Costs and effects of genetic screening with application to cystic fibrosis and fragile X syndrome

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Costs and effects of genetic screening with application to cystic fibrosis and fragile X syndrome

Kosten en effecten van genetische screening toegepast op cystische fibrose en fragiele X syndroom

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Marinus Frederik Wildhagen

geboren te Breda

Hey hey hey hey, it was the DNA
Hey hey hey hey, that made me this way

(Sheer Heart Attack, Queen, 1978)

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List of publications

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1. Wildhagen MF, Ten Kate LP, Habbema JDF. Screening for cystic fibrosis. British Medical Bulletin 1998;54(4):857-875.
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2. Wildhagen MF, Verheij JBGM, Verzijl JG, Gerritsen J, Bakker W, Hilderink HBM, ten Kate LP, Tijmstra T, Kooij L, Habbema JDF. The nonhospital costs of care of patients with CF in The Netherlands: results of a questionnaire. Eur Respir J 1996;9(11):2215-2219.
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4. Wildhagen MF, Hilderink HBM, Verzijl JG, Verheij JBGM, Kooij L, Tijmstra Tj, ten Kate LP, Habbema JDF. Costs, effects, and savings of screening for cystic fibrosis gene carriers. J Epidemiol Community Health 1998;52:459-67.
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5. Wildhagen MF, van Os TAM, Polder JJ, ten Kate LP, Habbema JDF. Explorative study of costs, effects and savings of screening for female fragile X premutation and full mutation carriers in the general population. Community Genet 1998;1(1):36-47.
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6. Wildhagen MF, van Os TAM, Polder JJ, ten Kate LP, Habbema JDF. The efficacy of cascade testing for fragile X syndrome. Accepted by the Journal of Medical Screening.
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8. Kooij L, on behalf of the Werkgroep Kosten en Effecten van screening CF-gendragerschap: Kooij L, Tijmstra T, Verheij JBGM, Hilderink HBM, Verzijl JG, Wildhagen MF, Habbema JDF, ten Kate LP. Screening op gendragerschap van cystische fibrose: voor- en nadelen van verschillende scenario's [Screening for cystic fibrosis gene carrier state: pros and cons of different scenarios]. Ned Tijdschr Geneeskd 1994;138(16):818-823.
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Part 1

Introduction

Chapter 1
Introduction

Two to six percent of all newborn children have a disorder with a genetic cause (1-3). For an increasing number of these diseases, the precise genetic cause is known and this can lead to new treatment opportunities (see Appendix A for a basic description of the mechanisms of genetic inheritance). However, for most disorders total cure is not yet possible. For example, complications in patients with cystic fibrosis can be reduced by intensive treatment, but many patients will still die of lung problems caused by the disease. For diseases for which cure is not yet possible genetic screening might be a (temporary) solution. For example, a genetic screening programme in most Western countries is the offer of amniocentesis to pregnant women of a specified age (36 years and older in The Netherlands) to detect Down syndrome. Women in whom a foetus with Down syndrome is detected can then decide to prepare for the birth of an affected child or to avoid its birth by induced abortion. A list with examples of tests to detect disorders with a genetic cause or component currently offered in The Netherlands is given in Table 1.1. Because of the increasing number of genetic diseases that can be detected early, this list will probably continue to be extended.

Table 1.1 Examples of testing for hereditary disorders and risk factors (source: Health Council of The Netherlands (4))

Disease	Target group	Screening test
Rhesus haemolytic disease	All pregnant women	Serological
Diabetes mellitus	All pregnant women	Biochemical
Down syndrome, neural tube defects or other chromosome abnormalities	Pregnant women, demand of the woman	Serum screening (triple test)
Trombocytes blood group	Pregnant women, on indication	Serological
Carriership of balanced chromosome abnormalities, sex-linked diseases or recessive hereditary diseases	Pregnant women, on indication	Cytogenetic, biochemical, DNA testing
Haemoglobinopathies or sickle cell disease	Certain ethnic groups of pregnant women	Hb electrophoresis
Congenital malformations and neural tube defects	Most pregnant women	Ultrasound
Phenylketonuria (PKT) and congenital hypothyroidism (CHT)	All neonates	Biochemical, on heel prick
Down syndrome and other chromosomal abnormalities	Pregnant women of 36 years and older	Chorionic villus sampling, amniocentesis
Carriership of balanced chromosome abnormalities, sex-linked diseases or recessive hereditary diseases	Women prior to conception, on indication	Cytogenetic, biochemical, DNA testing
Fragile X syndrome	Mentally handicapped individuals	DNA testing

Among the diseases for which general population carrier screening is under discussion at the moment are cystic fibrosis, one of the most frequent autosomal recessive disease with physical problems in Caucasian populations, and fragile X syndrome, the most common cause of mental retardation from a single gene defect. Screening for carriers of these two diseases is the subject of this thesis. For a description of the diseases, see Chapter 2 (cystic fibrosis) and Chapter 6 (fragile X syndrome).

1.1 Screening and test properties

Screening is the process of sorting out which apparently healthy persons (probably) have a given disease or risk factor from those who (probably) do not have the disease or risk factor. Its direct purpose thus is to divide the target population into a high-risk group (people with a positive test result) and a low-risk group (people with a negative test result). The high-risk group is offered a so-called diagnostic test that will demonstrate the presence of the disease ('true-positive screening test result') or absence of the disease ('false-positive screening test result').

The quality of the screening test is described by the terms *sensitivity*, *specificity* and *predictive value* (Table 1.2) (5). Sensitivity (or true-positive rate) is the probability that a person with the disease will have a positive test result; specificity (or true-negative rate) is the probability that a person without the disease will have a negative test result. A test is perfect if both sensitivity and specificity are 100 percent. The predictive value is the probability that a positive or negative test result turns out to be correct. For example, the predictive value of a positive test result gives the probability that a person has the disease if he or she has a positive test result. Predictive values do not only depend on the sensitivity and specificity of the screening test, but also on the prevalence of the disease: if the prevalence of the disease increases, the predictive value of a positive test increases and the predictive value of a negative test result decreases (5).

Table 1.2 Classification of screening test results

	Disorder present	Disorder absent	Total
Test positive	TP (true-positive)	FP (false-positive)	TP+FP
Test negative	FN (false-negative)	TN (true-negative)	FN+TN
Total	TP+FN	FP+TN	TP+FN+FP+TN

Sensitivity = TP / (TP+FN)
Specificity = TN / (FP+TN)
Predictive value of a positive test result = TP / (TP+FP)
Predictive value of a negative test result = TN / (TN+FN)

From a technical point of view most genetic tests only have a very small probability of giving an error in the test result. This would mean that if these tests are used for screening, the sensitivity and specificity of the screening are almost 100 percent. However, many tests can only detect one or a few specific mutations in a gene, while several diseases are caused by more than one mutation. For example, cystic fibrosis can be caused by hundreds of mutations in one gene (see Chapter 2). This would mean that many tests should be performed to detect all these mutations (some of which have been detected in only one patient until now) which would make screening prohibitively expensive. For this reason, cystic fibrosis screening is aimed at the most frequent mutations (for example those few mutations that together already account for over 90% of CF cases) so that the sensitivity of screening for cases will not be 100%, but only 90%. Fragile X syndrome on the other hand is mostly caused by one mutation in a gene, and could therefore have an almost perfect screening test. However, in this disease the inheritance pattern from parent to child is peculiar (Chapter 6) which leads to a trade-off that has to be made between having a high sensitivity or high specificity. For Down syndrome (described in Appendix C) the screening test in The Netherlands currently is the age of the mother, since the risk of having a foetus with Down syndrome rises with age. Pregnant women of 36 years and older (approximately 9% of all pregnant women) are offered prenatal diagnosis. Since 35% of Down syndrome patients are born to mothers of 36 years or older, screening will at most detect 35% of Down syndrome pregnancies (=sensitivity). On the other hand, since most women of 36 years and older will have a child without Down syndrome, 9% of the women have a false-positive screening test. For this reason, serum screening by the triple test is performed in some parts in The Netherlands if the woman asks for it. As shown in Appendix C, this screening test has a sensitivity of 67% and only 5% of the women will have a false-positive test result.

1.2 Types of (genetic) screening

In contrast to what the name suggests, almost no general population screening programme tests every member of the population, as for almost all screening programmes it is possible to define a group with higher-than-average risk. For example, screening for breast cancer is not offered to men and to women at a young age because they are at (very) low risk. Screening can be offered standalone (e.g. breast cancer screening) or in the form of multiphasic screening where a variety of screening tests is used for a variety of diseases on the same occasion (e.g. an annual

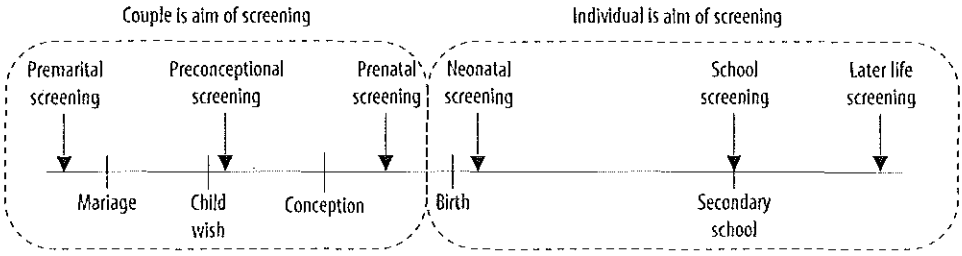


Figure 1.1 Points in time where genetic screening can take place

health check-up or the first visit in pregnancy). The advantage of multiphasic screening obviously is that an efficiency effect can be attained when a person is screened for several diseases at once and that the woman/couple is bothered only one time with screening; the disadvantage is that good information should be given to an individual for several diseases and for several screening tests at the same time which may be difficult. Information should include the fact that a negative (multiphasic) test result does not guarantee a healthy child as people are more inclined to think that they will have a healthy child if they are tested negatively for a large number for diseases.

Screening for genetic diseases may take place at various points of time in life (6-8). The main points of time are described for cystic fibrosis in Figure 1.1 and are described more extensively in Appendix B. As this thesis only deals with reproductive screening, screening in later life is not considered. There is consensus that an advantage of screening prior to pregnancy (preconceptional screening) over screening during pregnancy (prenatal screening) is that people have a choice not to conceive children after an unfavourable test result. And if they decide to have children, they have more time to consider if they want to have prenatal diagnosis, and this may lead to less anxiety (9, 10). Furthermore, they can decide to become pregnant by means of artificial insemination with donor sperm, egg cell donation or to have pre-implantation genetic diagnosis. Because it is difficult to reach people who are not yet pregnant, a preconceptional consultation centre has been proposed as a new health service provision where individuals or couples can go to for all questions regarding reproduction (11). Alternatively, couples with a child wish can consult their general práctitioner.

Specific to genetic diseases is the possibility to test relatives and offspring of detected patients and carriers (cascade testing). The advantage of this type of screening is that

the relatives or offspring of the so-called index case are at much higher-than-average risk of having the disease. Furthermore, when they have a relative with the disease, they are more or less familiar with the disease. Therefore, they can possibly make a better-informed choice concerning screening and reproduction than individuals in the general population. A disadvantage of cascade testing is that only relatives of an index case are offered screening. Since many children with a genetic disease are born in families where the disease has not yet occurred, the parents of these children will not have the possibility to have screening.

1.3 Is genetic screening indicated?

Genetic (and non-genetic) screening programmes will also have negative effects. For example, for each detected disease case (true-positive case) several people without the disease will also have a positive screening test result (false-positive cases), at least when the specificity of the screening test is less than 100%. All positive cases will however have a diagnostic test that in general can cause adverse effects, such as miscarriage after prenatal diagnosis. The World Health Organisation has issued ten criteria that have to be fulfilled in a screening programme in general (Table 1.3).
They had especially screening for chronic diseases in mind. However, there are also some problems specific to genetic screening. The main difference is that in a genetic screening programme aimed at reproduction the screened individual (mostly the mother or mother-to-be) is not the individual where the disease will occur (the child or child-to-be). Furthermore, genetic screening may also have repercussions for the other sibs, the partner and the family members of the screened individual. They can

Table 1.3 WHO guidelines for screening programmes (source: Wilson and Jungner (13))

1. The condition sought should be an important health problem
2. There should be an accepted treatment for patients with recognised disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognisable latent or early symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
8. There should be an agreed policy on whom to treat as patients
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10. Case-finding should be a continuing process and not a 'once and for all' project

also be affected by the genetic disease or they can be carrier of the disease, and perhaps they would have liked not to know it (12). Therefore genetic screening has to be dealt with great care. The Dutch State Secretary for Welfare, Health and Cultural Affairs requested a report from the Health Council of The Netherlands regarding genetic screening. In this report the Health Council described twelve criteria that have to be fulfilled before screening is carried out (4).

1.4 Criteria for genetic screening of the Health Council of The Netherlands

This section lists the criteria of the Health Council Committee in their 1994 report (4) and gives a short explanation.

1. *The genetic screening programme must concern a health problem or a condition that can lead to a health problem in those being tested, or in their descendants.* Unlike the WHO guidelines for screening programmes in general, the Health Council Committee deliberately avoided stating that screening should focus on important public health problems only. This implies that a quantitatively less important public health problem that can be detected and treated with simple and harmless methods (e.g. PKU) can be screened for using these criteria.
2. *The target population of the screening programme must be clearly defined.* The identity of the target group must be known before the acceptability and desirability of the screening programme can be assessed.
3. *The screening programme should enable participants to become aware of the presence or risk of a disorder or carrier status, and to take a decision based on that information.* This is the primary aim of (genetic) screening. Other potential consequences of screening, such as reducing health care costs, will only be secondary aims.
4. *Practical courses of action must be open to the participants.* For many genetic diseases, the 'practical course of action' will primarily be a choice between continuation and termination of pregnancy. If an individual with a high-risk screening test result does not want any course of action, he/she should generally be advised not to have a risky confirmatory test. For example, individuals/couples who know in advance that they will not decide for termination of pregnancy should be advised not to have invasive prenatal diagnosis since it carries an iatrogenic abortion risk (unless the mere knowledge of the disease status of the child offsets this risk to them).

5. *Participation in the genetic screening programme should be voluntary and conditional on consent based on good information.* This criterion goes without comment.
6. *The target group should be supplied with accurate, comprehensible information.* Accurate, comprehensible information forms the basis of voluntary consent described in the previous criterion.
7. *A test method should be available which is suited to the objective of the screening.* This criterion also goes without comment.
8. *There should be sufficient facilities for follow-up diagnostics, for carrying out the chosen courses of action and for informing and supporting the participants.* It is evident that there should be sufficient health care facilities. Furthermore, all options must be legally allowed, e.g. termination of pregnancy is only allowed before 22-24 weeks of pregnancy in The Netherlands.
9. *The procedures used for the storage of medical information and cellular material must incorporate adequate measures to protect both the personal privacy of the participants and their rights regarding their personal data and cellular material.* Screening programmes have to comply with legal standards such as the Data Protection Act (WPR). The procedures to be followed for using body material are described in another Health Council report (14).
10. *If scientific research is carried out within the framework of screening, the participants should be properly informed about this in advance.* Screening is subject to the Medical Experiments Bill (WME).
11. *Provision should be made for continuous quality assurance of the effectiveness, efficiency and safety of the test procedure and all follow-up procedures, as well as information and support given to the participants.* Every screening programme should always have the best test and the best information possible. However, because of the rapid pace of science in genetics this is even more important for genetic screening.
12. *The benefits for the participants in the programme should outweigh the disadvantages. To support this evaluation, those proposing a screening programme must provide information about:*

a. *The prevalence of the disease or disorder in the target group.* This item goes without comment.

b. *The natural course of the disorder, and the variation in degrees of severity.* The information about the natural course of the disorder should contain data about average life expectancy, nature and severity of the complications, treatment options and the probability of physical or mental handicap. For prenatal screening and diagnosis, the information should include the risks of spontaneous abortion and foetal death.
c. *The target group and the considerations which led to the choice of the proposed target group and the proposed time of testing.* In criterion 2 the proposed target group is already discussed. In this weighing item, all possible alternatives should be given including advantages and disadvantages. If a screening programme involves minors, consideration should be given to the question whether screening can be postponed to the age where they can decide for themselves.
d. *The specificity, sensitivity and predictive value of the test method and the burden which testing imposes on participants.* As for all screening programmes, the probability of having a true positive or true negative result should be weighed against the probability of false positive and false negative results.
e. *The available courses of action if a health problem or carrier status is revealed.* This item is obviously linked to criterion 4.
f. *The time allowed by the procedure for consideration and possible implementation of the selected course of action.* The more drastic the courses of action and the more latitude for consideration of these options required by the test result, the more time should be allowed for choosing the course of action.
g. *The possible psychological, social and other repercussions (both positive and negative) of an offer and of participation or non-participation in the screening for the person to be tested and for members of their family or for groups within the community.* The screening offer itself will lead to questions and anxiety for the individual, since he/she will be 'forced' to think about the disease. A point of concern is the imperative character of the screening offer, where some individuals feel themselves forced to accept a screening offer (15).
h. *The likelihood of erroneous results and their possible consequences for participants, and the measures taken to limit any harm which such an error might cause.* This item deals with so-called good practice.
i. *The safeguards for participants against unjustified impediments (as a result of their participation or non-participation in the screening programme or follow-up testing) to obtain employment or private insurance cover.* This item speaks for itself.

j. *The costs of the screening and of the necessary infrastructure.* The considerations of the benefits and drawbacks of the above criteria must reveal a clear benefit to the participants. If this condition is fulfilled, the costs and savings of the screening programme should be assessed to see whether the programme can be justified within total health care.

To see whether the criteria were practical in real life, we performed an assessment of the criteria for serum screening for Down syndrome (16). Although this thesis primarily concerns screening for cystic fibrosis and/or fragile X syndrome, the assessment is presented in Appendix C for illustrative purposes.

1.5 Economic evaluation

1.5.1 Types of economic analysis

The basic economic evaluation is *cost analysis*. This analysis only takes the costs and the induced (economic) savings of the screening programme into account, and can therefore be described as a partial form of economic appraisal. In *cost-effectiveness* analysis, the costs of the programme as calculated in a cost analysis are linked to the consequences ('effects') of the screening programme. These effects are measured in natural or physical units, for example the number of detected people with the disease, the number of life-years that are gained as a result of early diagnosis, or the number of detected carrier couples. In *cost-utility analysis*, the effects of the screening programme are valued using utility, a measure for the relative preference of an individual or group for given health outcomes. The most commonly used measure for this type of analysis is costs per quality adjusted life year (QALY) gained. Cost-utility analysis is usually performed when programmes target at diseases that do not (only) cause mortality but also morbidity, or if the screening programme is aimed to prevent mortality but at the expense of some morbidity. For example, screening for prostate cancer may possibly prevent mortality, but the treatment of prostate cancer (radical prostatectomy) can cause impotence or incontinence, which will influence the quality of life. The last type of analysis, *cost-benefit analysis*, is the most radical economic type of analysis. In this analysis the effects of the screening programme are valued in money terms. It is obvious that valuing effects is very hard and for some effects, e.g. knowing earlier of having a certain disease, it may be nearly impossible (but hard-core economists will try to reveal your values by asking what you are prepared to pay for this earlier knowledge).

1.5.2 Points of view

Some screening programmes will lead to costs for one person or institution, but to benefits for others. For example, a screening programme that is financed by the Ministry of Health can lead to a smaller number of patients with a disease with corresponding lower costs to for example the insurers. Therefore, it is important to determine in advance the point of view of an economic analysis. The points of view can include (from narrowest to broadest) patients, employers, the provider of the screening programme, the Ministry of Health, government and/or society. For most screening programmes the societal point of view is the most relevant because screening has implications on many sectors in society. Costs in the societal point of view do not automatically coincide with the charges and fees paid by the health care system. Most of these charges and fees are bargained prices that only have a remote relationship with the true costs. These costs, therefore, have to be estimated in a different way, namely by measuring each party's investments in manpower, equipment and supplies with relevant wages and prices. The resulting costs will differ from estimates based on the financial point of view of which the accounts of health insurance companies are typical. In that case commercial prices are used, including transfer payments such as profits, margins, value-added taxes and royalties.

1.5.3 Discounting

Costs and savings of a screening programme will not all occur at the same point in time. For example, costs of the screening test(s) itself (occurring at the start of the screening) form the largest part of the costs, while a large part of the savings are caused by future treatments of the disease which are not needed anymore. Furthermore, screening for the same disease can have different target populations (pregnant women, couples with a child wish, school children) which lead to different time profiles. It is generally accepted that earning an amount of money (EURO or Guilder or Dollar) today is preferred over earning the same amount next year because it can be put on a bank account where it will 'grow' because of interest. This concept is called time preference in economics. For example, if the 'real' interest rate (the interest without inflation) is 3% an amount of 1,000 will grow to 1,000 + 1,000 * 3% = 1,030 in one year. Reversely, the amount of 1,030 of next year can be regarded as equivalent to an amount of 1,000 in this year, provided the interest rate is 3%. The interest rate in the reverse reasoning is called discount rate and the amounts obtained by applying discount rates to future costs and savings are called present values.

Among health economists, the rate with which to discount costs is one of the most controversial issues at the moment. The most widely used discount rates (which are both used in this thesis) are 3% and 5%, but recommendations range from 0% to 10%. The most recent and authoritative recommendations are given by a working party convened by the US Public Health Service (17-19) and by a working party for the British Medical Journal (20). The American party (19) recommends a discount rate of 3%, but a 5% rate should also be given for at least the next 10 years. The British party (20) only indicates that "at present most recommendations seem to vary between 3% and 6%, and a common rate in the literature is 5% per year", and emphasises that the discount rate should be stated and justified.
Both working parties recommend discounting health effects and costs by the same rate, but the British party adds the suggestion to discount health effects with a lower rate for preventive (screening) programmes because the results of some studies seem to suggest it (21). Usually, the costs and benefits of a health care programme cover the same target population. In an intergenerational setting like genetic screening additional arguments apply, and we therefore decided not to discount effects (see also Chapter 10, General discussion).

1.6 The thesis

This thesis addresses the final criterion of the Health Council report by giving an assessment of the effects of screening programmes for carriers of the cystic fibrosis gene and/or the fragile X syndrome gene, of the (balance between) costs and savings of these screening programmes, and of the cost-effectiveness of these screening programmes. The ratio behind first assessing effects and costs of screening programmes before assessing the more important other criteria is that screening programmes will probably not be introduced in present times anyway if the economic balance will be very unfavourable. On the other hand, with a favourable economic balance, the decision whether or not to introduce screening will depend on other criteria without worry that economic considerations could stop an otherwise favourable screening programme.
The second part of the thesis concerns cystic fibrosis and starts with an introduction of the disease and screening. In the two following chapters, both the nonhospital costs of care and the age-specific and lifetime costs of care of cystic fibrosis are described. The part ends with a cost-effectiveness analysis of screening for cystic fibrosis-gene carriers. In the next part the disease fragile X syndrome and screening for fragile X

syndrome carriers are introduced first, followed by a cost-effectiveness analysis of screening for fragile X syndrome carriership. The last chapter of this part describes and uses a theoretical simulation model for cascade testing in order to explore its effectiveness. A multiphasic screening model is introduced in the last part of this thesis, where a combination of screening for cystic fibrosis and fragile X syndrome carriers is described.

For comparison purposes all amounts of money are converted to the new European currency EURO (€), where €1.00 is equal to 2.20371 Dutch Guilders, 0.671 Pounds Sterling and 1.111 American Dollars.

1.7 References

1. Pronk JC, Beemer FA, Geraedts JPM, Leschot NJ, Niermeijer MF. Medische genetica [Medical genetics]. (5th ed.) Utrecht: Wetenschappelijke Uitgeverij Bunge, 1994.
2. Modell B, Kuliev AM, Wagner M. Community genetics services in Europe. WHO Regional Publications, 1991. European series; vol 38).
3. UNSCEAR. Genetic and somatic effects of ionizing radiation. A report of the United Nations Scientific Committee of the Effects of Atomic Radiation. New York: United Nations, 1986.
4. Health Council of The Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994; no. 1994/22E.
5. Habbema JDF, van Oortmarssen GJ. Performance characteristics of screening tests. Clin Lab Med 1982;2(3):639-656.
6. Modell B. Cystic fibrosis screening and community genetics. J Med Genet 1990;27(8):475-479.
7. Mennie ME, Gilfillan A, Compton M, Curtis L, Liston WA, Pullen I, Whyte DA, Brock DJH. Prenatal screening for cystic fibrosis. Lancet 1992;340(8813):214-216.
8. Watson EK, Mayall E, Chapple J, Dalziel M, Harrington K, Williams C, Williamson R. Screening for carriers of cystic fibrosis through primary health care services. BMJ 1991;303(6801):504-507.
9. Shapiro DA, Shapiro LR. Pitfalls in Tay-Sachs carrier detection: physician referral patterns and patient ignorance. N Y State J Med 1989;89(6):317-319.
10. Ten Kate LP, Tijmstra T. Screenen op dragerschap van het cystische-fibrose-gen [Screening for carrier state of the cystic fibrosis gene]. Ned Tijdschr Geneeskd 1989;133(48):2402-2404.

11. Ten Kate LP. Genetische factoren [Genetic factors]. In: Van der Maas PJ, Hofman A, Dekker E, eds. Epidemiologie en gezondheidsbeleid [Epidemiology and public health policy]. Alphen aan den Rijn: Samsom Stafleu, 1989:133-144. Gezondheidsbeleid; vol 3).
12. Kooij L, Tijmstra TJ. Erfelijke ziekten zijn familieziekten [Hereditary diseases are family diseases]. Ned Tijdschr Geneeskd 1996;140(9):473-475.
13. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization, 1968. Public Health Papers 34.
14. Health Council of The Netherlands. Proper use of Human Tissue. The Hague: Health Council, 1994; no. 1994/01E.
15. Tijmstra TJ. Het imperatieve karakter van medische technologie en de betekenis van 'geanticipeerde beslissingsspijt' [The imperative character of medical technology and the significance of 'anticipated decision regret']. Ned Tijdschr Geneeskd 1987;131(26):1128-1131.
16. Wildhagen MF, Christiaens GCML, Habbema JDF. Serumscreening bij zwangeren voor Down-syndroom en open neurale-buisdefecten; toetsing aan de Gezondheidsraad-criteria voor genetische screening. [Serum screening in pregnant women for Down syndrome and open neural-tube defects; testing against the Health Council criteria for genetic screening]. Ned Tijdschr Geneeskd 1996;140(2):85-89.
17. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276(14):1172-1177.
18. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276(16):1339-1341.
19. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276(15):1253-1258.
20. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313(7052):275-283.
21. Parsonage M, Neuburger H. Discounting and health benefits. Health Econ 1992;1(1):71-76.

Part 2

Cystic fibrosis

Chapter 2
Cystic fibrosis

2.1 Introduction

Cystic fibrosis (CF) was first described in the medical literature in the 1930s (1, 2), and turned out to be inherited in an autosomal recessive pattern. In 1985, the CF gene was localised on chromosome 7 (3, 4). The cloning of the cystic fibrosis gene in 1989 (5) and the development of simple technical methods for the detection of the more prevalent mutations (6, 7) have made it possible to test for carriers in the general population.

2.2 The disorder

Cystic fibrosis is a disease with recurrent pneumonia, disturbances of the digestive tract, high sweat sodium concentration, malnutrition and obstructive azoospermia (8, 9). The disease has a great impact on the length and quality of life and requires a relatively high amount of medical care. Care of patients with CF is not only intensive, but demands support from relatives, friends, colleagues etc. and interferes with the normal daily life both of the patient and relatives.

Meconium ileus occurs in 10% to 20% of newborns with CF and may be the earliest clinical manifestation of the condition (8, 10). Most patients with CF need daily physiotherapy and repeated courses of antibiotics to treat pulmonary infections. The digestive problem usually results in underweight in children who require a high-energy diet, with 50% more food than the average child their age. Another characteristic of patients with CF is their reduced fertility (11). Although male infertility caused by CF is generally recognised, reduced fertility is also characteristic of women with CF (11, 12).

There have been considerable advances in the medical care of individuals with CF, including recombinant human DNase that reduces the viscosity of purulent airway secretions, heart-lung transplantation, and home therapy (9, 13-17). Current research in gene therapy may soon progress to the point of widespread clinical use. This progress in treatment will obviously have an impact on the length and quality of a patient's life, and will probably have a major influence on the use and type of home care. Despite the progress made in clinical management during the last three decades

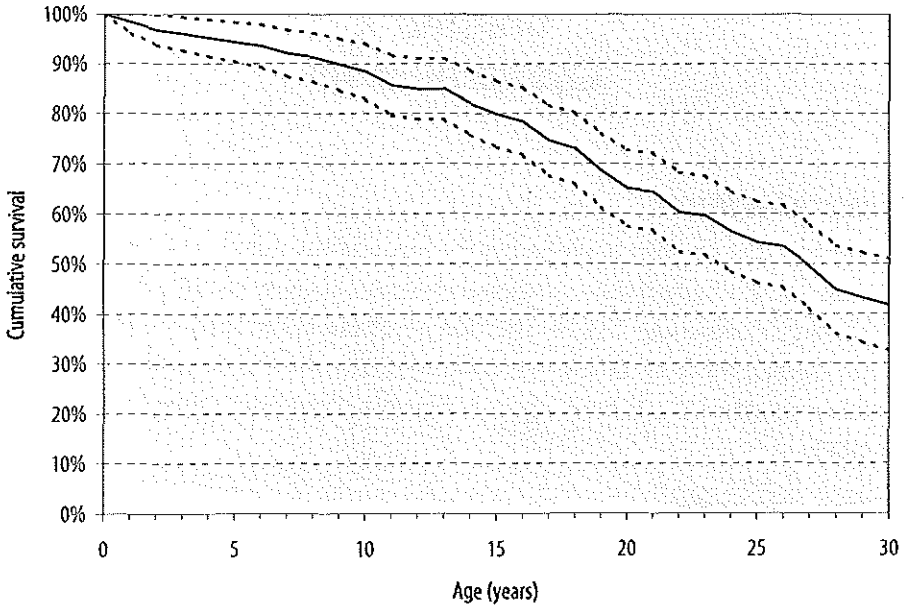


Figure 2.1 Survival curve of patients with cystic fibrosis (source: Collée et al. (18))

it remains, in most patients, a disease with a limited life expectancy (Figure 2.1). In The Netherlands the median cross-sectional survival was 27 years in the period 1985-1990 (18). Because of likely future improvement in treatment, the real life expectancy for children that are born now may be well over 30 years.

2.3 Genetics

Cystic fibrosis is one of the most common recessively inherited disorders in Caucasian populations. In 1989 the gene that is defective in people with cystic fibrosis was discovered (5, 6, 19). This so-called cystic fibrosis transmembrane conductance regulator (CFTR) gene codes for a protein that regulates a low-conductance chloride channel (20). Many, although not all, of the clinical manifestations of the disease can be explained by the lack of this function. Soon after the CF gene was cloned, it was realised that screening for carriers would be possible through direct mutation detection.

Since 1989, many different mutations in the CFTR gene have been discovered, and some of them have been detected in only one family. Currently more than

750 mutations have been identified (CF Genetic Analysis Consortium, http://www.genet.sickkids.on.ca/cftr/FullTable.html), the most common of which is the ΔF508 mutation, a three-base deletion in the gene. This mutation, together with a further 6-10 non-ΔF508 mutated genes, account for more than half of the population variation in CF mutations worldwide (Table 2.1). Remarkable is the relatively high frequency of the A455E mutation in The Netherlands. This mutation is associated with a mild form of CF if this mutation is present in one of the two copies of the CF gene (21).

Affected individuals have a CFTR gene mutation on both chromosomes number 7, but in carriers, who are not affected by the disorder and are healthy, there is only one CFTR gene mutation present. Couples in which both partners are carriers have a 1 in 4 risk with each pregnancy of having an affected child.

2.4 Prevalence

As in many genetic conditions, the diagnosis of an infant with CF often is the first clue that the genetic trait exists in the family. In fact, more than 80% of individuals with CF are born to families with no previous history of the illness (23).

The birth prevalence of CF in The Netherlands is 1 in 3,600 (24). This means that in The Netherlands each year approximately 50 children are born with CF, and the total number of patients in The Netherlands is about 1,000. Since the disorder is autosomal recessive, the carrier frequency in The Netherlands is 1 in 30 (24, 25). There are suggestions that the high frequency of carriers reflects past or present genetic

Table 2.1 Most frequent mutations in the CFTR-gene (source: CF Genetic Analysis Consortium (22) and Halley et al. (21))

	NL	North Europe	North America	World
ΔF508	73.6%	70.3%	66.1%	66.0%
A455E	3.5%	0.2%	0.3%	0.1%
G542X	2.0%	2.1%	2.2%	2.4%
1717-1G->A	1.8%	0.8%	0.4%	0.6%
R553X	1.2%	0.8%	0.9%	0.7%
R1162X	1.1%	0.2%	0.2%	0.3%
N1303K	1.0%	1.0%	1.2%	1.3%
S1251N	1.0%	not given	not given	not given
E60X	1.0%	not given	not given	not given
W1282X	0.5%	0.6%	2.3%	1.2%
G551D	0.1%	1.7%	2.0%	1.6%
Some other mutations	2.0%	2.8%	4.2%	2.9%
Total	88.8%	80.2%	79.9%	77.3%

advantage (26, 27), for example the gene may protect against cholera or typhoid fever which were major killers in the past (27, 28).
The prevalence of CF carrier status varies widely across different racial and ethnic groups, being very common among people in Northern Ireland (carrier prevalence 1 in 21 and birth prevalence 1 in 1,807) and relatively rare among Orientals (carrier prevalence 1 in 150 and birth prevalence 1 in 90,000) (29, 30). The carrier prevalence in the United States and the United Kingdom is about 1 in 25.

2.5 Screening and screening test

2.5.1 Carrier screening

CFTR mutations can be detected by molecular analysis on material obtained by a blood sample, mouthwash or bloodspot (31). Taking a blood sample is the most obvious procedure, but medical supervision is necessary when taking the sample. With the mouthwash procedure there is no need for medical supervision of sample collection and the risk of infection is eliminated. The molecular analysis on material obtained by a mouthwash has theoretically an almost perfect sensitivity and specificity, apart from laboratory errors (31). This relatively simple detection of CFTR mutations makes it possible to consider introducing a screening programme for carriers of the cystic fibrosis gene, where the primary aim is to assess carrier status and counsel couples whose members are both carrier of a CF gene mutation (32, 33). These couples can then be offered further diagnostic possibilities such as prenatal diagnosis by chorionic villus sampling or amniocentesis.
Because of the large number of mutations in the CFTR gene it is not feasible to test all individuals for all possible mutations. However, if individuals are tested with a panel of probes consisting of the mutations from Table 2.1, 87.3% of the carriers and 76.2% (87.3% of 87.3%) of the carrier couples can be detected in The Netherlands. Because of the imperfect test sensitivity, couples with one test-positive and one test-negative partner have an (increased) risk of 1 in 917 of having an affected child, compared to a 1 in 3,600 baseline risk. However, these individuals cannot be offered prenatal diagnosis.
Several screening strategies have been suggested (34-37). Of these, prenatal, preconceptional, school and neonatal screening can be considered for general population screening. For prenatal and preconceptional carrier screening, several strategies and definitions exist, and these can be distinguished with regard to the testing process and the information process (34, 38-40). Among the strategies are

stepwise screening, where one partner (usually the woman) is screened first, and only the partners of those found to be carriers will be offered screening. One disadvantage of the approach is that it generates anxiety in women identified as carriers. However, this anxiety appears to be short-lived and disappears among women whose partners test negative (41). In stepwise screening, three test outcomes are possible: both partners are test-positive (++ couples), one partner is test-positive and the other test-negative (+- couples), and one partner is test-negative and the other is not tested (-? couples). Another strategy is couple screening, where the couple is treated as an entity. Both partners submit a sample simultaneously, and if both are identified as carriers the couple is designated as being at high risk and reported as positive. In contrast, couples in which one partner is tested positive and one negative are designated negative although their risk of an affected infant is higher than the prior risk for the general population. One of the arguments for couple screening is that unnecessary anxiety can be avoided by identifying couples of mixed carrier status by simply treating all couples not at high risk as negative. This caused concern among geneticists as it was felt that the results of all genetic testing should be made available to those tested and not withheld (42). A compromise has been to make the results available on request rather than routinely. Early experience from pilot studies in The Netherlands shows that almost all couples want both partners to be tested and to obtain individual results (L. Henneman, personal communication).

Since stepwise screening also aims at the couple, the terminology 'stepwise' and 'couple' can be confusing. For this reason, the terms single-entry two-step (SETS) couple screening and double-entry two-step (DETS) couple screening have been proposed (Figure 2.2) (40). In these strategies both partners submit a sample. In single-entry two-step screening, one partner is tested first (first step) and if he/she is identified as a carrier the second partner is tested. The first partner is tested for the ΔF508 and other frequent mutations, while the second partner is tested for a larger number of less common mutations (second step). In double-entry two-step couple screening, both partners are tested for the ΔF508 and other frequent mutations (first step), and the test-negative partner of an identified carrier is tested for a larger number of less common mutations (second step). The advantage of DETS over SETS is that the remaining risk in couples with two negative partners (-- couples) in the DETS strategy is significantly lower than in couples with one test-negative partner and one individual that is not tested (-? couples) in the SETS strategy. On the other hand, approximately 5% of couples identified in the DETS approach will comprise one test

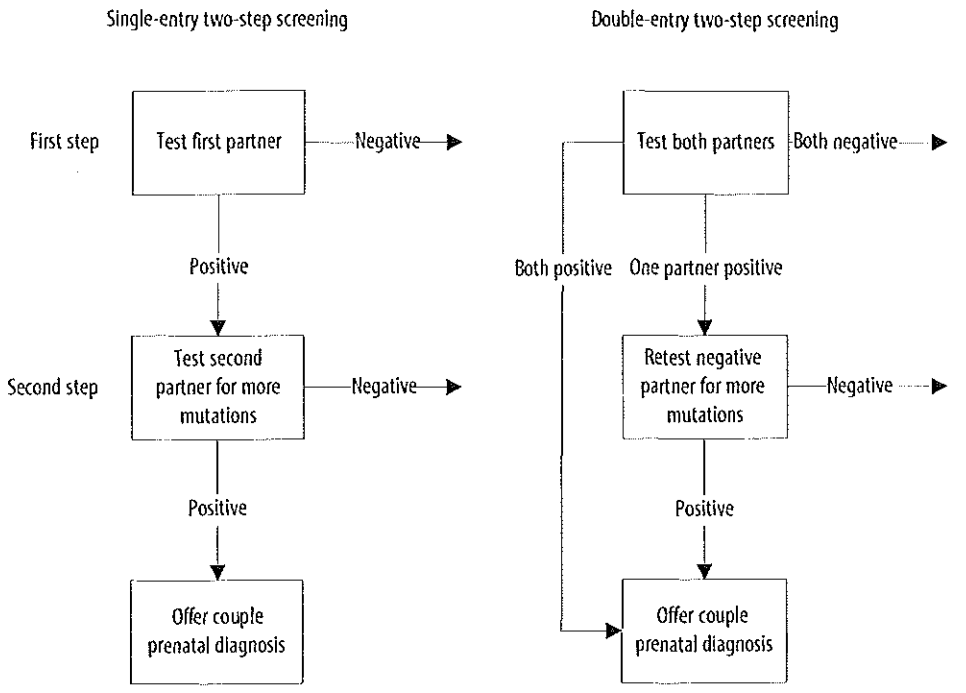


Figure 2.2 Single-entry two-step (SETS) screening and double-entry two-step (DETS) CF screening

positive partner and one test negative partner, compared with 2.5% for single-entry two-step screening. For these couples, the risk is not reduced with the current test sensitivities, but is higher than the risk in the general population (see Appendix D).

Several pilot studies of CF carrier screening have been reported and these are summarised according to screening strategy (Table 2.2-Table 2.3). Uptake is highest for prenatal screening (either stepwise or couple) with a weighted average of 75 percent. The average uptake of preconceptional screening is 7-9% when individuals or couples are invited for screening, 38% and 76% respectively for opportunistically offered screening of individuals and couples. Uptake is influenced by the method of invitation to screening (opportunistic contact or written or other invitation) as well as the setting, with rates as low as 2% reported when the invitation is sent by post (43), compared with rates as high as 87% when screening is offered to visitors of a family clinic by committed researchers (44) (not shown in the table). Only

two studies have been performed using a school setting: uptake was 42% in the Canadian study, and 42% and 75% in two high schools in Australia (45, 46).

The most common reason to decline CF carrier screening was unwillingness to terminate an affected pregnancy (54, 58, 59). However, once the couple has consented to be screened, most affected pregnancies were terminated. The results of published prenatal screening studies show that, of the 13 high-risk couples with an affected foetus identified as a consequence of screening in early pregnancy, all but one chose to terminate that pregnancy. Data for preconceptional screening are not available.

As said earlier, more than 80% of all CF cases are born to families without a history of the disease (23). Holloway and Brock calculated that 4-13% of all carriers in Scotland would be detected with a hypothetical cascade testing programme, which would result in 8-24% of all carrier couples detected (60, 61). In contrast, more than 50% of carrier couples can be detected by prenatal screening (Appendix D) (40). Therefore, Brock (61) concluded that with regard to effectiveness cascade testing should only be discussed in combination with general population screening.

Table 2.2 Summary of studies reporting prenatal screening for CF carriers

First author	Place	Population	Number of couples screened	Coverage (% population screened)	Affected pregnancies detected	Affected pregnancies terminated	% detected pregnancies terminated
Prenatal stepwise screening							
Harris (47)	Manchester	NA*	127	NA*	0	0	-
Schwartz (48)	Copenhagen	7,400	6,599	89%	1	1	100%
Jung (49)	Berlin	638	637	100%	1	1	100%
Cuckle (50)	Yorkshire	6,071	3,764	62%	NA*	NA*	NA*
Miedzybrodzka (51)	Aberdeen	1,629	1,475	91%	0	0	-
Brock (52)	Edinburgh	6,030	4,978	83%	2	2	100%
Doherty (53)	Maine	NA*	1,645	NA*	1	1	100%
Loader (54)	Rochester	5,646	3,334	59%	0	0	-
Witt (55)	N. California	6,617	5,161	78%	1	0	0%
Grody (56)	Los Angeles	4,739	3,192	67%	1	1	100%
All prenatal stepwise studies		38,770	29,140	75%	7	6	86%
Prenatal couple screening							
Harris (47)	Manchester	NA*	117	NA*	0	0	-
Miedzybrodzka (51)	Aberdeen	361	321	89%	0	0	-
Wald (57)	Oxford	810	543	67%	0	0	-
Brock (52)	Edinburgh	16,571	12,566	76%	6	6	100%
All prenatal couple studies		17,742	13,430	76%	6	6	100%

* "NA" means that data are not available; these are omitted in the calculation of totals

Table 2.3 Summary of studies reporting preconceptional screening for CF carriers

First author	Place	Population	Number of couples screened	Coverage (% population screened)	Method
Preconceptional stepwise screening					
Bekker (62)	London	3,951	234	6%	Invitation
Bekker (62)	London	1,208	556	46%	Opportunistic
Tambor (63)	Baltimore	2,713	101	4%	Invitation
Tambor (63)	Baltimore	608	143	24%	Opportunistic
Payne (43)	South Wales	739	166	22%	Invitation
Payne (43)	South Wales	802	303	38%	Opportunistic
All preconceptional stepwise studies		7,403	501	7%	Invitation
All preconceptional stepwise studies		2,618	1,002	38%	Opportunistic
Preconceptional couple screening					
Watson (44)	SW Hertfordshire	852	87	10%	Invitation
Watson (44)	SW Hertfordshire	944	714	76%	Opportunistic
Payne (43)	South Wales	135	2	2%	Invitation
Payne (43)	South Wales	NA*	29	NA*	Opportunistic
All preconceptional couple studies		987	89	9%	Invitation
All preconceptional couple studies		944	714	76%	Opportunistic

* "NA" means that data are not available; these are omitted in the calculation of totals

2.5.2 Neonatal patient screening

In 1968, Schutt and Isles reported excessive albumin in the meconium of patients with meconium ileus due to CF (64). This made neonatal screening for cystic fibrosis patients a possibility (65, 66). In 1979 Crossley et al. reported that immunoreactive trypsin (IRT) was raised in the serum of children with cystic fibrosis (67). Since neonatal screening using a dried blood-spot assay for IRT has a high sensitivity and because it was widely believed that an early diagnosis would improve outcome, neonatal screening programmes were developed in Europe, United States and Australia. The sensitivity of the IRT test (85.7%) and the specificity (99.8%) are improved by testing for the ΔF508 mutation in high-risk bloodspots (sensitivity 95.2%, specificity 99.9%), but false positives are still possible (68). Therefore the diagnosis is confirmed by a sweat test (69).

The rationale for neonatal screening to identify affected infants has been questioned. It has been argued that evidence is lacking that an early diagnosis will substantially improve outcome. While the findings of several studies have suggested that patients with CF who are diagnosed early, i.e. before the onset of clinical pulmonary

involvement, have a better prognosis than those whose diagnosis was made when pulmonary symptoms developed (70-78), all of these studies have some methodological problems.

In an article in the New England Journal of Medicine regarding the only randomised controlled trial for neonatal screening so far, Farell et al. concluded that "neonatal screening provides the opportunity to prevent malnutrition in infants with cystic fibrosis" (79). This article led to an editorial in the same issue that concluded "The results of this new study provide further evidence that the time has come for routine neonatal screening for cystic fibrosis" (80). However, an editorial in the British Medical Journal remarked that there are some methodological issues and concluded that "the present evidence is not encouraging and does not warrant any change in policy from that suggested by the National Institutes of Health consensus statement (81)", that concluded that newborns should not be screened.

Because the methodology of newborn patient screening is different from general population carrier screening, this thesis does not cover newborn patient screening.

2.6 References

1. Fanconi G, Uehlinger E, Knauer C. Das Coeliakiesyndrom bei angeborener zysticher Pankreasfibromatose und Bronchiektasien. Wien Med Wochenschr 1936;86:753-756.
2. Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. Am J Dis Child 1938;56:344-399.
3. Knowlton RG, Cohen-Haguenauer O, Van Cong N, Frezal J, Brown VA, Barker D, Braman JC, Schumm JW, Tsui LC, Buchwald M, Donis-Keller H. A polymorphic DNA marker linked to cystic fibrosis is located on chromosome 7. Nature 1985;318(6044):380-382.
4. Tsui LC, Buchwald M, Barker D, Braman JC, Knowlton R, Schumm JW, Eiberg H, Mohr J, Kennedy D, Plavsic N, Zsiga M, Markiewicz D, Akots G, Brown V, Helms C, Gravius T, Parker C, Rediker K, Donis-Keller H. Cystic fibrosis locus defined by a genetically linked polymorphic DNA marker. Science 1985;230(4729):1054-1057.
5. Rommens JM, Iannuzzi MC, Kerem BS, Drumm ML, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordan JR, Tsui LC, Collins FS. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 1989;245(4922):1059-1065.

6. Kerem BS, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui LC. Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245(4922):1073-1080.
7. Kerem BS, Zielenski J, Markiewicz D, Bozon D, Gazit E, Yahav J, Kennedy D, Riordan JR, Collins FS, Rommens JM, Tsui LC. Identification of mutations in regions corresponding to the two putative nucleotide (ATP)-binding folds of the cystic fibrosis gene. Proc Natl Acad Sci U S A 1990;87(21):8447-8451.
8. Welsh MJ, Tsui LC, Boat TF, Beaudet AL. Cystic fibrosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease. 7th ed. New York: McGraw-Hill, Inc., 1995:3799-3876. vol 3).
9. Rosenstein BJ, Zeitlin PL. Cystic fibrosis [review]. Lancet 1998;351(9098):277-282.
10. Ornoy A, Arnon J, Katznelson D, Granat M, Caspi B, Chemke J. Pathological confirmation of cystic fibrosis in the fetus following prenatal diagnosis. Am J Med Genet 1987;28(4):935-947.
11. Brugman SM, Taussig LM. The reproductive system. In: Taussig L, ed. Cystic fibrosis. New York: Thieme Stratton, 1984:323-337.
12. Buchwald M. Cystic fibrosis: from the gene to the dream. Clin Invest Med 1996;19(5):304-310.
13. Aitken ML, Burke W, McDonald G, Shak S, Montgomery AB, Smith A. Recombinant human DNase inhalation in normal subjects and patients with cystic fibrosis. A phase 1 study. Jama 1992;267(14):1947-1951.
14. Mylett J, Johnson K, Knowles M. Alternate therapies for cystic fibrosis. Semin Respir Crit Care Med 1994;15:426-433.
15. Tamm M, Higenbottam T. Heart-lung and lung transplantation for cystic fibrosis: world experience. Semin Respir Crit Care Med 1994;15:414-425.
16. Wilson JM. Cystic fibrosis: strategies for gene therapy. Semin Respir Crit Care Med 1994;15:439-445.
17. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, Rosenstein BJ, Smith AL, Wohl ME. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med 1994;331(10):637-642.
18. Collée JM, Cobben JM, ten Kate LP. Inventarisatie Cystic Fibrosis in Nederland. Verslag van de vijfde ronde (1990). Nederlandse CF registratie, Rijksuniversiteit Groningen, 1993.

19. Riordan JR, Rommens JM, Kerem BS, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL, Drumm ML, Iannuzzi MC, Collins F, Tsui LC. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989;245(4922):1066-1073.
20. Bear CE, Li CH, Kartner N, Bridges RJ, Jensen TJ, Ramjeesingh M, Riordan JR. Purification and functional reconstitution of the cystic fibrosis transmembrane conductance regulator (CFTR). Cell 1992;68(4):809-818.
21. Halley DJJ, van den Ouweland AMW, van der Hout AH, Scheffer H. Overzicht van 5 jaar DNA-diagnostiek voor cystische fibrose [Overview of 5 years DNA-diagnostics for cystic fibrosis]. LOD Nieuwsbrief 1995;2:8-10.
22. The Cystic Fibrosis Genetic Analysis Consortium. Population variation of common cystic fibrosis mutations. Hum Mutat 1994;4(3):167-177.
23. Blythe SA, Farrell PM. Advances in the diagnosis and management of cystic fibrosis. Clin Biochem 1984;17(5):277-283.
24. Ten Kate LP. Cystic fibrosis in The Netherlands. Int J Epidemiol 1977;6(1):23-34.
25. De Vries HG, Collée JM, de Walle HE, van Veldhuizen MH, Smit Sibinga CT, Scheffer H, ten Kate LP. Prevalence of delta F508 cystic fibrosis carriers in The Netherlands: logistic regression on sex, age, region of residence and number of offspring. Hum Genet 1997;99(1):74-79.
26. Turner G, Meagher W, Willis C, Colley P. Cascade testing for carrier status in cystic fibrosis in a large family. Med J Aust 1993;159(3):163-165.
27. Romeo G, Devoto M, Galietta LJV. Why is the cystic fibrosis gene so frequent? Hum Genet 1989;84(1):1-5.
28. Pier GB, Grout M, Zaidi T, Meluleni G, Mueschenborn SS, Banting G, Ratcliff R, Evans MJ, Colledge WH. Salmonella typhi uses CFTR to enter intestinal epithelial cells. Nature 1998;393(6680):79-82.
29. Wright SW, Morton NE. Genetic studies on Cystic Fibrosis in Hawaii. Am J Hum Genet 1968;20:157-168.
30. Roberts G, Stanfield M, Black A, Redmond A. Screening for cystic fibrosis: a four year regional experience. Arch Dis Child 1988;63(12):1438-1443.
31. De Vries HG, Collée JM, van Veldhuizen MHR, Achterhof L, Smit Sibinga CT, Scheffer H, Buys CHCM, ten Kate LP. Validation of the determination of deltaF508 mutations of the cystic fibrosis gene in over 11 000 mouthwashes. Hum Genet 1996;97(3):334-336.

32. Wilfond BS, Fost N. The cystic fibrosis gene: medical and social implications for heterozygote detection. JAMA 1990;263(20):2777-2783.
33. Anonymous. Statement of the American Society of Human Genetics on cystic fibrosis carrier screening. Am J Hum Genet 1992;51(6):1443-1444.
34. Brock DJH. Heterozygote screening for cystic fibrosis. J Med Screen 1994;1(2):130-133; discussion 133-134.
35. Dodge JA, Boulyjenkov V. New possibilities for population control of cystic fibrosis. Bull World Health Organ 1992;70(5):561-566.
36. Modell M. Screening for carriers of cystic fibrosis - a general practitioner's perspective. BMJ 1993;307(6908):849-852.
37. Raeburn JA. Screening for carriers of cystic fibrosis. Screening before pregnancy is needed. BMJ 1994;309(6966):1428-1429.
38. Wald NJ. Couple screening for cystic fibrosis. Lancet 1991;338(8778):1318-1319.
39. Livingstone J, Axton RAA, Gilfillan A, Mennie M, Compton M, Liston WA, Calder AA, Gordon AJ, Brock DJH. Antenatal screening for cystic fibrosis: a trial of the couple model. BMJ 1994;308(6942):1459-1462.
40. Ten Kate LP, Verheij JBGM, Wildhagen MF, Hilderink HBM, Kooij L, Verzijl JG, Habbema JDF. Comparison of single-entry and double-entry two-step couple screening for cystic fibrosis carriers. Hum Hered 1996;46(1):20-25.
41. Mennie ME, Gilfillan A, Compton M, Curtis L, Liston WA, Pullen I, Whyte DA, Brock DJH. Prenatal screening for cystic fibrosis. Lancet 1992;340(8813):214-216.
42. Miedzybrodzka Z, Dean J, Haites N. Screening for cystic fibrosis [letter]. Lancet 1991;338(8781):1524-1525.
43. Payne Y, Williams M, Cheadle J, Stott NCH, Rowlands M, Shickle D, West G, Meredith L, Goodchild M, Harper PS, Clarke A. Carrier screening for cystic fibrosis in primary care: evaluation of a project in South Wales. The South Wales Cystic Fibrosis Carrier Screening Research Team. Clin Genet 1997;51(3):153-163.
44. Watson EK, Mayall E, Chapple J, Dalziel M, Harrington K, Williams C, Williamson R. Screening for carriers of cystic fibrosis through primary health care services. BMJ 1991;303(6801):504-507.
45. Wake SA, Rogers CJ, Colley PW, Hieatt EA, Jenner CF, Turner GM. Cystic fibrosis carrier screening in two New South Wales country towns. Med J Aust 1996;164(8):471-474.

46. Mitchell J, Scriver CR, Clow CL, Kaplan F. What young people think and do when the option for cystic fibrosis carrier testing is available. J Med Genet 1993;30(7):538-542.
47. Harris H, Scotcher D, Hartley N, Wallace A, Craufurd D, Harris R. Cystic fibrosis carrier testing in early pregnancy by general practitioners. BMJ 1993;306(6892):1580-1583.
48. Schwartz M, Brandt NJ, Skovby F. Screening for carriers of cystic fibrosis among pregnant women: a pilot study. Eur J Hum Genet 1993;1(3):239-244.
49. Jung U, Urner U, Grade K, Coutelle C. Acceptability of carrier screening for cystic fibrosis during pregnancy in a German population. Hum Genet 1994;94(1):19-24.
50. Cuckle HS, Richardson GA, Sheldon TA, Quirke P. Cost effectiveness of antenatal screening for cystic fibrosis. BMJ 1995;311(7018):1460-1463; discussion 1463-1464.
51. Miedzybrodzka ZH, Hall MH, Mollison J, Templeton A, Russell IT, Dean JC, Kelly KF, Marteau TM, Haites NE. Antenatal screening for carriers of cystic fibrosis: randomised trial of stepwise v couple screening. BMJ 1995;310(6976):353-357.
52. Brock DJH. Prenatal screening for cystic fibrosis: 5 years' experience reviewed. Lancet 1996;347(8995):148-150.
53. Doherty RA, Palomaki GE, Kloza EM, Erickson JL, Haddow JE. Couple-based prenatal screening for cystic fibrosis in primary care settings. Prenat Diagn 1996;16(5):397-404.
54. Loader S, Caldwell P, Kozyra A, Levenkron JC, Boehm CD, Kazazian Jr. HH, Rowley PT. Cystic fibrosis carrier population screening in the primary care setting. Am J Hum Genet 1996;59(1):234-247.
55. Witt DR, Schaefer C, Hallam P, Wi S, Blumberg B, Fishbach A, Holtzman J, Kornfeld S, Lee R, Nemzer L, Palmer R. Cystic fibrosis heterozygote screening in 5,161 pregnant women. Am J Hum Genet 1996;58(4):823-835.
56. Grody WW, Dunkel-Schetter C, Tatsugawa ZH, Fox MA, Fang CY, Cantor RM, Novak JM, Bass HN, Crandall BF. PCR-based screening for cystic fibrosis carrier mutations in an ethnically diverse pregnant population. Am J Hum Genet 1997;60(4):935-947.
57. Wald NJ, George L, Wald N, MacKenzie IZ. Further observations in connection with couple screening for cystic fibrosis [letter]. Prenat Diagn 1995;15(6):589-590.

58. Livingstone J, Axton RA, Mennie M, Gilfillan A, Brock DJH. A preliminary trial of couple screening for cystic fibrosis: designing an appropriate information leaflet. Clin Genet 1993;43(2):57-62.
59. Mennie ME, Gilfillan A, Compton ME, Liston WA, Brock DJH. Prenatal cystic fibrosis carrier screening: factors in a woman's decision to decline testing. Prenat Diagn 1993;13(9):807-814.
60. Holloway S, Brock DJH. Cascade testing for the identification of carriers of cystic fibrosis. J Med Screen 1994;1(3):159-164.
61. Brock DJH. Heterozygote screening for cystic fibrosis [review]. Eur J Hum Genet 1995;3(1):2-13.
62. Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, Marteau T. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? BMJ 1993;306(6892):1584-1586.
63. Tambor ES, Bernhardt BA, Chase GA, Faden RR, Geller G, Hofman KJ, Holtzman NA. Offering cystic fibrosis carrier screening to an HMO population: factors associated with utilization. Am J Hum Genet 1994;55(4):626-637.
64. Schutt WH, Isles TE. Protein in meconium from meconium ileus. Arch Dis Child 1968;43(228):178-181.
65. Cain ARR, Deall AM, Noble TC. Screening for cystic fibrosis by testing meconium for albumin. Arch Dis Child 1972;47(251):131-132.
66. Ten Kate LP, Feenstra-de Gooyer I, Ploeg-de Groot G, Gouw WL, Anders GJPA. Should we screen all newborns for cystic fibrosis? Int J Epidemiol 1978;7(4):323-330.
67. Crossley JR, Elliott RB, Smith PA. Dried-blood spot screening for cystic fibrosis in the newborn. Lancet 1979;1(8114):472-474.
68. Gregg RG, Simantel A, Farrell PM, Koscik R, Kosorok MR, Laxova A, Laessig R, Hoffman G, Hassemer D, Mischler EH, Splaingard M. Newborn screening for cystic fibrosis in Wisconsin: comparison of biochemical and molecular methods. Pediatrics 1997;99(6):819-824.
69. Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. Pediatrics 1959;23:545-549.
70. Doershuk CF, Matthews LW, Tucker AS, Spector S. Evaluation of a prophylactic and therapeutic program for patients with cystic fibrosis. Pediatrics 1965;36:675-688.

71. Huang NN, Macri CN, Girone J, Sproul A. Survival of patients with cystic fibrosis. Am J Dis Child 1970;120(4):289-295.
72. Shwachman H, Redmond A, Khaw KT. Studies in cystic fibrosis. Report of 130 patients diagnosed under 3 months of age over a 20-year period. Pediatrics 1970;46(3):335-343.
73. Stern RC, Boat TF, Doershuk CF, Tucker AS, Primiano FPJ, Matthew LW. Course of cystic fibrosis in 95 patients. J Pediatr 1976;89(3):406-411.
74. Kraemer R, Hadorn B, Rossi E. Classification at time of diagnosis and subsequent survival in children with cystic fibrosis. Helv Paediatr Acta 1977;32(2):107-114.
75. Orenstein DM, Boat TF, Stern RC, Tucker AS, Charnock EL, Matthews LW, Doershuk CF. The effect of early diagnosis and treatment in cystic fibrosis: a seven-year study of 16 sibling pairs. Am J Dis Child 1977;131(9):973-975.
76. Wilcken B, Chalmers G. Reduced morbidity in patients with cystic fibrosis detected by neonatal screening. Lancet 1985;2(8468):1319-1321.
77. Bowling F, Cleghorn G, Chester A, Curran J, Griffin B, Prado J, Francis P, Shepherd R. Neonatal screening for cystic fibrosis. Arch Dis Child 1988;63(2):196-198.
78. Dankert-Roelse JE, te Meerman GJ, Martijn A, ten Kate LP, Knol K. Survival and clinical outcome in patients with cystic fibrosis, with or without neonatal screening. J Pediatr 1989;114(3):362-367.
79. Farrell PM, Kosorok MR, Laxova A, Shen G, Koscik RE, Bruns WT, Splaingard M, Mischler EH. Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. N Engl J Med 1997;337(14):963-969.
80. Dankert-Roelse JE, te Meerman GJ. Screening for cystic fibrosis--time to change our position? [editorial]. N Engl J Med 1997;337(14):997-999.
81. Anonymous. Genetic testing for cystic fibrosis. NIH Consens Statement 1997 Apr 14-16;15(4):1-37.

Chapter 3
The nonhospital costs of care of patients with CF in The Netherlands: results of a questionnaire

3.1 Introduction

Cystic fibrosis (CF) is the most frequent serious autosomal recessive disease in Caucasian populations. Characteristics of CF are chronic bronchopulmonary infections, pancreatic insufficiency, disturbances of the digestive tract, and high sweat-sodium concentration. The birth prevalence of CF in The Netherlands is 1 in 3,600 (1). This means that in The Netherlands each year approximately 50 children are born with CF. The total number of patients in The Netherlands is about 1,000.

The disease has a great impact on the length and quality of life and consumes a relatively high amount of medical care. Treatment starts from the diagnosis and continues throughout life, and consists of prescribing additional calories and vitamins and fighting the respiratory infections with antibiotics and intensive physiotherapy. Care of patients with CF is not only intensive, but demands support from relatives, friends, colleagues etc. and interferes with the normal daily life both of the patient and relatives (2).

In a previous study (see Chapter 4), the costs of medical care in the hospital were determined by reviewing the medical records of 81 patients (40 males and 41 females) of the Beatrix Children's Clinic of the University Hospital Groningen and the Leyenburg Hospital in The Hague for the years 1990 and 1991 (3). These hospital records contain mainly information regarding medical treatment and appointments, and lack data on medical costs outside the hospital, such as physiotherapy, visits to the general practitioner and home medication, as well as the costs of nonmedical (home) care, such as domestic help, diet, travelling because of CF and special facilities. The results of a questionnaire survey to determine these nonhospital costs are described.

3.2 Patients and methods

We developed a questionnaire containing items about nonhospital medical care, domestic help, diet, travelling because of CF, work/school, medication, and devices and special facilities at home, work or school. Nonhospital medical care was divided into care from general practitioner, physiotherapist and homeopath/acupuncturist. The questionnaires were supplied with a number so that a reminder could be sent if necessary; the list with numbers and names was destroyed immediately after the reminders were sent.

From the Beatrix Children's Clinic of the University Hospital Groningen, 23 children were selected in such a way that all age categories were represented. In the Leyenburg Hospital, 50 adult nonterminal patients were selected. These patients or their guardian (for children) were asked to fill in the questionnaire on a daily basis for 4 weeks in May 1993. The questionnaire was returned by 14 Groningen patients (average age 10 years; range 1-17 years) and 33 Leyenburg patients with an average age of 27 years (range 16-46 years) (Table 3.1). The total response was, therefore, 64% (47 out of 73). Data from one (adult) patient were not useful because this patient lived abroad. For validation purposes, six responding (parents of) patients, who had indicated they were willing to have a telephone interview, were telephoned and the questionnaire was talked through with them. It was concluded that the questionnaires were filled in carefully and meticulously. Because the questionnaire was anonymous, it could not be linked to the patient's records; therefore, it was not possible to stratify according to severity of disease.

Table 3.1 Age distribution of responders to questionnaire

Age (years)	Responders
0-4	3
5-9	2
10-14	6
15-19	10
20-24	8
25-29	6
30-34	6
35+	5
Total	46

The average consumption per patient was calculated by dividing the total units consumed of that item by the number of respondents. The average costs per patient per year were calculated by multiplying the average consumption by 13 (correction for a 4 weekly questionnaire period) and multiplying this result with the unit costs. If possible, unit costs were determined on the basis of insurer allowances. If this was not possible, data from the report "Cost calculation in health service research; guidelines for practice" (4) were used. The source of financing was not taken into account.

3.3 Results

The average consumption per item and the costs of nonhospital care per year for children and adults with CF are presented in Table 3.2 and Table 3.3, respectively. In these tables, ranges of consumption and costs are also shown, and the weighted average of the consumption and costs for an 'average' patient in The Netherlands, where 36% of the patients are adult (aged ≥18 years) (J.M. Collée, personal communication).

Table 3.2 Consumption of nonhospital care per year for patients with CF. Values are presented as average, and range in parenthesis

	Consumption per year				
	Children		Adults		Weighted average*
Nonhospital medical care					
General practitioner n	0.9	(0-13)	3.7	(0-26)	1.9
Physiotherapist n	26.0	(0-91)	33.7	(0-260)	28.8
Homeopath / acupuncturist n	0.9	(0-13)	3.3	(0-52)	1.8
Domestic help h	113	(0-1404)	148	(0-1248)	126
Diet items for CF n	1.2	(0-3)	1.0	(0-3)	1.1
Travelling because of CF	857	(120-3192)	4,194	(0-27774)	2,058
Work, school, absence					
Job contract % total	-	-	57	-	-
Part-time % employed	-	-	41	-	-
Absence % contract hours	8	(0-65)	18	(0-25)	-
Medication prescriptions n	5.6	(1-8)	8.7	(4-16)	6.7
Pancreatic enzymes	1.1	(1-2)	0.8	(0-1)	1.0
Pulmonary medicines	1.3	(0-3)	3.6	(0-7)	2.1
Vitamins	2.1	(0-5)	1.7	(0-4)	1.9
Oral antibiotics	0.4	(0-2)	0.4	(0-1)	0.4
Parenteral antibiotics	0.1	(0-1)	0.3	(0-1)	0.2
Other medication	0.6	(0-2)	1.9	(0-5)	1.1
Devices and special facilities at home, work or school % of patients					
Nebulizer	43	-	88	-	59
Home trainer	21	-	69	-	38
Infusion pump	7	-	13	-	9
PEP-mask†	43	-	16	-	33
Special features	0	-	34	-	12
Other	21	-	31	-	25

* per year for a Dutch CF patient

† positive expiratory pressure mask

Table 3.3 Nonhospital costs of care per year for a patient with cystic fibrosis (CF). Values are presented as average, and range in parenthesis

	Costs per year (€) Children		Adults		Weighted average*
Nonhospital medical care	545	(0-1755)	809	(0-5411)	640
Domestic help	1,028	(0-12742)	1,342	(0-11326)	1,141
Diet for CF	669	(0-2533)	1,084	(0-3937)	818
Travelling because of CF	245	(34-913)	1,199	(0-7940)	588
Pancreatic enzymes	2,145	(438-4699)	1,854	(0-4376)	2,040
Pulmonary medicines	488	(0-2757)	3,045	(0-14299)	1,408
Vitamins	170	(0-466)	280	(0-1306)	210
Oral antibiotics	1,237	(0-13316)	2,643	(0-6697)	1,743
Parenteral antibiotics	217	(0-1559)	1,328	(0-25812)	617
Other medication	99	(0-435)	1,177	(0-7159)	487
Devices and special facilities at home, work or school	101	(0-398)	561	(0-4153)	266
Total nonhospital costs of care	6,944	(1065-19852)	15,322	(2473-39751)	9,960

* costs per year for Dutch CF patients

3.3.1 General practitioner, physiotherapist and homeopath/acupuncturist

One child (7%) and eight adults (25%) consulted their general practitioner (GP) in the 4 weeks under study for a total of one and nine consultations, respectively. It was, therefore, estimated that a CF child has on average 0.9 GP consultations per year and an adult 3.7. At a cost per consultation of €15.28, this amounted to €14 per child with CF per year and €56 per adult.

Six children (43%) and 14 adults (44%) indicated that they had visited a physiotherapist for 4.7 and 5.9 times per respondent per 4 weeks, respectively. This means that a child with CF visited a physiotherapist on average 26 times a year and an adult 34 times. The corresponding costs were €501 per year for children and €650 for adults, at a cost of €19.29 per consultation.

Five persons (one child and four adults) consulted a homeopath or acupuncturist, of whom one patient had four consultations and one had two. Average consultations per year were 0.9 for children and 3.3 for adults. At a cost of €31.76 per consultation, this means that consultations with a homeopath or acupuncturist cost €29 per child per year and €103 per adult.

3.3.2 Domestic help

Fourteen adult patients (44%) responded that they had domestic help for an average of 26 hours during the 4 weeks. This corresponds to almost 148 hours per year per adult patient. With standardised costs of €9.08 per hour, this amounts to €1,342 per adult patient per year.

Caring for a child with CF costs the parents/guardians a lot of extra time in comparison with a child without CF; these costs were only taken into account if the parents had some domestic help. Three parents of children with CF (21%) received help from a caretaker or relative for 41 hours on average during the 4 weeks, which corresponds to 113 hours domestic help and €1,028 per child per year.

3.3.3 Diet for CF

Diet used by patients with CF aims at ameliorating the physical condition of the patient. Sixty-three percent (29 out of 46) of all patients indicated that they used a supplemental or special diet. Most patients used calorie concentrates: Fortisip® (used by 16 patients); Polycal® (12); Nutrison® (5); Nutrilon® (5) and Meritene and Protifar (1 each). Furthermore, snacks such as Evergreen®, Mars® and Nuts® were used by three patients, and other products such as shakes (two patients) and camomile tea, celery soup and cream (one patient each). Average costs for a CF-specific diet amounted to €669 per year for children and €1,084 for adults.

3.3.4 Travelling because of CF

Almost all respondents, 45 persons (98%), answered that during the 4 weeks they had travelled once or more because of CF, children on average 66 km and adults 333 km in the 4 weeks. This corresponded to 857 and 4,194 km per patient per year, costing €245 and €1,199 per year at €0.29 per km.

3.3.5 Work, school and absence

Fifty-seven percent (17 persons) of the adult patients reported that they held a contract of employment, of which almost 50% had a part-time job. During the 4 weeks, five persons had been absent due to CF for a total of 13 days (104 hours), which was 18% of the total contract hours of all 17 patients who had a contract (570 hours). As a comparison, in the general population absence due to sickness in The Netherlands in this period was 5.8% for males and 8.9% for females (5).

Three out of 18 patients (17%) who attended school had been absent for one or more days; average absence for these three patients in the 4 weeks was 9 days. This means

that a child with CF was on average absent from school for 19.5 days per year. National data concerning school absence are not known.

3.3.6 Medication

All patients used medication for CF (children on average 5.6 different medicines and adults 8.7). For a better overview, medication has been divided into six groups: pancreatic enzymes (14 children and 25 adults); pulmonary medicines (8 children and 29 adults); vitamins (11 children and 25 adults); oral antibiotics (5 children and 14 adults); parenteral antibiotics (2 children and 9 adults); and other medication (6 children and 25 adults).

The pancreatic enzymes were either pancrelipase (10 children and 23 adults) or pancreatin (5 children and 1 adult). Average costs per year amount to €2,145 for children and €1,854 for adults.

In the pulmonary medicines group, many different preparations were used. Salbutamol was used most frequently in this group (3 children and 18 adults), followed by colistin by nebulization (2 children and 17 adults), and acetylcysteine and ipratropium bromide (12 patients each). Other medicines were used less than 10 times. As mucolytic agent, mercaptoethanesulfonate was recorded 13 times and acetylcysteine 12 times. On average, 3.6 different prescriptions were taken by the users of pulmonary medicines (children 2.3 and adults 3.9). Average costs amounted to €488 per year for children and €3,045 for adults.

The vitamins A, B, C, D, E and K and multivitamins were prescribed in different combinations. The average costs per patient per year amounted to €170 for children and €280 for adults.

In the oral antibiotics group, eight different medicines were indicated in the questionnaire. Of these, co-trimoxazole was used most frequently (1 child and 6 adults). Two patients indicated that they used co-trimoxazole for a fixed period of 8 months and 3 weeks, respectively. The other patients did not indicate a fixed period of use. Ciproxin therapy was used by three patients for an average of 3 weeks per patient. Average costs for the oral antibiotics group were €1,237 per year for children and €2,643 for adults.

In the parenteral antibiotics group, three different medicines were noted: flucloxacillin (2 children and 7 adults), ceftazidime and tobramycin (both used by one adult). Flucloxacillin therapy was used by two patients for 3 weeks and 13 weeks,

respectively. Ceftazidime was used as a cure for 3 weeks. Average costs for the group parenteral antibiotics were €217 per year for children and €1,328 for adults.
In the 'other medication' group, 31 users recorded 70 medicines; the most widely used were insulin (7 adults, no children), ranitidine and ursodeoxycholic acid (both 5 adults, no children). Four patients used two homeopathic medicines on average. Average costs per patient per year amounted to €99 for children and €1,177 for adults.

3.3.7 Devices and special facilities at home, work or school

Three quarters of the respondents (6 children and 28 adults) used a nebulizer with (average) cost price of €711. Using an (annuity) amortisation scheme of 10 years and an interest rate of 5%, this amounted to €39 per year for children and €140 for adults. Almost a quarter of the respondents (6 children and 5 adults) used a positive expiratory pressure (PEP)-mask (cost price €109), average €13 per child per year and €5 per adult. For ameliorating or retaining the physical condition, 22 adult respondents and 3 children used a home trainer and/or rowing device (average cost price €334), or €5 per child per year and €32 per adult, with an amortisation scheme of 10 years. Four adults used an infusion pump at home (3 Cadd-plus and 1 Cadd-1), and one child used a Flocare device. Average costs for infusion pumps were €11 per child per year and €174 per adult. Other devices were extra diapers (1), vibracan (1), ambulant oxygen device (2), lung volume gauge (2) and air cleaner (1): average costs per year €32 for children and €81 for adults. Five persons (4 children and 1 adult) did not use any device.
For eight (adult) respondents, a special facility at home or at work had been made, e.g. a home trainer, shower and oxygen at work, a personal (handicapped) parking place and a shower-seat at home. The costs for an average adult patient with CF were €130 per year.
Average costs for devices and special facilities at home, work or school consequently amounted to €101 per year for children and €561 per year for adult patients.

3.4 Discussion

The disease CF has a great impact on the daily life of the patient and family. In this study, it was found that the majority of patients had a special diet and 74% sprayed with a nebulizer one or more times a day for about 30 minutes. Almost all patients had medical care outside the hospital during the survey period: whereas 43% had visited a physiotherapist, it can be assumed that the other 26 patients performed exercises

themselves. Total nonhospital costs of CF care in The Netherlands amounted to €6,944 per year for children and €15,322 for adults. However, the costs of nonhospital care of children should be considered with caution because data from only 14 children were collected.

This study is obviously most relevant to the Dutch situation, but a significant part of it could be used to assess costs for other (European) countries as well. Possible differences might be the rather low number of consultations with a general practitioner (0.9 per year for children and 3.3 for adults) and (reimbursed) visits to a physiotherapist (26 times per year for children and 34 times for adults).

Caring for a family member or friend with CF takes much time and energy. For example, almost half of the adult patients had domestic help. These 'direct costs' were taken into account in this analysis. On the other hand, caring for a child with CF takes more time for parents/guardians than caring for a child without CF. The use of these so-called 'indirect costs', mainly production losses, is disputed among economists. Therefore, these costs of caring and of absence from work were not included in the calculation.

CF is a disease for which tremendous progress is being made in the field of medical care. Some developments have already become reality since the time of our data collection, such as recombinant human deoxyribonuclease (DNase) I to decrease the viscosity of purulent airway secretions, and the increasing use of (heart-)lung transplantations. Other developments have the possibility of progressing to the point of widespread clinical use, such as gene therapy (6-9). This progress in treatment will obviously have an impact on the length and quality of a patient's life, and will probably have a major influence on the use and type of home care and, thus, on the costs of nonhospital care. The results of the present analysis should, therefore, be updated regularly.

The results of this analysis have been used in the calculation of the total costs of the disease cystic fibrosis (10). For this reason, the medical consumption per age category was determined and the nonhospital costs added. These totals were discounted with a 5% interest rate and corrected for the survival curve (median age 27 years) of the Dutch CF registration (11), which comprises 3,302 observed patient-years. In this way, the so-called lifetime costs of CF were determined at €245,901, of which €122,984 (=50%) were costs made outside the hospital. Considering the cost-effectiveness of, for example, continuous intravenous home treatment of airway infections (12), the shift from hospital to extramural care could eventually lead to lower costs of the

disease. On the other hand, an increase in the number of lung transplantations is expected to occur, so that the future total costs of care are difficult to predict.
The lifetime costs of CF have been used to prospectively evaluate costs of screening for carriers of the CF gene (13). A choice for or against genetic screening on the basis of economic motives is completely rejected by the authors. Recently, a committee of the Dutch Health Council has formulated a set of reasonable criteria for genetic screening programmes (14). Cost aspects can play a role in evaluating whether or not an otherwise desirable screening programme can be organised, or that costs of screening can be prohibitive. The results of our costs study (13) indicate that costs are probably not prohibitive for cystic fibrosis screening.

3.5 References

1. Ten Kate LP. Cystic fibrosis in The Netherlands. Int J Epidemiol 1977;6(1):23-34.
2. Gerritsen J, van der Laag H, Sinnema G, Knol K. Guidance of children and adolescents with cystic fibrosis. Lung 1990;168:474-480.
3. Verzijl JG, Hilderink HBM, Verheij JBGM, Kooij L, Habbema JDF, ten Kate LP. Costs of cystic fibrosis (CF) and costs of screening for CF carriers in The Netherlands. In: Escobar H, Baquero F, Suárez L, eds. Clinical ecology of cystic fibrosis. Madrid: Exerpta Medica, Elsevier Science Publishers B.V., 1993:313-318.
4. Rutten FFH, van Ineveld BM, van Ommen R, van Hout BA, Huijsman R. Kostenberekening bij gezondheidszorgonderzoek; richtlijnen voor de praktijk [Cost calculation in health care research; guidelines for practice]. Instituut voor Medische Technology Assessment, 1993.
5. Statistics Netherlands. Maandbericht gezondheid 94/5 [Monthly bulletin of health statistics 94/5]. Voorburg/Heerlen: Statistics Netherlands, 1994; no. 94/5.
6. Tamm M, Higenbottam T. Heart-lung and lung transplantation for cystic fibrosis: world experience. Semin Respir Crit Care Med 1994;15:414-425.
7. Mylett J, Johnson K, Knowles M. Alternate therapies for cystic fibrosis. Semin Respir Crit Care Med 1994;15:426-433.
8. Wilson JM. Cystic fibrosis: strategies for gene therapy. Semin Respir Crit Care Med 1994;15:439-445.
9. Rosenstein BJ. Cystic fibrosis in the year 2000. Semin Respir Crit Care Med 1994;15:446-451.

10. Wildhagen MF, Verheij JBGM, Verzijl JG, Hilderink HBM, Kooij L, Tijmstra T, ten Kate LP, Gerritsen J, Bakker W, Habbema JDF. Cost of care of patients with cystic fibrosis in The Netherlands in 1990-1. Thorax 1996;51(3):298-301.
11. Ten Kate LP, Halley DJJ. Genetische aspecten van 'cystic fibrosis' [Genetic aspects of 'cystic fibrosis']. Tijdschr Huisartsgeneeskd 1995;12:195-198.
12. Bakker W, Vinks AATMM, Mouton JW, de Jonge P, Verzijl JG, Heijerman HGM. Continue intraveneuze thuisbehandeling van luchtweginfecties met ceftazidim via een draagbare pomp bij patiënten met cystische fibrose; een multicentrisch onderzoek [Continuous intravenous home treatment of airway infections using ceftazidime administration via portable pump in patients with cystic fibrosis; a multicenter study]. Ned Tijdschr Geneeskd 1993;137:2486-2491.
13. Wildhagen MF, Hilderink HBM, Verzijl JG, Verheij JBGM, Kooij L, Tijmstra T, ten Kate LP, Habbema JDF. Costs, effects, and savings of screening for cystic fibrosis gene carriers. J Epidemiol Community Health 1998;52:459-467.
14. Health Council of The Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994; no. 1994/22E.

Chapter 4
Cost of care of patients with cystic fibrosis in The Netherlands in 1990-1991

4.1 Introduction

Cystic fibrosis is the most common serious autosomal recessive disease in many white populations. Despite the progress made in clinical management during the last three decades it remains, in most patients, a disease with a limited life expectancy. In The Netherlands the median survival is 27 years (1).

Research on the cost of care of patients with cystic fibrosis is scarce (2-5). Nowadays, however, there seems to be an increasing interest in this subject, possibly because of the recent discovery of the gene responsible for the disease which creates the possibility of population screening for carriers of the cystic fibrosis gene. The cost of care analysis presented here is part of a research project in which the costs, effects, and savings of screening for carriers of the cystic fibrosis gene in The Netherlands are estimated (6). We decided not to use data from the literature because we wanted to have age-specific cost estimates using primary data rather than using non-age-specific data and expert opinions.

The aim of the cost of care analysis is to estimate the following quantities using data collected from medical patient records and a patient questionnaire: (1) the age-specific medical consumption and medical costs of patients, and a breakdown of these costs into costs of hospital care, hospital and nonhospital medication, and home care with separate estimates for the (pre)terminal disease stage; (2) the lifetime medical costs of a patient by combining age-specific medical costs with recent survival figures of the Dutch cystic fibrosis registration (1); and (3) the cost of care of cystic fibrosis in The Netherlands by combining age-specific medical consumption with the number and age-distribution of patients in The Netherlands (1).

The estimate of the lifetime costs of medical consumption of patients with cystic fibrosis will be used for cost-effectiveness calculations of nationwide screening programmes for cystic fibrosis carriers for The Netherlands.

4.2 Methods

The costs of medical consumption of patients with cystic fibrosis were divided into costs of hospital care (hospital days, consultations, diagnostic tests), hospital and home medication, and home care (visits to a general practitioner, physiotherapy at home, help from relatives, diet, travelling expenses, and special aids).

4.2.1 Medical consumption

To determine the cost of hospital care we reviewed the medical records of 81 patients (40 men) treated in a cystic fibrosis centre for adults in The Hague and in the Groningen University Cystic Fibrosis Centre for Children. We confined ourselves to hospital care during the years 1990 and 1991 to reflect recent clinical practice. An inventory was made of all admissions to hospital (hospital days, admissions, and consultations), visits to outpatient departments (consultations), radiological procedures, surgical interventions, laboratory investigations (tests), and other activities that were taken in relation to cystic fibrosis. We also made an inventory of all medications taken in the hospital and at home. The cohort of patients analysed represents approximately 8% of all living patients in The Netherlands. The age distribution (median age 13; range 0-37 years) was similar to the age distribution of all patients in the Dutch cystic fibrosis registration which covers 3,302 observed patient-years and has a 75% survival at 17 years and a 50% survival at 27 years (1).

To gain insight into the medical consumption that is not covered in the medical records we asked 73 patients to keep a diary of visits to the general practitioner and physiotherapist and travelling expenses for one month. The response rate of this questionnaire was 64%. We also questioned the patients about the support received from their social environment (for example, relatives), their daily activities and their school/work life.

To check whether the medical consumption estimated from the medical records was in accordance with clinical experience, we interviewed several clinicians in charge of patients with cystic fibrosis. The results of the patient questionnaire were used to validate several data extracted from the patient records. The questionnaire itself was validated through interviews with some of the patients (or their parents) who completed the diaries.

The average age-specific medical consumption was obtained by dividing the age-specific consumption from the patient records and the patient questionnaires by the patient-years at risk in the age group concerned. Separate calculations were made for

patients in the preterminal or terminal stage, defined as the last two years of life, because we expected that their medical consumption would differ significantly from the non-(pre)terminal patients.

4.2.2 Costs

We estimated the costs from a societal point of view. Costs are measured by calculating invested manpower and materials with relevant wages and prices. These cost estimates will differ from those resulting from a financial point of view in which commercial prices are used including so-called transfer payments – for example, profits, margins, tariffs, taxes, royalties (7). Whenever possible we used real costs per unit of medical consumption known from other research or estimated by us. If the real costs were not known, reimbursements from health care insurers were used (Table 4.1). These reimbursements are the prices that insurers pay to hospitals, general practitioners, doctors, and other health care providers. The reimbursements are mostly settled in some form of negotiation between health care insurers and providers (for example, hospitals), and do not necessarily equate with real costs.

Most patients are treated in specialised cystic fibrosis centres or university hospitals. The costs of these hospital days are higher than for general hospitals because of the more intensive treatment. The costs of a hospital day include physiotherapy for 20 minutes a day. Children receive more physiotherapy (on average twice a day for 30 minutes) than adolescents who can perform their daily exercises mostly on their own; we therefore added the cost of 30 minutes physiotherapy to the costs of a hospital day for children.

The average age-specific medical costs are obtained by multiplying the average age-specific medical consumption by the corresponding unit cost figures. The age-specific

Table 4.1 Costs of several units of medical consumption by patients with cystic fibrosis based on estimates of real costs or on reimbursements

Unit	Cost figure	Based on
Hospital day	€229.42	Estimate of real costs
Consultation	€43.56	Estimate of real costs
Radiograph (average)	€36.81	Reimbursement
Ultrasound (average)	€77.69	Reimbursement
Doppler ultrasound	€62.62	Reimbursement
CT scan	€170.74	Reimbursement
Lung function test	€98.16	Reimbursement
Laboratory (weighted average)	€9.46	Reimbursement

figures were converted into the lifetime average consumption by using the Sum-Limit method (8), which corrects for the year-to-year survival of patients with cystic fibrosis. To discount these costs we used a 5% discount rate towards the time of birth. Survival of patients with cystic fibrosis in The Netherlands was estimated from the Dutch cystic fibrosis registration (1).

4.3 Results

The average consumption of the most important aspects of hospital care (except medication) is presented in Table 4.2. 'Consultations' include all visits of patients to the outpatients department. 'Laboratory tests' represent the number of results of laboratory investigations (from blood, urine, and stool).

The estimates of the costs of home medication and home care were based on the patient questionnaire. Costs of home care include materials, diet, and travelling expenses. On average a patient visited the general practitioner 2.8 times per year and the physiotherapist 31 times per year. Of all patients 74% used a nebulizer, 54% a hometrainer for daily workouts, 11% an infusion pump, and 24% a positive expiratory pressure (PEP) mask. Only 11% did not use any device. For the devices we calculated the average yearly costs on an annuity basis. From the questionnaire we also learned that 57% of all adults had a paid job and about half of them (47%) had part-time contracts.

The average cost of a patient with cystic fibrosis per year is €16,319. Table 4.3 presents the breakdown of these costs. The total cost of care of cystic fibrosis in The

Table 4.2 Age-specific average hospital consumption of patients with cystic fibrosis per patient per year

Age (years)	Number of Patients	Hospital days	Admissions	Consul-tations	Radio-graphs	(Doppler) Ultrasound scans	Lung function tests	Laboratory tests
0	3	68.8	2.5	13.7	6.5	0.5	0.0	146.8
1 – 4	11	7.2	0.4	6.4	2.5	0.1	0.2	57.5
5 – 9	11	5.9	0.5	5.7	2.6	0.3	5.8	64.8
10-14	21	4.9	0.4	5.3	2.3	0.4	7.9	87.1
15-19	18	22.4	0.9	6.5	4.4	1.0	10.4	134.2
20-24	9	52.6	1.6	7.4	8.8	0.9	7.3	216.2
25-29	2	25.1	1.9	8.9	4.9	0.5	2.4	128.2
30-34	5	6.5	0.7	8.2	3.1	0.7	4.3	141.8
35+	1	0.0	0.0	4.0	1.0	0.0	2.8	36.0
All	81	18.5	0.9	6.9	4.0	0.5	5.3	116.5

Table 4.3 Average cost of care (per patient per year) of patients with cystic fibrosis in 1991

	Cost	Percentage
Hospital care	€6,900	42%
Medication	€6,084	37%
Home care	€3,335	20%
Total	€16,319	100%

Netherlands in 1991 is estimated to be €16.3 million, which is approximately 0.07% of the total health care budget in The Netherlands. This figure is obtained by multiplying the average costs per year with the number of patients (estimated at 1,000 patients). The cost of age-specific hospital care, medication, and home care is presented in Figure 4.1. The five year moving average is obtained by averaging the costs of the index year with the costs of the two preceding and the two following years. We have to keep in mind that from age 25 onwards our estimates are based on a relatively small group of patients (age 25 years, n=8).

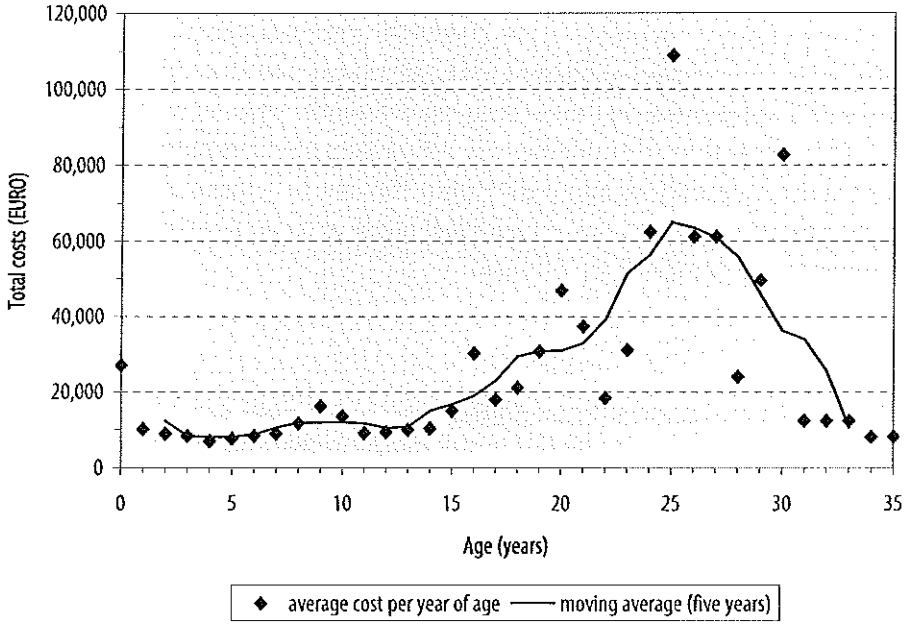


Figure 4.1 Average cost of care of patients with cystic fibrosis per year of age

A relatively high medical consumption occurs in the first year of life because the diagnostic process takes place in the first year of life in most (57%) patients (1). The increase in average costs after the age of 15 is mainly due to frequent antibiotic treatment and hospital days (Table 4.4) due to exacerbations or complications. Among the Dutch patients older than 31 years a relatively high proportion is diagnosed at an older age. Those patients have milder pulmonary disease, are less likely to suffer from pancreatic insufficiency or diabetes mellitus, and have consequently lower than average cost of care (9). The high values of the average costs at age 25 and 30 shown in Figure 4.1 are caused by two patients who underwent a lung transplantation (cost €122,521).

In order to arrive at the costs in The Netherlands we totalled the average cost per year of life up to the age of 35, which amounted to €919,464. When survival is taken into consideration, the lifetime costs of a patient with cystic fibrosis are €612,570. If we discount the lifetime costs to the time of birth using a discount rate of 5%, which is common in cost-effectiveness studies, they amount to €245,901.

The difference in costs between the average medical consumption of patients aged 15 and older who are not in the (pre)terminal phase and the average medical consumption of patients in the (pre)terminal stage amounts to €39,794 which is 71% of the costs of the (pre)terminal stage (Table 4.4). This difference is due to the large number of hospital days, radiographs, Doppler studies and laboratory tests that are required. It is noteworthy that there is no big difference between the average cost of care of all patients (€16,319) and the cost of care for patients older than 15 years who are not in the (pre)terminal phase (€16,609). This can be explained by the relatively small number of patients in the (pre)terminal phase (n=8) and the relatively low costs of patients under the age of 15 (€11,608).

Table 4.4 Average medical consumption (per patient per year) of patients with cystic fibrosis aged 15 or older not in the (pre)terminal stage compared with the average consumption of patients in the (pre)terminal stage

	Number of Hospital days	Admissions	Consul-tations	Radio-graphs	(Doppler) ultrasound scans	Lung function tests	Laboratory tests	Average medical consumption cost
15+ years	10.9	0.8	6.5	3.0	0.3	8.7	76.3	€16,609
(Pre)terminal	106.0	2.7	7.9	15.9	5.4	5.5	575.5	€56,404

4.4 Discussion

Our model of age-specific medical consumption seems plausible and the approach is also applicable to other countries. The lifetime costs of €245,901 differ from other estimates. The OTA report estimates the lifetime costs of a patient with cystic fibrosis for 1989 at €107,959 (3). This figure is obtained by discounting the average direct medical costs (average per year €8,405) by 5% per year and correcting for survival in the USA. The difference between the OTA estimate and ours is probably due to primary data collection in our research (instead of using expert estimates). Ginsberg et al. estimate the excess lifetime costs of patients to be €194,101 (4), which comes closest to our research. Although they made age-specific estimates of the costs, they did not always use data from real patients, and this may be the reason for the difference from our estimate.

All other known research on costs of cystic fibrosis differentiates between mild, moderate, and severe patients (2, 5). Robson et al. calculated costs to be between €4,177 and €29,852 per year with an average of €12,328 for an adult patient (2). From our calculations the costs of an adult patient (aged 15 or over), excluding home care costs (for comparability), are €21,650. In Denmark these costs were €58,291 for three year old patients, €54,802 for 12 year old patients, and €97,398 for a 20 year old patient (5). Our calculations for these patients are, respectively, €8,362 for patients of three years of age, €9,406 for patients aged 12, and €46,867 for those aged 20. These differences could again be the result of the use of expert estimates in the Danish study instead of using primary patient data.

Cystic fibrosis is a disease in which tremendous progress is being made in medical care. Some developments such as recombinant human DNase I to decrease the viscosity of purulent airway secretions, an increasing use of (heart-)lung transplantations, and home therapy have already become a reality since the time of this review, while others such as gene therapy have a possibility of progressing to the point of widespread clinical use (10-13). Although some of these developments can be very economical—for example, home therapy—most new developments are costly (14-18). Moreover, this progress in treatment will have an impact on the length and quality of a patient's life so that the cost of care for patients with cystic fibrosis will probably rise.

The indirect costs of patients have not been taken into consideration in this study. Indirect costs are mainly the result of production losses because patients (or their carers) are unable to work full time. Although American studies have tried to estimate

these costs (for example, Pauly estimated the total cost for the cystic fibrosis population per year at €66 million (19)), the use of such a method is disputed among economists. The so-called costs of 'replacement' have also not been calculated and can only be calculated if a child born with cystic fibrosis was foregone and replaced by a child not affected with cystic fibrosis.

The daily costs of patients with cystic fibrosis such as diet appear to be relatively stable. The additional costs of, for example, frequent admission to the hospital, and treatment with intravenous antibiotics fluctuate and depend on the age of the patient and stage of the disease. It is to be expected that daily costs will remain stable in the future, but additional costs will increase due to expensive new treatment and care provision. Because of better treatment and new medication, the lifetime cost of care will probably increase (higher medical consumption). This will lead to an ever increasing cost-savings balance of screening, as long as the growth in the costs of screening is lower than the growth in the lifetime costs of cystic fibrosis.

4.5 References

1. Ten Kate LP, Halley DJJ. Genetische aspecten van 'cystic fibrosis' [Genetic aspects of 'cystic fibrosis']. Tijdschr Huisartsgeneeskd 1995;12:195-198.
2. Robson M, Abbott J, Webb K, Dodd M, Walsworth-Bell J. A cost description of an adult cystic fibrosis unit and cost analyses of different categories of patients. Thorax 1992;47(9):684-689.
3. US Congress Office of Technology Assessment. Cystic Fibrosis and DNA tests: implications of carrier screening. Washington, DC: U.S. Government Printing Office, 1992.
4. Ginsberg G, Blau H, Kerem E, Springer C, Kerem B-S, Akstein E, Greenberg A, Kolumbos A, Abeliovich D, Gazit E, Yahav J. Cost-benefit analysis of a national screening programme for cystic fibrosis in an Israeli population. Health Economics 1994;3:5-23.
5. Nippert I, Clausen H. Evaluating Cystic Fibrosis carrier screening development in Northern Europe: Denmark, the Federal Republic of Germany, The Netherlands, and the United Kingdom. Dordrecht: Kluwer Academic Publishers Group, in press.

6. Verzijl JG, Hilderink HBM, Verheij JBGM, Kooij L, Habbema JDF, ten Kate LP. Costs of cystic fibrosis (CF) and costs of screening for CF carriers in The Netherlands. In: Escobar H, Baquero F, Suárez L, eds. Clinical ecology of cystic fibrosis. Madrid: Exerpta Medica, Elsevier Science Publishers B.V., 1993:313-318.
7. Drummond MF, Stoddard GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, 1987.
8. Van Hout BA. Harttransplantaties. Kosten, effecten en prognoses [Heart transplantations. Costs, effects and forecasts (summary in English)] [thesis]: Erasmus University Rotterdam, 1990.
9. Gan KH, Heijerman HGM, ten Kate LP, Scheffer H, Bakker W. Late diagnosis of cystic fibrosis: genetics and disease symptoms 7th Annual North American Cystic Fibrosis Conference. Dallas, Texas, October 13-16, 1993. Abstracts. Pediatr Pulmonol Suppl 1993;9:234.
10. Tamm M, Higenbottam T. Heart-lung and lung transplantation for cystic fibrosis: world experience. Semin Respir Crit Care Med 1994;15:414-425.
11. Mylett J, Johnson K, Knowles M. Alternate therapies for cystic fibrosis. Semin Respir Crit Care Med 1994;15:426-433.
12. Wilson JM. Cystic fibrosis: strategies for gene therapy. Semin Respir Crit Care Med 1994;15:439-445.
13. Rosenstein BJ. Cystic fibrosis in the year 2000. Semin Respir Crit Care Med 1994;15:446-451.
14. Bosso JA, Stephenson STH, Herbst JJ. Feasibility and cost savings of intravenous administration of aminoglycosides in outpatients with cystic fibrosis. Drug Intell Clin Pharm 1985;9:52-54.
15. Donati MA, Guenette G, Auerbach H. Prospective controlled study of home and hospital therapy of cystic fibrosis pulmonary disease. J Pediatr 1987;111(1):28-33.
16. Kane RE, Jennison K, Wood C, Black PG, Herbst JJ. Cost savings and economic considerations using home intravenous antibiotic therapy for cystic fibrosis patients. Pediatr Pulmonol 1988;4(2):84-89.
17. Strandvik B, Hjelte L, Malmborg AS, Widen B. Home intravenous antibiotic treatment of patients with cystic fibrosis. Acta Paediatr 1992;81(4):340-344.

18. Bakker W, Vinks AATMM, Mouton JW, de Jonge P, Verzijl JG, Heijerman HGM. Continue intraveneuze thuisbehandeling van luchtweginfecties met ceftazidim via een draagbare pomp bij patiënten met cystische fibrose; een multicentrisch onderzoek [Continuous intravenous home treatment of airway infections using ceftazidime administration via portable pump in patients with cystic fibrosis; a multicenter study]. Ned Tijdschr Geneeskd 1993;137:2486-2491.
19. Pauly MV. The economics of cystic fibrosis. In: Lloyd-Still JD, ed. Textbook of cystic fibrosis. Boston: John Wright PSG Inc, 1983:465-476.

Chapter 5
Costs, effects, and savings of screening for cystic fibrosis gene carriers

5.1 Introduction

Cystic fibrosis (CF) is the most frequent serious autosomal recessive disease in white populations. Characteristics of CF are chronic bronchopulmonary infections, pancreatic insufficiency, disturbances of the digestive tract, and high sweat sodium concentration. The disease has a great impact on the length and quality of life and causes a comparatively high medical consumption (1, 2). Treatment starts from the diagnosis and continues throughout life, and consists of prescribing additional calories, vitamins and pancreas enzymes, and fighting the respiratory infections with antibiotics and intensive physiotherapy.

In 1989, the gene responsible for cystic fibrosis was cloned (3-5). Nowadays, more than 600 mutations of this CFTR gene are known (CF Genetic Analysis Consortium). Of these, the so-called ΔF508 mutation, a three-base deletion in a part of the gene, is by far the most common in Western Europe, while a limited number of other mutations accounts for more than half of the non-ΔF508 mutated genes (6, 7). These mutations can be detected by polymerase chain reaction analysis with, apart from laboratory errors, a perfect sensitivity and specificity. This makes it possible to consider introducing a screening programme for carriers of the CF gene, where the primary aim is to detect carrier status and counsel couples whose members are both carrier of a CF gene mutation so that they can make deliberate decisions about reproduction.

Screening for CF gene carriers is under debate in many countries. There are health related, psychosocial, ethical, legal, and economic consequences associated with CF gene carrier screening, as with other genetic screening programmes. In The Netherlands, the Dutch Health Council recently formulated criteria for genetic screening programmes intended to ensure systematic assessment of such programmes before their introduction (8). The last criterion states that if the positive consequences clearly outweigh the negative consequences, costs and savings of the screening programme should be calculated and checked in view of a fair distribution of resources within the total area of the health services. We started a prospective

evaluation to determine the cost-savings balance of CF screening and related the costs to effect measures. If the economic balance will turn out to be unacceptably unfavourable, CF screening is not warranted anyhow. If, on the other hand, the economic balance is favourable, decision making can concentrate on the crucial non-economic aspects.

Several screening strategies have been suggested (9-12) and are being or have been analysed in a pilot study (13-21). Of these, prenatal, preconceptional, school, and neonatal screening can be considered for general population screening. For the prenatal and preconceptional screening strategies we considered both single-entry and double-entry two-step couple screening (see below). Analogously to Morris and Oppenheimer (22), we did not consider cascade screening (screening of relatives of patients) in this analysis, because the approach is completely different from general population screening. Furthermore, Holloway and Brock (23) have shown that cascade testing is not very effective, as only between 8% and 24% of all carrier couples would be detected if cascade testing were restricted to up to the second cousin level.

We calculated the costs, effects, and savings of the screening strategies and compared them with a situation in which there is no CF gene carrier screening. For a one year screening period, we simulated the effects on individuals and couples under certain assumptions concerning reproductive decision making. Although our main analysis uses population genetic figures and cost estimates for The Netherlands, other combinations of assumptions can be analysed as well with our model. In this paper, we will only analyse other carrier frequencies as they may occur in other countries.

5.2 Methods

We developed a simulation model for a screening programme for CF gene carriers. We prospectively evaluated four different screening strategies taking the Dutch situation as an example: prenatal screening, preconceptional screening, school screening, and neonatal carrier screening. For each screening strategy we calculated the expected costs, effects, and savings for a one year screening period. CF related costs and savings that occur after that year were taken into account using a five percent annual discount rate (24).

To see by what extent the cost-savings balance depends on our assumptions, we conducted two threshold analyses. In a single-variable threshold analysis, we determined for selected assumptions the maximal or minimal value of that assumption for which savings equal costs. In a multi-variable threshold analysis, we

varied these assumptions simultaneously and determined at what percentage change in all assumptions savings equal costs. Furthermore, we examined the influence of the CF gene carrier prevalence on the cost-savings balance. After a brief explanation of the screening strategies, we describe the assumptions and parameters that we used in our analysis.

5.2.1 Screening strategies

Prenatal screening

In the prenatal screening strategy, pregnant women and their partners are screened as early in their pregnancy as possible so that chorionic villus sampling may still be possible in case both are carriers. Prenatal screening is the only form of screening in which prevention of pregnancy is not possible. Only for the future children all reproductive options are open. Because almost all women who suspect to be pregnant consult a general practitioner or midwife, it is relatively easy to integrate this form of CF gene screening in the existing health care system. Observed participation rates in the UK range from 62% to 91% (18, 25-27).

Preconceptional screening

Preconceptional screening concerns couples who consider having a child and want to receive information about their carrier status. The screening result is known before the (potential) reproduction so that all reproductive options are open to the carrier couples, for example, accepting the risk of giving birth to a CF child, having prenatal diagnosis possibly followed by induced abortion, refraining from having (more) children, adoption, artificial insemination with donor sperm or egg cell donation and pre-implantation diagnosis. For most countries (including The Netherlands) an important obstacle to preconceptional screening is the absence of a preconceptional consultation system. Observed participation rates in the UK range from 4% to 87%, and depend very much on the way people are approached (13, 14, 28).

School screening

In the school screening strategy, acquisition of the testing material (for example, mouth washes) can take place within the school environment. For minimising the time between screening and (potential) reproduction, pupils in the last year of compulsory education (at the age of 16 in The Netherlands) should be offered the test. From a social-genetic perspective, this type of screening also offers a good

opportunity for teaching genetics. Good information is important because school screening takes place in a rather unstable stage of life, possibly leading to stigmatisation. Studies in Italy and Canada on thalassaemia and Tay-Sachs disease screening, and for CF carrier screening in Australia and Canada show that school screening is feasible (21, 29-31). Observed participation rates for screening in high schools range from 42% to 75% (21, 31).

Neonatal screening

In the neonatal carrier screening strategy, the target population consists of newborn children who are tested in the first months after birth. As almost all newborns are already tested on PKU/CHT by a blood spot, CF gene screening can easily be integrated into the existing screening programme. If a newborn child turns out to be a carrier the target population can be extended to the parents, and if both turn out to be a carrier they can use this information in making further reproductive choices.
However, there are also disadvantages for this strategy. Firstly, screening for curable diseases (PKU/CHT) which has a routine character will be combined with screening for carriership of a (still) incurable disease (CF). Secondly, the information regarding carriership only becomes relevant to the newborn for reproductive decisions after 20 to 30 years. This necessitates considerable efforts for retaining this information that can be helped by, for example, a computer database or an individual health passport.

Single-entry versus double-entry in prenatal and preconceptional screening

In the school and neonatal screening strategies, single persons are screened. For prenatal screening and preconceptional screening however, we deal with couples and the test can be offered with single or with double-entry (27, 32-34). We assumed that in the single-entry two-step screening framework (SETS), one partner is tested initially for carriership of the ΔF508 mutation only. In case he/she is a carrier, the sample of the second partner will be searched for a total of 17 mutations. For the double-entry two-step screening framework (DETS), we assumed that the mouth wash sample of both partners is initially tested for the ΔF508 mutation and that the sample of the negative partner in case of a positive/negative couple is searched for the other 16 mutations (32). We have assumed that testing material will be directly obtained from both partners, even in the SETS framework. In this way, the partner who is not tested initially does not have to make extra arrangements to be tested in case his/her partner is shown to be a carrier. For the school and neonatal screening programmes, we

assumed that for cost considerations the individuals are tested only for the ΔF508 mutation (see also the discussion).

5.2.2 Prevalence

The prevalence of CF gene carriers varies between populations; in The Netherlands it is one in 30 (35). The ΔF508 mutation is identified in 73.6 percent of all CF genes and 16 other mutations account for 11.9 percent (36). It is therefore possible to identify 85.5 percent of all mutations with a 17 mutations screening test. As a comparison, the prevalences in the United Kingdom and the United States are 1:25 to 1:28, while the ΔF508 mutation accounts for 70-77 percent of all CF genes and five to 11 other mutations for 15-20 percent, depending on racial and ethnic background (37, 38).
In The Netherlands, the presence of autosomal and sex chromosome abnormalities is checked for routinely when chorionic villi are analysed for CF. Therefore we took these abnormalities into account, with a prevalence at time of prenatal diagnosis of 1:500 for both autosomal and sex chromosome abnormalities (39).

5.2.3 Target populations

We assumed that the target population of prenatal screening consists of couples who are pregnant with their first child. We used the number of firstborn children, 85,030 in 1995 in The Netherlands (40), but corrected for the probability of spontaneous abortion between the time of screening and time of birth (3.5% for low-risk pregnancies (41)), leading to a target of 88,241 couples (see first line of Table 5.1). For preconceptional screening, the number of firstborn children was corrected with a 10% probability of a couple remaining infertile (42), so that the target of preconceptional screening consists of 94,478 couples. The target population of school screening consists of 183,060 people of 16 years (43). We assumed that 90% of them will form a couple that wants a child, and 10% of these couples remain infertile (44). For neonatal screening, the target population consists of all 190,513 children that were born in 1995 (40), again it is assumed that 90% of them will form a couple that wants a child and that 10% of these remain infertile (44).
We assumed that in all screening strategies, 84.9% of the people with a firstborn child will have a second child after 2.9 years on average (40, 44). For computational simplicity, we ignore in our calculations births of children who are thirdborn or more. This assumption will obviously not have effects on the costs per detected carrier couple, but will lead to a conservative estimate of the cost-savings balance.

Table 5.1 Assumptions that differ between CF gene screening strategies: size of target population, coverage, information preservation, and costs

	Screening strategy			
	Prenatal	Preconceptional	School	Neonatal
Size of target population	88,241	94,478	183,060	190,513
Coverage of screening	90%	50%	85%	95%
Information preservation	100%	100%	90%	70%
Mass information costs	€157,235	€262,058	€209,646	€157,235
Individual information costs	€2.72	€1.36	€0.68	€1.36
Organisation costs	€10.38	€10.38	€10.38	€0.00

5.2.4 Coverage and information preservation

As discussed in the description of the strategies, the coverage that may be achieved is probably highest for neonatal screening, somewhat lower for prenatal screening, and again somewhat lower for school screening; we set these values at 95%, 90% (18, 27), and 85% (45), respectively. For preconceptional screening, coverage depends very much on the existence of a preconceptional consultation system and on the way in which people are approached (13, 14); we took 50% coverage as baseline value.

In the Tay-Sachs disease prevention programme in Montreal, Zeesman et al. (30) found that after eight years 90% of the screened pupils were able to retrieve the test result regarding carriership. Because the time between testing and possible use of the carrier information for school screening is of the same order of magnitude (12 years in our analysis), we took this value for the information retention rate of school screening. For neonatal screening, the time between testing and possible use of the information equals 28 years in our analysis, leading to a lower retention rate. Moreover, carrier status information has to be passed from the parents to the screened child at some time. For these reasons we presumed an information retention rate of 70% for neonatal screening. Furthermore, we assumed that individuals who have not retained their test information will not be retested. We summarise the estimates for coverage and information preservation in the second and third row of Table 5.1.

5.2.5 Other assumptions

Furthermore, to assess the consequences of CF gene screening, we had to make a number of assumptions concerning reproduction and use of prenatal diagnosis. In the published pilot carrier screening studies that actually tested persons, 95% of all detected carrier couples opted for prenatal diagnosis and 92% of all affected foetuses were aborted subsequently (25-27, 46-51). However, these figures were based on very

small numbers, and the attenders in these pilot studies might be a selected group that is favourably biased towards screening, prenatal diagnosis, and abortion. Therefore, we decided to take somewhat more conservative estimates and presumed that 15% of the detected carrier couples refrain from having (more) children (52), that 85% of the carrier couples make use of prenatal diagnosis, that in 80% of diagnosed affected foetuses parents make the choice for selective abortion, and that prenatal diagnosis carries an attributable risk of iatrogenic abortion of 0.75% (53). Furthermore, we took into account spontaneous abortions. Most of the assumptions were subjected to a sensitivity analysis.

5.2.6 Economic factors

The costs of screening can be divided in three aspects: the costs of spread of information before the screening—for instance by mass media and leaflets—, the costs of the organisation of the screening and the testing itself, and the costs of aftercare. We estimated the costs from a societal point of view: costs are measured by calculating invested manpower and materials with relevant wages and prices. Resulting figures will differ from those obtained when using a purely financial point of view, where commercial prices of, for example, kits are used, including so-called transfer payments (for example, profits, margins, tariffs, taxes, royalties) (54). We regarded as economic savings the precluded lifetime medical costs of patients who will be born less as a result of the screening programme. Because costs of diagnosis and treatment of CF occur at a later point in time than the actual screening, they were recalculated to the (present) value in the year of screening using an annual discount rate of five percent (24).

Costs of information

We divided the information costs into two parts (see Table 5.1): the mass information costs that depend on the target group—for example, costs of mass media campaigns—and the individual information costs that are proportional to the number of individuals or couples—for instance costs of leaflets.

Van der Maas et al., studying the costs and effects of mass screening for breast cancer in The Netherlands, obtained €262,058 for the mass information costs and €1.36 for individual information (costs adjusted for inflation between 1990 and 1996) (55). As we may regard the way of information provision in the preconceptional screening strategy as somewhat analogous to that for the breast cancer screening programme, we took these values as baseline cost estimates for the preconceptional screening

programme. Because of its easy integration in the existing health care system, we set the mass information costs for prenatal and neonatal screening lower at 60% of the value for preconceptional screening and we took the school mass information costs at 80% because of the integration in the school setting.
The individual information costs are likely to be highest for prenatal screening because of the direct consequences and emotional sequelae of the test outcome. Therefore we estimated them as twice the costs of individual information for preconceptional screening at €2.72, which is comparable to the costs used by Cuckle et al. (26). We set the individual information costs lowest for school screening at 50% of the value of preconceptional screening. The individual information costs to the parents in the neonatal screening strategy were set at the same value as the costs in the preconceptional screening strategy.

Costs of testing

Costs of testing can be subdivided into costs of acquisition of the sample of an individual or couple, shipment of the samples to a laboratory, DNA extraction, DNA analysis, reporting of the results, and costs for the screenee. The so-called organisation costs of acquisition, shipment, and administration were estimated at €10.38 per couple for prenatal, preconceptional, and school screening. Organisation costs for neonatal screening were ignored because the CF test is assumed to supplement the already existing screening programme for PKU/CHT in The Netherlands; therefore costs of acquisition, shipment, and reporting of the results will not change or change only very slightly if a screening test is added to the PKU/CHT programme. Estimates of the costs of DNA testing for multiple mutations in the United Kingdom range from €34 to €45 (22, 26, 56). In our analysis, we took the cost estimate of Cuckle et al. (€37.89) (26) for the multiple mutations test. The ΔF508 mutation analysis can be performed with a comparatively cheap in house polymerase chain reaction, and is done in much larger quantities than the multiple mutations tests. Therefore we assumed that the cost of DNA testing for the ΔF508 mutation only would cost only a quarter of the multiple mutations test (€9.47). For the costs for the screenee, we took the costs of travelling by public transport and the costs of production loss (one hour for travelling to the screening, waiting time, and the time of screening) (57), totalling €6.57.

Costs of further diagnosis and treatment

Aftercare consists of counselling carrier couples and positive/negative couples and, depending on the choice of the couple, prenatal diagnosis for detected carrier couples and eventually, depending on the couples decision, abortion of an affected foetus. For counselling we took the costs of a qualified nurse in a clinical genetics centre, assuming that counselling a carrier couple takes one hour (22) and counselling a positive/negative couple takes a half hour. At an hourly wage of €19.06 and an overhead percentage of 40%, counselling costs to the clinical genetics centre are €26.68 for a carrier couple and €13.34 for a positive/negative couple. For the carrier couple, we added 15 minutes of waiting time and the costs of public transport to the counselling costs, totalling €10.50 for positive/positive couples and €7.88 for positive/negative couples (57). The costs of prenatal diagnosis, selective abortion, early spontaneous abortion, late spontaneous abortion, and iatrogenic abortion were based on Dutch reimbursements between health care providers, government, and insurance companies: €1,270.58, €221.01, €69.23, €444.36, and €69.23 respectively (58, 59).

Lifetime costs of a CF patient

By means of an examination of the medical records of 81 patients (40 men, 41 women) and a patient questionnaire among 73 patients (2), we estimated the age specific cost of illness of a CF patient. We converted this cost of illness into the average lifetime excess costs of care of a CF patient by adjusting for the survival figures of CF patients and discounting at five percent (1). The lifetime excess costs of care of a CF patient in The Netherlands were in this way estimated to be €273,967 (corrected for inflation).

5.3 Results

Lowest total costs of screening are achieved with single-entry preconceptional screening, and with neonatal screening (upper part of Table 5.2). The costs of the other strategies are much higher. The double-entry two-step (DETS) frameworks for preconceptional and prenatal screening have much higher costs than their single-entry counterparts (SETS), because the number of tests performed is almost twice as high.

Table 5.2 Costs, effects, and savings per year for a CF gene screening programme

	Screening strategy					
	Prenatal		Preconceptional		School	Neonatal
	SETS†	DETS†	SETS†	DETS†		
Costs of information*	€438,000	€438,000	€431,000	€431,000	€300,000	€465,000
Costs of testing*	€3,074,000	€4,386,000	€2,107,000	€2,895,000	€3,096,000	€1,999,000
Costs of aftercare*	€166,000	€229,000	€84,000	€122,000	€93,000	€186,000
Total costs of screening*	€3,679,000	€5,053,000	€2,621,000	€3,448,000	€3,489,000	€2,651,000
Detected carrier couples	56	63	33	38	36‡	112‡
Costs per detected carrier couple*	€66,000	€80,000	€79,000	€92,000	€97,000	€24,000
Number of avoided patients	18	21	10	12	8	13§
Costs per avoided patient*	€205,000	€247,000	€258,000	€298,000	€421,000	€206,000
Net economic savings (savings minus costs)*	€1,561,000	€869,000	€221,000	−€235,000	−€2,115,000	−€224,000

* costs and savings are rounded to €1,000

† SETS=single-entry two-step couple screening
DETS=double-entry two-step couple screening

‡ number of couples whose members both have retained their carrier information until their reproductive period

§ including seven patients born less because parents are shown to be a carrier couple due to their first carrier child being detected

With regard to the number of detected carrier couples, neonatal screening performs best (112 carrier couples detected). If testing of parents of diagnosed carrier newborns (which is an extra possibility of neonatal screening only) would not be included in the calculations, double-entry prenatal screening detects most carrier couples (63 couples). As expected, double-entry screening detects more carrier couples than single-entry screening (63 compared with 56 couples for prenatal screening). The costs per detected carrier couple are by far lowest for neonatal screening, because its organisation costs are set at zero. The SETS versions of prenatal and preconceptional screening perform much better than the DETS versions, for example, €66,000 and €80,000, respectively for prenatal screening.

When we want to carry the economic analysis of the screening programmes further, we need to calculate the number of patients that are born less as a result of the screening programme (third part of Table 5.2). This number is defined as the number of patients not born because the (would be) parents decide to refrain from having (more) children or to have an induced abortion in case of an affected foetus. In the neonatal screening strategy, some patients are born less because the first child is detected carrier, and in the follow-up his/her parents appear to be a carrier couple and decide to refrain from further children. The DETS framework of prenatal screening results in the highest number (21 patients) of avoided patients. Because we assumed

that individuals who have not retained their test information are not retested, school screening does not result in many avoided patients (eight patients). In the neonatal screening strategy, seven patients are born less because the first child is detected carrier. The number of avoided patients in the preconceptional screening strategy is rather small because of its low coverage.

The net economic savings (savings minus costs) are positive for both prenatal screening strategies and the single-entry version of preconceptional screening. The costs of double-entry preconceptional, school, and neonatal screening are higher than the economic savings, mainly because of the high polymerase chain reaction screening costs, which account for more than 25% of the total costs of these screening programmes. Maximum net economic savings are obtained in the SETS version of prenatal screening (€1.6 million).

5.3.1 Threshold analysis

We calculated for selected parameters the values for which savings exactly equal costs while keeping all other parameters at their baseline values (Table 5.3). Even if carrier couples never refrain from having more children, prenatal screening and SETS preconceptional screening have a favourable cost-savings balance. The savings of DETS preconceptional screening would be higher than its costs if more than 29% of all carriers would refrain from having children, while an unrealistic 96% of all carriers should refrain to achieve higher savings than costs for neonatal screening. Even if all carrier couples would refrain from having children, costs exceed savings for school screening.

For the prenatal screening programmes, the fraction of the carrier couples that will use prenatal diagnosis can decrease to 74% or less before costs exceed savings, and for SETS preconceptional screening the threshold is 78%. If more than 95% of all carriers would have prenatal diagnosis, even DETS preconceptional screening and neonatal screening would have higher savings than costs, while costs always exceed savings for school screening, even if all couples will use prenatal diagnosis. The threshold values for the fraction that decides to have an affected foetus aborted are similar to the thresholds for the fraction of the carrier couples that will use prenatal diagnosis, because these two parameters act 'multiplicatively' on the number of avoided patients.

Table 5.3 Single- and multi-variable threshold analyses. The table gives the threshold value for which costs of screening equal savings. Between parentheses: the ratio of threshold to baseline value. Costs and savings are discounted at 5% per year

	Screening strategy					
	Prenatal		Preconceptional		School	Neonatal
	SETS*	DETS*	SETS*	DETS*		
Single-variable threshold analysis						
Fraction of the carrier couples that will refrain from having a child (baseline: 15%)	†	†	†	29% x1.92	‡	96% x6.41
Fraction of the carrier couples that will use prenatal diagnosis (baseline: 85%)	63% x0.74	74% x0.87	78% x0.92	93% x1.09	‡	95% x1.12
Fraction of the affected foetuses that will be selectively aborted (baseline: 80%)	54% x0.67	67% x0.84	71% x0.89	87% x1.09	‡	89% x1.12
Coverage of screening	25% x0.27	40% x0.44	37% x0.74	66% x1.32	‡	‡
Information preservation	77% x0.77	89% x0.89	94% x0.94	‡	‡	94% x1.35
Costs of individual information	€19.21 x7.05	€12.16 x4.46	€3.65 x2.68	‡	‡	€0.34 x0.25
Cost of ΔF508 mutations test (baseline €9.47)	€25.79	€14.65	€13.01	€7.62	‡	€7.83
Cost of multiple mutations test (baseline €37.89)	€103.16 x2.72	€58.59 x1.55	€52.04 x1.37	€30.48 x0.80		€31.33 x0.83
Multi-variable threshold analysis§	8%	4%	2%	-3%	‡	-3%

* SETS = single-entry two-step couple screening, DETS = double-entry two-step couple screening

† for every value of the parameter, savings exceed costs

‡ for every value of the parameter, costs exceed savings

§ all parameter values can simultaneously decrease by this percentage (respective increase for costs of individual information and costs of testing) before costs will exceed savings

Coverage of screening does not influence the cost-savings balance very much because a large part of the costs are so-called variable costs that are proportional to coverage. However, savings in the DETS preconceptional screening strategy would be higher than its costs if a coverage higher than 66% is attained. Even if all people would be screened, costs of school and neonatal screening are higher than the savings. Attaining a high enough information preservation is rather important, as the costs exceed savings for SETS preconceptional screening and prenatal screening if many people would forget the test results. If an information preservation of more than 94% would be reached, savings of neonatal screening would be higher than the costs. For school screening and DETS preconceptional screening, costs are always higher than savings.

Because the costs of individual information do not form a large part of total costs, these costs do not influence the cost-savings balance very much: the costs can be more than two times higher before costs exceed savings for the prenatal and preconceptional SETS screening strategies. Even if the costs of individual information would be zero, costs exceed savings for school screening and DETS preconceptional screening.

Costs of testing form a large part of total screening costs, ranging from 24% in prenatal SETS screening to 48% in neonatal screening. For prenatal screening and SETS preconceptional screening, costs will be higher than savings only if the costs of tests rise by more than 37%. However, if the costs of the tests could be lowered by approximately 20% all screening strategies (except school screening) would have a positive cost-savings balance.

In the multi-variable threshold analysis, we determined by what percentage the parameter values mentioned in the single-variable threshold analysis could deteriorate simultaneously from the baseline values before costs exceed savings (see the last line of Table 5.3). As an increase in the parameter values (except for costs of information and costs of testing) leads to higher savings or lower costs, or both, we decreased these values by a given percentage, while we increased the costs by that same percentage. The conclusion of this multi-variable threshold analysis is that the parameter values for the prenatal screening programmes can deteriorate 4% or more, and the values for SETS preconceptional screening 2%. On the other hand, the parameter values of DETS preconceptional screening and neonatal screening should improve 3% before savings exceed costs, while school screening will never have a favourable cost-savings balance.

5.3.2 Other CF gene carrier prevalences

As the CF gene carrier prevalence varies between countries, we calculated the net economic savings for carrier prevalences between one in 35 and one in 25 (Figure 5.1). Using this figure, readers can determine the net economic savings in their country or situation, provided the costs structure is similar to the one we used.

As expected, the cost-savings balance worsens for all strategies if the carrier frequency is lower, but single-entry prenatal screening remains the best strategy from a costs point of view. The costs in this strategy will exceed the savings only if the carrier frequency is lower than 1:36. If the carrier frequency is higher than 1:28, both DETS preconceptional screening and neonatal screening will have a favourable cost-

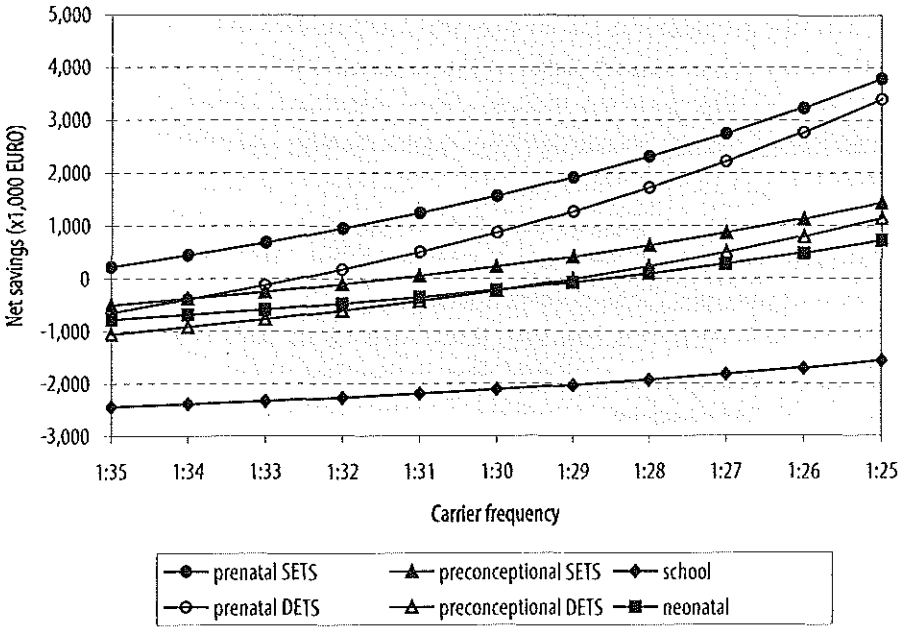


Figure 5.1 Net economic savings per year for six CF gene screening strategies for different CF gene frequencies

savings balance. This means that, other things being equal, prenatal, preconceptional, and neonatal screening would have higher savings than costs in countries (for example, UK and USA) where the CF gene carrier frequency is higher than one in 25. School screening will only have higher savings than costs with a theoretical carrier frequency of 1:18.

5.4 Discussion

Using a decision analytic model we found that there are no economic objections against prenatal screening and single-entry preconceptional screening for carriers of the CF gene when we take costs of care of CF patients into account. For double-entry preconceptional screening, neonatal screening, and school screening, costs are higher than savings. In a sensitivity analysis, this conclusion remained valid for prenatal and single-entry preconceptional screening programmes for a wide range of other plausible assumptions. For double-entry preconceptional screening and neonatal

screening programmes, a favourable cost-savings balance can only be obtained if uptake of screening, prenatal diagnosis or induced abortion would be higher than our assumptions, or if the costs of testing would be lowered by 20%. School screening will never have a favourable cost-savings balance.

We investigated if the poor performance of the neonatal and school screening strategies could be improved upon by testing all persons for 17 CF mutations. In this scenario more carrier couples are detected and more CF patients are avoided than in the baseline scenario, but the increased savings of the avoided patients does not offset the higher costs of screening. Consequently, this scenario has a worse cost-savings balance than the baseline scenario.

Although our model is primarily quantified for the Dutch situation of CF gene screening, it can be adapted for use in other countries or even for other autosomal recessive genetic diseases by changing the relevant parameter values. For example, because the carrier frequency in the United Kingdom is higher (1 in 25) than in The Netherlands (37), screening for CF gene carriers has a better cost-savings balance, provided the costs structure, and especially the relative magnitude of costs and savings, is similar to the Dutch situation. Using the 1 in 25 prevalence of CF gene carriers, we calculated a cost per detected carrier couple of €47,000 for prenatal SETS and €56,000 for DETS. These results are much higher than those of Cuckle et al. (26), who calculated a cost per detected carrier couple of €24,000 for sequential prenatal screening (SETS in our notation) and €27,000 for couple screening (almost similar to DETS). An explanation is that they took a 100% uptake of prenatal diagnosis and induced abortion and did not include costs of further diagnosis and treatment. Morris and Oppenheimer (22) concluded that sequential prenatal screening costs €45,000 per detected carrier couple and couple screening €44,000. These costs are somewhat lower than ours because we took the costs of further diagnosis and treatment into account.

It should be borne in mind that, even when savings exceed costs, financing a screening programme for CF gene carriers is not straightforward, because the screening budget has to be made available now, while the savings of the programme will only appear later. Moreover, savings may be realised in different budgets than the costs of screening are made, so that a conflict of interests may arise.

The reader should note that CF is a disease for which advances in medical treatment are or will (probably) be made, for example, lung transplantation and introduction of gene therapy (60, 61). This progress in treatment will most probably have an impact

on the length and quality of life of a CF patient (62). Whether lifetime costs of CF for such a patient will increase or decrease remains to be seen. And when—hopefully—treatment improves the life of CF patients even more, screening for CF gene carriers will be a thing of the past.

The present paper focussed deliberately on cost aspects. There is much more to be discussed in genetic screening than costs. Economic considerations should not be the primary goal of any screening programme, but a careful cost analysis and a discussion of cost-effectiveness and the cost-savings balance as reported in this paper, is an essential part of a full evaluation. Prenatal and single-entry preconceptional CF screening have from an economic point of view roughly comparable and reassuring cost prospects. When other aspects are also considered, single-entry preconceptional screening, which has a slightly worse cost-savings balance, possibly has to be preferred because with that strategy all reproductive options are still open for a carrier couple. Lack of participation will not be irreparable when prenatal screening is used as a 'safety net' for pregnant couples who did not attend the preconceptional screening programme.

5.5 References

1. Wildhagen MF, Verheij JBGM, Verzijl JG, Hilderink HBM, Kooij L, Tijmstra T, ten Kate LP, Gerritsen J, Bakker W, Habbema JDF. Cost of care of patients with cystic fibrosis in The Netherlands in 1990-1. Thorax 1996;51(3):298-301.
2. Wildhagen MF, Verheij JBGM, Verzijl JG, Gerritsen J, Bakker W, Hilderink HBM, ten Kate LP, Tijmstra T, Kooij L, Habbema JDF. The nonhospital costs of care of patients with CF in The Netherlands: results of a questionnaire. Eur Respir J 1996;9(11):2215-2219.
3. Kerem BS, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui LC. Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245(4922):1073-1080.
4. Riordan JR, Rommens JM, Kerem BS, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL, Drumm ML, Iannuzzi MC, Collins F, Tsui LC. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989;245(4922):1066-1073.

5. Rommens JM, Iannuzzi MC, Kerem BS, Drumm ML, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordam JR, Tsui LC, Collins FS. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 1989;245(4922):1059-1065.
6. European Working Group on CF Genetics (EWGCFG). Gradient of distribution in Europe of the major CF mutation and of its associated haplotype. Hum Genet 1990;85(4):436-445.
7. Zielenski J, Tsui LC. Cystic fibrosis: genotypic and phenotypic variations. Annu Rev Genet 1995;29:777-807.
8. Health Council of The Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994; no. 1994/22E.
9. Brock DJH. Heterozygote screening for cystic fibrosis. J Med Screen 1994;1(2):130-133; discussion 133-134.
10. Dodge JA, Boulyjenkov V. New possibilities for population control of cystic fibrosis. Bull World Health Organ 1992;70(5):561-566.
11. Modell M. Screening for carriers of cystic fibrosis - a general practitioner's perspective. BMJ 1993;307(6908):849-852.
12. Raeburn JA. Screening for carriers of cystic fibrosis. Screening before pregnancy is needed. BMJ 1994;309(6966):1428-1429.
13. Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, Marteau T. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? BMJ 1993;306(6892):1584-1586.
14. Watson EK, Mayall E, Chapple J, Dalziel M, Harrington K, Williams C, Williamson R. Screening for carriers of cystic fibrosis through primary health care services. BMJ 1991;303(6801):504-507.
15. Botkin JR, Alemagno S. Carrier screening for cystic fibrosis: a pilot study of the attitudes of pregnant women. Am J Public Health 1992;82(5):723-725.
16. Harris HJ, Scotcher D, Craufurd D, Wallace A, Harris R. Cystic fibrosis carrier screening at first diagnosis of pregnancy in general practice [letter]. Lancet 1992;339(8808):1539.
17. Livingstone J, Axton RAA, Gilfillan A, Mennie M, Compton M, Liston WA, Calder AA, Gordon AJ, Brock DJH. Antenatal screening for cystic fibrosis: a trial of the couple model. BMJ 1994;308(6942):1459-1462.
18. Mennie ME, Gilfillan A, Compton M, Curtis L, Liston WA, Pullen I, Whyte DA, Brock DJH. Prenatal screening for cystic fibrosis. Lancet 1992;340(8813):214-216.

19. Ranieri E, Lewis BD, Gerace RL, Ryall RG, Morris CP, Nelson PV, Carey WF, Robertson EF. Neonatal screening for cystic fibrosis using immunoreactive trypsinogen and direct gene analysis: four years' experience. BMJ 1994;308(6942):1469-1472.
20. Brambati B, Tului L, Fattore S, Férec C. First-trimester fetal screening of cystic fibrosis in low-risk population [letter]. Lancet 1993;342(8871):624.
21. Wake SA, Rogers CJ, Colley PW, Hieatt EA, Jenner CF, Turner GM. Cystic fibrosis carrier screening in two New South Wales country towns. Med J Aust 1996;164(8):471-474.
22. Morris JK, Oppenheimer PM. Cost comparison of different methods of screening for cystic fibrosis. J Med Screen 1995;2(1):22-27.
23. Holloway S, Brock DJH. Cascade testing for the identification of carriers of cystic fibrosis. J Med Screen 1994;1(3):159-164.
24. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313(7052):275-283.
25. Harris H, Scotcher D, Hartley N, Wallace A, Craufurd D, Harris R. Cystic fibrosis carrier testing in early pregnancy by general practitioners. BMJ 1993;306(6892):1580-1583.
26. Cuckle HS, Richardson GA, Sheldon TA, Quirke P. Cost effectiveness of antenatal screening for cystic fibrosis. BMJ 1995;311(7018):1460-1463; discussion 1463-1464.
27. Miedzybrodzka ZH, Hall MH, Mollison J, Templeton A, Russell IT, Dean JC, Kelly KF, Marteau TM, Haites NE. Antenatal screening for carriers of cystic fibrosis: randomised trial of stepwise v couple screening. BMJ 1995;310(6976):353-357.
28. Flinter FA, Silver A, Mathew CG, Bobrow M. Population screening for cystic fibrosis [letter]. Lancet 1992;339(8808):1539-1540.
29. Bianco I, Graziani B, Lerone M, Congedo P, Aliquo' MC, Ponzini D, Braconi F, Foglietta E, Modiano G. Prevention of thalassaemia major in Latium (Italy) [letter]. Lancet 1985;2(8460):888-889.
30. Zeesman S, Clow CL, Cartier L, Scriver CR. A private view of heterozygosity: eight-year follow-up study on carriers of the Tay-Sachs gene detected by high school screening in Montreal. Am J Med Genet 1984;18(4):769-778.

31. Mitchell J, Scriver CR, Clow CL, Kaplan F. What young people think and do when the option for cystic fibrosis carrier testing is available. J Med Genet 1993;30(7):538-542.
32. Beaudet AL, O'Brien WE. Advantages of a two-step laboratory approach for cystic fibrosis carrier screening [letter]. Am J Hum Genet 1992;50(2):439-440.
33. Ten Kate LP, Verheij JBGM, Wildhagen MF, Hilderink HBM, Kooij L, Verzijl JG, Habbema JDF. Comparison of single-entry and double-entry two-step couple screening for cystic fibrosis carriers. Hum Hered 1996;46(1):20-25.
34. Wald NJ. Couple screening for cystic fibrosis. Lancet 1991;338(8778):1318-1319.
35. Ten Kate LP. Cystic fibrosis in The Netherlands. Int J Epidemiol 1977;6(1):23-34.
36. Halley DJJ, van den Ouweland AMW, van der Hout AH, Scheffer H. Overzicht van 5 jaar DNA-diagnostiek voor cystische fibrose [Overview of 5 years DNA-diagnostics for cystic fibrosis]. LOD Nieuwsbrief 1995;2:8-10.
37. Brock DJH. Cystic fibrosis. In: Brock DJH, Rodeck CH, Ferguson-Smith MA, eds. Prenatal diagnosis and screening. London: Churchill Livingstone, 1992:441-460.
38. US Congress Office of Technology Assessment. Cystic Fibrosis and DNA tests: implications of carrier screening. Washington, DC: U.S. Government Printing Office, 1992.
39. UNSCEAR. Genetic and somatic effects of ionizing radiation. A report of the United Nations Scientific Committee of the Effects of Atomic Radiation. New York: United Nations, 1986.
40. Statistics Netherlands. Maandstatistiek bevolking 96/12 [Monthly bulletin of population statistics 96/12]. Voorburg/Heerlen: Statistics Netherlands, 1996; no. 96/12.
41. Hook EB, Topol BB, Cross PK. The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis which are not terminated electively: new data and estimates of the excess and relative risk of late fetal death associated with 47,+21 and some other abnormal karyotypes. Am J Hum Genet 1989;45(6):855-861.
42. Hille E, de Kroon M. Epidemiologie van infertiliteit [Epidemiology of infertility]. iMTA/iMGZ, Erasmus University Rotterdam, 1992; no. 92.15.
43. Statistics Netherlands. Maandstatistiek bevolking 96/8. [Monthly bulletin of population statistics 96/8]. Voorburg/Heerlen: Statistics Netherlands, 1996; no. 96/8.

44. Bonsel GJ, Maas PJ, van der. At the cradle of the future. Health scenarios concerning human reproduction 1995-2010. Summary of the Dutch STG report "Aan de wieg van de toekomst". Zoetermeer, The Netherlands: Foundation for Future Health Scenarios, 1996.
45. Cobb E, Holloway S, Elton R, Raeburn JA. What do young people think about screening for cystic fibrosis? J Med Genet 1991;28(5):322-324.
46. Schwartz M, Brandt NJ, Skovby F. Screening for carriers of cystic fibrosis among pregnant women: a pilot study. Eur J Hum Genet 1993;1(3):239-244.
47. Jung U, Urner U, Grade K, Coutelle C. Acceptability of carrier screening for cystic fibrosis during pregnancy in a German population. Hum Genet 1994;94(1):19-24.
48. Brock DJH. Prenatal screening for cystic fibrosis: 5 years' experience reviewed. Lancet 1996;347(8995):148-150.
49. Doherty RA, Palomaki GE, Kloza EM, Erickson JL, Haddow JE. Couple-based prenatal screening for cystic fibrosis in primary care settings. Prenat Diagn 1996;16(5):397-404.
50. Witt DR, Schaefer C, Hallam P, Wi S, Blumberg B, Fishbach A, Holtzman J, Kornfeld S, Lee R, Nemzer L, Palmer R. Cystic fibrosis heterozygote screening in 5,161 pregnant women. Am J Hum Genet 1996;58(4):823-835.
51. Wald NJ, George L, Wald N, MacKenzie IZ. Further observations in connection with couple screening for cystic fibrosis [letter]. Prenat Diagn 1995;15(6):589-590.
52. Decruyenaere M, Evers-Kiebooms G, Denayer L, van den Berghe H. Cystic fibrosis: community knowledge and attitudes towards carrier screening and prenatal diagnosis. Clin Genet 1992;41(4):189-196.
53. Anonymous. CDC publishes report on chorionic villus sampling and amniocentesis. Am Fam Physician 1995;52(4):1210.
54. Drummond MF, Stoddard GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, 1987.
55. Van der Maas PJ, van Ineveld BM, van Oortmarssen GJ, de Koning HJ, Lubbe JTN, Habbema JDF, Birnie E, Geerts AT, de Bruyn AE, Collette HJA, Rombach JJ, Verbeek ALM, Straatman H, Hendriks JHCL, van den Heuvel WJA. The costs and effects of mass screening for breast cancer. Rotterdam: Department of Public Health and Social Medicine, 1988.
56. Beech R, Bekker H. Planning the development of cystic fibrosis gene carrier screening. J Health Serv Res Policy 1996;1(2):81-92.

57. Rutten FFH, van Ineveld BM, van Ommen R, van Hout BA, Huijsman R. Kostenberekening bij gezondheidszorgonderzoek; richtlijnen voor de praktijk [Cost calculation in health care research; guidelines for practice]. Instituut voor Medische Technology Assessment, 1993.
58. Centraal Orgaan Tarieven Gezondheidszorg (COTG). Tarieven medisch specialistische hulp [Tariffs medical specialist care]. 1995.
59. Centraal Orgaan Tarieven Gezondheidszorg (COTG). Vademecum tarieven gezondheidszorg [Vademecum tariffs health care]. Utrecht: 1995.
60. Coutelle C, Caplen N, Hart S, Huxley C, Williamson R. Gene therapy for cystic fibrosis. Arch Dis Child 1993;68(4):437-440.
61. Wilson JM. Cystic fibrosis: strategies for gene therapy. Semin Respir Crit Care Med 1994;15:439-445.
62. Rosenstein BJ. Cystic fibrosis in the year 2000. Semin Respir Crit Care Med 1994;15:446-451.

Part 3

Fragile X syndrome

Chapter 6
Fragile X syndrome

6.1 Introduction

The first pedigree with clear familial X-linked mental retardation was reported in 1943 by J.P. Martin and J. Bell (1). They described a family in which eleven mentally retarded sons from two generations had been born from normally intelligent mothers, and concluded that the mental defect was due to a sex-linked recessive gene. Furthermore, they noted that in two known instances relatively slight mental retardation had occurred in females and suggested that in these two the causal mutation was incompletely recessive. Using metaphases of cells from patients with X-linked mental retardation, Lubs (2) was the first to describe a fragile site near the end of the long arm of the X chromosome, that appears as an unstained gap or break at a defined point on the X chromosome; therefore the disorder is named fragile X syndrome. Only a part of the patients show this fragile site in a part of their cells; this complicated the diagnosis of fragile X syndrome for a long time. In 1991, the gene responsible for fragile X syndrome was sequenced and cloned (3). It was shown that in almost all cases a large increase in the length of a part of this gene causes fragile X syndrome (see '6.3 Genetics'). Therefore, a distinction is generally made between normal (normal repeat length), premutation (a small increase in repeat length) and full mutation (a large increase in repeat length).

6.2 The disorder

Mental retardation is the most prominent feature of fragile X syndrome. IQ in most males with fragile X syndrome is below 70 (mean IQ approximately 40), and decreases with age in many patients (4). Eighty percent of all affected males have one or more of the following dysmorphic features: high forehead, large prominent ears, big jaw, macroorchidism, hyperextensibility of joints, and high-pitched, jocular speech (5-7). Not every patient shows all the physical symptoms, which are generally more apparent after childhood. Behavioural abnormalities include hand flapping and biting, excessive shyness (avoidance of eye contact), hyperactivity, and some have autistic features (6). Although it is most unusual for men with fragile X syndrome to have children, there are some exceptions described in literature (8-11); however the

presence of the full mutation in these patients has not been confirmed by DNA testing.

Approximately sixty percent of females with a full mutation has some mental retardation, and the degree of this retardation is on average less than in males (12-14). The behaviour problems are milder and fewer and the dysmorphic features less obvious (15, 16). In fragile X carrier females of normal intelligence there is an increase in psychiatric symptoms, particularly schizophrenia-spectrum disorders (17, 18). Premutations are not associated with a clinical phenotype (19, 20) and are found in female carriers and so-called normal transmitting males. Both full mutation and premutation women have similar numbers of pregnancies as non-carrier women, and the sex ratio of the children does not differ from those of normal women (21, 22). Furthermore, the survival of both full mutation and premutation carriers is the same as for the general population.

6.3 Genetics

The fragile X syndrome is the most common cause of mental retardation caused by a single gene defect and is associated with a fragile site, designated FRAXA, on the long arm of the X chromosome at Xq27.3 (23). The molecular basis for the syndrome usually is a large expansion of a repetitive CGG triplet sequence located in the 5' untranslated region of the fragile X gene, FMR1(3, 24-28). In rare cases (less than 5%), the syndrome is due to either a deletion of part or all of the FMR1 gene (29-36) or a point mutation within an RNA binding domain (37, 38). The phenotype of these individuals is indistinguishable from those with a large expansion; therefore it appears that absence of functioning FMR1 protein causes fragile X syndrome.

The length of the CGG repeat varies in the normal population (polymorphism) from 6 to 52 repeats with a mode of 30 and is stable on transmission (24, 39-42). Alleles that are not stable upon transmission can be divided into premutation alleles and full mutation alleles. Premutation alleles range from 43 to 200 repeats and exhibit instability, usually resulting in increases in repeat number in the offspring (25, 42-45). The most important risk factor for the instability of the premutation allele is the sex of the transmitting parent (46, 47). If a father transmits a premutation to his daughter, the premutation size usually increases or decreases by less than 10 repeats; males with a premutation are called normal transmitting males (48, 49). These premutations may however become unstable in their daughter's offspring (24, 50, 51). These findings explain the phenomenon known as the 'Sherman paradox' in which

penetrance of mental impairment is lower in the daughters of transmitting males than in their granddaughters (48). No well-defined boundary exists between the normal and premutation state. The term 'grey zone' has been used to describe this region of repeat numbers between approximately 45 and 55 repeats, which includes large normal and small premutation alleles.

In fragile X syndrome patients the CGG repeat is amplified beyond 200 copies (full mutation) (24) and the concomitant hypermethylation of the preceding CpG island represses the transcription of FMR1 (55-57). This results in the absence of the FMR1 protein (FMRP) leading to the fragile X phenotype (58, 59). Full mutations are always derived from full mutations or from maternal premutations, with the rate of transition being directly related to the maternal repeat length (Figure 6.1, Table 6.1). The smallest premutation size in a mother that expanded to a full mutation reported in the literature was 59 triplets (54). Published expansion risks from premutation to full mutation are almost certainly biased upwards, since they are obtained by analysing families that are detected by an index fragile X syndrome patient. They should therefore be used with caution if applied to general population screening where premutations might be somewhat more stable (60).

Approximately 15-20% of patients (so-called mosaics) has a full mutation in the majority of their cells, but carry a premutation in a small number of cells (12, 25, 47, 55, 57, 61). These patients exhibit variation in the DNA methylation, but in general do not appear to be less severely affected than patients with a full mutation (12). For this reason we consider in the analyses described in this thesis mosaics as belonging to the full mutation group.

Table 6.1 Probabilities of transmitting a full mutation to their offspring by premutation women

No. of CGG repeats	Fu (24) N=63	Heitz (50) N=131	Yu (51) N=89	Snow (39) N=75	Sherman (22) N=24	Turner (52) N=254	Väisänen (53) N=79	Fisch (43)* N=184	Nolin (54) N=393	Total† N=1,154
-69	8%	10%	-	20%	67%	56%	36%	18%	21%	32%
70-79	71%	47%	27%	28%	50%	56%	85%	39%	63%	50%
80-89	82%	69%	56%	79%	80%	78%	100%	77%	68%	72%
90-99	100%	90%	56%	100%	100%	78%	100%	89%	92%	87%
100-109	100%	93%	56%	100%	100%	78%	100%	91%	100%	91%
110-119	100%	100%	78%	100%	100%	87%	100%	100%	97%	95%
120-129	-	100%	96%	100%	-	87%	100%	100%	100%	97%
130-	-	100%	94%	-	-	87%	100%	95%	96%	92%
Total	70%	77%	69%	65%	88%	76%	62%	67%	80%	75%

* includes pedigrees from Fu (24), Snow (39)

† data from Fu (24), Snow (39) not included since they are included in Fisch (43)

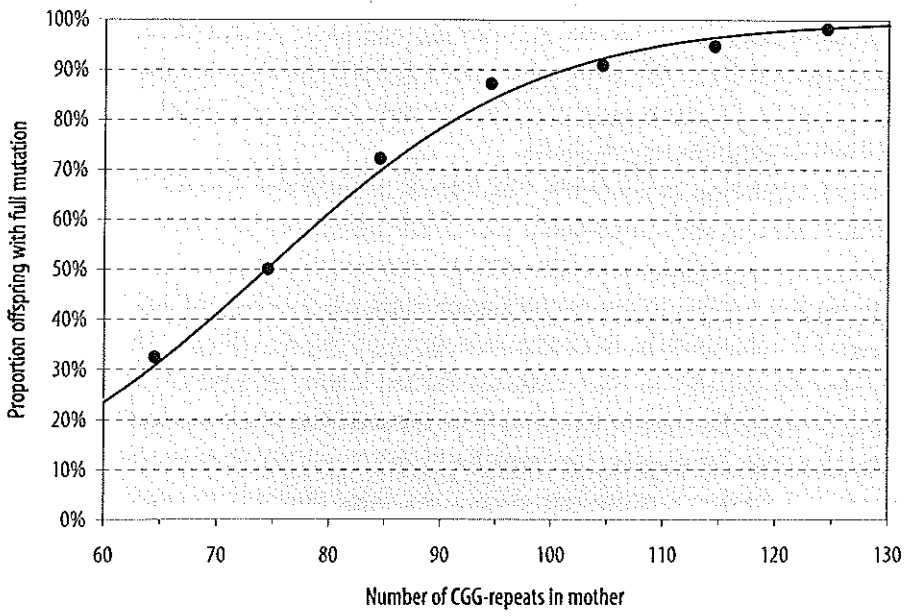


Figure 6.1 Proportion of offspring with a full mutation from premutation women, obtained by a logistic regression analysis. The closed circles represent the midpoints of the premutation categories in Table 6.1

In the normal population, one AGG triplet interrupts the CGG string every eight to twelve CGG repeats on average (41, 42, 44, 45, 62, 63). In premutation alleles the stretch of so-called pure CGGs (no interspersion of AGGs) is increased. Because it is postulated that the threshold for instability is about 34-38 pure CGGs (44), the risk for fragile X 'grey-zone' alleles to expand appears to depend on the absence of stabilising AGG repeats (45, 64).

Because affected males rarely reproduce, a very high mutation rate has been suggested to maintain the frequency of the disorder (65). If this would have been the case, variation between different ethnic groups would be minimal. However, no new mutations have been described for fragile X syndrome (51, 66-68). Actually, founder effects have now been identified through the demonstration of linkage disequilibrium, so that varying prevalence figures are to be anticipated in different ethnic populations (45, 68-74). For example, the broad geographical distribution of the 153-196 fragile X haplotype all over Finland indicates that it is of ancient origin

and that it was most likely present in the founder population of Finland about 100 generations ago (71, 75). As an alternative for founder chromosomes it has been suggested that this might be because certain haplotypes have a larger number of CGG repeats which might make them more mutable, and thus more likely to give rise to a premutation or full mutation (72, 76). The data of Buyle et al. (68) suggest that a founder effect of the fragile X mutation also exists in the Belgian and Dutch populations.

A four-allele model, which describes the CGG expansion process, postulates four distinct allele states based on overall length (75). In this model, the normal (N) allele with fewer than approximately 40 repeats is stable, the intermediate (S) allele with approximately 40-60 repeats is prone to conversion at a low rate to the unstable premutation (Z) allele with approximately 60-200 repeats, which in turn has a high likelihood of conversion to the full mutation (L) allele. This four-allele model has been generalised to nine alleles (77) and to *n* alleles by using empirically derived risk figures (78). However, because it is difficult to determine which of the S alleles are likely to be unstable by CGG repeat length determination, it has not been practical to apply these models clinically to determine accurately the risk of expansion for intermediate alleles detected within the 'grey zone'. Fisch et al. (79), using different CGG repeat numbers as cut-off criteria between general and premutation populations, concluded that no members from either the general or the premutation population were misclassified in their study if a cut-off of 55 CGG repeats was used, while one (out of 939) individuals from the general population would be misclassified as being from the premutation population if a cut-off of 50 CGG repeats would be used.

6.4 Prevalence

6.4.1 Fragile X syndrome and full mutations

The two biggest studies on the prevalence of fragile X syndrome were performed in England and Australia (80, 81). Webb et al. (80) carried out a clinical and cytogenetic study of 219 boys and 104 girls between 11 and 16 years of age who attended schools for the educationally handicapped or who were in residential accommodation in Coventry, England, and detected 16 boys and 10 girls with fragile X syndrome. Children who had a specific cause of mental retardation in their record were not included in the study. Correcting for parents who did not agree that their child was tested, and assuming that no patient was missed, they estimated the frequency of fragile X syndrome to be 1 in 1,360 for males and 1 in 2,073 for females. In that same

year, Webb et al. (82) gave an update on the previous study and presented a 1 in 952 prevalence of the fragile X mental retardation syndrome for all school age children.
After the discovery of a non-pathological fragile site at Xq27.2 (FRAXD, the 'common fragile site') (83), which may be confused with the mental retardation fragile site at Xq27.3 (FRAXA, the 'rare fragile site'), Webb et al. reanalysed their data and concluded that they mistakenly diagnosed 2 patients for sure and two patients probably as being FRAXA. Therefore they adjusted the prevalences to 1 in 1,039, approximately the same for both sexes (84). In 1991, after the cloning of the FMR1 gene, they retested the school children with molecular analysis (85). Fragile X syndrome was excluded in 13 of the children, so that the estimated frequency of fragile X syndrome dropped to 1 in 2,197.
Turner et al. (81) also cytogenetically tested children between 5 and 18 years in special schools and special classes in Sydney, Australia, and also screened persons of all ages who resided in institutions, day activity centres and sheltered workshops. Again, persons who had a recognised cause of mental retardation were excluded from the study, and the figures were corrected for persons who refused screening. They detected 28 male fragile X syndrome patients out of 599 tested and 12 female patients out of 322 tested, leading to a 1 in 2,610 frequency for males and 1 in 4,221 for females.
In 1996, Turner, Webb et al. updated the prevalence figures of their respective studies (94). They retested all boys who were identified by cytogenetic tests as having fragile X syndrome by molecular analysis and corrected the prevalence figures to 1 in 4,090 for Coventry (originally 1 in 952) and 1 in 4,350 for Sydney (originally 1 in 2,610). Since these estimates were almost similar, the authors concluded that "a more realistic figure based on molecular analysis is 1 in 4,000".
Since (almost) all male persons with a full mutation have fragile X syndrome (12), the prevalence of full mutations among males is the same as the prevalence of fragile X syndrome males, namely 1 in 4,000. There are no reasons to assume that the prevalence of full fragile X mutations would be different in females than in males as the paternally derived X chromosome does not show a full mutation. However, only 59% of females with a full fragile X mutation are mentally retarded (12), so that the prevalence of fragile X syndrome mentally retarded females is 1 in 4,000 times 59%, which is approximately 1 in 7,000.
In The Netherlands, de Vries et al. screened a representative sample of 3,352 individuals in schools and institutes for the mentally retarded (95). Assuming the same

prevalence in participating and non-participating individuals, they estimated a fragile X syndrome prevalence of 1 in 6,045 boys (95% confidence interval: 1 in 9,981 to 1 in 3,851), which is just not significantly lower than the consensus estimate of Turner et al. (94).

6.4.2 Premutations

With regard to premutations, the situation is not so clear-cut. There are a few small-scale studies performed that determined premutation prevalences ranging from 0 in 227 females to 1 in 197 (Table 6.2). The largest study performed on the normal population is that of Rousseau et al. (88). In this study, 41 premutation alleles were found in 10,624 persons from an unselected population, leading to a premutation-frequency of 1 in 259. Furthermore, using this premutation frequency and assuming that the risk of expansion of a premutation allele was the same as that in fragile X families (50), the authors of that study calculated a fragile X syndrome prevalence of 1 in 2,381 (42/100,000) in the French Canadian population, which is 68% higher than the consensus estimate of Turner, Webb et al. (94). However, there are indications of founder effects in the French Canadian population (96), so that the premutation frequency obtained from this population should be used with caution for other populations. Furthermore, Sherman speculated that women who are cognitively impaired were not included in this study, so that Rousseau et al. only estimated the frequency of premutation carrier females and did not attempt to determine the frequency of full mutation carrier females. Therefore, an estimate with regard to the premutation prevalence in an unselected population without founder effects would be 68% lower, which is 1 in 435. It is this figure that is used throughout the analyses performed in this thesis.

6.5 Screening and screening test

The cloning of the fragile X syndrome gene in 1991 has created a discussion whether a DNA screening programme for premutation and full mutation carriers in the general population should be investigated in a pilot study or even implemented (60, 97-103). The main goal of general population carrier screening is to identify premutation and full mutation carriers and thereby give them the possibility of an informed reproductive choice. For example, they can decide to become pregnant and to have prenatal diagnosis by DNA sampling of a chorionic villus sample or amniocentesis sample.

Table 6.2 Prevalence of premutations (≥55 CGG-repeats) in females and males in the general population

	Year	Female	Male
Snow et al. (39)	1993	1/197	0/50
Arinami et al. (86)	1993	0/227	0/370
Reiss et al. (87)	1994	1/561	0/416
Rousseau et al. (88)	1995	41/10,624	-
Brown et al. (89)	1996	6/2,500	-
Dawson et al. (90)	1995	2/735	3/778
Spence (91)	1996	3/745	-
Eichler et al. (92)	1995	-	0/406
Holden et al. (93)	1995	-	1/1,000
Total		54/15,589 (1/289)	4/3,020 (1/755)

Southern blot analysis is used for screening since the cloning of the gene (24, 25, 47, 104, 105). It detects premutations and full mutations (25, 28, 47), gives information about methylation (47) and, if the right probe is used, detects deletions in the FMR1 gene (106). However, Southern blot does not give a precise estimation of the number of CGG repeats (107) and misses some small premutations. Moreover, especially important for a general population screening programme, Southern blot is very labour-intensive and thus expensive at €67 in The Netherlands (108), takes a lot of time before the test result is known (2 weeks or more), and demands relatively large amounts of DNA.

PCR on the other hand gives a rather accurate estimation of the number of CGG repeats (24, 40) and does not miss small premutations. Furthermore, it gives a quick test result (1-2 days), is less expensive at €21 in The Netherlands (108) and does not need a large amount of DNA. On the other hand, PCR does not give information about methylation status and has its limitations in detecting deletions in the FMR1 gene. The most important disadvantage with regard to general population screening is that PCR can not detect very large premutations and full mutations (109), so that it can not discriminate between women with two X chromosomes of the same number of CGG repeats and women with a combination of one normal-size X chromosome and one large premutation or full mutation. The two groups of women, approximately 40% of all women (40), subsequently have to be retested with Southern blot analysis.

There are several arguments against general population carrier screening. An important argument (99, 102), acknowledged also by proponents of screening, is the inability to predict the intellectual status of a female foetus with a full mutation, since

only approximately 60% of these has some mental retardation (12-14). Methylation gives some indication about the degree of mental retardation, but is not a perfect prognostic value. This makes the decision whether or not to terminate a pregnancy of a female foetus with a full mutation very difficult and requires delicate counselling (110). The results from seven studies show that more than 57% of the pregnancies of female foetuses with a full mutation detected by prenatal diagnosis are terminated (111). Another problem is the inability to determine between large normal alleles (that can not expand to a full mutation) and small premutation alleles ('grey zone' alleles that can expand to a full mutation). Generally, opponents of general population screening point out that the complicated inheritance pattern of fragile X syndrome necessitates appropriate follow-up counselling (102). The advocates of general population screening on the other hand point out that this counselling is available in genetics clinics, so that population screening can be offered appropriately (100).

The American College of Medical Genetics (102) does not recommend population screening, except as part of a well-defined clinical research protocol. However, the College gave guidelines that the following special populations could be tested: patients with some form of mental retardation and/or features that are prominent of fragile X syndrome; patients with a family history of fragile X syndrome or undiagnosed mental retardation (cascade testing); foetuses of known carrier mothers.

Screening persons in institutions who do not have a definite diagnosis for their mental retardation has been done since a long time. First, the testing was done by cytogenetic detection of the fragile site in lymphocytes. After the cloning of the fragile X syndrome gene this was replaced by Southern blot analysis and PCR. Provided the tests are done with 'good laboratory practice', DNA testing for fragile X syndrome has an almost 100% sensitivity and specificity (47). Even opponents of patient screening acknowledge that "many parents of affected males who have had to trudge back and forth to their general practitioners trying to convince them that there is something wrong with their child" would benefit from neonatal patient screening (112). These patients can then be 'used' as so-called index patients to test relatives and give them an informed choice (cascade testing).

In Chapter 7 of this thesis, we analyse the cost, effects and savings of general population preconceptional, prenatal and school screening programmes for fragile X syndrome carriers, and in Chapter 8 we describe the effectiveness of cascade testing for fragile X syndrome. We would like to stress again that the most important 'gain' of screening is not the economic gain because less fragile X syndrome patients are born.

As Modell et al. (113) (cited by Turner et al. (114)) observed: "accepted affected children (born because informed parents decided not to have prenatal diagnosis or not to terminate an affected pregnancy) are a benefit not a cost".

6.6 References

1. Martin JP, Bell J. A pedigree of mental defect showing sex-linkage. J Neurol Neurosurg Psychiatry 1943;6:154-157.
2. Lubs HA. A marker X chromosome. Am J Hum Genet 1969;21(3):231-244.
3. Verkerk AJMH, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DPA, Pizzuti A, Reiner O, Richards S, Victoria MF, Zhang FP, Eussen BE, van Ommen GB, Blonden LAJ, Riggins GK, Chastain JL, Kunst CB, Galjaard H, Caskey CT, Nelson DL, Oostra BA, Warren ST. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 1991;65(5):905-914.
4. Fisch GS, Arinami T, Froster-Iskenius U, Fryns JP, Curfs LM, Borghgraef M, Howard-Peebles PN, Schwartz CE, Simensen RJ, Shapiro LR. Relationship between age and IQ among fragile X males: a multicenter study. Am J Med Genet 1991;38(2-3):481-487.
5. Sutherland GR, Hecht F. The fragile X: physical phenotype. Fragile sites on human chromosomes. New York: Oxford University Press, 1985:132-149.
6. Hagerman RJ. Physical and behavioral phenotype. In: Hagerman RJ, Silverman AC, eds. Fragile X syndrome: diagnosis, treatment and research. Baltimore and London: The Johns Hopkins University Press, 1991:3-68.
7. Sutherland GR, Richard RI. Fragile X syndrome. In: Brock DJH, Rodeck CH, Ferguson-Smith MA, eds. Prenatal diagnosis and screening. London: Churchill Livingstone, 1992:393-403.
8. Van Roy BC, De Smedt MC, Raes RA, Dumon JE, Leroy JG. Fragile X trait in a large kindred: transmission also through normal males. J Med Genet 1983;20(4):286-289.
9. Moric-Petrovic S, Laca Z. A father and daughter with fragile X chromosome. J Med Genet 1983;20(6):476-478.
10. Voelckel MA, Mattei MG, C NG, Philip N, Birg F, Mattei JF. Dissociation between mental retardation and fragile site expression in a family with fragile X-linked mental retardation. Hum Genet 1988;80(4):375-378.

11. Yu WD, Wenger SL, Steele MW. X chromosome imprinting in fragile X syndrome. Hum Genet 1990;85(6):590-594.
12. Rousseau F, Heitz D, Tarleton J, MacPherson J, Malmgren H, Dahl N, Barnicoat A, Mathew C, Mornet E, Tejada I, Maddalena A, Spiegel R, Schinzel A, Marcos JAG, Schorderet DF, Schaap T, Maccioni L, Russo S, Jacobs PA, Schwartz C, Mandel JL. A multicenter study on genotype-phenotype correlations in the fragile X syndrome, using direct diagnosis with probe StB12.3: the first 2,253 cases. Am J Hum Genet 1994;55(2):225-237.
13. Turner G, Brookwell R, Daniel A, Selikowitz M, Zilibowitz M. Heterozygous expression of X-linked mental retardation and X-chromosome marker fra(X)(q27). N Engl J Med 1980;303(12):662-664.
14. Mazzocco MMM, Hagerman RJ, Pennington BF. Problem solving limitations among cytogenetically expressing fragile X women. Am J Med Genet 1992;43(1-2):78-86.
15. Lachiewicz AM. Abnormal behaviors of young girls with fragile X syndrome. Am J Med Genet 1992;43(1-2):72-77.
16. Loesch DZ, Hay DA. Clinical features and reproductive patterns in fragile X female heterozygotes. J Med Genet 1988;25(6):407-414.
17. Reiss AL, Hagerman RJ, Vinogradov S, Abrams M, King RJ. Psychiatric disability in female carriers of the fragile X chromosome. Arch Gen Psychiatry 1988;45(1):25-30.
18. Hagerman RJ, Sobesky WE. Psychopathology in fragile X syndrome. Am J Orthopsychiatry 1989;59(1):142-152.
19. De Vries BB, Wiegers AM, de Graaff E, Verkerk AJ, Van Hemel JO, Halley DJJ, Fryns JP, Curfs LM, Niermeijer MF, Oostra BA. Mental status and fragile X expression in relation to FMR-1 gene mutation. Eur J Hum Genet 1993;1(1):72-79.
20. Reiss AL, Freund LS, Baumgardner TL, Abrams MT, Denckla MB. Contribution of the FMR1 gene mutation to human intellectual dysfunction. Nat Genet 1995;11(3):331-334.
21. Schwartz CE, Dean J, Howard-Peebles PN, Bugge M, Mikkelsen M, Tommerup N, Hull C, Hagerman R, Holden JJA, Stevenson RE. Obstetrical and gynecological complications in fragile X carriers: a multicenter study. Am J Med Genet 1994;51(4):400-402.

22. Sherman SL, Maddalena A, Howard-Peebles PN, Brown WT, Nolin S, Jenkins E, Schwartz C, Tarrelton J, Shapiro LR, Smits APT, et a. Characteristics of the transmission of the FMR1 gene from carrier females in a prospective sample of conceptuses. Am J Med Genet 1994;51(4):503-506.
23. Krawczun MS, Jenkins EC, Brown WT. Analysis of the fragile-X chromosome: localization and detection of the fragile site in high resolution preparations. Hum Genet 1985;69(3):209-211.
24. Fu YH, Kuhl DPA, Pizzuti A, Pieretti M, Sutcliffe JS, Richards S, Verkerk AJMH, Holden JJA, Fenwick Jr. RG, Warren ST, Oostra BA, Nelson DL, Caskey CT. Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. Cell 1991;67(6):1047-1058.
25. Oberlé I, Rousseau F, Heitz D, Kretz C, Devys D, Hanauer A, Boué J, Bertheas MF, Mandel JL. Instability of a 550-base pair DNA segment and abnormal methylation in fragile X syndrome. Science 1991;252(5010):1097-1102.
26. Yu S, Pritchard M, Kremer E, Lynch M, Nancarrow J, Baker E, Holman K, Mulley JC, Warren ST, Schlessinger D, Sutherland GR, Richards RI. Fragile X genotype characterized by an unstable region of DNA. Science 1991;252(5010):1179-1181.
27. Kremer EJ, Yu S, Pritchard M, Nagaraja R, Heitz D, Lynch M, Baker E, Hyland VJ, Little RD, Wada M, Toniolo D, Vincent A, Rousseau F, Schlessinger D, Sutherland GR, Richards RI. Isolation of a human DNA sequence which spans the fragile X. Am J Hum Genet 1991;49(3):656-661.
28. Kremer EJ, Pritchard M, Lynch M, Yu S, Holman K, Baker E, Warren ST, Schlessinger D, Sutherland GR, Richards RI. Mapping of DNA instability at the fragile X to a trinucleotide repeat sequence p(CCG)n. Science 1991;252(5013):1711-1714.
29. Gedeon AK, Baker E, Robinson H, Partington MW, Gross B, Manca A, Korn B, Poustka A, Yu S, Sutherland GR, Mulley JC. Fragile X syndrome without CCG amplification has an FMR1 deletion. Nat Genet 1992;1(5):341-344.
30. Wohrle D, Kotzot D, Hirst MC, Manca A, Korn B, Schmidt A, Barbi G, Rott HD, Poustka A, Davies KE, Steinbach P. A microdeletion of less than 250 kb, including the proximal part of the FMR-I gene and the fragile-X site, in a male with the clinical phenotype of fragile-X syndrome. Am J Hum Genet 1992;51(2):299-306.
31. Tarleton J, Richie R, Schwartz C, Rao K, Aylsworth AS, Lachiewicz A. An extensive de novo deletion removing FMR1 in a patient with mental retardation and the fragile X syndrome phenotype. Hum Mol Genet 1993;2(11):1973-1974.

32. Meijer H, de Graaff E, Merckx DML, Jongbloed RJE, de Die-Smulders CEM, Engelen JJM, Fryns JP, Curfs PMG, Oostra BA. A deletion of 1.6 kb proximal to the CGG repeat of the FMR1 gene causes the clinical phenotype of the fragile X syndrome. Hum Mol Genet 1994;3(4):615-620.
33. De Graaff E, Rouillard P, Willems PJ, Smits APT, Rousseau F, Oostra BA. Hotspot for deletions in the CGG repeat region of FMR1 in fragile X patients. Hum Mol Genet 1995;4(1):45-49.
34. Quan F, Zonana J, Gunter K, Peterson KL, Magenis RE, Popovich BW. An atypical case of fragile X syndrome caused by a deletion that includes the FMR1 gene. Am J Hum Genet 1995;56(5):1042-1051.
35. Hirst M, Grewal P, Flannery A, Slatter R, Maher E, Barton D, Fryns JP, Davies K. Two new cases of FMR1 deletion associated with mental impairment. Am J Hum Genet 1995;56(1):67-74.
36. Lugenbeel KA, Peier AM, Carson NL, Chudley AE, Nelson DL. Intragenic loss of function mutations demonstrate the primary role of FMR1 in fragile X syndrome. Nat Genet 1995;10(4):483-485.
37. De Boulle K, Verkerk AJ, Reyniers E, Vits L, Hendrickx J, Van Roy B, Van den Bos F, de Graaff E, Oostra BA, Willems PJ. A point mutation in the FMR-1 gene associated with fragile X mental retardation. Nat Genet 1993;3(1):31-35.
38. Siomi H, Choi M, Siomi MC, Nussbaum RL, Dreyfuss G. Essential role for KH domains in RNA binding: impaired RNA binding by a mutation in the KH domain of FMR1 that causes fragile X syndrome. Cell 1994;77(1):33-39.
39. Snow K, Doud LK, Hagerman R, Pergolizzi RG, Erster SH, Thibodeau SN. Analysis of a CGG sequence at the FMR-1 locus in fragile X families and in the general population. Am J Hum Genet 1993;53(6):1217-1228.
40. Brown WT, Houck Jr. GE, Jeziorowska A, Levinson FN, Ding X, Dobkin C, Zhong N, Henderson J, Brooks SS, Jenkins EC. Rapid fragile X carrier screening and prenatal diagnosis using a nonradioactive PCR test. JAMA 1993;270(13):1569-1575.
41. Hirst MC, Grewal PK, Davies KE. Precursor arrays for triplet repeat expansion at the fragile X locus. Hum Mol Genet 1994;3(9):1553-1560.
42. Kunst CB, Warren ST. Cryptic and polar variation of the fragile X repeat could result in predisposing normal alleles. Cell 1994;77(6):853-861.
43. Fisch GS, Snow K, Thibodeau SN, Chalifaux M, Holden JJ, Nelson DL, Howard-Peebles PN, Maddalena A. The fragile X premutation in carriers and its effect on mutation size in offspring. Am J Hum Genet 1995;56(5):1147-1155.

44. Eichler EE, Holden JJA, Popovich BW, Reiss AL, Snow K, Thibodeau SN, Richards CS, Ward PA, Nelson DL. Length of uninterrupted CGG repeats determines instability in the FMR1 gene. Nat Genet 1994;8(1):88-94.
45. Snow K, Tester DJ, Kruckeberg KE, Schaid DJ, Thibodeau SN. Sequence analysis of the fragile X trinucleotide repeat: implications for the origin of the fragile X mutation. Hum Mol Genet 1994;3(9):1543-1551.
46. Sherman SL, Morton NE, Jacobs PA, Turner G. The marker (X) syndrome: a cytogenetic and genetic analysis. Ann Hum Genet 1984;48(Pt 1):21-37.
47. Rousseau F, Heitz D, Biancalana V, Blumenfeld S, Kretz C, Boue J, Tommerup N, Van Der Hagen C, DeLozier-Blanchet C, Croquette MF, Gilgenkrantz S, Jalbert P, Voelckel MA, Oberlé I, Mandel JL. Direct diagnosis by DNA analysis of the fragile X syndrome of mental retardation. N Engl J Med 1991;325(24):1673-1681.
48. Sherman SL, Jacobs PA, Morton NE, Froster-Iskenius U, Howard-Peebles PN, Nielsen KB, Partington MW, Sutherland GR, Turner G, Watson M. Further segregation analysis of the fragile X syndrome with special reference to transmitting males. Hum Genet 1985;69(4):289-299.
49. Murray A, Macpherson JN, Pound MC, Sharrock A, Youings SA, Dennis NR, McKechnie N, Linehan P, Morton NE, Jacobs PA. The role of size, sequence and haplotype in the stability of FRAXA and FRAXE alleles during transmission. Hum Mol Genet 1997;6(2):173-184.
50. Heitz D, Devys D, Imbert G, Kretz C, Mandel JL. Inheritance of the fragile X syndrome: size of the fragile X premutation is a major determinant of the transition to full mutation. J Med Genet 1992;29(11):794-801.
51. Yu S, Mulley J, Loesch D, Turner G, Donnelly A, Gedeon A, Hillen D, Kremer E, Lynch M, Pritchard M, Sutherland GR, Richards RI. Fragile-X syndrome: unique genetics of the heritable unstable element. Am J Hum Genet 1992;50(5):968-980.
52. Turner AM, Robinson H, Wake S, Laing SJ, Leigh D, Turner G. Counselling risk figures for fragile X carrier females of varying band sizes for use in predicting the likelihood of retardation in their offspring. Am J Med Genet 1994;51(4):458-462.
53. Väisänen ML, Kähkönen M, Leisti J. Diagnosis of fragile X syndrome by direct mutation analysis. Hum Genet 1994;93(2):143-147.
54. Nolin SL, Lewis FA, 3rd, Ye LL, Houck Jr. GE, Glicksman AE, Limprasert P, Li SY, Zhong N, Ashley AE, Feingold E, Sherman SL, Brown WT. Familial transmission of the FMR1 CGG repeat. Am J Hum Genet 1996;59(6):1252-1261.

55. Pieretti M, Zhang FP, Fu YH, Warren ST, Oostra BA, Caskey CT, Nelson DL. Absence of expression of the FMR-1 gene in fragile X syndrome. Cell 1991;66(4):817-822.
56. Sutcliffe JS, Nelson DL, Zhang F, Pieretti M, Caskey CT, Saxe D, Warren ST. DNA methylation represses FMR-1 transcription in fragile X syndrome. Hum Mol Genet 1992;1(6):397-400.
57. McConkie-Rosell A, Lachiewicz AM, Spiridigliozzi GA, Tarleton J, Schoenwald S, Phelan MC, Goonewardena P, Ding X, Brown WT. Evidence that methylation of the FMR-I locus is responsible for variable phenotypic expression of the fragile X syndrome. Am J Hum Genet 1993;53(4):800-809.
58. Verheij C, Bakker CE, de Graaff E, Keulemans J, Willemsen R, Verkerk AJMH, Galjaard H, Reuser AJJ, Hoogeveen AT, Oostra BA. Characterization and localization of the FMR-1 gene product associated with fragile X syndrome. Nature 1993;363(6431):722-724.
59. Devys D, Lutz Y, Rouyer N, Bellocq JP, Mandel JL. The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutation. Nat Genet 1993;4(4):335-340.
60. Bundey S, Norman E. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):770.
61. Malmgren H, Steén-Bondeson ML, Gustavson KH, Seémanova E, Holmgren G, Oberlé I, Mandel JL, Pettersson U, Dahl N. Methylation and mutation patterns in the fragile X syndrome. Am J Med Genet 1992;43(1-2):268-278.
62. Eichler EE, Macpherson JN, Murray A, Jacobs PA, Chakravarti A, Nelson DL. Haplotype and interspersion analysis of the FMR1 CGG repeat identifies two different mutational pathways for the origin of the fragile X syndrome. Hum Mol Genet 1996;5(3):319-330.
63. Zhong N, Yang W, Dobkin C, Brown WT. Fragile X gene instability: anchoring AGGs and linked microsatellites. Am J Hum Genet 1995;57(2):351-361.
64. Zhong N, Ju W, Pietrofesa J, Wang D, Dobkin C, Brown WT. Fragile X "gray zone" alleles: AGG patterns, expansion risks, and associated haplotypes. Am J Med Genet 1996;64(2):261-265.
65. Brown WT. The fragile X: progress toward solving the puzzle. Am J Hum Genet 1990;47(2):175-180.

66. Smits APT, Smeets D, Hamel B, Dreesen J, van Oost B. High prevalence of the fra(X) syndrome cannot be explained by a high mutation rate. Am J Med Genet 1992;43(1-2):345-352.
67. Smits APT, Dreesen JCFM, Post JG, Smeets DFCM, de Die-Smulders C, Spaans-van der Bijl T, Govaerts LCP, Warren ST, Oostra BA, van Oost BA. The fragile X syndrome: no evidence for any recent mutations. J Med Genet 1993;30(2):94-96.
68. Buyle S, Reyniers E, Vits L, De Boulle K, Handig I, Wuyts FLE, Deelen W, Halley DJJ, Oostra BA, Willems PJ. Founder effect in a Belgian-Dutch fragile X population. Hum Genet 1993;92(3):269-272.
69. Richards RI, Holman K, Friend K, Kremer E, Hillen D, Staples A, Brown WT, Goonewardena P, Tarleton J, Schwartz C, Sutherland GR. Evidence of founder chromosomes in fragile X syndrome. Nat Genet 1992;1(4):257-260.
70. Oudet C, Mornet E, Serre JL, Thomas F, Lentes-Zengerling S, Kretz C, Deluchat C, Tejada I, Boue J, Boue A, Mandel JL. Linkage disequilibrium between the fragile X mutation and two closely linked CA repeats suggests that fragile X chromosomes are derived from a small number of founder chromosomes. Am J Hum Genet 1993;52(2):297-304.
71. Oudet C, von Koskull H, Nordstrom AM, Peippo M, Mandel JL. Striking founder effect for the fragile X syndrome in Finland. Eur J Hum Genet 1993;1(3):181-189.
72. Hirst MC, Knight SJ, Christodoulou Z, Grewal PK, Fryns JP, Davies KE. Origins of the fragile X syndrome mutation. J Med Genet 1993;30(8):647-650.
73. Zhong N, Dobkin C, Brown WT. A complex mutable polymorphism located within the fragile X gene. Nat Genet 1993;5(3):248-253.
74. Macpherson JN, Bullman H, Youings SA, Jacobs PA. Insert size and flanking haplotype in fragile X and normal populations: possible multiple origins for the fragile X mutation. Hum Mol Genet 1994;3(3):399-405.
75. Morton NE, Macpherson JN. Population genetics of the fragile-X syndrome: multiallelic model for the FMR1 locus. Proc Natl Acad Sci U S A 1992;89(9):4215-4217.
76. Richards RI, Sutherland GR. Dynamic mutations: a new class of mutations causing human disease. Cell 1992;70(5):709-712.
77. Kolehmainen K. Population genetics of fragile X: a multiple allele model with variable risk of CGG repeat expansion. Am J Med Genet 1994;51(4):428-435.

78. Morris A, Morton NE, Collins A, Macpherson J, Nelson D, Sherman S. An n-allele model for progressive amplification in the FMR1 locus. Proc Natl Acad Sci U S A 1995;92(11):4833-4837.
79. Fisch GS, Nelson DL, Snow K, Thibodeau SN, Chalifoux M, Holden JJA. Reliability of diagnostic assessment of normal and premutation status in the fragile X syndrome using DNA testing. Am J Med Genet 1994;51(4):339-345.
80. Webb TP, Bundey SE, Thake AI, Todd J. Population incidence and segregation ratios in the Martin-Bell syndrome. Am J Med Genet 1986;23(1-2):573-580.
81. Turner G, Robinson H, Laing S, Purvis-Smith S. Preventive screening for the fragile X syndrome. N Engl J Med 1986;315(10):607-609.
82. Webb TP, Bundey S, Thake A, Todd J. The frequency of the fragile X chromosome among schoolchildren in Coventry. J Med Genet 1986;23(5):396-399.
83. Sutherland GR, Baker E. The common fragile site in band q27 of the human X chromosome is not coincident with the fragile X. Clin Genet 1990;37(3):167-172.
84. Webb T, Bundey S. Prevalence of fragile X syndrome [letter]. J Med Genet 1991;28(5):358.
85. Morton JE, Rindl PM, Bullock S, Bundey S, Webb T. Fragile X syndrome is less common than previously estimated [abstract]. J Med Genet 1995;32:144-145.
86. Arinami T, Asano M, Kobayashi K, Yanagi H, Hamaguchi H. Data on the CGG repeat at the fragile X site in the non-retarded Japanese population and family suggest the presence of a subgroup of normal alleles predisposing to mutate. Hum Genet 1993;92(5):431-436.
87. Reiss AL, Kazazian Jr. H, Krebs CM, McAughan A, Boehm CD, Abrams MT, Nelson DL. Frequency and stability of the fragile X premutation. Hum Mol Genet 1994;3(3):393-398.
88. Rousseau F, Rouillard P, Morel ML, Khandjian EW, Morgan K. Prevalence of carriers of premutation-size alleles of the FMRI gene--and implications for the population genetics of the fragile X syndrome. Am J Hum Genet 1995;57(5):1006-1018.
89. Brown WT, Nolin S, Houck Jr. G, Ding X, Glicksman A, Li SY, Stark-Houck S, Brophy P, Duncan C, Dobkin C, Jenkins E. Prenatal diagnosis and carrier screening for fragile X by PCR. Am J Med Genet 1996;64(1):191-195.
90. Dawson AJ, Chodirker BN, Chudley AE. Frequency of FMR1 premutations in a consecutive newborn population by PCR screening of Guthrie blood spots. Biochem Mol Med 1995;56(1):63-69.

91. Spence WC, Black SH, Fallon L, Maddalena A, Cummings E, Menapace-Drew G, Bick DP, Levinson G, Schulman JD, Howard-Peebles PN. Molecular fragile X screening in normal populations. Am J Med Genet 1996;64(1):181-183.
92. Eichler EE, Hammond HA, Macpherson JN, Ward PA, Nelson DL. Population survey of the human FMR1 CGG repeat substructure suggests biased polarity for the loss of AGG interruptions. Hum Mol Genet 1995;4(12):2199-2208.
93. Holden JJA, Chalifoux M, Wing M, Julien-Inalsingh C, Lawson JS, Higgins JV, Sherman S, White BN. Distribution and frequency of FMR1 CGG repeat numbers in the general population. Developmental Brain Dysfunction 1995;8:405-407.
94. Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. Am J Med Genet 1996;64(1):196-197.
95. De Vries BBA, van den Ouweland AMW, Mohkaming S, Duivenvoorden HJ, Mol E, Gelsema K, van Rijn M, Halley DJJ, Sandkuijl LA, Oostra BA, Tibben A, Niermeijer MF. Screening and diagnosis for the fragile X syndrome among the mentally retarded: an epidemiological and psychological survey. Collaborative Fragile X Study Group. Am J Hum Genet 1997;61(3):660-667.
96. Sherman SL. The high prevalence of fragile X premutation carrier females: is this frequency unique to the French Canadian population? [editorial]. Am J Hum Genet 1995;57(5):991-993.
97. Bonthron D, Strain L. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):769-770.
98. Howard-Peebles PN, Maddalena A, Black SH, Schulman JD. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):770.
99. Palomaki GE, Haddow JE. Is it time for population-based prenatal screening for fragile-X? [letter]. Lancet 1993;341(8841):373-374.
100. Howard-Peebles PN, Maddalena A, Spence WC, Levinson G, Fallon L, Bick DP, Black SH, Schulman JD. Fragile X screening: what is the real issue? [letter]. Am J Med Genet 1994;53(4):382.
101. Palomaki GE. Population based prenatal screening for the fragile X syndrome. J Med Screen 1994;1(1):65-72.
102. Park V, Howard-Peebles PN, Sherman S, Taylor A, Wulfsberg E. Policy statement: American College of Medical Genetics. Fragile X syndrome: diagnostic and carrier testing. Am J Med Genet 1994;53:380-381.

103. Anonymous. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. Am J Hum Genet 1995;57(5):1233-1241.
104. Tarleton JC, Saul RA. Molecular genetic advances in fragile X syndrome. [review]. J Pediatr 1993;122(2):169-185.
105. Sutherland GR, Gedeon A, Kornman L, Donnelly A, Byard RW, Mulley JC, Kremer E, Lynch M, Pritchard M, Yu S, Richards RI. Prenatal diagnosis of fragile X syndrome by direct detection of the unstable DNA sequence. N Engl J Med 1991;325(24):1720-1722.
106. Mulley JC, Yu S, Gedeon AK, Donnelly A, Turner G, Loesch D, Chapman CJ, Gardner RJ, Richards RI, Sutherland GR. Experience with direct molecular diagnosis of fragile X. J Med Genet 1992;29(6):368-374.
107. Levinson G, Maddalena A, Palmer FT, Harton GL, Bick DP, Howard-Peebles PN, Black SH, Schulman JD. Improved sizing of fragile X CCG repeats by nested polymerase chain reaction. Am J Med Genet 1994;51(4):527-534.
108. Wildhagen MF, van Os TAM, Polder JJ, ten Kate LP, Habbema JDF. Explorative study of costs, effects and savings of screening for female Fragile X premutation and full mutation carriers in the general population. Community Genet 1998;1(1):36-47.
109. Warren ST, Nelson DL. Advances in molecular analysis of fragile X syndrome [review]. JAMA 1994;271(7):536-542.
110. Oostra BA, Halley DJJ. Complex behavior of simple repeats: the fragile X syndrome [review]. Pediatr Res 1995;38(5):629-637.
111. Murray J, Cuckle H, Taylor G, Hewison J. Screening for fragile X syndrome. Health Technol Assessment 1997;1(4).
112. Moore DY. Diagnosing fragile X syndrome. Lancet 1993;342(8886-8887):1563-1564.
113. Modell B. The need for a science of community genetics - lecture. 8th international congress of human genetics. Washington, 1991.
114. Turner G, Robinson H, Laing S, van den Berk M, Colley A, Goddard A, Sherman S, Partington M. Population screening for fragile X. Lancet 1992;339(8803):1210-1213.

Chapter 7
Explorative study of costs, effects and savings of screening for female fragile X premutation and full mutation carriers in the general population

7.1 Introduction

The fragile X syndrome is the commonest cause of mental retardation from a single gene defect. It is transmitted in an X-linked semi-dominant fashion, with females being typically more mildly affected than males (1). Affected males may show suggestive physical features (the Martin-Bell phenotype), consisting of long face and ears, rather coarse features and macroorchidism. However, the phenotype may go unnoticed and cannot be relied upon to make the diagnosis. The dysmorphic features in females with fragile X syndrome are less obvious (2).

The syndrome is characterised by the amplification of a CGG repeat present in the 5' untranslated region of the FMR1 gene (3-6). The length of the CGG repeat varies in the normal population from 6 to 52 repeats and is stable on transmission (7). Premutation alleles ranging from 43 to 200 repeats exhibit instability, usually resulting in increases in repeat number in the offspring. Premutations are not associated with a clinical phenotype and are found in female carriers and so-called normal transmitting males. In fragile X syndrome patients, the CGG repeat is amplified beyond 200 copies (full mutation) and the concomitant hypermethylation of the preceding CpG island represses the transcription of FMR1 (8). This results in the absence of the FMR1 protein leading to the fragile X syndrome phenotype (9, 10).

The cloning of the gene and the knowledge of the inheritance pattern of the fragile X syndrome make it possible to consider a screening programme for premutation and full mutation carriers in the general population (11-18). Several general-population-based screening strategies have been suggested for genetic diseases and are being or have been analysed in a pilot study (19). Of these, prenatal, preconceptional, and school screening can, on technical grounds, also be considered for general population fragile X screening. Neonatal carrier screening cannot be considered for general

population screening because Southern blot analysis on a blood spot does not appear to be feasible.

The primary aim of a fragile X screening programme is to detect carrier status and counsel women who are carriers of a premutation or full mutation so that they have an informed choice about reproduction, but there are also many health-related, psychosocial, ethical, legal and economic consequences. In The Netherlands, the Dutch Health Council has recently provided a number of criteria for genetic screening programmes intended to ensure systematic assessment of such programmes before their introduction (20). The last criterion in this report states that if the favourable non-economic consequences for the participants clearly outweigh the unfavourable consequences, costs and effects of the screening programme should be calculated and checked in view of a fair distribution of resources within the total area of the health service. We started a prospective evaluation of the cost-savings balance of screening for fragile X carriers to determine whether there are economic arguments to decide against a screening programme and what kind of programme is the most favourable one from an economic point of view. Also, we relate costs to effect measures. The methodology of this evaluation has also been used for an evaluation of the costs, effects and savings for screening for carriers of the cystic fibrosis gene (21).

7.2 Materials and methods

We developed a decision-analytic model for a screening programme for fragile X female premutation and full mutation carriers. We divided the premutation categories according the number of CGG repeats using 55 CGG repeats as a cut-off between general population and premutation alleles (22): CGG repeats between 55 and 59, 60-69, 70-79, 80-89 and 90-200 CGG repeats. We made two full mutation categories: full mutation with and without mental retardation.

We prospectively evaluated three different screening strategies taking the Dutch situation as an example: prenatal screening, preconceptional screening, and school carrier screening. For each screening strategy we calculated the expected costs, effects and savings for a 1-year screening period. Fragile X-related effects, costs and savings that occur later were taken into account using a 3% annual discount rate for the costs and savings; effects were not discounted. For comparison, we also calculated results of a maximum yield scenario in which we set information preservation and uptake of screening, prenatal diagnosis and induced abortion at 100%. Because prenatal and preconceptional screening are probably more desirable than school

screening, we will discuss these two strategies in more detail in the 'Results' section.
The knowledge about and experience with fragile X screening is not very large. Therefore a relatively large number of assumptions have to be made in our analysis. For this reason, we conducted a sensitivity analysis to assess the stability of the results of our analysis. In this analysis, we varied the values of selected assumptions while keeping all other parameters at their baseline values. We also varied the values of all selected assumptions simultaneously in a multi-variable sensitivity analysis. After a brief explanation of the screening strategies, we describe the assumptions and parameters that we used in our analysis (Table 7.1).

7.2.1 Screening strategies

Prenatal screening

In the prenatal screening strategy, a pregnant woman is screened as early in her pregnancy as possible so that chorionic villus sampling (CVS) is still possible in case she is a detected carrier. Prenatal screening provides a suitable gateway for genetic screening because questions concerning familial disease often arise in early pregnancy. Furthermore, it is relatively easy to integrate this form of fragile X screening in the existing health care system because almost all women who suspect to be pregnant consult a general practitioner or midwife. Prenatal screening is the only form of screening in which not all reproductive options are possible: the carrier couple can obviously not decide to refrain from conceiving children, to adopt a child or to have egg cell donation. Furthermore, the reproductive choices that are still possible (accepting the risk of giving birth to a fragile X syndrome child or having prenatal diagnosis possibly followed by induced abortion) have to be made in a relatively short time span. Only for subsequent children all reproductive options are open.

Table 7.1 Assumptions used in the analysis of fragile X carrier screening

Fragile X prevalences			
Females with premutation	1:435	Females with full mutation	1:4,000
Males with premutation	1:871	Males with full mutation	1:4,000

Probabilities	
Probability of a new premutation	0%
Probability of a back-mutation from premutation size to normal size	0%
Full-mutation boys with mental retardation	100%
Full-mutation girls with mental retardation	59%
Probability of a couple being unwantedly childless	10%
Probability of a couple being deliberately childless	10%
Autosomal chromosome abnormalities at birth	1:500
Sex chromosome abnormalities at birth	1:500
Recurrence risk of chromosome abnormalities	1.50%
Iatrogenic abortion after CVS	0.75%
No amplification of PCR	10%
1 DNA band at PCR	40%
Southern blot fails	10%

Costs			
DNA-extraction	€7.96	Induced abortion	€221.01
Costs for the screenee	€7.00	Early spontaneous abortion	€69.23
PCR test	€21.27	Late spontaneous abortion	€444.36
Southern blot	€66.68	Iatrogenic abortion	€69.23
Counselling a carrier	€101.03	Discount rate for costs	3%
Prenatal diagnosis	€1,270.58		

Screening-dependent parameters	Prenatal	Preconceptional
Target group size	100,000	100,000
Coverage of people without fragile X mental retardation	75%	50%
Coverage of people with fragile X mental retardation	37.5%	25%
Coverage of people who were not screened for their 1st child	25%	25%
Information retention	100%	100%
Mass information costs	€314,470	€524,116
Personal information costs	€5.45	€2.72
Organisation costs	€17.23	€17.23

Parameters depending on carrier status of the screened	Norm	Premutation	Full mutation
Persons who refrain from having children	0%	15%	15%
Uptake of prenatal diagnosis	0%	75%	75%

Parameters depending on the status of the foetus	Norm or PM	FM boys	FM girls	Aut.abn.	Sex.abn.
Early spontaneous abortion	1.95%	1.95%	1.95%	21.21%	6.15%
Late spontaneous abortion	1.55%	1.55%	1.55%	19.70%	2.79%
Uptake of induced abortion	0%	90%	45%	95%	75%
Costs of care of patient	€0	€847,472	€472,232	€663,854	€0

Preconceptional screening

Preconceptional screening concerns women who consider having a child and want to receive information about their carrier status. The screening result is known prior to the (potential) reproduction so that all reproductive options are open to the carriers. Since some women need time to psychologically accept that they are carrier (23), many people advocate preconceptional screening rather than prenatal screening. In most countries (including The Netherlands), a major obstacle to preconceptional screening is the absence of a preconceptional consultation system, so that a high coverage of screening is unlikely. Furthermore, coverage will probably depend on the way in which people are approached, as has been shown for cystic fibrosis carrier screening (24-26).

School screening

In the school screening strategy, acquisition of the testing material can take place within the school environment. To minimise the time between screening and (potential) reproduction, pupils in the last year of compulsory education (in The Netherlands at the age of 16) should be offered the test. Studies in Italy and Canada on thalassaemia and Tay-Sachs disease screening show that school screening for carriership of genetic diseases is feasible (27, 28). From a community-genetic perspective, this type of screening can offer an opportunity for teaching genetics, but this has also been questioned (29). One concern is the lack of confidentiality of test results. Furthermore, good information is important because school screening takes place at a rather unstable stage of life and might lead to stigmatisation.

7.2.2 Target populations and coverage

Premutation and full mutation males never pass a full mutation X chromosome to their children. Because the aim of a fragile X screening programme is to inform carriers who are at risk of having a fragile X syndrome child, only women are the target of screening.

In The Netherlands, 189,521 children were born in 1996 of whom 85,792 were firstborns (30). The average age of a primigravida is 28.9 years; the mean interval between two subsequent pregnancies is 2.9 years (30). In our calculations, we work for ease of interpretation with a simplified stable population of 100,000 couples.

We corrected for the probability of spontaneous abortion between the time of screening and time of birth (see below). If applicable, we corrected with a 10%

probability of a couple being infertile (31) and assumed in the school screening strategy that 90% of females will later form a couple that wants a child (32). Furthermore, we assumed that in all screening strategies 85% of the people with a firstborn child will have a second child after 3 years on average (32, 33). For computational simplicity, we ignore in our calculations the birth of children who are thirdborn or more. This assumption will obviously not have effects on the costs per detected carrier couple, but will lead to a conservative estimate of the cost-savings balance.

As discussed in the description of the strategies, coverage is probably highest for prenatal screening and somewhat lower for school screening. For preconceptional screening, coverage depends very much on the existence of a preconceptional consultation system and on the way in which people are approached (24, 26). As (arbitrary) basic assumptions, we set the coverage values at 75% for prenatal screening and 50% for preconceptional and school screenings. For the coverage of women with fragile X syndrome, we took half of these baselines, as several studies have shown that they participate less in screening programmes (34, 35). For people who did not attend screening for their first child, we took an attendance rate for the second child of 25% for people without fragile X syndrome and 12.5% for people with fragile X syndrome.

7.2.3 Information preservation

In the Tay-Sachs disease prevention programme in Montreal, Zeesman et al. (28) found that after 8 years 90% of the screened pupils were able to retrieve the test result regarding carriership. Because the time between testing and possible use of the carrier information for school screening is of the same order of magnitude (12-13 years in our analysis), we took this value for the information retention rate of school screening. Although there is also a time lag between screening and use of information in the preconceptional screening strategy (1 year in our analysis), we assumed an information retention rate of 100% for this strategy. Furthermore, we assumed that someone who has not retained the carrier information will not be retested.

7.2.4 Tests

The samples of people in the target group are tested with a polymerase chain reaction (PCR) test that takes approximately 8 hours. In about 10% of the samples no amplification will occur so that a repeat PCR test has to be performed (G. Pals, personal communication). In 40% of the samples, the PCR test will show only one

band, either because a person has two alleles of the same size or two alleles that differ by only one CGG repeat, or because a person has one normal-size allele and one long DNA sequence (large premutation or full mutation) which escapes detection in the PCR test (36). In these cases, Southern blot analysis is performed which will fail for technical reasons in 10% of the cases so that a repeat Southern blot is needed (G. Pals, personal communication). In the model we presume that after these tests the number of CGG repeats or the presence of a full mutation is known with certainty and that both PCR and Southern blots are performed on one blood sample.
If the woman is pregnant and decides to have prenatal diagnosis, CVS is performed at 10-12 weeks gestation. The sample is examined in the same way as the sample of the woman with PCR and Southern blot. In addition to these tests, the villi are routinely tested for maternal contamination and for chromosomal abnormalities. We presumed a 100% sensitivity and specificity of the DNA tests. In The Netherlands, karyotyping of the foetus is offered to women of advanced maternal age (36 years and older), and approximately 50% of the women make use of this offer (37). Since approximately 88% of the births are from women younger than 36 years (30), only a small percentage of pregnant women will have karyotyping of the foetus. Because of this, and because triple marker screening for Down syndrome and neural tube defects is not actively being offered in The Netherlands, the number of detected foetuses with chromosome abnormalities mentioned in this article can almost completely be accredited to the fragile X screening programme.

7.2.5 Prevalence, risk and recurrence

The prevalence of both males and females with a full mutation has been estimated as 1:4,000 by Turner et al. (38). In The Netherlands, de Vries et al. (39) screened a representative sample of 3,352 individuals in schools and institutes for the mentally retarded. They estimated a fragile X syndrome prevalence of 1 in 6,045 boys (95% confidence interval: 1 in 9,981 to 1 in 3,851). Since the 1:4,000 estimate is based on larger groups and since this estimate is contained in the confidence interval of de Vries et al., we used the 1:4,000 prevalence.
In the largest general population-screening programme to date, Rousseau et al. (40) detected 41 women with 55 CGG repeats or more among 10,624 women. They estimated a frequency of full mutation carriers in French Canada of 42:100,000, which is approximately 1.68 times the figure of Turner et al. (38). Because there are indications of founder effects in the French Canadian population (41), we decided to

divide the premutation frequencies obtained by Rousseau et al. by 1.68, assuming that a decrease in premutation frequency will cause a similar decrease in full mutation frequency. Therefore we took a premutation frequency of 1:435 in females. Male premutation prevalences were taken as half of those of females, and mosaics were not taken into account. For the transition from premutation in the parent to a full mutation in the foetus, we used the logistic model of Fisch et al. (42). In this model, the probability of transition to full mutation depends on the length of the mother's CGG repeat. For example, the risk of expansion is 20% if the mother has 60-69 CGG repeats, and is 71% for 80-89 repeats.

We assumed that all boys and 59% of the girls with a full mutation have mental retardation (1). The probabilities of a new premutation and a back-mutation from premutation size to normal size were taken to be zero.

The prevalences at birth of serious autosomal chromosomal abnormalities and sex chromosome abnormalities in the general population are both 1:500 (43). The recurrence risk for a chromosomal abnormality of a child, if there is a first child with a chromosomal abnormality, was estimated at 1.5%.

7.2.6 Refraining, prenatal diagnosis and induced abortion decisions

We assumed that in the preconceptional and school screening strategies, 0% of the non-carrier women and 15% of the carriers will refrain from a first child. Of the women who have not refrained from a first child, 25% will refrain from a second child if an abnormality or disease is found at prenatal diagnosis or birth of the first child.

Uptake of prenatal diagnosis is set at 75% for both premutation and full mutation carriers, and people without a premutation or full mutation will not take prenatal diagnosis. If a woman has been screened and (not) had prenatal diagnosis for her first child, she will also (not) have prenatal diagnosis for her second child. In The Netherlands, 95% of foetuses with serious autosomal abnormalities, detected prenatally, and 75% of the foetuses with a sex chromosome abnormality were selectively aborted (37). We assumed that 90% of the detected males and 45% of the female foetuses with a full mutation would be selectively aborted; that if an induced abortion has been done for a first child with a given disease/abnormality, the second foetus will also be selectively aborted if it has the same disease/abnormality, and that the second foetus will not be aborted if the first foetus has not been aborted.

7.2.7 Spontaneous and iatrogenic abortion

We divided the risk of spontaneous abortion into two parts: the risk of a spontaneous abortion occurring between the time of prenatal testing and the time of a possible induced abortion ('early spontaneous abortion') and a spontaneous abortion occurring after the time of a possible induced abortion ('late spontaneous abortion'). The distinction between early and late spontaneous abortions is important, both from a psychological and an economic point of view because if the abortion occurs in the first days after CVS, the woman might (falsely) ascribe a spontaneous abortion to the CVS procedure. On the other hand, ending an affected pregnancy by induced abortion when the pregnancy would otherwise have ended in a late spontaneous abortion is unfavourable, both because of the induced abortion-associated grief and because of the costs of unnecessary actions. For autosomal abnormalities, the risk for early and late spontaneous abortion is 21.21% and 19.70% and for sex chromosome abnormalities 6.15% and 2.79%, respectively (44). The risk of spontaneous abortion after the moment of prenatal testing in normal pregnancies is 3.5% (44) and is assumed the same for premutation and full mutation carriers (45). We subdivided this risk into 'early' and 'late' using the relative proportions of the respective early and late abortion risks for autosomal and sex chromosome abnormalities. In this way, we obtained 1.95% as the risk for early spontaneous abortion and 1.55% for the risk of late abortion. Furthermore, we presumed that CVS carries an attributable risk of iatrogenic abortion of 0.5-1.0% (46) (midpoint 0.75%).

7.2.8 Economic factors

The costs of screening can be divided into three categories: the costs of information dissemination prior to the screening - for instance by mass media and leaflets; the costs of testing and organisation of the screening programme, and the costs of aftercare. We estimated the costs from a societal point of view, the recommended way of analysing costs in screening programmes (47, 48), by calculating invested manpower, equipment and materials at relevant wages and prices. These cost estimates will differ from the results using a purely financial point of view. In the latter case, commercial prices are used including transfer payments (profits, margins, taxes, and royalties) (49). We regarded as economic savings, the precluded lifetime medical costs of patients who will be born less because of the screening programme ('avoided patients'). Because costs of diagnosis and treatment of fragile X syndrome occur at a later point in time than the actual screening, they were transformed to the (present)

value in the year of screening using an annual discount rate of 3%. Cost figures were converted from Dutch guilders (NLG) to EUROs (€) using an exchange rate of €1 = NLG 2.20371.

Costs of information

We divided the information costs into two parts: the mass information costs that depend on the target group—for example costs of mass media campaigns—and the individual information costs that are proportional to the number of individuals—for instance costs of leaflets.

Fragile X syndrome is not very well known in the general population, contrary to, for example, breast cancer. Van der Maas et al. (50), studying the costs and effects of mass screening for breast cancer in The Netherlands, obtained €262,058 for mass information costs and €1.36 for individual information costs (costs adjusted for inflation). Because fragile X syndrome is less well known, we decided to take twice these values as baseline cost estimates for the preconceptional screening programme for fragile X carriers. Because of its easy integration in the existing screening programme, we set the mass information costs for prenatal screening at 60% of the value for preconceptional screening and we took the school mass information costs at 80% because of the integration in the school setting.

The individual information costs are likely to be highest for prenatal screening because of the direct consequences and emotional sequelae of the test outcome. Therefore, we estimated them as twice the costs of individual information for preconceptional screening. The individual information costs were set lowest for school screening at 50% of the value of preconceptional screening.

Costs of testing

Costs of testing can be subdivided into costs of acquisition of the blood sample by a general practitioner, midwife or nurse, shipment of the samples to a laboratory, DNA extraction, PCR analysis, Southern blot analysis, reporting of the results, and costs for the screenee. We estimated the so-called organisation costs of acquisition, shipment and administration at €17.23 per individual. The cost of DNA extraction was estimated at €7.96 per sample (G. Pals, personal communication). One sample provides enough DNA to perform the PCR analysis at €21.27 and, if necessary, the Southern blot at €66.68 (G. Pals, personal communication). All figures include costs for staff, equipment, materials, disposables and overhead. For the costs for the screenee, we took the costs of travelling by public transport and the costs of

production loss (1 hour for travelling back and forth to the screening, waiting time and the time of screening) (51), totalling €7.00.

Costs of further diagnosis and treatment

Aftercare consists of counselling carriers and, depending on the choice of the carrier, prenatal diagnosis for detected carriers and eventually, depending on the carrier's decision, abortion of an affected foetus. For counselling, we took the costs of a qualified nurse in a clinical-genetics centre, assuming that counselling a carrier takes 3 hours. At an hourly wage of €19.06 and an overhead percentage of 40%, counselling costs to the clinical-genetics centre are €80.05 per carrier. For the carrier couple, we added to the counselling time 15 minutes of waiting time and the costs of public transport to the counselling costs, totalling €20.98 (51). The costs of prenatal diagnosis, selective abortion, early and late spontaneous abortion, and iatrogenic abortion were based on Dutch reimbursements: €1,270.58, €221.01, €69.23, €444.36, and €69.23 respectively (52, 53). These reimbursements are the prices that insurers pay to hospitals, general practitioners, doctors, and other health care providers, and are mostly settled in some form of negotiation between health care insurers and providers (for example, hospitals). Therefore, they do not necessarily equate with real costs.

Lifetime costs of care of patients

People with fragile X syndrome stay in institutions for people with a mental handicap or surrogate family units, live with their parents or are self-supporting. In The Netherlands, 38% of the male patients and 8% of the females stay in institutions, and 18% of both males and females stay in surrogate family units. 35% of the male and 38% of the female patients live with their parents, while the other 9% of males and 36% of females are self-supporting (A.P.T. Smits, personal communication). For these types of services the age- and sex-specific costs of care for fragile X syndrome are known (54-56). We adjusted the age- and sex-specific costs for the survival figures of the general population and with a discount percentage of 3%. In that way, the so-called lifetime costs of care for fragile X syndrome patients were estimated at €847,472 for males and €472,232 for females. These figures are somewhat lower than the figure of Turner et al. (57) who estimated the costs at approximately €889,000. Therefore, the use of our own estimates will lead to a more conservative estimate of the cost-savings balance.

We considered the costs of care of people with Down syndrome as representative for those of people with autosomal chromosome abnormalities. To obtain the lifetime costs of care for these patients, we used the methodology described above, but we used a survival table for Down syndrome patients (58) and assumed that the proportions of patients in the above-mentioned institutions are distributed evenly. In that way, the costs of care for (male and female) patients with an autosomal chromosomal abnormality were estimated at €663,854. Because people with sex chromosome abnormalities in general do not have many complications, we decided to ignore these costs.

7.3 Results

In Table 7.2-Table 7.4, we give the results of our analysis for prenatal and preconceptional screenings. The results of school screening are not described in the tables for the sake of clarity. Total costs of screening are lower for preconceptional screening than for prenatal screening (Table 7.2) because it has a low coverage of screening. With regard to the number of detected carriers (Table 7.3), prenatal screening outperforms preconceptional screening (200 detected carriers) because of its higher coverage. The potential number of detected carriers (maximum yield scenario), however, is equal for both strategies at 255 detected carriers. The baseline prenatal screening strategy detects 200/255 = 78% of the maximum number of detectable carriers. As for all strategies, this percentage can be obtained by taking the weighted average of the uptake rate of screening for the first child and the additional uptake rate of screening for the second child.

Table 7.2 Costs per year of two fragile X screening programmes

	Screening strategy	
	Prenatal	Preconceptional
Spread of information*	€885,000	€820,000
Organisation and testing*	€6,975,000	€5,132,000
Aftercare*	€358,000	€198,000
Total with baseline assumptions*	€8,219,000	€6,151,000
Maximum yield scenario*	€10,244,000	€10,026,000

* costs and savings are rounded to €1,000

When we want to carry the economic analysis of the screening programmes further, we need to calculate the number of avoided patients. These numbers are defined as the number of patients not born because the would-be parents decided to refrain from having (more) children or to have an induced abortion in case a foetus has the full mutation or a chromosomal abnormality. The number of avoided patients is lower in the preconceptional screening strategy because of its low coverage. As a

percentage of the maximum yield, prenatal screening avoids the birth of most patients (28 out of a maximum of 68 = 41%).

The costs per detected carrier are comparable, but somewhat lower for prenatal screening, €41,100 (Table 7.4). The cost-effectiveness ratio of the preconceptional screening strategy is €41,400 per detected carrier, and the ratio for school screening is €39,300. The net economic savings (savings minus costs) are positive for all strategies at €12 million for prenatal screening, €8 million for preconceptional screening and €2 million per year for school screening.

To assess the stability of the conclusions, we varied the values of some assumptions and determined the costs per detected carrier and the net economic savings per year for each programme. As expected, varying the prevalence of premutation carriers has a large impact on the cost-effectiveness ratio (Figure 7.1) and on the net economic savings (Figure 7.2a). Varying the coverage on the other hand has less influence on the net savings (Figure 7.2b).

Table 7.3 Numbers of detected carriers, avoided patients and negative side effects per year of two fragile X screening programmes

	Screening strategy	
	Prenatal	Preconceptional
Detected carriers		
Baseline assumptions	200	149
Maximum yield scenario	255	255
Avoided patients		
Boy with full mutation and MR (baseline)	21	14
Girl with full mutation and MR (baseline)	6	5
Child with autosomal abnormality (baseline)	1	0
Child with sex chromosome abnormality (baseline)	0	0
Total (baseline assumptions)	28	19
Total (maximum yield scenario)	68	61
Negative side effects		
Avoided girls with full mutation without MR	4	3
Avoided normal or premutation children	5	27
Iatrogenic abortions	2	1

Table 7.4 Cost-effectiveness measures and savings per year of two fragile X screening programmes

	Screening strategy	
	Prenatal	Preconceptional
Costs per detected carrier		
Baseline assumptions	€41,100	€41,400
Maximum yield scenario	€40,200	€39,400
Savings of affected children born less		
Baseline assumptions	€20,580,000	€14,018,000
Maximum yield scenario	€47,173,000	€41,219,000
Net savings per year		
Baseline assumptions	€12,361,000	€7,868,000
Maximum yield scenario	€36,929,000	€31,194,000

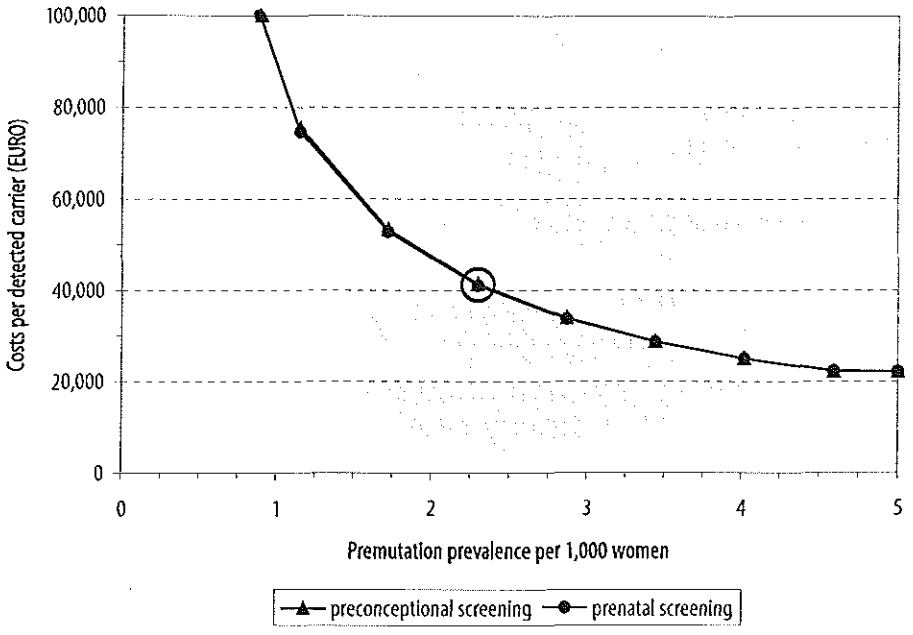


Figure 7.1 Dependency of the cost-effectiveness ratio on premutation carrier prevalence. Note that the costs per detected carrier are almost equal for both strategies so that the lines overlap. ○: baseline value of the parameter

The costs of care play no role in the cost-effectiveness ratio, but they have a somewhat larger influence on the net savings than the prevalence of carriers (Figure 7.2c). For the other assumptions, the balance is rather insensitive to a change in the values.

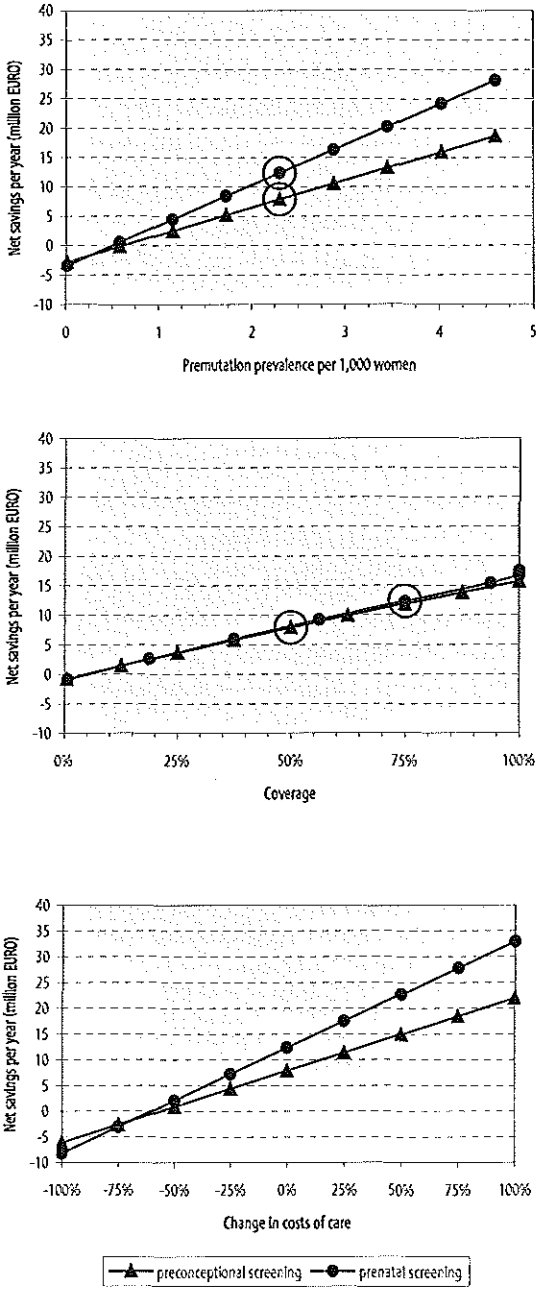


Figure 7.2 Dependency of the net savings on selected assumptions. O: baseline value of the parameter

Looking at the threshold values of the parameters (the percentage increase/decrease of the parameter for which costs of the programme equal the savings), we can conclude that costs of prenatal and preconceptional screening programmes will never exceed savings for a wide range of assumptions (Table 7.5). For example, in these strategies, costs will only be higher than savings if the prevalence of premutation and full mutation carriers is less than 43% of the baseline values (i.e. 1/1,011 for premutation carriers and 1/9,287 for full mutation carriers), if information preservation is less than 50% of the baseline values or if the costs of care of patients are lower than 44% of the baseline values. Although coverage has a considerable influence on the costs and the savings, the costs will only become higher than the savings in these strategies if coverage is lower than 5% (the prenatal threshold is 6% of a 75% baseline coverage and the preconceptional threshold is 9% of a 50% baseline). Although the thresholds are somewhat stricter for school screening, costs will not exceed savings for a wide range of assumptions also. For example, costs exceed savings only if the prevalence of carriers is 74% of the baseline value.

In the multi-variable sensitivity analysis (Figure 7.3) we varied ten parameters simultaneously to see how sensitive the cost-savings balance is if all these parameters had been estimated too optimistically or too pessimistically. The conclusion of this multi-variable sensitivity analysis is that for prenatal and preconceptional screenings the parameter values can deteriorate to 86% of the baseline values before the costs of screening exceed the savings, while parameter values of school screening could only deteriorate by 5%.

Table 7.5 Threshold values for favourable cost-savings balance of screening programmes (% of baseline values depicted in Table 7.1, pos = savings are higher than costs for all parameter values)

	Screening strategy	
	Prenatal	Preconceptional
Threshold for prevalence of carriers	39%	43%
Threshold for coverage	6%	9%
Threshold for costs of care	40%	44%
Threshold for information preservation	49%	50%
Threshold for refraining from children	pos	pos
Threshold for uptake of prenatal diagnosis	39%	28%
Threshold for uptake of induced abortion	37%	27%
Threshold for costs of tests	386%	347%
Threshold for costs of individual information	2,304%	2,906%
Multi-variable threshold	86%	86%

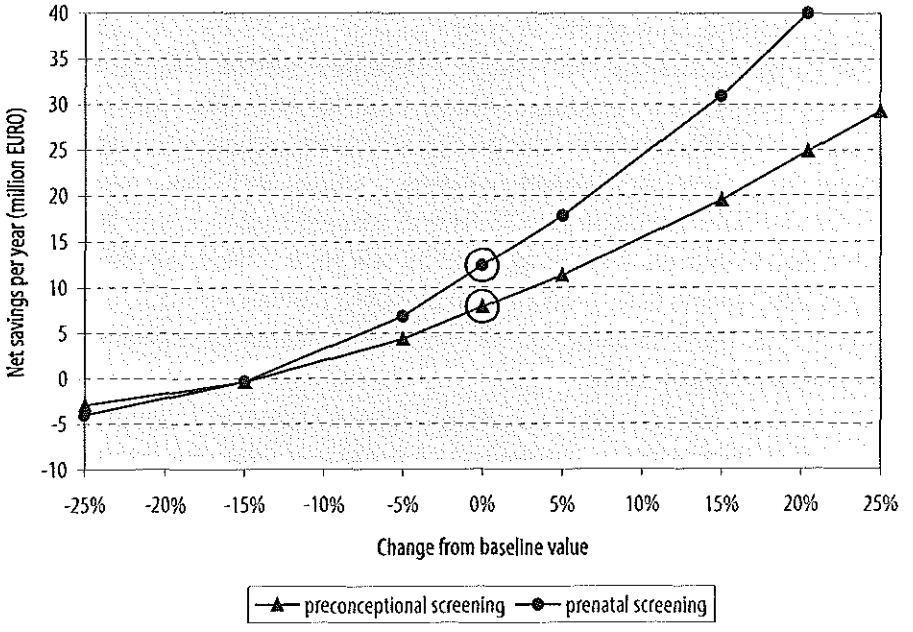


Figure 7.3 Multi-variable sensitivity analysis of the net savings per year. Assumptions that are simultaneously varied in favourable (+) and unfavourable (-) direction from their baseline value: coverage, information preservation, carrier prevalence, refrain percentage, uptake of prenatal diagnosis, percentage of induced abortions, discount percentage of the costs, costs of care, costs of the screening tests, costs of individual information. O: baseline value of the parameter

7.4 Discussion

Using a decision-analytic model, we found that there are no economic objections against screening for carriers of the fragile X gene, since the costs of screening are (amply) recovered later. In a sensitivity analysis, this conclusion remained valid for a wide range of other plausible assumptions.

The distinction between high-end normals and low-end premutation alleles is not always clear because repeats of similar size differ markedly in their intergenerational stability. We decided to use 55 CGG repeats as a cut-off between normals and premutation alleles. Using this cut-off, 1.3% of the women with 55 CGG repeats or

more are incorrectly classified as having a premutation allele (false-positives) (22). This means, for example, that of the 49 tested women with 55-59 CGG repeats in the prenatal screening strategy, on average one woman will be false-positive. If this woman chooses prenatal diagnosis, she has a 0.75% risk of iatrogenic abortion. On the other hand, 1% of the women with 50-54 repeats, and perhaps a few with less than 50 repeats, are incorrectly classified as having a normal allele (false-negatives) (22). Assuming a 2:1 ratio of women with 50-54 CGG repeats to women with 55-59 repeats (59), this means that on average one woman will have a false-negative test result. However, this woman has a very small probability of giving birth to a fragile X syndrome child. These percentages will of course be altered by changing the cut-off value to higher or lower values.

The difference in intergenerational stability between normal and premutation alleles suggests that differences in sequence content may play an essential role in determining an allele's predisposition to instability. A normal fragile X CGG repeat has some dispersed AGG repeats, normally one AGG for every 9-10 CGGs. In unstable premutations, the number of AGGs is diminished or absent (60, 61). However, determining the number of AGGs requires expensive sequencing that will influence the cost-effectiveness balance.

The full mutation creates a problem of interpretation in female foetuses because the intellectual outcome is so variable. For example, 41% of the females with a full mutation will not have mental retardation (1). At present there is no prenatal test to determine which of the female foetuses with the full mutation will be affected, but some studies indicate that the degree of methylation of the FMR1 gene correlates with mental function in both females and males (62, 63). A decision whether or not to terminate a pregnancy of a female foetus with a full mutation must therefore be based on the knowledge of a 59% likelihood of the foetus having fragile X syndrome. For this reason, it has been proposed to first test for the sex of the foetus and to only test male foetuses for the fragile X gene. Therefore we also determined the cost-savings balance if no female foetuses with a full mutation were aborted. In this scenario, savings will still exceed costs by €1 to €10 million.

In our analysis, we did not consider screening in special schools or other forms of large-scale cascade testing. We feel that it is inappropriate to simply compare relative costs because both the ethics and methodology involved in the testing process are different from general population screening. For example, the first step in cascade testing is the diagnosis of (index) cases with fragile X syndrome whose carrier-parents

could also have been detected by a general population screening. In case of a general population screening, however, these parents would have had more reproductive options, such as refraining from children. On the other hand, an earlier diagnosis of the index case is an advantage (64). Therefore we have also developed a computer model with which we calculate the efficiency of cascade testing (see Chapter 8).

It should be borne in mind that, even when savings exceed costs, financing a screening programme for fragile X gene carriers is not straightforward because the screening budget has to be made available now while the savings of the programme will only appear (much) later. Moreover, savings may be realised in other budgets than where the costs of screening are made so that conflicting interests may arise.

We used a 3% discount rate to transform the streams of future costs and savings to the (present) value in the year of screening. If the effects were also discounted, carriers detected in the future would count less than carriers detected now. Because of this intergenerational setting of genetic screening, we decided not to discount the effects. Recently, an authoritative American Panel on Cost-Effectiveness in Health and Medicine recommended this 3% discount rate for both costs and effects, and suggested to also use a 5% and 0% discount rate for comparability with other studies (65). The costs per detected carrier will only be slightly affected by varying discount rates for costs since most costs occur in the year of screening and are therefore not discounted. On the other hand, net savings of all screening strategies will change considerably since the relative importance of the costs of care of avoided patients is higher for lower discount rates. For example, the net savings of prenatal screening range from €42.1 million at 0% discounting to €12.4 million at 3% discounting and to €5.7 million at 5% discounting. For preconceptional screening the net savings range from €29.3 million at 0% discounting to €7.9 million at 3% discounting and to €3.2 million at 5% discounting. This means that savings exceed costs regardless of the choice of discount factor. Only for school screening, will costs exceed savings by €1.7 million when using a 5% discount factor.

In The Netherlands, all chorionic villi are routinely tested for chromosomal abnormalities. If this routine test were not performed, the costs of aftercare would obviously decrease and, because foetuses with chromosomal abnormalities are not detected anymore, the savings of affected children born less decrease. However, the savings of the avoided children decrease more than the costs of screening. Therefore the cost-savings balance of all screening strategies deteriorates somewhat (e.g. net savings of preconceptional screening decrease from €7.9 million to €7.7 million).

The present paper focused deliberately on cost aspects. There is of course much more to be discussed in genetic screening than costs, see e.g. the criteria list of the Dutch Health Council (20). Economic considerations should never be the primary goal of any screening programme, but a careful cost analysis and a discussion of cost-effectiveness measures as reported in this paper are an essential part of a full evaluation. When other aspects are also considered, preconceptional screening, which has the second-best cost-savings balance, possibly has to be preferred because with that strategy all reproductive options are still open for a carrier couple. Lack of participation will not be irreparable when prenatal screening, the optimal strategy from an economic point of view, is used as a 'safety net' for pregnant women who did not attend the preconceptional screening programme.

7.5 References

1. Rousseau F, Heitz D, Tarleton J, MacPherson J, Malmgren H, Dahl N, Barnicoat A, Mathew C, Mornet E, Tejada I, Maddalena A, Spiegel R, Schinzel A, Marcos JAG, Schorderet DF, Schaap T, Maccioni L, Russo S, Jacobs PA, Schwartz C, Mandel JL. A multicenter study on genotype-phenotype correlations in the fragile X syndrome, using direct diagnosis with probe StB12.3: the first 2,253 cases. Am J Hum Genet 1994;55(2):225-237.
2. Loesch DZ, Hay DA. Clinical features and reproductive patterns in fragile X female heterozygotes. J Med Genet 1988;25(6):407-414.
3. Verkerk AJMH, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DPA, Pizzuti A, Reiner O, Richards S, Victoria MF, Zhang FP, Eussen BE, van Ommen GB, Blonden LAJ, Riggins GK, Chastain JL, Kunst CB, Galjaard H, Caskey CT, Nelson DL, Oostra BA, Warren ST. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 1991;65(5):905-914.
4. Oberlé I, Rousseau F, Heitz D, Kretz C, Devys D, Hanauer A, Boué J, Bertheas MF, Mandel JL. Instability of a 550-base pair DNA segment and abnormal methylation in fragile X syndrome. Science 1991;252(5010):1097-1102.
5. Yu S, Pritchard M, Kremer E, Lynch M, Nancarrow J, Baker E, Holman K, Mulley JC, Warren ST, Schlessinger D, Sutherland GR, Richards RI. Fragile X genotype characterized by an unstable region of DNA. Science 1991;252(5010):1179-1181.

6. Kremer EJ, Yu S, Pritchard M, Nagaraja R, Heitz D, Lynch M, Baker E, Hyland VJ, Little RD, Wada M, Toniolo D, Vincent A, Rousseau F, Schlessinger D, Sutherland GR, Richards RI. Isolation of a human DNA sequence which spans the fragile X. Am J Hum Genet 1991;49(3):656-661.
7. Fu YH, Kuhl DPA, Pizzuti A, Pieretti M, Sutcliffe JS, Richards S, Verkerk AJMH, Holden JJA, Fenwick Jr. RG, Warren ST, Oostra BA, Nelson DL, Caskey CT. Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. Cell 1991;67(6):1047-1058.
8. Pieretti M, Zhang FP, Fu YH, Warren ST, Oostra BA, Caskey CT, Nelson DL. Absence of expression of the FMR-1 gene in fragile X syndrome. Cell 1991;66(4):817-822.
9. Verheij C, Bakker CE, de Graaff E, Keulemans J, Willemsen R, Verkerk AJMH, Galjaard H, Reuser AJJ, Hoogeveen AT, Oostra BA. Characterization and localization of the FMR-1 gene product associated with fragile X syndrome. Nature 1993;363(6431):722-724.
10. Devys D, Lutz Y, Rouyer N, Bellocq JP, Mandel JL. The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutation. Nat Genet 1993;4(4):335-340.
11. Bonthron D, Strain L. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):769-770.
12. Bundey S, Norman E. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):770.
13. Howard-Peebles PN, Maddalena A, Black SH, Schulman JD. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):770.
14. Palomaki GE, Haddow JE. Is it time for population-based prenatal screening for fragile-X? [letter]. Lancet 1993;341(8841):373-374.
15. Howard-Peebles PN, Maddalena A, Spence WC, Levinson G, Fallon L, Bick DP, Black SH, Schulman JD. Fragile X screening: what is the real issue? [letter]. Am J Med Genet 1994;53(4):382.
16. Palomaki GE. Population based prenatal screening for the fragile X syndrome. J Med Screen 1994;1(1):65-72.
17. Park V, Howard-Peebles PN, Sherman S, Taylor A, Wulfsberg E. Policy statement: American College of Medical Genetics. Fragile X syndrome: diagnostic and carrier testing. Am J Med Genet 1994;53:380-381.

18. Anonymous. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. Am J Hum Genet 1995;57(5):1233-1241.
19. Chapple JC. Genetic screening. In: Brock DJH, Rodeck CH, Ferguson-Smith MA, eds. Prenatal diagnosis and screening. London: Churchill Livingstone, 1992:579-593.
20. Health Council of The Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994; no. 1994/22E.
21. Wildhagen MF, Hilderink HBM, Verzijl JG, Verheij JBGM, Kooij L, Tijmstra T, ten Kate LP, Habbema JDF. Costs, effects, and savings of screening for cystic fibrosis gene carriers. J Epidemiol Community Health 1998;52:459-467.
22. Fisch GS, Nelson DL, Snow K, Thibodeau SN, Chalifoux M, Holden JJA. Reliability of diagnostic assessment of normal and premutation status in the fragile X syndrome using DNA testing. Am J Med Genet 1994;51(4):339-345.
23. Ryynänen M, Kirkinen P, Mannermaa A, Saarikoski S. Carrier diagnosis of the fragile X syndrome--a challenge in antenatal clinics. Am J Obstet Gynecol 1995;172(4 Pt 1):1236-1239.
24. Watson EK, Mayall E, Chapple J, Dalziel M, Harrington K, Williams C, Williamson R. Screening for carriers of cystic fibrosis through primary health care services. BMJ 1991;303(6801):504-507.
25. Flinter FA, Silver A, Mathew CG, Bobrow M. Population screening for cystic fibrosis [letter]. Lancet 1992;339(8808):1539-1540.
26. Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, Marteau T. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? BMJ 1993;306(6892):1584-1586.
27. Bianco I, Graziani B, Lerone M, Congedo P, Aliquo' MC, Ponzini D, Braconi F, Foglietta E, Modiano G. Prevention of thalassaemia major in Latium (Italy) [letter]. Lancet 1985;2(8460):888-889.
28. Zeesman S, Clow CL, Cartier L, Scriver CR. A private view of heterozygosity: eight-year follow-up study on carriers of the Tay-Sachs gene detected by high school screening in Montreal. Am J Med Genet 1984;18(4):769-778.
29. Holtzman NA. Genetic screening: for better or for worse. Pediatrics 1977;59(1):131-133.

30. Statistics Netherlands. Maandstatistiek bevolking 97/11. [Monthly bulletin of population statistics 97/11]. Voorburg/Heerlen: Statistics Netherlands, 1997; no. 97/11.
31. Hille E, de Kroon M. Epidemiologie van infertiliteit [Epidemiology of infertility]. iMTA/iMGZ, Erasmus University Rotterdam, 1992; no. 92.15.
32. Bonsel GJ, Maas PJ, van der. At the cradle of the future. Health scenarios concerning human reproduction 1995-2010. Summary of the Dutch STG report "Aan de wieg van de toekomst". Zoetermeer, The Netherlands: Foundation for Future Health Scenarios, 1996.
33. Statistics Netherlands. Maandstatistiek bevolking 96/12 [Monthly bulletin of population statistics 96/12]. Voorburg/Heerlen: Statistics Netherlands, 1996; no. 96/12.
34. Ryynänen M, Pulkkinen L, Kirkinen P, Saarikoski S. Fragile-X syndrome in east Finland: molecular approach to genetic and prenatal diagnosis. Am J Med Genet 1994;51(4):463-465.
35. Curtis G, Dennis N, MacPherson J. The impact of genetic counselling on females in fragile X families. J Med Genet 1994;31(12):950-952.
36. Brown WT, Houck Jr. GE, Jeziorowska A, Levinson FN, Ding X, Dobkin C, Zhong N, Henderson J, Brooks SS, Jenkins EC. Rapid fragile X carrier screening and prenatal diagnosis using a nonradioactive PCR test. JAMA 1993;270(13):1569-1575.
37. Jaarverslagcommissie Werkgroep Prenatale Diagnostiek. Jaarverslag 1990 [Annual report 1990]. Utrecht: Werkgroep Prenatale Diagnostiek van de Nederlandse Vereniging voor Obstetrie en Gynaecologie en de Vereniging Klinische Genetica Nederland, 1993.
38. Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. Am J Med Genet 1996;64(1):196-197.
39. De Vries BBA, van den Ouweland AMW, Mohkaming S, Duivenvoorden HJ, Mol E, Gelsema K, van Rijn M, Halley DJJ, Sandkuijl LA, Oostra BA, Tibben A, Niermeijer MF. Screening and diagnosis for the fragile X syndrome among the mentally retarded: an epidemiological and psychological survey. Collaborative Fragile X Study Group. Am J Hum Genet 1997;61(3):660-667.
40. Rousseau F, Rouillard P, Morel ML, Khandjian EW, Morgan K. Prevalence of carriers of premutation-size alleles of the FMRI gene--and implications for the population genetics of the fragile X syndrome. Am J Hum Genet 1995;57(5):1006-1018.

41. Sherman SL. The high prevalence of fragile X premutation carrier females: is this frequency unique to the French Canadian population? [editorial]. Am J Hum Genet 1995;57(5):991-993.
42. Fisch GS, Snow K, Thibodeau SN, Chalifaux M, Holden JJ, Nelson DL, Howard-Peebles PN, Maddalena A. The fragile X premutation in carriers and its effect on mutation size in offspring. Am J Hum Genet 1995;56(5):1147-1155.
43. UNSCEAR. Genetic and somatic effects of ionizing radiation. A report of the United Nations Scientific Committee of the Effects of Atomic Radiation. New York: United Nations, 1986.
44. Hook EB, Topol BB, Cross PK. The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis which are not terminated electively: new data and estimates of the excess and relative risk of late fetal death associated with 47,+21 and some other abnormal karyotypes. Am J Hum Genet 1989;45(6):855-861.
45. Schwartz CE, Dean J, Howard-Peebles PN, Bugge M, Mikkelsen M, Tommerup N, Hull C, Hagerman R, Holden JJA, Stevenson RE. Obstetrical and gynecological complications in fragile X carriers: a multicenter study. Am J Med Genet 1994;51(4):400-402.
46. Anonymous. CDC publishes report on chorionic villus sampling and amniocentesis. Am Fam Physician 1995;52(4):1210.
47. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313(7052):275-283.
48. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276(14):1172-1177.
49. Drummond MF, Stoddard GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, 1987.
50. Van der Maas PJ, van Ineveld BM, van Oortmarssen GJ, de Koning HJ, Lubbe JTN, Habbema JDF, Birnie E, Geerts AT, de Bruyn AE, Collette HJA, Rombach JJ, Verbeek ALM, Straatman H, Hendriks JHCL, van den Heuvel WJA. The costs and effects of mass screening for breast cancer. Rotterdam: Department of Public Health and Social Medicine, 1988.

51. Rutten FFH, van Ineveld BM, van Ommen R, van Hout BA, Huijsman R. Kostenberekening bij gezondheidszorgonderzoek; richtlijnen voor de praktijk [Cost calculation in health care research; guidelines for practice]. Instituut voor Medische Technology Assessment, 1993.
52. Centraal Orgaan Tarieven Gezondheidszorg (COTG). Tarieven medisch specialistische hulp [Tariffs medical specialist care]. 1995.
53. Centraal Orgaan Tarieven Gezondheidszorg (COTG). Vademecum tarieven gezondheidszorg [Vademecum tariffs health care]. Utrecht: 1995.
54. Centraal Administratiekantoor AWBZ. Jaarverslag 1994 en additionele tabellen [Annual report 1994 and additional tables]. Den Haag: 1995.
55. Nationaal Ziekenhuis Instituut (NZI). Landelijke registratie zorg- en dienstverlening aan mensen met een verstandelijke handicap, landelijke tabellen 1993 [National registration care of and services to people with mental handicap, national tables 1993]. Utrecht: Nederlandse Vereniging voor Gehandicaptenzorg, 1995.
56. Fiadt-Wdt. Gebruikers geïnventariseerd, 1990-1993 [Inventarisation of users, 1990-1993]. Utrecht: 1995.
57. Turner G, Robinson H, Laing S, Purvis-Smith S. Preventive screening for the fragile X syndrome. N Engl J Med 1986;315(10):607-609.
58. Baird PA, Sadovnick AD. Life tables for Down syndrome. Hum Genet 1989;82(3):291-292.
59. Brown WT, Nolin S, Houck Jr. G, Ding X, Glicksman A, Li SY, Stark-Houck S, Brophy P, Duncan C, Dobkin C, Jenkins E. Prenatal diagnosis and carrier screening for fragile X by PCR. Am J Med Genet 1996;64(1):191-195.
60. Eichler EE, Holden JJA, Popovich BW, Reiss AL, Snow K, Thibodeau SN, Richards CS, Ward PA, Nelson DL. Length of uninterrupted CGG repeats determines instability in the FMR1 gene. Nat Genet 1994;8(1):88-94.
61. Zhong N, Yang WH. Evidence that fragile X gene (FMR-1) instability occurs within the 3' end of the triplet repeat region. Am J Hum Genet 1994;55(3):A 1474.
62. Malmgren H, Steén-Bondeson ML, Gustavson KH, Seémanova E, Holmgren G, Oberlé I, Mandel JL, Pettersson U, Dahl N. Methylation and mutation patterns in the fragile X syndrome. Am J Med Genet 1992;43(1-2):268-278.

63. McConkie-Rosell A, Lachiewicz AM, Spiridigliozzi GA, Tarleton J, Schoenwald S, Phelan MC, Goonewardena P, Ding X, Brown WT. Evidence that methylation of the FMR-I locus is responsible for variable phenotypic expression of the fragile X syndrome. Am J Hum Genet 1993;53(4):800-809.
64. Moore DY. Diagnosing fragile X syndrome. Lancet 1993;342(8886-8887):1563-1564.
65. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276(15):1253-1258.

Chapter 8
The efficacy of cascade testing for fragile X syndrome

8.1 Introduction

The cloning of the FMR1 gene and the knowledge of the inheritance pattern of the fragile X syndrome (1-4) have made testing programmes for fragile X carriership a possibility (5-12). One of these testing strategies identifies (index) cases from a high-risk population – e.g. special schools or institutions for mentally handicapped persons – and offers fragile X carrier testing to relatives of the persons (13-18). Some authors use the term 'screening' for this strategy, but we prefer to call this cascade testing, as screening is generally thought to be offered to a more general target population (19, 20). The term cascade testing was first proposed by Super et al. (21) to describe a procedure for testing the extended members of families where the proband had cystic fibrosis. Although family testing was already being carried out, their suggestion was that cascade testing should be pro-active.

Because of the genetic nature and because the probability of new mutations in the FMR1 gene is (close to) zero, cascade testing in fragile X syndrome families might seem the obvious way to detect fragile X carriers. However, some authors consider cascade testing not effective as it requires extensive family tracing, testing, and counselling (10). Moreover, since the fragile X syndrome family is identified by an index case with fragile X syndrome, individuals only have reproductive options for potential future children.

This paper quantifies, using a simulation model, the (hypothetical) detection rate of fragile X syndrome patients for three levels of cascade testing: testing only first-degree relatives, testing relatives up to the third degree, and testing relatives up to the fifth degree.

8.2 Materials and methods

We developed a micro simulation model for cascade testing using Borland Delphi version 3.02. With this model we simulate a number of pedigrees of five generations in order to obtain a population where some nuclear families are (closely) connected

with others and some are not. In this way we analyse how many carriers would be detected by cascade testing in the optimal case.
When starting a cascade testing programme, patients of all generations are used as an index case. After all these families with index cases have been tested in this 'start-up phase', only newly diagnosed fragile X syndrome persons are used as index case (the stabilised 'long-term phase'). Since we are primarily interested in the long-term performance of a cascade testing programme we presume first that only patients of the current generation are used as index case. After that, we describe the start-up phase and determine the number of generations to be tested in order to detect a given percentage of carriers.

8.2.1 Simulation of a pedigree

The model starts by generating a first-generation couple. Using a random number generator, both partners of this couple are assigned a carrier status using the prevalences of a theoretic general population (see section '8.2.3 Prevalence and transition probabilities'). Next, the number of children from this couple is determined which depends on the carrier status of both partners (see section '8.2.5 Other assumptions'). For each of these children, two random numbers are generated to determine sex and carrier status (see '8.2.3 Prevalence and transition probabilities'), and a partner of this child is simulated (see '8.2.4 Carrier status of a partner'). This procedure is repeated for children of these children and so on until a five-generation pedigree is obtained.

8.2.2 Testing strategies

We analyse a (long-term) situation where cascade testing takes place in one (=current =fourth) generation (Figure 8.1). If a person in this generation is mentally retarded, his/her family is tested in three ways: 1. only parents and brothers/sisters of index cases are tested ('first-degree relatives'); 2. grandparents and cousins/nieces of index cases are also tested ('third-degree relatives'); and 3. great-grandparents and second cousins/nieces of index cases are also tested ('fifth-degree relatives'). Offspring of tested persons who are not carrier is not tested for fragile X syndrome carriership.
For all three strategies, we determine the number of families with at least one index case in the current generation and the number of families with at least one carrier but no index case in the current generation. Furthermore, we calculate the number of children with and without fragile X syndrome that will be born in both types of families in the next (fifth) generation.

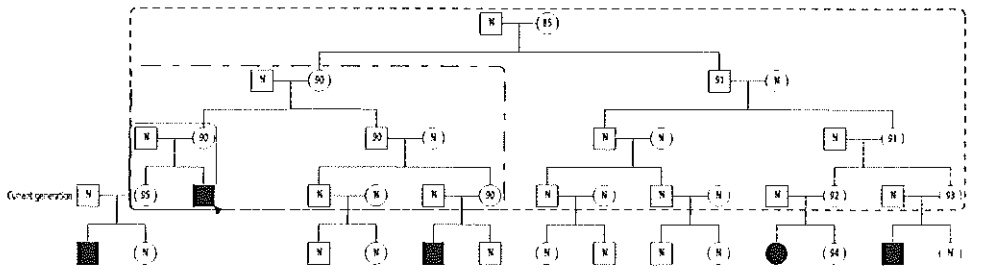
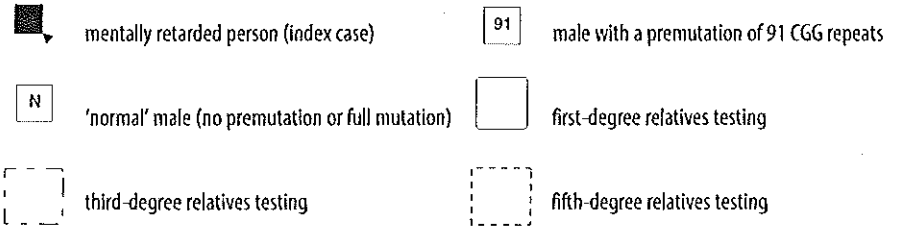


Figure 8.1 Sample pedigree. For simplicity we show two children per couple



8.2.3 Prevalence and transition probabilities

We assumed eight carrier classes: one normal class (no premutation or full mutation), two full mutation classes (with and without mental retardation) and five premutation carrier classes (CGG repeats between 55 and 59, 60-69, 70-79, 80-89 and 90-200 CGG repeats). We used 55 CGG repeats as a cut-off between normal alleles and premutation alleles (22), as no full mutation child has been identified having a mother with an allele size of less than 55 CGG repeats.

For the prevalence of these classes in the absence of disturbances because of screening (Table 8.1), we constructed a theoretical population genetics model analogous to that of Kolehmainen (23) and determined the equilibrium frequencies of the classes using the following assumptions: 1. the prevalence of both males and females with a full mutation is 1:4,000 (24); 2. a normal allele can not mutate directly to a full mutation; 3. the probability of a back-mutation from premutation- or full mutation-size to normal-size is zero; 4. the transition from premutation in the mother to a full mutation in the foetus is calculated with the logistic model of Fisch et al. (25); 5. the transition probability from premutation in the father to a full mutation in the daughter is zero; 6. transition probabilities from a premutation mother/father to

Table 8.1 Prevalence of fragile X syndrome premutations and full mutations per 100,000 in the general (theoretical) population

	Female	Male
Normal	49,923	49,958
Premutation	65	29
of which 55-59 repeats	39	19
of which 60-69 repeats	7	3
of which 70-79 repeats	6	3
of which 80-89 repeats	3	1
of which 90-200 repeats	10	3
Full mutation	12	13
of which no mental retardation	5	0
of which mental retardation	7	13
Total	50,000	50,000

premutation child are given by Fu et al. (1) and Yu et al. (26); the transition probability from mother to child does not depend on the sex of the child (Table 8.2); 7. all boys and 59% of the girls with a full mutation have mental retardation (17); 8. the reproductive fitness of women with a full mutation and mental retardation is 0.12 (27); 9. fathers with a full mutation and mental retardation do not reproduce.

A cascade testing programme obviously reduces the prevalence of premutations and full mutations in the population, since detected carriers can decide to refrain from production or to have prenatal diagnosis and induced abortion of a fragile X foetus. The extent of this reduction is unknown. We will assume in our calculations no reduction of the prevalences. This assumption will lead to an upper limit on the detection rate of fragile X syndrome carriers.

8.2.4 Carrier status of a partner

Individuals in the simulated pedigrees can be assumed to have a partner who is not part of the same pedigree. Furthermore, it can be assumed that this partner is not part of a family that is already identified as being a fragile X syndrome family, as he/she will then belong to another simulated pedigree. Therefore, the carrier prevalences of these partners are not the same as the general population prevalences. For this reason, we determined in the first run of our simulation the carrier prevalences of individuals who are not in a known fragile X syndrome family, and used this distribution of prevalences for partners of individuals in the simulated pedigrees.

Table 8.2 Transition probabilities of the alleles from mother to child and father to daughter

Mother	Child Normal	55-59	60-69	70-79	80-89	90-200	Full mutation
Normal	1.00*	0.00*	0	0	0	0	0
CGG 55-59	0	0.65	0.13	0.13	0	0.00	0.09
CGG 60-69	0	0	0.06	0.15	0.32	0.27	0.20
CGG 70-79	0	0	0.14	0	0	0.42	0.44
CGG 80-89	0	0	0	0	0.05	0.24	0.71
CGG 90-200	0	0	0	0	0	0.05	0.95
Full mutation	0	0	0	0	0	0	1.00

Father	Daughter Normal	55-59	60-69	70-79	80-89	90-200	Full mutation
Normal	1.00*	0.00*	0	0	0	0	0
CGG 55-59	0	0.72	0.14	0.14	0	0	0
CGG 60-69	0	0	0.07	0.19	0.41	0.33	0
CGG 70-79	0	0	0.24	0	0	0.76	0
CGG 80-89	0	0	0	0	0.18	0.82	0
CGG 90-200	0	0	0	0	0	1.00	0
Full mutation	0	0	0	0	0	1.00	0

* parameter values determined by the model. Rounded to four decimals the figures are 0.9999 and 0.0001, respectively

8.2.5 Other assumptions

Because the average number of children per couple has declined over the last decades, we presume that first- and second-generation couples where both partners are not mentally retarded have four children, that those of the third generation have three children and that those of the fourth generation have two children. Thus, the number of couples in the pedigrees increase over the five generations from 1 to 4 to 16 to 48 to 96. Couples where the male is mentally retarded do not have any children and couples where the female is mentally retarded have 0.12 times the baseline number on average since the reproductive fitness of those women is 0.12 (27). Furthermore, we assumed that all persons will have a partner, that there is no competing mortality (i.e. mortality before or during reproductive life), that all index patients will be diagnosed at or shortly after birth, and that test information of all individuals is available (best-case scenario).

8.3 Results

We sampled 100,000 pedigrees in which there were 723 persons with fragile X syndrome in the current generation who can serve as index case and 3,086 carriers

who are at risk to conceive children with fragile X syndrome. As a check of the predictions of our simulation model, we compared the prevalences in the fifth generation predicted by our simulation model with those of the general (theoretical) population denoted in Table 8.1 and concluded that the figures are rather similar. We will first describe the three long-term testing strategies, where we assume that there has been no start-up phase for cascade testing. After that, we describe the start-up phase of cascade testing. Only families that are not known from the start-up phase as fragile X syndrome family need to be tested in the long-term strategies. Although the absolute numbers will change when taking into account this start-up phase, the relative percentages will not change.

8.3.1 First-degree testing

When testing only relatives up to the first degree, the 723 persons with fragile X syndrome in the current generation appear to belong to 548 different nuclear families (Table 8.3). In 2,131 other nuclear families there are no persons with fragile X syndrome in the current generation, but there is at least one (female) carrier who is at risk of conceiving next-generation children with fragile X syndrome. In the remaining 1.6 million nuclear families (16 x 100,000) there are no carriers or persons with fragile X syndrome, these families are not at risk of conceiving next-generation children with fragile X syndrome.

In the 548 nuclear families with a fragile X syndrome person, 66 (current generation) couples will have one (next-generation) child with fragile X syndrome, and 22 couples will have two. These 88 couples can, in principle, be detected with cascade testing before they conceive children, which means that they will have a reproductive choice with cascade testing. In the families where there are no fragile X syndrome patients

Table 8.3 Results for first-degree testing

	Current-generation couples in these families will have ... next-generation Frax children				
	1 FraX child	2 FraX children	No FraX children	Total	%
Families in the current generation with:					
- at least one index case	66	22	460	548	0.03%
- at least one carrier but no index case	1,021	191	919	2,131	0.13%
- no index case or carrier	-*	-*	1,596,387	1,596,387	99.83%
Total number of families	1,087	213	1,597,766	1,599,066	100%
%	0.07%	0.01%	99.92%	100%	

* non-carriers can not conceive children with fragile X syndrome

but at least one carrier in the current generation, 1,021 couples will have a (next-generation) child with fragile X syndrome, and 191 couples will have two affected children. These 1,212 couples can not be detected by cascade testing, as there are no current-generation index cases with fragile X syndrome.
Summarising, 88 current-generation couples (=7%) who will have at least one child with fragile X syndrome in the next generation can have an informed choice with first-degree cascade testing and 1,212 (=93%) will not have an informed choice. If all the recognised couples at risk would have prenatal diagnosis and induced abortion of a fragile X syndrome foetus, 110 patients (=7% of all fragile X syndrome patients) will not be born due to cascade testing.

8.3.2 Third-degree testing

When testing relatives up to the third degree, the 723 fragile X syndrome patients appear to belong to 483 extended families (Table 8.4). In 1,817 other families, there are no fragile X syndrome patients but there is at least one female carrier.
In the 483 extended families with a fragile X syndrome patient, 122 current-generation couples will have one next-generation child with fragile X syndrome, and 36 couples will have two fragile X syndrome children; these 158 couples can be detected with third-degree testing. In the 1,817 families with at least one carrier and no index case, 965 current-generation couples will have one child with fragile X syndrome, and 177 couples will have two.
This means that 158 couples (=12%) who will have at least one child with fragile X syndrome can have an informed choice with third-degree cascade testing, and 1,142 couples (88%) will not have this advantage. If again all recognised couples at risk would choose prenatal diagnosis and induced abortion, 194 (=13% of all) fragile X syndrome children will not be born.

Table 8.4 Results for third-degree testing

	Current-generation couples in these families will have ... next-generation FraX children				
	1 FraX child	2 FraX children	No FraX children	Total	%
Families in the current generation with:					
- at least one index case	122	36	325	483	0.12%
- at least one carrier but no index case	965	177	675	1,817	0.45%
- no index case or carrier	-*	-*	397,519	397,519	99.42%
Total number of families	1,087	213	398,519	399,819	100%
%	0.27%	0.05%	99.67%	100%	

* non-carriers can not conceive children with fragile X syndrome

8.3.3 Fifth-degree testing

Per definition, fifth-degree cascade testing will lead to the lowest number of (extended) families with at least one index case (461 families) and with at least one carrier without an index case (1,725 families) in the current generation, but these families are much larger (Table 8.5). In the families with an index case, 200 current-generation couples (=15%) will have at least one child with fragile X syndrome, while 1,100 couples (=85%) in the families with a carrier but no index case will have at least one fragile X syndrome child. This means that 244 (=16%) children with fragile X syndrome will not be born if all detected foetuses were aborted.

8.3.4 The start-up phase

In the start-up phase of a cascade testing programme, people of all generations are used as possible index cases. This scenario results in 576 extended families with index cases, and in these detected fragile X syndrome families 179 current-generation couples will have one fragile X syndrome child and 50 couples will have two (Table 8.6). In the 1,818 carrier families without an index case, 908 couples will not have an informed choice for one fragile X syndrome child and 163 for two. Consequently, 229 (18%) couples who will have at least one fragile X syndrome child will have an informed reproductive choice, and 1,071 couples (82%) will not have this choice, and 279 fragile X syndrome patients (18%) will not be born.

These figures are not dramatically different from those of fifth-degree testing. The reason for this is that fragile X syndrome males do not reproduce, and that fragile X syndrome females do reproduce less. Therefore, only a small percentage of fragile X syndrome children is born from fragile X syndrome parents. Because of this most parents of a fragile X syndrome child turn out to be a premutation carrier, so that the

Table 8.5 Results for fifth-degree testing

	Current-generation couples in these families will have ... next-generation FraX children				
	1 FraX child	2 FraX children	No FraX children	Total	%
Families in the current generation with:					
- at least one index case	156	44	261	461	0.46%
- at least one carrier but no index case	931	169	625	1,725	1.73%
- no index case or carrier	-*	-*	97,814	97,814	97.81%
Total number of families	1,087	213	98,700	100,000	100%
%	1.09%	0.21%	98.70%	100%	

* non-carriers can not conceive children with fragile X syndrome

Table 8.6 Results for the start-up phase

	Current-generation couples in these families will have ... next-generation FraX children				
	1 FraX child	2 FraX children	No FraX children	Total	%
Families in the current generation with:					
- at least one index case	179	50	347	576	0.58%
- at least one carrier but no index case	908	163	747	1,818	1.82%
- no index case or carrier	-*	-*	97,606	97,606	97.61%
Total number of families	1,087	213	98,700	100,000	100%
%	1.09%	0.21%	98.70%	100%	

* non-carriers can not conceive children with fragile X syndrome

probability for brothers/sisters of the index case of having fragile X syndrome is less than 50%.

8.3.5 Number of generations to be tested

Cascade testing will detect a large proportion of carriers with large premutations, but will detect only a small proportion of small premutations. For example, only 20.9% of the carriers with 60-69 CGG repeats will be detected in the start-up phase, and can thus be followed-up. Using the fifth-degree testing strategy, only 20.3% of the carriers with 60-69 CGG repeats who are not detected in the start-up phase will be detected so that 36.9% of the carriers with 60-69 CGG repeats are known after the combined effort. In the next testing round, again 20.3% of the remaining 63.1% will be detected, which means that 49.7% of these carriers are detected when following the start-up phase two generations are tested. The same calculations can be done for other premutation categories and for full mutations. Taking into account the relative prevalences of the premutations and full mutations, a weighted average of the carriers detected can be calculated (Figure 8.2). In this way, we predict that testing only the current generation with fifth-degree relatives testing, including the start-up phase, detects 48.1% of all carriers, testing two generations detects 59.8% and three generations 68.5%. This would mean that, in order to detect 90% of all premutation and full mutation carriers, one would have to keep on testing for at least eight generations. This can be seen as another measure for the performance of a cascade testing programme.

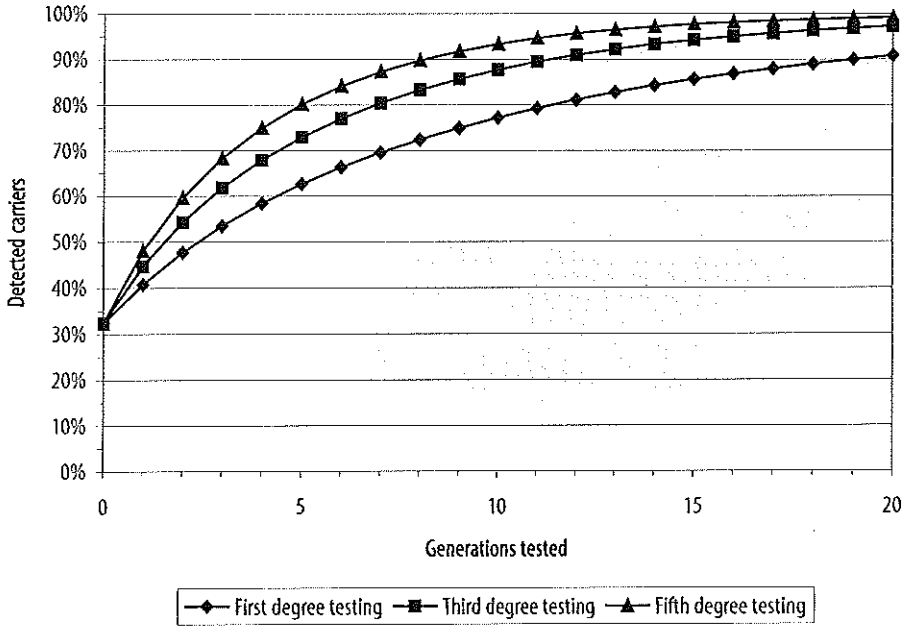


Figure 8.2 Percentage of carriers detected by number of generations tested

8.4 Discussion

Cascade testing is not very effective in detecting couples who will have a fragile X syndrome child in the future. For example, if only first-degree relatives are tested, 7% of the couples who will have a child with fragile X syndrome are detected through an index case and thus have a reproductive choice, while 93% of the couples are not detected and do not have this choice. Probably the maximally feasible testing scenario in practice is fifth-degree testing, although even this scenario will be difficult to complete as in today's society many families have lost touch with distant relatives so that a lot of work is needed to construct the pedigrees. In the ideal situation that in this scenario all persons agree to be tested, only 15% of all couples who will have a child with fragile X syndrome are detected. This means that still 85% of all couples bound to have a fragile X syndrome child do not have a reproductive choice. Compared to the results obtained by Holloway and Brock (28), cascade testing for fragile X syndrome up to the second cousin level is somewhat less effective than

cascade testing for cystic fibrosis where up to 24% of all carrier couples would be detected if cascade testing were restricted to up to the second cousin level (28). This higher effectiveness of cystic fibrosis cascade testing is caused by the higher prevalence of the cystic fibrosis gene and because of the different inheritance patterns of both diseases.

Testing seventh-degree relatives will improve the percentage of couples detected slightly. On the other hand, it will usually not be possible to obtain samples from great-great-grandparents because most of them will be deceased. Because of this, offspring of non-carrier great-great-grandparents is also tested which makes the programme less effective.

The main reason for the rather ineffectiveness in detecting carrier couples is the inheritance of fragile X syndrome. Brothers and sisters of an index case only have a 50% chance of also having inherited the premutation or full mutation, while cousins and nieces of the index case only have a 25% probability of having inherited the premutation or full mutation. Furthermore, if a premutation is passed on, it does not always expand to a full mutation, and only 59% of all females with a full mutation have fragile X syndrome (17).

We assumed that patients with fragile X syndrome do not reproduce or reproduce less than other people. There are however no physiologic reasons known for this. Therefore we also analysed a situation in which fragile X syndrome patients have the same number of children as individuals without fragile X syndrome. In this situation, the percentage of detected families bound to have a fragile X syndrome child increases from 7% to 19% for first-degree testing and from 15% to 31% for fifth-degree testing. For the start-up phase, the detection rate increases from 18% to 35%.

The effectiveness of cascade testing obviously depends on the number of children per couple. Therefore, we also analysed the performance of cascade testing if all people would have five children. In this scenario, the percentages of fragile X syndrome families and premutation families rise only slightly, and the percentage of detected families who will have a fifth-generation fragile X syndrome child rises for all three testing strategies. For example, 20.0% of the families who will have at least one fragile X syndrome child would be detected in the ideal fifth-degree testing scenario, while this percentage is 15.4% in the baseline scenario. In order to detect at least 90% of all premutation and full mutation carriers, only six generations have to be tested in this scenario, as opposed to eight generations in the baseline analysis.

A well-known efficiency measure is the number of tested individuals per case detected ('number needed to test'). Using a rough calculation we estimated that with our assumptions a maximum of approximately 130 individuals in the start-up phase need to be tested to detect one couple who will have a fragile X syndrome child, if all eligible individuals participate in the cascade testing. For general population screening this figure will increase to approximately 5,000 couples that have to be tested; thus cascade testing needs approximately a factor 35-40 times fewer tests to detect one carrier couple who will have a fragile X syndrome child than general population screening. Of course, it is much more difficult to identify couples that need to be screened in cascade testing than in general population screening, and relatives may refuse to be tested which will make cascade testing less efficient. However, even if these factors would have been taken into account, cascade testing will remain much more efficient than general population testing.

Therefore, although general population screening is more effective in giving the highest number of carrier couples an informed choice concerning reproduction, cascade testing has a better efficiency and has the advantage that the detected carrier couples have in general better knowledge of the fragile X syndrome because they usually know the index case who has the syndrome. As economical factors may never be the primary factor in deciding whether or not to introduce genetic screening or testing, maybe the decision whether to perform general population screening or cascade testing should depend on whether one considers it more preferable to give the informed choice to a large number of carriers by general population screening versus giving the choice to a smaller number of carriers who are already involved in the disease anyhow by cascade testing.

8.5 References

1. Fu YH, Kuhl DPA, Pizzuti A, Pieretti M, Sutcliffe JS, Richards S, Verkerk AJMH, Holden JJA, Fenwick Jr. RG, Warren ST, Oostra BA, Nelson DL, Caskey CT. Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. Cell 1991;67(6):1047-1058.
2. Oberlé I, Rousseau F, Heitz D, Kretz C, Devys D, Hanauer A, Boué J, Bertheas MF, Mandel JL. Instability of a 550-base pair DNA segment and abnormal methylation in fragile X syndrome. Science 1991;252(5010):1097-1102.

3. Verkerk AJMH, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DPA, Pizzuti A, Reiner O, Richards S, Victoria MF, Zhang FP, Eussen BE, van Ommen GB, Blonden LAJ, Riggins GK, Chastain JL, Kunst CB, Galjaard H, Caskey CT, Nelson DL, Oostra BA, Warren ST. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 1991;65(5):905-914.
4. Yu S, Pritchard M, Kremer E, Lynch M, Nancarrow J, Baker E, Holman K, Mulley JC, Warren ST, Schlessinger D, Sutherland GR, Richards RI. Fragile X genotype characterized by an unstable region of DNA. Science 1991;252(5010):1179-1181.
5. Bonthron D, Strain L. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):769-770.
6. Bundey S, Norman E. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):770.
7. Howard-Peebles PN, Maddalena A, Black SH, Schulman JD. Population screening for fragile-X syndrome [letter]. Lancet 1993;341(8847):770.
8. Palomaki GE, Haddow JE. Is it time for population-based prenatal screening for fragile-X? [letter]. Lancet 1993;341(8841):373-374.
9. Howard-Peebles PN, Maddalena A, Spence WC, Levinson G, Fallon L, Bick DP, Black SH, Schulman JD. Fragile X screening: what is the real issue? [letter]. Am J Med Genet 1994;53(4):382.
10. Palomaki GE. Population based prenatal screening for the fragile X syndrome. J Med Screen 1994;1(1):65-72.
11. Park V, Howard-Peebles PN, Sherman S, Taylor A, Wulfsberg E. Policy statement: American College of Medical Genetics. Fragile X syndrome: diagnostic and carrier testing. Am J Med Genet 1994;53:380-381.
12. Anonymous. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. Am J Hum Genet 1995;57(5):1233-1241.
13. Webb TP, Bundey SE, Thake AI, Todd J. Population incidence and segregation ratios in the Martin-Bell syndrome. Am J Med Genet 1986;23(1-2):573-580.
14. Nolin SL, Snider DA, Jenkins EC, Brown WT, Krawczun M, Stetka D, Houck Jr. G, Dobkin CS, Strong G, Smith-Dobransky G, Victor A, Hughes K, Kimpton D, Little A, Nagaraja U, Kenefick B, Sullivan C. Fragile X screening program in New York State. Am J Med Genet 1991;38(2-3):251-255.

15. Smits APT, van Oost BA, de Haan AFJ, Hamel BCJ, Dreesen JCFM, Smeets DFCM. Penetrance of fra(X) gene: influence of grandparental origin of the gene, mental status of the carrier mother, and presence of a normal transmitting male. Am J Med Genet 1992;43(1-2):365-372.
16. Turner G, Robinson H, Laing S, van den Berk M, Colley A, Goddard A, Sherman S, Partington M. Population screening for fragile X. Lancet 1992;339(8803):1210-1213.
17. Rousseau F, Heitz D, Tarleton J, MacPherson J, Malmgren H, Dahl N, Barnicoat A, Mathew C, Mornet E, Tejada I, Maddalena A, Spiegel R, Schinzel A, Marcos JAG, Schorderet DF, Schaap T, Maccioni L, Russo S, Jacobs PA, Schwartz C, Mandel JL. A multicenter study on genotype-phenotype correlations in the fragile X syndrome, using direct diagnosis with probe StB12.3: the first 2,253 cases. Am J Hum Genet 1994;55(2):225-237.
18. De Vries BBA, Wiegers AM, Smits APT, Mohkamsing S, Duivenvoorden HJ, Fryns JP, Curfs LMG, Halley DJJ, Oostra BA, van den Ouweland AMW, Niermeijer MF. Mental status of females with an FMR1 gene full mutation. Am J Hum Genet 1996;58(5):1025-1032.
19. US Congress Office of Technology Assessment. Cystic Fibrosis and DNA tests: implications of carrier screening. Washington, DC: U.S. Government Printing Office, 1992.
20. Health Council of The Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994; no. 1994/22E.
21. Super M, Schwarz MJ, Malone G. Screening for cystic fibrosis carriers [letter]. Lancet 1992;340(8817):490-491.
22. Fisch GS, Nelson DL, Snow K, Thibodeau SN, Chalifoux M, Holden JJA. Reliability of diagnostic assessment of normal and premutation status in the fragile X syndrome using DNA testing. Am J Med Genet 1994;51(4):339-345.
23. Kolehmainen K. Population genetics of fragile X: a multiple allele model with variable risk of CGG repeat expansion. Am J Med Genet 1994;51(4):428-435.
24. Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. Am J Med Genet 1996;64(1):196-197.
25. Fisch GS, Snow K, Thibodeau SN, Chalifaux M, Holden JJ, Nelson DL, Howard-Peebles PN, Maddalena A. The fragile X premutation in carriers and its effect on mutation size in offspring. Am J Hum Genet 1995;56(5):1147-1155.

26. Yu S, Mulley J, Loesch D, Turner G, Donnelly A, Gedeon A, Hillen D, Kremer E, Lynch M, Pritchard M, Sutherland GR, Richards RI. Fragile-X syndrome: unique genetics of the heritable unstable element. Am J Hum Genet 1992;50(5):968-980.
27. Sherman SL, Morton NE, Jacobs PA, Turner G. The marker (X) syndrome: a cytogenetic and genetic analysis. Ann Hum Genet 1984;48(Pt 1):21-37.
28. Holloway S, Brock DJH. Cascade testing for the identification of carriers of cystic fibrosis. J Med Screen 1994;1(3):159-164.

Part 4

Concluding remarks

Chapter 9
Combining genetic screening programmes - the example of cystic fibrosis and fragile X syndrome screening

9.1 Introduction

Population based screening programmes have been proposed for several genetic diseases (1, 2). For some diseases, screening programmes have already been introduced in many countries, e.g. screening for Down syndrome and neural tube defects in pregnancy, and Tay-Sachs carrier screening in Ashkenazi Jews. For other diseases, possible introduction of screening programmes is being contemplated, e.g. for cystic fibrosis, fragile X syndrome and Duchenne muscular dystrophy. A discussion is taking place whether some of these separate screening programmes could better be combined in one single screening programme in which a panel of tests is performed (combined screening, or multiplex screening) (3-6).

Combined screening is already taking place in medical care. For example, neonates are screened for both PKU and CHT, and screening for open neural tube defects (NTDs) by assessing serum alpha-foetoprotein has been extended to a screening programme for NTDs and Down syndrome by including serum human chorionic gonadotropin and serum unconjugated oestriol, taking also maternal age into consideration. Also, as a 'side effect' of some screening programmes, some disorders will be detected which are not the primary aim of the screening programme. For example, Becker muscular dystrophy is detected when searching for Duchenne muscular dystrophy. However, since these disorders are not the direct aim, we will not call this combined screening.

The main advantage of combined screening programmes is that the couple or individual is confronted with only one screening offer instead of several, and that they can therefore be informed in one counselling session. Because there is some information to be given in common, the duration (and thus the costs) of the pre-test counselling session will be shorter than the combined length of the separate counselling sessions. Furthermore, combining screening programmes leads to lower

total costs because of efficiency effects in e.g. organisation, information, and the time and travel costs spent by the couple ('indirect costs').
In previous articles, we have described cost-effectiveness analyses of separate screening programmes for cystic fibrosis carriers and for fragile X syndrome carriers (7, 8). These analyses show that there is a favourable economic balance for prenatal and preconceptional screening for carriership for these diseases, but that the economic feasibility of school carrier screening is less clear cut. If the two screening programmes would be offered and organised together, the advantages of combined screening would apply. In this article we estimate the costs, effects and savings of combined cystic fibrosis and fragile X syndrome screening programmes, in comparison to those of separate screening programmes.

9.2 Materials and methods

We developed a decision-analytic model for a combined screening programme for cystic fibrosis (CF) and fragile X syndrome (FraX) carriers. The structure of the model is similar to that of (separate) screening for CF carriers and FraX carriers (7, 8). We analysed the present situation in The Netherlands, where in the absence of maternal serum screening additional chromosome analysis is performed routinely in samples obtained for prenatal diagnosis of CF or FraX and presumed a 100% sensitivity and specificity of the prenatal diagnosis test.
In our analysis, we used the baseline assumptions of the analyses of the separate screening programmes, except for assumptions that are influenced by combining the programmes. Furthermore, as new mutation detection methods have been developed, we changed the sensitivity and costs of the screening test.

9.2.1 Screening strategies

For general population carrier screening, three strategies are considered: prenatal, preconceptional, and school screening (9-11). Since Southern blot analysis (the second step in FraX carrier screening) can not be performed on a blood spot, neonatal screening can not be considered for separate FraX or combined CF-FraX carrier screening. For the same reason mouth washes for CF carrier screening have to be replaced by blood samples.
Because CF is an autosomal recessive disease, a child with CF can only be born from a couple in which both parents are carriers. For this reason, (prenatal and preconceptional) CF screening is targeted towards couples (12-15). In FraX screening, the primary target of screening is the woman because a FraX child can only be born

from carrier mothers. Therefore, the best strategy for CF-FraX screening is to test the woman first, and if she appears to be a CF carrier, to test her partner ('single-entry two-step screening').

We assumed that the woman is tested for CF carriership with the allele-specific-oligonucleotide hybridisation method using the reverse dot blot detection format using 32 mutations (ASO) (16), which has a sensitivity of 90% and costs €45.29. If necessary, her partner is tested with a DGGE test that screens all exons of the CF-gene at once on a denaturing gradient gel by two-dimensional DNA electrophoretic separation of polymerase chain reaction amplified exons (17) which has a sensitivity of 98% and costs €178.07, excluding DNA extraction. (H. Scheffer, personal communication).

9.2.2 Assumptions equal to the separate screening programmes

In this section we summarise the basic assumptions made in the earlier separate cost-effectiveness analyses of CF screening and FraX screening and we describe the assumptions that differ from the earlier analyses (Table 9.1). As the recommended discount rate for costs has changed from 5% to 3% between the time of our analysis of CF screening and FraX screening (18), the first assumption that differs from that of the CF analysis is the discount percentage of 3%.

Table 9.1 Parameter values used in the analysis of combined screening for CF and FraX carriers. The parameter values denoted by * differ from those used in the separate analyses (7, 8)

Probabilities	
Probability of a new FraX premutation	0%
Probability of a back-mutation from FraX premutation-size to normal-size	0%
Percentage of full FraX mutation boys with mental retardation	100%
Percentage of full FraX mutation girls with mental retardation	59%
Probability of a couple being unwanted childless	10%
Probability of a couple being wanted childless	10%
Recurrence risk of chromosome abnormalities	1.5%
Iatrogenic abortion after chorionic villus sampling	0.75%
Sensitivity of ASO test	90%
Sensitivity of DGGE test	98%
No amplification of PCR	10%
1 DNA band at PCR	40%
Southern blot fails	10%

Prevalences	
CF-carrier prevalence	1:30
Females with full FraX mutation	1:4,000
Males with full FraX mutation	1:4,000
Females with FraX premutation	1:435
Males with FraX premutation	1:871
Autosomal chromosome abnormalities at birth	1:500
Sex chromosome abnormalities at birth	1:500

Costs	
DNA extraction	€7.96
PCR test for FraX	€21.27
ASO test	€45.29
DGGE test	€178.07
Southern blot	€66.68
Costs to screenee	€7.00
Counselling a FraX carrier	€101.03
Counselling a CF carrier couple	€37.19
Counselling a (+-) couple for CF	€21.22
Prenatal diagnosis	€1,270.58
Induced abortion	€221.01
Early spontaneous abortion	€69.23
Late spontaneous abortion	€444.36
Iatrogenic abortion	€69.23
Discount rate for costs	3%*

Screening-dependent parameters	Prenatal	Preconceptional	School
Target population size	100,000	100,000	100,000
Coverage of people without FraX mental retardation	75%*	50%*	50%*
Coverage of people with FraX mental retardation	37½%	25%	25%
Information retention	100%	100%	90%
Mass information costs	€393,087*	€655,145*	€524,116*
Personal information costs	€6.81*	€3.41*	€1.70*
Organisation costs	€17.23	€17.23	€17.23

Parameters depending on carrier status of the screened	Norm	FraX premutation	FraX full mutation	(++) for CF	(+-) for CF
Refrain from having children	0%	15%	15%	15%	0%
Uptake of prenatal diagnosis among pregnant women	0%	75%	75%	85%	0%

Parameters depending on carrier status of the foetus	FraX status			CF	Autosomal abnormality	Sex chromosome abnormality
	Norm or PM	FM boys	FM girls			
Early spontaneous abortion	1.95%	1.95%	1.95%	1.95%	21.21%	6.15%
Late spontaneous abortion	1.55%	1.55%	1.55%	1.55%	19.70%	2.79%
Uptake induced abortion	0%	90%	45%	80%	95%	75%
Costs of care of patient	€0	€847,472	€472,232	€382,832	€663,854	€0

Prevalence and risk

The prevalence of CF-gene carriers varies between populations; in The Netherlands it is one in thirty (19, 20). The prevalence of both males and females with a full mutation in the FraX gene has been estimated by Turner et al. as 1:4,000 (21). Rousseau et al. (22) detected 41 women with a premutation (55 CGG repeats or more) in 10,624 women, and estimated a frequency of full mutation carriers in French Canada of

42:10,000, which is 68% higher than the figure of Turner et al. (21). Because there are indications of founder effects in the French Canadian population (23), we adjusted the premutation prevalence obtained by Rousseau et al. by dividing their premutation frequency by 1.68. In this way a premutation frequency in females of 1:435 was obtained. Male premutation prevalences were taken half of those of females, and mosaics were not taken into account. For the transition from premutation in the parent to a full mutation in the foetus we used the logistic model of Fisch et al. (24). We assumed that all boys and 59% of the girls with a full mutation have mental retardation (25). New premutations and back-mutations from premutation-size to normal-size were assumed not to occur.

The prevalence at birth of serious autosomal chromosomal abnormalities and of sex chromosome abnormalities in the general population are both 1:500 (26). The recurrence risk for a chromosomal abnormality of a child, given a first child with a chromosomal abnormality, was estimated at 1.5%.

Target population and information preservation

The target populations of screening can be derived from the number of firstborn children (85,792) and the number of girls of 16 years (91,782) in The Netherlands in 1996 (if necessary corrected with a 10% probability of a couple being unwanted childless and a 10% probability of a couple being wanted childless) (27-29). For ease of interpretation, we work in our analyses with a simplified stable population of 100,000 firstborn children and 100,000 girls of 16 years. Furthermore, we assumed that in all screening strategies 84.9% of the people with a firstborn child will have a second child after 2.9 years on average (30, 31) and we ignore in our calculations births of children who are thirdborn or more. Because the time between testing and possible use of the carrier information is similar to that of the Tay-Sachs screening programme of Zeesman et al. (32), we took their ninety percent information preservation as an estimate of information preservation of school screening.

9.2.3 Assumptions specific of combined screening

Coverage in a combined screening programme needs not be the same as in separate screening programmes. On the one hand there will be some people who would not consider separate screening but will consider a combined screening. On the other hand some people who would consider e.g. separate testing for CF (which is a physical disease) will not consider combined screening that includes carrier testing for FraX (which is mainly a mental disorder). Because of this, we decided to take the

coverage equal to the coverage of FraX screening (which in our earlier analysis was lower than that of CF screening), and will consider other coverages in a sensitivity analysis.

If screening programmes are combined, efficiency effects will occur for some costs. For example, information costs will be lower than the sum of the costs of the separate screening programmes because of the overlapping information need. We therefore assumed that the mass information and individual information costs of the combined screening programme are 25% higher than those of a separate screening programme for FraX.

The DNA extraction costs for CF and FraX PCR analysis are assumed to be the same as the extraction costs for a separate FraX screening programme at €7.96. Since there exists no combined PCR for CF and FraX however, the PCR analyses for CF mutations and FraX premutations or full mutations can not be done in one pass. Therefore, there are no efficiency effects assumed in the PCR costs for a combined CF-FraX DNA analysis.

9.3 Results

In Table 9.2-Table 9.4, we give a comparison of the yearly costs, effects and savings of separate and combined screening programmes for three screening strategies. Because we assumed in the original analysis of CF screening (7) a higher coverage and discount rate and other screening tests, we have in this paper reanalysed CF screening with the new assumptions.

Since we took all assumptions except costs equal to those of the separate screening programmes, the effect measures of screening (the number of detected carriers, the number of avoided patients and healthy persons, and the number of iatrogenic abortions) in the combined screening programmes are the same as the sum of the respective numbers in the separate screening programmes.

Table 9.2 Prenatal screening: comparison of the yearly costs, effects and savings of separate and combined CF-FraX programmes

	Separate CF programme	Separate FraX programme	Sum of separate programmes*	Combined CF-FraX programme
Total costs of screening	€6,217,000	€8,219,000	€14,435,000	€9,356,000
Detected carrier couples	74	200	274	274
- CF carrier couples	74	-	74	74
- FraX carrier couples	-	200	200	200
Costs per detected carrier	€85,000	€41,000	€53,000	€34,000
Number of avoided patients	23	28	51	51
Health care savings	€8,834,00	€20,580,000	€29,414,000	€29,414,000
Net economic savings	€2,618,000	€12,361,000	€14,979,000	€20,058,000
Negative side effects				
Avoided non-diseased children (normal children, CF carrier children, FraX premutation children, girls with FraX full mutation but no mental retardation)	3	9	12	12
Iatrogenic abortions	1	2	3	3

* for the costs per detected carrier, the figure is calculated by dividing the sum of the total costs of screening by the total number of detected carriers

Because of efficiency effects, combined screening reduces total costs: while the sum of the costs of two separate prenatal screening programmes is €14.4 million, the combined programme costs 35% less with €9.4 million per year. The decrease in total costs of screening for preconceptional and school screening is similar with 32% and 33%, respectively. Since the effects of combined and separate screening are the same, the costs per detected carrier are also 35%, 32% and 33% lower than those of the separate screening programmes, respectively. The health care savings obviously do not change since the number of avoided patients is equal. Compared to the sum of the net savings (savings minus costs) of the separate screening programmes, net savings increase by 34% for prenatal screening and by 40% for preconceptional screening.

A separate school screening programme for CF carriers has €3.2 million higher costs than savings, and these are not completely offset by the €1.9 million net savings of a FraX screening programme. The savings of a combined screening programme however are €2.2 million higher than its costs, which is 12% higher than the net savings of a separate FraX screening programme. This means that there are also no economic objections against combined school carrier screening.

Table 9.3 Preconceptional screening: comparison of the yearly costs, effects and savings of separate and combined CF-FraX programmes

	Separate CF programme	Separate FraX programme	Sum of separate programmes*	Combined CF-FraX programme
Total costs of screening	€4,622,000	€6,151,000	€10,773,000	€7,272,000
Detected carrier couples	49	149	198	198
- CF carrier couples	49	-	49	49
- FraX carrier couples	-	149	149	149
Costs per detected carrier	€94,000	€41,000	€54,000	€37,000
Number of avoided patients	15	20	35	35
Health care savings	€5,482,000	€14,018,000	€19,500,000	€19,500,000
Net economic savings	€859,000	€7,868,000	€8,727,000	€12,228,000
Negative side effects				
Avoided non-diseased children (normal children, CF carrier children, FraX premutation children, girls with FraX full mutation but no mental retardation)	11	31	42	42
Iatrogenic abortions	0	1	1	1

* for the costs per detected carrier, the figure is calculated by dividing the sum of the total costs of screening by the sum of detected carriers

9.3.1 Sensitivity analysis

In our baseline analysis we assumed a coverage of combined screening that is equal to that of the separate FraX screening programme from an earlier paper. To assess the influence of a higher or lower coverage on the net savings, we show in Figure 9.1 the net savings of combined screening for varying uptake rates, and compare these with the sum of net savings of the two separate programmes. For example, the sum of the net economic savings of two separate preconceptional screening programmes is €8.7 million, as denoted by the open triangle in the figure. Following the dashed line originating from this triangle, it can be seen that these €8.7 million net savings are obtained in a preconceptional multiplex screening programme if the uptake of screening is 38%. In other words, if more than 12% of the people who would present themselves to separate CF or FraX carrier screening would not show up for combined screening, the net savings of a multiplex screening programme will be lower than the sum of the net savings for two separate screening programmes. For a prenatal screening programme, the uptake rate should be higher than 58% in order to have an efficiency effect of combined screening compared to the baseline uptake of 75%, while the coverage of school screening should be higher than 6%, which is 44% lower

Table 9.4 School screening: comparison of the yearly costs, effects and savings of separate and combined CF-FraX programmes

	Separate CF programme	Separate FraX programme	Sum of separate programmes*	Combined CF-FraX programme
Total costs of screening	€4,508,000	€5,733,000	€10,242,000	€6,813,000
Detected carrier couples	20	146	166	166
- CF carrier couples	20	-	20	20
- FraX carrier couples	-	146	146	146
Costs per detected carrier	€223,000	€39,000	€62,000	€41,000
Number of avoided patients	5	15	20	20
Health care savings	€1,312,000	€7,669,000	€8,981,000	€8,981,000
Net economic savings	-€3,196,000	€1,936,000	€1,260,000	€2,168,000
Negative side effects				
Avoided non-diseased children (normal children, CF carrier children, FraX premutation children, girls with FraX full mutation but no mental retardation)	3	24	27	27
Iatrogenic abortions	0	1	1	1

* for the costs per detected carrier, the figure is calculated by dividing the sum of the total costs of screening by the sum of detected carriers

than the baseline uptake rate. Compared to a separate FraX carrier screening programme however, the coverage of combined school screening can only decrease by 2% in order not to lose efficiency effects.

9.4 Discussion

People want their children to be healthy and not just free of one particular disease. For this reason, a multiplex screening programme for serious genetic disease might be more appropriate than multiple separate screening programmes. In this analysis we showed that a combined screening programme for CF carriers and FraX carriers has a better economic performance than two separate programmes. For school carrier screening, this would mean that the health care savings are higher than the screening costs for combined screening, because the net costs of a separate CF carrier screening programme are more than compensated by the net savings of a separate FraX carrier screening programme. Furthermore, the net savings of a combined school screening programme are also higher than those of a separate FraX school screening programme. In a sensitivity analysis we showed that the economic performance of combined screening would only be worse than the performance of the separate screening programmes if a (large) part of the people who would present themselves

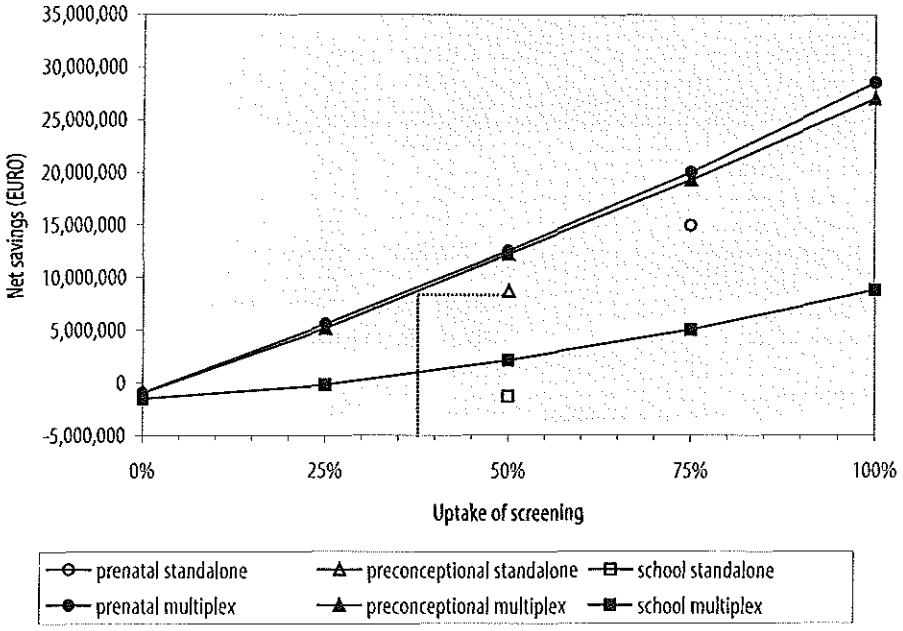


Figure 9.1 Net savings of combined and separate screening CF-FraX programmes for varying uptake rates of screening. Uptake rates are weighted averages of the respective uptake rates of people with and without mental retardation

for separate screening do not take up the offer of combined screening. However, we think that this is unlikely, as coverage of combined screening will probably be higher than coverage of separate screening.

It should also be noted from Figure 9.1 that the net economic savings are largely determined by coverage, and that the effect of combined screening is, in this respect, comparable to the effect of a 10 to 15% increase in uptake. But, as said before, non-economic considerations like persons not being exposed repeatedly to a screening process may even be more important considerations for combined screening.

There is a consensus that informed consent, which requires pre-test counselling, is mandatory for all screening programmes. This might be a problem for combined screening programmes, because it may be difficult to inform the patient extensively about all or most diseases concerned and about the implications of the information from the screening tests. To avoid this information overload, 'generic consent' has

been proposed by Elias and Annas (3). Here broader concepts and common-denominator issues are used in the counselling sessions and the couple or individual does not give informed consent for screening for a given disease but for screening for (offspring with) a number of diseases with serious physical and/or mental causes, as is done in amniocentesis and serum screening.

How should it be decided which diseases and disorders should be included in a combined screening programme? First there can be a (public) negotiation debate between patient organisations, 'experts' such as geneticists, psychologists and ethicists, and government. Another way of establishing the list has been proposed by Biesecker (4) who suggests an analysis of resources that are required for patient autonomy and informed consent for each screening test and a selection of those tests that can be implemented given the total current and envisaged resources (both workload and financial) within the health sector. Even more than for separate screening programmes, economic considerations are no argument against a combined CF-FraX screening programme. An individual or couple should always have the right not to have a screening test for some or all diseases, which means that a social climate is necessary in which there is room and support for handicapped persons (11).

9.5 References

1. Bamforth FJ. Laboratory screening for genetic disorders and birth defects [review]. Clin Biochem 1994;27(5):333-342.
2. Motulsky AG. Predictive genetic diagnosis [editorial]. Am J Hum Genet 1994;55(4):603-605.
3. Elias S, Annas GJ. Generic consent for genetic screening. N Engl J Med 1994;330(22):1611-1613.
4. Biesecker LG, Wilfond BS. Generic consent for genetic screening [letter]. N Engl J Med 1994;331(15):1024.
5. Wells RJ. Generic consent for genetic screening [letter]. N Engl J Med 1994;331(15):1024.
6. Elias S, Annas GJ. Generic consent for genetic screening [reply]. N Engl J Med 1994;331(15):1025.
7. Wildhagen MF, Hilderink HBM, Verzijl JG, Verheij JBGM, Kooij L, Tijmstra T, ten Kate LP, Habbema JDF. Costs, effects, and savings of screening for cystic fibrosis gene carriers. J Epidemiol Community Health 1998;52:459-467.

8. Wildhagen MF, van Os TAM, Polder JJ, ten Kate LP, Habbema JDF. Explorative study of costs, effects and savings of screening for female Fragile X premutation and full mutation carriers in the general population. Community Genet 1998;1(1):36-47.
9. Brock DJH. Heterozygote screening for cystic fibrosis. J Med Screen 1994;1(2):130-133; discussion 133-134.
10. Dodge JA, Boulyjenkov V. New possibilities for population control of cystic fibrosis. Bull World Health Organ 1992;70(5):561-566.
11. Health Council of The Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994; no. 1994/22E.
12. Beaudet AL, O'Brien WE. Advantages of a two-step laboratory approach for cystic fibrosis carrier screening [letter]. Am J Hum Genet 1992;50(2):439-440.
13. Ten Kate LP, Verheij JBGM, Wildhagen MF, Hilderink HBM, Kooij L, Verzijl JG, Habbema JDF. Comparison of single-entry and double-entry two-step couple screening for cystic fibrosis carriers. Hum Hered 1996;46(1):20-25.
14. Miedzybrodzka ZH, Hall MH, Mollison J, Templeton A, Russell IT, Dean JC, Kelly KF, Marteau TM, Haites NE. Antenatal screening for carriers of cystic fibrosis: randomised trial of stepwise v couple screening. BMJ 1995;310(6976):353-357.
15. Wald NJ. Couple screening for cystic fibrosis. Lancet 1991;338(8778):1318-1319.
16. Wall J, Cai S, Chehab FF. A 31-mutation assay for cystic fibrosis testing in the clinical molecular diagnostics laboratory. Hum Mutat 1995;5(4):333-338.
17. Wu Y, Hofstra RM, Scheffer H, Uitterlinden AG, Mullaart E, Buys CH, Vijg J. Comprehensive and accurate mutation scanning of the CFTR gene by two-dimensional DNA electrophoresis. Hum Mutat 1996;8(2):160-167.
18. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276(15):1253-1258.
19. Ten Kate LP. Cystic fibrosis in The Netherlands. Int J Epidemiol 1977;6(1):23-34.
20. De Vries HG, Collée JM, de Walle HE, van Veldhuizen MH, Smit Sibinga CT, Scheffer H, ten Kate LP. Prevalence of delta F508 cystic fibrosis carriers in The Netherlands: logistic regression on sex, age, region of residence and number of offspring. Hum Genet 1997;99(1):74-79.
21. Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. Am J Med Genet 1996;64(1):196-197.

22. Rousseau F, Rouillard P, Morel ML, Khandjian EW, Morgan K. Prevalence of carriers of premutation-size alleles of the FMRI gene--and implications for the population genetics of the fragile X syndrome. Am J Hum Genet 1995;57(5):1006-1018.
23. Sherman SL. The high prevalence of fragile X premutation carrier females: is this frequency unique to the French Canadian population? [editorial]. Am J Hum Genet 1995;57(5):991-993.
24. Fisch GS, Snow K, Thibodeau SN, Chalifaux M, Holden JJ, Nelson DL, Howard-Peebles PN, Maddalena A. The fragile X premutation in carriers and its effect on mutation size in offspring. Am J Hum Genet 1995;56(5):1147-1155.
25. Rousseau F, Heitz D, Tarleton J, MacPherson J, Malmgren H, Dahl N, Barnicoat A, Mathew C, Mornet E, Tejada I, Maddalena A, Spiegel R, Schinzel A, Marcos JAG, Schorderet DF, Schaap T, Maccioni L, Russo S, Jacobs PA, Schwartz C, Mandel JL. A multicenter study on genotype-phenotype correlations in the fragile X syndrome, using direct diagnosis with probe StB12.3: the first 2,253 cases. Am J Hum Genet 1994;55(2):225-237.
26. UNSCEAR. Genetic and somatic effects of ionizing radiation. A report of the United Nations Scientific Committee of the Effects of Atomic Radiation. New York: United Nations, 1986.
27. Statistics Netherlands. Maandstatistiek bevolking 97/11. [Monthly bulletin of population statistics 97/11]. Voorburg/Heerlen: Statistics Netherlands, 1997; no. 97/11.
28. Hille E, de Kroon M. Epidemiologie van infertiliteit [Epidemiology of infertility]. iMTA/iMGZ, Erasmus University Rotterdam, 1992; no. 92.15.
29. Statistics Netherlands. Maandstatistiek bevolking 97/8. [Monthly bulletin of population statistics 97/8]. Voorburg/Heerlen: Statistics Netherlands, 1997; no. 97/8.
30. Bonsel GJ, Maas PJ, van der. At the cradle of the future. Health scenarios concerning human reproduction 1995-2010. Summary of the Dutch STG report "Aan de wieg van de toekomst". Zoetermeer, The Netherlands: Foundation for Future Health Scenarios, 1996.
31. Statistics Netherlands. Maandstatistiek bevolking 96/12 [Monthly bulletin of population statistics 96/12]. Voorburg/Heerlen: Statistics Netherlands, 1996; no. 96/12.

32. Zeesman S, Clow CL, Cartier L, Scriver CR. A private view of heterozygosity: eight-year follow-up study on carriers of the Tay-Sachs gene detected by high school screening in Montreal. Am J Med Genet 1984;18(4):769-778.

Chapter 10
General discussion

10.1 Summary of the results

10.1.1 General

Genetic carrier screening is technically feasible for both cystic fibrosis and fragile X syndrome. Preconceptional carrier screening has the advantage over prenatal carrier screening that the carriers have more reproductive possibilities (Appendix B); however the cost-savings balance of preconceptional screening is somewhat less favourable than the balance of prenatal screening, and organisational problems for preconceptional screening could be prohibitive for the time being (Chapter 5 and Chapter 7). Because school carrier screening and neonatal carrier screening involve testing minors and because of the long time frame between screening and possible use of the test results, these two screening strategies should only be considered if both preconceptional and prenatal screening would not be possible.

10.1.2 Cystic fibrosis

The nonhospital excess costs of care of patients with cystic fibrosis are relatively high at €9,960 per year (Chapter 3). However, many of the patients seem to have a 'normal' daily life since 57% of the adult patients have a job contract and only 17-18% had been absent from work or school during a four week period registered by us. Total costs of care of patients with cystic fibrosis are estimated at €16,163 per year; the lifetime excess costs of care are €245,901 using a five percent discount rate (Chapter 4), and €343,613 using a three percent discount rate.

For cystic fibrosis carrier screening, the screening costs per detected carrier couple are lowest for neonatal screening at €24,000 and are much higher for the other screening strategies (range €66,000-€97,000). The net economic savings (savings minus costs) are highest for prenatal screening, but are also positive for single-entry preconceptional screening. Double-entry preconceptional screening, school screening and neonatal screening on the other hand have higher costs than savings. These conclusions hold for a wide range of assumptions (Chapter 5).

10.1.3 Fragile X syndrome

The screening costs per detected carrier for the fragile X syndrome screening programmes are much lower than their counterparts in cystic fibrosis screening (range €39,000-€41,400). The net savings of prenatal and preconceptional fragile X syndrome carrier screening are higher than for cystic fibrosis, and the savings of school screening also exceed its costs for fragile X syndrome carrier screening (Chapter 7). Cascade testing is not very effective in early detection of carriers who will have a child with fragile X syndrome, but it is more efficient than general population screening in the sense that less people need to be screened per carrier detected (Chapter 8). Therefore a good strategy might be to perform general population screening followed by cascade testing on all detected carriers; this should be confirmed by a (cost-effectiveness) analysis.

10.1.4 Cystic fibrosis and fragile X syndrome

A combination of cystic fibrosis and fragile X syndrome screening will have efficiency effects: the screening costs per detected (cystic fibrosis or fragile X syndrome) carrier for a combined programme are more than 30% lower than those of the separate screening programmes, and the net savings of prenatal and preconceptional screening increase by 34% and 40%, respectively (Chapter 9). While the savings of a separate school screening programme for CF carriers are lower than the costs, the savings of a combined CF-FraX school screening programme exceed costs by €2.2 million.

10.2 New data with respect to CF screening in The Netherlands

Obviously, the results in this thesis depend on the assumptions made. Some of these assumptions have already changed since the chapters in this thesis have been written. For example, the recommended discount rate has changed from 5% to 3% during the time of the CF analysis. Furthermore, several new mutation detection methods have been developed such as allele-specific-oligonucleotide hybridisation using the reverse dot blot detection format for 32 mutations (ASO test) (1) and screening all exons of the CF-gene at once on a denaturing gradient gel by two-dimensional DNA electrophoretic separation of polymerase chain reaction amplified exons (DGGE test) (2). The sensitivities of these two methods are assumed to be 90% and 98% per individual, respectively (H. Scheffer, personal communication). Of course, the costs of

testing will also change if these tests are used since ASO costs €45.29 and DGGE costs €178.07 (3). In the original analysis, we presumed a sensitivity of 73.6% for the ΔF508 test and 85.5% for the seventeen mutations test while the costs were €9.47 and €37.89, respectively. Therefore, the analysis of Chapter 5 is redone with accordingly changed assumptions for four different tests or test combinations.
As can be seen in Table 10.1 the changes in assumptions have a large impact on the costs and effects of screening, and the costs of some strategies become higher than the savings. The net economic savings of the first test combination (the ΔF508 test in the first step and a test for 17 mutations in the second step) for single-entry two-step screening are even higher than in the original analysis. The savings of double-entry two-step screening are higher than its costs, while in the original analysis the costs were higher than the savings. The main reason for this is that the discount percentage has decreased from 5% to 3%, which primarily affects costs of care upwards.
If only one test is used (situations 2 and 3), the effects of the SETS version and the DETS version are the same since the sensitivity of the first and second step are the same. However, the costs of screening of the DETS version are much higher than those of the SETS version since partners of test-negative individuals are also tested in the DETS version, as opposed to the SETS version. Furthermore, twice as many couples will be designated as being positive-negative in the DETS version than in the SETS version. If the sensitivity of the screening test is lower than 97%, they have an increased risk of having a CF child but cannot be offered prenatal diagnosis. On the

Table 10.1 Costs, effects and savings of single-entry two-step (SETS) and double-entry two-step (DETS) preconceptional couple screening for CF

Test or test combination	1. ΔF508 in 1st step, 17 mut. in 2nd step	2. Only ASO test	3. Only DGGE test	4. ASO in 1st step, DGGE in 2nd step
Single-entry two-step (SETS)				
Costs of screening	€2,169,000	€4,378,000	€12,765,000	€4,623,000
Detected carrier couples	35	45	53	49
Costs per detected carrier couple	€62,000	€97,000	€239,000	€94,000
Number of avoided patients	11	15	17	16
Net economic savings	€1,987,000	€902,000	- €6,548,000	€1,105,000
Double-entry two-step (DETS)				
Costs of screening	€2,987,000	€6,936,000	€21,772,000	€7,059,000
Detected carrier couples	40	45	53	53
Costs per detected carrier couple	€75,000	€154,000	€408,000	€133,000
Number of avoided patients	13	15	17	17
Net economic savings	€1,714,000	- €1,655,000	- €15,555,000	- €882,000

other hand, the risk of having a CF child for couples in which the first partner tested negative in the SETS version (-? couples) is 7.5 times higher than for negative couples in the DETS version (-- couples). However, both risks fall in the 'very small risk' category, and do not warrant extensive attention by prospective parents.

For the fourth test combination (ASO in the first step, DGGE in the second), the economic savings are higher than the costs for single-entry two-step screening, but not for double-entry two-step screening. The main reason for this is that in the first step a test with sensitivity of 90% is used which means that in the second step only a small percentage of the carriers can be detected.

Of the programmes with higher savings than costs, the first test combination (the ΔF508 test in the first step and a test for 17 mutations in the second step) has highest net economic savings, while the fourth test combination detects most carrier couples and leads to the highest number of avoided patients. Comparing the first to the fourth scenario, the fourth scenario has €882,000 less of net economic savings for the SETS version while it detects 14 carrier couples more, so that the incremental costs are €63,000 per detected carrier couple. This means that if one regards these incremental costs not to be prohibitive, one should opt for the fourth testing scenario. For the DETS version, the incremental costs are €197,000 per detected carrier couple, more than three times the incremental costs of the SETS version.

As the coverage has a rather large influence on the net savings of a screening programme, we have determined the net savings for varying uptake rates (Figure 10.1) and we have calculated the minimum uptake rate for which savings of screening are higher than or equal to its costs (threshold analysis, Table 10.2). For the SETS version of the first test combination, the uptake rate should be higher than 10% for SETS in order to have higher savings than costs, and for the DETS version the uptake rate should be higher than 12%. For the SETS versions of the second situation the uptake rate should be higher than 24%, while even a 100% uptake rate for the

Table 10.2 Threshold analysis: the threshold coverage for which costs of screening equal savings

Test or test combination	1. ΔF508 in 1st step, 17 mut. in 2nd step	2. Only ASO test	3. Only DGGE test	4. ASO in 1st step, DGGE in 2nd step
Threshold coverage for SETS	10%	24%	none	21%
Ratio of threshold to baseline value	x0.20	x48	none	x0.42
Threshold coverage for DETS	12%	none	none	none
Ratio of threshold to baseline value	x0.23	none	none	none

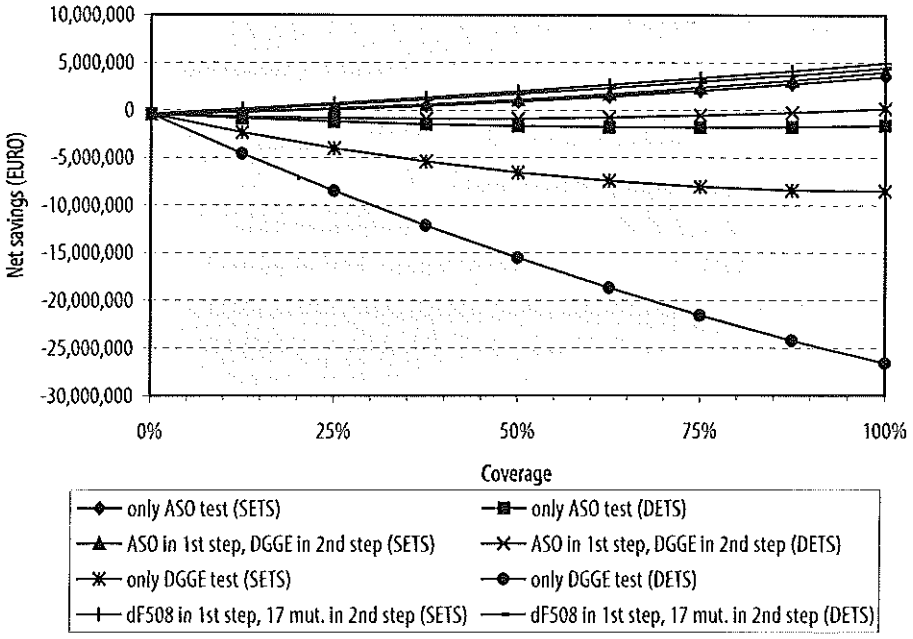


Figure 10.1 Net savings of preconceptional screening for several test combinations and uptake rates

DETS version of the second combination and both versions of the third combinations lead to higher costs than savings. The uptake rate of the fourth combination should be higher than 21%, but for the DETS version of the fourth combination costs are always higher than savings.

The above analysis is a more detailed version of Verheij et al. (3). For example, spontaneous abortions and chromosome abnormalities are modelled, and costs for the screenees are taken into account.

10.3 Assessing the criteria of the Health Council

This thesis has shown that there is a favourable economic balance for screening for cystic fibrosis and/or fragile X syndrome carriers under most realistic assumptions. However, as this is only the last subcriterion in the Health Council report (4), the screening programmes analysed in this thesis have been checked in Table 10.3 against the criteria of the Health Council Committee on Genetic Screening (note that

economic considerations are addressed in 12j). The criteria that are not (completely) satisfied are:

- criteria 3 and 5 ('awareness and informed consent'): minors are tested in school screening and neonatal screening, and legally they can not give informed consent. Therefore, preconceptional screening and prenatal screening are better methods of screening with regard to these criteria;
- criterion 4 ('actions'): the value of the information from screening for carriers detected as newborns or school aged children lies far in the future, by which time they may have 'forgotten' their test results. Since preconceptional screening gives the carrier couple more options than prenatal screening (avoiding pregnancy, artificial insemination, pre-implantation diagnosis), preconceptional screening can be considered preferable with regard to this criterion;
- criterion 6 ('information'): there is a debate about the amount of information to be given to couples in cystic fibrosis carrier screening where one partner is identified as carrier and the other not when the screening test does not have a 100% sensitivity. Since the negatively tested partner may have a mutation that is not detectable with currently available screening tests, these couples have a higher risk of an affected child than the untested general population but they do not have the option of prenatal diagnosis. Understanding these and other implications of genetic testing for CF and fragile X syndrome requires a high degree of genetic knowledge about test sensitivity, carrier status, patterns of inheritance, risk/probability and genotype-phenotype correlations (5). Given the recognised gaps in genetic knowledge among the general public, it is essential that any genetic testing programme includes educational and counselling components and written informed consent (6). Involvement of patient's associations is important for a balanced information (7);

Table 10.3 Check of screening programmes to the criteria of the Health Council

	Criterion, applied to carrier screening for:	CF		FraX		CF-FraX	
	Strategy:	Prec Pren	Schl Neon	Prec Pren	Schl	Prec Pren	Schl
a.	Absolute criteria						
1.	The programme concerns a health problem or condition that can lead to a health problem	+	+	+	+	+	+
2.	The target population is clearly defined	+	+	+	+	+	+
3.	The programme enables participants to become aware of the disease or carrier status	+	+/-	+	+/-	+	+/-
4.	Practical courses of action are open to the participants	+	+/-	+	+/-	+	+/-
5.	Participation is voluntary and consent is based on good information	+	+/-	+	+/-	+	+/-
6.	The target group is supplied with accurate and comprehensible information	+/-	+	+/-	+/-	+/-	+/-
7.	A suitable test method is available	+	+	+	+	+	+
8.	There are sufficient facilities for every step in screening and diagnosis	+/-	+/-	+	+	+/-	+/-
9.	The personal privacy of the participants is protected	+	+	+	+	+	+
10.	If scientific research is carried out, participants are properly informed about this	+	+	+	+	+	+
11.	There is continuous quality assurance regarding tests, follow-up and participant information	+	+	+	+	+	+
b.	Weighing criteria. There should be information about						
12a.	The prevalence of the disease or disorder	Y	Y	N	N	Y/N	Y/N
12b.	The natural course of the disorder	Y	Y	Y	Y	Y	Y
12c.	All possible target groups and the considerations which led to the selection of the target group and the time in life for testing	Y	Y	Y	Y	Y	Y
12d.	The performance of the screening test, including the burden which testing imposes on the participants	Y	Y	Y	Y	Y	Y
12e.	The available courses of action after a positive test result	Y	Y	Y	Y	Y	Y
12f.	The time allowed for consideration and possible implementation of the courses of action	Y	Y	Y	Y	Y	Y
12g.	The possible psychological, social and other repercussions of the offer, participation and non-participation to participants and other people	N	N	N	N	N	N
12h.	The possibility and consequences of erroneous results	Y	Y	Y	Y	Y	Y
12i.	The guarantees to prevent participants experiencing unjustified impediments from obtaining employment or private insurance cover as a result of (non-)participation in the screening and follow-up testing	Y	Y	Y	Y	Y	Y
12j.	The costs which are linked to the screening and to the attainment of the requisite infrastructure	Y	Y	Y	Y	Y	Y

+: the criterion is or can be satisfied
+/-: the criterion is not completely satisfied
Y: there is enough knowledge with regard to this criterion
N: there is not enough knowledge with regard to this criterion

- criterion 8 ('facilities'): using the assumptions of Chapter 5 for CF prenatal and preconceptional screening, between 33 and 63 carrier couples can be expected to be detected by screening in The Netherlands per year. For these carrier couples, there would be sufficient facilities for counselling in clinical genetic centres. This might not be the case for couples where one partner is identified as a carrier and the other is not, given that, each year, 1,355 to 3,881 of these couples may be identified through screening. It has been suggested that these couples could be counselled by trained paramedics ('project-nurses'), who might also have a role in testing family members of detected carriers (8). There are likely to be adequate facilities for performing between 40 and 99 prenatal diagnoses and between 8 and 20 induced abortions. The same applies for fragile X syndrome screening: between 149 and 200 carriers can be expected per year (Chapter 7), the number of prenatal diagnoses ranges from 147 to 263 and the number of induced abortions from 17 to 31;
- criteria 9, 10, 12i ('privacy, research and guarantees against impediments'): these criteria can only be assessed for completely specified screening programmes. There should be no difficulties in fulfilling these criteria in The Netherlands;
- although criterion 11 ('continuous quality assurance') can, in principle, be satisfied in any CF screening programme, special attention has to be given to the quality control of CFTR typing. In a European concerted action on cystic fibrosis, Cuppens and Cassiman (9) found that only 25 of 40 (=62.5%) participating laboratories throughout Europe were able to type correctly all nine samples with various CFTR alleles, and that four laboratories (10%) typed three or more alleles incorrectly. However, a significantly lower error rate was observed in laboratories from the United Kingdom, which is believed to be a direct consequence of their participation in a quality control scheme. This quality control testing has been operational for more than three years since the time of the study of Cuppens and Cassiman (9);
- criterion 12a ('prevalence'): the prevalence of fragile X syndrome premutations has not yet been determined in The Netherlands; as a matter of fact they have not yet been established in a large-scale study, except in the Canadian situation with possibly large founder effects;
- criterion 12b ('natural course'): only about half of the female foetuses with a full fragile X syndrome mutation will have mental retardation. Therefore, the parents-to-be have a difficult decision to make;

- criterion 12g ('repercussions'): insufficient knowledge is available regarding adverse psychological, social and other repercussions. Factors such as anticipated decision regret, perception of the severity of the condition as well as perception of risk influence the decisions to accept or decline screening (10). The complexity of the concept of 'carrier status' and its implications for family members may also make the screening decision difficult (11). Possible anxiety caused by the screening result appears to be short-lived, with most of those accepting the offer of screening expressing a preference for "certainty" over "not knowing" (12). Furthermore carriership could influence the self-perception and the perceptions of others who are no carrier. For example, in one study carriers viewed their future health with less optimism than people who are no carrier (13). Most CF patients and their families appear to have a positive attitude to carrier screening and termination of affected pregnancies (14, 15). For fragile X syndrome carrier screening, such comprehensive studies have not yet been published. No adverse repercussions from a medical point of view have been reported;
- criterion 12j ('costs'): this thesis shows that there are no economic objections against preconceptional or prenatal carrier screening and to multiplex school screening but that the costs of neonatal and separate school screening exceed the savings. This means that if it is decided to introduce school or neonatal carrier screening in The Netherlands, funds have to be made available in the health care budget.

10.4 Recommendations

There are no technical, organisational or economic objections against cystic fibrosis carrier screening. With regard to psychological and social consequences, there might be some adverse effects, but these are not yet studied in The Netherlands.

The WBO committee of the Dutch Health Council, instituted as a result of the Dutch Population Screening Act (WBO) to advise central government, concluded in their report (16) that there are no categorical arguments against a pilot preconceptional screening programme for cystic fibrosis carriers in The Netherlands, and that it would have advised the Dutch Minister of Health to grant the license if it would have assessed a regular license application. The KNMG (Royal Dutch Society for the Promotion of Medicine) also does not have moral objections against preconceptional screening for CF carriers if the screening is aimed at making possible an informed choice concerning reproduction (17). Therefore, a pilot study in The Netherlands is

recommended that focuses on the psychological and social consequences, and determines uptake rates of screening, diagnosis and therapy. As preconceptional CF screening will probably involve the general practitioners in the Dutch situation, special emphasis should be drawn on whether the general practitioners will take part in the study and how to inform couples that their practitioner participates in the pilot study. If this pilot study shows that carrier screening is feasible from these points of view, introduction of general population carrier screening for cystic fibrosis in The Netherlands should be seriously considered.

For a fragile X syndrome screening study, the focus should presently be on determining the prevalence of full mutations and premutations in The Netherlands, since these are not known in the Dutch general population. Furthermore, a pilot study should determine the attitude of Dutch women concerning fragile X syndrome screening in general and the problem of predicting mental retardation in female foetuses with a full mutation.

A combined screening programme of cystic fibrosis and fragile X syndrome carriers might not seem obvious, given the diversity of information for two different disorders to be given to individuals. Combining two screening programmes for physical disorders or combining two screening programmes for mental disorders on the other hand might be more feasible as the information concerns two similar disorders. As couples will probably be seen once in the preconceptional scenario for screening, they may be offered the choice between screening for physical disorders or mental disorders or both which will obviously lead to concepts as generic consent (18).

Summarising, the main focus of future studies regarding carrier screening in general should be on the psychological and social consequences of screening, and on how to involve general practitioners best in preconceptional screening.

10.4.1 Discounting

The above recommendations follow directly from the results of this thesis. A methodological issue concerns discounting effects in genetic screening. The reasons for not discounting health effects are (19):

- it is difficult to conceive of individuals investing in health or trading flows of healthy years through time;
- discounting for example years of life gained in the future gives less weight to future generations in favour of the present one. This makes only sense if one expects future generations to have better therapeutic technologies available.

The reasons in favour of discounting health effects are (19):

- discounting costs while not discounting effects will lead to inconsistencies in reasoning, e.g. it is better to defer spending now so that progressively less cost-effective programs can be mounted in the future (20, 21);
- contrary to the first reason for not discounting effects, one can conceive of investments in health and the trading of health through time. If this were not the case, people would not refrain from pleasurable but in the long run potentially risky actions, such as smoking, or short run relatively dangerous activities, such as skydiving.

As already said in the introduction of this thesis, both the working party convened by the US Public Health Service (22-24) and the working party for the British Medical Journal (25) recommend discounting health effects by the same discount rate as discounting the costs, but the British party adds the suggestion to discount the health effect with a lower rate for preventive (screening) programmes. On top of the debate how to discount costs and effects for health interventions in general, genetic screening deals with future generations, which means that future generations can be discriminated if effects are discounted. For example, detecting 100 carrier couples one year from now is valued equal to detecting 100/(1+0.05)=95 carrier couples at this moment at five percent discounting. This problem also plays a role in environmental economics, where some alternative discounting methods are proposed (26). For genetic screening, these methods would be:

- only costs should be discounted, and not the effects. In this way, detecting a carrier (couple) in 10 years is valued equally important as detecting a carrier (couple) now (we have used this method in the thesis);
- cost-benefit ratios are weighed differently for subsequent generations. This means that a cost-benefit ratio is calculated per generation from the perspective of time 0, the moment of the investment decision. The ratios are weighed with a factor that can be progressive, regressive etc. The problem obviously is how to determine the weighing factor(s);
- the point in time is set to 0 every time a new generation occurs. This means that costs and effects are discounted to the year of birth of the generation, and not to some point in time in the (far) history. In this method, the standard discounting formula of section 1.5.3 is replaced by a more complex formula (27). The problem with this method is that it assumes a stable population with the same number of persons in every age group, and every individual is assumed to die at the end of

the average life expectancy. A second problem is that the discounting formula is based on the idea that costs and effects are distributed equally in the population. For the costs, this is no problem, but contrary to most environmental issues, this is not so obvious for the effects since health effects occur in identifiable individuals of known ages.

Obviously, the problems of discounting in genetic screening have not (yet) been resolved. Therefore more research, in particular from health economists, is necessary to resolve this special form of the discounting debate.

10.4.2 Diagnosis and treatment

Great advances in treatment and diagnosis are taking place with regard to the diseases described in this thesis. For example, in cystic fibrosis treatment a shift is taking place from hospital care to home care, (heart-)lung transplantations are increasingly performed, and recombinant human deoxyribonuclease (DNase) I is used to decrease viscosity of purulent airway secretions (28, 29). Furthermore, clinical trials are already performed on gene therapy for CF, although clinical widespread use may not be expected in the near future (30-33). These developments are aimed at giving patients with CF a better life expectancy and quality of life, but will also have repercussions on the costs of care for patients with cystic fibrosis. If the costs of care of patients rise, this will lead to a 'paradox' with regard to screening. On one hand will the savings of preventing the birth of a patient with the disease increase (an economic tendency in favour of screening), but on the other hand the quality and length of life in the absence of screening are improving (a tendency against screening). There is no question that carrier screening would then be a thing of the past, but, on the other hand, neonatal patient screening can be contemplated. Firstly, as suggested by the latest paper by Farrell et al. (34) describing nutritional benefits of neonatal patient screening, an early diagnosis probably affects the long-term individual health benefits. Secondly, "there are real prospects that effective, if not curative, treatment based on an understanding of the pathophysiology of cystic fibrosis at the cellular level will be available before long" (35). Thirdly, neonatal (patient and carrier) screening allows parents to have a reproductive option for subsequent pregnancies. However, the (cost)effectiveness of neonatal patient screening should be investigated to see whether neonatal screening is a good public health measure.

A new approach to prenatal diagnosis of fragile X syndrome was published, where the absence or presence of the FMRP protein in cells is used as a diagnostic tool (36, 37). Since this protein is responsible for the mental retardation in fragile X syndrome, using a rapid and simple antibody test can predict the mental status of the foetus. Validation studies show that this method is reliable for male foetuses (38).
Approximately one in a million cells in maternal blood are of foetal origin (39). At the moment it is possible to 'harvest' these cells by labour-intensive laboratory methods, but less labour-intensive methods are under development (40). These cells can be analysed with PCR or fluorescent in situ hybridisation (FISH). Using this method prenatal diagnosis of trisomy 21 is already technically possible, and there are no technical reasons that in the future cystic fibrosis or fragile X syndrome can not be detected using this method. Harvesting cells from male foetuses is no problem, since cells in the blood originating from males per definition are of a foetus and not of the mother. For female foetuses, more laborious methods are needed to distinguish a maternal cell from a foetal cell. A second problem is that cells of previous pregnancies or miscarriages may remain in maternal blood and thus may complicate the diagnosis (41). If these complications can be resolved, invasive prenatal diagnosis by amniocentesis or chorionic villus sampling with its associated risk of miscarriage will not be necessary in the future for these diseases.

10.4.3 Information

It is very important that the target group receives adequate and balanced information. It should include at least the test characteristics, a description of the severity of the disease and inheritance patterns. The offer of testing should be made to enable couples who wish to avoid the birth of a child with CF to do so, without influencing those who do not. Care should be taken to ensure that the decision to have testing is completely voluntary (6). An important point of attention in future research should be how to transfer probability measures in inheritance patterns to individuals, as many individuals are inclined to dichotomise probabilities into "yes" or "no". This leads to many people accepting rather far-reaching procedures in order to prevent that their child has a disease, however small the probability. For example, Tijmstra and Bajema (42) found that many people would take part in a screening programme in which all three-day-old children would have to be in an incubator for 24 hours in order to save the life of 2 out of 180,000 children with a fatal disease yearly. The authors conclude that there are no limits as far as the public is concerned:

if people have the impression that distress can be prevented by means of medico-technical interventions, they will make use of the technology en masse (42). This means that the public will probably accept combined screening for a large number of diseases in order to rule out most of the serious diseases, so that the demand side of the 'health care market' does not limit the number of diseases to screen for. Therefore, as we already remarked in Chapter 9, a public negotiation debate between patients organisations, experts and government should establish a priority list of diseases to screen for.

10.4.4 Computer models

As for all evaluation analyses, the assumptions used in analysing the (cost)effectiveness of genetic screening are important. Computer models make these assumptions explicit and therefore force the user to consider what plausible value(s) the assumptions can have. In order to have a consistent approach in calculating (cost)effectiveness measures, it would be advisable to have one model that can be used for screening for several diseases, standalone or in a multiphasic way. The model should enable individuals with different backgrounds (e.g. medical doctors, economists, and politicians) to analyse screening programmes. Therefore, it should be very user-friendly and flexible. The (spreadsheet) models that were used in the analysis of general population screening in this thesis can, in principle, be extended for the analysis of several diseases, but the models become increasingly complex and inflexible. Therefore, a microsimulation programme comparable to the MISCAN-programme for analysis of cancer screening (43), might be the proper way to follow.

10.5 References

1. Wall J, Cai S, Chehab FF. A 31-mutation assay for cystic fibrosis testing in the clinical molecular diagnostics laboratory. Hum Mutat 1995;5(4):333-338.
2. Wu Y, Hofstra RMW, Scheffer H, Uitterlinden AG, Mullaart E, Buys CHCM, Vijg J. Comprehensive and accurate mutation scanning of the CFTR gene by two-dimensional DNA electrophoresis. Hum Mutat 1996;8(2):160-167.
3. Verheij JBGM, Wildhagen MF, Hofstra RMW, Pals G, Habbema JDF, ten Kate LP. Preconceptional couple screening for carriers of cystic fibrosis: a prospective evaluation of effects, costs and savings. Submitted 1998.
4. Health Council of The Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994; no. 1994/22E.

5. Decruyenaere M, Evers-Kiebooms G, Denayer L, van den Berghe H. Cystic fibrosis: community knowledge and attitudes towards carrier screening and prenatal diagnosis. Clin Genet 1992;41(4):189-196.
6. Anonymous. Genetic testing for cystic fibrosis. NIH Consens Statement 1997 Apr 14-16;15(4):1-37.
7. Black RB, Weiss JO. A professional partnership with genetic support groups. Am J Med Genet 1988;29(1):21-33.
8. Shickle D, Harvey I. 'Inside-out', back-to-front: a model for clinical population genetic screening. J Med Genet 1993;30(7):580-582.
9. Cuppens H, Cassiman JJ. A quality control study of CFTR mutation screening in 40 different European laboratories. The European Concerted Action on Cystic Fibrosis. Eur J Hum Genet 1995;3(4):235-245.
10. Tijmstra TJ. Het imperatieve karakter van medische technologie en de betekenis van 'geanticipeerde beslissingsspijt' [The imperative character of medical technology and the significance of 'anticipated decision regret']. Ned Tijdschr Geneeskd 1987;131(26):1128-1131.
11. Tambor ES, Bernhardt BA, Chase GA, Faden RR, Geller G, Hofman KJ, Holtzman NA. Offering cystic fibrosis carrier screening to an HMO population: factors associated with utilization. Am J Hum Genet 1994;55(4):626-637.
12. Mennie ME, Compton ME, Gilfillan A, Liston WA, Pullen I, Whyte DA, Brock DJH. Prenatal screening for cystic fibrosis: psychological effects on carriers and their partners. J Med Genet 1993;30(7):543-548.
13. Marteau TM, van Duijn M, Ellis I. Effects of genetic screening on perceptions of health: a pilot study. J Med Genet 1992;29(1):24-26.
14. Conway SP, Allenby K, Pond MN. Patient and parental attitudes toward genetic screening and its implications at an adult cystic fibrosis centre. Clin Genet 1994;45(6):308-312.
15. Decruyenaere M, Evers-Kiebooms G, Denayer L, Welkenhuysen M. Uptake and impact of carrier testing for cystic fibrosis. A review and a theoretical framework about the role of knowledge, health beliefs and coping. Community Genet 1998;1(1):23-35.
16. Gezondheidsraad: Commissie Wet bevolkingsonderzoek. Proeve van toepassing Wet bevolkingsonderzoek: cystische fibrosse [Test of assesment Population Screening Act: cystic fibrosis]. Den Haag: Gezondheidsraad, 1996; no. 20.

17. KNMG. Artsen en genen. Aanbevelingen inzake genetica van het hoofdbestuur van de KNMG voor de Algemene Vergadering [Doctors and genes. Recommendations concerning genetics of the executive board of the KNMG for the general assembly]. Medisch Contact 1998;53(16):551-555.
18. Elias S, Annas GJ. Generic consent for genetic screening. N Engl J Med 1994;330(22):1611-1613.
19. Drummond MF, Stoddard GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, 1987.
20. Keeler EB, Cretin S. Discounting of life-savings and other nonmonetary effects. Management Science 1983;29(3):300-306.
21. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977;296(13):716-721.
22. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276(14):1172-1177.
23. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276(16):1339-1341.
24. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276(15):1253-1258.
25. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313(7052):275-283.
26. Price C. Time, discounting and value. Oxford: Blackwell, 1993.
27. Kula E. Economics of natural resources, the environment and politics. (2 ed.) Chapman & Hall: 1994. London.
28. Aitken ML, Burke W, McDonald G, Shak S, Montgomery AB, Smith A. Recombinant human DNase inhalation in normal subjects and patients with cystic fibrosis. A phase 1 study. Jama 1992;267(14):1947-1951.
29. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, Rosenstein BJ, Smith AL, Wohl ME. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med 1994;331(10):637-642.

30. Wilson JM. Cystic fibrosis: strategies for gene therapy. Semin Respir Crit Care Med 1994;15:439-445.
31. Rosenstein BJ. Cystic fibrosis in the year 2000. Semin Respir Crit Care Med 1994;15:446-451.
32. Mylett J, Johnson K, Knowles M. Alternate therapies for cystic fibrosis. Semin Respir Crit Care Med 1994;15:426-433.
33. Alton EWFW, Geddes DM. Gene therapy for cystic fibrosis: steady progress, should do well [editorial]. Eur Respir J 1997;10(2):257-259.
34. Farrell PM, Kosorok MR, Laxova A, Shen G, Koscik RE, Bruns WT, Splaingard M, Mischler EH. Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. N Engl J Med 1997;337(14):963-969.
35. Dodge JA. Neonatal screening for cystic fibrosis. Cystic fibrosis should be added to diseases sought in all newborn babies. BMJ 1998;317(7155):411.
36. Willemsen R, Mohkamsing S, de Vries B, Devys D, van den Ouweland A, Mandel JL, Galjaard H, Oostra B. Rapid antibody test for fragile X syndrome. Lancet 1995;345(8958):1147-1148.
37. Willemsen R, Los F, Mohkamsing S, van den Ouweland A, Deelen W, Galjaard H, Oostra B. Rapid antibody test for prenatal diagnosis of fragile X syndrome on amniotic fluid cells: a new appraisal. J Med Genet 1997;34(3):250-251.
38. Willemsen R, Smits APT, Mohkamsing S, van Beerendonk H, de Haan A, de Vries B, van den Ouweland A, Sistermans E, Galjaard H, Oostra BA. Rapid antibody test for diagnosing fragile X syndrome: a validation of the technique. Hum Genet 1997;99(3):308-311.
39. Senyei AE, Wassman ER. Fetal cells in the maternal circulation. Technical considerations for practical application to prenatal diagnosis. [review]. Obstet Gynecol Clin North Am 1993;20(3):583-598.
40. Tanke HJ, Oosterwijk JC, Mesker WE, Ouwerkerk van-Velzen MCM, Knepflé CFHM, Wiesmeyer CC, van Ommen GJB, Kanhai HHH, Vrolijk J. Detection of 'rare event' fetal erythroblasts in maternal blood using automated microscopy. Early Hum Dev 1996;47 Suppl:S89-93.
41. Iverson GM, Bianchi DW, Cann HM, Herzenberg LA. Detection and isolation of fetal cells from maternal blood using the flourescence-activated cell sorter (FACS). Prenat Diagn 1981;1(1):61-73.

42. Tijmstra TJ, Bajema C. 'Je zult die ene maar zijn'; risicobeleving en keuzegedrag rond medische technologie ['You should be that one exception'; risk perception and choice behavior in medical technology]. Ned Tijdschr Geneeskd 1990;134(39):1884-1885.
43. Habbema JDF, van Oortmarssen GJ, Lubbe JTN, van der Maas PJ. The MISCAN simulation program for the evaluation of screening for disease. Comput Methods Programs Biomed 1985;20(1):79-93.

Part 5

Appendices

Appendix A
A short introduction to genetics

Human genetic material is contained in the cell nucleus and outside cell nuclei, in the mitochondria. In the cell nucleus, it consists of 22 pairs of non-sex determining chromosomes (called autosomes), numbered from 1 to 22, and two sex determining chromosomes, called X and Y, where women have two X chromosomes and men one X and one Y chromosome. Each individual inherits one set of autosomes (one of each pair) from the mother and one set from the father. Furthermore, they inherit one of the two sex determining chromosomes from the mother and one from the father.

A.1 Genes

Each chromosome contains a number of genes, a length of DNA (deoxyribonucleic acid) that caries information relating to one particular function. Information is based on four building stones: adenine, thiamine, guanine and cytosine (abbreviated A, T, G and C). Most genes are unknown, and of most known genes the function is unknown.
Each set of chromosomes inherited from a parent contains 50,000-100,000 genes (1). Because the paternal and maternal chromosomes have the same genes, individuals also have all genes in duplicate. Up to February 1999, 10,181 genes have been described and 7,030 of these have been located (http://www.ncbi.nlm.nih.gov/omim). The DNA sequence of the other genes is expected to be known in the beginning of the next century as a consequence of the Human Genome Project (2).
Molecular 'errors' in DNA can arise during cell division. Errors may consist of the substitution of one or more building blocks (point mutation), loss of (part of) a gene (deletion) or of rearrangements such as insertions, duplications or the repetition of a given sequence of building blocks.

A.2 Disorders

A classic distinction between hereditary disorders is chromosomal disorders, monogenic disorders and multifactorial disorders (3).

A.2.1 Chromosomal disorders

Chromosomal disorders are disorders in the number or structure of the chromosomes. An important chromosomal disorder is Down syndrome (see Appendix C). In Down

syndrome, there are three chromosomes 21 instead of the usual two. Most of the times, this is caused by a spontaneous error in one of the divisions resulting in the egg cell, the risk of which increases with maternal age. Most pregnancies with gross chromosomal disorders miscarry in pregnancy. For example, approximately 30% of all Down syndrome pregnancies end in miscarriage in the second or third trimester of pregnancy (4).

A.2.2 Monogenic disorders

Monogenic disorders (or Mendelian or single-gene disorders) can be distinguished in autosomal recessive, autosomal dominant and X-linked diseases.

In autosomal dominant disorders individuals with one mutated gene, either the paternally or maternally derived one, have the disorder. This means that the child of a patient with an autosomal disorder has a 50% probability of being a patient (Figure A.1). Examples of autosomal dominant disorders are familiar hypocholesterolemia and Huntington's disease.

If the disorder is autosomal recessive, offspring will have the disease only if both parents transmit the mutated gene (see Figure A.2). If one of the parents has transmitted a mutated gene and the other parent has transmitted a 'normal' gene, the child will not have the disease but can transmit the mutated gene to his/her offspring. Individuals with one mutated and one 'normal' gene are called carrier. In Chapter 2 to Chapter 5 the autosomal recessive disorder cystic fibrosis is described.

Most X-linked disorders are recessive. This means that men with a single abnormal gene on the X chromosome have the disorder, while women usually are protected by the second (normal) X chromosome. A son always inherits the X chromosome from the mother (and the Y chromosome from the father), so if the mother has a mutated X chromosome the son has a 50% probability of inheriting this chromosome and thus having the disease (Figure A.3). Daughters inherit an X chromosome from both the

Figure A.1 Inheritance pattern of autosomal dominant disorders

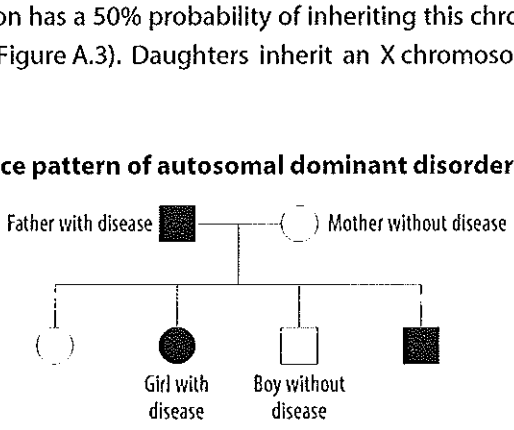
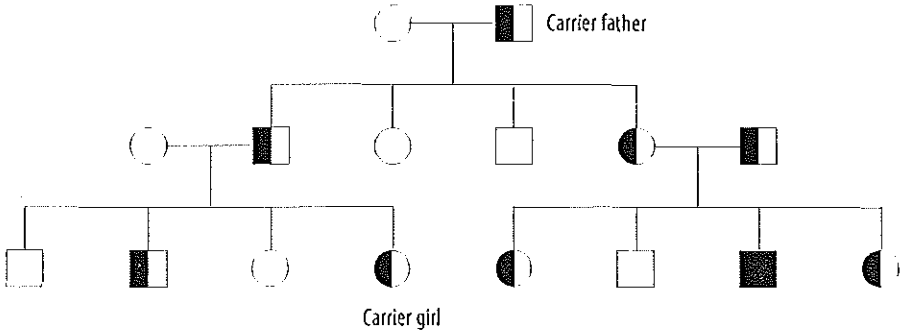


Figure A.2 Inheritance pattern of autosomal recessive disorders

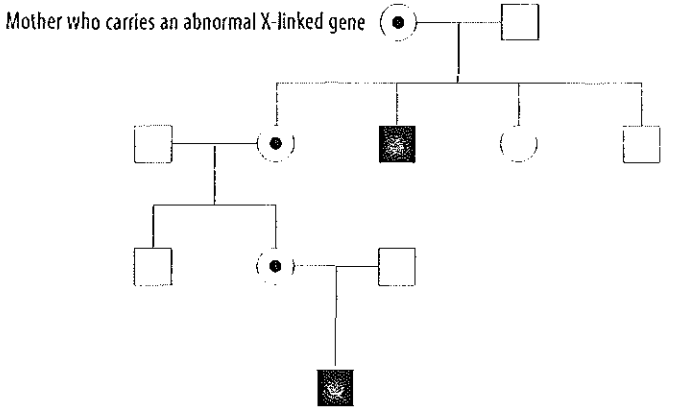


mother and the father, so they do not have the disease but may be a carrier. In Chapter 6 to Chapter 8 fragile X syndrome is described. In this disease the mode of inheritance is very complex, this is described in Chapter 6.

A.2.3 Multifactorial disorders

Multifactorial disorders are disorders with a considerable genetic component, but with as yet no clear pattern of inheritance or detectable chromosomal abnormality. They result from an additive effect of several independent genes and several exogenous factors (environmental influences). This group includes most congenital disorders (e.g. neural tube defects) and major chronic diseases of later life (e.g. diabetes mellitus).

Figure A.3 Inheritance pattern of X-linked disorders



A.3 Founder effects

Particularly in communities that originate from the migration of small groups, a few of the founders of the community contribute a lot to the so-called genetic makeup of the next generations. If one of them has a particular genetic trait, this can lead to a relatively high number of people with the trait in the future generations; this is called founder effect. Founder effects can also occur if existing populations become first smaller and than larger ('bottle neck'). Founder effects exist e.g. in populations in Finland, South Africa, Quebec and the U.S.A.

A.4 PCR test

With the technique of PCR (Polymerase Chain Reaction), a method of increasing the amount of DNA (amplification) developed in the mid-1980s (5, 6), it is possible to perform tests on DNA from just a few cells, or even from a single cell. This method can be important for prenatal testing using foetal cells isolated from the mother's blood, or which have been taken from an embryo produced by test tube fertilisation (so-called pre-implantation genetic diagnosis).

A.5 References

1. Guyer MS, Collins FS. How is the Human Genome Project doing, and what have we learned so far? Proc Natl Acad Sci U S A 1995;92(24):10841-10848.
2. McKusick VA. HUGO news. The Human Genome Organisation: history, purposes, and membership. Genomics 1989;5(2):385-387.
3. Pronk JC, Beemer FA, Geraedts JPM, Leschot NJ, Niermeijer MF. Medische genetica [Medical genetics]. (5th ed.) Utrecht: Wetenschappelijke Uitgeverij Bunge, 1994.
4. Hook EB, Topol BB, Cross PK. The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis which are not terminated electively: new data and estimates of the excess and relative risk of late fetal death associated with 47,+21 and some other abnormal karyotypes. Am J Hum Genet 1989;45(6):855-861.
5. Saiki RK, Scharf S, Faloona F, Mullis KB, Horn GT, Erlich HA, Arnheim N. Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. Science 1985;230(4732):1350-1354.
6. Eisenstein BI. The polymerase chain reaction. A new method of using molecular genetics for medical diagnosis. N Engl J Med 1990;322(3):178-183.

Appendix B
Screening for cystic fibrosis gene carrier state: pros and cons of different scenarios

B.1 Introduction

The increasing possibilities of DNA diagnostics have given genetic testing a completely new dimension. For hundreds of genetic disorders the exact gene defect has been found already (1). Through this the possibilities for direct DNA diagnostics increase; for example it is possible to identify carriers of recessive inheritable disorders. One of these disorders is the serious autosomal recessive inheritable disorder cystic fibrosis (CF). The basic defect of this (still) incurable disease consists of mutations in the so-called 'cystic fibrosis transmembrane conductance regulator' (CFTR)-gene on chromosome 7. With a birth prevalence of 1 in 3,600, CF is the most frequent autosomal recessive inheritable disease in The Netherlands (2). Most of the children with CF are born in families in which this disease had not occurred earlier.

Approximately 1 in 30 individuals in The Netherlands is carrier (heterozygote) of the CF gene. This means that in our country approximately half a million people are carrier. Carriers do not have health problems as a consequence of this carriership. However, if two partners are carriers, each child of them has a 25% probability of having CF. With the discovery in 1989 of the gene that causes CF and of the most occurring mutation ΔF508 it is possible to detect carriers of this genetic disorder by direct mutation detection (3-5). In The Netherlands the ΔF508 mutation occurs in approximately 77% of the CF chromosomes (6, 7). Furthermore, at least 13 other mutations have been identified in our country, so that with the present diagnostic tests a mutation can be detected in approximately 90% of the CF chromosomes in our country (D.J.J. Halley and H. Scheffer, personal communication). With this it is, in principle, possible to detect 90% of the carriers and 81% of the carrier couples. At this moment carrier detection in The Netherlands takes place mainly in CF families and in partners of carriers who are found in this way, but there are research projects in several European countries and the United States where carrier detection is also offered to persons without these risk-increasing factors. The advantage of this

screening is that it informs people about their risk. At the same time, carrier detection raises psychosocial, ethical and social questions (8).
When it is decided to also offer carrier screening to persons without CF-family history in this country, the question arises at what moment and to what persons screening should be offered. As to the time of the screening offer, the following five possibilities can be considered: shortly after birth (neonatal screening); during secondary school (school screening); at the moment of child wish (preconceptional screening); during pregnancy (prenatal screening); early in pregnancy (embryonic screening). This article gives an overview of the possible scenarios for a screening offer and the advantages and disadvantages of each type.
The aim of a large-scale carrier screening offer for CF is that it enables people to make deliberate reproductive choices on the basis of information. People should have the freedom to make the choice themselves. This is only possible when they are informed in advance of all possible implications and results of carrier screening. When weighing the advantages and disadvantages of the various scenarios it is more important to offer the possibility to people to choose for CF carrier screening themselves than to aim for a coverage as high as possible.

B.2 Neonatal screening

The large advantage of choosing neonatal screening is that it can be simply added to the phenylketonuria/congenital-hypothyroidism (PKU/CHT) screening so that the coverage can be almost 100% (9). This also means that screening for treatable diseases is combined with screening for a (yet) untreatable disorder. This will inevitably have consequences for the existing PKU/CHT screening; at least it will mean that the routine character of the heel pricks will no longer be natural for every individual.
With neonatal screening, not only children who are carrier of the CF gene are detected, but also children who have the disease CF. Advocates of neonatal screening see this as a big advantage: an early diagnosis makes treatment in an early stage possible (10). As long as the sensitivity of the test is not 100%, the diagnosis CF can only be made if a CF mutation is found on both chromosomes 7. If a CF mutation is found on one of the chromosomes, a sweat test has to determine whether the individual is carrier or patient: there is a chance that a non-detectable mutation is present on the other chromosome.

Table B.1 Frequency of cystic fibrosis mutations in 200,000 neonates in The Netherlands

Mutations on chromosome 7	Frequency in %	Absolute number (n = 200,000)
On neither chromosome	96.64	193,277
Mutation at one chromosome (carriership)	3.33	6,667
Mutation at both chromosomes (disease)	0.03	56

Assuming 200,000 births per year in The Netherlands, approximately 6,700 children will be carrier of the CF gene (Table B.1). Because of the incomplete sensitivity of the test not all children with a CF mutation will be detected (Table B.2). Depending on the test sensitivity used, approximately 5,100 children (when screened for only the mutation ΔF508) resp. 6,000 children (when screened for several mutations) in whom a mutation is found at one of the chromosomes will need a sweat test to determine whether they are CF gene carrier or CF patient. Ultimately, more than 5,000 children know at a very early age that they are gene carrier of a heritable disease. Clearly, there can be no self-determination about participation or informed consent.

With neonatal screening, the knowledge of being a carrier will be relevant only after 20-40 years. There is a probability that at that time the sensitivity of the test is increased and that neonates in whom no mutation has been detected have to be rescreened. Furthermore it is possible than people do not know (anymore) what the result of the screening is or what the significance of the result is.

When a child is a detected CF gene carrier, both parents have to be tested for carriership if they want to have more children. After all there is a considerable chance that both are carrier. This possibility to inform parents on the basis of the test result is often named as one of the advantages of neonatal screening. In some cases this information will arise only after a child with CF has been born. Furthermore, in some at risk couples the risk will be undetected; after all there is a probability of 25% in each pregnancy that the child has no mutation on either chromosome.

Table B.2 Detection of carriers and patients with cystic fibrosis for 200,000 births, depending on the sensitivity of the screening test

Sensitivity	Gene carrier		Patient	
	Detected	Missed	Detected*	Missed
77%	5,134	1,533	43	13
90%	6,000	667	50	6

* detected provided every neonate with one detected mutation has a sweat test

B.3 School screening

In school screening, obtaining the samples can take place within the school situation. To make the time between screening and the moment of reproduction as short as possible, scholars in the last phase of (compulsory) education can be screened.
From a social-genetic perspective this type of screening gives a good possibility for genetic education: the information can be aimed directly at the target group and fitted into the school system. Various studies have shown that scholars themselves have a positive attitude against school carrier screening (11, 12). Screening at schools has been especially successful in Italy for screening for carriership of thalassaemia and in Canada for screening for carriership of Tay-Sachs disease (13, 14).
School screening concerns testing of minors. This means that the final decision to participate is with the parents, and not with the scholars themselves. Also, knowledge regarding carriership is not directly applicable with school screening and the chance exists that the individual needs to be rescreened at the time this knowledge is relevant. In a screening programme for carriership of Tay-Sachs disease it appeared that 10% of the screened secondary scholars had forgotten the test result after 8 years (15).
With school screening there is a rather large probability of stigmatisation, especially with contemporaries. There is a possibility that, despite good information, the carriers are regarded as divergent. At an age where youths conform themselves especially to contemporaries this can have a negative consequence.

B.4 Preconceptional screening

Preconceptional screening concerns a screening offer to individuals and couples in the reproductive age with a (future) child wish. This type of screening aims at the group for which screening is most relevant: there is a wish for children, but there is not yet a pregnancy. This means that there is enough time for information and preparation for the screening. When, after screening, there appears to be an increased risk to have a child with CF, all reproductive options are open for the persons involved: accepting the increased risk; primary prevention by refraining from offspring; having prenatal diagnosis, possibly followed by selective abortion in case of a foetus with CF; adoption; reproduction by means of artificial insemination with donor sperm; egg cell donation or pre-implantation diagnostics. The target group of this type of screening can not be reached without a special effort. A possible offer could therefore be announced without obligation via the media and primary care. The way in which this

will be done will be of decisive importance for the extent of interest of the intended target group. In a pilot study in London, aimed at people in the reproductive age, the average participation was 17% for those who received a written invitation. With a personal offer by a member of the research team, where screening was directly possible, the participation was a lot higher (70%). With the same offer, where first an appointment for taking the research material at another day was planned, the participation was 25% (15). A possibility for such an aimed offer in our country would be to set up a preconceptional consultation system.

Preconceptional screening can be offered both to individuals and to couples. Because the probability of having a child with CF is only present when both partners are carrier of the CF gene, there is a reason to let the couple be the object of screening, and not the individual. A positive result of an individual test means a risk of 1 in 120 for a child with CF. In more than 97% of the cases screening of the partner will reduce this estimated risk. Screening aimed at couples not only gives a more realistic picture of the risk, but also has the advantage that, if desired, both partners can be approached simultaneously. In couple screening namely, there are two strategies possible: stepwise screening or simultaneous screening (16). Stepwise screening means that first one partner is tested. Only with a positive test result the other partner is tested. In simultaneous screening both partners are tested directly. If screened for only the ΔF508 mutation the test material of the second partner can be tested for more mutations if one of the partners has a positive test result. The advantage of simultaneous screening is that couples are given more certainty about their risk. The number of couples where one partner has a positive test result and the other a negative result is twice as large in simultaneous screening as in stepwise screening (Table B.3). A disadvantage however is that with the current test sensitivities the

Table B.3 Hypothetical results of carrier screening for cystic fibrosis for 200,000 couples in The Netherlands, assuming a carrier frequency of 1:30

	Number of persons (%) screened with a test of					
	Incomplete sensitivity*				Complete sensitivity†	
Carrier status of the couple	Stepwise screening‡		Simultaneous screening			
Negative/negative	194,867	(97.43)	189,865	(94.93)	186,889	(93.44)
Positive/unknown or positive/negative	4,979	(2.49)	9,959	(4.98)	12,889	(6.44)
Positive/positive	154	(0.08)	176	(0.09)	222	(0.11)

* assuming a test sensitivity of 77% for screening of the first partner and of 90% for screening of the second partner

† assuming a not (yet) existing test sensitivity of 100%

‡ one partner is tested first; if he/she is positive, the second partner is also tested

estimated risk is not reduced for positive-negative couples (Table B.4); without screening the risk is 1:3,600. This disadvantage is present in all strategies, but is most prominent with an offer aimed at couples. Only with a detection rate of approximately 97% screening will also reduce the estimated risk for these couples.
Considering the problems that screening gives to couples with a positive-negative result some institutes have chosen a policy where a couple is only informed about carriership if both partners are carrier (16, 17). This prevents in many cases unnecessary anxiety and has furthermore the advantage that counselling can aim completely at couples with a high risk. Results of a pilot study show that this type of selective information has no effect on the participation (18). Selective information however deprives some people of the possibility to make a choice regarding procreation on the basis of information. This is in conflict with the starting point of the screening offer.

B.5 Prenatal screening

Prenatal screening is aimed at those for whom the need for information about possible congenital abnormalities is most actual. Therefore the participation can be high. The advantage of prenatal screening is that it is easy to integrate in the existing health care system. At the first contact in relation to pregnancy, women can be informed about screening by general practitioner, gynaecologist or midwife. An important disadvantage of the offer of prenatal screening is that not all options are possible for participating couples: there is already a pregnancy. With an increased risk there is a large possibility that, considering the time pressure, decisions are made too quickly. This can later lead to feelings of regret and blame. To decrease the time pressure, the offer of screening should be made as soon as possible in pregnancy.

Table B.4 Estimated probability that a couple in The Netherlands will have a child with cystic fibrosis after carrier screening

Mutations detected by screening	Screening result* One partner tested		Both partners tested		
	Negative	Positive	Both negative	One positive and one negative	Both positive
77%	1:15,250	1:120	1:64,604	1:508	1:4
90%	1:35,076	1:120	1:338,724	1:1,164	1:4
96%	1:87,690	1:120	1:2,108,304	1:2,904	1:4
97%	1:116,920	1:120	1:3,745,515	1:3,871	1:4

* the frequency of carriers in The Netherlands is 1:30, so the probability of a child with cystic fibrosis without screening is 1:3,600.

Results of a pilot project in Manchester show that such an offer is experienced positively (19). More than 80% of the participating women had the opinion that they had enough time to decide whether or not to have screening after having been informed. This does not remove the fact that pregnant women prefer screening before pregnancy to screening during pregnancy (20). The results of carrier screening programmes for other recessive inheritable disorders show that screening during pregnancy is most common. From a report published in 1989 in the U.S.A. regarding carrier screening for Tay-Sachs disease, 80% of the participants had screening only during pregnancy (21). In Sardinia there is a shift in thalassaemia screening: interest increases in couples for preconceptional screening (22).

Also with prenatal screening there is the question whether to offer screening stepwise or simultaneously. With stepwise screening it seems logical to first screen the pregnant woman since she already has medical help. For couples where the woman is identified as carrier, this means however a large burden to wait for the test result of the male. Results of a pilot study in the United Kingdom indicate that this stress decreases quite quickly after the negative test result of the partner becomes known (23). However, with a negative result for the partner there is still a risk that is approximately 5 times as high as the general risk. This indicates that for understanding and interpreting risk figures all kinds of psychological mechanisms play a role independent of the quantitative risk.

When all future parents make use of the possibility of prenatal screening, approximately 97.4% (stepwise screening) and 94.9% (simultaneous screening) of the couples will have a negative-negative test result (Table B.3). They have a very small probability of having a child with CF. For the other couples the test brings about that they are confronted with an increased probability of having a child with CF. Table B.3 shows that with the still incomplete test sensitivity not all couples at risk are detected who have a 25% probability of having a child with CF. Furthermore, a relatively large number of the positive-negative couples is missed, especially with stepwise screening. For the positive-positive couples there is a possibility for prenatal diagnosis (chorionic villus sampling, amniocentesis). With this diagnostic test there is a 100% guarantee whether the foetus is affected or not. Despite their increased risk, the positive-negative couples can not have prenatal diagnosis, because at most it can be demonstrated that the foetus is a carrier. This disadvantage obviously applies to all screening scenarios, but is the most relevant for prenatal screening.

B.6 Embryonic screening

A fifth possibility of carrier screening is embryonic screening. Only recently this form of diagnosis has been published. In The Lancet of September 1993 Brambati et al. describe a screening programme performed by them in Italy of embryonic screening in women who qualified for chorionic villus sampling because of the increased risk of having a child with chromosomal abnormalities (24). Villi obtained by the CVS were screened for the presence of the CF gene. In this type of screening, both foetuses with the CF gene on one chromosome as affected foetuses with the CF gene on both chromosomes are detected. In the screening programme one affected foetus was detected; this pregnancy was terminated because of the test result. In 12 of the more than 880 screened foetuses the ΔF508 mutation was present at one chromosome. Because not all mutations are detectable, these foetuses have an increased risk of CF. Two couples decided for this reason to terminate the pregnancy. In a comparable screening programme in the United States none of the participating couples broke off the pregnancy when only one CF mutation was detected. In some cases a sweat test was performed shortly after birth at the request of the parents (25).
Probably the advocates of embryonic screening point out that it is important to extract as much information from the villi as possible on an indication of CVS (26).

B.7 Discussion

Technological developments offer new possibilities to people. This is also true for carrier detection: it enables an informed choice with regard to reproduction and with this the prevention of distress. The discovery of the CF gene and the most common mutations enables screening not only within CF families but also outside the families. A complicating factor is the still incomplete sensitivity as a result of the large number of mutations that can cause the disorder. If it is decided to offer carrier screening outside CF families, the question is how this should happen. Screening of neonates is possible. The objections to neonatal screening are so large however that this type of screening seems no serious possibility. This also applies to screening of scholars. Although in this case the target group can be informed well, there are large objections: the information is not directly relevant and minor scholars can not decide completely themselves about participation. It seems logical to choose as a target group people in the reproductive age. Knowledge about carriership after all becomes relevant when reproduction is possible. When the advantages and disadvantages of preconceptional and prenatal screening are weighed, an offer of preconceptional

screening is preferred. In this type of screening the most relevant target group is reached. This group has, contrary to the target group of prenatal screening, still all reproductive options open after screening. Many people however turn out to need screening during pregnancy. A preconceptional screening offer where screening can happen before and during pregnancy would give in most to the wishes.

A discussion point with regard to an offer of preconceptional screening constitutes the question whether this offer should be aimed in a stepwise or simultaneous way. The advantage of simultaneous screening is that a more realistic image is obtained of the risk. If both partners are tested simultaneously, more certainty can be given about the risk also. Simultaneous screening however leads to twice as many positive-negative couples as stepwise screening. With the present still incomplete test sensitivity, screening will not reduce the risk for these couples. Furthermore, these couples do not have the possibility of prenatal diagnosis. A second important consequence of the still incomplete test sensitivity is that not all couples at risk are detected. In The Netherlands, approximately 60% of the carrier couples can be detected if screened for the most occurring mutation ΔF508. When screened for the mutation ΔF508 and for 13 other mutations 81% of the carrier couples can be detected. The gain of screening with a larger test sensitivity is that more carrier couples can be informed about their risk of having a child with CF.

The primary problem in an offer of embryonic screening is the impossibility to distinguish with another test (such as the sweat test in neonatal screening) carriers from patients. Furthermore this type of screening can only be used if for some other reason foetal material is collected. An offer of embryonic screening to all pregnant women would bring about a too large risk, given the probability of a spontaneous miscarriage after CVS. In our opinion embryonic screening can not be regarded as a serious possibility of carrier screening. This type of screening is not aimed at identifying carriers, but at detecting affected foetuses. In this sense embryonic screening should rather be seen as a form of prenatal diagnosis.

B.8 References

1. Schellekens H. De principes van de biotechnologie [The principles of biotechnology]. Med J Delft 1993;1:37-42.
2. Ten Kate LP. Erfelijkheid en epidemiologie van kystische fibrose (mucoviscidose) [Hereditability and epidemiology of cystic fibrosis (mucoviscidosis)]. Ned Tijdschr Geneeskd 1979;123(24):1020-1027.

3. Rommens JM, Iannuzzi MC, Kerem BS, Drumm ML, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordan JR, Tsui LC, Collins FS. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 1989;245(4922):1059-1065.
4. Riordan JR, Rommens JM, Kerem BS, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL, Drumm ML, Iannuzzi MC, Collins F, Tsui LC. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989;245(4922):1066-1073.
5. Kerem BS, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui LC. Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245(4922):1073-1080.
6. Halley DJJ, Veeze HJ, Sandkuyl LA, Wesby-van Swaay E, van Damme NH, Deelen WH, Witte JE, Niermeijer MF. The mutation delta F508 on Dutch cystic fibrosis chromosomes: frequency and relation to patients age at diagnosis. Hum Genet 1990;85(4):407-408.
7. Scheffer H, Bruinvels DJ, te Meerman GJ, Verlind E, Penninga D, Dankert J, ten Kate LP, Buys CHCM. Frequency of the delta F508 mutation and XV2c,KM19 haplotypes in cystic fibrosis families from The Netherlands: haplotypes without delta F508 still in disequilibrium. Hum Genet 1990;85(4):425-427.
8. Kooij L, Tijmsta T. Psychosociale implicaties van screening op gendragerschap van cystic fibrosis [Psychosocial implications of screening for gene carriership of cystic fibrosis]. Rijksuniversiteit Groningen, Vakgroep Gezondheidswetenschappen / Noordelijk Centrum voor Gezondheidsvraagstukken, 1994.
9. Verkerk PH, Derksen-Lubsen G, Vulsma T, Loeber JG, de Vijlder JJM, Verbrugge HP. Evaluatie van een decennium neonatale screening op congenitale hypothyreoidie in Nederland [Evaluation of a decade of neonatal screening for congenital hypothyroidism in The Netherlands]. Ned Tijdschr Geneeskd 1993;137(43):2199-2205.
10. Dankert-Roelse JE, te Meerman GJ, Martijn A, ten Kate LP, Knol K. Survival and clinical outcome in patients with cystic fibrosis, with or without neonatal screening. J Pediatr 1989;114(3):362-367.
11. Cobb E, Holloway S, Elton R, Raeburn JA. What do young people think about screening for cystic fibrosis? J Med Genet 1991;28(5):322-324.

12. Williamson R, Allison MED, Bentley TJ, Lim SM, Watson E, Chapple J, Adam S, Boulton M. Community attitudes to cystic fibrosis carrier testing in England: a pilot study. Prenat Diagn 1989;9(10):727-734.
13. Bianco I, Graziani B, Lerone M, Congedo P, Aliquo' MC, Ponzini D, Braconi F, Foglietta E, Modiano G. Prevention of thalassaemia major in Latium (Italy) [letter]. Lancet 1985;2(8460):888-889.
14. Zeesman S, Clow CL, Cartier L, Scriver CR. A private view of heterozygosity: eight-year follow-up study on carriers of the Tay-Sachs gene detected by high school screening in Montreal. Am J Med Genet 1984;18(4):769-778.
15. Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, Marteau T. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? BMJ 1993;306(6892):1584-1586.
16. Wald NJ. Couple screening for cystic fibrosis. Lancet 1991;338(8778):1318-1319.
17. Brock DJH. Antenatal community screening for cystic fibrosis. Newsletter of the European Community concerted action for cystic fibrosis 1993;2:4-5.
18. Livingstone J, Axton RA, Mennie M, Gilfillan A, Brock DJH. A preliminary trial of couple screening for cystic fibrosis: designing an appropriate information leaflet. Clin Genet 1993;43(2):57-62.
19. Harris H, Scotcher D, Hartley N, Wallace A, Craufurd D, Harris R. Cystic fibrosis carrier testing in early pregnancy by general practitioners. BMJ 1993;306(6892):1580-1583.
20. Botkin JR, Alemagno S. Carrier screening for cystic fibrosis: a pilot study of the attitudes of pregnant women. Am J Public Health 1992;82(5):723-725.
21. Shapiro DA, Shapiro LR. Pitfalls in Tay-Sachs carrier detection: physician referral patterns and patient ignorance. N Y State J Med 1989;89(6):317-319.
22. Cao A, Rosatelli MC, Galanello R. Population-based genetic screening [review]. Curr Opin Genet Dev 1991;1(1):48-53.
23. Mennie ME, Gilfillan A, Compton M, Curtis L, Liston WA, Pullen I, Whyte DA, Brock DJH. Prenatal screening for cystic fibrosis. Lancet 1992;340(8813):214-216.
24. Brambati B, Tului L, Fattore S, Férec C. First-trimester fetal screening of cystic fibrosis in low-risk population [letter]. Lancet 1993;342(8871):624.
25. Black SH, Bick DP, Maddalena A, Schulman JD, Jones SL, Fallon L, Cummings E, Menapace-Drew G. Pregnancy screening for cystic fibrosis [letter]. Lancet 1993;342(8879):1112-1113.

26. Young ID. Pregnancy screening for cystic fibrosis. Lancet 1993;342(8871):569-570.

Appendix C
Serum screening for Down syndrome and open neural tube defects in the second trimester of pregnancy – does it satisfy the criteria of the Committee Genetic Screening of the Dutch Health Council?

C.1 Introduction

Serum screening for Down syndrome and open neural tube defects in the unborn child is carried out on a large scale in several countries. In The Netherlands there is debate whether the present programme for detection of Down syndrome in pregnancy by diagnostic amniocentesis or chorionic villus sampling, which is limited to women over 35, should be replaced by a serum screening offer to all pregnant women (1-4).

The Dutch Population Screening Act (WBO) requires that central government approves certain screening programmes before they are implemented. Because genetic screening has some special implications, a committee of the Health Council (hereafter called 'the committee') has issued a report on genetic screening (5). In this report, the committee formulated eleven absolute criteria and ten weighing criteria for the admission of genetic screening programmes, taking the criteria of Wilson and Jungner (6) as a starting point. In this article we assess serum screening for Down syndrome and open neural tube defects in the unborn child against the criteria of the committee and indicate gaps in knowledge for making decisions in The Netherlands. We address screening for both Down syndrome and open neural tube defects, unless explicitly noted otherwise.

C.2 Assessing the criteria of the Health Council Committee

According to the Health Council Committee, genetic screening has to meet three groups of criteria. The first group (1-5) consists of absolute criteria that do not depend on the particularities such as design and organisation of a specific screening programme. The second group (6-11) has to be assessed for a specific screening

programme, and the third group (12a-j) is composed of ten weighing criteria where the overall balance should be directed towards the benefits. We discuss the criteria groupwise.

C.2.1 Absolute criteria, independent of the specific screening programme

1. *The genetic screening programme must concern a health problem or a condition that can lead to a health problem in those being tested, or in their descendants.*

Down syndrome and neural tube defects are serious health problems for the persons involved and their family.

2. *The target population of the screening programme must be clearly defined.*

Serum screening targets pregnant women with a gestational age of 15-18 weeks.

3. *The screening programme should enable participants to become aware of the presence or risk of a disorder or carrier status, and to take a decision based on that information.*

The individual risk of a Down syndrome child or a child with an open neural tube defect can be calculated by an algorithm using the concentration of serum markers and maternal age. Above a cut-off risk defined beforehand, the couple can choose for a diagnostic test such as ultrasound examination and/or amniocentesis. In case of a serious abnormality, the parents can opt for termination of pregnancy or for continuation of pregnancy, preparing themselves for the birth of the child. In the latter case, adequate care around delivery can be agreed on and organised in an earlier stage.

4. *Practical courses of action must be open to the participants.*

See discussion of criterion 3. The Dutch abortion law allows termination of pregnancy until neonatal viability. Reckoning with possible inaccuracies in calculating gestational age (GA) this means until 22-24 weeks depending on the way of determining GA. The time schedule of serum screening allows decisions to be taken before that time (see also criterion 12f).

5. *A test method should be available which is suited to the objective of the screening.*

Serum screening is currently based on the measurement of alpha-foetoprotein (αFP), unconjugated oestriol (uE3), and (free-β) human chorionic gonadotropin (hCG) levels in maternal blood. In combination with maternal age, the concentration of these analytes predicts the individual risk for a Down syndrome or open neural tube foetus in that pregnancy. The test characteristics of serum screening are expected to improve with the introduction of new markers. Also screening in the first trimester will

eventually become possible, with as most promising candidate serum markers free-βhCG and Pregnancy Associated Plasma Protein A (PAPP-A) (7).

C.2.2 Conclusion with regard to the independent absolute criteria

Serum screening for Down syndrome and neural tube defects fulfils the absolute criteria set by the committee.

C.2.3 Absolute criteria that have to be met in a specific programme

6. *Participation in the genetic screening programme should be voluntary and conditional on consent based on good information.*

Voluntary and well informed participation has to be realised in the screening programme itself; whether counselling has been comprehensible and non-directive can only be checked afterwards. High uptake rates of prenatal blood tests suggest passive acceptance, while uptake is lower in case more non-directive information is passed on to the woman (8). The way in which routine prenatal screening is presented will not always lead to well-informed decisions; health care providers should be well trained in how to inform people about the advantages and disadvantages of serum screening (9).

7. *The target group should be supplied with accurate, comprehensible information.*

The information given before the screening should at least discuss the conditions possibly detected by the screening (Down syndrome and open neural tube defects), the likelihood of detection, the test method, the significance of low-risk and high-risk test results including diagnostic tests, the options after a diagnosis 'Down syndrome' or 'open neural tube defect', and how further information can be obtained (10). At this moment there is considerable debate in the British literature whether this information should be detailed or simple (8, 11-14).

8. *There should be sufficient facilities for follow-up diagnostics, for carrying out the chosen courses of action and for informing and supporting the participants.*

Using a risk cut-off of 1 in 250 for Down syndrome or open neural tube defects, 4.5% of the pregnancies will be classified as high risk for Down syndrome (cf. criterion 12d) and 1.9% as high risk for open neural tube defects (15). Using uptake rates from literature (16-26), 5,500-10,200 amniocenteses would be performed annually if serum screening were to replace maternal age screening in The Netherlands (±200,000 pregnancies per year). In 1993 more than 7,000 invasive prenatal diagnoses were done for advanced maternal age reasons in The Netherlands. The potential number of

amniocenteses as a consequence of serum screening is thus in the same order as the number of amniocenteses for advanced maternal age currently done.
The most recent number of induced abortions of Down syndrome foetuses for all indications in The Netherlands was 86 (=92% of all detected foetuses) (27). If the age indication would be replaced by serum screening, between 55 and 165 extra induced abortions would be performed. Annually 30,242 legal abortions are done in The Netherlands (28). Therefore no more resources are required in case age-based screening by amniocentesis is replaced by serum screening.
Facilities for performing the amniocenteses indicated through results of serum screening and terminations when requested are sufficient. However, a major problem are the facilities required for informing pregnant women adequately before and after the test, and for assisting those ending with a termination of pregnancy because of foetal anomaly.

9. *Provision should be made for continuous quality assurance of the effectiveness, efficiency and safety of the test procedure, and all follow-up procedures, as well as information and support given to the participants.*

The laboratories have to continuously evaluate the serum determinations by means of quality standards. In The Netherlands invasive prenatal diagnosis is regulated by law and can only be done in authorised centres. These have the obligation to keep quality standards and report annually. Evaluation of information and counselling demands labour-intensive psychosocial research and can therefore only be performed in a research framework.

10. *If scientific research is carried out within the framework of screening, the participants should be properly informed about this in advance.*

Because the conserved sera may be traced to the individual woman, consent of the participants has to be obtained if additional research is done that exceeds evaluation of the test characteristics (29).

11. *The procedures used for the storage of medical information and cellular material must incorporate adequate measures to protect both the personal privacy of the participants and their rights regarding their personal data and cellular material.*

The Dutch Data Protection Act ('Wet Persoonsregistratie') and the ministerial order about sensitive data ('Besluit Gevoelige Gegevens') state that only data that are essential to the treatment of the patient can be filed conditional on the patient's approval. Rules on use of registered data, blood, storage periods and procedures for file clearing have to be made for this purpose and transmitted to the patient.

C.2.4 Conclusion with regard to the programme-dependent absolute criteria

Facilities for follow-up diagnostic tests and for different courses of action will be no problem in The Netherlands. When serum screening becomes a large scale event, a huge effort will be needed to inform and train health care providers, to adequately inform the patients, and to evaluate both the screening performance and the social and psychological impact. The question whether to give detailed or simple information to the participants has to be answered. The other absolute programme-dependent criteria have to be assessed in the specific screening programme by continuous evaluation.

C.2.5 Weighing criteria

12. The benefits for the participants in the programme should outweigh the disadvantages. To support this evaluation, those proposing a screening programme must provide information about:

a. The prevalence of the disease or disorder in the target group.

Approximately 1.2-1.3 per 1,000 births are affected by Down syndrome, making it the most common congenital cause of mental handicap (10, 30). The incidence of Down syndrome rises steeply with increasing maternal age (30) and hence depends on the age distribution of the target population in The Netherlands. Approximately 9 percent of all pregnancies (maternal age higher or equal to 36 years at 18 weeks gestation) is 'responsible' for the birth of 35 percent of the children with Down syndrome (32).

The birth incidence of a child with a neural tube defect for the years 1980-1986 was 1.4 per 1,000 in the northern part of The Netherlands (0.66/1,000 anencephaly and 0.58/1,000 spina bifida) and 3.2/1,000 in the United Kingdom (1.28/1,000 anencephaly and 1.58/1,000 spina bifida) (33). The risk for neural tube defects is not age-dependent.

b. The natural course of the disorder, and the variation in degrees of severity.

Of all liveborn Down syndrome patients, thirty percent has a congenital heart disease. A quarter of the patients with congenital heart disease dies within a year after birth, while fifty percent reaches the age of thirty. Of the Down syndrome patients without congenital heart disease, nine percent dies within the first year of life and 80 percent reaches the age of thirty (34). In the majority of patients there are age-dependent degenerative changes in the brain which are typical of Alzheimer's disease.

Anencephaly is not compatible with life. Children with spina bifida can be kept alive through a variety of operations, both shortly after birth and later in life. They are almost always physically –and frequently also mentally – handicapped (35).

c. *The target group and the considerations which led to the choice of the proposed target group and the proposed time of testing.*

Down syndrome occurs in pregnant women of all ages. Because the predictive value of the test is much lower for younger women than for older women (Table C.1), some people advocate restricting serum screening to older age categories. On the other hand a serum screening programme only for women younger than 35 years of age has been proposed in the United States of America, to be used complementary to direct amniocentesis or chorionic villus sampling in women older than 35 years (36). Strategies and risk cut-offs will depend on current national policies and resources and on preferences in society.

Ideally, screening should be performed as early as possible in pregnancy. At present there is sufficient information for making a good risk estimation for screening in the second trimester of pregnancy, but not for screening in the first trimester.

d. *The specificity, sensitivity and predictive value of the test method and the burden which testing imposes on participants.*

Ten projects have shown a combined sensitivity (detection percentage) of 67 percent for Down syndrome (Table C.2). Assuming a 100% uptake of screening, 4.5 percent of the women who are not pregnant of a child with Down syndrome will be offered amniocentesis because of a high-risk test result (false positive), that is a specificity of 95.5 percent. For comparison: a risk estimation on the basis of maternal age (36 years or older at 18 weeks gestation) with a 100 percent uptake detects 35 percent of Down syndrome foetuses with a specificity of 91 percent. The predictive value of a high-risk

Table C.1 Calculation of the number of false-positive serum test results per detected Down syndrome foetus

Maternal age	Prevalence at prenatal diagnosis (per 1,000 women) (a), (30)	Detection percentage* (sensitivity) (b), (31)	False positive percentage* (1-specificity) (c), (31)	Number of false positive test (FP) results (per 1,000 women) d = (1-a)*c	Number of true-positive test (TP) results (per 1,000 women) e = a*b	Number of FP results per TP result f = d/e
35	3.8	72%	11%	110	3	40.1
40	13.3	90%	33%	326	12	27.2
45	45.3	98%	68%	649	44	14.6

* cut-off risk 1:250, gestational age determined with ultrasound

test result (cut-off 1:250) is 1:68 if the gestational age is based on the last menstrual period and 1:53 for a gestational age determined through ultrasound (31).
For open spina bifida the detection percentage of the αFP-test for a risk cut-off of 2.5 MoM (multiples of the normal median) is 75 if the gestational age is based on the last menstrual period and 90% for an ultrasonically detected gestational age. The percentages of women with a false-positive test result are 3.3 and 2.8 respectively. Some of them have a child with another abnormality such as exomphalos and gastroschisis. The predictive value for open spina bifida of a high-risk test result after ultrasound dating is 1:31 for a birth prevalence of 1/1,000 and 1:16 for a birth prevalence of 2/1,000 (31). For anencephaly the detection percentage is at least 90 percent with a predictive value of about 1:23 (35). The burden for the participants is discussed under criterion 12g.

e. The available courses of action if a health problem or carrier status is revealed.

See also criterion 3. Furthermore it should be noted that pregnancies with a high αFP- and/or high hCG-concentration that can not be explained by the presence of a Down syndrome or neural tube defect foetus have a higher risk of obstetric complications (37-40). These pregnancies should therefore be labelled as high-risk pregnancies. Research should clarify which cut-off value is optimal and whether the findings have clinically useful consequences. This finding of an enhanced obstetric risk has special significance in the organisation of prenatal care in The Netherlands where in 70% of pregnant women, prenatal care is initially provided by GP's or midwives.

f. The time allowed by the procedure for consideration and possible implementation of the selected course of action.

Serum analysis can be performed daily if there are more than 50 samples a day, so that the time between blood sampling and the availability of the test result for the woman is 3-5 days. In case of a high-risk test result, prenatal diagnosis can be performed within seven days, depending on the time the woman needs to make her decision. The result of ultrasound examination is known immediately, while the result of the amniocentesis is known within 10-14 days. Consequently, if blood sampling is performed between 15 and 18 weeks, the result of amniocentesis can be known between 17 and 22 weeks. Because the Dutch abortion law states that termination of pregnancy has to be performed before 22 weeks gestation (see above), the woman has between a few days and five weeks to decide whether or not to terminate the pregnancy.

Table C.2 Results of ten pilot studies of second-trimester serum screening

	No. of pregnancies in study	Mean age (range)	Risk cut-off †	Down's pregnancies ‡	Detected Down's pregnancies	Detection percentage (sensitivity)	False-positive percentage (100–specificity)	Positive predictive value	Amniocentesis uptake	Participation
Haddow et al. (17)	25,207	27.0 (16-41)	1:190 m	36	21	58	3.8	1:38	79	not given
Phillips et al. (18)	9,530	24.5 (12-34)	1:274 m	7	4	57	3.2	1:77	68	not given
Wald et al. (19)	12,603	not given	1:250 b	25	12	48	4.1	1:43	75	74%
Burton et al. (20)	8,233	28.1 (13-48)*	1:270 m	12	10	83	5.9	1:48	81	not given
Cheng et al. (21)	7,718	28.7	1:195 m	22	20	91	6.0	1:23	69	not given
Wenstrom et al. (22)	18,712	not given	1:190 m	27	13	48	3.6	1:51	78	not given
Goodburn et al. (23)	25,359	27.0 (15-53)*	1:200 b	48	36	75	4.0	1:28	85	77%
Piggott et al. (24)	6,990	not given	1:250 b	11	8	73	3.0	1:26	76	67%
Benn et al. (25)	11,434	not given	1:270 m	20	14	70	5.9	1:48	67	not given
Kellner et al. (26)	10,605	29.7 (14-44)	1:270 b	16	12	75	7.2	1:64	90	not given
All	136,391	-	-	224	150	67	4.5	1:40	80	-

* median age

† b=at birth, m=mid-trimester

‡ detected and undetected

g. *The possible psychological, social and other repercussions (both positive and negative) of an offer and of participation or non-participation in the screening for the person to be tested and for members of their family or for groups within the community.*

Adverse psychological consequences are to be expected during the decision process whether or not to have serum screening, during the waiting for the screening results, and after a high-risk test result. The consequences of a high-risk test result for a non-Down syndrome pregnancy are mainly short-term: the anxiety generated by the serum screening results generally subsides rapidly when diagnostic tests are reassuring (41-46). There has not been research on psychological consequences of having a Down syndrome child after low-risk test results. Positive psychological effects of serum screening are the autonomy and self-determination allowed to the patient and consequently her enhanced possibilities to detect or exclude some of the most serious foetal abnormalities.

Amniocentesis causes iatrogenic loss of pregnancy in about 0.3 percent of cases (47). If amniocentesis detects a serious abnormality, the woman can choose to terminate the pregnancy, which has a risk of 1-2 percent of medical complications (47) and induces a long period of perinatal grief (48).

h. *The likelihood of erroneous results, the possible consequences of this for participants and the measures taken to limit any harm which such an error might cause.*

See also criteria 12d and 12g. In order to reach a uniformly high standard of serum screening, the sera should be examined in a limited number of laboratories. These laboratories have to communicate intensively with the departments of obstetrics in which the counselling is done and the invasive prenatal diagnosis is performed. Centres for prenatal diagnosis have a pivot role as advisors and instructors for other pregnancy care providers.

i. *The safeguards for participants against unjustified impediments (as a result of their participation or non-participation in the screening programme or follow-up testing) to obtain employment or private insurance cover.*

The insurance implications of genetic testing are more and more a concern (49). We are not aware of any cases in the world literature where difficulties in getting insured have occurred because people opted out of prenatal screening, prenatal diagnosis, or termination of pregnancy of a foetus with severe illness.

j. The costs of the screening and of the necessary infrastructure.

Several studies have estimated the costs of serum screening for Down syndrome and/or open neural tube defects prospectively and retrospectively for various countries and various situations (19, 50-59). Per 100,000 pregnant women these costs have been estimated between €2,097,000 and €3,835,000 for Great Britain (19, 55, 56, 59). For the situation in the United States of America, which we regard less comparable with the Continental European situation, much higher costs have been estimated (57). For the Dutch situation no calculations are available.

C.2.6 Discussion of weighing criteria

For the Dutch situation data are available for most (12a-12f, 12h-12i), but not all criteria (12g, 12j). The psychological, social and other repercussions to the tested people and/or their family (criterion 12g) as well as the costs of a screening programme (criterion 12j) have been studied in the UK. Part of the data is probably valid for the Dutch situation. Ideally Dutch studies should be conducted to make the final weighing.

C.3 General discussion

Insofar they can be checked, the absolute criteria for genetic screening of the Health Council Committee are fulfilled. Contrary to researchers in other countries we cannot yet assess the weighing criteria for The Netherlands because the individual psychological and social consequences of serum screening and the costs of a programme have not yet been examined. One of the reasons of this gap in knowledge is that there is no tradition of αFP-screening for open neural tube defects in The Netherlands, as opposed to for example Great Britain (1-4). Before we contemplate to introduce a larger-scale serum screening programme in The Netherlands, we should investigate a number of issues, amongst others optimal ways of informing the patient and psycho-emotional consequences as well on the individual level as on society as a whole (8, 11-14).

If the introduction of serum screening is considered, we propose the following preparatory steps:

- diffusion of knowledge through the departments of obstetrics where invasive prenatal diagnosis is performed (the 'centres for prenatal diagnosis');
- training of current health care providers and/or special counsellors who can assist (individually or on a group basis) patients with their choices concerning screening

(not only for Down syndrome but for example also for cystic fibrosis) and diagnostic procedures;
- uniform information (written or on tape) in various languages;
- close collaboration between laboratories analysing sera, centres for prenatal diagnosis, and health care providers.

Once introduced, the quality of the programme should be monitored by a committee installed for that purpose. Training of health care providers and development of information material should be a continuing effort. We are ultimately in favour of:
- individual information and reporting of results through general practitioner, midwife or gynaecologist;
- follow-up of the course of pregnancy and outcome of all patients for instance through the nationwide obstetric registration.

These steps ask for a large logistic and financial effort and a long time of preparation. The success of such a programme depends on the willingness to make these efforts and requires a dedication of the persons involved. Because screening for disease takes a growing share of the health care (for example cystic fibrosis) such a restructuring of information and follow-up has to be done anyway.

Counselling should contain only comprehensible information and should never be directive or coercive. In order to really make decisions in freedom, a social climate is necessary in which there is room and support for handicapped persons. The committee of the Health Council duly gives this strong emphasis in her report.

C.4 References

1. Van den Boer-van den Berg JMA, Dupuis HM. De triple-serumtest voor detectie van Down-syndroom en neurale-buisdefecten; het probleem van een risicoschattende test [The triple-serum test for detection of Down syndrome and neural tube defects; the problem of a risk assessment test]. Ned Tijdschr Geneeskd 1993;137(26):1286-1289.
2. Beekhuis JR, Mantingh A, de Wolf BTHM, van Lith JMM, Breed ASPM. Serumscreening van zwangeren op foetale neurale-buisdefecten èn Down-syndroom; eerste ervaringen in Nederland [Serum screening of pregnant women for fetal neural tube defects and Down syndrome; initial experiences in The Netherlands]. Ned Tijdschr Geneeskd 1993;137(26):1303-1307.

3. Giltay JC. De triple-serumtest voor detectie van Down-syndroom en neurale-buisdefecten; het probleem van een risicoschattende test [brief] [Triple serum test for the diagnosis of Down syndrome and neural tube defects; the problem of a risk assessment test (letter)]. Ned Tijdschr Geneeskd 1993;137(33):1681.
4. Beekhuis JR, Mantingh A, de Wolf BTHM, van Lith JMM, Breed ASPM. De triple-serumtest voor detectie van Down-syndroom en neurale-buisdefecten; het probleem van een risicoschattende test [brief] [The triple serum test for the diagnosis of Down syndrome and neural tube defects; the problem of a risk assessment test (letter)]. Ned Tijdschr Geneeskd 1993;137(33):1682.
5. Health Council of The Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994; no. 1994/22E.
6. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization, 1968. Public Health Papers 34.
7. Wald NJ, Kennard A, Smith D. First trimester biochemical screening for Down's syndrome. Ann Med 1994;26(1):23-29.
8. Thornton JG, Hewison J, Lilford RJ, Vail A. A randomised trial of three methods of giving information about prenatal testing. BMJ 1995;311(7013):1127-1130.
9. Marteau TM, Slack J, Kidd J, Shaw RW. Presenting a routine screening test in antenatal care: practice observed. Public Health 1992;106(2):131-141.
10. The Royal College of Obstetricians and Gynaecologists (RCOG). Report of the RCOG Working Party on biochemical markers and the detection of Down's syndrome. London: RCOG, 1993.
11. Boyd PA. Serum screening for Down's syndrome. Private patients may receive less counselling [letter]. BMJ 1994;309(6965):1372.
12. Reynolds T, John R. Serum screening for Down's syndrome. National policy would ensure consistency [letter]. BMJ 1994;309(6965):1372-1373.
13. Allaby M. Serum screening for Down's syndrome. Counselling should emphasise possible outcomes of screening [letter]. BMJ 1994;309(6965):1373.
14. Barrow M, Falconer Smith J, Stewart C. Serum screening for Down's syndrome. Keeping the concept of risk simple [letter]. BMJ 1994;309(6965):1373.
15. Kriek R, Korenromp MJ, Hagenaars AM, Christiaens GCML, Bruinse HW. Screening op foetale neuraalbuisdefecten. Alfa-foetoproteïneconcentratie in maternaal serum [Screening for fetal neural tube defects. Alpha-fetoprotein concentration in maternal serum]. Med Contact 1994;49(9):321-324.

16. Spencer K, Carpenter P. Prospective study of prenatal screening for Down's syndrome with free beta human chorionic gonadotrophin. BMJ 1993;307(6907):764-769.
17. Haddow JE, Palomaki GE, Knight GJ, Williams J, Pulkkinen A, Canick JA, Saller DNJ, Bowers GB. Prenatal screening for Down's syndrome with use of maternal serum markers. N Engl J Med 1992;327(9):588-593.
18. Phillips OP, Elias S, Shulman LP, Andersen RN, Morgan CD, Simpson JL. Maternal serum screening for fetal Down syndrome in women less than 35 years of age using alpha-fetoprotein, hCG, and unconjugated estriol: a prospective 2-year study. Obstet Gynecol 1992;80(Pt 1):353-358.
19. Wald NJ, Kennard A, Densem JW, Cuckle HS, Chard T, Butler L. Antenatal maternal serum screening for Down's syndrome: results of a demonstration project. BMJ 1992;305(6850):391-394.
20. Burton BK, Prins GS, Verp MS. A prospective trial of prenatal screening for Down syndrome by means of maternal serum alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol. Am J Obstet Gynecol 1993;169(3):526-530.
21. Cheng EY, Luthy DA, Zebelman AM, Williams MA, Lieppman RE, Hickok DE. A prospective evaluation of a second-trimester screening test for fetal Down syndrome using maternal serum alpha-fetoprotein, hCG, and unconjugated estriol. Obstet Gynecol 1993;81(1):72-77.
22. Wenstrom KD, Williamson RA, Grant SS, Hudson JD, Getchell JP. Evaluation of multiple-marker screening for Down syndrome in a statewide population. Am J Obstet Gynecol 1993;169(4):793-797.
23. Goodburn SF, Yates JRW, Raggatt PR, Carr C, Ferguson-Smith ME, Kershaw AJ, Milton PJD, Ferguson-Smith MA. Second-trimester maternal serum screening using alpha-fetoprotein, human chorionic gonadotrophin, and unconjugated oestriol: experience of a regional programme. Prenat Diagn 1994;14(5):391-402.
24. Piggott M, Wilkinson P, Bennett J. Implementation of an antenatal serum screening programme for Down's syndrome in two districts (Brighton and Eastbourne). The Brighton and Eastbourne Down's Syndrome Screening Group. J Med Screen 1994;1(1):45-49.

25. Benn PA, Horne D, Briganti S, Greenstein RM. Prenatal diagnosis of diverse chromosome abnormalities in a population of patients identified by triple-marker testing as screen positive for Down syndrome. Am J Obstet Gynecol 1995;173(2):496-501.
26. Kellner LH, Weiss RR, Weiner Z, Neuer M, Martin GM, Schulman H, Lipper S. The advantages of using triple-marker screening for chromosomal abnormalities. Am J Obstet Gynecol 1995;172(3):831-836.
27. Jaarverslagcommissie Werkgroep Prenatale Diagnostiek. Jaarverslag 1990 [Annual report 1990]. Utrecht: Werkgroep Prenatale Diagnostiek van de Nederlandse Vereniging voor Obstetrie en Gynaecologie en de Vereniging Klinische Genetica Nederland, 1993.
28. Statistics Netherlands. Statistisch Jaarboek 1995 [Statistical yearbook 1995]. Voorburg/Heerlen: SDU, 1995.
29. Health Council of The Netherlands. Proper use of Human Tissue. The Hague: Health Council, 1994; no. 1994/01E.
30. Hook EB. Prevalence, risks and recurrence. In: Brock DJH, Rodeck CH, Ferguson-Smith MA, eds. Prenatal diagnosis and screening. London: Churchill Livingstone, 1992:351-392.
31. Wald NJ, Cuckle HS. Biochemical screening. In: Brock DJH, Rodeck CH, Ferguson-Smith MA, eds. Prenatal diagnosis and screening. London: Churchill Livingstone, 1992:563-577.
32. Statistics Netherlands. Maandstatistiek bevolking 94/8 [Monthly bulletin of population statistics 94/8]. Voorburg/Heerlen: Statistics Netherlands, 1994; no. 94/8.
33. Eurocat Working Group. Prevalence of neural tube defects in 20 regions of Europe and the impact of prenatal diagnosis, 1980-1986. J Epidemiol Community Health 1991;45(1):52-58.
34. Baird PA, Sadovnick AD. Life expectancy in Down syndrome. J Pediatr 1987;110(6):849-854.
35. Gezondheidsraad. Neuraalbuisdefecten [Neural tube defects]. Den Haag: Gezondheidsraad, 1988; no. 15.
36. Down syndrome screening. Washington, DC: American College of Obstetricians and Gynecologists Committee Opinion, 1994; no. ACOG 141.
37. Katz VL, Chescheir NC, Cefalo RC. Unexplained elevations of maternal serum alpha-fetoprotein. Obstet Gynecol Surv 1990;45(11):719-726.

38. Waller DK, Lustig LS, Smith AH, Hook EB. Alpha-fetoprotein: a biomarker for pregnancy outcome [review]. Epidemiology 1993;4(5):471-476.
39. Gonen R, Perez R, David M, Dar H, Merksamer R, Sharf M. The association between unexplained second-trimester maternal serum hCG elevation and pregnancy complications. Obstet Gynecol 1992;80(1):83-86.
40. Morssink LP, Kornman LH, Beekhuis JR, De Wolf BTHM, Mantingh A. Abnormal levels of maternal serum human chorionic gonadotropin and alpha-fetoprotein in the second trimester: relation to fetal weight and preterm delivery. Prenat Diagn 1995;15(11):1041-1046.
41. Burton BK, Dillard RG, Clark EN. The psychological impact of false positive elevations of maternal serum alpha-fetoprotein. Am J Obstet Gynecol 1985;151(1):77-82.
42. Earley KJ, Blanco JD, Prien S, Willis D. Patient attitudes toward testing for maternal serum alpha-fetoprotein values when results are false-positive or true-negative. South Med J 1991;84(4):439-442.
43. Abuelo DN, Hopmann MR, Barsel Bowers G, Goldstein A. Anxiety in women with low maternal serum alpha-fetoprotein screening results. Prenat Diagn 1991;11(6):381-385.
44. Marteau TM, Slack J. Psychological implications of prenatal diagnosis for patients and health professionals. In: Brock DJH, Rodeck CH, Ferguson-Smith MA, eds. Prenatal diagnosis and screening. London: Churchill Livingstone, 1992:663-673.
45. Marteau TM, Cook R, Kidd J, Michie S, Johnston M, Slack J, Shaw RW. The psychological effects of false-positive results in prenatal screening for fetal abnormality: a prospective study. Prenat Diagn 1992;12(3):205-214.
46. Statham H, Green J. Serum screening for Down's syndrome: some women's experiences. BMJ 1993;307(6897):174-176.
47. Heckerling PS, Verp MS. A cost-effectiveness analysis of amniocentesis and chorionic villus sampling for prenatal genetic testing. Med Care 1994;32(8):863-880.
48. Korenromp MJ, Iedema-Kuiper HR, van Spijker HG, Christiaens GCML, Bergsma J. Termination of pregnancy on genetic grounds; coping with grieving. J Psychosom Obstet Gynaecol 1992;13:93-105.
49. Anonymous. Have you had a gene test? [editorial]. Lancet 1996;347(8995):133.
50. Henderson JB. An economic appraisal of the benefits of screening for open spina bifida. Soc Sci Med 1982;16(5):545-560.

51. Layde PM, Allmen SDv, Oakley Jr. GP. Maternal serum alpha-fetoprotein screening: a cost-benefit analysis. Am J Public Health 1979;69(6):566-573.
52. Gill M, Murday V, Slack J. An economic appraisal of screening for Down's syndrome in pregnancy using maternal age and serum alpha fetoprotein concentration. Soc Sci Med 1987;24(9):725-731.
53. Nightingale EO, Meister SB, eds. Prenatal screening, policies, and values: the example of neural tube defects. Cambridge, MA: Division of Health Policy Research and Education, Harvard University, 1987.
54. Tosi LL, Detsky AS, Roye DP, Morden ML. When does mass screening for open neural tube defects in low-risk pregnancies result in cost savings? Can Med Assoc J 1987;136(3):255-265.
55. Sheldon TA, Simpson J. Appraisal of a new scheme for prenatal screening for Down's syndrome. BMJ 1991;302(6785):1133-1136.
56. Shackley P, McGuire A, Boyd PA, Dennis J, Fitchett M, Kay J, Roche M, Wood P. An economic appraisal of alternative pre-natal screening programmes for Down's syndrome. J Public Health Med 1993;15(2):175-184.
57. Haddow JE, Palomaki GE, Knight GJ, Cunningham GC, Lustig LS, Boyd PA. Reducing the need for amniocentesis in women 35 years of age or older with serum markers for screening. N Engl J Med 1994;330(16):1114-1118.
58. Seror V, Muller F, Moatti JP, Le Gales C, Boue A. Economic assessment of maternal serum screening for Down's syndrome using human chorionic gonadotropin. Prenat Diagn 1993;13(4):281-292.
59. Fletcher J, Hicks NR, Kay JDS, Boyd PA. Using decision analysis to compare policies for antenatal screening for Down's syndrome. BMJ 1995;311(7001):351-356.

Appendix D
Comparison of single-entry and double-entry two-step couple screening for cystic fibrosis carriers

D.1 Introduction

Cystic fibrosis (CF) is the most common life-shortening recessive disorder affecting people of European descent (1). For instance, in the United States of America alone, 1,700-2,000 babies are born with CF annually (1). Disregarding rare instances of uniparental disomy (2) or pseudodominance, both parents of CF patients are carriers of one mutated copy of the so-called CFTR gene (3). The number of Americans who are CF carriers is estimated to be 8 million (1). However, only children of couples where both partners are carriers are at a high 1-in-4 risk of being affected with CF. In the United States, 1 in every 625 couples is supposed to have this 1-in-4 risk with each pregnancy (1). If couples with such a high risk are identified before birth or conception of a CF child, they can be informed about their high risk and consider all options, including prenatal diagnosis. In theory, the identification of all at risk couples can be achieved by population screening programmes, and many pilot studies are currently undertaken (4-9). The number of Americans of reproductive age who could theoretically be involved in CF carrier screening amounts to 125 million (1). With such high numbers, all possible strategies need to be carefully considered.

One of the main technical problems with CF carrier screening is that there is no single screening method that detects all carriers. Screening is performed through mutation detection by DNA technology. Several hundred different mutations have been identified so far (10). One mutation, ΔF508, has a particular high frequency in most white populations, representing 60-80% of all mutated CFTR genes (11). Some other mutations, each with an individual frequency of 1 to a few percent, together make up 10-15% of mutated CFTR genes. So, in most populations, 5-30% of all CFTR mutations cannot be detected easily because they are either rare or still unknown. Several strategies have been proposed to minimise the disadvantages associated with the incomplete sensitivity of present screening methods.

In this paper we will compare the arithmetic consequences of two types of couple screening: single-entry two-step screening (SETS) and double-entry two-step screening (DETS). In SETS, one starts with testing one member of the couple first (first step), and proceeds to test the other member (second step) only if the first member is identified as a carrier. In view of the large number of possible mutations, one might choose for economic reasons to employ a test with a lower sensitivity in testing the first member than in testing the second member. For instance, one could screen only for the ΔF508 mutation in the first member of the couple, and screen for ΔF508 and as many mutations as possible in the second member. In DETS, both members of the couple are tested initially for one or a few mutations (first step) and partners of identified carriers, who themselves are not identified as carriers in the first step, are tested for more mutations (second step).

The differences between SETS and DETS are the following. In SETS, only one member (single-entry) and in DETS both members (double-entry) of the couple are involved in the first step of the procedure. In SETS, the sensitivity of the second test may be chosen to be the same as the sensitivity of the first test, although a higher-sensitivity second test has potential advantages. In DETS, a second test always aims to increase the number of mutations for which the partner of an already identified carrier is tested. SETS and DETS have in common that the couple rather than the individual is the target of the screening, but in SETS one member of the couple will usually remain untested.

SETS and DETS will be compared here with regard to the frequency of identified carrier couples and resulting detection rate, the frequency of couples with one identified carrier and their (remaining) risk for CF in a child, and the frequency of couples without an identified carrier and their (remaining) risk.

D.2 Methods

Figure D.1 and Figure D.2 depict schematically the possible outcomes of SETS and DETS, respectively. The areas in each figure are separated from each other by lines representing carrier frequency (cfr), sensitivity of the first step (sens1) or sensitivity of the second step (sens2). In Figure D.1 (concerning SETS) area a represents couples with both partners identified as carriers (++ couples). Couples with one identified carrier (+- couples) are included in areas d and i, and couples without identified carriers (-? couples) are contained in areas b, c, e, f, g and h. However, couples included in areas b, c and d are in fact not-identified couples with both partners

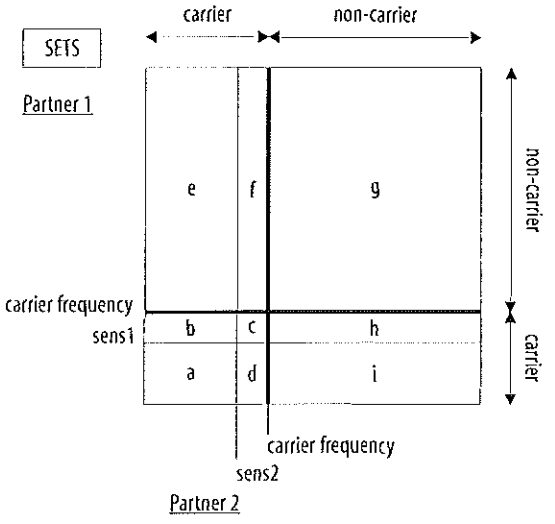


Figure D.1 Diagram showing all possible outcomes in SETS couple screening. Sens1 = sensitivity of the first screening step; sens2 = sensitivity of the second screening step. Partner 1 is the first partner of the couple to be tested. Partner 2 is tested only if the first partner tests positive. For the pictorial presentation the carrier frequency has been inflated. See text for full explanation

carriers. In Figure D.2 (concerning DETS), ++ couples are found in areas a, b and d, +- couples in areas e, i, k and q and -- couples in areas c, f, g, h, l, m, n, o and p. Here couples included in areas c, e, f, g, h and i are not-identified couples with both partners carriers. From inspection of the figures the following formulae can be derived.

For SETS:

1 prevalence of ++ couples = $a = sens1 * sens2 * cfr^2$;

2 detection rate of ++ couples = $\frac{a}{a+b+c+d} = sens1 * sens2$;

3 prevalence of +- couples = $d+i = sens1 * cfr * (1 - sens2 * cfr)$;

4 residual risk in +- couples = $0.25 * \frac{d}{a+i} = 0.25 * (1 - sens2) * \frac{cfr}{1 - sens2 * cfr}$;

5 prevalence of -? couples = $b+c+e+f+g+h = 1 - sens1 * cfr$;

6 residual risk in -? couples = $0.25 * \frac{b+c}{b+c+e+f+g+h} = 0.25 * (1 - sens1) * \frac{cfr^2}{1 - sens1 * cfr}$;

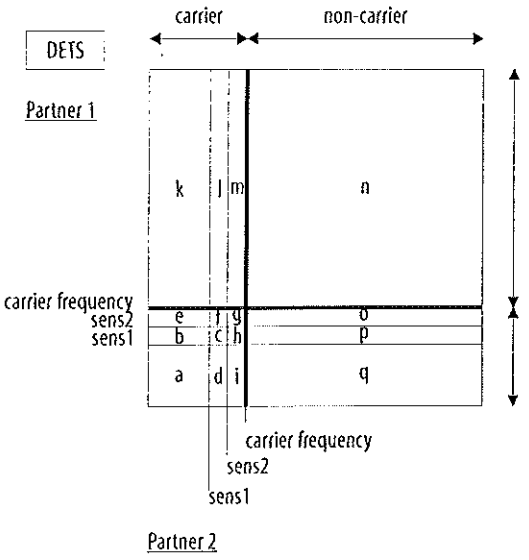


Figure D.2 Diagram showing all possible outcomes in DETS couple screening. Sens1 = sensitivity of the first screening step; sens2 = cumulative sensitivity of the first and second screening step. Partners 1 and 2 are both tested in the first screening step. Partners of identified carriers who test negative in the first test are tested for more mutations in a second step. For the pictorial presentation the carrier frequency has been inflated. See text for full explanation

For DETS:

7 prevalence of ++couples = $a+b+d=(sens2^2-(sens2-sens1)^2)*cfr^2$;

8 detection rate of ++ couples = $\frac{a+b+d}{a+b+c+d+e+f+g+h+i}=sens2^2-(sens2-sens1)^2$;

9 prevalence of +- couples = $e+i+k+q=2*sens1*cfr*(1-sens2*cfr)$;

10 residual risk in +- couples = $0.25*\frac{e+i}{e+i+k+q}=0.25*(1-sens2)*\frac{cfr}{1-sens2*cfr}$;

11 prevalence of -- couples = $c+f+g+h+i+m+n+o+p=(1-sens1*cfr)^2$

12 residual risk in -- couples = $0.25*\frac{c+f+g+h}{c+f+g+h+l+m+n+o+p}=0.25*\frac{((1-sens1)*cfr)^2}{(1-sens1*cfr)^2}$.

D.3 Results

Results of calculations with a carrier frequency of 0.04 and several sensitivities for the first and second test, starting at 75%, are shown in Table D.1 For DETS, the sensitivity

Table D.1 Results of SETS and DETS couple screening at different combinations of first- and second-test sensitivities

		SETS						DETS					
		Detection	++	+-		-?		Detection	++	+-		–	
Sens1	Sens2	rate (in %)	freq 1 in	freq 1 in	risk 1 in	freq (in %)	risk 1 in	rate (in %)	freq 1 in	freq 1 in	risk 1 in	freq (in %)	risk 1 in
0.75	0.75	56.25%	1,111	34.4	388	97.00%	9,700	56.25%	1,111	17.2	388	94.09%	37,636
	0.80	60.00%	1,042	34.4	484	97.00%	9,700	63.75%	980	17.2	484	94.09%	37,636
	0.85	63.75%	980	34.5	644	97.00%	9,700	71.25%	877	17.3	644	94.09%	37,636
	0.90	67.50%	926	34.6	964	97.00%	9,700	78.75%	794	17.3	964	94.09%	37,636
	0.95	71.25%	877	34.7	1,924	97.00%	9,700	86.25%	725	17.3	1,924	94.09%	37,636
	0.99	74.25%	842	34.7	9,604	97.00%	9,700	92.25%	678	17.4	9,604	94.09%	37,636
	1.00	75.00%	833	34.7	∞	97.00%	9,700	93.75%	667	17.4	∞	94.09%	37,636
0.80	0.80	64.00%	977	32.3	484	96.80%	12,100	64.00%	977	16.1	484	93.70%	58,564
	0.85	68.00%	919	32.3	644	96.80%	12,100	72.00%	868	16.2	644	93.70%	58,564
	0.90	72.00%	868	32.4	964	96.80%	12,100	80.00%	781	16.2	964	93.70%	58,564
	0.95	76.00%	822	32.5	1,924	96.80%	12,100	88.00%	710	16.2	1,924	93.70%	58,564
	0.99	79.20%	789	32.5	9,604	96.80%	12,100	94.40%	662	16.3	9,604	93.70%	58,564
	1.00	80.00%	781	32.6	∞	96.80%	12,100	96.00%	651	16.3	∞	93.70%	58,564
0.85	0.85	72.25%	865	30.4	644	96.60%	16,100	72.25%	865	15.2	644	93.32%	103,684
	0.90	76.50%	817	30.5	964	96.60%	16,100	80.75%	774	15.3	964	93.32%	103,684
	0.95	80.75%	774	30.6	1,924	96.60%	16,100	89.25%	700	15.3	1,924	93.32%	103,684
	0.99	84.15%	743	30.6	9,604	96.60%	16,100	96.05%	651	15.3	9,604	93.32%	103,684
	1.00	85.00%	735	30.6	∞	96.60%	16,100	97.75%	639	15.3	∞	93.32%	103,684
0.90	0.90	81.00%	772	28.8	964	96.40%	24,100	81.00%	772	14.4	964	92.93%	232,324
	0.95	85.50%	731	28.9	1,924	96.40%	24,100	90.00%	694	14.4	1,924	92.93%	232,324
	0.99	89.10%	701	28.9	9,604	96.40%	24,100	97.20%	643	14.5	9,604	92.93%	232,324
	1.00	90.00%	694	28.9	∞	96.40%	24,100	99.00%	631	14.5	∞	92.93%	232,324
0.95	0.95	90.25%	693	27.4	1,924	96.20%	48,100	90.25%	693	13.7	1,924	92.54%	925,444
	0.99	94.05%	665	27.4	9,604	96.20%	48,100	97.85%	639	13.7	9,604	92.54%	925,444
	1.00	95.00%	658	27.4	∞	96.20%	48,100	99.75%	627	13.7	∞	92.54%	925,444
0.99	0.99	98.01%	638	26.3	9,604	96.04%	240,100	98.01%	638	13.1	9,604	92.24%	23,059,204
	1.00	99.00%	631	26.3	∞	96.04%	240,100	99.99%	625	13.2	∞	92.24%	23,059,204
1.00	1.00	100.00%	625	26.0	∞	96.00%	∞	100.00%	625	13.0	∞	92.16%	∞

of the second test is represented as the cumulative sensitivity of the first and second tests. Inspection of the table reveals the following.

As expected, the proportion of ++ couples (couples with both partners identified as carriers) is the same for SETS with similar first- and second-test sensitivities and DETS with a similar first-test sensitivity and no second test. To obtain this result almost twice as many tests have to be performed in DETS than in SETS.

The proportion of ++ couples and with it the detection rate of couples with both members carriers increases with increasing sensitivity of the first and second tests, but

the increase with increasing sensitivity of the second test is sharper in DETS than in SETS.

The proportion of +- couples (couples with one identified carrier) varies primarily with the screening strategy (SETS or DETS), to some extent with the sensitivity of the first test and only marginally with the sensitivity of the second test. The proportion of +- couples is twice as large in DETS as in SETS.

The remaining risk of CF in a child of a +- couple is determined by the sensitivity of the second test. For sensitivities less than 1/(1+cfr), which equals approximately (1-cfr), the after-testing risk is higher than the before-testing risk. With a 99% sensitivity of the second test, the remaining risk of +- couples does not decrease further than to about one quarter of the initial frequency.

As expected, the proportion of -? SETS couples and -- DETS couples (couples without identified carriers) varies with the screening strategy and the sensitivity of the first test.

The remaining risk in -- and -? couples varies with the sensitivity of the first test. This risk is significantly lower in DETS than in SETS.

D.4 Discussion

In trying to devise efficient and economical methods for carrier screening, Beaudet and O'Brien (12) have advocated a two-step laboratory strategy for testing couples, in which both partners are tested for fewer mutations in a first step and only partners of identified carriers are tested for additional mutations. They demonstrated that the detection rate of carrier couples is very little affected by studying fewer mutations in the first step. This can also be illustrated by our calculations on DETS. For instance, testing both members of a couple with one test with a 85% sensitivity yields an only 1% increase in detection rate over a two-step procedure in which the first test has a sensitivity of 75% and the second test a sensitivity of 85%.

With regard to the detection rate in DETS, we thus agree with the conclusion of Beaudet and O'Brien (12) that it is far more efficient and economic to test more mutations on samples of partners of known carriers than to test an increasing number of mutations on all samples. However, with regard to the remaining risk in couples without identified carriers, it is far more beneficial to test both member of the couple for as many mutations as possible in one step than to start with a first step with a lower sensitivity and proceed to a second step with a higher sensitivity. In the example given above, the remaining risk for these couples in a one-test procedure

with 85% sensitivity is about 3-fold lower than in a two-step procedure with 75% sensitivity in the first test and 85% sensitivity in the second test.

If one compares DETS to SETS, other disadvantages of DETS emerge. The most important disadvantage of DETS over SETS is the doubling of the proportion of +- couples (couples with one identified carrier) in DETS, while the remaining risk of such couples is the same in SETS and DETS (we do not go into the possibility of withholding the +- result as suggested by Brock (13)). Another disadvantage of DETS over SETS seems to be that DETS requires twice as many tests as SETS. However, savings obtained by DETS may be greater than by SETS (see Chapter 5).

Comparing all the pros and cons of the different strategies does not in itself reveal the most optimal procedure. Preceding decisions are needed with regard to desirable detection rate, proportion of +- couples and their remaining risk, and the remaining risk in -- couples. For instance, one could regard carrier screening only justified when the detection is 80% of greater, when the number of +- couples is as low as possible, when the remaining risk of such couples does not exceed 1 in 1,000 and when the remaining risk of -- couples is less than 1 in 25,000. As Table D.1 shows, these conditions can best be met by SETS with a high sensitivity (91% or more) of the first test. The calculations presented here can also be used as a basis for cost and savings considerations, if costs of screening, cost of care of CF patients, uptake rate and the distribution of reproductive decisions of carrier couples found by screening are known (see Chapter 5).

D.5 References

1. Nishimi RY. From the Office of Technology Assessment. JAMA 1993;269(15):1921.
2. Spence JE, Perciaccante RG, Greig GM, Willard HF, Ledbetter DH, Hejtmancik JF, Pollack MS, WE OB, Beaudet AL. Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet 1988;42(2):217-226.
3. Riordan JR, Rommens JM, Kerem BS, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL, Drumm ML, Iannuzzi MC, Collins F, Tsui LC. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989;245(4922):1066-1073.
4. Watson EK, Mayall E, Chapple J, Dalziel M, Harrington K, Williams C, Williamson R. Screening for carriers of cystic fibrosis through primary health care services. BMJ 1991;303(6801):504-507.

5. Mennie ME, Gilfillan A, Compton M, Curtis L, Liston WA, Pullen I, Whyte DA, Brock DJH. Prenatal screening for cystic fibrosis. Lancet 1992;340(8813):214-216.
6. Botkin JR, Alemagno S. Carrier screening for cystic fibrosis: a pilot study of the attitudes of pregnant women. Am J Public Health 1992;82(5):723-725.
7. Harris H, Scotcher D, Hartley N, Wallace A, Craufurd D, Harris R. Cystic fibrosis carrier testing in early pregnancy by general practitioners. BMJ 1993;306(6892):1580-1583.
8. Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, Marteau T. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? BMJ 1993;306(6892):1584-1586.
9. Livingstone J, Axton RAA, Gilfillan A, Mennie M, Compton M, Liston WA, Calder AA, Gordon AJ, Brock DJH. Antenatal screening for cystic fibrosis: a trial of the couple model. BMJ 1994;308(6942):1459-1462.
10. Tsui LC. The spectrum of cystic fibrosis mutations. Trends Genet 1992;8(11):392-398.
11. The Cystic Fibrosis Genetic Analysis Consortium. Worldwide survey of the delta F508 mutation--report from the cystic fibrosis genetic analysis consortium [letter]. Am J Hum Genet 1990;47(2):354-359.
12. Beaudet AL, O'Brien WE. Advantages of a two-step laboratory approach for cystic fibrosis carrier screening [letter]. Am J Hum Genet 1992;50(2):439-440.
13. Brock DJH. Heterozygote screening for cystic fibrosis [review]. Eur J Hum Genet 1995;3(1):2-13.

Summary

In this thesis the costs, effects and savings of genetic screening programmes for carriers of cystic fibrosis and fragile X syndrome are studied. In *chapter 1* genetic screening in general is described focussing on the points in time where genetic screening can be offered: prenatal screening (screening of pregnant women), preconceptional screening (screening of non-pregnant women with a child wish), school screening (screening of 16-year old scholars in the last year of compulsory education) and neonatal screening (screening of newborns). Furthermore, this chapter discusses criteria that in the view of the Committee Genetic Screening of the Dutch Health Council have to be fulfilled by a genetic screening programme. In the last part of the chapter several types of economic evaluation are presented.

Chapter 2 gives an introduction to the disease cystic fibrosis, a genetic disorder with recurrent pneumonia, disturbances of the digestive tract, high sweat sodium concentration, malnutrition and fertility problems. Cystic fibrosis is an autosomal recessive disorder, which means that only couples where both partners have an affected gene are at risk to have a child with cystic fibrosis. Because approximately 1 in 30 persons in The Netherlands have an affected gene, about 1 in 3,600 Dutch newborns have cystic fibrosis. Most patients have daily physiotherapy and often use antibiotics to fight respiratory infections. In the period 1985-1990 the median life expectancy of patients was 27 years. Because of the cloning of the affected gene in 1989 and the development of simple technical methods to detect the most prevalent mutations in the gene, screening for (carriers of) cystic fibrosis has become a possibility. In the last part of the chapter possibilities and impossibilities of such a programme are described.

Chapter 3 describes a questionnaire aimed at the costs outside the hospital of patients with cystic fibrosis. Questionnaires were sent to 73 patients with cystic fibrosis who were seen in two Dutch hospitals: the Leyenburg hospital in The Hague and the Beatrix Children's Clinic in Groningen. In total 14 (parents of) children and 33 adults returned the questionnaire. The average costs outside the hospital amount to €6,944 per child per year (range €1,065-€19,852) and €15,322 for adults (range €2,473-€39,751). Medical care outside the hospital is responsible for 8% of these costs for children and 5% for adults, domestic help for 15% and 9% respectively, diet for 10% and 7%, travelling costs because of the disease for 4% and 8%, medication for

63% and 67%, and devices and special facilities at home, work or school for 1% and 4%. The conclusion of the analysis is that costs outside the hospital are very high for patients with cystic fibrosis, and that these add up to almost half of the total (medical and nonmedical) costs of cystic fibrosis during the life of a patient.

In *chapter 4* the total costs of care of Dutch patients with cystic fibrosis in 1990 and 1991 are described. The age-specific medical consumption is estimated by an examination of medical records and the questionnaire described in chapter 3. A distinction is made between costs of hospital care, medication in and outside the hospital, and home care. The costs per year are calculated by multiplying the yearly amount of care by the costs per unit. The average yearly costs in 1991 were €16,319 (hospital care 42%, medication 37%, home care 20%). The costs of cystic fibrosis in The Netherlands, with about 1,000 patients, are estimated at more than €16 million per year; this is 0.07% of the total health care budget. When the survival is taken into account and the costs are discounted at 5% per year to the birth year of the patient, the costs during the life of a patient are about €250,000.

The results of chapters 3 and 4 are used in the analysis of the costs, effects and savings of a screening programme for carriers of the cystic fibrosis gene presented in *chapter 5*. A general computer model was constructed with which prenatal, preconceptional, school, and neonatal carrier screening is evaluated. For prenatal and preconceptional screening two strategies are analysed: single-entry and double-entry screening of couples. In singe-entry screening one partner is tested for carriership, and only if he/she is carrier the second partner is tested; in double-entry screening both partners are tested for carriership. Of all screening strategies, neonatal screening gives most carrier couples (112 couples) the possibility of an informed choice concerning reproduction, followed by prenatal screening (63 couples). Prenatal and single-entry preconceptional screening for carriers of the cystic fibrosis gene have a favourable cost-savings balance in The Netherlands for a wide variety of assumptions, and single-entry prenatal screening has highest savings (€1.5 million per year). For double-entry and neonatal screening relatively favourable assumptions concerning coverage and, uptake of prenatal diagnosis and induced abortions are necessary to have a favourable cost-savings balance, while carrier screening of scholars has an unfavourable balance for a wide range of assumptions (in the baseline analysis the costs of school screening are €2 million higher than the savings). The conclusion of the analysis is that costs will not form an obstacle for prenatal or single-entry preconceptional screening.

Chapter 6 discusses fragile X syndrome, the most common single-gene cause of mental retardation. Many patients with fragile X syndrome have one or more of the following physical symptoms or behavioural abnormalities: high forehead, large prominent ears, enlarged testicles, hyperactivity, excessive shyness and autistic features. The symptoms are milder in women with fragile X syndrome than in men. In most cases the cause of fragile X syndrome is a large expansion of the number of CGG repeats in a part of the fragile X gene (full mutation). Persons with a smaller number of repeats in the gene (so-called premutation) have no symptoms, but women with a premutation run the risk of having a child with fragile X syndrome because the premutation 'grows' to a full mutation. Men with a premutation can give this premutation to their child, but it will never grow to a full mutation. This means that men with a premutation do not run the risk of having a child with fragile X syndrome. Moreover, as (almost) no men with fragile X syndrome do conceive children, only women have to be tested in a screening programme. In the last part of the chapter screening for carriers of the fragile X gene is described.

The costs, effects and savings of a screening programme for the fragile X gene is discussed in *chapter 7*. Prenatal screening detects the highest number of carriers (200 carriers) and prevents the highest number of births of patients (28 patients). The costs per detected carrier are almost equal for all screening strategies (€40,000), and all screening strategies have a favourable cost-savings balance: €12 million for prenatal screening, €8 million for preconceptional screening and €2 million for school screening. This means that from an economical point of view there are no obstacles to fragile X syndrome carrier screening, and that the decision whether or not to screen can concentrate on medical, social, psychological and ethical aspects.

Another strategy to detect carriers, described in *chapter 8*, is cascade testing (testing of relatives of a patient) for fragile X syndrome. With a computer-simulation model 100,000 five-generation pedigrees are constructed and the maximal number of detected carriers is calculated for three scenarios: 1. only first-degree relatives of the patients are tested; 2. relatives up to the third degree are tested; 3. relatives up to the fifth degree are tested. In the start-up phase of a cascade testing programme, 19% of the couples that will have a child with fragile X syndrome are detected. After this start-up phase, a cascade testing programme will detect 8% of the undetected couples who will have a child with fragile X syndrome if only first-degree relatives are tested, 13% if relatives up to the third degree are tested, and 16% if relatives up to the fifth degree are tested. This means that at least eight generations have to be tested in

order to find 90% of all carriers. The results of the analysis show that the effectiveness of cascade testing is not high, but the cost-effectiveness probably is favourable.
Questions can be raised whether separate genetic screening programmes can and should be combined (*chapter 9*). The advantages of a combined programme are that the couples is confronted with only one screening offer and one counselling session, and that there will be efficiency effects in the costs of for example organisation and information. Therefore the combination of screening programmes for carriers of cystic fibrosis and fragile X syndrome is analysed. Because all assumptions, except for some costs, are taken the same as the assumptions in the analyses of chapter 5 and 7, the effect measures (like the number of detected couples and the number of prevented patients) of a combined screening programme are the same as those of the separate screening programmes. The conclusion of this analysis is that indeed considerable gains can be obtained when combining screening programmes for cystic fibrosis and fragile X syndrome carriers.
In *chapter 10* the research results are summarised and an updated analysis of the costs, effects and savings of preconceptional screening for carriers of the cystic fibrosis gene is presented. For example, the recommended discount rate is reduced from 5% to 3% and new screening tests are analysed. In the updated analysis preconceptional screening is cost-saving for three out of four test combinations, but double-entry preconceptional screening is only cost-saving for one of the test combinations. Considering the criteria of the Committee Genetic Screening of the Health Council a number of gaps in knowledge are noticed, for example the psychological and social consequences of screening in The Netherlands are not examined sufficiently. In the last part of the chapter recommendations for further research are made. A pilot study for preconceptional screening in The Netherlands is proposed in which the psychosocial aspects of screening should be investigated. Because the knowledge of screening for carriers of the fragile X syndrome gene is not sufficient to consider a screening programme, a pilot study is proposed in which the prevalence of carriers is examined and in which the attitude of Dutch women towards fragile X syndrome screening is analysed. Furthermore, the development of a general computer model for analysing both separate and combined genetic screening programmes is proposed so that a standardised and comparable way of performing cost-effectiveness analysis is possible.

Samenvatting

In dit proefschrift worden de kosten, effecten en besparingen van genetische bevolkingsonderzoeken (screening) naar dragerschap van cystische fibrose en het fragiele X syndroom bestudeerd. In *hoofdstuk 1* wordt genetische screening in het algemeen beschreven waarbij aandacht geschonken wordt aan de verschillende tijdstippen in het leven waarop genetische screening uitgevoerd kan worden: prenatale screening (screening van zwangere vrouwen), preconceptionele screening (screening van niet-zwangere vrouwen met een kinderwens), scholieren screening (screening van 16-jarige scholieren in het laatste jaar van het verplichte onderwijs) en neonatale screening (screening van pasgeborenen). Verder worden in dit hoofdstuk criteria besproken waaraan een genetisch bevolkingsonderzoek in de ogen van de Commissie Genetische Screening van de Gezondheidsraad moet voldoen, en wordt in het laatste deel verschillende vormen van economische evaluatie gepresenteerd.
Hoofdstuk 2 geeft een inleiding tot de ziekte cystische fibrose, een genetische aandoening met onder andere steeds terugkerende longontstekingen, problemen met het spijsverteringskanaal, een hoog zoutgehalte in het zweet, ondervoeding en fertiliteitproblemen. Cystische fibrose is een autosomaal recessieve aandoening, wat betekent dat alleen paren waarin beide partners een aangedaan gen hebben het risico lopen op een kind met cystische fibrose. Omdat ongeveer 1 op de 30 personen in Nederland het aangedane gen hebben, heeft ongeveer 1 op de 3.600 pasgeborenen in Nederland cystische fibrose. De meeste patiënten krijgen dagelijks fysiotherapie en gebruiken vaak een antibioticakuur om longinfecties te bestrijden. In de periode 1985-1990 werd meer dan 50% van alle patiënten ouder dan 27 jaar. Door de ontdekking van het aangedane gen in 1989 en de ontwikkeling van simpele technische methoden om de meest voorkomende mutaties in het gen te detecteren is bevolkingsonderzoek op (dragerschap van) cystische fibrose mogelijk geworden. In het laatste deel van het hoofdstuk worden de mogelijkheden en onmogelijkheden van zo'n bevolkingsonderzoek beschreven.
Hoofdstuk 3 beschrijft een dagboekenquête naar de ziektekosten van patiënten met cystische fibrose buiten het ziekenhuis. Dagboeken werden verzonden naar 73 patiënten met cystische fibrose die onder controle waren in twee Nederlandse ziekenhuizen: het Leyenburg ziekenhuis in 's Gravenhage en het Beatrix Kinderziekenhuis in Groningen. In totaal 14 (ouders van) kinderen en 33 volwassenen

vulden de vragenlijst in. De gemiddelde kosten buiten het ziekenhuis bedragen €6.944 per kind per jaar (bereik €1.065-19.852) en €15.322 per volwassene (bereik €2.473-39.751). Medische zorg buiten het ziekenhuis is verantwoordelijk voor 8% van deze kosten voor kinderen en 5% voor volwassenen, huishoudelijke hulp voor respectievelijk 15% en 9%, dieet voor 10% en 7%, reiskosten wegens de ziekte voor 4% en 8%, medicatie voor 63% en 67%, en hulpmiddelen en speciale voorzieningen thuis, op het werk of op school voor 1% en 4%. De conclusie van de analyse luidt dat kosten van ziekte buiten het ziekenhuis erg hoog zijn voor patiënten met cystische fibrose, en dat deze ongeveer de helft uitmaken van de totale (medische en niet-medische) kosten van cystische fibrose gedurende het leven van een patiënt.

In *hoofdstuk 4* worden de totale kosten van zorg van Nederlandse patiënten met cystische fibrose in 1990 en 1991 besproken. De leeftijdspecifieke medische consumptie is geschat met behulp van een statusonderzoek en de enquête die besproken is in hoofdstuk 3. Onderscheid is gemaakt tussen kosten van ziekenhuiszorg, medicatie in en buiten het ziekenhuis, en thuiszorg. De kosten per jaar zijn berekend door de jaarlijkse hoeveelheid zorg te vermenigvuldigen met de kosten per eenheid zorg. Gemiddeld waren de jaarlijkse kosten in 1991 gelijk aan €16.319 (ziekenhuiszorg 42%, medicatie 37%, thuiszorg 20%). De kosten van cystische fibrose in Nederland, met ongeveer 1.000 patiënten, zijn geschat op ruim €16 miljoen per jaar; dit is 0,07% van het totale gezondheidszorgbudget. Als de overleving in beschouwing wordt genomen en de kosten met 5% per jaar worden verdisconteerd naar het geboortejaar van een patiënt, zijn de kosten gedurende het hele leven van een patiënt gelijk aan een kleine €250.000.

De resultaten van de hoofdstukken 3 en 4 worden gebruikt in de in *hoofdstuk 5* gepresenteerde analyse naar de kosten, effecten en besparingen van een bevolkingsonderzoek op dragerschap van het cystische fibrose-gen. Hiertoe is een algemeen computermodel geconstrueerd waarmee prenatale, preconceptionele, scholieren, en neonatale dragerschapsscreening wordt geëvalueerd. Voor de prenatale en preconceptionele screening zijn twee strategieën bekeken: stapsgewijs en gelijktijdig screenen van paren. In de stapsgewijze strategie wordt eerst één partner getest op dragerschap, en alleen als deze drager is wordt de tweede partner getest; in de gelijktijdige strategie worden beide partners getest op dragerschap. Van alle screeningsstrategieën geeft neonatale screening de meeste dragerschapsparen (112 paren) de mogelijkheid van een geïnformeerde keuze omtrent reproductie, met op de tweede plaats prenatale screening met 63 paren. Prenatale en stapsgewijze

preconceptionele screening op dragerschap van het cystische fibrose-gen hebben in Nederland een gunstige kosten-besparingsbalans onder wijd uiteenlopende aannames, waarbij stapsgewijze prenatale screening het meest bespaart (€1,5 miljoen per jaar). Voor gelijktijdige preconceptionele screening en neonatale screening zijn relatief gunstige aannames over opkomst bij screening, keuze voor prenatale diagnostiek en geïnduceerde abortus nodig om een gunstige kosten-besparingsbalans te verkrijgen, terwijl dragerschapsscreening van scholieren een ongunstige balans heeft onder uiteenlopende aannames (in de basisvariant zijn de kosten van scholierenscreening €2 miljoen hoger dan de besparingen). De conclusie van de analyse luidt dat kosten geen obstakel zullen vormen voor prenatale of stapsgewijze preconceptionele screening.

Hoofdstuk 6 bespreekt het fragiele X syndroom, de meest voorkomende oorzaak van mentale retardatie waarbij een enkel gen betrokken is. Veel patiënten met het fragiele X syndroom hebben fysieke symptomen of gedragsstoornissen zoals een hoog voorhoofd, grote vooruitstekende oren, vergrote testikels, hyperactiviteit, overmatige verlegenheid en autistische kenmerken. De symptomen zijn milder bij vrouwen met het fragiele X syndroom dan in mannen. In de meeste gevallen is een grote verhoging van het aantal CGG-herhalingen in een deel van het fragiele X gen (volle mutatie) de oorzaak van het fragiele X syndroom. Mensen met een kleiner aantal herhalingen in het gen (zogenaamde premutaties) hebben geen symptomen, maar vrouwen met een premutatie hebben wel kans op een kind met het fragiele X syndroom doordat de premutatie 'groeit' tot een volle mutatie. Mannen met een premutatie kunnen de premutatie wel doorgeven aan hun kind, maar deze zal niet doorgroeien naar een volle mutatie. Dit betekent dat mannen met een premutatie geen kans hebben op een kind met het fragiele X syndroom. Omdat mannen met het fragiele X syndroom bovendien (bijna) geen kinderen krijgen, hoeven in een eventueel screeningsprogramma alleen vrouwen getest te worden. In het laatste deel van het hoofdstuk wordt screening op dragers van het fragiele X gen beschreven.

De kosten, effecten en besparingen van een bevolkingsonderzoek op het fragiele X gen worden besproken in *hoofdstuk 7*. Prenatale screening detecteert het hoogste aantal dragers en voorkomt de geboorte van de meeste patiënten met het fragiele X syndroom. De kosten per gedetecteerde drager zijn ongeveer gelijk voor alle screeningsstrategieën (€40.000), en alle screeningsstrategieën hebben een gunstige kosten-besparingsbalans: €12 miljoen voor prenatale screening, €8 miljoen voor preconceptionele screening en €2 miljoen voor screening van scholieren. Dit

betekent dat er vanuit het gezichtspunt van kosten geen obstakels zijn voor fragiele X syndroom dragerschapsscreening, en dat de beslissing om wel of niet te screenen zich kan concentreren op medische, sociale, psychologische en ethische aspecten.
Een andere strategie om dragers te detecteren, beschreven in *hoofdstuk 8*, is cascade testen (testen van familieleden van een patiënt) op het fragiele X syndroom. Met een computer-simulatiemodel zijn 100.000 stambomen van vijf generaties geconstrueerd en is gekeken wat het maximaal aantal gedetecteerde dragers is voor drie scenario's: 1. alleen eerstegraads verwanten van de patiënt worden getest; 2. verwanten tot in de derde graad worden getest; 3. verwanten tot in de vijfde graad worden getest. In de opstartfase van een cascade-programma worden 19% van de paren die een kind met het fragiele X syndroom zullen krijgen gedetecteerd. Na deze opstartfase zal een cascade-programma 8% van de nog niet gedetecteerde paren die een kind met het fragiele X syndroom zullen krijgen opsporen als alleen eerstegraads verwanten worden getest, 13% als eerste- tot derdegraads verwanten worden getest, en 16% als eerste- tot vijfdegraads verwanten worden getest. Dit betekent dat minimaal acht generaties getest moeten worden om 90% van alle dragers te vinden. De resultaten van de analyse laten zien dat de effectiviteit van cascade testen niet groot is, maar waarschijnlijk is de kosteneffectiviteit wel gunstig.
De vraag is of afzonderlijke genetische screeningsprogramma's gecombineerd zouden kunnen en moeten worden (*hoofdstuk 9*). De voordelen van een gecombineerd programma zijn dat het paar met slechts één screeningsaanbod en één counselingsessie wordt geconfronteerd, en dat er efficiëntie-effecten in de kosten van bijvoorbeeld organisatie en informatie zullen optreden. Daarom is gekeken naar een combinatie van een screeningsprogramma op dragerschap van cystische fibrose en het fragiele X syndroom. Omdat, uitgezonderd enkele kosten, alle aannames gelijk zijn genomen aan de aannames in de analyses van hoofdstuk 5 en 7, verschillen de effectmaten (zoals het aantal gedetecteerde paren en het aantal voorkomen patiënten) van een gecombineerd programma niet met die van afzonderlijke screeningsprogramma's. De conclusie van deze analyse is dat er inderdaad aanzienlijke voordelen behaald kunnen worden bij het combineren van screeningsprogramma's op dragerschap van cystische fibrose en het fragiele X syndroom.
In *hoofdstuk 10* tenslotte worden de onderzoeksresultaten samengevat waarna een geactualiseerde analyse van de kosten, effecten en besparingen van preconceptionele screening op dragerschap van het cystische fibrose-gen wordt

gepresenteerd. Zo is bijvoorbeeld het aanbevolen verdisconteringpercentage verlaagd van 5% naar 3% en zijn er nieuwe screeningstesten geanalyseerd. Bij de geactualiseerde analyse is preconceptionele screening kostenbesparend voor drie van de vier onderzochte testcombinaties, maar is gelijktijdige preconceptionele alleen kostenbesparend voor een van de vier testcombinaties. Bij het nalopen van de criteria van de Commissie Genetische Screening van de Gezondheidsraad worden een aantal leemtes in kennis geconstateerd, waarbij vooral de psychologische en sociale gevolgen van screening in Nederland nog niet voldoende zijn onderzocht. In het laatste deel van het hoofdstuk worden onderzoeksaanbevelingen gedaan. Zo wordt onder meer gepleit voor een vooronderzoek in Nederland naar preconceptionele screening op dragerschap van het cystische fibrose-gen waarin vooral de psychosociale aspecten van screening onderzocht moeten worden. Aangezien de kennis van screening op dragerschap van het fragiele X syndroom nog niet toereikend is om een screeningsprogramma nu reeds te overwegen wordt voorgesteld eerst een vooronderzoek uit te voeren waarin de prevalentie van dragerschap wordt onderzocht, en waarin de houding van de Nederlandse vrouwen jegens fragiele X syndroom screening wordt bekeken. Tevens wordt voorgesteld een algemeen computermodel te ontwikkelen voor zowel afzonderlijke als gecombineerde genetische screeningsprogramma's zodat een gestandaardiseerde en daardoor onderling vergelijkbare manier van kosteneffectiviteitsanalyse voor diverse genetische screeningsprogramma's kan worden bereikt.

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Costs and effects of genetic screening with application to cystic fibrosis and fragile X syndrome

Kosten en effecten van genetische screening toegepast op cystische fibrose en fragiele X syndroom

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr. P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 7 april 1999 om 13.45 uur

door

Marinus Frederik Wildhagen

geboren te Breda

Promotiecommissie

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