disorder affects an estimated one in 4000 males and one in 8000 females. The disorder is worse in males than in females. Affected males are generally unable to live independently, while affected females have learning difficulty but may live independently. There is no cure for FXS. Management of affected individuals is through specific educational and psychosocial interventions and treatment of any clinical symptoms.[1,2]

The total population in England and Wales was about 53 million (26 million males and 27 million females) in 2000.[3] There are about 10,000 FXS patients in England and Wales, based on the estimated prevalence of one in 4000 males and one in 8000 females. Since the annual cost to the NHS for managing a moderately affected adult was approximately £20,000 (1995 data),[2] the total annual cost of managing FXS patients can be estimated to be £200 million in England and Wales.

Technology development during the last decade has made population-based screening for FXS possible. The identification of carrier status may prompt FXS carriers to modify their reproductive behaviour, resulting in a reduction in births of children with FXS. Other benefits of screening for FXS may include a possible improvement in the management of FXS patients, improved quality of life for parents and other family members and the reduction of anxiety in at-risk women with normal testing results. However, population-based programmes of screening for FXS are costly and not risk-free. For example, false-positive results may cause unnecessary psychological harm and the invasive prenatal diagnosis may cause the loss of foetuses.[1]

Genetic features of FXS

The disorder displays an unusual inheritance pattern in an X-linked fashion.[4] Both females and males could be affected or be unaffected carriers. The children (sons or daughters) of unaffected female carriers have a risk of being affected. Sons of unaffected male carriers [normal transmitting males (NTMs)] cannot be affected or be carriers, while all daughters of NTMs will be unaffected carriers.

These observations were explained following the discovery of the causative gene, *FMR1*, in 1991.[5] This gene is located in the Xq27.3 region of the long arm of the X chromosome. It contains a variable trinucleotide repeat, cytosine–guanine–guanine (CGG), which can become unstable over successive generations. The number of CGG repeats within a gene will determine whether the individual has a normal allele (<55 repeats), premutation (approximately 55–200 repeats), or a full mutation (≥200 repeats).

The premutation (PM) can become unstable on maternal transmission, and the risk of expanding to a full mutation (FM) depends upon the number of repeats in the maternal allele and other factors. Evidence indicated that the risk for PMs to expand may depend on the absence of stabilising adenine–guanine–guanine (AGG) repeats, which interrupt the CGG repeat region.[6] The PM may be defined differently in terms of cut-off values of CGG repeats size, and there is a 'grey zone' from 40 to 60 CGG repeats. The stability of 40–60 CGG repeats and their clinical importance are uncertain and controversial.

Children with PM are not affected in general. When the expansion of CGG repeats reaches a critical size (>200 repeats), hypermethylation of the CGG repeat and its flanking regions within exon 1 of the *FMR1* gene will result in a shutdown of transcription and the absence of FMR1 protein (FMRP).[2] All males with a hypermethylated FM and about 50% of females with a hypermethylated FM are affected. It is not yet possible to predict whether a female foetus with FM will be affected with learning difficulty. The phenotypic expression of people with FM may be different. Generally, learning difficulty in FM females is less severe than that in FM males. Another reason for varying severity of learning difficulty is mosaicism, which refers to the fact that some individuals may have both FM and PM in their body cells.

The complex genetics of this disorder and the uncertainty regarding the risk of expansion of CGG repeats of differing sizes lead to difficulties in communicating inheritance and risk information in counselling situations.

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Diagnostic testing technologies

There are several technologies for testing FXS: cytogenetic tests, Southern blotting of genomic DNA, DNA amplification by polymerase chain reaction (PCR) and antibody testing for detecting FMRP.[1,2] Cytogenetic testing could be used to detect FMs but not PMs, and it is time consuming and expensive. The method for detecting FMRP may be cheap, but it is not suitable for detecting FMs in females and PMs. Thus, the following discussion will focus on Southern blotting and PCR.

Southern blotting

This procedure was developed for testing FXS in 1991, using different restriction enzymes. It can be used to detect FM, methylation and large PMs, but small PMs may be missed. It requires high quality/quantity of DNA sample, and is relatively time consuming (at least 1 week from receipt of sample) and labour intensive. The cost per test using Southern blot is about £50–75.[1]

DNA amplification by PCR

PCR is a relatively rapid and cheap test for detecting FXS mutations, by using the enzyme DNA polymerase to process and copy a specified sequence. It is suitable for the detection of normal alleles or PMs, but not FMs, because large FMs may fail to amplify. In addition, the results are not interpretable if one of the two bands is missing in females. It was estimated that for a high throughput, the cost per sample could be as low as £10.[1]

Combination of PCR and selective Southern blotting

It has been generally accepted that the most appropriate protocol of testing FXS is to combine PCR and selective Southern blotting.[1,2] First, all samples are tested by PCR. Then Southern blotting is used when there is a failure to amplify or there is a single band in females. It has been estimated that about one-third of females may need to be tested by Southern blotting. A combination of PCR and selective Southern blotting is considered to be the definitive test for FXS.[2] In the existing models of screening for FXS, the accuracy of testing the number of CGG repeats has been assumed to be 100%.[7,8]

Screening strategies

The purposes of screening are (1) to identify women at high risk of transmitting FXS to any offspring and (2) to diagnose affected individuals at an early stage in order that they may achieve the maximum benefit from health and educational interventions. There are several possible strategies of screening for FXS.[1,2]

Prenatal screening

All pregnant women with unknown status of FXS mutation are eligible to be tested. For carriers detected, prenatal diagnosis could be carried out to test foetal mutation status. The efficiency may be low because it has to test a large number of women at low risk, although it could be modified to test only pregnant women with family history of FXS or learning difficulty in general. Prenatal testing for FXS can be incorporated into existing screening programmes for other foetal disorders (e.g. Down's syndrome). However, since the general public and medical professionals may be less familiar with FXS and its complicated inheritance pattern, genetic counselling in screening for FXS will be more difficult and require more time than that in screening for Down's syndrome.

For prenatal diagnosis of foetal carrier status, there are three different invasive procedures: amniocentesis, chorionic villus sampling (CVS) and peripheral umbilical cord blood sampling (PUBS). The estimated rate of foetal loss was 0.5–1.0% by amniocentesis or CVS and 1.4% by PUBS.[1]

The interpretation of the DNA test is not always straightforward. Male foetuses with FM are certainly affected, whereas only about half of female foetuses with FM will be affected. Hence it may be difficult for parents to decide whether the detected female foetuses with FM should be terminated.

Preconceptual screening

All females of reproductive age are eligible to be tested for PM or FM. Since women can be informed about their mutation status before being pregnant, they have a full range of reproductive choices. The major disadvantages include low uptake rate and some ethical issues such as privacy, confidentiality, peer pressure and stigmatisation.[2] The efficacy of preconceptual screening for FXS may be lower than prenatal screening.

Cascade screening

It is an established approach in clinical genetics that relatives of FXS patients are tested for carrier status. Systematic cascade screening may be more efficient because members of affected families will have a high risk of being carriers. It can only detect carriers in affected families. Hence its

impact on the detection of FXS depends on the distribution of carriers between the affected families and the general population. In addition, births of further affected children may occur in families before the diagnoses of index cases.[9]

Neonatal and paediatric testing

Guthrie blood spot screening is routinely conducted for phenylketonuria and hypothyroidism in the UK. Testing neonates for FXS could also be incorporated. Furthermore, children with learning difficulty or development delay may be tested for FXS. The detection of children with FXS may help the identification of their relatives at high risk of carrier status. However, the early diagnosis of affected children has limited benefits to the affected children themselves, because of lack of effective interventions.

Current service provision

Routine screening for FXS is not currently available in the UK, although limited neonatal screening and screening of relatives of affected individuals (cascade screening) are performed in the UK. The UK National Screening Committee does not currently support a national screening programme for FXS; however, the committee wished to review this position following the publication of two HTA reports on screening for FXS.[1,2]

A survey of current practice

We sent a questionnaire (Appendix 2) to 25 centres of clinical genetics services across the UK in early 2002, to obtain basic information about the current practice of diagnosis and counselling for FXS. Twenty-one completed questionnaires were received. All the 21 centres offer genetic counselling to families affected by FXS. Patients are generally referred from community paediatrics, and the patients have usually undergone molecular genetic testing. More than half of the centres (13/21) have a designated FXS register or procedures for reviewing cases.

Genetic counselling may be provided by genetic counsellors, or nurses, or consultants. The usual first or pre-clinic contact methods include home visit ($n = 8$), at a hospital outpatient clinic ($n = 7$), by telephone ($n = 1$), or a mix of these methods ($n = 4$). After the first contact, the genetic counselling is usually at a hospital outpatient clinic ($n = 19$). The genetic counselling typically lasts 45–60 minutes. Most centres (20/21) stated that genetic counsellors, nurses or consultants discuss issues about carrier testing and prenatal diagnosis with pregnant women in the affected families. Discussions may take as long as necessary, but usually less than 60 minutes.

Where feasible and acceptable, carrier testing is offered to family members of the proband. PM is generally defined as the CGG repeat sizes from 55 to 200 (12 centres), although the cut-off values of 50, 53, 59 and 61 are also used. The turnaround time from the receipt of sample in the laboratory to the receipt of the result by the clinicians ranges from 11 to 56 days for routine carrier testing and from 2 to 14 days for prenatal diagnosis.

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Chapter 3

Review methods

A protocol for the Cochrane review on screening for FXS stated that only randomised controlled trials (RCTs) will be included.[10] RCTs can provide the most valid evidence about the effectiveness of different screening strategies. However, because there is no evidence from relevant RCTs, we have to rely on data from observational studies. An assessment of the two HTA reports and published reviews suggests that a modelling approach may be useful to synthesise data from various sources.

We first conducted an assessment of published literature, to bring together and update the findings of two previous HTA reviews. Then efforts were focused on the development of a model that could be used to synthesise data from various sources, to estimate cost-effectiveness of different strategies and to conduct sensitivity analyses according to different assumptions.

Methods for literature review

Search strategy

The literature searches were restricted to electronic databases (MEDLINE and EMBASE) and citations in included papers. The search strategy was broad, by searching the MeSH subject headings and keywords about all aspects of FXS (Appendix 3), and covered all relevant literature published between 1991 and 2001. The two previously published HTA reviews included searches at least up to 1996.[1,2] In this rapid review, therefore, we focused on the literature published from 1996 to 2001.

Inclusion and exclusion criteria

Relevant studies of all designs were considered for inclusion. A study was considered relevant if it was about

- performance of diagnostic tests for FXS, including DNA amplification technology and Southern blotting
- prevalence of FXS and frequency of PMs and FMs
- risk of expansion from PM to FM and associated factors
- outcomes of screening for FXS
- costs of screening for FXS
- costs of managing patients with FXS
- quality of life of FXS patients and their carers
- feasibility and acceptability of screening for FXS
- modelling of screening for FXS.

Decisions about inclusion and exclusion of studies were made independently by two reviewers (VS and FS). Retrieved references were downloaded into a Reference Manager database. To facilitate their retrieval from the database, included references were coded according to their subject content (Appendix 4).

MEDLINE search yielded a total of 957 studies published between 1991 and September 2001. Based on an assessment of titles and abstracts, 569 of the 957 studies were considered to be potentially relevant by at least one of the two reviewers. Twenty-two of the 566 studies were published in non-English languages. Although there was no language restriction in the literature search, we reviewed only English language studies. First, this was because of limited resources and time available. In addition, by checking titles and abstracts, we judged that conclusions based on studies published in the English language were unlikely to be changed by including studies published in other languages.

Because a large number of studies were potentially relevant, we had to focus on studies that were highly relevant to screening for FXS. A study was considered to be highly relevant if it reported empirical data on any of

- the prevalence or frequency of FXS and mutations (Chapter 4)
- risk of expansion from PM to FM and associated factors (Chapter 5)
- findings of practical screening programmes (Chapter 6)
- modelling of screening for FXS (Chapter 7).

Data extraction, synthesis, and quality assessment

Data from relevant studies were extracted into tables in relevant chapters by one reviewer (FS). The characteristics, quality and findings of included studies are summarised in tables. Where it was judged necessary and appropriate, results from

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different studies were quantitatively combined. Because of the complexity of included studies and lack of a generally agreed framework for assessing quality of non-RCTs, we did not carry out a formal quality assessment of included studies, but have commented on the key features about validity of study findings in relevant tables and chapters.

Modelling screening for FXS

Based on findings from the literature review, we developed a new model that can be used to compare outcomes of different strategies of screening for FXS. It is a deterministic model for simulating population dynamics in England and Wales, and calculations were implemented using Microsoft Excel. We used the model to estimate multiple outcomes from different screening strategies and to simulate short-term and long-term consequences of different screening strategies. Details of the model's structure and assumptions are described in Chapter 8.

Chapter 4

Prevalence of FXS and mutation

Prevalence of FXS in people with learning difficulty

Findings of the previous HTA reports

Murray and co-workers summarised data from 10 studies about the prevalence of FXS among males in institutions.[1] The studies were published between 1983 and 1996, conducted in the UK, USA, Japan, Finland, Germany, Italy and Poland. The males were with known or unknown aetiology of learning difficulty, and all FXS cases were confirmed by DNA analysis. The reported frequency of FXS in males with learning difficulty varied greatly, from 3 to 16%, with an average of 6% (131/2019). Murray and co-workers suggested that the observed variation in the reported prevalence of FXS may be attributable to the following factors:

- admission patterns for the institution
- completeness of ascertainment due to patient and parental non-compliance with diagnostic testing
- selection criteria for testing (e.g. some studies included only those with typical features of FXS)
- definition of the denominator population.

In the 2001 HTA report, Pembrey and co-workers[2] estimated the prevalence of FXS in people with learning difficulty, based on a review by de Vries and co-workers,[11] which included studies conducted in England, Australia, USA and The Netherlands. The pooled frequency of FXS among people with learning difficulty was 0.7% (24/3353) for males and 0.5% (6/1317) for females.

Updated review

Table 1 presents studies included in the two previous HTA reports, plus studies newly identified by our updated literature search (more details are given in Appendix 5). The studies were conducted in different countries, and the patients were included according to different selection criteria.

For males with learning difficulty, there were 42 studies and a total of 16,006 patients. The prevalence of FXS was on average 2.3%, ranging from 0.3 to 16%. Studies could also be separated according to whether the cause of learning difficulty was known. For males, the prevalence of FXS was 3.5% in studies that included males with learning difficulty of unknown cause. It was 1.7% in studies that included males with any learning difficulty.

For females, there were 22 studies and a total of 8677 patients. The prevalence of FXS in females with learning difficulty was on average 0.7%, ranging from 0 to 8%. There was no difference between studies that included learning difficulty of unknown cause and studies that included any learning difficulty.

In seven studies, the people with learning difficulty could not be separated according to sex. The prevalence of FXS in the seven studies was 1.8%, which is similar to 1.7% when all studies were combined.

Preselection for DNA testing in people with learning difficulty

The proportion of FXS in people with learning difficulty was low, about 2.3% for males and 0.7% for females, according to the updated literature review. To improve the efficiency of screening for FXS, de Vries and co-workers[12] applied a seven-item checklist for clinical preselection for DNA testing in 896 males and 685 females with learning difficulty of unknown cause. The seven items were family history of learning difficulty, face, ears, joints, skin, testes and personality. They found that "the seven item checklist allowed exclusion from further testing in 86% of the retarded males (95% CI 0.83–0.88) without missing either any of the newly diagnosed cases or, in retrospect, any of the 50 previously diagnosed cases known to our department". The proportion of FXS was 6.7% in all males with learning difficulty. Using a score of $\geqslant 5$ as the selection criterion, only 119 of the 896 males with learning difficulty would need to be tested and the frequency of FXS would be 50% among the tested.[12]

A similar finding was also reported in a study by Arvio and co-workers;[13] 344 males with learning difficulty of unknown cause were tested and six (1.74%) new FXS were detected. Only 44 would need to be tested according to a check list and clinical examination in order to detect these six (13.6%) new cases.

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TABLE 1 *Prevalence of FXS in people with learning difficulty*

Study	**Country**	**Subjects**[a]	**Sex**	**FM**	***N***	**%**
Elango[18]	India	LD	Both	20	1111	1.80
Hou[19]	China (Taiwan)	LD	Both	233	11892	1.96
Wang[20]	China (Taiwan)	LD	Both	0	349	0.00
Zhong[21]	China	LD	Both	32	1127	2.84
Subtotal – both (LD)				285	14479	1.97
Saha[22]	India	LD(unk)	Both	7	98	7.14
Patsalis[23]	Canada	LD(unk)	Both	0	1550	0.00
Patsalis[23]	Canada	LD(unk)	Both	0	550	0.00
Subtotal – both [LD(unk)]				7	2198	0.32
All – both sexes				**292**	**16677**	**1.75**
Cora[24]	Turkey	LD	Female	1	25	4.00
Crawford[25]	USA	LD(SEN)	Female	0	872	0.00
Elbaz[26]	French West Indies	LD	Female	0	85	0.00
Gerard[27]	France	LD	Female	1	171	0.58
Hagerman[28]	USA	LD	Female	3	140	2.14
Iqbal[29]	Saudi Arabia	LD	Female	2	46	4.35
Jacobs[30]	UK	LD	Female	0	74	0.00
Sharma[31]	India	LD	Female	1	37	2.70
Slaney[32]	UK	LD(SEN)	Female	0	51	0.00
Turner[33]	Australia	LD	Female	39	5554	0.70
Tzeng[34]	China (Taiwan)	LD	Female	1	160	0.63
Subtotal – female (LD)				48	7215	0.67
Angel[35]	Mexico	LD(unk)	Female	0	9	0.00
Arrieta[36]	Spain	LD(unk)	Female	2	42	4.76
de Vries[11]	The Netherlands	LD(unk)	Female	2	685	0.29
Jara[37]	Chile	LD(unk)	Female	0	86	0.00
Kwon[38]	Korea	LD(unk)	Female	0	24	0.00
Mila[39]	Spain	LD(unk)	Female	0	40	0.00
Millan[40]	Spain	LD(unk)	Female	4	51	7.84
Pang[41]	China	LD(unk)	Female	1	81	1.23
Patsalis[42]	Greece/Cyprus	LD(unk)	Female	0	255	0.00
Syrrou[43]	Greece/Cyprus	LD(unk)	Female	0	176	0.00
Tuncbilek[44]	Turkey	LD(unk)	Female	0	13	0.00
Subtotal – female [LD(unk)]				9	1462	0.62
All – female				**57**	**8677**	**0.66**
Cora[24]	Turkey	LD	Male	5	95	5.26
Crawford[25]	USA	LD(SEN)	Male	5	1979	0.25
Elbaz[26]	French West Indies	LD	Male	11	163	6.75
Froster-Iskenius[45]	Germany	LD	Male	15	242	6.20
Gerard[46]	France	LD	Male	10	403	2.48
Haddad[47]	Brazil	LD	Male	5	256	1.95
Hagerman[28]	USA	LD	Male	1	299	0.33
Hofstee[48]	Japan	LD	Male	11	305	3.61
Iqbal[29]	Saudi Arabia	LD	Male	24	259	9.27
Jacobs[30]	UK	LD	Male	4	180	2.22
Lantigua-Cruz[49]	Cuba	LD	Male	7	54	12.96
Mazurczak[50]	Poland	LD	Male	6	201	2.99
Murray[51]	UK	LD(SEN)	Male	5	1013	0.49

continued

TABLE 1 *Prevalence of FXS in people with learning difficulty (continued)*

Study	Country	Subjects[a]	Sex	FM	*N*	%
Murray[52]	UK	LD(SEN)	Male	20	3738	0.54
Neri[53]	Sicily	LD	Male	12	155	7.74
Sharma[31]	India	LD	Male	9	93	9.68
Slaney[32]	UK	LD	Male	4	103	3.88
Tan[54]	Singapore	LD(SEN)	Male	6	255	2.35
Turner[55]	Australia	LD	Male	10	472	2.12
Tzeng[34]	China (Taiwan)	LD	Male	11	415	2.65
Webb[56]	UK	LD	Male	6	219	2.74
Subtotal – male (LD)				187	10899	1.72
Angel[35]	Mexico	LD(unk)	Male	2	53	3.77
Arrieta[36]	Spain	LD(unk)	Male	8	92	8.70
Arvio[13]	Finland	LD(unk)	Male	6	344	1.74
Butler[57]	USA	LD(unk)	Male	4	201	1.99
de Vries[11]	The Netherlands	LD(unk)	Male	9	896	1.00
Faradz[58]	Indonesia	LD(unk)	Male	4	262	1.53
Fryns[59]	Belgium	LD(unk)	Male	57	354	16.10
Jara[37]	Chile	LD(unk)	Male	4	214	1.87
Kahkonen[60]	Finland	LD(unk)	Male	6	150	4.00
Kwon[38]	Korea	LD(unk)	Male	1	77	1.30
Limprasert[61]	Thailand	LD(unk)	Male	16	237	6.75
Mila[39]	Spain	LD(unk)	Male	11	182	6.04
Millan[40]	Spain	LD(unk)	Male	15	186	8.06
O'Dwyer[62]	UK	LD(unk)	Male	1	138	0.72
Paika[63]	USA	LD(unk)	Male	6	44	13.64
Pang[41]	China	LD(unk)	Male	1	243	0.41
Patsalis[42]	Greece/Cyprus	LD(unk)	Male	8	611	1.31
Primrose[64]	UK	LD(unk)	Male	7	100	7.00
Syrrou[43]	Greece/Cyprus	LD(unk)	Male	4	257	1.56
Tuncbilek[44]	Turkey	LD(unk)	Male	5	166	3.01
Tuncbilek[65]	Turkey	LD(unk)	Male	5	300	1.67
Subtotal – male [LD(unk)]				180	5107	3.52
All – male				**367**	**16006**	**2.29**
Total				**716**	**41360**	**1.73**

[a] LD, learning difficulty; LD(unk), learning difficulty with unknown cause; LD(SEN), from special educational needs schools.

It should be noted that the suggested checklists for preselection have not been fully validated for children under 6 years old. Since the phenotype is less well developed in preschool children, the use of such a screening checklist might miss affected children in this age group. Warburton and co-workers[14] reported (in a conference poster) a clinical questionnaire-based method for the preselection of children up to 5 years old. They found that the introduction of this questionnaire preselection reduced the molecular workload in FRAXA (fragile site associated with FXS) screening from 23 to 6% in 6 months.

Prevalence of FXS in the general population

The prevalence of FXS in the general population can be estimated indirectly. The commonly used method was first to detect FXS cases among people with learning difficulty. Then the number of identified cases of FXS was related to the size of population of the same age from which they were drawn. The prevalence of FXS or FM was about one in 4000 (or 2.5 per 10,000) in the male population, according to two previous HTA reports.[1,2] It was generally accepted that the

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***TABLE 2** Indirectly estimated prevalence of FXS in the general population[a]*

Study	Place	Subjects tested	No. tested	No. of cases	Rate/10,000 (95% CI)[b]	1 in *N* (95% CI)[b]
Arvio[13]	Southern Hame, Finland	Male LD	344	38	2.27	1 in 4400
Crawford[25]	Atlanta, USA	Male LD	1979	5	2.5 (1.36, 4.57)	1 in 3968 (2188, 7353)
de Vries[11]	The Netherlands	Male LD	1519	39	1.65 (1.0, 2.6)	1 in 6045 (3851, 9981)
Elbaz[26]	French West Indies	Male LD	163	11	4.2	1 in 2381
Morton[66]	Coventry, UK	Male LD	219	6	2.4	1 in 4090
Murray[52]	Wessex, UK	Male LD	3738	20	1.81 (1.12, 2.50)	1 in 5530 (4007, 8922)
Patsalis[42]	Cyprus	Male LD	611	8	2.36	1 in 4246
Turner[55]	Sydney, Australia	Male LD	472	10	3.00	1 in 3333
Pooled			**8701**	**137**	**2.42 (or 2.26)**	**1 in 4132 (or 4425)**

[a] Pooled estimates were simply the average of results of seven studies (or the weighted average, weighted by the number of FXS cases).
[b] CI = confidence interval

***TABLE 3** Studies that provided direct data on the frequency of FM in population*

Study	Country	Subjects	Sex	FM	No. tested	Rate/10,000
Geva[67]	Israel	Normal	Female	0	9660	0.00
Pesso[68]	Israel	Normal (high risk)	Female	3	1033	29.04
Pesso[68]	Israel	Normal (low risk)	Female	1	8426	1.19
Rousseau[69]	Canada	Normal	Female	0	10624	0.00
Ryynanen[70]	Finland	Normal	Female	0	1477	0.00
Toledano-Alhadef[17]	Israel	Normal	Female	3	14334	2.09
Wenstrom[71]	USA	Normal	Female	0	263	0.00
Subtotal (female)				7	45817	1.53
Larsen[72]	Greenland	Normal	Male	0	101	0.00
Larsen[73]	Denmark	Normal	Male	0	2012	0.00
Patsalis[42]	Canada	Normal	Male	0	2073	0.00
Subtotal (male)				0	4186	0.00
All studies				**7**	**50003**	**1.40**

frequency of FM in females is the same as that in males. Since only half of females with FM are affected, the prevalence of FXS in females could be estimated to be about one in 8000 (or 1.25 per 10,000).

Table 2 presents the results of eight studies of indirectly estimated prevalence of FXS in the general population, based on identified FXS cases from males with learning difficulty. The proportion of FXS ranged from 1.8 to 4.2 per 10,000 population (or from 1 in 2400 to 1 in 6000). Based on a total of 137 affected males, the pooled proportion was 2.42 per 10,000 (or 2.26 per 10,000 if weighted by the number of affected cases), which is equivalent to 1 in 4132 (or 1 in 4425 if weighted by the number of affected cases)

Several studies reported detected FMs in samples from the general population (*Table 3*). The sample sizes in these studies were small, and many have included only healthy volunteers or excluded people with family history. Consequently, many studies did not find any affected cases, and the pooled frequency of FM was low (1.4 per 10,000).

Prevalence of PM in the general population

Findings in the two previous HTA reports

The most common CGG repeat size is about 30, ranging from 5 to 54, in the unaffected population. The PM is often defined as the CGG

TABLE 4 *Frequency of PM in the general population*

Study	Country	Subjects	Sex	Cut-off[a]	PM	N	%
Arinami[b 74]	Japan	DNAtest[d]	Female		0	227	0.000
Arrieta[36]	Spain	Normal (NS)[e]	Female		0	72	0.000
Chen[75]	China	Normal (NS)	Female		0	41	0.000
Dawson[b 76]	Canada	Guthrie cards	Female	55	2	735	0.272
Geva[67]	Israel	Prenat/concept[f]	Female	55	61	9660	0.631
Pang[41]	China	Volunteers	Female		0	350	0.000
Pesso[68]	Israel	Prenat/concept	Female	54	70	8426	0.831
Reiss[b 77]	USA	DNAtest	Female	75	1	561	0.178
Rousseau[b 78]	Canada	Outpatient	Female	55	41	10624	0.386
Ryynanen[70]	Finland	Prenat	Female	50	18	1477	1.219
Snow[b 79]	USA	Blood donors	Female	57	1	197	0.508
Spence[b 16]	USA	DNAtest/eggD[g]	Female	60	3	745	0.403
Toledano-Alhadef[17]	Israel	Prenat/concept	Female	55	124	14334	0.865
Wenstrom[71]	USA	Prenat(HR)[h]	Female		0	263	0.000
All female					**321**	**47712**	**0.673 (1 in 149)**
Arrieta[36]	Spain	Normal (NS)	Male		0	98	0.000
Arinami[b 74]	Japan	DNAtest	Male		0	370	0.000
Chen[75]	China	Normal (NS)	Male		0	42	0.000
Dawson[b 76]	Canada	Guthrie cards	Male	57	3	778	0.386
Eichler[b 80]	USA	Blood donors	Male		0	406	0.000
Faradz[81]	Indonesia	Volunteers	Male	55	4	1069	0.374
Holden[b 82]	Canada	Guthrie cards	Male	61	1	1000	0.100
Larsen[72]	Greenland	Newborn	Male		0	101	0.000
Larsen[73]	Denmark	Newborn	Male	56	3	2012	0.149
Murray[c 1]	UK	Normal (NS)	Male	65	1	543	0.184
Pang[41]	China	Volunteers	Male		0	299	0.000
Patsalis[23]	Canada	Newborn	Male	53	4	2073	0.193
Reiss[b 77]	USA	DNAtest	Male		0	416	0.000
Rousseau[b 78]	Canada	Not specified	Male		14	10572	0.132
Snow[b 79]	USA	Blood donors	Male		0	50	0.000
Sucharov[83]	Brazil	Normal (NS)	Male	130	1	100	1.000
All male					**31**	**19929**	**0.156 (1 in 643)**
Patsalis[84]	Cyprus	DNAtest	X Chr	56	7	1132	0.618
Poon[85]	China	Volunteers	X Chr	52	5	858	0.583
Syrrou[86]	Greece/Cyprus	Normal (NS)	X Chr	50	1	323	0.310
Tzeng[87]	China (Taiwan)	Outpatient	X Chr	95	1	300	0.333
Wang[20]	China (Taiwan)	Volunteers	X Chr		0	350	0.000
Female or male (X chromosomes)					**14**	**2963**	**0.472 (1 in 212)**

[a] Cut-off: defined PM cut-off value, or reported lowest PM repeats size.
[b] Used in Murray and co-workers, 1997[1] (HTA report, p. 38).
[c] Result from a study by A Murray, reported in 2001 HTA report.[2]
[d] DNAtest: People having DNS test unrelated to learning difficulty.
[e] Normal (NS): not specified.
[f] Prenat/concept: prenatal or preconceptual women.
[g] EggD: egg donors.
[h] HR: with family history of unspecified learning difficulty.

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repeat sizes from 55 to 200. However, there is a grey zone between the PM and normal alleles. Published studies may have used different cut-off values for PM, which have important implications on the estimated frequency of PM in the population. The 2001 HTA report[2] prompted the use of following definitions:

- minimum of <11 repeats (rare)
- common 11–40 repeats (approximately 98%)
- intermediate 41–60 (about 2%)
- premutation 61–200
- full mutation >200.

The 1997 HTA report by Murray and co-workers[1] summarised data from nine studies about frequency of PM in the general population. The pooled proportion of PM was 0.37% (1 in 273) in 13,089 females, and 0.125% (1 in 800) in 13,592 males. In these studies, the cut-off value for defining PM repeats size was about 54. The distribution of PM sizes in females was also provided, based on 48 identified carriers.

In the 2001 HTA report, Pembrey and co-workers[2] included data from an unpublished UK study, in which one PM (65 CGG repeats) and two borderline alleles (51 and 52 repeats) were detected among 543 normal boys around Bristol (Pembrey and co-workers, personal communication with A Murray and co-workers). In a newly published study from Israel by Drasinover and co-workers,[15] the proportion of PM (CGG repeats size 61–135) was 1 in 271.

Murray and colleagues discussed possible bias in the study by Spence and co-workers,[16] in which women were tested on a self-payment basis and the uptake rate was low. This bias was also discussed in the 2001 HTA report,[2] with regard to an Israeli study.[15] Selection bias can be introduced if relatives of women who have been diagnosed as carriers were more likely to take up the subsequent testing. A further problem is that a founder effect may partly explain the high prevalence of PM (and also FM) in some populations.

Updated literature review

Table 4 shows findings of studies about the frequency of PM in the general population. There are 14 studies which provided data for females and 16 studies for males. Five studies did not report the results separately for females and males, and the number of X chromosomes was used as denominator for calculating the prevalence.

Subjects in these studies were women who participated in prenatal or preconceptual screening programmes, ordinary outpatients, blood or egg donors or those receiving DNA tests unrelated to learning difficulty. The cut-off value for PM was 54 or 55 in most studies. By pooling data from these studies, the proportion of PM was 0.67% (1 in 149) in females and 0.16% (1 in 643) in males. Pooling results from the five studies of X chromosomes yielded a rate of 0.47% (1 in 212 X chromosomes).

The proportion of PM in the general population was higher in this updated review than that reported previously. The founder effect and biased selection of participants in screening programmes may exist. If there is bias in the selection of relatives of identified carriers in screening programmes, the proportion of people with positive results will increase as screening programmes proceed. The earlier results of the Israeli study by Toledano-Alhadef and co-workers[17] were also reported in Drasinover and co-workers.[15] A comparison of the earlier and later results is presented in *Table 5*, which shows that the prevalence of PM (repeats size 51–200) was statistically significantly higher in the later stage of the programme (1.8% versus 1.3%). The limited data indicate the existence of the selection bias suspected.

Risk of PM in families with FXS

The risk of PM in members of families of FXS may be estimated according to the mechanism of PM and FM transmissions from generation to generation. Following an example provided by Pembrey and co-workers,[2] *Figure 1* presents the

TABLE 5 *Selection bias in estimating the prevalence of PM in the general population – a comparison of earlier and later results from an Israeli study*

	No. of PM	Total women screened	% (exact 95% CI)
Earlier	138	10587	1.30 (1.10 to 1.54)
Later	69	3747	1.84 (1.44 to 2.32)
All	207	14334	1.44 (1.26 to 1.65)

Data are from Drasinover and co-workers[88] and Toledano-Alhadef and co-workers.[17]

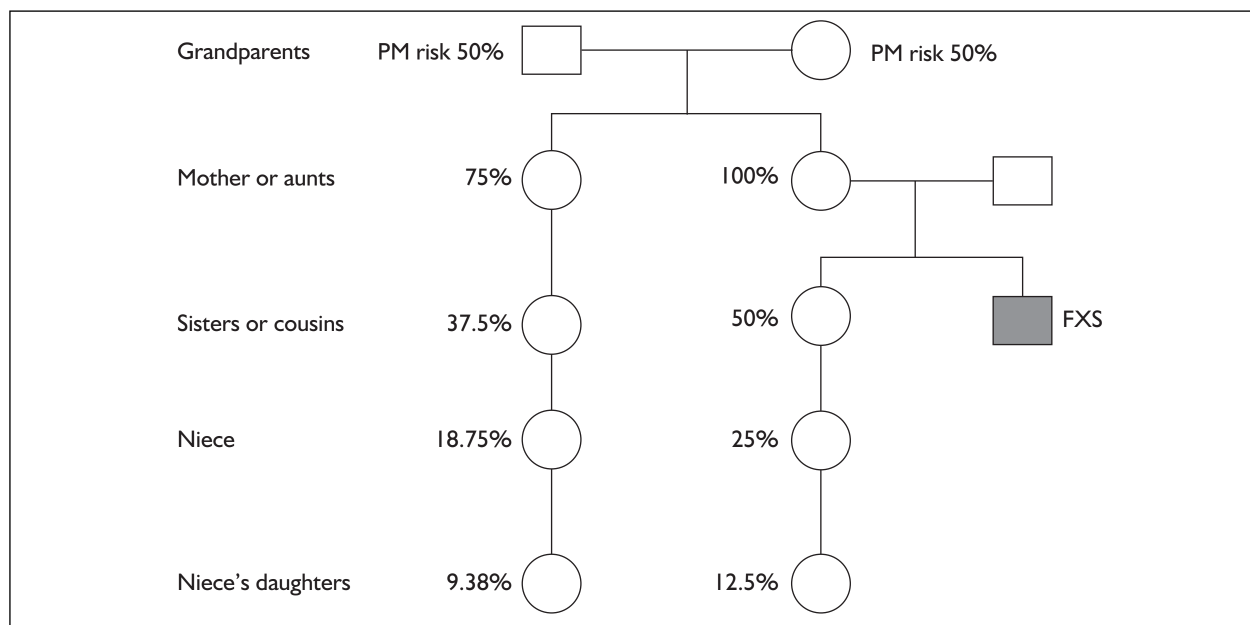

FIGURE 1 *Risk of PM among female relatives of FXS patients*

estimated risk of being carriers among female relatives of FXS patients.

Distribution of PM CGG repeats size

The distribution of PM repeats size in 461 females from the general population is summarised in *Table 6*. The frequency of PM declines greatly when the CGG repeats size increases; 37% of all PMs are smaller than 55 repeats, which means that the number of PMs will be reduced by 37% if the cut-off value for PM changed from 52 to 55. It will be reduced by about 63% if the cut-off value for PM increased from 52 to 60.

TABLE 6 *Distribution of PM in general female population*

PM category	No. of PMs	% (>52)	% (>55)	% (>60)
52–54	170	36.9		
55–59	120	26.0	41.2	
60–64	63	13.7	21.6	36.8
65–69	42	9.1	14.4	24.6
70–74	27	5.9	9.3	15.8
75–79	12	2.6	4.1	7.0
80–84	10	2.2	3.4	5.8
85–89	7	1.5	2.4	4.1
90–94	7	1.5	2.4	4.1
>95	3	0.007	1.0	1.8
All	461	100.0	100.0	100.0

Note: % (>52), % (>55) and % (>60) are the distribution of PM using different cut-off values of CGG repeats size.

The distribution of PM sizes in the general population could be compared with that in FXS families (*Figure 2*). The PM repeats size in the general population was much smaller than that in FXS families, which may partially explain the fact that the risk of expansion from PM to FM is much smaller in the general population than in affected families (see the next chapter for details).

Summary

The overall prevalence of FXS was on average 2.3%, ranging from 0.3 to 16% in males with learning difficulty. The prevalence of FXS was 3.5% in males with unspecified learning difficulty and 1.7% in males with any learning difficulty. For females with learning difficulty, the prevalence of FXS was on average 0.7%, ranging from 0 to 8%, according to 8677 patients from 22 studies. No difference was observed between unspecified learning difficulty and any learning difficulty in females.

Preselection according to family history and clinical features can increase the proportion of detected FXS cases among people with learning difficulty who were DNA tested.

Using the indirect method and data from eight studies, the prevalence of FXS in the general population was estimated to be 2.3/10,000 (or 1 in

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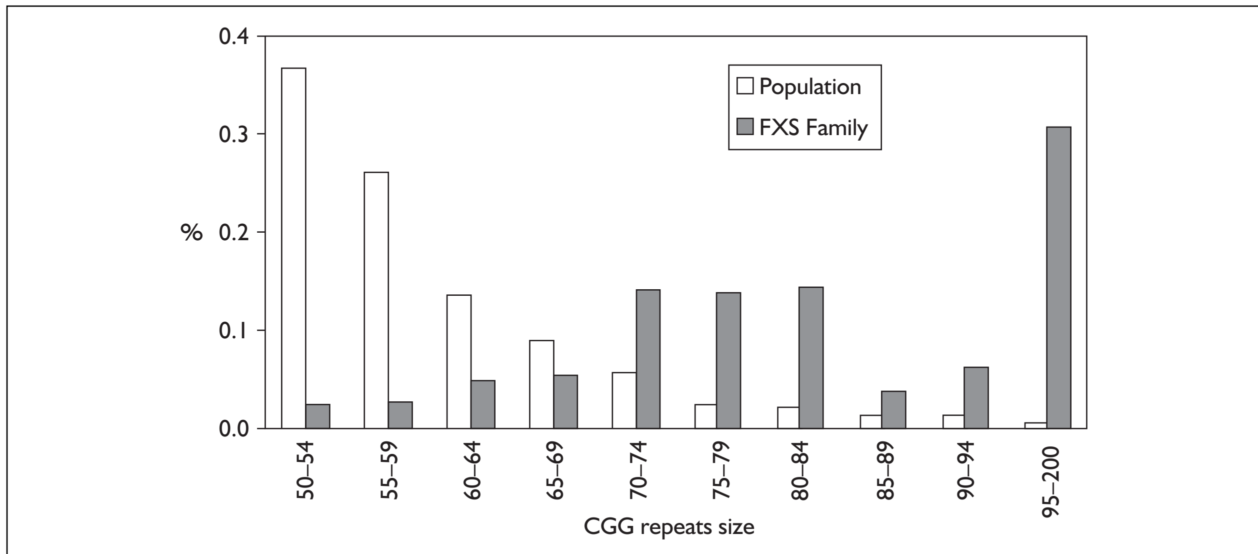

***FIGURE 2** Distribution of PM repeats sizes in the general population and in FXS families. Data for the PM in general population from Murray and co-workers,[1] Ryynanen and co-workers,[70] Toledano-Alhadef and co-workers,[17] Geva and co-workers,[67] and Pesso and co-workers.[68] Data for FXS families from Fisch and co-workers,[89] Moutou and co-workers,[90] Ashley-Koch and co-workers,[91] Nolin and co-workers,[92] Murray and co-workers,[1] and Milewski and co-workers.[93]*

4425). The use of the indirect method may underestimate the prevalence of FXS in the general population, because of the possible incompleteness of detection of FXS among people with learning difficulty.

Pooling data from identified studies (16 for males and 14 for females), the prevalence of PM was 0.16% (1 in 643) among the general male population and 0.67% (1 in 149) among the general female population. These may have overestimated the prevalence of PM in the general population because of the possible founder effect and biased selection in screening programmes.

The estimated prevalence of PM was sensitive to the cut-off value of CGG repeat size used to define the PM. The PM repeat sizes in the general population were generally much smaller than that in the affected families.

Chapter 5

Risk of expansion from PM to FM

Findings in the previous HTA reports

Children may inherit FM alleles by the direct transmission of mothers' FM or by the expansion of mothers' PM during transmission. There are some factors that are associated with the instability of transmitted PM alleles:

- Sex of PM carriers is the most important factor. PMs never expand to FM when transmitted from fathers to daughters.
- The risk of expansion from PM to FM is associated with the CGG repeat size of PM in mothers. The greater the size of CGG repeats, the greater is the risk of expansion to FM.
- The sequence of the CGG triplet repeats and the flanking haplotype may also be risk factors. The loss of AGG may be associated with the instability of CGG repeat sizes.[94]

The risk of expansion from PM to FM in maternal transmission may be different between FXS families and the general population. First, this is because the PM repeat sizes were greater in FXS families than that in the general population (*Figure 2*). In addition, there may be other unknown factors that cause the PM transmissions to be more unstable in FXS families.

It has been generally recognised that there may be 'ascertainment bias' in studies of FXS families, owing to the unrepresentative sample in which the offspring with FM may be more likely to be included. The commonly used method for the correction of ascertainment bias is to exclude one offspring with FM from each family, although this may lead to an over-correction. A related bias is also possible because female PM carriers with no FXS child may be less likely to be included in family studies.[1]

In the 1997 HTA report, Murray and co-workers summarised data from published studies and estimated that the risk of expansion from PM to FM in maternal transmission was on average 60% (269/447) in affected families, after correcting for ascertainment bias.[1] They also carried out a logistic regression analysis about the expansion risk and PM repeat size using data from affected families. A clear association between the risk of expansion and the size of CGG repeat size was observed. Using the data in the HTA report by Murray and co-workers, the estimated regression model was

$$\text{Risk} = \frac{1}{1 + e^{8.238 - 0.1075 \times \text{PM size}}}$$

In 1997, there were no studies that reported the risk of expansion from PM to FM in the general population. Murray and co-workers used two indirect methods to estimate such risk: (1) from PM size distribution in the general population and (2) by working backwards. Applying the estimated regression model to the PM size frequency distribution in the general population, they estimated that the risk of expansion from PM to FM was on average from 27 to 37%, which was still too high to be consistent with the PM and FM prevalence in the population.

By working backwards, Murray and co-workers estimated that the expansion risk was about 10% in the general population. Several assumptions were made in this approach. It was assumed that the frequency of FM in the population was 1 per 4000; the frequency of female PM carriers was 1 per 273; the reproductive fitness of FM carrier women was 50%; and the segregation ratio was the same for mutated and normal alleles.[1]

In the 2001 HTA report, Pembrey and co-workers[2] discussed the results from the 1997 HTA report and provided some sensitivity analyses using different assumptions. They also found some empirical data from recently published studies by Drasinover and co-workers[15] and by Ryynanen and co-workers.[70] It was concluded that identified empirical data on PM expansion risk in the general population fell in with the range estimated by Murray and co-workers.[1]

Updated literature review

We identified 14 studies that reported empirical data about risk of expansion from PM to FM in maternal transmissions (Appendix 6). Four studies reported data about the general population,[17,67,68,70] and 10 studies were about affected families.[89–92,94–99]

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PM expansion risk in affected families

The identified studies of affected families were carried out in North America, Finland, The Netherlands, France and the UK. One difficulty in extracting data from identified studies is that the same data may have been used in different publications, although it was not always clear whether or what part of the data have been previously reported. For example, data reported in Fu and co-workers[95] were also included in Fisch and co-workers.[89] By checking authors' names and reported methods, two studies[95,98] were excluded because of duplicate publication. A study by Kallinen and co-workers[97] was also excluded because the ascertainment bias may not be corrected. We excluded part of the data (PM repeat sizes <90) from Nolin and co-workers[92] because the same data were used in Ashley-Koch and co-workers.[91]

A total of 1111 maternal PM transmissions were included in the analysis (fourth column in *Table* 7). It was found that 704 of the 1111 maternal PM transmissions expanded to FM, with a rate of 63.4% (95% CI: 60.5 to 66.2%). This was similar to the 61.2% (95% CI: 55.6 to 64.7%) based on 447 maternal PM transmissions in the review by Murray and co-workers,[1] and to the 66.8% (95% CI: 60.0 to 73.6%) based on 184 cases in Fisch and co-workers.[89]

We carried out a logistic regression analysis of the 1111 maternal PM transmissions using the midpoint values for PM size categories and obtained the following model:

$$\text{Risk} = \frac{1}{1 + e^{8.6434 - 0.1114 \times \text{PM size}}}$$

The risk of expansion from PM to FM is clearly associated with the size of PM CGG repeats (see the fourth and fifth columns in *Table* 7). According to this model, the expansion risk is 8, 20, 43, 70, 87 and >95% for CGG repeats size 50–59, 60–69, 70–79, 80–89, 90–99 and >100, respectively.

It may be interesting to compare this model with two previous models by Murray and co-workers[1] and Fisch and co-workers.[89] *Figure 3* indicates that the results of logistic regression analyses using data summarised in Fisch and co-workers, in Murray and co-workers and in this updated review are almost identical.

TABLE 7 *Risk of expansion from PM to FM in the general population and in FXS families*

PM repeat size	Population data (*N*)	Population expected	FXS family data (*N*)	FXS family expected
50–59	0.000 (109)	0.012	0.125 (48)	0.075
60–69	0.075 (40)	0.041	0.157 (153)	0.197
70–79	0.214 (14)	0.134	0.456 (287)	0.428
80–89	0.333 (6)	0.355	0.669 (181)	0.695
90–99+	0.714 (14)	0.663	0.905 (116)	0.874
100–109		0.875	0.958 (143)	0.955
110–119		0.962	0.982 (56)	0.985
120–129+		0.989	0.984 (127)	0.995
130–139		0.997		0.998
140–		0.999		0.999
Total	0.098 (18/183)		0.634 (704/1111)	

Studies used for risk of expansion in the general population: Geva and co-workers,[67] Toledano-Alhadef and co-workers,[17] Pesso and co-workers[68] and Ryynanen and co-workers.[70]
Studies used for estimating risk of expansion in FXS families: Fisch and co-workers,[89] Ashley-Koch and co-workers,[91] Nolin and co-workers,[92] Moutou and co-workers,[90] Murray and co-workers,[94] Heitz and co-workers[96] and Vaisanen and co-workers.[99]
For general population data, the group of repeat size 90–99 also included all PMs >99. For the FXS family data, the group of repeat size 120–129 included all PMs >129.
Expected risk for the general population was estimated by using

$$\text{logit}(p) = -11.41296 + 0.1272674 \times \text{PM size}$$
(SE 1.75486 and 0.0219348)

Expected risk for affected families was estimated by using

$$\text{logit}(p) = -8.643433 + 0.1113986 \times \text{PM size}$$
(SE 0.5825642 and 0.0073177)

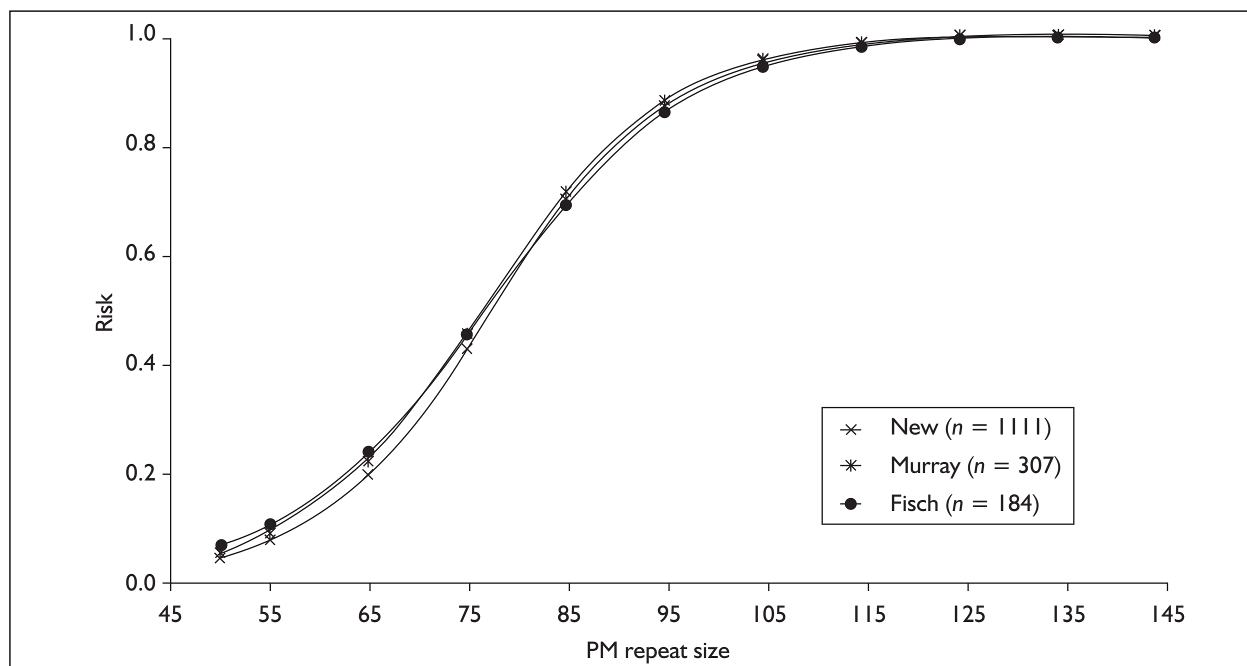

FIGURE 3 *Risk of expansion from PM to FM in FXS-affected families – regression analysis results from different reviews*

General population studies

We also identified four recently published studies that reported data about risk of PM expansion to FM in the general population (Appendix 6).[17,67,68,70]

Of the four studies, Ryynanen and co-workers[70] reported four maternal PM transmissions from a programme of prenatal screening for FXS in Finland. Two of the four PM transmissions expanded to FM in foetuses. The number of cases reported in this study was too small to be very useful.

The important data are from three studies about preconceptual or prenatal screening programmes in Israel.[17,67,68] They have seemingly adopted a similar screening protocol: preconceptual or pregnant women were tested for FXS mutation on a self-payment basis. Women had to bear the cost of the test, although the prenatal diagnosis (when necessary) was publicly financed. The women with a family history of FXS were excluded. Self-referred and highly motivated women in these studies may not be truly representative of the general population. Compared with other studies of the general populations, these three studies reported a higher prevalence of PM (see Chapter 4).

By pooling data from these four population studies (*Table 7*), there was a total of 183 maternal PM transmissions and 18 expanded to FM. The risk of expansion to FM was therefore 9.8% (95% CI: 5.5 to 14.2%). This rate is much lower than 63.4% in FXS families, and almost identical with 10% estimated by working backwards in Murray and co-workers.[1]

Again, the risk of expansion from PM to FM is clearly related to the size of PM CGG repeats. No PM has expanded to FM when CGG repeats size was smaller than 60 in the general population. The rate was about 8, 21, 33 and 71% for PM size 60–69, 70–79, 80–89 and >90, respectively. A logistic regression analysis using data from the general population was also conducted (*Table 7* and *Figure 4*).

General population versus FXS families

The updated review confirms that the risk of expansion from PM to FM is strongly associated with the size of CGG repeats in both FXS families and in the general population. The expansion risk is much greater in FXS families than that in the general population (*Table 7* and *Figure 4*). This is attributable to the fact that CGG repeats size of PMs tended to be smaller in the general population than that in FXS families (see Chapter 4). In addition, given the same PM CGG repeats size, PMs in the general population were still associated with a significantly lower risk of expansion to FM. For example, given a repeats size of 85, the expected risk of expansion to FM is about 36% in the general population and 70% in affected families (*Table 7* and *Figure 4*).

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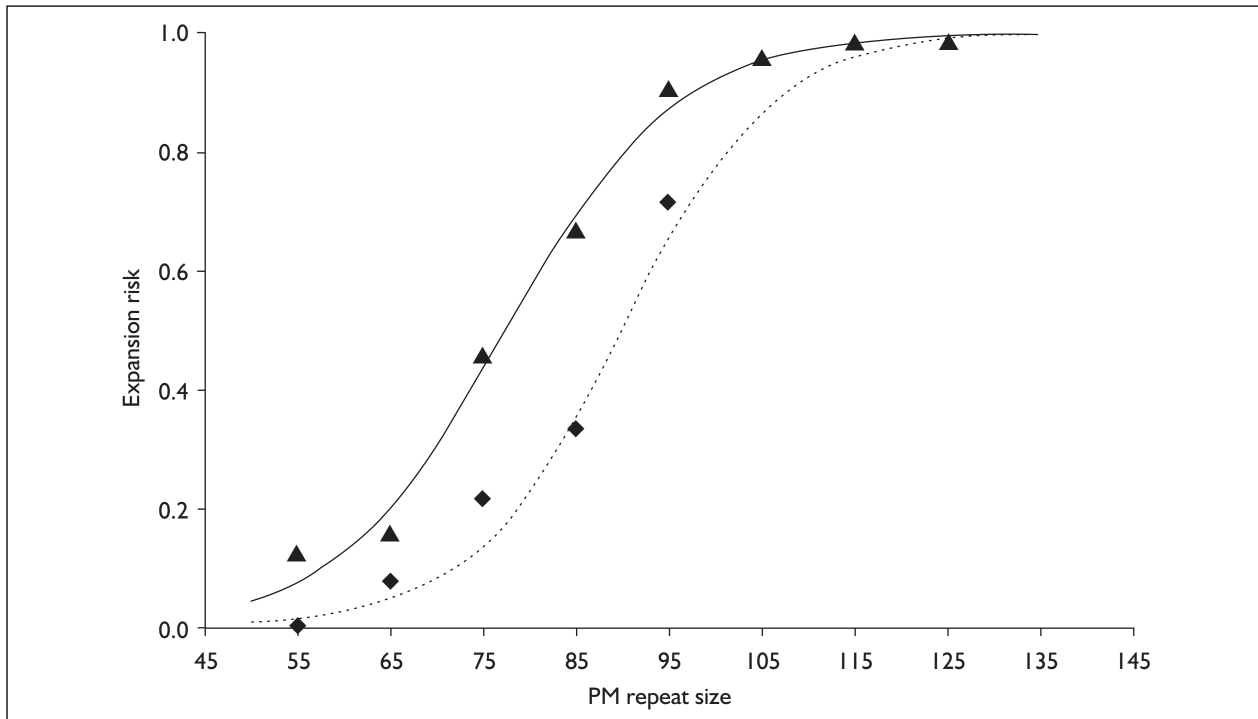

FIGURE 4 *Risk of expansion from PM to FM in the general population (diamond points and dashed line) and in FXS families (triangles and solid line)*

Summary

- The risk of expansion from PM to FM in maternal transmission is significantly related to the size of CGG repeats. The greater the size of CGG repeats, the greater is the risk of expansion.
- The risk of expansion from PM to FM in the general population is significantly lower than that in FXS families.
- Based on data of 1111 maternal PM transmissions, the pooled rate of expansion from PM to FM was 63.4% (95% CI: 60.5 to 66.2%) in PM carriers from FXS families.
- According to data of 183 maternal PM transmissions, the pooled rate of expansion from PM to FM was 9.8% (95% CI: 5.5 to 14.2%) in PM carriers identified from the general population.

Chapter 6

Findings of practical screening programmes

Several studies have reported findings from practical programmes of screening for FXS (all the identified studies are summarised in Appendix 7). These screening programmes were carried out in different countries, including preconceptual or prenatal screening in Israel and cascade screening in Australia. They provided empirical data about the feasibility, acceptance and consequences of screening for FXS.

Preconceptual or prenatal screening in Israel

Three studies reported results of preconceptual or prenatal screening for FXS in Israel.[17,67,68] The methods used in the three studies were similar. Preconceptual or pregnant women were tested for FXS from 1992 to 2000 in three centres. Women had to pay for the test, although the subsequent prenatal diagnosis when necessary was publicly financed. Women with a family history of X-linked learning difficulty were excluded (or separated from those without a family history in one study).

The total number of women tested was 14,334 in the study by Toledano-Alhadef and co-workers,[17] 9660 in the study by Geva and co-workers,[67] and 9459 in the study by Pesso and co-workers.[68] The prevalence of PM (>50 repeats) detected was 1/69, 1/114 and 1/73, respectively.[17,67,68] The reported prevalence of FM was 1/4778 by Toledano-Alhadef and co-workers[17] and 1/8400 by Pesso and co-workers.[68]

Compared with other studies, the prevalence of PM was high in these studies, possibly owing to the selection of high-risk women (this issue has been discussed in Chapter 4). Self-referred women may not be representative of the population. The prevalence of PM and FM may be overestimated, because relatives of detected carriers may be more likely to ask for the test. However, this selection bias may improve the effectiveness of a screening programme in practice.

It is also important to note that the estimated prevalence of abnormal alleles was highly sensitive to the cut-off value for the definition of PM. For example, in the study by Pesso and co-workers,[68] the prevalence of PM was 1/68 when the cut-off value for PM was 51 repeats. The prevalence of PM will decrease dramatically when the cut-off value for PM increases. It became 1/145 when the cut-off value for PM increased to 55 repeats and 1/383 when the cut-off value was 60 repeats.[68]

A high proportion of pregnant carriers underwent prenatal diagnosis procedures. The rate of acceptance in pregnant carriers was 89–92%. All foetuses with FM were terminated in two studies[17,68] (the study by Geva and co-workers[67] did not report termination). The probability of expansion from PM to FM in maternal transmission was 4.5–15.2%. Geva and co-workers[67] compared their results with those of previous studies, and concluded that "the likelihood of fragile X premutation expansion to full mutation is significantly lower in individuals ascertained by general prenatal carrier testing than in those from known fragile X families".

Screening practices in Finland

Prenatal screening

From 1995 to 1996, at the Kuopio City Health Centre in Finland, DNA testing for FXS was offered, free of charge and on a strictly voluntary basis, to pregnant women who were seeking prenatal care and being registered between the sixth and tenth weeks of pregnancy.[70] The study included women without a family history of FXS. At the first visit, all pregnant women received a brochure describing the syndrome and counselling from specially trained health care providers (mostly midwives).

The acceptance rate was 85% (1477/1738) (note that this is the acceptance rate for prenatal carrier testing; Israeli studies reported only the acceptance rate for prenatal diagnosis in pregnant carriers, since women were self-referred). Of the 1477 women tested, 1416 had a normal *FMR1* gene, 43 had 40–50 repeats, 12 had 50–60 repeats, and six carriers (>60 repeats) were detected. Invasive prenatal diagnosis was performed in six of the 43 women with 40–50 repeats, in all women with 50–60 repeats ($n = 12$) and PM carriers ($n = 6$). Foetal *FMR1* was normal

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in all of the six women with 40–50 repeats. One PM foetus (>60 repeats) was diagnosed in the 12 women with 50–60 repeats. In the six carriers, prenatal diagnosis found one foetal PM, one foetal FM and one foetal mosaicism. No affected foetuses were terminated in this study.[100]

The authors concluded that "antenatal screening provides an effective way of identifying carriers and incorporating prenatal testing into this process". According to a questionnaire survey, most carriers (76%) felt very anxious after receiving the test results. Women whose foetuses were confirmed normal by prenatal diagnosis considered the test to have had an overall positive influence on their pregnancy. It was estimated that the total cost of detecting one foetal FM was £34,000.

Cascade screening

Ryynanen and co-workers[101] identified 59 index cases of FXS in a population of 900,000 from 1991 to 1993. After contacting the parents, guardians or closest family members, 1071 relatives were identified to have an increased risk (⩾25%) of FXS. Of the 1071 relatives (48%), 515 accepted the carrier screening. The carrier was defined as an unaffected female with PM or FM or an unaffected male with PM. The number of female relatives tested per index case was on average five, and the number of male relatives per index case was on average four.

In 288 female relatives, the cascade testing detected 133 PMs and 46 FMs (1/2.2 and 1/6, respectively). In 219 male relatives, it detected 30 PMs and 20 FMs (1/7 and 1/11, respectively). All the pregnant female carriers (n = 21) underwent prenatal diagnosis (CVS) and three foetuses with PM and nine foetuses with FM were detected. All pregnancies with FM were terminated.

The offer of carrier screening was accepted by 49.4% of relatives of the index cases. About 8% of relatives were not certain about carrier screening but later accepted. Only 4% of relatives expressed an absolutely negative attitude. About 39% of the remaining relatives expressed an interest but dropped out later.

Screening women undergoing invasive prenatal diagnosis

Kallinen and co-workers[102] reported results of screening for FXS, aspartylglycosaminuria and infantile neuronal ceroid lipofuscinosis in women undergoing invasive prenatal diagnosis at the University Hospital of Kuopio in Finland in 1997–8. The indications for invasive prenatal diagnosis were advanced age, family history, maternal serum screening, ultrasound finding or other reasons (but not for screening for FXS). About 92% (220/239) of the eligible women accepted the gene tests for FXS. The programme detected one PM carrier (62 CGG repeats), seven aspartylglycosaminuria and two infantile neuronal ceroid lipofuscinosis. The authors concluded that carrier screening for single gene disorders was feasible and well accepted among pregnant women undergoing invasive prenatal testing.

Case finding and cascade screening in Australia

In 1986, a programme of case finding and cascade screening for FXS was established in New South Wales, Australia.[33,103,104] By 1990, the programme had screened 14,225 people attending adult and child institutions for learning difficulty, and offered FXS testing to a total of 8172 patients. Consent for physical examination and blood testing was given by 79% (6490/8172) of parents or guardians. Chromosome tests were performed in 3862 of the 6490 consented individuals (not all consented patients due to changes in the criteria for blood testing). The programme identified 253 probands (70% of them were newly diagnosed). In the extended families, 818 female relatives at 25–50% risk of being carriers were interviewed and counselled.

Turner and co-workers[33] interviewed 90 people from FXS families who received genetic counselling. It was found that "the single most important factor in patient satisfaction with the information received about fragile X was their recall of the amount of time spent with the genetic counsellor" (from 20 minutes to 4 hours).

By 1996, a total of 245 index cases or probands from 225 families were identified.[104] Up to first degree of relatives were tested in 54 families and up to third degree in 91 families, and extensive cascade testing in 44 families. The other 36 families had minimal testing (we were not able to find the definition of 'minimal testing'). It could be estimated that the number of female relatives tested per proband was 5.6 (1363/245). Diagnosis and counselling reduced the birth rate in FXS families by 20%, and 78% of pregnant relatives (presumably pregnant relatives with PM or FM) received prenatal diagnosis. All male foetal FMs and 60% of female foetal FMs were terminated.[103] It was reported that the prevalence of FXS was reduced from 2.5 per 10,000 to about 1 per

10,000 newborn males in known relatives of probands. (The method and definition in this calculation are not clear, because the rate of 2.5/10,000 is presumably for the general population.) Reproductive confidence in members of the extended families was restored.

Cascade screening in The Netherlands

Van Rijn and co-workers[105] newly identified 19 FXS families between 1991 and 1995 at a Department of Clinical Genetics. They informed 124 relatives up to fourth degree about their risk of being a carrier of FXS, and eventually tested 94 relatives. The overall rate of acceptance was 76% (94/124), with the highest participation among first-degree relatives (90%). The average number of relatives tested per family was five (or 3.7 for female relatives only).

Among 70 female relatives tested, they found 26 (37%) normal *FMR1* genes, 33 (47%) PMs and 11 (16%) FMs. On average, only one new FXS patient and two additional carriers per family were identified by this cascade screening. The authors suggested that the low yield may be due to the small number of relatives informed and tested per family. Information about the heredity of FXS was disseminated by family members to only one-third of eligible relatives.

Screening pregnant women in the USA

At a genetics and IVF centre

From 1993 to 1995, DNA testing for FXS was offered during routine prenatal or genetic counselling to all pregnant women at the Genetics and IVF Institute, Fairfax, USA.[16] Most women were referred for the indication of advanced maternal age. A brochure on FXS was sent to each woman and reviewed by a counsellor or physician during the counselling session. The rate of acceptance was 21% (688/3345) among pregnant women who were offered the test. PM was detected in three women (60, 64 and 67 repeats) among 474 women without a family history of learning difficulty. Interestingly, among 214 women who had a family history of learning difficulty, no PM or FM was detected. Three pregnant PM carriers underwent prenatal diagnosis and no foetal FM was diagnosed.

In the same study, 271 potential egg donors were also tested, and two women with 50–59 CGG repeats were found.

The overall frequency of PM (⩾60 repeats) was estimated to be 1/248 (3/745) in women without a family history of learning difficulty. The authors concluded that "screening for pregnant or preconceptual populations for fraX carrier status using DNA testing is accepted by many patients and is an important addition to current medical practice".

Testing of high-risk pregnant women

Brown and co-workers[106] reported results of testing for FXS in different groups. From 1992 to 1995, 344 pregnant women with a family history of learning difficulty of unknown cause were tested. The testing found two women with FM and four with PM (70, 59, 59 and 56 repeats). The frequency of FM and PM (>55 repeats) in these high-risk women was therefore 1/172 and 1/86, respectively. Three of the four PM carriers underwent prenatal diagnosis and no foetal FM was detected.

In another group of 40 pregnant women who were members of previously identified FXS families (but whose carrier status was unknown), 10 carriers were detected. Eight carriers underwent prenatal diagnosis and two foetal FMs were detected.[106]

Summary

- Three Israeli studies provided the most important empirical data about preconceptional or prenatal screening for FXS. An Australian study provided the most important empirical data about case finding and cascade screening for FXS. Studies conducted in Finland also provided important data. Limited data were provided by studies conducted in the USA.
- The empirical evidence suggested that preconceptual or prenatal screening, case finding and cascade screening are feasible and acceptable by affected families and the general population. The identified screening programmes were effective in detecting carriers, but a comparison of different strategies was not possible.
- The prevalence of PM reported by practical population programmes was higher than in other studies, possibly owing to positive selection of high-risk individuals. Biased selection of women at high risk may result in an overestimation of FXS mutations in the general population, but may improve the efficiency of screening programmes in practice.
- The included studies also provided data about risk of expansion from PM to FM in population.

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Chapter 7

A review of published models

This chapter reviews published models of population-based screening for FXS. All identified studies are summarised in Appendix 8. A model by Meadows and Sherman[107] was included in the table but it is not discussed further in this chapter, because the prevalence of FM was based on the cytogenetic test.

Antenatal screening model by Murray and co-workers

Murray and co-workers[1] presented a simple model of allele dynamics in a hypothetical population of one million couples (*Figure 5*). They estimated that the prevalence of PM was 1/273 in females and 1/800 in males. The frequency of FM was 1/4000. By working backwards, the risk of expansion from PM to FM was estimated to be 10% in the general population. They also estimated the unit costs for different procedures in prenatal screening, including information provision (£2), DNA testing (£30), genetic counselling (£25) and prenatal diagnosis (£275).

Murray and co-workers[1] suggested that the effectiveness of a screening programme should be measured by "the extent to which it reduces the birth prevalence of the disorder or improves prognosis". Positive predictive value was the principal outcome in this model. A positive result was defined as the detection of PM or FM. "If the woman has a pregnancy affected with fragile X syndrome it is a true positive result; otherwise, it is a false positive." That is, true positive results include all affected foetuses (whether or not birth is avoided) with a positive test result (i.e. detected mothers with PM or FM).

This model estimated that there were 184 true positives (women with FXS children) and 3601 false positives (women with PM or FM but whose children were born without FXS) by antenatal screening of one million couples. This corresponded to a positive predictive value of 1/20 (184/3785) and a false-positive rate of 0.4% (3601/999,816). Compared with a 1/50 positive predictive value and a 5% false-positive rate by antenatal screening for Down's syndrome,[108] the antenatal screening for FXS may be more effective.

Assuming a 100% acceptance and termination of affected pregnancies and that each couple has two pregnancies, the cost of preventing an affected birth was on average £93,000. This ratio is not markedly related to the uptake rate (assuming that a reduction in uptake will result in a reduction in costs), but will increase by 20% if only half of the affected female foetuses are terminated. Murray and co-workers concluded that "unless there are future technical developments which obviate the need for Southern blotting in a third of pregnancies, screening for fragile X syndrome will be more expensive than other antenatal screening tests".[1] For instance, maternal serum screening for Down's syndrome costs about £30,000 per affected pregnancy detected.

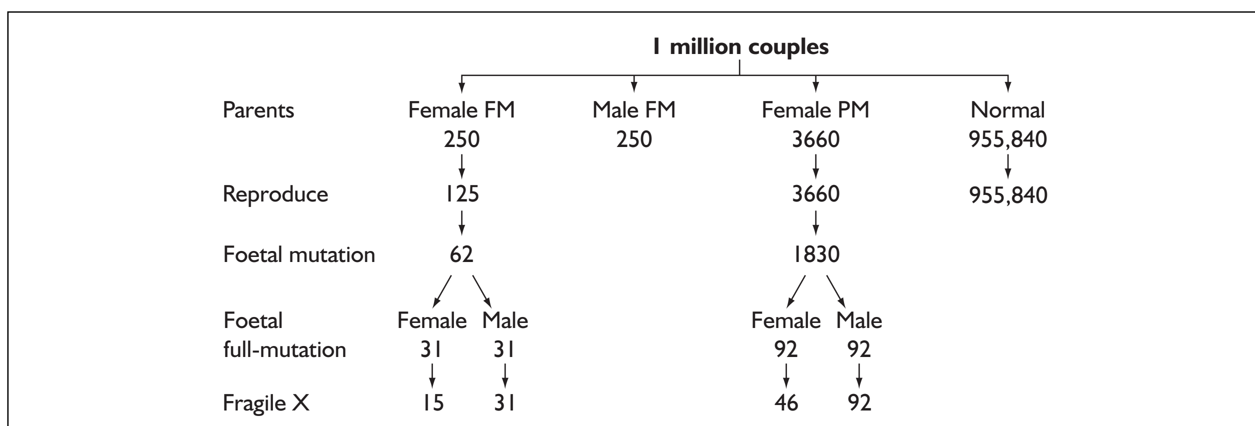

FIGURE 5 *A simple population model of allele dynamics. Source: 1997 HTA report by Murray and co-workers.[1]*

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Murray and co-workers' model does not allow a comparison between different screening strategies. The definition of true positive in this model seems sensible but confusing, because the concepts of positive predictive value and true positive have been used mainly to assess the accuracy of a diagnostic test. For the effectiveness of a screening programme, the accuracy of the test and the efficacy of the following interventions are similarly important. It may be better to restrict the use of true positive and predictive value to the accuracy of the diagnostic test (i.e. identification of carriers of PM and FM). It may be more appropriate to estimate the effectiveness of the programme by measuring (1) the proportion of identified carriers in total carriers (PM and FM), (2) the proportion of normal women confirmed, (3) the number of affected children prevented and (4) side-effects related to the programme.

A descriptive framework by Pembrey and co-workers

A descriptive framework of screening for FXS was provided in the 2001 HTA report by Pembrey and co-workers.[2] Consequences and costs of different screening strategies were discussed. Consequences of screening programmes included social, psychological, organisational and changes in reproductive behaviour and prevalence of FXS. They listed resources and costs required for each programme in terms of staffing, DNA testing, and prenatal diagnosis. The main conclusions were as follows:

- Current practice will result in only a slow rise in the proportion of FXS families identified.
- A 5-year programme of systematic case finding among adults with learning disabilities has the potential to substantially increase FXS cases known to the genetics services.
- A retrospective programme of systematic case finding in children with learning disabilities would produce a low yield.
- Screening newborn males on the basis of the Guthrie card is unlikely to be feasible at present.
- Prenatal screening is likely to pose major difficulties by generating results that are uninterpretable for those with intermediate size repeats, and in the uncertainty associated with the risk in women with 55–65 CGG repeats.
- There is a possible case for offering screening for PM to women with premature ovarian failure (POF).

The framework is very comprehensive but narrative, although some quantitative data have been provided. A 5-year programme of cascade screening was recommended. It is difficult to compare consequences and costs of different strategies, owing to a lack of quantitative assessment.

A model of prenatal, preconceptual and school screening in The Netherlands

Wildhagen and co-workers[8] provided a decision analytic model to compare prenatal, preconceptual and school screening for FXS over a 1-year period in a hypothetical population of 100,000 couples in The Netherlands (the analyses were actually focused on the comparison of prenatal and preconceptual screening). The structure of the model was not explicitly presented in the paper.

Assumptions used in the model were based on literature reviews and expert opinions. Prevalence of FM was estimated to be 1 in 4000. It was assumed that 59% of females with FM had learning difficulty (rather than 50% as in Murray and co-workers[1]). The prevalence of PM was estimated to be 1/435 in females and 1/871 in males. The PM was further divided into five categories: 55–59, 60–69, 70–79, 80–89 and 90–200 CGG repeats. The probability of expansion from PM to FM in maternal transmission was based on Fisch's logistic model.[89] The coverage was assumed differently for different strategies and for different patients. For prenatal screening, the coverage was assumed to be 75% for population without FXS, 37.5% for FXS patients and 25% for people who were not screened for their first child. The corresponding coverage was 50, 25 and 25% for preconceptual screening.

The costs of screening programmes included costs of information dissemination, testing, organisation and aftercare. The lifetime cost for an FXS patient was estimated to be US$957,734 for males and $533,673 for females. The measured outcomes included avoided FXS children, carriers detected, side-effects and savings due to fewer affected cases.

The findings of this model suggested that all screening strategies have a favourable cost-saving balance (saving US$14 million by prenatal screening, US$9 million by preconceptual screening and US$2 million by school screening). The number of carriers (PM or FM) detected was 200 (78%) by prenatal screening and 149 (58%) by preconceptual screening. The number of avoided children born with FXS was greater by prenatal screening (28/68) than that by preconceptual screening (19/61). The cost per carrier detected

was about US$45,000. Sensitivity analyses found that the prevalence of PM has a large impact on the cost-effectiveness of population-based screening for FXS.

Assumptions were clearly presented in a table, but the structure of the model was not provided in the article. The risk of expansion from PM to FM in the general population was overestimated because the model used findings from studies of affected families. Although the evaluated screening programme was for a 1-year period, the long-term consequences were incorporated by assuming a second pregnancy per woman and lifetime savings due to prevented FXS children.

Tejada and Duran[109] commented on this model. They suggested that possible screening for FXS was much more complicated than was first thought, and theoretical assumptions used in the model were not applicable in clinical practice. They also used their own data from case series (in Spain) to indicate that prenatal screening should not be carried out, for reasons of a high prevalence of PM in their sample, difficulties in the interpretation of 'grey zone' PMs (>45 repeats) and difficulty for women to assimilate information on FXS.

A simulation modelling of cascade testing in The Netherlands

Wildhagen and co-workers[110] developed a micro-simulation model, simulating pedigrees of five generations to obtain a population where some nuclear families were connected with others and some were not. Then the simulation data were used to estimate the efficacy of cascade testing for FXS. The assumptions about the prevalence and expansion risk from PM to FM were similar to that in a model of population screening programmes.[8]

The first generation contained 100,000 couples and each partner of these couples was assigned a carrier status. The number of children of reproductive couples was assumed to be four for the first- and second-generation couples, three for the third-generation couples and two for the fourth-generation couples. Children's carrier status was randomly determined according to their parents' carrier status and assumed transition probabilities. In the model, the fourth generation was considered to be the current generation and the fifth generation was the future generation to estimate how many affected children could be prevented by cascade screening.

Simulation results suggested that there were 723 patients with FXS in the current population. It has been claimed that the predicted prevalence of FXS in the fifth generation was similar to that assumed. However, it seems that the predicted prevalence became lower in the simulated fourth (1/6639) and fifth (1/6345) generations than the assumed initial value (1/5000). This may be due to assumed transition probabilities (from PM to FM) or the distribution of PM. Costs of the screening programme were not considered.

The model predicted that 18% of couples who will have an FXS child could be detected in the start-up phase of a cascade testing programme. With the stabilised cascade testing programme, it is 7% by testing first-degree relatives, 12% by testing third-degree relatives, or 15% by testing fifth-degree relatives. To detect 90% of all PM and FM carriers, at least eight consecutive generations need to be tested. It was concluded that cascade testing is not very effective in detecting carriers, because a large proportion of FXS children are born in families without index cases. However, cascade testing is more efficient, with a better number needed to test (130 to be tested for detecting one carrier) than population prenatal screening (5000 to be tested for detecting one carrier).[110]

Cost–benefit of preconceptual or prenatal testing in Israel

A decision analysis was conducted to compare costs and benefits of prenatal or preconceptual screening versus no screening for FXS in Israel.[17] The input assumptions were based on a literature review and findings of a study of 14,334 women. According to this study, the prevalence of PM (>54 repeats) was 1/113, the prevalence of FM was 1/2867 and the transition probability from PM to FM was 4.2%. Costs of the screening programme included costs of publicity, DNA testing, prenatal diagnosis, counselling and iatrogenic abortion. It has been estimated that the extra lifetime cost of a patient with FXS was US$680,000.

It was estimated that the net benefit from running the screening programme is about US$5,500,000 per year in Israel. The net benefit remains positive over a wide range of acceptance rates. The calculated cost of lifetime care for a patient with learning difficulty in Israel (US$680,000) is well above the cut-off point based on financial considerations. The authors concluded that, because of the high prevalence of PM and FM alleles in the general population, and because of

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the cost-effectiveness of the programme, preconceptual or prenatal screening for female carriers should be carried out on a wide scale.[17]

The major part of the economic evaluation is presented in the Appendix of the paper by Toledano-Alhadef and co-workers.[17] The high prevalence of PM and FM in this study may be partially due to the possibility that relatives of women with positive testing results were more likely to participate subsequently in this self-paid programme.

A model of cost–benefit of prenatal screening in the USA

A cost–benefit equation was developed based on the premise that the cost of the prenatal screening programme should be equal to or less than the cost of the current practice.[7] The following equation represents the cost–benefit of the programme in its full maturity, from a societal perspective:

$$C_{FX} = \frac{C_{test}A}{2} + \frac{C_{amnio}A}{250} + C_{FX}(1 - T_{AB})$$

where C_{FX} is the lifetime cost for an FXS patient, C_{test} is the cost per prenatal screening test, A is the number of women needed to be tested for one case of FXS, C_{amnio} is the cost for the amniocentesis package (including ultrasound, amniocentesis procedure, genetic counselling and amniotic fluid analysis) and T_{AB} is the proportion of abortion of detected FM foetuses (therapeutic abortion). The calculation was based on the assumption that there were 4 million births a year in the USA.

It was assumed that the prevalence of FXS was 1/4000, frequency of carriers was 1/250 and the acceptance rate was 50–80%. In the equation, testing costs were divided by two (fertility rate) because there is no need to repeat the screening test in subsequent pregnancies. The prenatal diagnosis (amniocentesis) was needed in A/250 pregnant women. The rate of procedure-related foetal loss was assumed to range from 1/100 to 1/250 and the rate of therapeutic abortion ranged from 50 to 100%. The additional lifetime cost per FXS child was assumed to be US$500,000 (1998).

It was found that a policy of routine prenatal carrier testing may be beneficial only if the cost per screening test is less than US$120 during the first year of the programme, or less than US$240 when the programme reaches its full maturity. Invasive procedures for prenatal diagnosis may result in about 46–115 foetal lives to be lost.

The model is simple and its assumptions are clearly presented. The effectiveness or efficacy of the programme cannot be evaluated.

Summary

- Murray and co-workers[1] quantitatively considered the effectiveness and costs of prenatal screening in the UK. According to the most optimistic scenario, the cost of preventing an affected birth was about £93,000.
- Pembrey and co-workers[2] provided a descriptive framework for different strategies, and recommended a 5-year programme of active case finding and cascade screening in the UK.
- Wildhagen and co-workers[8] developed a decision analytic model to compare prenatal, preconceptual and school screening for FXS in The Netherlands. They found that all strategies have a favourable cost-saving balance. Prenatal screening may prevent more FXS births than preconceptual screening. The estimated cost was US$45,000 per detected carrier.
- Wildhagen and co-workers[110] used a micro-simulation model to assess the cascade testing for FXS in The Netherlands. Cascade testing may be more efficient in terms of a better NNT (number needed to test for one detected carrier) than prenatal screening. However, it may not be very effective, because a large proportion of FXS children are born in families without index cases.
- Toledano-Alhadef and co-workers[17] carried out a cost–benefit analysis according to a literature review and results of a prenatal/preconceptual screening programme in Israel. The estimated net benefit from the programme was about US$5,500,000 per year in Israel.
- Vintzileos and co-workers[7] provided an equation to calculate the cost–benefit of prenatal screening for FXS in the USA. They concluded that a prenatal screening programme may become beneficial only if the cost per test could be further reduced.
- These models provided useful information about the efficacy and/or effectiveness of different strategies of screening for FXS. The major weaknesses of the existing models are that (1) the prenatal screening and cascade screening have not been directly compared and (2) the long-term impact of different strategies on the burden of the disease in the population has not been assessed.

Chapter 8

A new model for screening for FXS

The two major strategies of screening for FXS (prenatal screening and active cascade screening) have not been directly compared in trials or in the existing models. To compare these two strategies, a population cohort model was built (FXS Model), which provides a tool for estimating changes in the frequency of PM and FM in the population under different assumptions.

Figure 6 shows the basic structure of the FXS Model. The model is a deterministic simulation model, and was constructed using Microsoft Excel. There are three major components in the FXS Model: population cohort, cascade screening and prenatal screening. In this chapter, we describe the model's structure and estimate input parameters under the assumption of no interventions (theoretical scenario). In the next chapter, the model is used to compare three screening strategies: current practice (low level of cascade testing), active cascade screening and prenatal screening.

Population cohort model

The model is a population cohort model operating on an annual cycle. The population is divided by age into 1-year bands from age 0 to 84 years, with all persons of age 85 years or over combined into a single age group. Within each age group, the population is further divided into subgroups as shown in *Table 8*.

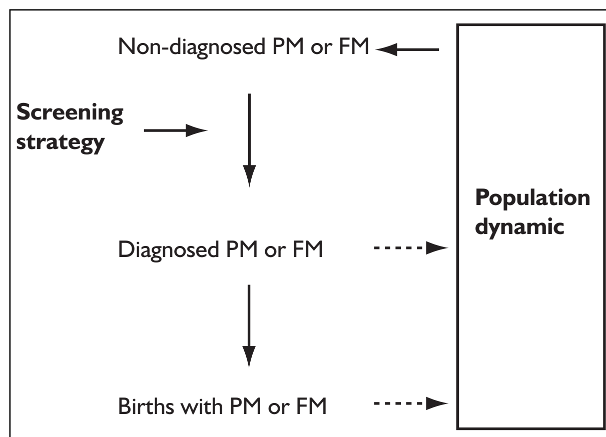

FIGURE 6 *Basic structure of the FXS model*

Initialisation

The model is initialised with an estimated population for England and Wales at mid-2000.[111] It is assumed that the initial proportions of PM and FM are independent of age and that the FXS carrier status of the entire population is untested.

Updating the model

Except for age 0, the population in each age, sex and mutation status 1 year later is found by applying the age- and sex-specific death rate to the previous year's population. It is assumed that the death rate is independent of mutation status. The numbers within the subgroups are adjusted according to the screening policy under consideration.

The main part of the model is the way in which the numbers of new births were calculated. New births are grouped first by the status of the parents as defined in *Table 8*. Possible combinations of mother

TABLE 8 *Population subgroups considered*

Sex	Subjects	Status
Female	Normal	Untested tested
	PM in the general population	Undiagnosed Diagnosed
	PM in FXS families	Undiagnosed Diagnosed
	FM without FXS	Undiagnosed Diagnosed
	FM with FXS	Undiagnosed Diagnosed: family members not screened Diagnosed: family members screened
Male	Normal	
	NTM in the general population	Undiagnosed Diagnosed
	NTM in FXS families	Undiagnosed Diagnosed
	FM	Undiagnosed Diagnosed: family members not screened Diagnosed: family members screened

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TABLE 9 *Mutation status of parents and their children*

Parents[a]	Children	
	Girls	**Boys**
Normal mother Normal father	Normal (100%)[b]	Normal (100%)
Normal mother NTM father	PM (100%)	Normal (100%)
PM mother Normal father	Normal (50%) PM[c] FM[c]	Normal (50%) PM[c] FM[c]
FM mother Normal father	Normal (50%) FM (50%)	Normal (50%) FM (50%)

[a] Births from PM or FM mother and NTM father are assumed to be negligible. It is assumed that FM males cannot be fathers.
[b] A normal *FMR1* gene may expand and become PM during its transmission. The rate of expansion from normal to PM should be very low, and will be estimated using the FXS Model in the simulation of a theoretical scenario.
[c] The proportion of children with PM or FM when parents are a combination of PM mother and normal father will depend on the risk of expansion from PM to FM.

and father are any category of mother with a normal father, or a normal mother with an NTM father (*Table 9*). Births from non-normal mothers and NTM fathers are assumed to be negligible in number and are not considered in the model. FM fathers are assumed to be impossible.[1] The expected number of births in each subgroup is based on the number of women in the relevant (5-year) age group and mutation status, adjusted for the mutation status of the father. This is then multiplied by a lifetime fertility figure of 1.8, adjusted for reduction in the number of births to diagnosed PM and FM mothers, and by a further factor reflecting the distribution of births by age of the mother. These births are then allocated to the population categories defined in *Table 8*, allowing for new mutations and expansion from PM to FM.

Diagnosis of PM and FM

Diagnosis of PM or FM in the model results from three possible causes: natural diagnosis of FXS, prenatal screening and cascade screening.

Natural diagnosis

First, there is behaviourally diagnosed FXS. This is assumed to occur during the first 10 years of life. *Figure 7* shows the assumed age distribution

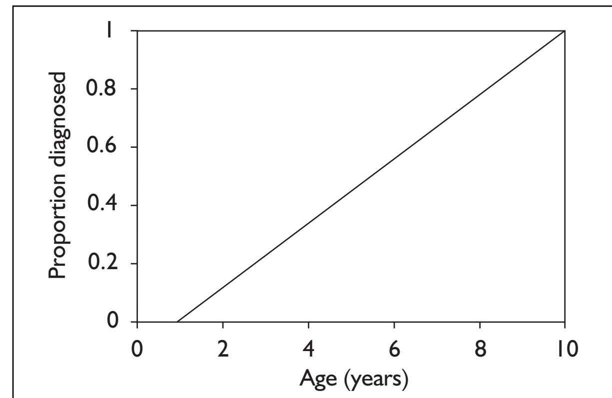

FIGURE 7 *Age distribution of natural diagnosis of FXS*

among those whose FXS is diagnosed in this way. Combining the distribution in *Figure 7* with the overall proportion of individuals with FXS who are behaviourally diagnosed gives the age-dependent probability that any individual with FXS will be diagnosed in the next year.

Prenatal screening

The second reason for diagnosis is through prenatal screening (*Figure 8*). When women with unknown status of FXS mutation become pregnant, depending on the uptake rate, all or a proportion of them can be tested by a prenatal screening programme. The mutation status of women tested will be known, and the model is then updated accordingly. The probability that a previously untested woman will be screened is found in a similar way to the calculation for the number of births attributed to such women. This proportion will be zero unless the prenatal screening option is selected in the model.

Cascade screening

Cascade screening provides the remaining reason for diagnosis (*Figure 9*). FXS patients may be diagnosed through behavioural diagnosis or active case finding. Depending on the uptake rate, a proportion of diagnosed FXS patients can be used as index cases to identify a group of female relatives with unknown status of FXS mutation. For each index case, an average number of female relatives with unknown carrier status to be tested is assumed. It is assumed that the female relatives tested are uniformly distributed between the ages of 0 and 44 years, and within each age group they are divided according to the assumed distribution of mutation status. Calculating the number of females to be tested in this way gives the proportion of females to be tested as a result of cascade screening. This proportion will be zero unless the cascade screening option is selected in the model.

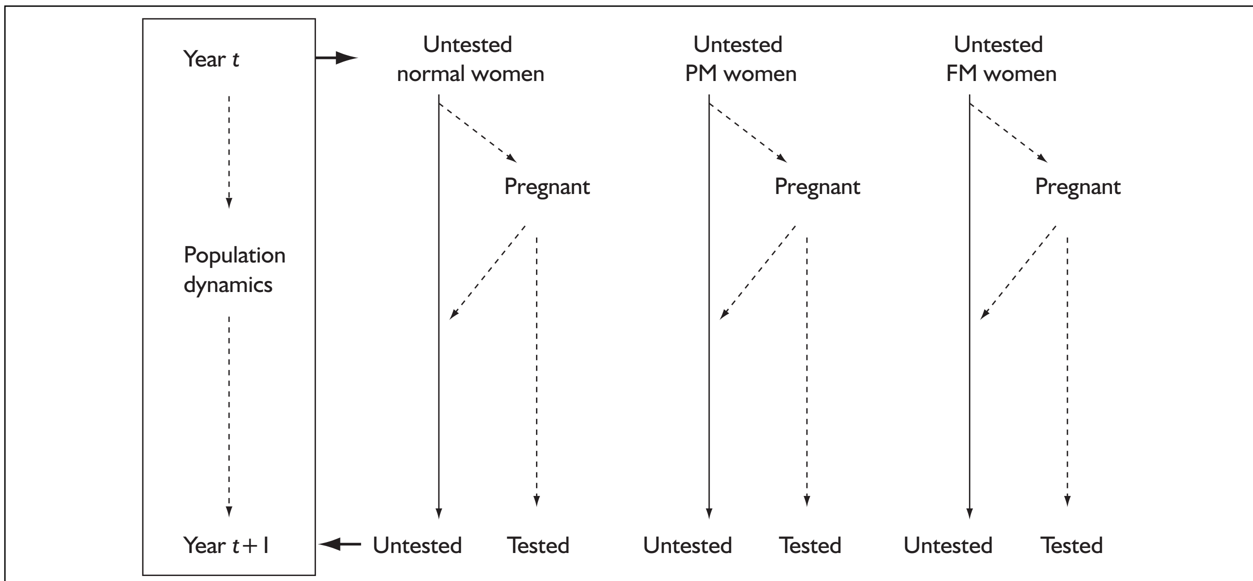

FIGURE 8 *Prenatal screening for FXS*

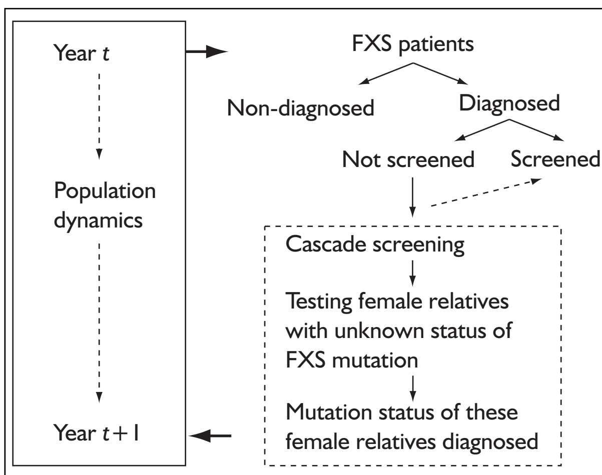

FIGURE 9 *Cascade screening for FXS*

Estimating key parameters by a theoretical simulation

In the theoretical scenario, it is assumed that no FXS patients would be diagnosed and the frequency of PM and FM is constant in the population over the period of simulation. Several key input parameters need to be estimated, including:

- the frequency of FM and PM in the general population and in affected families
- the distribution of PM carriers between the general population and affected families
- the risk of expansion from PM to FM in maternal transmission
- the rate of new PMs among children of normal mothers and normal fathers.

Whenever possible, assumptions for the input parameters are initially based on findings of the literature review in previous chapters (Chapters 4–7). Data from various sources are often different and possibly biased. When there is lack of empirical data, initial values for a few input parameters are decided arbitrarily. The initial values are then modified by a test running of the model, under assumptions that there is no intervention and the frequency of PM and FM in the population is constant over the period of simulation (100 years). Our approach is similar to (but not exactly the same as) the approach of working backwards used by Murray and co-workers.[1]

Initial values for input parameters

Frequency of FM

The indirectly estimated prevalence of FM in the population is 2.3 per 10,000 (Chapter 4). This is similar to generally accepted FM prevalence of 2.5 per 10,000 (or 1 in 4000). Therefore, the initial input value for the prevalence of FM in both the male and female population is assumed to be 2.3/10,000.

Frequency of PM

Our literature review in Chapter 4 suggested that the prevalence of PM is 0.67% among females and 0.16% among males. These values are used as initial input values. The cut-off points to define PM are different in the published literature. The working definition of PM in the model may be considered as CGG repeats size ⩾55, according to the cut-off points used in most studies.

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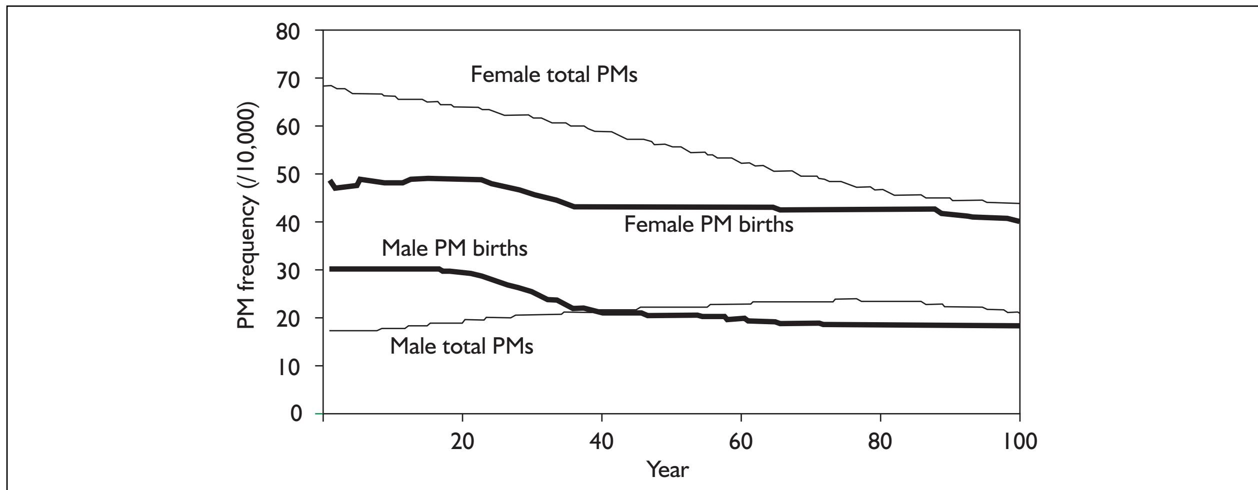

FIGURE 10 *Frequency of PM in population and in new births: simulation results based on the initial values*

Expansion risk from PM to FM

The risk of expansion from PM to FM in maternal transmission is associated with the size of PM CGG repeats. The greater the repeats size, the greater is the risk of expansion. In addition, the expansion risk is much greater in FXS families than that in the general population, because of (1) greater repeats size and (2) greater expansion risk given the same repeats size in affected families.

In the FXS Model, the PM carriers are separated as PMs in the population and PMs in affected families, but not separated by the size of CGG repeats. This simplifies the model greatly (in terms of model's structure and data requirement), and is judged to be sufficient for the purpose of comparing strategies of screening for FXS. Based on a literature review (Chapter 5), the initial value of expansion risk from PM to FM is assumed to be 10% in the general population and 63% in FXS families.

FXS mutations in affected families

For evaluating cascade screening, PM carriers are separated into two categories: PM carriers in the general population and PM carriers in affected families. We are not aware of any empirical data, so its initial value was arbitrarily decided, by assuming that 4% of all PM carriers are from the affected families. This initial value is arbitrary but can be modified according to the results of the model's test running.

To maintain a constant proportion of PM carriers in FXS families, it is necessary to allocate some newborn PMs in the general population to FXS families. It is initially assumed that every new female FM corresponds to a new PM being allocated to FXS families.

New PM mutations from normal mother and father

To maintain a stable frequency of PM in population, new PMs need to be added to the pool of total PMs. There are no empirical data about the rate of new PM from normal mothers and normal fathers. A rate of 1/10,000 was arbitrarily used as the initial value. This initial rate was modified after testing the model.

Testing the model

When the above assumed initial values were tested in the model, the frequencies of PM and FM were not constant over the projection years (*Figures 10* and *11*). The frequency of PM decreases (from 0.67 to 0.43%) in females and increases (from 0.16 to 0.22%) in males. As a result of an initially high frequency of FM in new births (4.6/10,000), the frequency of FM in population increases from 2.3/10,000 to 4.3/10,000 over the simulation period. Therefore, the initial input values had to be modified in order to achieve a constant level of frequency of PM and FM.

By means of many times of experimental (trial-and-error) runnings of the model, we selected a set of input values that yield a constant frequency of PM and FM in the population (*Table 10*). The major changes were as follows:

- The modified frequency of FM in population became slightly greater (2.5/10,000 vs 2.3/10,000).
- The modified frequency of PM in females is about half of that from the literature review (0.35% vs 0.67%).
- The modified rate of new PMs in offspring of normal parents is greater than that initially assumed (3.5/10,000 vs 1/10,000).

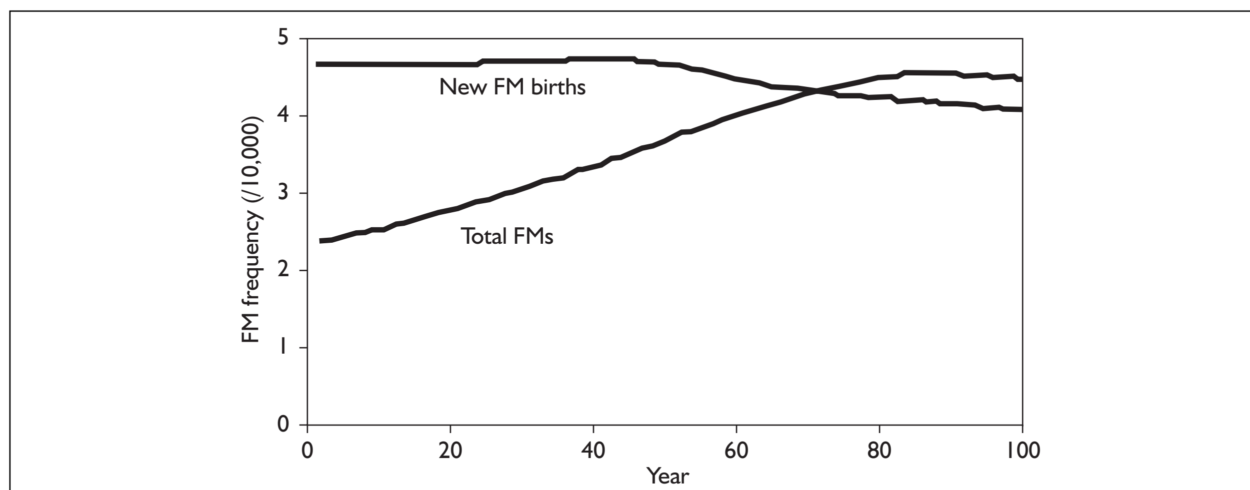

FIGURE 11 *Frequency of FM in population and in new births: simulation results based on the initial input values*

TABLE 10 *Initial input values versus modified input values for theoretical simulation*

	Initial value	Modified value
Frequency of FM		
Female	2.3/10,000	2.5/10,000
Male	2.3/10,000	2.5/10,000
Frequency of PM		
Female	0.67%	0.35%
Male	0.16%	0.16%
New PM from normal parents	1/10,000	3.5/10,000
FXS family PM/total PM		
Female	4%	6%
Male	4%	3%
Family PM/new FM	1	1
Expansion risk from PM to FM		
Population	10%	8%
FXS family	63%	50%
Fertility rate		
Normal mother and father	1.8	1.8
Normal mother and NTM father	1.8	1.8
PM mother and normal father	1.8	1.8
FM mother and normal father	0.9	0.9

- Initial values for the risk of expansion from PM to FM were reduced, both in the general population (8% vs 10%) and in affected families (50% vs 63%).
- The assumed proportion of PM carriers in affected families was increased from 4% to 6% in females and reduced to 3% in males.

The results of the modified test running are shown in *Figures 12* and *13*. The frequency of FM and PM in population and among new births is almost unchanged over the simulation period.

Under the theoretical scenario, the model estimated that <50% of all newborns with FM are from affected families. This is estimated by including all FM newborns from PM carriers in affected families and those from all FM carriers (affected or not).

Remarks

Any model is necessarily a simplification of reality. Because the risk of expansion from PM to FM depends on the number of CGG repeats in the affected gene, the ideal model would group PM carriers according to the size of CGG repeats. This would also allow for expansion of PM short of a FM (for example, from 70 to 100 CGG repeats). Such a model would, however, be considerably more cumbersome than the existing model. The present model was selected as a reasonable compromise between the conflicting requirements of manageability and completeness.

The model presented here is better suited to the simulation of prenatal screening than to cascade screening. For cascade screening it requires

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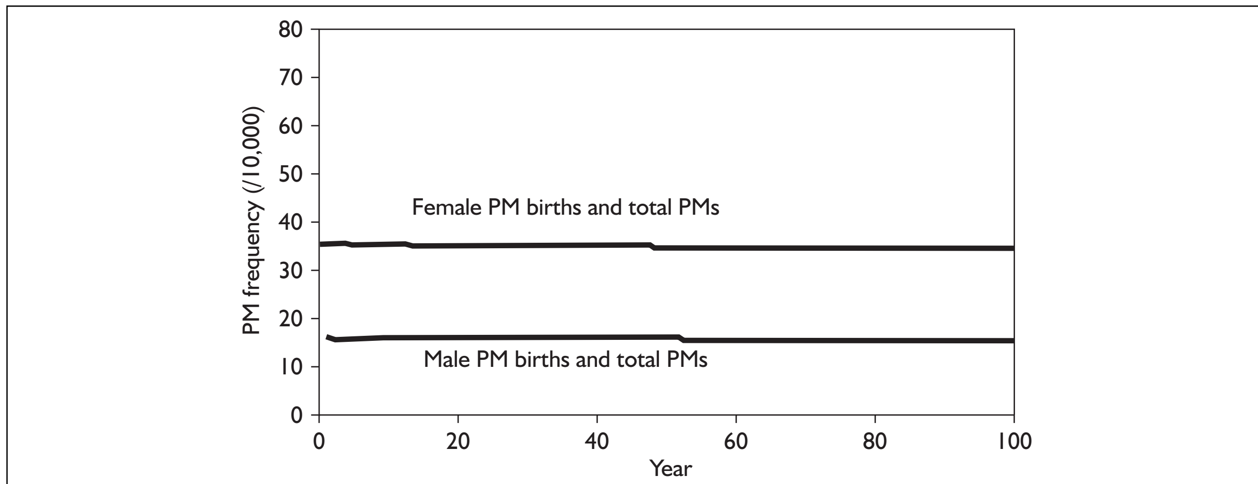

FIGURE 12 *Frequency of PM in population: results of theoretical scenario*

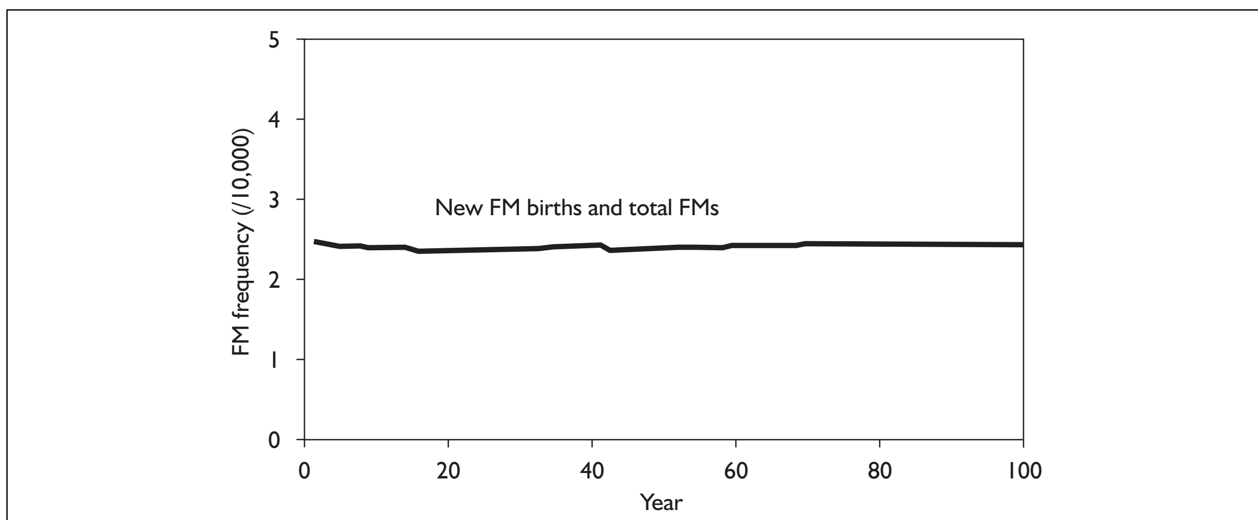

FIGURE 13 *Frequency of FM in population: results of theoretical scenario*

information about the (average) distribution of mutations among family members of index cases. In estimating this information, we have been helped by a model constructed by Wildhagen and co-workers,[110] which was specifically constructed to assess cascade screening, but not to handle other screening methods.

The key parameters to the model are decided according to the assumption that the frequency of FM and PM in the population is constant over the simulation period (100 years). This assumption may not be exactly true in the real world, but it seems to be more acceptable than any other alternative assumptions.

Chapter 9

Comparison of screening strategies by the FXS Model

In this chapter, the FXS Model is used to compare different strategies for screening for FXS. The strategies compared are current practice, active cascade screening and prenatal screening. We first describe the strategy-specific assumptions and then present the results of our simulation modelling.

Assumptions for each strategy

Some input parameters used in the theoretical scenario (*Table 10*) remain the same in all simulation scenarios. Several are used as baseline values but may change during the period of simulation. Such baseline parameters include the prevalence of FM, prevalence of PM and the proportion of family PMs in total PMs. For example, the prevalence of FM at baseline is 2.5/10,000 for all simulation scenarios. Then it may remain the same or decrease in the simulated population, depending on different screening strategies. Several other parameters are constant during the simulation. Such parameters include the incidence of new PM from normal parents, number of family PMs per new FM and the risk of expansion from PM to FM.

The strategy-specific assumptions used in the model are summarised in *Table 11*. The current practice scenario involves only the most likely estimates. The active cascade screening and the prenatal screening scenario contain the most likely estimates and a range of values for some key parameters. The pessimistic and optimistic values of important parameters are used in sensitivity analyses.

Strategy 1: current practice

Current practice is assumed to be a low level of cascade testing of female relatives of diagnosed FXS patients (*Table 11*). The rate of natural diagnosis of FXS is assumed to be 40% in females and 80% in males; 10% of the diagnosed but unscreened FXS patients and all newly diagnosed FXS patients are eligible as index cases for cascade screening. The rate of test uptake is assumed to be 40%. Three female relatives with unknown carrier status are tested for each index case. The fertility rate of diagnosed PM females is assumed to be lowered from 1.8 to 1.6. The rate of undergoing prenatal diagnosis is assumed to be 60% for PM carriers and 70% for FM carriers. It is assumed that 80% of diagnosed male foetal FMs and 40% of diagnosed female FM foetuses are terminated.

To evaluate the cascade screening strategy, it is necessary to estimate the distribution of normal, PM and FM alleles in FXS families. Based on data from Turner and co-workers,[104] 52% of the tested female relatives in FXS families were with normal alleles, 16% with FM and learning difficulty and 32% with PM or FM without learning difficulty. Suppose about half of females with FM are affected with learning difficulty, it could be estimated that about 16% of female relatives are with PM. Hence the proportion of female relatives of FXS patients is assumed to be 52% for normal alleles, 16% for PM, 16% for FM without FXS and 16% for FM with FXS.

Considering the fact that cascade screening has been performed in practice for many years, a proportion of FXS patients and carriers have been diagnosed at time when proposed screening programmes start. It is therefore necessary to estimate the baseline distribution of diagnosed and non-diagnosed FXS cases or carriers. Results of a 10-year running of the current practice scenario were used to estimate these baseline proportions (Appendix 9). The proportions of diagnosed carriers presented in Appendix 9 were used in the FXS model as initial values for all screening strategies.

Strategy 2: active cascade screening

This strategy is similar to current practice but involves more active case finding, a higher uptake rate of screening and a greater number of female relatives tested. This scenario assumes that 80% (range: 60–100%) of females with FXS and 90% (range: 85–100%) of males with FXS are diagnosed by active programmes of case finding. 50% (range: 20–100%) of diagnosed but unscreened cases and all newly identified FXS patients are eligible to be index cases. The uptake

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TABLE 11 *Assumptions used in different screening strategies*

Item	Subjects[a]	Current practice	Active cascade screening			Prenatal screening		
		Point	Point	Pessimistic	Optimistic	Point	Pessimistic	Optimistic
Fertility rate	Normal mother, normal father	1.8	1.8	1.8	1.8	1.8	1.8	1.8
	Normal mother, NTM father	1.8	1.8	1.8	1.8	1.8	1.8	1.8
	Diag popuPM mother	1.6	1.6	1.6	1.6	1.6	1.6	1.6
	Non-diag popuPM mother	1.8	1.8	1.8	1.8	1.8	1.8	1.8
	Diag familyPM mother	1.6	1.6	1.6	1.6	1.6	1.6	1.6
	Non-diag familyPM mother	1.8	1.8	1.8	1.8	1.8	1.8	1.8
	Diag FM mother	0.9	0.9	0.9	0.9	0.9	0.9	0.9
	Non-diag FM mother	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Screening uptake rate		0.4	0.8	0.6	1.0	0.7	0.4	0.9
Natural diagnosis rate of FM	Female	0.4	0.8	0.6	1.0	0.4	0.4	0.9
	Male	0.8	0.9	0.85	1.0	0.8	0.8	0.9
Rate of antenatal diagnosis	PopuPM carriers	0.0	0.0	0.0	0.0	0.8	0.4	0.9
	FamilyPM carriers	0.6	0.8	0.6	1.0	0.8	0.6	1.0
	FM carriers	0.7	0.8	0.7	0.9	0.8	0.7	0.9
Abortion rate	Male FM foetus	0.8	0.9	0.8	1.0	0.9	0.8	1.0
	Female FM foetus	0.4	0.5	0.4	0.8	0.5	0.4	0.8
Number tested per index case	Female relatives	3	6	4	9			
	Male relatives	0	0	0	0			
Rate of testing unscreened	All cases	0.1	0.5	0.2	1.0			
	Active years	100	100	100	100			

[a] PopuPM, PM carriers in the general population; familyPM, PM carriers in FXS families; NTM, male PM carriers; diag, non-diag, diagnosed or non-diagnosed carriers.

TABLE 12 *Simulation results for current practice scenario*

Simulation year	New cases identified	Index cases	Female relatives tested	Total prenatal diagnosis	Total aborted FM foetuses	All cases detected	Number of FXS births	Frequency of FM births (10,000)	Frequency of total FMs (10,000)	Rate of detection of female PMs (%)	Rate of detection of FMs (%)
1	87	197	592	70	17	406	109	2.24	2.50	1.23	56.19
2	80	190	571	73	18	390	107	2.23	2.50	1.33	57.59
3	74	184	553	75	18	377	105	2.22	2.49	1.43	58.87
4	70	178	534	77	19	365	103	2.21	2.48	1.53	60.04
5	66	172	517	79	19	354	101	2.20	2.47	1.62	61.13
6	64	167	502	81	19	345	99	2.19	2.47	1.72	62.20
7	61	162	487	83	20	336	98	2.18	2.46	1.81	63.29
8	59	158	473	85	20	329	96	2.17	2.45	1.90	64.34
9	58	153	460	87	21	322	95	2.16	2.45	1.98	65.35
10	57	149	448	88	21	316	94	2.16	2.44	2.07	66.26
15	52	132	395	93	21	288	93	2.14	2.42	2.46	69.51
20	51	118	354	94	22	268	93	2.14	2.39	2.80	72.18
25	51	108	323	91	21	251	91	2.14	2.37	3.11	74.62
30	50	99	297	85	19	235	88	2.14	2.35	3.38	76.87
35	49	91	274	78	18	220	85	2.13	2.33	3.61	78.86
40	47	85	255	74	17	207	83	2.13	2.31	3.80	80.33
45	46	80	240	70	16	196	81	2.13	2.29	3.93	81.33
50	46	76	228	67	15	188	80	2.13	2.27	4.01	81.99
60	45	71	212	61	14	177	77	2.14	2.23	3.99	82.68
70	42	67	200	56	13	167	73	2.14	2.19	3.81	83.03
80	41	64	191	53	12	159	70	2.15	2.16	3.61	83.28
90	39	61	183	50	12	152	67	2.15	2.14	3.45	83.18
100	37	58	174	47	11	145	63	2.15	2.14	3.34	83.14

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TABLE 13 *Simulation results for active cascade screening (point estimates)*

Simulation year	New cases identified	Index cases	Female relatives tested	Total prenatal diagnosis	Total aborted FM foetuses	All cases detected	Number of FXS births	Frequency of FM births (10,000)	Frequency of total FMs (10,000)	Rate of detection of female PMs (%)	Rate of detection of FMs (%)
1	98	1186	7115	145	37	3586	94	1.95	2.50	3.02	65.46
2	85	747	4482	159	39	2316	90	1.89	2.49	3.76	66.43
3	76	484	2901	157	38	1547	89	1.89	2.48	3.80	67.27
4	69	326	1955	154	38	1085	87	1.89	2.47	3.84	68.02
5	64	229	1375	152	37	800	86	1.89	2.46	3.88	68.65
6	61	170	1021	150	37	626	85	1.89	2.45	3.91	69.22
7	57	133	801	149	36	516	84	1.89	2.44	3.94	69.80
8	55	111	665	147	36	448	83	1.89	2.43	3.97	70.32
9	53	97	581	146	36	405	83	1.89	2.42	4.00	70.82
10	52	88	528	145	36	378	82	1.89	2.41	4.03	71.30
15	51	77	464	145	35	346	82	1.89	2.37	4.17	73.73
20	51	77	460	142	35	343	82	1.89	2.33	4.34	76.31
25	51	76	458	135	33	338	81	1.90	2.30	4.54	78.93
30	51	75	449	124	30	329	78	1.89	2.26	4.75	81.51
35	50	72	434	115	28	316	75	1.88	2.23	4.97	83.88
40	48	70	418	110	26	304	72	1.87	2.19	5.14	85.68
45	47	68	405	106	26	294	71	1.87	2.15	5.16	86.65
50	46	66	397	104	25	288	70	1.87	2.11	5.17	87.59
60	44	64	383	98	24	277	66	1.87	2.04	5.21	89.25
70	42	60	361	93	22	262	63	1.86	1.97	5.29	90.34
80	40	57	344	88	21	249	60	1.86	1.90	5.35	90.94
90	38	55	329	84	20	238	57	1.86	1.88	5.39	90.86
100	36	52	313	80	19	226	54	1.86	1.87	5.42	90.86

TABLE 14 *Simulation results for prenatal screening (point estimates)*

Simulation year	Total women tested	Total prenatal diagnosis	Total aborted FM foetuses	All cases detected	Number of FXS births	Frequency of FM births (10,000)	Frequency of total FMs (10,000)	Rate of detection of female PMs (%)	Rate of detection of FMs (%)
1	428,442	1356	70	2163	70	1.44	2.50	2.85	55.23
2	399,651	1352	69	2062	67	1.42	2.48	4.47	55.88
3	373,290	1346	69	1967	65	1.40	2.46	6.01	56.47
4	349,885	1339	68	1883	64	1.39	2.44	7.46	57.02
5	328,799	1331	68	1806	62	1.37	2.42	8.83	57.52
6	311,382	1326	67	1744	61	1.36	2.41	10.14	57.99
7	296,393	1319	67	1689	59	1.35	2.39	11.41	58.46
8	283,935	1314	66	1644	58	1.34	2.38	12.63	58.90
9	273,760	1310	66	1607	58	1.34	2.36	13.81	59.29
10	265,223	1308	66	1577	57	1.33	2.35	14.96	59.66
15	242,916	1315	65	1510	56	1.31	2.27	20.40	61.48
20	234,477	1320	65	1486	55	1.30	2.20	25.65	63.32
25	227,066	1295	62	1435	53	1.26	2.13	30.79	65.24
30	218,488	1244	58	1351	49	1.21	2.06	35.81	67.16
35	211,223	1191	54	1267	44	1.15	1.99	40.80	68.82
40	206,474	1146	51	1204	42	1.11	1.90	45.43	69.97
45	203,432	1117	49	1164	40	1.10	1.82	49.71	70.86
50	199,984	1095	48	1133	39	1.08	1.73	53.48	71.51
60	189,486	1036	45	1058	37	1.06	1.55	57.52	71.67
70	179,971	968	42	986	34	1.04	1.38	58.62	70.98
80	172,713	918	40	934	32	1.02	1.22	59.14	70.69
90	164,339	868	37	880	30	1.01	1.14	59.58	70.98
100	156,434	817	35	828	28	0.99	1.10	59.82	70.91

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rate is assumed to be 80% (range: 60–100%). Six (range: 4–9) female relatives for each index case are tested. The rate of prenatal diagnosis is assumed to be 80% (range: 60–100%) for PM carriers and 80% (range: 70–90%) for FM carriers.

Strategy 3: prenatal screening

This strategy aims to test all pregnant women with unknown carrier status in the population. The uptake rate is assumed to be 70% (range: 40–90%). The rate of natural diagnosis of FXS is assumed to be the same as in current practice. The rate of prenatal diagnosis and the rate of abortion of PM and FM foetuses are the same as in active cascade screening.

Results of different screening strategies

The simulation results for different screening strategies are shown in *Tables 12–14*, *Figures 14* and *15*.

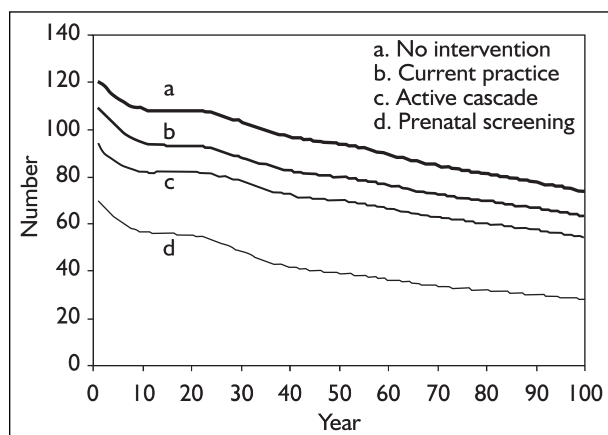

FIGURE 14 *Number of new births of FXS children – different screening scenarios*

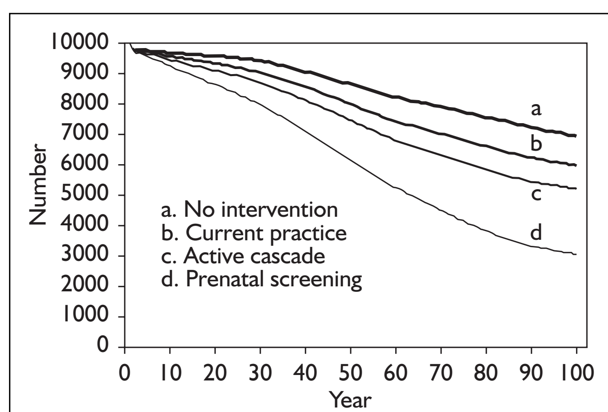

FIGURE 15 *Number of all FXS patients – different screening scenarios*

Current practice scenario

Table 12 shows the simulation results for the current practice scenario. During the first 10 years of simulation, the number of index cases screened is from 197 to 149 per year, the number of female relatives tested ranges from 592 to 448 per year and the number of women undergoing prenatal diagnosis is from 70 to 88 per year. As a consequence of this low-level cascade testing, the rate of detection of female PM carriers is 1.23–2.07% during the first 10 years and up to 4% during the whole simulation period. The proportion of detected FM carriers is 56–66% during the first 10 years and up to 83% in year 100. The number of aborted FM foetuses is 17–21 per year and the number of newborn FXS children is 109 in year 1 and 94 in year 10.

Active cascade screening scenario

In the active cascade scenario, the number of index cases is greatest in year 1 ($n = 1186$); then it becomes smaller in subsequent years because of the success of active case finding in previous years. The number of female relatives tested is 7115 in year 1 and 528 in year 10. In spite of a decrease in the number of index cases and female relatives tested, the proportion of known carriers in total carriers is still increasing. The proportion of diagnosed female PM carriers is 3.0% in year 1, 4.0% in year 10 and 5.4% in year 100. Active case finding is successful in detecting the majority of FM carriers in the population. During the first 10 years of simulation 65–71% of all FM carriers are detected. It is estimated that about 37 FM foetuses per year are aborted during the first 10 years. The frequency of FM births is further lowered in this scenario (*Table 13*), as compared with that in the current practice scenario (*Table 12*).

Prenatal screening scenario

In the prenatal screening scenario, all pregnant women with unknown carrier status are eligible for testing. The number of pregnant women tested is 428,442 in year 1 and 265,223 in year 10 (*Table 14*). The number of women undergoing prenatal diagnosis is similar during the first 10 years of simulation (1356 in year 1 and 1308 in year 10). The number of aborted FM foetuses is also similar (70 in year 1 and 66 in year 10). The proportion of diagnosed female PM carriers increases from 3% in year 1 to 15% in year 10 and to about 60% in year 100. The estimated frequency of FM in population declines steadily, from 2.5 per 10,000 in year 1 to 2.35 per 10,000 in year 10, 1.9 per 10,000 in year 40 and 1.1 per 10,000 in year 100.

***TABLE 15** Incremental number of avoided births of children with FXS (no intervention as the reference standard)*

		Active cascade screening			Prenatal screening		
Years	**Current practice**	**Point**	**Pessimistic**	**Optimistic**	**Point**	**Pessimistic**	**Optimistic**
1	11	26	13	46	51	21	92
2	11	29	14	45	51	21	91
3	12	28	16	45	51	22	90
4	12	28	16	44	51	22	89
5	12	27	17	43	51	22	88
6	13	27	18	43	51	22	88
7	13	27	18	42	51	22	87
8	13	27	18	42	51	22	86
9	14	26	18	42	51	22	86
10	14	26	18	41	51	22	86
15	15	26	18	41	52	23	86
20	15	26	18	41	53	23	87
25	15	26	18	41	54	23	87
30	15	26	18	41	55	23	86
35	15	25	18	41	55	24	85
40	14	25	17	40	55	24	84
45	14	25	16	39	55	24	82
50	14	24	16	38	54	24	81
60	13	23	15	37	53	24	78
70	12	22	14	35	51	23	74
80	11	21	13	34	49	22	71
90	11	20	13	33	48	22	68
100	10	19	12	31	46	21	65

***TABLE 16** Incremental number of avoided births of children with FXS (current practice as the reference standard)*

	Active cascade screening			Prenatal screening		
Years	**Point**	**Pessimistic**	**Optimistic**	**Point**	**Pessimistic**	**Optimistic**
1	15	2	35	40	10	81
2	17	3	34	40	10	80
3	16	4	33	40	10	78
4	16	4	32	39	10	77
5	15	5	31	39	10	76
6	14	5	30	39	9	75
7	14	5	29	38	9	74
8	13	5	29	38	9	73
9	13	5	28	38	9	72
10	12	5	28	38	9	72
15	11	4	27	37	8	71
20	11	3	26	38	8	72
25	11	3	26	39	8	72
30	11	3	26	40	8	71
35	11	2	26	41	9	70
40	10	2	25	41	10	69
45	10	2	25	41	10	68
50	10	2	25	41	10	67
60	10	2	24	40	11	65
70	10	2	23	39	11	62
80	10	2	23	38	11	60
90	9	2	22	37	11	57
100	9	2	21	35	11	55

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Comparison of results of three strategies

Figure 14 shows the estimated number of new births of FXS children in England and Wales over a period of 100 years. The absolute number of newborn FXS children will reduce, even if there is no intervention because the population size becomes smaller (total fertility rate 1.8). Current practice will reduce the births of FXS children, and active cascade screening can reduce the births of FXS children further. Prenatal screening is the most effective in reducing births of FXS children.

Table 15 presents the incremental number of avoided births of children with FXS, as compared with the reference standard of no intervention. During the first 10 years of simulation, current practice prevents about 12 newborn FXS children per year. Active cascade screening will prevent more FXS births than the current practice; the likely point estimate is about 27 (range: 17–43) per year during the first 10 years. Prenatal screening is able to prevent many more births of children with FXS. Each year, it prevents births of about 51 (range: 22–88) FXS children.

Using the current practice as the reference standard, the incremental number of avoided births of FXS children per year is about 15 (range: 4–31) by the active cascade screening and about 39 (range: 9–76) by prenatal screening during the first 10 years of screening (*Table 16*).

The total number of FXS patients in the population decreases correspondingly (*Figure 15*). Compared with current practice, there will be 137 fewer FXS patients with active cascade screening or 388 fewer FXS patients with prenatal screening 10 years after starting the screening programmes in England and Wales. After 20 years, there are 252 and 759 fewer FXS patients, respectively.

Results of sensitivity analyses

Sensitivity analyses were carried out using the range of values provided in *Table 11*. The results of the sensitivity analyses are presented as the pessimistic and optimistic estimates (*Tables 15* and *16*). It can be seen that a programme of population prenatal screening has greater potential in reducing the number of births of FXS children, as compared with a programme of active case finding and cascade screening.

Chapter 10

Economic evaluations

In this chapter we first review the published economic evaluations of screening for FXS, then the FXS Model is used to evaluate the cost-effectiveness of prenatal screening and cascade screening.

Published economic evaluations of screening for FXS

We identified six studies that reported data on the cost of screening for FXS (*Table 17*). Five of these studies evaluated the cost-effectiveness or cost–benefit of prenatal or preconceptual screening programmes.[1,7,8,17,70] One review by Pembrey and co-workers[2] provided data about unit costs of some screening procedures. No study has evaluated the cost-effectiveness of cascade screening for FXS.

The cost-effectiveness of prenatal screening was reported in a Finnish study by Ryynanen and co-workers.[70] The cost per FM foetus detected was about £34,000. In a UK study, Murray and co-workers[1] estimated that the cost per FXS foetus diagnosed by prenatal screening was £93,000–124,000, depending on the uptake rate of screening and prenatal diagnosis. According to Wildhagen and co-workers' model,[8] the cost per detected carrier was about US$47,000 for prenatal screening or preconceptual screening.

Four studies evaluated the cost–benefit of prenatal screening for FXS.[7,8,17,70] Three of the four studies concluded that prenatal screening for FXS was beneficial, including two evaluations of empirical data from screening programmes[17,70] and one using simulation modelling.[8] A cost–benefit study by Vintzileos and co-workers[7] concluded that prenatal screening for FXS was not beneficial, unless the cost of a DNA test could be lowered from US$250 to less than US$240.

In summary, there is a lack of economic evaluation about different strategies of screening for FXS. The two most important strategies (prenatal and cascade) have not been compared head-to-head in published studies. The outcomes of interest in the published studies varied, including the number of carriers detected, the number of FM foetuses detected and the number of FXS children avoided. Because of a lack of comparison of different strategies, the cost-effectiveness ratios were generally average, not incremental.

***TABLE 17** Published economic evaluations of screening for FXS*

Study	Unit cost	Outcomes
Murray *et al.*, 1997[1] Prenatal screening UK	(UK£, 1997) Information given to all pregnant women: £2 DNA testing (screened women): £30 Genetic counselling (women with positive results): £25 Prenatal diagnosis: £275 (including £200 for diagnostic procedure and £75 for Southern blotting)	*Cost per case detected* Uptake prenatal diagnosis 100% 100% £93,000 75% 100% £95,000 100% 75% £122,000 75% 75% £124,000 (cases: FXS births)
Pembrey *et al.*, 2001[2] UK	Information from MENCAP indicated the annual cost per adult with moderate FXS would be at least £20,000 (UK£, 1995). Laboratory cost (the Wessex 1998/9): £50 per genotype. PCR: the centrally negotiated cost to the NHS (2000?), £2.80 for a single PCR and £5.60 for multiple testing of a family. Automated sequencer: £100,000	

continued

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TABLE 17 *Published economic evaluations of screening for FXS (continued)*

Study	Unit cost	Outcomes
Wildhagen *et al.*, 1998[8] Prenatal or preconceptual The Netherlands	Separating screening costs into three categories: information dissemination prior to the screening; testing and organisation of the programme; and aftercare US$ (year, unknown) DNA extraction: $9.00 Costs for the screener (travelling and time): $7.91 PCR test: $24.04 Southern blot: $75.36 Counselling a carrier: $114.18 Prenatal diagnosis: $1435.90 Induced abortion: $249.77 Early spontaneous abortion: $78.24 Late spontaneous abortion: $502.18 Iatrogenic abortion: $78.24 Discount rate for costs: 3% *Screening dependent: prenatal preconceptual* Mass information costs: $355,385 $592,308 Personal information costs: $6.15 $3.08 Organisation costs (acquisition, shipment and administration): $19.47 $19.47 *Lifetime costs of care of patient:* Norm or PM: $0. FM: $957,734 for boys and $533,673 for girls	*Prenatal screening* Costs/detected carrier: $46,400 Savings of affected children born less: $23,257,000 Net savings per year: $13,970,000 *Preconceptual screening* Costs/detected carrier: $46,800 Savings of affected children born less: $15,842,000 Net savings per year: $8,891,000
Vintzileos *et al.*, 1999[7] Cost–benefit of prenatal screening USA	(US$, 1998) Lifetime cost per FXS child: $500,000 (incremental) Current cost per screening test: $250 Amniocentesis package: $1300 (including ultrasound $163; the invasive procedure $225; genetic counselling $90; laboratory analysis of amniotic fluid $850)	Net losses per prenatally-diagnosed case of FXS (80% uptake rate) *Therapeutic abortion rate 50%:* First year of programme: $770,833 Programme fully mature: $270,833 *Therapeutic abortion rate 100%:* First year of programme: $520,833 Programme fully mature: $20,833
Ryynanen *et al.*, 1999[70] Prenatal screening Finland	DNA testing: PCR £36; selective Southern blotting £72; average £45/woman. Lifetime costs for the care of an affected child: £570,000–700,000	Including the prenatal diagnosis, the cost of detecting one FM foetus: £34,000
Toledano-Alhadef *et al.*, 2001[17] Cost–benefit of prenatal screening Israel	US$ (year, unknown) Publicity for each person in the target population: $1 DNA testing and expenses for tested women: $110 Amniocentesis and karyotype: $155 DNA testing of the foetus: $98 Genetic counselling following foetal diagnosis: $51 Iatrogenic abortion: $658 Cost of genetic counselling following foetal diagnosis: $128 Cost of abortion (iatrogenic or therapeutic): $483 Cost of genetic counselling following diagnosis of carrier status: $27 Lifetime care of a person with learning difficulty: $680,000 Lost foetuses due to either iatrogenic abortion or termination of an unaffected female with FM: $36,500	Net benefit in Israel per year: $5,500,000

TABLE 18 *Assumptions about unit cost for different procedures*

Procedure	Unit cost and range estimates (UK£, 1997)[a]
Information given	2 (1–3)
Preselection for DNA test[b] (case finding in cascade screening)	10 (5–15)
DNA testing	30 (24–36)
Genetic counselling	25 (20–30)
Prenatal diagnosis	275 (220–330)
Therapeutic abortion[c]	300 (225–325)

[a] The unit costs are mainly based on Murray and co-workers (1997).[1]
[b] Because of no objective data, cost of giving information to patients and cost of pre-selection for DNA testing are arbitrarily assumed.
[c] Range for abortion is 25th and 75th percentile. Ranges for other procedures are assumed to be 20% lower or higher than the point estimates.

Economic evaluation using the FXS Model

Our cost-effectiveness analysis is from the view of the NHS. The effectiveness data are from the FXS Model (see Chapter 9). Assumptions about costs are mainly based on Murray and co-workers,[1] except the unit cost of therapeutic abortion, which is from Acute Care 97/98 (UK National Statistics 1996–7).[112] The assumed unit costs for different procedures are summarised in *Table 18*. Only the direct costs for listed procedures are considered, following the similar approach by Murray and co-workers.[1] The cost is measured in UK£ (1997).

It is further assumed that the frequency of FXS patients in people with learning difficulty of unknown cause is 1% (range: 1.0–1.5%). After preselection, about 7 (range: 7–10) patients with learning difficulty need to be genetically tested for identifying a new FXS case in the cascade screening. These estimates are based on data from a study by Arvio and co-workers.[13]

Estimated costs of different strategies

Based on the assumed parameters for different screening programmes (*Table 11*) and assumed unit costs (*Table 18*), we estimated the total costs of different strategies for screening FXS in England and Wales (*Table 19*). Over the period of simulation, the total annual cost for any screening strategies will decrease. This is due to the fact that the screening candidates need to be tested only once and the total number of women with unknown carrier status will be reduced by the screening programmes. The total annual cost of the current practice (low level of cascade testing) is from £256,000 in year 1 and £186,000 in year 10. The active cascade screening programme will cost more than current practice, from £744,000 in year 1 to £201,000 in year 10. The most expensive strategy is prenatal screening. The prenatal

TABLE 19 *Estimated costs of different strategies in England and Wales (UK£, 1997)*

Simulation year	Current practice	Active cascade	Prenatal screening
1	256,124	744,493	14,508,189
2	239,833	544,096	13,558,619
3	227,639	417,947	12,688,236
4	217,423	338,055	11,915,208
5	209,365	287,469	11,218,328
6	202,860	254,792	10,642,932
7	196,644	232,279	10,147,144
8	192,109	217,597	9,735,114
9	188,867	208,125	9,398,944
10	185,639	201,167	9,116,897
15	173,534	195,264	8,383,993
20	168,297	193,628	8,107,228
25	164,837	191,315	7,855,077
30	159,827	186,148	7,556,558
35	153,452	179,255	7,300,554
40	147,399	172,755	7,130,406
45	142,653	167,786	7,021,241
50	139,364	164,422	6,901,184
60	133,840	158,156	6,537,858
70	126,733	149,279	6,204,575
80	120,915	142,094	5,951,045
90	115,935	135,994	5,660,769
100	110,380	129,201	5,385,573

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TABLE 20 *Results of modelling: cost per carrier (case) detected*

Year	Average cost (reference: no intervention)			Incremental cost (reference: current practice)	
	Current	Cascade	Prenatal	Cascade	Prenatal
1	618	205	6698	152	8103
2	601	230	6567	155	7960
3	589	263	6439	157	7827
4	580	301	6317	160	7697
5	575	345	6199	163	7572
6	571	390	6092	167	7455
7	567	429	5996	170	7346
8	566	462	5911	174	7246
9	567	487	5835	176	7155
10	569	504	5768	176	7069
15	581	533	5541	300	6709
20	605	534	5443	284	6506
30	656	539	5579	245	6614
40	689	543	5910	232	6992
50	715	544	6078	222	7148
60	733	545	6166	214	7255
70	737	545	6279	208	7406
80	739	545	6362	205	7511
90	741	545	6420	202	7602
100	740	545	6490	201	7705

Carriers (cases) included all detected PM or FM carriers and PM or FM foetuses.

screening programme costs £14,508,000 in year 1 and £9,117,000 in year 10.

Costs per carrier detected

Table 20 shows the costs per carrier detected. The denominator of the ratio of cost-effectiveness includes all new FXS cases identified, all PM or FM carriers detected among pregnant women or relatives in FXS families and all PM or FM foetuses diagnosed. Compared with no intervention, active cascade screening is the most efficient strategy, while the current practice is similarly efficient. The cost per carrier detected by the prenatal screening programme is highest among the three strategies, from £6700 in year 1 to £5800 in year 10.

The incremental cost-effectiveness of active cascade screening and prenatal screening using current practice as a reference are relatively constant over the years of simulation (*Table 20*). The incremental cost per extra carrier detected by active cascade screening is £152 in year 1 and £176 in year 10. The incremental cost per carrier detected by prenatal screening is £8103 in year 1 and £7069 in year 10.

Murray and co-workers[1] estimated that the cost per case (FXS foetus) detected by prenatal screening ranges from £93,000 (100% uptake rate) to £124,000 (75% uptake rate), depending on the uptake rate of screening and prenatal diagnosis. Using the same definition of cases detected, our estimate of cost per FXS foetus detected is £194,267 in year 1, £129,243 in year 10 and 116,859 in year 20. Our estimates are therefore similar to Murray and co-workers' estimate of £124,000 when the assumed uptake rate of screening and prenatal diagnosis was 75%.

Costs per FXS child avoided

The cost per FXS child avoided by different screening strategies is presented in *Table 21*. Using current practice as the reference standard, the incremental cost per extra FXS child avoided is £31,943 in year 1 and £1262 in year 10 by active cascade screening. Prenatal screening is less efficient than active cascade screening, which is associated with an incremental cost of £357,299 in year 1 and £237,997 in year 10 for each extra FXS child prevented.

Cost–benefit analyses

The costs (UK£ 1997, standardised) for lifetime care of FXS patients were estimated to be about £600,000 for boys and £330,000 for girls by Wildhagen and co-workers,[8] £300,000 by Vintzileos and co-workers,[7] £500,000–£610,000 by

TABLE 21 *Modelling results: cost per FXS child prevented*

	Average cost (reference: no intervention)			Incremental cost (reference: current practice)	
Year	**Current**	**Cascade**	**Prenatal**	**Cascade**	**Prenatal**
1	23312	28334	285172	31943	357299
2	21026	18972	264859	17616	334767
3	19359	14809	247162	11559	314847
4	17971	12158	231684	7681	297426
5	16855	10491	218055	5214	282095
6	15917	9408	206702	3623	269463
7	15072	8677	197294	2597	259230
8	14408	8206	189449	1933	250782
9	13855	7905	182877	1517	243888
10	13383	7686	177378	1262	237997
15	11890	7500	161520	1900	220050
20	11207	7418	153306	2285	209660
30	10712	7282	138084	2473	185830
40	10193	6921	129070	2415	171220
50	10152	6829	126828	2421	166198
60	10379	6838	123450	2376	159843
70	10486	6752	121850	2249	156508
80	10560	6695	120609	2167	153865
90	10647	6685	119050	2122	151249
100	10651	6638	118132	2068	149751

TABLE 22 *Estimated cost–benefit of screening for FXS*

	Current practice	**Active cascade**	**Prenatal screening**
Annual costs (£)	211,650	344,602	11,292,961
No. of FXS avoided per year	13	27	51
Lifetime cost per FXS (£)	380,000	380,000	380,000
Net benefit (£)	4.7 million	9.9 million	8.1 million

The annual costs of screening programmes and the number of FXS children avoided per year are the averages of the first 10 years of simulation.

Ryynanen and co-workers,[70] and £400,000 by Toledano-Alhadef and co-workers.[17] Pembrey and co-workers[2] reported that it costs the NHS about £20,000 per year (1995, UK£) for managing a moderately affected adult in the UK. Applying this unit cost to patients aged from 10 to 64 years and an annual discount rate of 6%, the costs for lifetime care of an affected patient may be estimated to be about £380,000 in the UK (1997, UK£).

Comparing the estimated costs of lifetime care for an FXS patient versus the costs per FXS child prevented (*Table 21*), even the most expensive strategy of prenatal screening is still economically beneficial. *Table 22* compares the cost–benefits of different screening strategies. The net saving to the NHS is £4.7 million by current practice and £9.9 million by active cascade screening in England and Wales. In spite of prenatal screening's high total costs, the net saving by prenatal screening (£8.1 million) is similar to that by active cascade screening.

Figure 16 shows the cumulative net costs for prenatal screening and active cascade screening. The cumulative net costs are incremental, using current practice as the reference standard. They are calculated by considering both savings due to fewer FXS patients and the costs of screening programmes. Both savings and costs are discounted by 6% annually. Active cascade screening starts to save money to the NHS soon (2 years) after its introduction. Cumulatively, it may save about £11 million after 10 years and £30 million after 20 years, as compared with current practice. Prenatal screening starts to save money after about 30 years. After about 60 years, the

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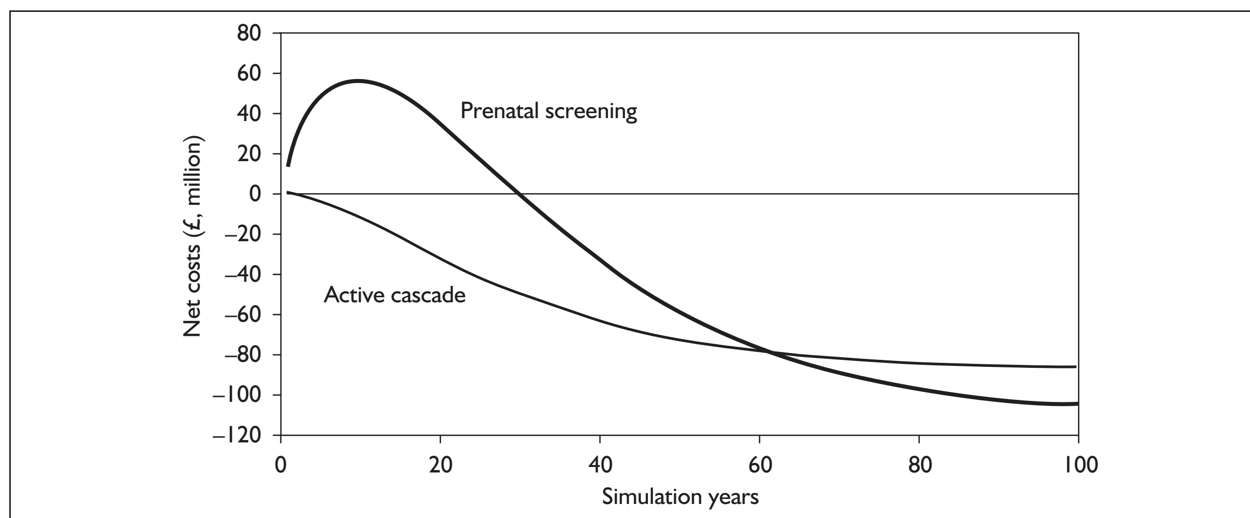

FIGURE 16 *Cumulative incremental net costs (savings) of prenatal screening or active cascade screening for FXS in England and Wales. The reference standard is the current practice. The incremental net costs are the difference between the savings due to fewer FXS patients and the costs of the screening procedures. The savings and costs are discounted at 6% annually. A positive value indicates that costs are greater than savings, while a negative value indicates that costs are less than savings. The annual cost to the NHS for managing each FXS patient is assumed to be £22,556 (1997 price)*

TABLE 23 *Results of sensitivity analyses – incremental cost per extra carrier detected*

	Active cascade screening			Prenatal screening		
Years	**Point**	**Pessimistic**	**Optimistic**	**Point**	**Pessimistic**	**Optimistic**
Reference standard: no intervention						
1	205	582	165	6698	10135	4956
5	345	596	209	6199	9682	4541
10	504	708	218	5768	9277	4184
20	534	991	218	5443	8926	3943
40	543	1211	215	5910	9224	4451
60	545	1257	215	6166	9444	4682
80	545	1257	215	6362	9623	4850
100	545	1258	215	6490	9746	4957
Reference standard: current practice						
1	152	243	126	8103	15413	5741
5	163	177	134	7572	14692	5338
10	176	147	114	7069	13946	4959
20	284	341	118	6506	12594	4596
40	232	623	106	6992	12439	5184
60	214	593	108	7255	12493	5440
80	205	555	108	7511	12755	5655
100	201	546	107	7705	13011	5811

Pessimistic scenario: pessimistic values for assumed effectiveness and high values for assumed costs. Optimistic scenario: optimistic values for assumed effectiveness and low values for assumed costs.

savings from active cascade screening and prenatal screening will be similar (about £73 million). Then prenatal screening starts to save more than active cascade screening.

Sensitivity analyses

There is great uncertainty in the assumptions about effectiveness and costs of different screening strategies. To explore the impact of different assumptions on the estimated cost-effectiveness, assumed lower and higher values for the input parameters about effectiveness (*Table 11*) and costs (*Table 18*) are used to provide pessimistic and optimistic estimates. The pessimistic scenario is based on the lower values for the assumed effectiveness and higher values for the costs,

TABLE 24 *Results of sensitivity analyses – incremental cost per extra FXS child avoided*

	Active cascade screening			Prenatal screening		
Years	**Point**	**Pessimistic**	**Optimistic**	**Point**	**Pessimistic**	**Optimistic**
Reference standard: no intervention						
1	28334	53078	5251	285172	529368	153725
5	10491	27346	3005	218055	424522	116489
10	7686	20169	2581	177378	359948	93817
20	7418	17767	2522	153306	328617	80906
40	6921	17402	2199	129070	273743	73532
60	6838	18653	2144	123450	257770	72103
80	6695	18794	2102	120609	246163	71914
100	6638	18813	2083	118132	236897	71305
Reference standard: current practice						
1	31943	113224	3783	357299	1063039	173309
5	5214	16312	1175	282095	935425	134301
10	1262	6707	762	237997	901025	110745
20	2285	5758	959	209660	925821	96793
40	2415	8268	867	171220	654670	87985
60	2376	12136	896	159843	545525	85515
80	2167	11160	866	153865	481790	84838
100	2068	10541	843	149751	445537	83986

whereas the optimistic scenario is based on the higher estimates of effectiveness and lower estimates of costs. The results are shown in *Tables 23* and *24*.

The incremental cost-effectiveness in the sensitivity analyses is calculated by using no intervention or current practice as the reference standard. Compared with current practice, the pessimistic estimate of cost per FXS child avoided by active cascade screening is on average £27,314 during the first 10 years of simulation, which is much lower than the cost of lifetime care for an FXS patient (£380,000). For prenatal screening, the pessimistic estimate of cost per FXS child prevented during the first 10 years is on average £950,572, which is higher than the lifetime cost for managing an FXS patient.

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Chapter 11

Discussion and conclusions

The possible strategies of screening for FXS include newborn screening, prenatal screening, preconceptual screening, cascade screening and paediatric screening. We have focused on a comparison of prenatal screening and cascade screening, because each of these two strategies was advocated by one of the two HTA reviews.[1,2]

Murray and co-workers[1] recommended that "pilot studies should be carried out to assess the feasibility of routine antenatal screening". They were sceptical about "the impact of cascade screening on the total population birth prevalence of fragile X syndrome". In contrast, Pembrey and co-workers[2] recommended that "a trial of systematic case-finding and cascade testing to evaluate the benefits and costs of such an approach would be based on reasonably secure risk figures for counselling". They suggested that a trial of population (prenatal) screening will be problematic because of the uncertainty about the risks for women from the general population with 55–65 repeats. However, the difficulty in the interpretation of borderline PMs is relevant not only to the prenatal screening of population, but also to the cascade screening of affected families (see *Figure 4*).

Usefulness and weaknesses of the FXS Model

Our model is the first that can be used to compare directly prenatal screening and active cascade screening and to estimate the long-term impact of the two strategies on population. It provides a framework to incorporate available data from various sources, and to be used to test 'what-if' questions. The assumptions about input parameters are from literature reviews and the model's test running. There are great uncertainties about the assumptions used in the model. When new data from research become available, the assumed values for input parameters in the FXS Model could be modified.

Both the benefits and costs of screening for FXS may have not been fully incorporated. The benefits of screening for FXS in the model include the detection of carriers and avoided births of FXS children. The improved quality of life for parents and other family members of avoided FXS children may also be important, but has not been considered in the model.

Only the direct costs to the NHS are considered in the model. The costs required for the infrastructure, professional training and public education have not been included, or the anxiety and emotional problems due to the uncertain or false-positive results. Because it is still impossible to predict whether a female FM foetus will be affected, some terminated female FM foetuses would in fact have had a normal life if they had been born. In addition, symptoms in the affected females are generally less severe than that in the affected males.

Major modelling results

Simulation results by the FXS Model showed that, over the first 10 years of simulation, active cascade screening will on average detect about 4% of all female PM carriers and 70% of all FM carriers (*Table 13*). Prenatal screening will on average detect about 10% of female PM carriers and 58% of all FM carriers during the first 10 years (*Table 14*). The maximal proportion of detected FM carriers by active cascade screening is slightly higher than that by prenatal screening (91% versus 71%). However, the maximal rate of detection of female PM carriers by active cascade screening (6%) is much lower than that by prenatal screening (60%).

It should be noted that this modelling result is determined by the assumed proportion of PM carriers in affected families versus PM carriers in the general population, which needs to be confirmed by empirical evidence. The detected PMs by cascade screening have a greater risk of full expansion than those detected by prenatal screening of the general population (50% versus 8%). In addition, carriers detected by cascade screening may already have knowledge about FXS, and be more able to make informed choices than carriers detected by population-based prenatal screening.

During the first 10 years of simulation, the additional number of births of FXS children that

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can be avoided each year is estimated to be about 15 (range: 4–31) by active cascade screening, and about 39 (range: 9–76) by prenatal screening. The prenatal screening programme is more effective than active cascade screening, but it will also cost much more. During the first 10 years, the estimated direct cost per year to the NHS in England and Wales is £0.7–0.2 million by cascade screening and £14.5–9.1 million by a programme of prenatal screening (*Table 19*). During the first 10 years of simulation, the incremental cost per carrier detected (using current practice as the reference standard) is on average only £165 (range: £129–182) by active cascade screening and £7543 (range: £5316–14,636) by prenatal screening (*Table 23*). The incremental cost per FXS child avoided is on average £8494 (range: £1367–27,314) by active cascade screening and £284,779 (range: £135,510–950,572) by prenatal screening (*Table 24*).

Therefore, prenatal screening is more efficacious and potentially has a greater impact on population, but it will also cost more and be less efficient than the active cascade screening. Considering that the lifetime care of each FXS patient will cost the NHS about £380,000 and the total annual cost of care of FXS patients to NHS is about £200 million, the most expensive strategy (population prenatal screening) is still cost-saving in the long term. The estimated net savings per year in England and Wales are about £10 million by active cascade screening and £8 million by prenatal screening (*Table 22*).

Aims of screening for FXS

Murray and co-workers[1] suggested that the principal aim of screening for FXS is to reduce the birth prevalence of the disorder, and a secondary aim is to bring forward the diagnosis of affected individuals. However, Pembrey and co-workers[2] believed that the aim of medical genetics (presumably including screening for FXS) is to "help those families with a genetic disadvantage live and reproduce as normally as possible". The major concern was not to put pressure on women "to abort an affected foetus or remain childless". Pembrey and co-workers[2] pointed out that their definition of living and reproducing normally is culturally dependent, and could be interpreted differently.

It seems that Pembrey and co-workers' definition of aim of screening is comprehensive, but lacks details and cannot be easily measured. In addition, for many affected families (or not yet affected families), prevention of birth of FXS children may help them "to live and reproduce normally". Thus, the prevention of births of FXS children, and at the same time to help the families to have unaffected children, could be the most important aim of screening for FXS, as long as families have freedom to make their own informed choices.

The European Society of Human Genetics suggested that "the benefits of genetic screening include pre-symptomatic detection of disease or susceptibility to diseases for prevention, early diagnosis, care and treatment; the detection of genetic predisposition to adverse effects of environmental factors to facilitate avoidance of harm, and detection of carrier status to enable reproductive or lifestyle decision".[113] The diagnosis of FXS has very limited benefit to affected patients themselves, because there are no effective treatments. Thus large-scale screening for FXS is unlikely to be justifiable only by the diagnosis of FXS patients. The detection of carrier status to enable reproductive or lifestyle decisions is also important. Since it is not possible to predict with certainty the foetus' mutation status before conception, termination of affected foetuses or childless are the two options for carriers to avoid the birth of affected children.

For cultural, ethical and religious reasons, abortion of affected foetuses is controversial, and so is any genetic screening programme that may result in the voluntary termination of affected foetuses. As observed by Jallinoja in Finland,[100] "the description of the aim of the screening or screening procedure ended at the 'option' of prenatal diagnosis, or 'final prenatal diagnosis'", although "all … researchers really wanted to do was to screen all pregnant women and, for example, to make mothers abort foetuses with gene defects in order to save money". Therefore, the problem cannot be solved by excluding the prevention of affected births from the aims of the genetic screening for FXS. Doing so may cause more harm, because of possible misleading or incomplete information provided to people when they decide whether or not to participate in the screening programme. For families that are childless or for whom termination of an affected foetus is definitely not an option, they are unlikely to benefit from the detection of carrier status, so they may not wish to be screened in the first place. This is relevant not only to the population-based prenatal screening, but also to cascade screening of affected families.

Feasibility and acceptability

The empirical evidence suggested that both prenatal screening and cascade screening are feasible and acceptable. A study of prenatal screening in Finland reported that the rate of acceptance was 85%.[70] A large number of women participated in self-paid programmes of preconceptual or prenatal screening for FXS in Israel.[17,67,68] There was a high degree of acceptability (79%) among families of patients with learning difficulty.[33] The acceptance rate of cascade screening by relatives of FXS cases was reported to be about 50% in Finland[101] and 76% in The Netherlands.[105] Among pregnant carriers, the acceptance rate for prenatal diagnosis is high (89% in Pesso and co-workers[68] or 92% in Toledano-Alhadef and co-workers[17]).

In a study of screening FXS among people with learning difficulty in The Netherlands, 70% of the parents/guardians accepted the testing, and the major reasons for participating included the wish to obtain a diagnosis (82%), the hereditary implications (81%) and the support of research into learning difficulty.[11]

Carmichael and co-workers[114] surveyed 413 members of the UK Fragile-X Society who were parents of affected children. The benefits of having a diagnosis to affected children include appropriate intervention, tolerance and financial help. Genetic counselling following the diagnosis is considered to be an important benefit to parents, siblings and wider family. The disadvantages include stigma, labelling, reduced expectations, anxiety (about other children and carrier status), family tension and guilty feelings. Overall, they found that “most families feel that having a diagnosis is a benefit rather than a disadvantage”.

McConkie-Rosell and co-workers[115] reported self-concept in 42 women (aged ⩾18 years) at risk for inheriting the FXS before and after carrier testing. These women had a 50% *a priori* risk of being a carrier, and carrier testing revealed 20 positive results. It was found that the global self-concept was stable during the 6 months after carrier testing, and there was no significant difference between carriers and non-carriers. Feelings about self were improved in non-carriers. However, there were situational-specific changes in feelings about self in carriers, regarding the implications of a positive carrier test for their own children, a possible barrier to having biological children if their family was not completed, possible expression of clinical features of FXS in themselves, an altered or a heightened awareness of their own genetic identity and regret over not having known sooner.[115]

Conclusions

The empirical evidence suggested that both prenatal screening and cascade screening are feasible and acceptable.

Both prenatal screening and active cascade screening can reduce the number of births of FXS children. Theoretically, the maximum number of FM births that could be prevented is nearly 100% by a population-based prenatal screening programme, and less than half by a case finding and cascade screening. Hence population-based prenatal screening is more efficacious and has a greater impact on the population, but it will also cost more and be less efficient than active cascade screening.

Active cascade screening is more efficient and requires much less resources than population-based prenatal screening. If adopted, this screening approach is warranted for only a few years, because of the anticipated success in reducing the number of undiagnosed cases. Indeed, the 2001 HTA report recommended a 5-year programme of systematic case finding.[2] After a few years, the estimated costs of active cascade screening will be only slightly higher than those of the current practice scenario (*Table 19*).

Considering that the lifetime care of each FXS patient will cost the NHS about £380,000, the most expensive strategy (population prenatal screening) is still cost-saving. This is based on the assumption that a large proportion of affected foetuses are terminated.

Since both prenatal screening and active cascade screening have advantages and disadvantages, both strategies should be evaluated in large-scale trials. It may also be important to explore and evaluate whether and how the different strategies could be simultaneously or sequentially combined.

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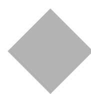

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Contributions of authors

All authors contributed to the development of review protocols, and commented on the draft manuscript. Vicky Sleightholme and Fujian Song wrote the review protocol. Anne Fry-Smith designed search strategies and searched electronic databases. Vicky Sleightholme designed a survey questionnaire. Vicky Sleightholme and Fujian Song assessed identified studies for inclusion. Fujian Song extracted and synthesised data from included studies. Pelham Barton, Fujian Song and Lily Yao developed the model. Fujian Song wrote the report and takes the major responsibility for any errors and mistakes.

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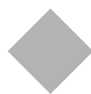

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Appendix 1

Major features of two HTA reports of screening for FXS

	Murray *et al.*, 1997[1]	**Pembrey *et al.*, 2001[2]**
Objectives	To provide information needed to decide whether to use DNA testing to screen for FXS.	To assess the feasibility and acceptability of population screening for FXS, in the context of existing services for families with FXS.
Literature search	Up to August 1996. Sources of literature: MEDLINE; SCI via BIDS; CINAHL; reference lists in identified papers; searching SCI for descendant papers; handsearching most relevant journals; SIGLE; workshop/conference proceedings; newsletters from UK and US patient groups/societies. Keywords/phrases to describe fragile X and the relevant genetics were used to ensure a high retrieval rate.	For the biomedical literature: MEDLINE (no date parameters were given). For the psychological literature: MEDLINE (1980–August 1995); PsycINFO (1984–August 1995); BIDS; reference lists of identified papers. No information on search terms. Questionnaires were sent to UK genetics services (1995 and 1998) regarding current services, data held, etc.
Inclusion and exclusion criteria	Studies were excluded if: outside scope of review; results were biased; based on anecdotal information; case reports; DNA status of participants unclear. No information on data extraction, quality assessment. Studies were entered into a meta-analysis where appropriate.	No information.
Background information	The natural history, prevalence and genetics of FXS were described. The risk of expansion from PM to FM was estimated.	The clinical features, biology and prevalence of FXS were discussed. In particular, the evidence regarding the prevalence and significance of different sizes of PMs and their risk of expansion were discussed, and the difficulties of interpreting this data in clinical practice. Recent evidence regarding premature ovarian failure in female FM carriers was also discussed.
Screening tests	Cytogenetic methods are unsuitable as they will only detect an FM. Southern blotting can be used but is inaccurate in measuring the size of small PMs, plus there is a long turnaround time and it is relatively expensive. Best method is to use DNA amplification (PCR) on all samples, and where there is a failure to amplify, use Southern blotting	DNA analysis can reliably detect CGG repeat number and detect FMs, but a combination of PCR and Southern blotting is required in laboratories which limits high throughput. Routine cytogenetic analysis of fragile sites is not accurate or cost-effective.
Screening strategies	Possible strategies are: routine antenatal testing of apparently low risk pregnancies; preconceptual testing of young women; systematic testing in affected families ('cascade screening'); active paediatric and neonatal screening – however, no evidence of direct benefit from early diagnosis	Less than half of individuals with FXS are likely to be known to UK regional genetics centres. Systematic case finding can increase this figure. In addition to cascade testing and counselling of relatives, this can lead to a 60% reduction in birth prevalence. Simulations suggest that case-finding and cascade testing/counselling can only reach half of the PM carriers (and most of these individuals would be at highest risk)

continued

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	Murray *et al.*, 1997[1]	Pembrey *et al.*, 2001[2]
	Little published information on the practical consequences of offering antenatal or preconceptual testing. Preconceptual screening only reported in potential egg donors for IVF. Active cascade screening programmes have been reported; the largest carried out in Australia resulted in ~26% reduction in pregnancies. Affected male foetuses are generally terminated; up to 64% of female foetuses with a FM are reported to be terminated.	Affected families are generally supportive of screening. The benefits to the patients with FXS of making a diagnosis, and the benefits to the families at risk of FXS of genetic counselling were discussed.
Current practice	Children with learning difficulties and developmental delay to be tested to exclude FXS.	The possible integration of FXS screening into current genetics services was discussed. The implementation of disease-specific centres is not necessary, and the development of services for fragile X families needs to be considered within an integrated policy framework.
Modelling	A simple model of allelic inheritance was constructed to illustrate a general population screening situation. The authors pointed out that due to uncertainty regarding PM to FM expansion rates, a range of values needs to be considered within the model.	A descriptive framework for evaluating screening for FXS, based on a hypothetic 3 million population covered by a regional clinical genetics centre in the UK.
Human costs of screening for FXS	Up to 1% foetal loss rate through invasive prenatal diagnosis. Psychological considerations of fragile X screening include anxiety generated through the screening itself, in addition to anxiety as a result of reproductive decisions made subsequent to a screening test. There are also specific counselling issues in explaining the complex risks and inheritance, in particular to female FM carriers who may have subtle learning difficulties.	The costs of FXS are social as well as financial. The costs to the individual and family of an FXS diagnosis include stigmatisation and guilt. The human cost of screening is mainly anxiety.
Financial costs of screening for FXS	Average cost of preventing an affected birth has been estimated to be AUS$14,200 (New South Wales, 1986) and US$12,740 (Spain, 1992), for example. These estimates were made using cytogenetic screening techniques and did not account for births avoided as a result of screening. Thus, these are likely to be overestimations of the actual costs of screening. Routine antenatal screening would be estimated to cost between £90,000 and £143,000 per case detected, depending upon the uptake. Future technical developments may reduce this cost. The estimated lifetime care cost for an affected individual is a minimum of $1,000,000 (USA)	Current estimates of the healthcare costs of prenatal and other population screening strategies suggest a cost-saving balance, but the prevalence figures on which these are based may be misleading, so the consequences of alternative hypothetical estimates were discussed. Systematic case finding and cascade testing are a partial alternative to population screening but require more staff and laboratory resources at regional genetics level to be feasible. Information from MENCAP indicated that the annual cost per FXS adult would be at least £20,000 (UK£, 1995).
Conclusions and recommendations	Current practice of limited neonatal screening and some cascade screening in many centres should continue. More research is needed before active screening programmes should be implemented in NHS, in particular: assess current practice of neonatal screening when there is developmental delay; a national audit of cascade screening should be initiated; the psychosocial implications of having a PM should be assessed; the feasibility of routine antenatal screening should be evaluated in a pilot study; a central register of DNA-based diagnoses should be set up.	Systematic case finding and cascade testing could achieve benefits for women most at risk. Any trials would be based on reasonably reliable counselling data. Uncertainty about risks for women from the general population with 55–65 repeats is not known, so a population screening programme would not be feasible.

Appendix 2

Questionnaire for current practice survey

Survey of current practice for diagnosis, testing and counselling for Fragile X syndrome in UK clinical genetics centres

Instructions:
Please indicate your response to the questions by marking the appropriate box, and elaborating where necessary.
Space is provided at the end of the questionnaire for further information and comments.

Section 1: Genetic counselling

1. Does your centre offer genetic counselling for families affected by Fragile X syndrome?

   ☐ Yes (go to Q2) ☐ No – nearest centre that does .... (go to section 2)

2. In general, have the individuals referred to your centre for genetic counselling for Fragile X syndrome already undergone molecular genetic testing prior to referral?

   ☐ Yes, patients are *typically* referred for counselling due to a positive Fragile X genetic test result.
   ☐ No, patients are *typically* referred for genetic investigation into causes of developmental delay/learning difficulty etc.

3. Which clinical speciality is the most frequent source of new Fragile X referrals to your centre?

   ....

4. Does your centre have a designated Fragile X register, or procedure for reviewing cases?

   ☐ Yes ☐ No

   If yes, please give brief details ....

5. Which members of staff typically make the first/pre-clinic contact with the proband/family members? (*please tick all that apply*):

   ☐ Genetic Counsellor/Associate/Nurse
   ☐ Consultant
   ☐ Non-consultant medical staff
   ☐ Other, please specify ....

6. What is the usual first/pre-clinic contact method?

   ☐ By telephone
   ☐ Visit to proband/family member's home
   ☐ At a hospital outpatient clinic
   ☐ Other, please specify ....

7. Please state how long is typically allocated for the first/pre-clinic contact: ....

8. Please briefly describe the main purpose of the first/pre-clinic contact:

   ....

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9. Are patients usually invited to a clinic following their first/pre-clinic contact?

☐ Yes
☐ No
☐ Depends on outcome of pre-clinic contact (please give brief details):

....

10. Who usually sees the proband/family members in clinic? (*please tick all that apply*):

☐ Genetic Counsellor/Associate/Nurse
☐ Consultant
☐ Non-consultant medical staff
☐ Other, please specify ....

11. Where is the patient usually seen during this contact?

☐ At a hospital outpatient clinic
☐ Other, please specify ....

12. Please briefly describe the main purpose of this clinic contact: ....

13. Please state how long is typically allocated for this contact: ....

14. Carrier testing: does your centre typically offer carrier testing for the following family members of the proband, where feasible and acceptable?

	Yes	No	Specific conditions (e.g. lower age limits etc.):
Mother of the proband?	☐	☐	....
Siblings of the proband?	☐	☐	....
Offspring of a female FM carrier?	☐	☐	....
Offspring of an individual with a PM?	☐	☐	....
Other family members of a proband?	☐	☐	....

....

Section 2: Diagnosis/testing procedures

15. Does your centre offer a laboratory service for the diagnosis/testing for Fragile X syndrome?

☐ Yes ☐ No – nearest centre/service that does ....

16. Please indicate the techniques used for diagnosis/testing in a *clinical testing* capacity by your centre:

☐ Chromosome analysis technique(s) ....
☐ Protein testing technique(s) ....
☐ Molecular genetic testing (*FMR1*) technique(s) ....
☐ Other technique(s) ....

17. What are the CGG repeat lengths used by your laboratory service for reporting different alleles?

Normal ....
Grey zone ....
PM ....
FM ....

18. What is the typical turnaround time from the receipt of the blood sample in the laboratory to the receipt of the result by the clinical geneticist/referring clinician?

Routine carrier testing .... Prenatal diagnosis..

Section 3: Prenatal diagnosis/testing

19. Do pregnant Fragile X family members have prenatal contact with the clinical genetics service to discuss carrier and prenatal testing options?

☐ Yes ☐ No

20. Which members of staff typically make the prenatal contact? (*tick all that apply*):

☐ Genetic Counsellor/Associate/Nurse
☐ Consultant
☐ Non-consultant medical staff
☐ Other, please specify ....

21. What is the usual contact method?

☐ Telephone
☐ At proband's/relative's home
☐ At hospital outpatient clinic
☐ Other, please specify ....

22. Please state how long is typically allocated for this contact: ....

23. For carriers who choose to have prenatal diagnosis, who explains the procedure to them?

☐ Genetic Counsellor/Associate/Nurse
☐ Member of prenatal diagnosis nursing staff
☐ Consultant
☐ Non-consultant medical staff
☐ Other, please specify ....

24. Where is this usually done?

☐ Via telephone
☐ At proband/relative's home
☐ At hospital outpatient clinic
☐ Other, please specify ....

25. Please state how long is typically allocated for this contact: ....

26. Who reports the result to the patient?

☐ Genetic Counsellor/Associate/Nurse
☐ Member of prenatal diagnosis nursing staff?
☐ Consultant
☐ Non-consultant medical staff
☐ Other, please specify ....

27. Where is this usually done?

☐ Via telephone
☐ At proband/relative's home
☐ At hospital outpatient clinic
☐ Other, please specify ....

28. Please state how long is typically allocated for this contact: ....

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Section 4: Further comments

Please use this page to elaborate any responses or to provide any further comments:
....
....
....

Thank you for your time in answering these questions

It would be very helpful if you could provide us with a contact name in case we need any further information. If you would be agreeable to this, please provide the details below:

Contact name: ....
Position: ....
E-mail address: ....
Telephone number: ....

Appendix 3

Literature search strategies

MEDLINE search strategy

1 Fragile X Syndrome/(2175)
2 fragile x syndrome$.ti,ab. (1358)
3 fra X.mp. (428)
4 martin bell syndrome$.mp. (129)
5 x linked mental retard$.mp. (428)
6 (xlmr or fraxa or fraxd or fraxf or fmr1).mp. (628)
7 or/1–6 (2774)
8 limit 7 to yr = 1991–1995 (920)
9 limit 7 to yr = 1996–2001 (957)

EMBASE (Ovid) 1980–September 2001

1 fragile x syndrome/
2 fragile x syndrome.ti,ab.
3 fra x.mp.
4 martin bell syndrome$.mp.
5 x linked mental retard$.mp.
6 (xlmr or fraxa or frax or fraxd or fraxf or fmr1).mp.
7 or/1–6
8 limit 7 to human
9 limit 8 to yr = 1991–1995
10 limit 8 to yr = 1996–2001

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Appendix 4

Coding for included studies

Papers should be coded according to their subject content as follows. The code should be entered into the CODE field in the references database. Many of the papers will overlap in subject content, in which case the papers should be coded with as many subjects as appropriate.

Subject of paper	Database code
Costs of screening for Fragile X or managing individuals with Fragile X	COST
Feasibility and **acceptability** of screening	FASC
Frequency of **PMs** and **FMs**	FREQ
General **review**	GENR
Modelling allele dynamics	MOD
Performance of **diagnostic tests** (including PCR and Southern blotting)	PERF
Prevalence of Fragile X syndrome	PREV
Quality of life of patients with Fragile X, or their carers	QOL
Risks of expansion of a PM to a FM, and associated factors	RISK
Screening outcomes for Fragile X	SCRN
Systematic review	SYSR
Any **other** aspect of Fragile X syndrome, not covered above (please specify the general focus of the paper in OTHER FRAX CONTENT field)	OTH

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Appendix 5

Studies of prevalence of PM or FM

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Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Angel *et al.*, 2000[35] Mexico Children with learning difficulty of unknown cause (MRUC)	62 children, aged 3 months to 17 years, referred to a Genetics Department, with learning difficulty of unknown cause. 71 chromosomes from 53 males and 9 females.		2 FXS males were diagnosed. The prevalence of FXS in children with learning difficulty of unknown cause was 3.2% (2/62). In MRUC males, it was 3.8% (2/53).	
Arrieta *et al.*, 1999[36] Spain (Basque) Idiopathic learning difficulty	134 (92 males and 42 females) individuals with idiopathic learning difficulty from institutions and special schools from Biscay province.		8 males and 2 females cases were identified. Prevalence of FXS: Male 8.7% (8/92) Female 4.8% (2/42) Overall 7.5% (10/134)	
Arrieta *et al.*, 1999[116] Spain (Basque) General population	242 X chromosomes, from 170 unrelated individuals of Basque origin (98 males, 72 females).	None. Range of CGG repeats: 19–43.		
Arvio *et al.*, 1997[13] Finland Unknown cause of learning difficulty	344 males with learning difficulty without an aetiology. Screening programme comprised 3 steps: a clinical checklist used by a specialist nurse, a clinical examination by a physician and the FRAXA-locus gene test.		The DNA analysis was performed in 44 males selected by the checklist and clinical examination. 6 new fragile X males detected. The minimum prevalence of the FXS was calculated to be 1:4400 males in general population.	
Chen *et al.*, 1997[117] China (Hong Kong and Guang Zhou) General population	83 normal southern Chinese (42 males and 41 females).	None. Range of CGG repeats: 17–37.		Also reported that 3 clinically diagnosed FXS patients did not have a greatly expanded CGG segment. It is possible that the expansion of the CGG repeats may not be as frequent a cause of FXS in southern Chinese as in other ethnic groups.

continued

Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Cora *et al.*, 2000[24] Turkey (Konya) Children with learning difficulty	120 children from 11 special subclasses for borderline intelligent to mildly retarded children.		5 males with FXS (5.3%, 5/95) and 1 female with FXS (4%, 1/25). Overall prevalence in people with learning difficulty: 5% (6/120).	
Crawford *et al.*, 1999[25] Atlanta, GA, USA Children attending special education needs (SEN) classes	Samples were from 2873 children, aged 7–10, attended SEN classes. Participation rate was 46%.	Two PMs (>60 repeats) were detected in females. The estimated prevalence of PM in white females was 1/317 (CI: 1/832 to 1/79).	(1) 5 FM males (5/1979) and no FM female (0/872) were diagnosed (all cases known previously). (2) The prevalence of FM was estimated to be 1/396 in male SEN population. (3) The estimated prevalence of FXS was 1/3968 (CI:1/7353 to 1/2188) in general male population.	Estimation of prevalence was based on some assumptions.
de Vries *et al.*, 1997[11] The Netherlands People with learning difficulty	3352 individuals in schools and institutes for learning difficulty. Inclusion criteria: unknown cause of learning difficulty, no cerebral palsy and no previous testing for *FMR1* gene. 70% of the parents/guardians of 2170 eligible patients consented to participation.		Including 9 newly detected and 30 previous known cases, the prevalence of FXS was 0.0198 in mildly retarded males, and 0.0244 in moderate/severe retarded males. The prevalence of FXS in the general male population in the Netherlands was estimated to be 1/6045 (95% CI: 1/3851 to 1/9981).	All newly diagnosed male patients showed the high-risk phenotype. Clinical preselection for DNA testing in males with learning difficulty is feasible using a simple scoring list, which will increase the efficiency of further testing eightfold (de Vries *et al.*, 1999).[12]
Elango and Verma, 1996[18] India (New Delhi) People with learning difficulty	1111 patients with learning difficulty. Cytogenetic test was provided to 55 of the 1111 patients who met the criteria: with clinical features of FXS; no physical malformations except facial dysmorphism; and with a positive family history of learning difficulty of unknown cause.		20 FXS identified. 1.8% (20/1111)	It is possible that there were FXSs among those (n = 1056) who were not tested.

continued

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Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Elbaz *et al.*, 1998[26] French West Indies (Caribbean Island) Learning difficulty	163 boys and 85 girls with learning difficulty, aged 7–18, attending specialised schools.		11 FM boys (6.7%, 11/163) and 0 FM girls. Overall 4.4% (11/248). The estimated minimal prevalence of FXS was 0.42/1000 (or 1/2381) among male births.	No FRAXE detected.
Faradz *et al.*, 1999[118] Indonesian Development disability	293 boys with mild development disability, minimal dysmorphism, absence of typical Down syndrome phenotype and no other chromosomal abnormalities. 262 successful DNA analyses.	One had a premutation (CGG repeat size 83)	Two FM and two mosaic. The frequency of FXS was 1.9% (5/262).	It is not clear why one PM was included in the calculation of overall prevalence of FXS. Without this PM case, the frequency was 1.5% (4/262).
Faradz *et al.*, 2000[81] Indonesia General population	1069 male volunteers from 12 Indonesian sub-populations.	4 PM detected (with 55, 55, 57 and 57 CGG repeats), with a total prevalence of 1/267. (All 4 PMs from the 120 males of Hiri Island.)		A high frequency of small premutation alleles (4/120) was identified in the Moluccan population of Hiri Island.
Gerard *et al.*, 1997[27] France People with learning difficulty	574 children (403 boys and 171 girls) with learning difficulty.		10 FXS boys: 2.5% (10/403) 1 FXS girls: 0.6% (1/171)	Clinical examination, especially in the youngest children, was often unremarkable, and the only reason for suspecting FXS was the presence of learning difficulty.
Geva *et al.*, 2000[67] Israel Normal pregnant or preconceptual women	9660 preconceptual or pregnant women.	85 PM (>50 repeats) carriers identified. (1/114 = 85/9660). Following data were based on 68 PM carriers who were pregnant and had no family history of learning difficulty: 50–59: 34 60–69: 20 70–79: 6 80–89: 3 ⩾90: 3	No mention of FM.	The likelihood of FX PM expansion to FM is significantly lower in individuals from the general population. Had 55 repeats been used as the lower cutoff, the carrier frequency would have been 1/159.

continued

Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Giangreco *et al.*, 1996[119] USA (Pittsburgh) Patients referred for FXS testing	Retrospective analysis of data from 273 boys and 62 girls referred for FXS testing.			With a simplified 6-item clinical checklist, 60% of testing could have been eliminated, thereby improving the cost-effectiveness of FXS testing and increasing the proportion of cases with positive results threefold.
Haddad *et al.*, 1999[47] Brazil (Belo Horizonte) People with learning difficulty	256 boys with learning difficulty from special schools.		5 FXS cases identified: 2% (5/256).	
Hecimovic *et al.*, 1998[120] Croatia Children with high-risk FXS	108 children (81 boys and 27 girls) with clinical indications of FXS: learning difficulty of unknown cause or positive family history and presence of at least one physical or behavioural characteristic of FXS.		14 FXS boys identified: 13% (14/108 all) or 17% (14/87 boys).	Simple preselection criteria can considerably increase the proportion of identified FXS cases.
Hou *et al.*, 1998[19] China (Taiwan) Children with learning difficulty	11,892 children (6937 boys and 4955 girls) with learning difficulty, from a large-scale cytogenetic study of the causes of ID in children from special schools and institutions in Taiwan between 1991 and 1996.		233 FXS from 182 families: 2% (233/11892).	
Iqbal *et al.*, 2000[29] Saudi Arabia Patients with learning difficulty, development delay or clinical suspicion of FXS.	259 male and 46 female patients. Majority <20 years old.		24 male and 2 female patients were found to express the fragile X site at q27.3. The prevalence of FXS in these patients was 9.27% (24/259) for males and 4.35% (2/46) for females.	It seems the calculation of prevalence (%) in the paper was not correct.

continued

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Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Jara *et al.*, 1998[37] Chile (Santiago) Unspecified learning difficulty	300 patients (214 male) aged 4–26, with unspecified learning difficulty.		4 male FXS cases identified: 1.9% (4/214 males) or 1.3% (4/300 overall).	
Kwon *et al.*, 2001[38] Korea Children with learning difficulty of unknown aetiology	101 children (77 males and 24 females) from the paediatric neurology clinic, suffering from learning difficulty of undetermined cause (63), autism spectrum (31) and learning disability (7).	None.	One FM identified (1%, 1/101).	Expanded long template PCR may be used as the first screening test for detecting FXS.
Lantigua-Cruz *et al.*, 1999[49] Cuba (Havana) Severe learning difficulty males	54 males with severe learning difficulty and belonged to aetiological categories of prenatal, because of suggestive facial features, X-linked inheritance, prenatally unknown, psychosis and untraceable.		7 cases were found (13%, 7/54) in the tested subjects. The overall prevalence could be estimated as >2.3% (7/306)	A total of 306 SLD males included in this aetiological study, but not all had been tested for FXS.
Larsen *et al.*, 1999[72] Greenland General population	101 newborn boys sampled randomly from the Greenland population.	None. CGG repeats range: 17–44.		
Larsen *et al.*, 2000[73] Denmark General population	Blood spots on filter-paper, used for newborn screening, were used as sample material. A total of 2012 samples from new born males were randomly collected from the daily routine. The CGG repeats were determined by PCR from 1686 samples (326 failed to amplification).	3 PM alleles (size 56, 60 and 91 repeats) were detected. The prevalence of PM in newborn males was 1/562 (3/1686). 151 alleles were in the grey-zone range (34–60 CGG repeats).	None.	This paper is mainly about the haplotype and AGG-interspersion analysis of *FMR1* alleles.
Limprasert *et al.*, 1999[61] Thailand Development delay	237 Thai boys (<15 y) from three medical centres, with development delay or learning difficulty of unknown cause.		16 FXS boys identified: 6.8% (16/237)	Family members of the 16 index cases were screened: 31 PM carrier females, 4 PM males were identified. Data may also be presented in Ruangdaraganon *et al.*, 2000[121] and in Jinorose *et al.*, 1997.[122]

continued

Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Mazzocco *et al.*, 1997[123] USA (Baltimore) Academic difficulty (without learning difficulty)	1014 school-age children (673 boys and 341 girls) with academic difficulties but without learning difficulty.	1 boy had a PM (67 CGG repeats).	None.	Neither the *FMR1* nor the *FMR2* mutation is a common aetiology of academic failure among school-age children without learning difficulty and the prevalence of the *FMR1* PM is no more frequent in children with academic failure than it is in the general population.
Mila *et al.*, 1997[39] Spain (Barcelona) People with learning difficulty	222 unrelated children with learning difficulty (4–20 y, 182 males and 40 females) from 9 special education schools. Excluded were learning difficulty of known cause.		11 FM males: 5% (11/222) or 6% (11/182 males only). 1 FRAXE-positive boy identified.	By contacting families of the 11 FXS cases, 16 individuals were screened, detecting 1 FXS boy, 7 female PM carriers and 2 female FM carriers.
Milewski *et al.*, 1996[93] Poland Family members of FXS cases	85 individuals (42 males and 43 females) from 18 families of 28 male and 9 female with learning difficulty. The patients were classified on the basis of clinical features and expression of the fragile X site (FRAXA).	Premutations were found in 17 females (39.5%, 17/43) and in one transmitting male (2.4%, 1/42): 65–75: 1 75–85: 6 85–95: 6 95–200: 4	FM was found in all affected males and in all FX positive females irrespective of their mental status.	Index cases were also included in the analysis.
Millan *et al.*, 1999[40] Spain (Valencia) People with learning difficulty	(1) Outpatients with learning difficulty referred to a genetics unit of a hospital; (2) children from 8 special education schools. Excluded were those children diagnosed with well-characterised syndromes.		Hospital outpatients: 8% (male 8.1%, 15/186; female 7.8%, 4/51) Special education schools: 1.9% (male 3.3%, 3/91; female 0%, 0/64).	
Morton *et al.*, 1997[66] UK (Coventry) General school children	A re-analysis of data from a population based study of school children (age 11–16) in Coventry.		Frequency of FXS: 1/2197.	It was a short abstract.

continued

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Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Murray *et al.*, 1996[51] UK (Hampshire) Boys with learning difficulty	1013 boys with unexplained learning difficulties, age 5–18, in the state school system. DNA from 726 mothers of boys were obtained. The X chromosome passed from mother to son is considered the 'experimental' chromosome, whereas that not transmitted is the 'control' chromosome.	1 PM boy identified (152 repeats). Grey zone size: Exptl / Ctrl 51–52: 3 / 1 53–54: 2 / 1 55–56: 1 / 0 57–59: 2 / 0	5 FRAXA FM identified (3 were newly identified) (0.5%, 5/1013). The estimated population prevalence of FXS was 1/4995. No FRAXE FM.	Data presented were preliminary findings from the programme. More updated information was reported in the abstract by Murray *et al.*, 2000.[52]
Murray *et al.*, 2000[52] UK (Hampshire) Learning difficulty	3738 males with learning difficulty, aged 5–18.	There was an excess of intermediate sized FRAXA (41–60 repeats) and FRAXE (31–60) alleles in males with learning disability compared with controls.	20 FRAXA FM (0.5%) and 1 FRAXE FM (0.027%). The population prevalence of FXS was estimated to be 1/5530 (95% CI 1/8922, 1/4007).	It was an abstract only
O'Dwyer *et al.*, 1997[62] UK (Leeds and Sheffield) Idiopathic learning disability (ILD)	138 male patients, aged 19–82, with learning disability of unknown cause (varied from mild to profound).		1 FM identified (0.7%, 1/138).	Authors concluded that indiscriminate mass screening of those with learning disability for FXS is probably not useful because, in adults, physical signs and a family history of learning disability can predict those likely to have the disorder.
Pang *et al.*, 1999[41] China (Hong Kong) Normal and people with learning difficulty	649 (299 males and 350 females; 999 X chromosomes) healthy voluntary staff. 324 (243 males and 81 females; 405 X chromosomes) patients with mild learning difficulty of unknown cause.	In normal subjects: CGG repeats range 19–54. In people with learning difficulty without FM: CGG repeats range: 20–47.	In normal subjects: none. In people with learning difficulty: 1 male and 1 female FM identified (0.6% 2/324 patients, or 0.5% 2/405 alleles).	Authors suggested that a large-scale screening programme would be worthwhile to determine the prevalence of FXS in the Chinese population.

continued

Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Patsalis *et al.*, 1999[42] Greece and Cyprus ILD	866 unrelated ILD individuals (611 males and 255 females), aged 3–25, referred to laboratory based on a detailed clinical and laboratory examination that excluded obvious clinical syndromes, chromosomal anomalies and metabolic disorders.	2 PM boys identified. These 2 PM boys had borderline learning difficulty and some of the behavioural problems of FXS.	8 FM males identified Male: 1.3% (8/611) Overall: 0.9% (8/866) Based on the total population aged 3–25 and prevalence of ILD, it was estimated that the prevalence of FXS was 1/4246 in the Cyprus general population.	Data in this study may have been used in Syrrou *et al.*, 1998[43] No FRAXE mutation identified.
Patsalis *et al.*, 1999[23] Canada and Cyprus Normal and patients with development disability (DD)	4 groups of subjects: (1) Cyprus DD – 550 patients with idiopathic DD from Cyprus (2) Cyprus control – 1132 individuals with β-thalassaemia carriers but no other clinical disorder or learning difficulty (3) Canadian DD – 1550 patients with idiopathic DD from Canada (4) Canadian control – 2073 anonymous newborn males and no clinical information	40–49, 50–54, 55–69 (%) Cy-DD 15 (2.7), 2 (0.4), 1 (0.2) Cy-Ctrl 32 (2.8), 0 (0.0), 7 (0.6) Can-DD 61 (3.9), 8 (0.5), 6 (0.4) Can-Ctrl 74 (3.6), 3 (0.14), 1 (0.05). (More detailed data are available from Table 1 in the paper).	None.	There was an increased frequency of PM-size alleles in the Cyprus control group, a finding which may reflect a founder effect since the controls are β-thalassaemia carriers. The observation of an increased frequency of PM in the Canadian DD group may represent a true increased risk of DD in persons with PM in families without a family history of FXS.
Patsalis *et al.*, 1999[84] Cyprus General population	750 individuals (both male and female) from 100 three-generation families. Referred for thalassaemia-carrier studies at an institute. 1132 chromosomes.	PM/chromosomes 56: 3/1132 59: 3/1132 60: 1/1132		

continued

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Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Pesso *et al.*, 2000[68] Israel Normal pregnant or preconceptual women	9459 women aged 19–44 were tested. Excluded those who had a known family history of FXS. However, women were separated as at high risk if there were any family history of learning difficulty or development problems in the extended family.	123 PM in 8426 low-risk women and 7 PM in 1033 high-risk women identified: Low-risk (*n* = 8426) / High-risk (*n* = 1033) 52–53: 53 / 3 54–55: 20 / 1 56–60: 32 / 0 61–69: 11 / 0 70–79: 3 / 0 80–89: 2 / 1 ⩾90: 2 / 2	1 FM among 8426 low-risk women and 3 FM from 1033 high-risk women were identified.	Concluded that screening for FXS among women of reproductive age should be more widely available, because of high rate of PM in the population. More detailed data for premutation repeats size were available.
Poon *et al.*, 2000[85] China (Hong Kong and Dalian) General population	Normal Chinese in (1) Hong Kong (497 voluntary medical staff and students) and (2) Dalian (42 medical students). A total of 858 X chromosomes.	5 CGG repeats were >50 (52, 53, 53, 53 and 54).	None.	Detailed data available for distribution of CGG repeats among normal people.
Rousseau *et al.*, 1995[69] Canada (Quebec) General population	10,624 unselected women. Leftover samples from the haematology laboratory of a general hospital.	41 PM carriers (>54 CGG repeats) were identified, with a prevalence of 1/259 (95% CI: 1/373 to 1/198): 55–59: 11 60–64: 12 65–69: 4 70–74: 8 75–79: 2 80: 1 86: 1 99: 1 101: 1	None.	If using the number of alleles as the denominator, the prevalence will be reduced by half: 41/21,248.
Ryynanen *et al.*, 1995[101] Finland Relatives of FXS cases	219 male and 288 female relatives of identified FXS patients. These relatives were of at least 12.5% risk of FXS.	PM (65–200 CGG repeats) Male: 30/219 Female: 133/288 (Not able to separate further into different sizes.)	FM: Male: 20/219 Female: 46/288	

continued

Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Ryynanen *et al.*, 1999[70] Finland Normal pregnant women	1477 pregnant women attending a prenatal screening programme. Excluded were those with a family history of FXS.	*N* = 1477. 40–50: 43 50–60: 12 >60: 6	None.	Concluded that antenatal screening provides an effective way of identifying carriers. No more detailed data available.
Saha *et al.*, 2001[22] India (Calcutta) Unclassified learning difficulty	98 subjects who showed unclassified learning difficulty and attending institutions or referred to authors' department.		6 men and one woman with full mutations (7%, 7/98).	Not able to separate males and females.
Sharma *et al.*, 2001[31] India (New Delhi) Learning difficulty individuals	130 individuals with mild/moderate learning difficulty, and with the FXS clinical phenotype, from institutionalised population.	14 PM carriers identified, all of whom were females and belonged to FXS families.	9 FM males (10%, 9/93) and 1 FM female (2.7%, 1/37). The overall frequency of FXS was 7.7% (10/130) in these samples of LD individuals.	
Sucharov *et al.*, 1999[83] Brazil (Rio de Janeiro) Normal population	100 X chromosomes from the normal male Brazilian.	3 alleles were >43 repeats (46, 47 and 130 repeats).		No details about sample source. 130 CGG repeats not mentioned in the discussion.
Syrrou *et al.*, 1998[43] Greece or Cyprus People with learning difficulty	433 unselected individuals (257 males and 176 females), aged 3–25 years with non-specific learning difficulty. None had the typical phenotypic features of the FX syndrome or family history.	1 PM boy (80 repeats) with borderline mental status (speech delay and learning difficulties)	4 FM boys identified. Male: 1.6% (4/257) Overall: 0.92% (4/433)	No FRAXE mutation identified. See Patsalis *et al.*, 1999[42] for possible duplication in data
Syrrou *et al.*, 1998[86] Greece or Cyprus General population	199 normal individuals (75 males and 124 females). CGG data from 323 chromosomes are included.	Range of CGG repeats: 17–55. 1 with CGG repeats>50.	None.	
Tan *et al.*, 2000[54] Singapore Learning difficulty individuals	255 males with unexplained cause for learning difficulties from 8 special schools.		6 new cases of FXS were detected (2.4%, 6/255).	Clinical features have been found to be generally not predictive.

continued

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Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Toledano-Alhadef *et al.*, 2001[17] Israel Normal pregnant or preconceptual women	14,334 preconceptual or pregnant women, on their own initiative or on the advice of their physician. Women with family history of learning difficulty were excluded from the analysis.	204 PM (>50 repeats) carriers identified among 14334 women. 50–54: 80 55–60: 62 61–65: 15 66–70: 25 71–75: 4 76–80: 9 81–200: 9	3 FM carriers identified. (3/14,334).	Authors recommended that screening should be carried out on a wide scale.
Tuncbilek *et al.*, 1999[44] Turkey People with learning difficulty	179 children (166 males and 13 females) with development disability of unknown cause, who were referred either by a paediatric neurologist or a paediatrician to a Genetics Department.		5 FXS boys identified (2.8%, 5/179). All cases were in the high-risk group according to a checklist of clinical finding.	If patients with learning difficulty of unknown aetiology are evaluated with the fragile X checklist prior to DNA testing, those in the low-risk group can be excluded from the more expensive DNA analysis. Also see Tuncbilek *et al.*, 2000.[65]
Tuncbilek *et al.*, 2000[65] Turkey People with learning difficulty	300 males with learning difficulty of unknown cause, attending special education schools.	None.	5 FXS identified (1.7%, 5/300).	Screening was based on a non-invasive antibody test of FMRP in hair root. All confirmed by DNA analysis.
Turner *et al.*, 1992[33] Australia and UK People with learning difficulty	14,225 individuals attending adult and child facilities for learning difficulty. Only 3862 were tested (after clinical examination, consents requests and consents receiving).		214 male and 39 female FXS identified. Male: 2.5% (214/8671 screened) or 10.1% (214/2122 tested) Female: 0.7% (39/5554 screened) or 3.5% (39/1125 tested)	
Turner *et al.*, 1996[55] Australia and UK People with learning difficulty	Reassessment of prevalence of FXS by Southern Blot testing in two studies.[33,56]	Not reported.	Prevalence of FXS in males: 1/4350 (Sydney) 1/4090 (Coventry)	

continued

Study, country and subjects	Sample and methods	PM prevalence	FM prevalence	Other findings/comments
Turner *et al.*, 1997[104] Australia Relatives of FXS cases	Relatives of FXS patients	Included with FM	Combined PM and FM carriers Female relatives: 47.8% (651/1363) Male relatives: 57.5% (560/974)	
Tzeng *et al.*, 1999[124] China (Taiwan) General population	100 women and 100 men (300 X chromosomes) were randomly and anonymously collected from an outpatient clinic.	1 PM (CGG repeats: 95) was identified. Frequency: 1/300 alleles.		Further technical improvement may be needed to be more cost-effective for a wide screening of all pregnant women.
Tzeng *et al.*, 2001[34] China (Taiwan) People with learning difficulty	415 male and 160 female individuals with learning difficulty.		Prevalence of FXS in people with learning difficulty: Male 2.6% (11/415) Female 0.63% (1/160).	Part of the data were used in a previous publication (Tzeng *et al.*, 2000)[125]
Wang *et al.*, 2000[20] China (Taiwan) Normal individuals and people with learning difficulty	316 healthy individuals (350 X chromosomes) who were college students or faculty members. 349 people with learning difficulty (429 X chromosome) from a rehabilitation institute.	None. Range of CGG repeats: 16–45.	None.	
Wenstrom *et al.*, 1999[71] USA (Birmingham) Pregnant women with a family history of non-specific learning difficulty	263 pregnant women who report a family history of non-specific learning problems, attention deficit–hyperactivity disorder, cerebral palsy or any features of autism. Women from known FXS families undergoing FXS testing were excluded.	None.	None.	Testing the affected proband is superior to screening the pregnant relative of the proband for identification of families at risk for FXS.
Zhong *et al.*, 1999[21] China (4 cities plus Hong Kong) People with learning difficulty	People with learning difficulty attending special education schools from 4 cities of mainland China (Tonglin, Wuhan, Xian, Tianjin) and Hong Kong.		32 FM identified: 2.7% (32/1127)	Males and females not separately reported.

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Appendix 6

Studies of risk of expansion from PM to FM

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Study	Subjects	Results/data	Major findings	Other/comments
Geva *et al.*, 2000[67] Israel General population *n* = 44 foetuses inherited the mutated alleles.	Women testing positive for PM in a population based prenatal *FMR1* carrier detection programme. No family history of FXS or known PM or FM.	No. of FM/total foetuses with mutations: 50–59: 0/17 60–69: 0/12 70–79: 0/4 80–89: 0/3 90–: 5/8	The overall probability of expansion to FM in PM transition was 11.4% (5/44). It seems that the likelihood of FraX PM expansion to FM is significantly lower in individuals ascertained by general prenatal carrier testing than in those from known FraX families.	Authors calculated the likelihood of expansion to FM from PM using the no. of mother carriers. It may be more appropriate to use the no. of foetal abnormal alleles as the denominator.
Toledano-Alhadef *et al.*, 2001[17] Israel General population *n* = 89 transmission of *FMR1* PM from mother to foetus.	173 pregnant carriers from a preconceptual or prenatal screening programme. Women with a family history of learning difficulty were excluded.	Foetal FM/total PM transmissions: 50–55: 0/39 56–60: 0/22 61–65: 0/8 66–70: 2/12 71–75: 0/3 76–80: 1/3 81–200: 1/2	The overall risk of expansion to FM in female PM transition was 4.5% (4/89).	
Pesso *et al.*, 2000[68] Israel General population *n* = 46 transmission of *FMR1* PM from mother to foetus.	130 PM carriers were identified by a preconceptual or prenatal screening programme (123 without a family history of learning difficulty).	Foetal FM/total PM transmissions: 50–60: 0/30 61–70: 1/8 71–79: 1/2 80–89: 1/2 90–99: 1/1 100–150: 3/3	The overall risk of expansion to FM in female PM transition was 15.2% (7/46).	Self-referred women may not be representative of the general population as a whole (similarly, also as in Geva *et al.*, 2000[67] and in Toledano-Alhadef *et al.*, 2001[17]).
Ryynanen *et al.*, 1999[70] Finland General population *n* = 4 transmissions from PM mother to foetus.	Cases were from a programme of prenatal screening.	Foetal FM/total PM transmissions: 56: 0/1 70: 0/1 70: 1/1 90: 1/1		Very small sample size.

continued

Study	Subjects	Results/data	Major findings	Other/comments
Ashley-Koch *et al.*, 1998[91] Australia, USA From families with FXS *n* = 432 offspring of PM females.	Data were from 4 centres (one in Australia and 3 in USA). The prospective cases of 50 PM transmission have been reported in Sherman *et al.*, 1996.[98]	No. of FM/all with mutated genes: 50–59: 5/43 60–69: 6/71 70–79: 104/218 80–89: 63/100	(1) The difference between female and male transmissions may be due to selection against FM sperm. (2) Increasing maternal age was associated with increasing risk of expansion to the FM, possibly owing to selection for smaller alleles within the offspring's soma over time. (3) Female and male offspring are equally likely to inherit the FM.	Linear and logistic regression was used to examine factors that may be associated with instability of the *FMR1* CGG repeat.
Fisch *et al.*, 1995[89] North America FXS families *n* = 174 (offspring with mutated *FMR1* gene).	Data were from 4 centres (many have been reported previously in the literature). Offspring from 140 females with PM was assessed. To avoid ascertainment bias, all index cases were removed from the analysis. There remained 110 female PM carriers who bore 174 offspring with *FMR1* gene mutations.	Percentage of FM (offspring with mutations): 50–59: 20% (5) 60–69: 17% (23) 70–79: 39% (38) 80–89: 76% (39) 90–99: 89% (35) 100–109: 91% (11) 110–119: 100% (9) 120–129: 100% (4) 130–: 95% (20)	There was an increase in risk to offspring for the FM as the size of the mother's PM increases. A logistic regression model was fitted (only graph presented, not equation). Using the data we obtained the following equation: $\mathrm{logit}(p) = -7.588 + 0.09863$ PM Size. Weighted by the frequency of PM, the aggregated risk that an offspring of the female with a PM would manifest the FM was 70% (±35%).	Findings of this study have been used by others in modelling effectiveness of screening for FXS. Some data in this study have been reported previously in Fu *et al.*, 1991,[95] and Snow *et al.*, 1993[79]
Fu *et al.*, 1991[95] North America and The Netherlands Not described but likely to be FXS families *n* = 63 female PM transmissions.	Not described.	Risk of expansion to FM in female transmissions: 50–59: 0/7 60–69: 1/6 70–79: 10/14 80–89: 14/17 90–99: 12/12 100–113: 7/7	Variation of the CGG repeat number is the basis of fragile X syndrome.	The data were also used in Fisch *et al.*'s 1995 study.[89] Discussed so-called 'Sherman paradox'.

continued

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Study	Subjects	Results/data	Major findings	Other/comments
Heitz *et al.*, 1992[96] France FXS families *n* = 175 maternal PM transmissions.	102 PM carrier mothers. The ascertainment bias was corrected by excluding one affected proband from each family.	Size / All cases / Bias adjusted 55–70: 4/22 2/20 70–90: 15/22 9/16 90–110: 64/69 45/50 110–130: 33/33 24/24 130–150: 18/18 15/15 >150: 11/11 6/6 Total: 145/175 (83%) 101/131 (77%)		
Kallinen *et al.*, 2000[97] Finland FXS families (mainly) and population screening *n* = 20 foetuses with mutated *FMR1* gene.	89 at-risk pregnancies: 74 identified by cascade screening, 12 by antenatal screening and 3 by offering tests to women undergoing amniocentesis or CVS for other reasons.	No. of FM/total foetuses with mutations: 40–59: 0/3 60–80: 1/7 80–100: 8/9 100–200: 1/1	The range of 40–59 repeats was safe. The risk of full mutation was low among the subjects with a repeat size between 60 and 80, whereas the risk increased significantly after 80 repeats. Maternal premutation size was positively correlated with the risk of having a full mutation offspring.	Table 2 provided a comparison with previous studies. Not able to separate cases according to sample sources.
Moutou *et al.*, 1997[90] France From FXS families *n* = 212 children with an PM, a FM or mosaic pattern of 112 PM carrier mothers.	Not described.	FM (including mosaic)/all children with mutated genes: 50–59: 0/6 60–69: 6/19 70–79: 18/27 80–89: 46/52 90–99: 34/36 100–104: 15/16 105–: 55/55	We found no effect of maternal PM size on incidence of mosaicism in leucocytes. A transition at an early morula stage (before day 3) cannot be formally excluded.	This study was mainly about whether expansion is postzygotic, including a simulation and some empirical data.
Murray *et al.*, 1997[94] UK Families ascertained from a regional genetic service or cascade screening. *n* = 61 maternal transmission of FRAXA PM.	136 families were selected because an allele of interest was segregating within them. For estimating likelihood of expanding to FM from maternal PM, probands in each family were excluded to correct for ascertainment bias.	No. of offspring with FM/total maternal transmission of PM alleles: 61–70: 4/17 71–80: 4/9 81–90: 9/14 91–100: 8/10 101–: 11/11	There was no clear correlation between haplotype and probability of expansion of FRAXA PM. Instability at FRAXA or FRAXE was more often observed in conjunction with a second instability at an independent locus suggesting general genomic instability as a possible mechanism by which at least some FRAXA and FRAXE mutations arise.	In Table 2, the number of PM size for each carriers was presented, which may be used for the modelling of risk. But it seems the number was not consistent with that in Figure 1.

continued

Study	Subjects	Results/data	Major findings	Other/comments
Nolin *et al.*, 1996[92] USA From FXS families *n* = 393 PM transmissions.	Most of the 191 families with FXS were clinically referred. To correct for ascertainment bias, one offspring with a full mutation was excluded from each sibship. (From names of co-authors, it is possible that data had been published in other papers)	No. of FM/meioses: 56–59: 3/12 60–69: 4/21 70–79: 44/70 80–89: 45/66 90–99: 61/66 100–109: 70/70 110–119: 38/39 120–129: 22/22 130–199: 26/27		Also presented results from a study by Snow *et al.*, 1993.[79]
Sherman *et al.*, 1996[98] USA Not described but likely from FXS relatives *n* = 80 PM transmissions.	Subjects were from collaborators of a Collaborative Prospective Fragile X Study. An individual is eligible if he or she is known to be a carrier prior to the presentation of their pregnancy.	Expansion of PM to FM: 50–59: 0/6 60–69: 3/8 70–79: 10/11 80–89: 10/16 ⩾90: 38/39	The risk of expansion to the FM may be correlated with maternal age and to the parental origin of premutation of carrier women.	
Vaisanen *et al.*, 1994[99] Finland FXS families *n* = 122 maternal PM transmissions.	134 nuclear families with FXS. The ascertainment bias was corrected by using Weinberg's method, excluding one affected proband from each family.	Size / All cases / Bias adjusted 60-70: 12/26 (46%) / 8/22 (36%) 70-80: 13/27 (48%) / 8/22 (35%) 80-90: 23/25 (92%) / 10/12 (83%) 90-100: 9/9 / 5/5 100-110: 5/5 / 1/1 110-120: 11/11 / 8/8 >120: 19/19 / 9/9 Total: 92/122 (75%) / 49/79 (62%)	In the maternal transmissions, the risk of expansion of a premutation to a full mutation appeared to depend on its size.	

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Appendix 7

Findings from empirical screening programmes

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Study	Programmed details	Main findings	Other/comments
Toledano-Alhadef *et al.*, 2001[17] Israel Preconceptual or prenatal testing	Between January 1992 and October 2000, preconceptual or pregnant women (*n* = 14,334) were tested with Southern blotting or followed by PCR (self-initiated). Excluded were women with a family history of learning difficulty. All carriers (>50 repeats) were offered genetic counselling. Pregnant carriers were provided with information about prenatal diagnosis (amniotic fluid or CVS; financed by Israel government).	Of 207 carriers (>50 repeats) identified (1/69), 3 women were carriers of full mutation. (Table 1 presents the no. of carriers for each range of CGG repeats). 173 of the 207 carriers were pregnant; 2 had miscarriages and 14 refused prenatal diagnosis. Acceptance rate was 92% (157/171). 177 prenatal diagnosis procedures (some women were pregnant more than once or with twins) were performed in pregnant carriers of PM or FM. The allele containing >50 repeats was transmitted in 90 (50.8%); 4 of the 5 with FM were expanded from PM (risk of expansion from PM to FM: 4.5%, 4/89). No FM was found in the foetuses of mothers with <70 CGG repeats. All 5 foetuses with confirmed FM were terminated.	Very high prevalence of PM and FM compared with other studies. From reported results of early 10,587 women (Drasinover *et al*., 2000[15]), it could be calculated that the frequency of PM was 1/77 and 1/57 in the early and late samples, respectively. So there may be bias owing to relatives of women with positive findings being more likely to participate in this self-paid study. (This bias, however, may be a good thing in practice for better efficiency of screening programme.)
Geva *et al*., 2000[67] Israel Preconceptual or prenatal testing	Over a 4-year period (1994–8), 9660 women underwent DNA test for FXS at a single medical centre. Prior to testing, genetic counselling was given regarding fragile X learning difficulty, etc. A 3-generation pedigree was obtained for each detected carrier (≥ 50 repeats). Results presented in this paper were pregnant carriers with no family history of X-linked learning difficulty.	Prevalence of premutation was 1/114 (85 women with 50–199 repeats) or 1/159 (had premutation defined as 55–199 repeats). 7 of these 85 carriers reported a family history of X-linked learning difficulty or *FMR1* mutation. 68 women (without family history) with 74 pregnancies agreed to undertake prenatal diagnoses. Abnormal allele was transmitted to the foetuses in 44 pregnancies and 5 expanded to full mutation (11.4%, 5/44). All carriers with full expansion (*n* = 3) were carriers of >90 repeats. This result was compared with findings of previous studies. It was concluded that the likelihood of fragile X premutation expansion to full mutation is significantly lower in individuals ascertained by general prenatal carrier testing than in those from known fragile X families.	Mentioned that for carriers with >70 repeats there appears to be a selective transmission of the premutated rather than the normal allele. There may be similar selection bias as in the study by Toledano-Alhadef *et al*., 2001.[17] In Table 2, likelihood of full expansion from PM was calculated using the number of women who transmitted abnormal allele. Is it more appropriate to use the total number of abnormal alleles transmitted?
Pesso *et al*., 2000[68] Israel Preconceptual or prenatal testing	From January 1994 to March 1999, a total of 9459 (self-funded) women (aged 19–44) were tested for FXS mutation. 1033 (high-risk women) reported a family history of learning difficulty and 8426 (low-risk women) did not. All detected carriers were referred to genetic counselling and offered prenatal diagnosis during the current or subsequent pregnancies.	134 carriers (≥ 52 repeats) were detected (1/70). In the low-risk group, there were 123 PM (1/68) and 1 FM (1/8400). In the high-risk group, there were 7 PM (1/150) and 3 FM (1/340). Carrier status of 111 foetuses was known. 9 with an FM (1/12); 4 belong to the low-risk group and 5 to the high-risk group. All FM foetuses were terminated. The probability of expansion from PM to FM was 15.2% (7/46); all from a PM >62 repeats. The uptake of invasive prenatal diagnosis was very high in carriers (89%, 101/113).	Mentioned that self-referred women may not be representative of the population as a whole. 11% were self-reported to have a family history of learning difficulty. To raise the cut-off for screening to >55 or 60 repeats would markedly reduce the required prenatal diagnosis (low risks, 1/69, 1/145, 1/383 respectively; high risks, 1/148, 1/258 and 1/258, respectively).

continued

Study	Programmed details	Main findings	Other/comments
Ryynanen *et al*., 1999[70] Finland Prenatal screening	From July 1995 to December 1996, DNA test was offered to 1477 pregnant women (1st trimester) at a health centre, free of charge, following counselling given by midwives. Detected carriers received detailed counselling and offered prenatal diagnosis testing.	The acceptance rate was 85% (1477/1738). Of the 1477 tested, 1416 had a normal *FMR1* gene, 43 with 40–50 repeats, 12 with 50–60 repeats and 6 carriers (>60 repeats) (1/246). 24 invasive prenatal diagnoses were performed (6 for 40–50 repeats, 12 for 50–60 repeats and 3 for >60 repeats). 1 foetal PM was detected in 12 women with 50–60 repeats; 1 PM, 1 FM and 1 size mosaic was detected in foetuses of 6 carriers (>60 repeats). Although most carriers (76%) were very anxious after receiving the test results, those confirmed by prenatal diagnosis as having normal foetuses considered the test to have had an overall positive influence on their pregnancy. It was estimated that the total cost of detecting one FM was £34,000.	2 FM foetuses in a total of 4 PM transmissions (2/4, including 1 of 12 with 50–60 repeats). This may be by chance, giving the small number of cases. Authors concluded that antenatal screening provides an effective way of identifying carriers and incorporating prenatal testing into this process.
Ryynanen *et al*., 1995[101] Finland Cascade screening	In a population of 900,000, 59 (53 males and 6 females) index cases of FXS were detected. PM was defined as 65–200 CGG repeats. Male or female relatives (with at least 12.5% risk of FXS) were cascade screened.	48% of (515/1071) relatives of the index cases who had increased risk of FXS (>12.5%) accepted the carrier screening. The number of female relatives tested per index case was 5 and male relatives 4. Among 288 female relatives, 133 PM and 46 FM were detected. Among 219 male relatives, 30 PM and 20 FM were detected. All pregnant female carriers ($n = 21$) underwent prenatal diagnosis (CVS); 3 foetal PM and 9 foetal FM were diagnosed. All FM foetuses were terminated.	Also reported that 7.6% were less certain concerning screening but accepted it later, and an absolutely negative attitude was expressed by 4.3% of the relatives. Suggested that carrier testing should be offered to pregnant women with a family history of learning difficulty of unknown cause.
Kallinen *et al*., 2001[102] Finland Applicability of carrier screening in women undergoing invasive prenatal diagnosis	From January 1997 to December 1998, 92.1% of 239 women undergoing invasive prenatal diagnosis (not for reasons of carrier screening) accepted an offer of gene tests for FXS, aspartylglycosaminuria and infantile neuronal ceroid lipofuscinosis (free of charge).	The programme detected 1 carrier of premutation of FXS, 7 aspartylglycosaminuria and 2 infantile neuronal ceroid lipofuscinosis. Foetuses were unaffected. Conclusion: carrier screening for single-gene disorders is feasible and well accepted among pregnant women undergoing invasive prenatal testing. Incorporation of genetic testing into foetal karyotyping gives more security to future parents.	Women included are a highly selective sample.

continued

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Study	Programmed details	Main findings	Other/comments
Turner *et al*., 1992,[33] 1997[103] Robinson *et al*., 1996[103] Australia Case finding and cascade screening	The programme was established in 1986. Case finding was through schools workshops, and institutions. Testing included a short physical examination and chromosomal analysis, which was later confirmed by molecular studies. Cascade testing was offered to the 1st-, 2nd- or 3rd-degree relatives. (1992 paper: 79% gave consent. The amount of time spent with the genetic counsellor varied from 20 minutes to 4 hours.)	By December 1996, a total of 245 index cases or probands from 225 families were identified and confirmed. 36 families had minimal testing; 1st-degree relatives were tested in 54 families; up to 3rd-degree relatives in 91 families; and extensive cascade testing in 44 families (see Figure 2 for details). The prevalence of FXS was reduced from 2.5/10,000 to 1/10,000 males in known relatives of probands. Reproductive confidence in members of the extended family was restored. Diagnosis and counselling reduced the birth rate in families with FXS by 20% and 78% of pregnant women will have prenatal diagnosis made. All male foetuses with FM and 60% of female foetuses with FM were terminated[106].	5.6 female relatives per proband (1363/245). Normal female relatives but with FM or PM per proband: 2.66. No. of female relatives who had learning difficulty and with FM per proband: 0.91. The reported numbers were somehow different in different published papers. Results in 1997 paper may be more reliable and updated. 1992 paper reported number of all screened children with learning difficulty. The rate of FXS in total consents received and chromosome tested was 3.9%.
van Rijn *et al*., 1997[105] The Netherlands Cascade testing	Between 1991 and 1995, 19 FXS families were newly identified at authors' department (clinical genetics). 124 relatives (1st–4th degree) were informed and 94 were tested for carrier status.	Number of relatives tested per family: total 4.95 (female: 3.7). DNA test results in relatives of FXS patients: Normal / PM / FM / Total Female: 26 / 33 / 11 / 70 Male: 12 / 6 / 6 / 24	Authors also reported that information about the heredity of FXS was only disseminated by family members to 1/3 of the relatives with *a priori* risk of being a carrier.
Brown *et al*., 1996[106] USA Prenatal testing of high-risk pregnant women	Group A: 344 pregnant women with a family history of learning difficulty of unknown cause over a 4-y period (1992–5). Group B: 40 pregnant women who were members of previously identified FXS families. Group C: 84 pregnancies of FX carrier women. Group D: 806 males with a clinical history of learning difficulty.	Group A: 2 women with FM, 4 had PM (70, 59, 59 and 56 repeats). 3 of the 4 PM carriers underwent prenatal diagnosis and no FM foetuses were detected. Group B: 10 carriers were detected. Of the 8 who underwent prenatal diagnosis, 2 pregnancies had FM foetuses. Group C: FM detected in 31 foetal samples and PM in 6. Group D: Among 806 males with a clinical history of learning difficulty or developmental delay of unknown cause, 33 (4.1%) gave a positive result.	Interesting discussion about the development of DNA test for FXS. Also reported results of testing 2500 unrelated X chromosomes with fewer than 60 repeats. The average repeat was about 30, and 80% had different-sized alleles (heterozygosity).

continued

Study	Programmed details	Main findings	Other/comments
Spence *et al*., 1996[16] USA Screening of pregnant women referred to a Genetics and IVF institute	Most women were referred for the indication of advanced maternal age. A brochure on FXS sent to each woman and reviewed by a counsellor or physician during the counselling session. PM defined as >60 repeats.	From December 1993 to June 1995, 3345 patients were offered the test (on a voluntary and self-pay basis) and 688 (21%) accepted. Among 474 women with no family history of learning difficulty, 3 had PM (60, 64, 67 repeats). Among 214 with a family history of learning difficulty, no PM or FM detected. 271 potential donors were also tested: with 2 repeats sized between 50 and 59 repeats. The overall frequency of PM was 1/248 (3/745) in women without a family history.	3 pregnant PM carriers underwent prenatal diagnosis; no FM diagnosed.
Wenstrom *et al*., 1999[71] USA Pregnant women with family history of non-specified learning difficulty	From 1994 to 1998, 1234 pregnant women were screened at a prenatal genetic clinic. DNA test was provided to 263 pregnant women who reported a family history of non-specific learning problems, attention deficit–hyperactivity disorder, cerebral palsy or any features of autism. Women from known FXS families undergoing FXS testing were excluded.	263 of the 12,349 (2.1%) had a positive family history and accepted test. No PM (>55) or FM were identified. In contrast, 18 FM (1.1%) and 13 PM (0.8%) were identified by testing 1637 specimens from affected probands during the same time period.	Authors concluded that testing the affected proband is superior to screening the pregnant relative of the proband for identification of families at risk for FXS.

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Appendix 8

Published studies about modelling screening for fragile X syndrome

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Study/objectives	Approach/methods	Key input variables	Key output variables	Main results	Conclusions/comments
Meadows and Sherman, 1996[107] USA Cost-effectiveness of newborn screening, prenatal screening, preconceptual screening and screening school-aged children with development delay	Simple population model was used, based on an assumed population of 100,000 females or 100,000 males, the prevalence of FM and PM.	Female population: Prevalence of FM: 1/2000 Prevalence of PM: 1/424 Male population: Prevalence of FM: 1/2000 Prevalence of PM: 1/685 Costs: DNA test: $50 Antibody test: $2 Amniocentesis: $1000	Costs per carrier detected.	Newborn testing: US$20,747/carrier detected (all mutations), or $100,000/male FM carrier detected. Newborn antibody test: $4543/male FM carrier detected Prenatal screening: $58,245/foetal FM carrier detected Preconceptual screening: $17,483/carrier LD children screening: $1429/carrier.	The prevalence rate for FM is too high, based on the cytogenetic tests. The results are the most optimistic estimates (100% uptake).
Murray *et al.*, 1997[1] UK Assessment of screening potential, focusing on the prenatal testing (although other strategies also discussed)	A simple population model of allele dynamics, based on a hypothetical population of 1 million couples. Assuming 2 children per couple.	PM frequency: female 1/273, male 1/800 FM frequency: 1/4000 Risk of expansion from PM to FM: 10%, by working backwards Cost of information giving: £2 Cost of DNA testing: £30 Cost of genetic counselling: £25 Cost of prenatal diagnosis: £275	True positive (defined as: detected women have a pregnancy affected with FXS). Positive predictive value. Cost per true positive case detected.	Antenatal screening in a general population of 1 million couples will yield 184 true positives and 3601 false positives. This is a false-positive rate of 0.4% and a positive predictive value of 1 in 20. The cost per true positive case detected ranges from £93,000 to £124,000.	Unless there are future technical developments which obviate the need for Southern blotting in 30% of pregnancies, screening for FXS will be more expensive than other antenatal screening tests. Others: quoted figures of lifetime costs of care for an affected individual are $1–4 million.

continued

Study/objectives	Approach/methods	Key input variables	Key output variables	Main results	Conclusions/comments
Pembrey *et al*., 2001[2] UK Discussion of consequences and costs of different strategies	Provide a descriptive framework for comparing different screening/testing approaches for FXS in the UK. Based on 3 million population (covered by a regional clinical genetics centre).	FM and PM prevalence. FXS in adults or children with learning disabilities.	Consequences: very broad, including social, psychological, organisational and changes in reproductive behaviour and prevalence of FXS. Costs required: including staffing, DNA testing, prenatal diagnosis.	Current practice will result in only a slow rise in the % of FXS families identified. A 5-y programme of systematic case-finding among adults with learning disabilities has the potential to substantially increase FXS cases known to the genetics services. (Continue to the right column)	(Continue from the left column) A retrospective programme of systematic case finding in children with learning disabilities would produce a low yield. Screening newborn males on the basis of the Guthrie card is unlikely to be feasible at present. Prenatal screening is likely to pose major difficulties by generating results that are uninterpretable for those with intermediate size repeats, and in the uncertainty associated with the risk in women with 55–65 CGG repeats. There is a possible case for offering screening for premutation carriers of their 16% chance of the menopause occurring before the age of 40 years.
Toledano-Alhadef *et al*., 2001[17] Israel Cost–benefit analysis of preconceptual or prenatal testing	A decision analysis tree to compare costs/benefits of screening versus no screening for FXS in Israel. The input parameters were estimated based on the current study and published literature.	Prevalence of PM (1/113) Prevalence of FM (1/2867) FM in mother carriers (4.2%) Acceptance rate (50%) Cost of publicity, DNA testing, prenatal diagnosis, counselling, iatrogenic abortion, etc. Lifetime cost of FXS ($680,000; but a sensitivity analysis conducted).	Net benefit.	The net benefit from running the screening programme is about $5,500,000 per year in Israel. The net benefit remains positive over a wide range of acceptance rates. The calculated cost of lifetime care for a patient with learning difficulty in Israel ($680,000) is well above the cut-off point based on financial considerations.	Because of the high prevalence of fragile X premutation or full mutation alleles, even in the general population, and because of the cost-effectiveness of the programme, we recommend that screening to identify female carriers should be carried out on a wide scale. Others: The major part of the economic evaluation is presented in the Appendix of the paper. Possible bias due to founder effect.

continued

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Study/objectives	Approach/methods	Key input variables	Key output variables	Main results	Conclusions/comments
Vintzileos *et al.*, 1999[7] USA Cost–benefit analysis of prenatal testing	A cost–benefit equation was developed based on the premise that the cost of the prenatal screening programme should be equal to or less than the cost of the current practice without such testing. Assuming 4 million births per year in USA. The formula represents the cost–benefit of the programme in its full maturity. Societal perspective.	Prevalence of FXS (1/4000) Frequency of carriers (1/250) Acceptance rate (50–80%) Procedure related foetal loss rate (1/100–1/250) Therapeutic abortion rate (50–100%) Test sensitivity, specificity (100%) Life time cost per FXS child ($500,000, incremental) Cost of testing Costs for amniocentesis package.	The maximum allowable costs per screening test. Total annual costs in the USA. Number of foetal lives to be lost.	A policy of routinely offering prenatal carrier testing may be beneficial only if the cost per screening test is less than $120 during the 1st year of the programme, or less than $240 when the programme reaches its full maturity. Approximately 46–115 foetal lives may be lost due to invasive genetic procedures in the USA.	Prenatal screening for FXS may be economically beneficial only if the cost of the prenatal screening test for carrier identification is considerably less than the current cost. Others: Mentioned advantage and disadvantage of screening for FXS in the Introduction. Mentioned that the American College of Medical Genetics does not recommend routine screening because of a primary concern with the issue of patient education and counselling.
Wildhagen *et al.*, 1998[8] The Netherlands Cost-effectiveness of three strategies for screening female fragile X pre- and full-mutation (prenatal, preconceptional, school carrier screening)	Decision analytic model for a 1-y period, based on a stable population of 100,000 couples. Assumptions based on literature review, expert opinions, prices and tariffs. Costs/savings discounted at 3% annually. Societal perspective.	Prevalence of FM (1/4000) LD % of female FM (59%) Frequency of PM (1/435 female, and 1/871 male) Transition from PM to FM (Fisch's logistic model) Risk of spontaneous abortion Lifetime costs of care for FXS patient ($957,734 for male and $533,673 for female) Costs of information dissemination Costs of testing and organisation Costs of aftercare.	Avoided patients with FXS. Detected carriers. Side-effects. Savings of fewer affected cases.	All screening strategies have a favourable cost-saving balance (US$14 million for prenatal screening, $9 million for preconceptual and $2 million for school screening). Prenatal screening will detect most carriers and will lead to the highest number of avoided FXS patients (41% vs 31%). The cost per detected carrier is around $45,000. Sensitivity analyses: varying % of premutation carriers has a large impact on the cost-effectiveness ratio.	From an economic point of view, there is no obstacle to FXS screening. The decision whether to screen or not can (and should) therefore concentrate on discussion of medical, social, psychological and ethical considerations. Others: Reproductive choice after prenatal +test: (1) accepting the risk of having an FXS child; (2) undertaking prenatal diagnosis, possibly followed by induced abortion; (3) all options for subsequent children (egg cell donation, adoption, etc.). See comments by Tejada and Duran, 1999.[109]

continued

Study/objectives	Approach/methods	Key input variables	Key output variables	Main results	Conclusions/comments
Wildhagen *et al.*, 1999[110] The Netherlands Efficacy of cascade testing for FXS with 3 scenarios: testing only 1st-degree relatives; or relatives up to 3rd degree; or up to 5th degree Cost not considered	A micro-simulation model was used to simulate a number of pedigrees of 5 generations to obtain a population where some nuclear families are connected with others and some are not. The model started from 50,000 couples (1st generation).	Prevalence of FXS, FM, PM Transition from PM to FM Carrier status of partner Number of children per family.	Percentage of FXS children avoided. No. of generations to be tested to detect 90% of all PM and FM.	In the start-up phase, 18% of couples who will have a FXS child are detected. With the stabilised cascade testing programme, it is 7% (1st-degree), or 12% (up to 3rd-degree) or 15% (up to 5th-degree relatives). To detect 90% of all PM and FM carriers at least 8 consecutive generations need to be tested.	Cascade testing is not very effective in detecting carriers. Others: According to number needed to test, authors estimated that cascade testing is more efficient (130 to be tested for one carrier) than population screening (5000 need to be tested for one carrier). In practice, it may be important to combine different strategies (prenatal + cascade).

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Appendix 9

Initial distribution of diagnosed versus non-diagnosed carriers in population (based on a 10-year running of current practice scenario)

Age	Female normal tested	Female normal untested	Female popuPM tested	Female popuPM untested	Female famPM tested	Female famPM untested	Female FXS diag & screened	Female FXS diag & unscreened	Female FXS non-diag	Female FM without FXS diag	Female FM without FXS non-diag	Male normal	PopuNTM diag	PopuNTM non-diag	FamNTM diag	FamNTM non-diag	Male FXS diag & screened	Male FXS diag & unscreened	Male FXS non-diag
0	0.0	1.0	0.0	1.0	0.035	0.965	0.000	0.112	0.888	0.112	0.888	1.0	0.0	1.0	0.159	0.841	0.000	0.100	0.900
1	0.0	1.0	0.0	1.0	0.031	0.969	0.011	0.109	0.880	0.102	0.898	1.0	0.0	1.0	0.141	0.859	0.014	0.103	0.882
2	0.0	1.0	0.0	1.0	0.057	0.943	0.021	0.165	0.814	0.151	0.849	1.0	0.0	1.0	0.123	0.877	0.029	0.108	0.863
3	0.0	1.0	0.0	1.0	0.082	0.918	0.039	0.228	0.733	0.199	0.801	1.0	0.0	1.0	0.105	0.895	0.053	0.129	0.817
4	0.0	1.0	0.0	1.0	0.108	0.892	0.058	0.288	0.654	0.246	0.754	1.0	0.0	1.0	0.087	0.913	0.079	0.151	0.770
5	0.0	1.0	0.0	1.0	0.133	0.867	0.080	0.342	0.578	0.292	0.708	1.0	0.0	1.0	0.069	0.931	0.106	0.173	0.721
6	0.0	1.0	0.0	1.0	0.157	0.843	0.102	0.393	0.506	0.336	0.664	1.0	0.0	1.0	0.052	0.948	0.134	0.195	0.671
7	0.0	1.0	0.0	1.0	0.181	0.819	0.125	0.438	0.437	0.379	0.621	1.0	0.0	1.0	0.034	0.966	0.163	0.217	0.620
8	0.0	1.0	0.0	1.0	0.205	0.795	0.146	0.474	0.380	0.421	0.579	1.0	0.0	1.0	0.017	0.983	0.186	0.222	0.592
9	0.0	1.0	0.0	1.0	0.229	0.771	0.166	0.507	0.327	0.463	0.537	1.0	0.0	1.0	0.000	1.000	0.205	0.227	0.568
10	0.0	1.0	0.0	1.0	0.302	0.698	0.203	0.731	0.066	0.508	0.492	1.0	0.0	1.0	0.000	1.000	0.216	0.488	0.296
11	0.0	1.0	0.0	1.0	0.334	0.666	0.283	0.717	0.000	0.562	0.438	1.0	0.0	1.0	0.000	1.000	0.295	0.490	0.215
12	0.0	1.0	0.0	1.0	0.325	0.675	0.286	0.714	0.000	0.546	0.454	1.0	0.0	1.0	0.000	1.000	0.300	0.492	0.208
13	0.0	1.0	0.0	1.0	0.333	0.667	0.286	0.714	0.000	0.559	0.441	1.0	0.0	1.0	0.000	1.000	0.298	0.492	0.210
14	0.0	1.0	0.0	1.0	0.325	0.675	0.283	0.717	0.000	0.546	0.454	1.0	0.0	1.0	0.000	1.000	0.300	0.491	0.208
15	0.0	1.0	0.0	1.0	0.314	0.686	0.278	0.722	0.000	0.528	0.472	1.0	0.0	1.0	0.000	1.000	0.300	0.492	0.208
16	0.0	1.0	0.0	1.0	0.315	0.685	0.274	0.726	0.000	0.528	0.472	1.0	0.0	1.0	0.000	1.000	0.295	0.482	0.224
17	0.0	1.0	0.0	1.0	0.303	0.697	0.266	0.729	0.005	0.510	0.490	1.0	0.0	1.0	0.000	1.000	0.287	0.471	0.241
18	0.0	1.0	0.0	1.0	0.300	0.700	0.265	0.722	0.014	0.503	0.497	1.0	0.0	1.0	0.000	1.000	0.278	0.464	0.258
19	0.0	1.0	0.0	1.0	0.306	0.694	0.260	0.728	0.012	0.514	0.486	1.0	0.0	1.0	0.000	1.000	0.270	0.456	0.274
20	0.0	1.0	0.0	1.0	0.308	0.692	0.260	0.727	0.013	0.518	0.482	1.0	0.0	1.0	0.000	1.000	0.264	0.448	0.287
21	0.0	1.0	0.0	1.0	0.305	0.695	0.257	0.719	0.024	0.512	0.488	1.0	0.0	1.0	0.000	1.000	0.258	0.440	0.302
22	0.0	1.0	0.0	1.0	0.315	0.685	0.249	0.727	0.024	0.529	0.471	1.0	0.0	1.0	0.000	1.000	0.245	0.431	0.324
23	0.0	1.0	0.0	1.0	0.319	0.681	0.246	0.726	0.028	0.535	0.465	1.0	0.0	1.0	0.000	1.000	0.236	0.421	0.344
24	0.0	1.0	0.0	1.0	0.320	0.680	0.239	0.721	0.040	0.537	0.463	1.0	0.0	1.0	0.000	1.000	0.222	0.410	0.367
25	0.0	1.0	0.0	1.0	0.334	0.666	0.227	0.732	0.041	0.561	0.439	1.0	0.0	1.0	0.000	1.000	0.204	0.399	0.398
26	0.0	1.0	0.0	1.0	0.332	0.668	0.228	0.730	0.041	0.558	0.442	1.0	0.0	1.0	0.000	1.000	0.202	0.399	0.399
27	0.0	1.0	0.0	1.0	0.333	0.667	0.228	0.731	0.041	0.559	0.441	1.0	0.0	1.0	0.000	1.000	0.201	0.399	0.400
28	0.0	1.0	0.0	1.0	0.326	0.674	0.229	0.722	0.049	0.548	0.452	1.0	0.0	1.0	0.000	1.000	0.202	0.399	0.399
29	0.0	1.0	0.0	1.0	0.323	0.677	0.226	0.717	0.056	0.543	0.457	1.0	0.0	1.0	0.000	1.000	0.202	0.399	0.399
30	0.0	1.0	0.0	1.0	0.336	0.664	0.223	0.736	0.040	0.565	0.435	1.0	0.0	1.0	0.000	1.000	0.198	0.399	0.403
31	0.0	1.0	0.0	1.0	0.359	0.641	0.227	0.765	0.008	0.603	0.397	1.0	0.0	1.0	0.000	1.000	0.196	0.399	0.406
32	0.0	1.0	0.0	1.0	0.361	0.639	0.236	0.764	0.000	0.607	0.393	1.0	0.0	1.0	0.000	1.000	0.201	0.399	0.401
33	0.0	1.0	0.0	1.0	0.342	0.658	0.237	0.745	0.019	0.575	0.425	1.0	0.0	1.0	0.000	1.000	0.205	0.399	0.396
34	0.0	1.0	0.0	1.0	0.327	0.673	0.233	0.723	0.045	0.549	0.451	1.0	0.0	1.0	0.000	1.000	0.205	0.399	0.396

continued

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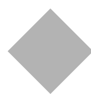
Age	Female normal tested	Female normal untested	Female popuPM tested	Female popuPM untested	Female famPM tested	Female famPM untested	Female FXS diag & screened	Female FXS diag & unscreened	Female FXS non-diag	Female FM without FXS diag	Female FM without FXS non-diag	Male normal	PopuNTM diag	PopuNTM non-diag	FamNTM diag	FamNTM non-diag	Male FXS diag & screened	Male FXS diag & unscreened	Male FXS non-diag
35	0.0	1.0	0.0	1.0	0.314	0.686	0.228	0.705	0.067	0.527	0.473	1.0	0.0	1.0	0.000	1.000	0.204	0.399	0.397
36	0.0	1.0	0.0	1.0	0.295	0.705	0.225	0.678	0.096	0.496	0.504	1.0	0.0	1.0	0.000	1.000	0.207	0.399	0.394
37	0.0	1.0	0.0	1.0	0.278	0.722	0.220	0.655	0.125	0.468	0.532	1.0	0.0	1.0	0.000	1.000	0.206	0.399	0.395
38	0.0	1.0	0.0	1.0	0.264	0.736	0.215	0.635	0.150	0.443	0.557	1.0	0.0	1.0	0.000	1.000	0.205	0.399	0.396
39	0.0	1.0	0.0	1.0	0.268	0.732	0.208	0.640	0.152	0.450	0.550	1.0	0.0	1.0	0.000	1.000	0.201	0.399	0.400
40	0.0	1.0	0.0	1.0	0.258	0.742	0.212	0.626	0.163	0.433	0.567	1.0	0.0	1.0	0.000	1.000	0.204	0.399	0.398
41	0.0	1.0	0.0	1.0	0.256	0.744	0.207	0.624	0.169	0.431	0.569	1.0	0.0	1.0	0.000	1.000	0.201	0.399	0.400
42	0.0	1.0	0.0	1.0	0.249	0.751	0.208	0.614	0.178	0.419	0.581	1.0	0.0	1.0	0.000	1.000	0.203	0.399	0.398
43	0.0	1.0	0.0	1.0	0.245	0.755	0.205	0.608	0.187	0.411	0.589	1.0	0.0	1.0	0.000	1.000	0.203	0.399	0.399
44	0.0	1.0	0.0	1.0	0.241	0.759	0.204	0.603	0.193	0.405	0.595	1.0	0.0	1.0	0.000	1.000	0.203	0.399	0.399
45	0.0	1.0	0.0	1.0	0.242	0.758	0.202	0.604	0.195	0.406	0.594	1.0	0.0	1.0	0.000	1.000	0.201	0.399	0.400
46	0.0	1.0	0.0	1.0	0.246	0.754	0.201	0.610	0.188	0.414	0.586	1.0	0.0	1.0	0.000	1.000	0.199	0.399	0.402
47	0.0	1.0	0.0	1.0	0.230	0.770	0.210	0.580	0.209	0.386	0.614	1.0	0.0	1.0	0.000	1.000	0.199	0.399	0.402
48	0.0	1.0	0.0	1.0	0.212	0.788	0.211	0.550	0.239	0.356	0.644	1.0	0.0	1.0	0.000	1.000	0.199	0.399	0.402
49	0.0	1.0	0.0	1.0	0.196	0.804	0.209	0.524	0.267	0.330	0.670	1.0	0.0	1.0	0.000	1.000	0.197	0.399	0.404
50	0.0	1.0	0.0	1.0	0.173	0.827	0.209	0.488	0.302	0.291	0.709	1.0	0.0	1.0	0.000	1.000	0.198	0.398	0.403
51	0.0	1.0	0.0	1.0	0.149	0.851	0.203	0.453	0.343	0.250	0.750	1.0	0.0	1.0	0.000	1.000	0.199	0.398	0.402
52	0.0	1.0	0.0	1.0	0.124	0.876	0.195	0.419	0.386	0.209	0.791	1.0	0.0	1.0	0.000	1.000	0.199	0.398	0.403
53	0.0	1.0	0.0	1.0	0.098	0.902	0.186	0.384	0.430	0.164	0.836	1.0	0.0	1.0	0.000	1.000	0.198	0.398	0.403
54	0.0	1.0	0.0	1.0	0.068	0.932	0.174	0.346	0.479	0.114	0.886	1.0	0.0	1.0	0.000	1.000	0.199	0.398	0.403
55	0.0	1.0	0.0	1.0	0.034	0.966	0.162	0.305	0.532	0.057	0.943	1.0	0.0	1.0	0.000	1.000	0.202	0.398	0.399
56	0.0	1.0	0.0	1.0	0.000	1.000	0.142	0.266	0.593	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.201	0.398	0.401
57	0.0	1.0	0.0	1.0	0.000	1.000	0.133	0.266	0.602	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.200	0.398	0.402
58	0.0	1.0	0.0	1.0	0.000	1.000	0.135	0.266	0.599	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.203	0.398	0.399
59	0.0	1.0	0.0	1.0	0.000	1.000	0.137	0.266	0.598	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.203	0.398	0.399
60	0.0	1.0	0.0	1.0	0.000	1.000	0.137	0.265	0.598	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.204	0.398	0.398
61	0.0	1.0	0.0	1.0	0.000	1.000	0.140	0.265	0.595	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.207	0.398	0.395
62	0.0	1.0	0.0	1.0	0.000	1.000	0.141	0.265	0.594	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.209	0.398	0.394
63	0.0	1.0	0.0	1.0	0.000	1.000	0.115	0.265	0.620	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.180	0.397	0.422
64	0.0	1.0	0.0	1.0	0.000	1.000	0.133	0.265	0.602	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.201	0.397	0.402
65	0.0	1.0	0.0	1.0	0.000	1.000	0.134	0.265	0.600	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.202	0.397	0.401
66	0.0	1.0	0.0	1.0	0.000	1.000	0.130	0.265	0.605	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.197	0.397	0.406
67	0.0	1.0	0.0	1.0	0.000	1.000	0.127	0.265	0.608	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.194	0.397	0.409
68	0.0	1.0	0.0	1.0	0.000	1.000	0.128	0.265	0.607	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.195	0.396	0.409
69	0.0	1.0	0.0	1.0	0.000	1.000	0.139	0.265	0.596	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.207	0.396	0.397
70	0.0	1.0	0.0	1.0	0.000	1.000	0.135	0.265	0.600	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.203	0.396	0.402
71	0.0	1.0	0.0	1.0	0.000	1.000	0.133	0.265	0.602	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.202	0.395	0.403
72	0.0	1.0	0.0	1.0	0.000	1.000	0.132	0.264	0.603	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.201	0.395	0.404
73	0.0	1.0	0.0	1.0	0.000	1.000	0.133	0.264	0.603	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.201	0.394	0.405
74	0.0	1.0	0.0	1.0	0.000	1.000	0.132	0.264	0.604	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.201	0.394	0.405
75	0.0	1.0	0.0	1.0	0.000	1.000	0.132	0.264	0.604	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.200	0.393	0.407
76	0.0	1.0	0.0	1.0	0.000	1.000	0.134	0.263	0.602	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.202	0.393	0.405
77	0.0	1.0	0.0	1.0	0.000	1.000	0.136	0.263	0.601	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.206	0.392	0.402
78	0.0	1.0	0.0	1.0	0.000	1.000	0.137	0.263	0.601	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.204	0.391	0.405
79	0.0	1.0	0.0	1.0	0.000	1.000	0.134	0.262	0.603	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.202	0.390	0.407
80	0.0	1.0	0.0	1.0	0.000	1.000	0.132	0.262	0.605	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.202	0.390	0.409
81	0.0	1.0	0.0	1.0	0.000	1.000	0.133	0.262	0.606	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.203	0.388	0.408
82	0.0	1.0	0.0	1.0	0.000	1.000	0.135	0.261	0.604	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.205	0.387	0.408
83	0.0	1.0	0.0	1.0	0.000	1.000	0.135	0.261	0.605	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.206	0.386	0.408
84	0.0	1.0	0.0	1.0	0.000	1.000	0.134	0.260	0.606	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.202	0.385	0.413
85+	0.0	1.0	0.0	1.0	0.000	1.000	0.134	0.259	0.606	0.000	1.000	1.0	0.0	1.0	0.000	1.000	0.204	0.383	0.413
Total	0.0	1.0	0.0	1.0	0.178	0.822	0.268	0.503	0.229	0.307	0.693	1.0	0.0	1.0	0.010	0.990	0.347	0.385	0.268

Notes: popuPM – premutation in the general population; popuNTM – normal transmitting males in the general population; diag – diagnosed; non-diag – non-diagnosed; famPM – Premulation in affected families.



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We look forward to hearing from you.

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