

University of Groningen

## Effects of neonatal screening for cystic fibrosis

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

1988

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Dankert-Roelse, J. E. (1988). *Effects of neonatal screening for cystic fibrosis*. s.n.

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## SUMMARY.

Newborn screening for cystic fibrosis (CF), the most common autosomal recessive heritable disorder with a chronic disabling nature and a shortened life span in many Causasian populations, often appears to be a matter of much controversy. This controversy originates from doubts on the usefulness of such a screening, because no causal therapy is, as yet, available.

Although several long term studies into the effects of early diagnosis and treatment on survival and clinical outcome have been carried out, the question of the potentially beneficial influences of a newborn screening programme for CF still need to be clarified.

The studies described in this thesis were carried out during a follow-up study, which was started in 1980, after an experimental neonatal screening programme for cystic fibrosis had been carried out in the north of the Netherlands in the period from 1973 to 1979. The screening test used in that programme, the meconium test (BM-test) manufactured by Boehringer-Mannheim, appeared to have an disappointingly high false-negative and false-positive rate. The aims of the follow-up study are mentioned in Chapter I. These were to evaluate the effects of neonatal screening for CF on primary prevention, as well as on survival and clinical outcome if compared to non-screening, and to assess the occurrence of side effects, e.g. of the induction of parental anxiety by false-positive screening test results.

When organizing mass screening for CF one would expect to achieve the following results, as a consequence of very early diagnosis: first, a reduction in the subsequent birth of more (affected) children in the same family. Furthermore, an improvement of survival and quality of life of the CF-patients. The high false-positive rate of the used screening test has led to an increased awareness that a screening program also may produce side-effects. The third aim of the study was, therefore, adressed to evaluate these side-effects.

In Chapter IIA and IIB the effects of neonatal screening on the influence of genetic counselling respectively on reproduction and attitudes towards reproductive behaviour are discussed.

In Chapter IIA the influence of genetic counselling on family planning was measured comparing the number of births, that could be expected on the basis of population statistics with the actual number of births in the families in this study. Genetic counselling clearly had an influence as can be seen from the estimated 50% reduction in childbirth after counselling. A greater reduction was found in those families where a CF diagnosis had been made by means of screening than in families where CF had been diagnosed clinically, but this difference was not statistically significant.

In the families where the index case had been screened for CF, the earlier diagnosis by screening caused a significant reduction in the number of children born after the index case, but prior to the CF diagnosis, as described in Chapter IIB. In the "screened" families only one child was born before the CF diagnosis was made, in the "non-screened" families 10 children were born among whom 2 with CF. No differences were noted in attitudes towards reproductive behaviour and in understanding of important genetic facts.

The effects on survival and clinical outcome are described in Chapter III. In Chapter IIIA investigations were carried out on three scoring systems for assessing chest radiographs in CF. Although no significant differences were noted between the methods, the Chrispin-Norman scoring system was recommended as the best choice, because differences in scoring appeared to be more interpretable. A lot of the variability in scoring appeared to be caused by random errors, indicating the need for properly designed studies in the case of scoring for investigational purposes.

The differences observed between screened and non-screened patients, in favour of the screened group of patients, in the first study (Chapter IIIB) became more evident in the second evaluation (Chapter IIIC). In this latter study the cumulative survival rate was significantly better for the screened

population. However, management differences probably were a second factor having influenced the survival rate. At the age of 9 significantly better clinical and chest X-ray scores, lower immunoglobulin-G levels and higher vitamin A levels were observed in the screened patients, after several years of similar treatment. This suggests that neonatal screening may prevent serious early lung damage, thus, leading to a better pulmonary condition at a later age.

One possible side effect of a screening programme is the occurrence of false alarms, as described in Chapter IV. The parental anxiety and concern that may occur after a false-positive screening test result appeared to be caused mainly by insufficient information being provided prior to the screening and the often long diagnostic procedure before reassurance was finally given.

Although this study to assess the effects of neonatal screening for CF was not initially set up as a randomized controlled trial, it appeared to fulfil most criteria of such a study.

In Chapter V the demands and pitfalls of such trials are discussed, as well as the possible implications of instituting routine newborn screening for CF in the Netherlands. Benefits that might be expected from such a screening program are the avoidance of the birth of a maximum of 7 CF-patients per annum in the Netherlands, as a consequence of early genetic counselling and the availability of prenatal diagnosis. Another benefit might be an improvement in survival as well as in the clinical condition of CF-patients.

This improvement in health care would initially cost about f50000 more per detected CF-patient, but these costs would possibly be retrieved if expenses would decrease as a consequence of less hospital admissions.

Finally, some recommendations for the organisation of such a screening programme are made based on the results of this study.