Cost-effectiveness of DNA-diagnosis for four monogenic diseases

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Abstract

In this paper the costs and benefits associated with DNA-diagnosis of individuals who are at risk of a child with a monogenic disease and who seek genetic counselling because of their reproductive plans are predicted under various assumptions using a mathematical model. Four monogenic diseases have been considered: cystic fibrosis, Duchenne muscular dystrophy, myotonic dystrophy and fragile X syndrome. Counselling (triggered by prior information) on the basis of DNA-diagnosis is compared to the situation that only risk evaluation based on pedigree analysis is possible. The results show for each disease that with DNA-diagnosis couples can be more confident in choosing (further) offspring leading to the birth of more healthy children while the number of affected children is reduced. The costs minus savings within the health care sector depend on the prior risks and to the future burden of the monogenic illness considered. DNA-diagnosis of relative "low" prior risks of a child with CF (e.g. 1:180, 1:240 and 1:480) leads to costs in stead of savings. For higher prior risks of CF and for the three other diseases DNA-diagnosis induces considerable savings. This result remains valid when assumptions regarding behaviour regarding reproduction and receiving DNA-diagnosis under different circumstances are varied.

Introduction

DNA-diagnosis has become an important part of genetic counselling as DNA-analyses are being applied to a growing number of monogenic diseases for carrier screening and prenatal diagnosis. Seven genetic centres perform DNA-diagnosis in The Netherlands. The Health Insurance Executive Board initiated an economic appraisal study in 1992 to support a decision about reimbursement and about licensing of these facilities, which we report on here.

This study focuses on the costs and benefits associated with DNA-diagnosis of individuals who are at risk of a child with a monogenic disease and who seek genetic counselling because of their reproductive plans. 'At risk' in this research means that couples who ask for information are related to an affected person. This complies with the indications for genetic counselling of monogenic hereditary diseases in the Netherlands. In genetic counselling there are two situations to which DNA-diagnosis may apply: (i) when a person at risk wants to know if he or she is a carrier of a genetic disease (carrier screening or presymptomatic diagnosis) and (ii) when a pregnant couple wants to know if the fetus is disadvantaged (prenatal diagnosis). Both applications are considered here.

The costs and benefits of DNA-diagnosis are predicted under various assumptions on reproduction decisions using a mathematical model (figure 1) and are represented for four monogenic diseases: cystic fibrosis, Duchenne muscular dystrophy, myotonic dystrophy and fragile X syndrome.

Methods

Alternatives

In cost-effectiveness analysis, the costs and benefits of a defined health care programme are compared with costs and benefits of one or more alternatives. This study compares DNA-diagnosis with the situation that only risk evaluation based on pedigree analysis is possible. As the situation with DNA-diagnosis is technically superior to other diagnostic tests the proposed comparison is the most relevant for demonstrating the benefits of genetic counselling in general and DNA-diagnosis in particular. In both situations retrospective counselling (triggered by prior information) is the policy under consideration here. This means that genetic counselling is only provided after the birth of the first affected child in a family (or after the identification of an index patient in a family). The availability of DNA-diagnosis may prevent the parents from having a second affected child and provides the possibility of having at least one other healthy child by making use of prenatal diagnosis. Other relatives of an affected child may also be screened if such information is useful (e.g. in relation to a reproductive decision).

[here about figure 1]

Decisions on reproduction and associated chances

A model (figure 1) is used incorporating assumptions about several decisions on reproduction and about associated chances of healthy progeny. The decisions on reproduction are derived from published research or expert opinion. Almost no disease-specific information about these decisions was available, so for all diseases, except cystic fibrosis, baseline assumptions are used to measure the costs and benefits of the compared interventions. The successive assumptions regarding reproductive decisions and the references to the literature are mentioned in table 1. Furthermore a number of probabilities regarding incidence of illness are incorporated in the model; risk of infertility: 10% [1], risk of induced abortion after chorionic-villus sampling: 1%

[2] and conditional risks of an affected or a healthy child.

[table 1]

Effects

The objective of genetic counselling, according to the definition of the WHO, is to help people with a genetic disadvantage to live and to reproduce as normally as possible [13]. This means that DNA-diagnosis for retrospective genetic counselling enables couples at risk to take informed decisions about (further) reproduction. In this way they may complete their families with minimal risk. A traditional cost-effectiveness analysis, where costs per life year gained or per QALY (quality adjusted life year) gained are measured, is not appropriate here since the different dimensions in which benefits can be expressed, cannot be aggregated to one unique summary outcome measure. The effects relate to information about genetic risks available to a family, a better chance of healthy posterity and, on the negative side, a higher risk of a terminated pregnancy. Thus the effects in this analysis are presented as the differences between the situation with DNA-diagnosis and the situation that only pedigree analysis is possible as regards the numbers of:

- couples choosing (further) offspring and getting pregnant.
- healthy children
- affected children
- terminated pregnancies

Costs

Only the costs within the health care system, shown in table 2, are considered here.
The costs of diagnosis (carrier screening and prenatal diagnosis) are based on the average costs of a test in 4 major DNA-laboratories in the Netherlands. The costs of deliveries and the costs of selective or induced abortion are based on Dutch tariffs and the costs of treatment of the monogenic diseases are based on global "burden of illness" studies or published research [14]. Expert-panels provided information on the profile of resource use in the treatment of the other three diseases, and cost studies were performed to estimate the relevant unit costs of these resource-use items. The total burden of illness was calculated by multiplying the volumes of used resources with the unit costs.

Table 2 shows the estimated life time cost and the discounted costs for each disease. To allow comparison of the burden of illness across diseases and to set this against the investment in DNA-diagnosis, the flow of costs over time has to be expressed in a total amount representing the present value of that flow. This is done by discounting costs in later periods using a discount rate of 5%.

[here about table 2]

Results

Effects

Table 3 shows the effects of DNA-diagnosis for the selected illnesses in distinct risk groups. These effects are the result of calculations based on the mathematic model shown in figure 1. The effects are calculated for each disease in a group of 100 couples that consult a genetic counsellor. As an example we will explain how these effects are calculated in case of CF. It is

assumed that couples already have an affected child. In the situation that no form of carrier or prenatal diagnosis is available 30% of parents at risk choose further offspring, the risk of a CF child being 25%. This results in: 30 pregnancies, 7.5 affected children and 22.5 healthy children per 100 consulting couples. In the situation that DNA diagnosis is available 85% of the carriers chooses further offspring, 90% chooses to perform prenatal diagnosis and 99% of the couples chooses to terminate the pregnancy when the child is affected. Results: 85 pregnancies, 2.3 affected children, 63.2 healthy children and 19.5 terminated pregnancies (including 1% induced abortions after chorionic-villus sampling) per 100 consulting couples. The comparison of the two above mentioned situations results in +55 pregnancies, +40.7 healthy children, -5.2 affected children and +19.5 terminated pregnancies as effects of DNA-diagnosis for 100 consulting couples.

[here about table 3]

In table 4 the effects per disease with a specific distribution of prior risks are shown.

[here about table 4]

The results for every individual disease are discussed below.

Cystic fibrosis

Cystic fibrosis (CF) is a severely debilitating chronic disease and causes a short life expectancy. In families where a CF mutation is already known the mutation can definitely be identified or excluded. Analysis of the ten most frequent mutations identifies 85% of all CF mutations [15]. The results show that with DNA-diagnosis couples in all risk categories (parents, man or woman is: sibling, uncle/aunt, nephew/niece) can be more confident in choosing (further) offspring, leading to the birth of more healthy children while the number of affected children can be reduced.

Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is a lethal, recessive, X-linked neuromuscular disease. DNA-diagnosis can identify or exclude a DMD mutation in 96.5% of female carriers or male fetuses in families where the mutation is already known (pers. comm. Dr. B. Bakker, 1994). The other 3.5% of the female carriers or male fetuses in these families have a risk of 1:2 for a DMD mutation. The results of DNA-diagnosis are again calculated for four risk groups of 100 couples related to a DMD patient (woman is: mother and sister, mother, sibling, niece). Also here similar positive results can be reported as in the case of cystic fibrosis.

Myotonic dystrophy

Myotonic dystrophy (DM) is an autosomal dominant disorder and is generally considered as a disease of adult life or adolescence. The patients' illness is more severe when the clinical symptoms are presented at an earlier age [16]. The congenital variant is the most severe form of MD and is only seen in the offspring of mothers who have the adult variant of DM [17]. A combination of mutation analysis, marker analysis and clinical symptoms identifies or excludes DM defenitely [18]. This study only takes into account the congenital form of DM (CDM) and is based on calculations of two groups of 100 consultands at risk of a CDM child (women is DM patient and mother of CDM child, women is DM patient). Therefore, the true effects and savings taking into account also the positive effects as a consequence of minor DM disorders will be higher than reported here. Here the number of affected children avoided is higher but at the cost of more terminated pregnancies, because the two risk groups that are analysed have larger prior risks of an affected (CDM) child than the analysed risk groups of CF and DMD.

Fragile X syndrome

Fragile X syndrome (fra(X)) is the most frequent hereditary form of mental retardation. The mutation in men always results in severe mental retardation, as against ranging from completely normal to severely retarded in women. DNA-diagnosis can definitely identify or exclude the

fra(X) mutation [19, 20]. Costs and effect measurement in this analysis is limited to the risk of a son with the fra(X) (lower bound estimate of positive effects) and is done for two groups of 100 couples with prior risks of 45% and 22.5% of a son with the fra(X) (woman has son with fra(X), woman is sister of fra(X) patient. Also here positive effects of the use of DNA-diagnosis can be reported.

Costs

Table 5 shows the costs minus savings of the four diseases. The costs minus savings relate strongly to the prior risks and to the burden of illness. DNA-diagnosis of relative "low' prior risks of a child with CF (e.g. 1:180, 1:240 and 1:480 or the prior risk of a Cf child in case one of the parents is a sibling, an aunt/uncle or nephew/niece, respectively of a CF child) leads to costs in stead of savings. For all other risks groups, DNA-diagnosis induces considerable savings.

[here about table 5]

Sensitivity-analysis

A univariate sensitivity analysis was done by varying subsequently all base line assumptions. The results per disease with a specific distribution of prior risks (like in table 4) are presented in table 6.

Under various assumptions regarding the choice for reproduction when no DNA-diagnosis is available and the choice for prenatal diagnosis the effects of DNA-diagnosis in CF couples remain positive. Only when sixty percent of the couples, with a 1 in 4 risk at a child with CF, uses prenatal diagnosis, there will be a slight increase in the number of births of affected children in a group of 100 consultants and consequently additional costs of DFL 12.000 per consulting couple instead of savings. When seventy percent, or more, of these couples at risk makes use of

prenatal diagnosis the number of affected children will decrease. In the sensitivity analysis for DMD, DM and fra(X) the positive effects and savings of the base line estimates do not change into any negative consequences.

[here about table 6]

Also when other assumptions are varied (use of DNA-diagnosis 60-100%; further offspring with DNA-diagnosis 60-100%; sensitivity of carrier diagnosis 0.9 - 1.0; costs of diagnosis DFL 500 - 2,500; costs of illness DFL 250,000 - 2,500,000) the effects of DNA-diagnosis remain positive.

Discussion

The effects of DNA-diagnosis are in general positive for each disease and for all risk groups considered: an increase in the number of couples choosing for (further) offspring, an increase in births of healthy children and a decrease in the number of affected children. On the negative side an increase is expected in the number of affected pregnancies that may be terminated. The availability of DNA-diagnosis also results in an increase in the number of births of healthy carriers. Furthermore, DNA-diagnosis induces considerable savings in the health care budget with the exception of the situation where both parents have a prior risk of 1:45 or lower to be carriers of the CF mutation. The savings increase with the burden of care for a particular disease and with higher prior risks.

Although the results differ across disease categories they suggest that positive effects and savings may also be produced in other disease categories where the health care expenditure for treatment is considerable and where prior risks of affected children are above the level of about 1%. As DNA-diagnosis appears to be rather cost-effective in the diseases considered here, one may like to investigate a broader application of this counselling service, e.g. by not only helping

couples presenting themselves with a request for counselling but though actively searching for families with high risk profiles (e.g. by testing mentally disabled for fra(X)). In cost-effectiveness research of CF-screening there are indications that a program for CF screening leads to savings [21].

On the basis of the results reported here the Health Insurance Executive was informed that the current Dutch practice of genetic counselling is a rather cost-effective health care intervention. The board subsequently decided to incorporate this activity into the package of health care services available to all publicly insured in the Netherlands.

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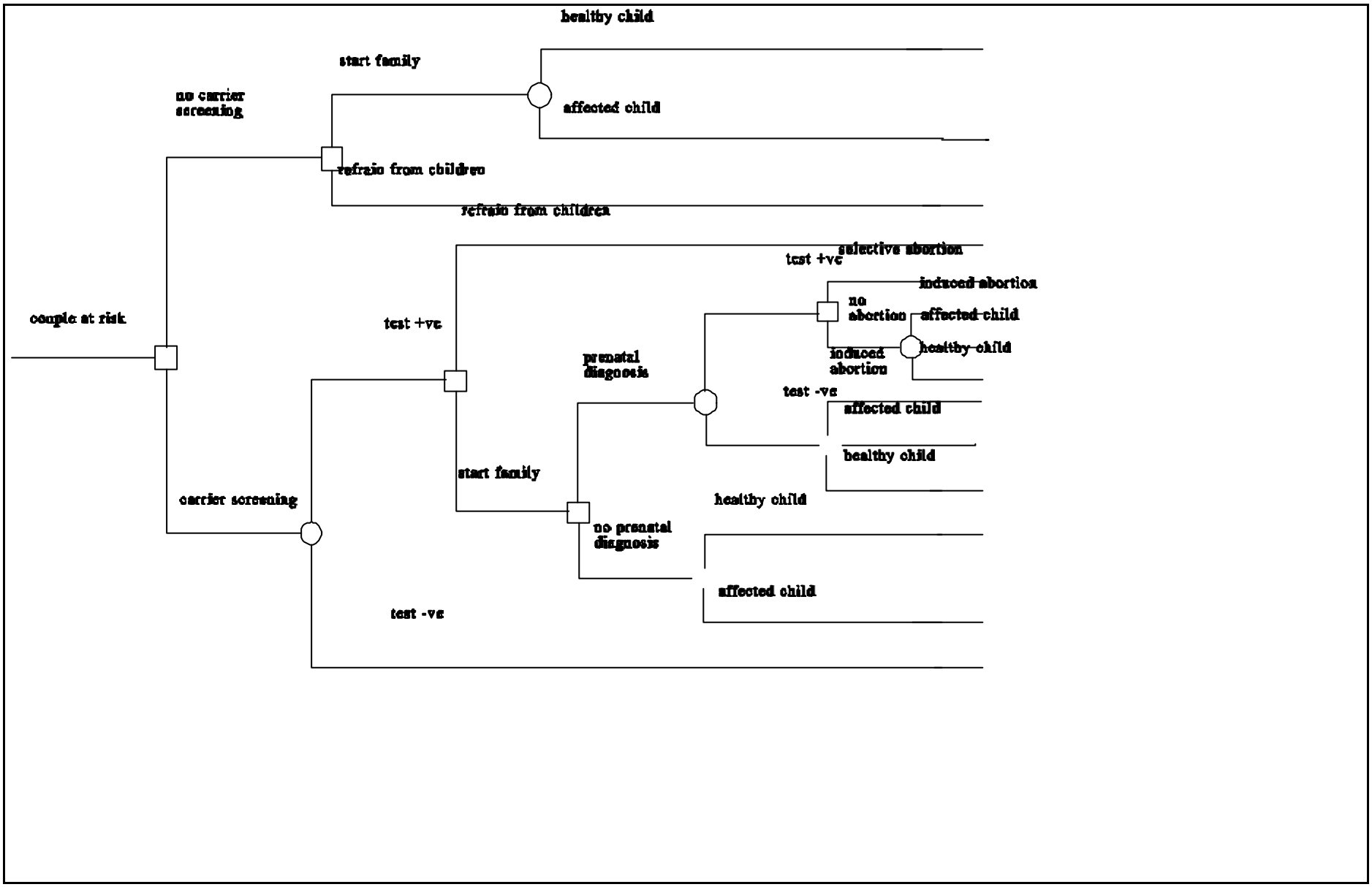
healthy child
start family
no carrier screening
affected child
refrain from children
refrain from children
selective abortion
test +ve
induced abortion
no abortion
affected child
couple at risk
test +ve
healthy child
induced abortion
prenatal diagnosis
test -ve
affected child
healthy child
start family
carrier screening
healthy child
no prenatal diagnosis
affected child
test -ve

Table 1: Assumptions about reproductive decisions of couples at risk (ranges used in sensitivity analyslis)

Interventions	% at risk couples choosing	risk affected child >10% a)	risk affected child <10% b)
No form of carrier or prenatal diagnosis available	(further) offspring	50% c) CF 30% d) (30%-70%)	80% e)
DNA-diagnosis available	carrier screening	100% f)	90% g) (60%-100%)
	(further) offspring	85% h) (60%-100%)	
	prenatal diagnosis	90% i) (60%-100%)	
	termination of pregnancy when the fetus is affected	99% j)	

Risk of an affected child>10% when a couple already has an affected child or when carrier screening gives an unfavourable testresult

Prior risk of an affected child <10% when a couple is related to an affected child

Emery et al,1979[3]; Sorenson et al, 1987 [4]; Frets, 1990 [5]

Average of: Dankert-Roelse, 1988 [6]; Kaback et al, 1984 [7]; Leonard et al, 1972 [8]

Average of: Sorenson et al, 1987 [4]; Frets, 1990 [5]

Diagnosis to confirm that a parent is a carrier of disease after the birth of an affected child

Pers. comm. with genetic clinicians of four clinical centres in Groningen, Leiden, Rotterdam and Nijmegen

Frets, 1990 [5]

Tybkjaer, 1992 [9]; Pers. comm. with genetic clinicians of four clinical centres in Groningen, Leiden, Rotterdam and Nijmegen

Kloosterman, 1990 [10]; Brandenburg, 1992 [11]; Beekhuis et al, 1993 [12]

Table 2: Cost estimates used in the model in DFL 1994(exchange rate US$

	Baseline estimate	Ranges sensitivity analysis
DNA test	1,200	500 - 2,500
Delivery	3,916	
Abortion (13 weeks)	987	
Curettment	668	
Life time cost of cystic fibrosis 1) Discounted with 5%	1,319,284 545,968	250,000 - 2,500,000
Life time cost of Duchenne muscular disease 2) Discounted with 5%	747, 173 487,723	250,000 - 2,500,000
Life time cost of cong. myotonic dystrophia 2) Discounted with 5%	1,187,919 424,635	250,000 - 2,500,000
Life time cost of fragile X syndrome 2) Discounted with 5%	4,107,920 820,017	250,000 - 2,500,000

1) Study Group Costs and Effects of CF carrier screening, 1994. iMGZ, Erasmus University Rotterdam

2) Global burden of illness studies by study group costs and effects of DNA diagnosis, 1994. iMTA, Erasmus University Rotterdam

Table 3: Effects of "DNA-diagnosis" versus "pedigree analysis" in distinct risk groups

Disease + prior risks	Effects of DNA-diagnosis for 100 consulting couples			
prior risk of parents being carriers (affected child)	couples getting pregnant	healthy children	affected children	terminated pregnancies
CF 1 (1:4)	+ 55.0	+ 40.7	- 5.2	+ 19.5
CF 1:45 (1:180)	+ 17.8	+ 17.7	- 0.2	+ 0.3
CF 1:60 (1:240)	+ 17.8	+ 17.8	- 0.2	+ 0.2
CF 1:120 (1:480)	+ 17.9	+ 17.9	- 0.1	+ 0.1
DMD 1 (1:2)	+ 35.0	+ 25.6	- 10.2	+ 19.6
DMD 2:3 (1:3)	+ 40.0	+ 38.3	- 7.3	+ 9.0
DMD 1:3 (1:6)	+ 41.0	+ 41.7	- 2.8	+ 2.0
DMD 1:6 (1:12)	+ 16.0	+ 18.0	- 2.6	+ 0.6
CMD 1 (1:2)	+ 35.0	+ 17.1	- 20.4	+ 38.3
CMD 1 (1:3)	+ 32,9	+ 10.1	- 8.3	+ 31
FraX 1 (45%)	+ 35.0	+ 25.9	- 7.9	+ 17
FraX 1:2 (22.5%	+ 38.9	+ 38.4	- 3.0	+ 3.4

Table 4: Effects of DNA-diagnosis versus pedigree analysis in distributed risk groups

Disease	Effects of DNA-diagnosis for 100 consulting couples	
Cystic fibrosis (a)	+ 38	couples choosing (further) offspring
	+ 30	healthy children
	- 3	affected children
	+ 11	terminated pregnancies
Duchenne muscular disease (b)	+ 33	couples choosing (further) offspring
	+ 31	healthy children
	- 6	affected children
	+ 8	terminated pregnancies
Myotonic dysthropy (c)	+ 34	couples choosing (further) offspring
	+ 14	healthy children
	- 15	affected children
	+ 35	terminated pregnancies
Fragile X syndrome (d)	+ 37	couples choosing (further) offspring
	+ 32	healthy children
	- 5	affected children
	+ 10	terminated pregnancies

Percentages of couples with different prior risks of an affected child
a) (55% 1:4) (15% 1:180) (15% 1:240) (15% 1:480)
b) (25% 1:2)(25% 1:3) (25% 1:6) (25% 1:12)
c) (50% 1:2)(50% 1:3)
d) (50% 0.45)(50% 0.225)

Table 5: Additional (+) costs or savings (-) of DNA-diagnosis versus pedigree analysis per consulting couple in DFL

Disease	Prior risk of parents being carriers (prior risk of affected child)	Costs minus savings for one consulting couple
Cystic fibrosis	1(1:4)	- 62,621
Cystic fibrosis	1:45 (1:180)	+ 42
Cystic fibrosis	1:60 (1:240)	+ 854
Cystic fibrosis	1:120 (1:480)	+ 2,075
Duchenne muscular dystrophy	1 (1:2)	- 71,751
Duchenne muscular dystrophy	2:3 (1:3)	- 50,200
Duchenne muscular dystrophy	1:3 (1:6)	- 16,956
Duchenne muscular dystrophy	1:6 (1:12)	- 16,254
Myotonic dystrophy	1 (1:2)	- 226,347
Myotonic dystrophy	1 (1:3)	- 90,223
Fragile X syndrome	1 (±45%)	- 321,417
Fragile X syndrome	1:2 (±22.5%)	- 118,034

Table 6: Results sensitivity analysis: Effects DNA-diagnosis versus pedigree analysis for 100 consulting couples in distributed risk groups

Disease	% couples getting pregnant with only pedigree analysis (variation 30%-70%) risk of affected child >10%			% couples choosing (DNA) prenatal diagnosis (variation 60% -100%)		
	30%	70%		60%	100%	
Cystic fibrosis	+38	+16	couples getting pregnant	+38	+38	couples getting pregnant
	+30	+14	healthy children	+30	+30	healthy children
	- 3	- 8	affected children	+ 1	- 4	affected children
	+11	+11	terminated pregnancies	+ 7	+12	terminated pregnancies
	- 34,000	-107,000	cost - savings per couple in DFL	+12,000	- 49,000	cost - savings per couple in DFL
Duchenne muscular dystrophy	+48	+19	couples getting pregnant	+33	+33	couples getting pregnant
	+43	+19	healthy children	+31	+31	healthy children
	- 3	- 8	affected children	- 3	- 7	affected children
	+ 8	+ 8	terminated pregnancies	+ 5	+ 9	terminated pregnancies
	- 20,000	- 58,000	cost - savings per couple in DFL	- 21,000	- 45,000	cost - savings per couple in DFL
Myotonic dystrophy	+53	+15	couples getting pregnant	+34	+34	couples getting pregnant
	+25	+ 3	healthy children	+14	+14	healthy children
	- 6	- 22	affected children	- 3	- 18	affected children
	+35	+35	terminated pregnancies	+23	+39	terminated pregnancies
	- 68,000	-250,000	cost - savings per couple in DFL	- 30,000	- 201,000	cost - savings per couple in DFL
Fragile X syndrome	+56	+18	couples getting pregnant	+37	+37	couples getting pregnant
	+48	+16	healthy children	+32	+32	healthy children
	- 3	- 9	affected children	- 2	- 7	affected children
	+10	+10	terminated pregnancies	+ 7	+11	terminated pregnancies
	- 107,729	-347,467	cost - savings per couple in DFL	- 79,680	- 266,443	cost - savings per couple in DFL