A long-term simulation model for Fragile X screening

Lily Yao
Pelham Barton
Health Economics Facility

Fujian Song
Department of Public Health and Epidemiology

University of Birmingham

Correspondence:

Lily Yao
HSMC
Park House
40 Edgbaston Park Road
BIRMINGHAM
B15 2RT

Acknowledgment:

This work is part of a project funded through the National Co-ordinating Centre for Health Technology Assessment as an HTA rapid review: The clinical effectiveness and cost effectiveness of different strategies for screening for fragile X syndrome (Project code: 01/32/01). The authors take full responsibility for all statements made here.

Background

Fragile X syndrome (FXS) is an inherited disorder that causes learning difficulties and developmental delay, and is the second most common cause of learning disability after Down's syndrome.[1;2] The disorder affects an estimated one in 4000 males and one in 8000 females, and has a tendency to be more severe in males, who may not be able to live independently as a result of the symptoms. There is no cure for FXS and management of affected individuals is through specific educational and psychosocial interventions, and treatment of any clinical symptoms.[1;2]

According to the prevalence of 1/4000 in males and 1/8000 in females, there are about 10,000 FXS patients in England and Wales. The annual cost to the NHS of managing a moderately affected adult was estimated to be approximately £20,000 (1995 data).[2] Thus, the total cost of managing FXS patients per year is about £200 million in England and Wales. A reduction in the number of births of children with FXS will reduce the costs required for caring such patients. Other benefits of screening for FXS may include the reduction of anxiety in women with normal testing results, a possible improvement in the management of patients with FXS, and improved quality of life for parents and other family members.

Routine screening for FXS is not currently available in the United Kingdom; however, limited neonatal screening and screening of relatives of affected individuals ('cascade screening') is carried out in many UK genetics centres. Although the UK National Screening Committee does not currently support a national screening programme for FXS, the committee wished to review this position following the publication of the two HTA reports on screening for FXS.[1;2] Further research is required to consolidate the existing evidence, and to provide effectiveness and economic information on pre-natal screening and systematic case finding to inform the possible development of FXS screening strategies.

The disorder displays an unusual inheritance pattern, and the severity of the disorder can increase over generations within a family. This observation was explained following the discovery of the causative gene, *FMR1* in 1991.[3] This gene 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 premutation (approximately 55-200 repeats), or a full mutation (200 repeats and over). 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 (known and unknown). There is evidence that the risk for PMs to expand may depend on the absence of stabilising AGG repeats, which interrupt the CGG repeat region.[4] Children with PM are not affected; but a FM leads to the development of FXS in all male offspring and about 50% of female offspring. A male with PM is also known as a normal transmitting male (NTM).

A new model for Fragile X syndrome

The two major strategies of screening for FXS (population prenatal screening and active cascade screening programme) have not been directly compared in trials or in the existing models. To estimate the impact of these two strategies, we built a population simulation model (here called the FXS model). The FXS model provides a tool for estimating changes in the number (frequency) of premutation (PM) and full mutation (FM) in the population of England and Wales under varying assumptions (Figure 1). We first show that the model can theoretically project the number (and frequency) of PM and FM in the population under the assumption of no interventions (theoretical scenario). Then it is used to compare three screening strategies: current practice (low level of cascade testing), active cascade screening, and prenatal screening.

There are three major components in the FXS model: population cohort, cascade screening and prenatal screening. The FXS model's structure and input parameters for the theoretical scenario are described below.

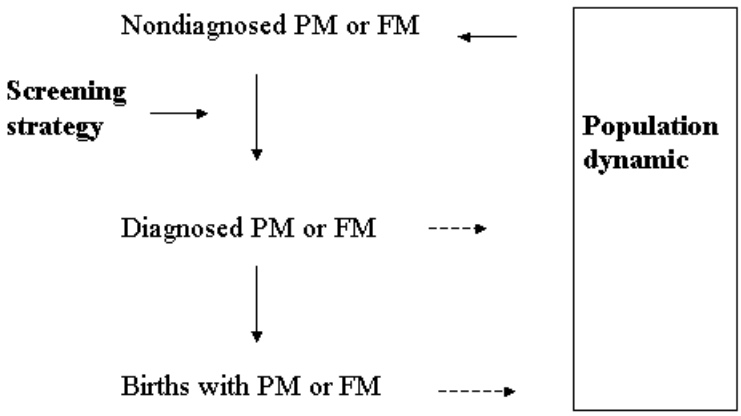

Figure 1. Basic structure of the model

Basic Structure

The FXS model is a population cohort model operating on an annual cycle. It has been constructed using Microsoft Excel. The population is divided by age into one-year

bands from age 0 to 84, with all persons of age 85 or over combined into a single age group. Within each age group, the population is divided into 17 subgroups as shown in Table 1. The model operates by means of detailed calculations of the population in one year's time given the current population. Time is advanced in the model by a macro which replaces the numerical values for the current population by the population one year later, storing appropriate summary data for the final results.

females:	normal	untested
		tested
	PM 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
males:	normal	
	NTM (PM)	undiagnosed
		diagnosed
	FM	undiagnosed
		diagnosed: family members not screened
		diagnosed: family members screened

Table 1. Population subgroups

Initialisation

The FXS model was initialised with an estimated population for England and Wales at mid-2000 based on National Statistics. It was assumed that the initial proportions of PM and FM were independent of age, and that the entire population was untested.

Updating the model

Given the population at any time, the population one year later is found as follows:

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

The main part of the FXS model is the way the numbers of new births were calculated. New births were grouped firstly by the status of the parents as defined in Table 1. Possible combinations were: any category of mother with a normal father, or a normal mother with an NTM father. Births from non-normal mothers and NTM fathers were assumed to be negligible in number, and were not considered in the model. FM fathers are assumed to be impossible.[1] These groupings were then further divided according to the age of the mother. The expected number of births in each subgroup was based on the number of women in the relevant (five-year) age group and mutation status, adjusted for the status of the father. This was 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 were then allocated to the population categories defined in Table 1, allowing for new mutations and expansion from PM to FM.

Testing and Diagnosis of PM and FM

Testing and diagnosis for either 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 15 years of life. Figure 2 shows the assumed age distribution among those whose FXS is diagnosed in this way. Combining the distribution in Figure 2 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.

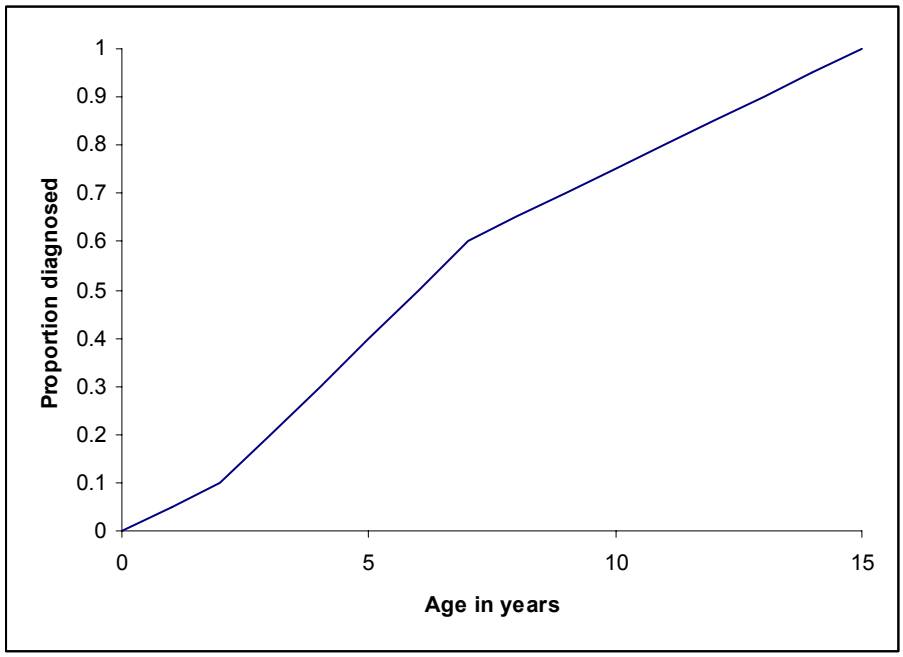

Figure 2. Assumed age distribution for natural diagnosis

Prenatal screening

The second reason for diagnosis is through prenatal screening (Figure 3). When the 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 FXS mutation status of women tested will become 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.

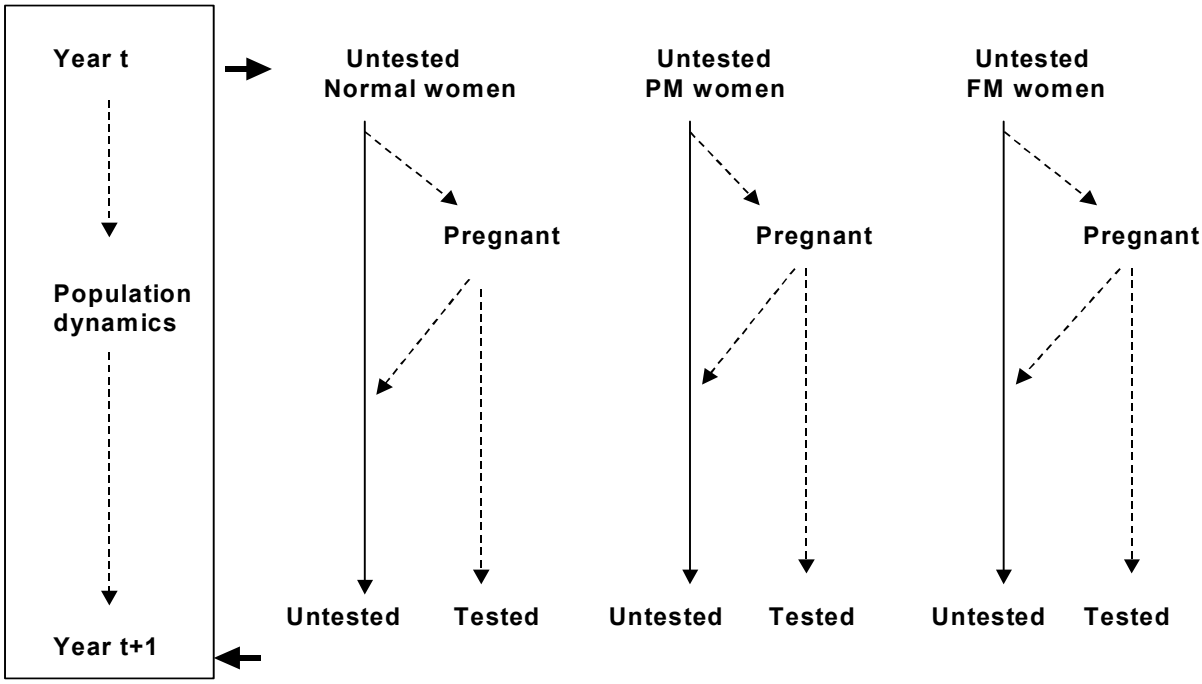

Figure 3. Prenatal screening

Cascade screening

Cascade screening provides the remaining reason for diagnosis (Figure 4) FXS patients may be diagnosed through behavioural diagnosis or active case finding programmes. 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 status of FXS mutation to be tested is assumed. These are assumed to be uniformly distributed between the ages of 0 and 44, and within each age group they are divided according to the assumed distribution of mutation status among FXS relatives. Calculating the number of females to be tested 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.

For evaluating the cascade screening strategy, it is necessary to estimate the distribution of normal, PM and FM alleles in relatives of FXS families. Based on data from Turner et al, 52% of the tested female relatives in FXS families were with normal alleles, 16%

with FM and mental retardation, and 32% with PM or FM and without mental retardation. Suppose about half of females with FM are mentally retarded, it could be estimated that about 16% of female relatives are with PM. Thus, 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.

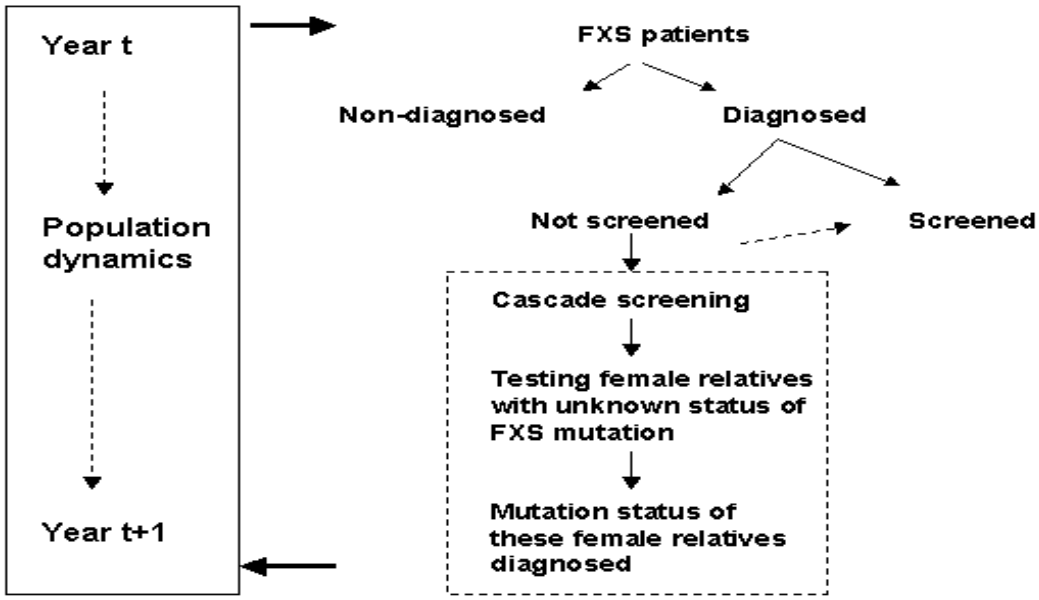

Figure 4. Cascade screening

Combined screening effects

Adding the proportions to be tested as a result of the three reasons listed above gives the total proportion among the untested population groups to be tested in any year.

Model Parameters

Model parameters were based on a systematic review of the literature (to be reported). Rates of new mutation, and of expansion from PM to FM, were estimated so that the proportions of PM and FM would be constant in a theoretical scenario where there was no screening at all. The values used are reported in Table 2.

Frequency of FM	
Female	2.5/10000
Male	2.5/10000
Frequency of PM	
Female	0.35%
Male	0.16%
New PM from normal parents	3.5/10000
FXS family PM/Total PM	6.5%
Family PM/New FM	1.15
Expansion risk from PM to FM	
Population	8%
FXS family	50%
Fertility rate	
Normal mother and father	1.8
Normal mother and NTM father	1.8
PM mother and normal father	1.8
FM mother and normal father	0.9

Table 2. Basic model parameters

The model was then run under three different scenarios: current practice, active cascade screening and prenatal screening. The main differences in parameters used are shown in Table 3. Figures in brackets indicate ranges for sensitivity analysis.

Costs are estimated from a UK NHS perspective. Assumptions about costs are mainly based on Murray *et al*[1], except the unit cost of therapeutic abortion which is from Acute Care 97/98 Healthcare Resource Groups (UK National Statistics 1996/97). The assumptions about the unit costs for different procedures are summarised in Table 4. Only the direct costs for listed procedures are considered, following the same approach used by Murray *et al*[1]. The cost is measured in 1997 UK£. Cost per preselection for DNA testing is assumed. The sensitivity analysis range for the cost of abortion are the 25th and 75th percentile costs. All other values have been set at fixed percentages below and above the point estimates.

	Current practice	Active cascade	Prenatal screening
Screening uptake rate	0.4	0.8 (0.4-1.0)	0.7 (0.4-0.9)
Natural diagnosis rate of FM			
Female	0.4	0.8 (0.4-1.0)	0.4 (0.4-0.9)
Male	0.6	0.9 (0.6-1.0)	0.6 (0.6-0.9)
Number tested per index case	3	6 (3-9)	NA
Rate of screening unscreened cases	0.1	0.5 (0.1-1.0)	NA
Rate of prenatal diagnosis in identified carriers			
PM carriers (population)	NA	NA	0.8 (0.4-0.9)
PM carriers (FXS family)	0.6	0.8 (0.6-1.0)	0.8 (0.6-0.9)
FM carriers	0.8	0.9 (0.8-1.0)	0.9 (0.8-0.9)
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)
Fertility rate			
Diagnosed PM mother	1.6	1.6	1.6
Diagnosed FM mother	0.9	0.9	0.9

Table 3. Parameters for different scenarios

Procedure	Unit cost and range estimates(UK£, 1997)
Information given	2 (1, 3)
Pre-selection for DNA test (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	300 (225, 325)

Table 4. Unit costs

Results

The main results from the model are the costs of different strategies, and the effects measured in FXS births prevented. These are shown in Tables 5 and 6 respectively. Cost-effectiveness ratios are given in Table 7.

Year	Current practice	Casacade	Prenatal
1	141515.65	657438.94	14511364.42
2	139179.09	429500.09	13561681.63
3	141716.83	334228.65	12691191.90
4	144625.05	274952.97	11918074.24
5	147950.99	238477.83	11221112.57
6	151609.34	216841.92	10645661.11
7	155310.95	203215.17	10149828.24
8	155025.25	190362.36	9737761.55
9	154891.61	184406.47	9401569.21
10	155008.36	181574.27	9119505.55
20	148266.24	178616.89	8109916.59
40	120693.03	156315.87	7138998.43

Table 5. Estimated costs of different strategies (1997 UK£).

Years	Compared with no intervention				Compared with current practice	
	Current practice	Active cascade	Prenatal screening		Active cascade	Prenatal screening
1	3	24	51		21	48
2	4	31	51		27	48
3	5	31	52		27	47
4	5	31	52		25	46
5	6	30	52		24	46
6	7	30	52		23	45
7	8	29	52		22	44
8	8	29	52		21	44
9	9	29	52		20	43
10	10	29	52		19	42
20	15	29	54		14	40
40	15	26	55		11	40

Table 6. Estimated FXS births prevented

Year	Average cost (reference: no intervention)			Incremental cost (reference: current practice)	
	Current	Cascade	Prenatal	Cascade	Prenatal
1	49417.94	27583.70	285034.00	24602.13	299076.85
2	37497.42	13954.67	264045.59	10726.20	281692.77
3	31232.12	10758.46	245822.36	7256.64	266500.04
4	27037.27	8983.92	229960.38	5160.29	253314.79
5	24073.27	7906.92	216038.40	3769.63	241801.14
6	21858.99	7274.41	204450.17	2851.94	232509.19
7	20132.41	6896.44	194851.36	2202.27	225225.34
8	18271.17	6522.12	186838.24	1706.90	219616.36
9	16752.77	6363.11	180133.77	1495.57	215307.28
10	15517.50	6302.60	174504.82	1411.56	212076.70
20	10148.17	6234.58	149470.52	2161.85	200810.98
40	7935.19	6026.83	129289.96	3320.92	175426.48

Table 7. Estimated cost per FXS birth prevented

As part of the sensitivity analysis, we considered pessimistic and optimistic estimates. The pessimistic scenario is based on the lower values for the assumed effectiveness and higher values for the costs, while the optimistic scenario is based on the higher estimates of effectiveness and lower estimates of costs. The results are shown in Table 8.

Year	Cascade screening		Prenatal screening	
	Pessimistic	Optimistic	Pessimistic	Optimistic
1	89346	9972	628484	156482
5	43277	2948	482954	118199
10	27846	2350	394877	94980
20	18128	2301	336910	81895
40	14335	2113	277637	76066

Table 8. Sensitivity analysis on cost per FXS birth prevented

Discussion

A number of issues are raised by the model. They may conveniently be classified as issues relating to model structure and to interpretation of the model results.

Model Structure

Any model is necessarily a simplification of reality. In this model, individuals with PM have simply been categorised according to family history of mutation. Risk of expansion from PM to FM in reality depends on the number of CGG repeats in the affected gene. The ideal model would group individuals according to the number of CGG repeats. This would also allow for expansion of premutations short of a full mutation (for example, from 70 CGG repeats 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 description of prenatal screening than to cascade screening. For cascade screening it requires 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 *et al*[5], which was specifically constructed to assess cascade screening, but not to handle other screening methods.

In its present form, the model assumes a constant pattern of births by age of the mother. This is clearly not the case. However, any reasonable assumption about changes in the birth pattern could be accommodated within the model structure with very little difficulty. Similarly, the model treats England and Wales as a closed system. Again, any desired pattern of migration could be included.

Interpretation of Model Results

The results presented here are in terms of cost per FXS birth prevented in any given year. Because the results are presented separately for each year, there was no need to discount costs or effects. However, they do not take account of the benefit of screening

in terms of reducing the prevalence of PM and FM in the population as a whole over time. Some means of aggregation of these results is necessary and it is not at present at all clear how to do this.

In the full report from which this paper has been derived, results will also be presented in terms of carriers detected. It would clearly be helpful to aggregate the benefits: again, it is not at all clear how this may be done.

Finally, the results show that cascade screening is less expensive, but less effective, than prenatal screening. At least on a year by year basis, it would be easy to calculate an incremental cost-effectiveness ratio between the two strategies. However, the interpretation of such a ratio depends on comparing the value of an FXS birth prevented with more conventional measures of health benefit such as QALYs.

Conclusion

A new model has been developed which provides a framework for comparing different approaches to screening for Fragile X syndrome. It allows projections to be made of the prevalence of PM and FM over time under a wide variety of assumptions.

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