Evaluating Cystic Fibrosis Carrier Screening Development in Northern Europe:

Denmark, the Federal Republic of Germany, the Netherlands, and the United Kingdom

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Preface

In 1989 the primary mutation, ΔF508, that causes Cystic Fibrosis (CF) was identified. At that time it was assumed that the way CF-carrier screening would find its way into West-European and USA health services would demonstrate what might happen if testing for carrier genes was expanded and widely available. There were worries how the availability of the test might impact society. Scenarios were imagined that companies would rush forward to market diagnostic test kits on a large scale without providing proper counselling and information.

Therefor, a set of studies were funded in Europe by the European Union’s ”Ethical, Social and Legal Aspects of the Human Genome Analysis Program” (ESLA/1990-1992) and funded in the United States by the ”Ethical, Legal and Social Implications” (ELSI) Program at the National Center for Human Genome Research to investigate the social and ethical issues that were connected with the new test.

In Europe a multidisciplinary group of scientists (including physicians, social scientists and psychologists) from Denmark (H. Clausen), Germany (I. Nippert), the Netherlands (P. Frets/M. Niermeijer) and the United Kingdom (M. Modell) started in 1992 the comparative study ”Evaluating Cystic Fibrosis Carrier Screening Development in Northern Europe: Denmark, the Federal Republic of Germany, the Netherlands, and the United Kingdom” (funded by ESLA) to find out how CF-carrier testing might fare in these countries.

To discuss the findings an international workshop was held at the John F. Kennedy Institute, Copenhagen-Glostrup, Denmark, November, 19-20, 1992. An international group of experts, including representatives of the CF-patients organisations was invited. From the USA two distinguished experts, N.A. Holtzman (Johns Hopkins University, Baltimore, MD) and D.C Wertz (The Shriver Center, Waltham, MA), were invited to comment on the European data.

Although the publication of the findings of the study and the proceedings of the workshop is somewhat delayed, the findings and the proceedings present a unique document. They highlight the different point of views expressed by providers, parents and patients on the risks and benefits that come with new genetic tests. They clearly show the different interests at stake and how various uptake rates are influenced by provider behaviour, by how the test is offered and to whom the test is offered (high uptake rates by pregnant women, low uptake rates by others).

They also demonstrate the scrutiny that went internationally into the efforts to safeguard new genetic testing.

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1. Introduction and Acknowledgements

I. Nippert

In 1989 the Cystic Fibrosis transmembrane conductor regulator (CFTR) gene was cloned and the common mutation was identified as the deletion of phenylalanine 508 (ΔF508). Today, more than 600 different mutations causing Cystic Fibrosis (CF) are identified. The proportion of CF-mutations that are ΔF508 is relatively high in Denmark, the F.R.G., the Netherlands, and the UK, ranging from 88%-73%. The most common six CF-alleles comprise appr. 83% - 90% of the CF-alleles prevalent in these countries. Thus carrier screening of CF, the commonest recessively inherited disease among Northeuropeans (prevalence of CF: -1:2 500/4 700; carrier frequency -1:25/34) becomes feasible. Pilot carrier screening programs were started in 1990 in Denmark, the UK and in the F.R.G.

CF-population based carrier screening has been widely debated among professionals and the public and compelling arguments for and against starting screening programs now have been put forward (s. U.S. Congress, Office of Technology Assessment, Cystic Fibrosis and DNA Tests: Implications of Carrier Screening, OTA-BA-532 (Washington, DC: U.S. Government Printing Office, August 1992); B. Modell, Cystic fibrosis screening and community genetics; J Med Genet 27:475-479, 1990). When the mutation was identified it was widely believed that carrier testing for CF would become the first large-scale experience with population based carrier screening in Northern Europe by means of direct DNA-analysis. Earlier experiences with population screening for haemoglobin disorders and Tay-Sachs-Disease in Southern Europe and the United States had demonstrated the necessity to build up an interconnected comprehensive infrastructure of services, to educate physicians and the population to be screened not only about the nature of the disorder itself but also about the limits of the tests that are available to avoid unnecessary harm, such as stigmatisation of carriers (C.L. Clow, C.R. Scriver, Knowledge about and attitudes toward genetic screening among high school students: the Tay-Sachs experience. Paediatrics 59:86-91, 1977) and discrimination in employment and insurance.

Therefor, consensus had been reached in the public debate that if CF-carrier-testing would be offered on a population basis a number of complex problems had to be solved, i.e.: Who should be offered testing and in what setting (pregnant women, through primary health care providers and/or community based screening programs)? How should the lack of public understanding of genetics and genetic testing be dealt with? How should the insufficient number of adequately trained health care providers be reduced? How could individual autonomy and
confidentiality be safeguarded? What kind of procedures should be taken to ensure the quality of genetic counselling? Using qualitative research methods (oral interviews and document analysis), we assessed the onset of CF-carrier screening development and the problems inherent in this process in those EU-countries that have a high CF-carrier frequency: Denmark, the F.R.G., the Netherlands, and the UK. An international multidisciplinary group including social/behavioural scientists, geneticists and representatives from the countries' CF-associations gave advice on the study design and instruments.

1.1 Objectives

The study compares and contrasts the status of Denmark's, the F.R.G.'s, the Netherlands', and the UK's approaches in the early 1990s to implement or not to implement and to diffuse or not to diffuse CF-screening into their health care systems from a health policy/public health perspective. The aim of the study is to identify "key-factors" that are affecting the implementation and diffusion process and to learn how these factors operate to influence the provision of CF-screening services. The study documents and analyses the views of "key-persons" (= those who are likely to influence the implementation and diffusion process of CF-screening, i.e. health professionals, health administrators, health policy decision makers, legal experts, lay persons coming from consumer and patient groups, etc.) from different professional and social backgrounds to learn what their interests and concerns are at the present stage and for the future. The study aims to lay a groundwork for social, ethical and legal policy discussion regarding the question whether and how population based screening for CF-carriers could or should be implemented. The study reviews from an interdisciplinary public health perspective - combining a social science health system analysis approach with genetic scientific expertise - the field of CF-carrier-testing at a time when CF-carrier screening programs in Northern Europe either are in their conceptualisation phase or piloting-testing stage before policies and strategies have stabilised.

1.2 Study Design and Methods

The study is outlined as an empirical comparative study that investigates the views of key-persons in Denmark, the F.R.G., the Netherlands, and the UK. To document the views the project used open structured (narrative) oral interviews. The issues that were covered by the interview were developed together with the country co-ordinators from each country with the assistance of a panel of consultants.

The Oral Interview Focussed on the Following Issues:
- preferred infrastructure of screening programs
- the role of primary health care providers in screening programs
- community approaches to screening programs
- preferred target population of screening programs
- quality control of genetic counselling performance
- need for professional and public education
- safeguarding of parental/client choices
- individual autonomy and confidentiality
- required knowledge on the part of the providers and the potential recipients on CF and CF-test limits
- medico-legal aspects such as protection of privacy from third parties, foreseeable malpractice suits from women that have not been informed about the possibility of prenatal CF-screening
- equal access to services
- cultural factors that may affect screening programs

Beside the interview data the study employed descriptive document analysis using available epidemiological data from CF-studies and data covering the country's health care system (national health care program) to describe the existing infrastructure of genetic services, counselling capacities, manpower/staff requirements, financing of the services, number of people to be screened, carrier population, etc. Additionally the study relied on empirical data stemming from empirical studies which were under way: (1) "Decision Making in Prenatal Diagnosis". The study includes more than 2000 pregnant women in the F.R.G., the project covers attitudes of pregnant women toward CF-carrier screening (I. Nippert, J. Horst, Die Anwendungsproblematik der pränatalen Diagnose aus der Sicht von Beratenen und Beratern - unter besonderer Berücksichtigung der derzeitigen und zukünftig möglichen Nutzung genetischer Tests -, Gutachten im Auftrag des Büros für Technikfolgen-Abschätzung im Deutschen Bundestag, Bonn 1994). (2) Current pilot projects conducted in Denmark, the F.R.G. and the UK.

**Sample Size**

Due to the short time period available for this study, the sample of persons interviewed within each country had to be kept at a manageable size. As the study's aim is to document the views of "key-persons" the standard of selecting a person for an interview were put relatively high so that the choice was kept among a few representative persons. Each country co-ordinator with the assistance of the country consultants determined on his/her own how many persons he/she asked for an interview. On the whole 61 persons were interviewed.
1.3 The Country Co-Ordinators and Consultants

The country co-ordinators are:

H. Clausen PhD, Denmark; I. Nippert PhD, F.R.G.; P. Frets PhD, the Netherlands; M. Modell (MD, FRCP, FRCGP), UK.

The consultants are:

M. Mikkelsen (clinical geneticist, em. professor, MD, PhD, at that time head of the department of medical genetics, John F. Kennedy Institute, Glostrup), Denmark.

H.W. Tybkjaer (exec. director of the Danish CF-Association, Viborg), Denmark.

G. Wolff (clinical geneticist, professor, MD, head of the genetic counselling centre (Leiter der Genetischen Beratungsstelle), Albert-Ludwigs-Universität Freiburg), F.R.G.

J. Schmidtke (clinical geneticist, professor, MD, head of the department of human genetics, Medizinische Hochschule Hannover), F.R.G.

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M. Weggen (Dutch CF-Association, Baarn), the Netherlands.

B. Modell (MD, PhD, FRCP, perinatal centre, department of obstetrics and gynaecology, University College and Middlesex School of Medicine, London), UK.

M. Scott (DSc, PhD, representative of the British CF-trust, Bromley), UK.

The consultants advised the country co-ordinators on the issues to be covered by the oral interview; assisted the country co-ordinators in the selection of key-persons for their country and served as "door openers" to facilitate the access to key-persons; assisted in reviewing the preliminary country reports; attended the two international
workshops to prepare and discuss the country reports. On account of their expertise in international issues in social, ethical and legal aspects of human genetics which include several surveys on social aspects and genetics N.A. Holtzman (professor, MD, MPHA, Johns Hopkins University, Baltimore, MD, USA) and D.C. Wertz (senior scientist, PhD, The Shriver Center, Waltham, MA, USA) acted as international consultants and attended the international workshop, Copenhagen 19.11.-20.11.1992 to comment the preliminary country reports.

During the study two workshops were held, one in London, February, 14, 1992 at the University College and Middlesex School of Medicine, where the final issues covered by the oral interviews were developed and the key persons to be interviewed were selected. A final workshop was held in Copenhagen, November, 19-20, 1992 at the John F. Kennedy Institute to discuss the preliminary country reports (see also the "Table of Contents of the Proceedings" at the end of this book). At this workshop the country co-ordinators and country consultants agreed to adopt in the final report the Office of Technology Assessment's use of the terms of genetic screening and genetic testing:

"OTA defines genetic testing as the use of specific assay to determine the genetic status of individuals already suspected to be at high risk for a particular inherited condition. While any individual can be considered "at high risk" for a particular unknown trait, and hence be "tested", "at high risk" in this report denotes the presence of a family history or clinical symptoms. The terms genetic test, genetic assay, and genetic analysis are used inchangeably to mean the actual laboratory examination of samples. Genetic screening usually uses the same assays employed for genetic testing, but it is distinguished from genetic testing by its target population. OTA uses the term "screening" selectively. In this report, it refers to analysing samples from individuals without a family history of the disorder, groups of these individuals, or populations. Carrier screening for CF (or CF-carrier screening), then, involves performing tests on persons for whom no family history of the disorder exists to determine whether they have one normal and one aberrant copy of the CF-gene, but not the disorder (which results from having two aberrant CF-genes). In contrast, OTA uses the term CF-screening (or screening for CF), to mean screening individuals to diagnose the presence or absence of the actual disorder, in the absence of medical indications of the disease or a family history of CF. This type of diagnostic screening usually involves new-borns, but is rarely done for CF except in Colorado and Wisconsin. CF-testing of new-borns is common if family history of the condition exists."

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**E. Bulmahn**, MdB, member of the Federal Parliament (Mitglied des Bundestages), Bonn, F.R.G.

**W.M. Catenhusen**, MdB, member of the Federal Parliament (Mitglied des Bundestages), at that time chairman of the Committee for Research, Technology and Technology Assessment of the German Federal Parliament (Vorsitzender des Ausschusses für Forschung, Technologie und Technikfolgenabschätzung im Deutschen Bundestag), Bonn, F.R.G.

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R. Harris, geneticist, em. professor, MD, department of medical genetics, St. Mary's Hospital, Manchester, UK. Professor of medical genetics, chairman of a confidential enquiry into counselling for genetic disorders.

W. Holzgreve, obstetrician, professor, MD, head of the Universitäts-Frauenklinik, Kantonsspital, Basel, Switzerland, at that time head of the department of prenatal medicine, Westfälische Wilhelms-Universität Münster, F.R.G.

A. Hunt, MD, Genetic Interest Group (GIG), c/o institute of molecular medicine, Radcliffe Hospital, University of Oxford, UK. Chairwoman of GIG, which is an umbrella group of more the 60 voluntary organisations for patients with genetic disorders.

O. Jensen, PhD, member of the Danish Council of Ethics, Denmark. The Danish Council of Ethics advises the parliament and the Minister of Health on all legal and ethical issues concerning new biomedical techniques.

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L. de Neergaard, MD, the National Board of Health, Denmark.

J. and B. Nielsen, a family with a CF-child, who has chosen not to make use of PD, Denmark.

S. and K. Nielsen, a family with a CF-child, who have chosen to make use of PD, Denmark.

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Dave, Louise, Mark and Pat. Four adults who suffer from CF. One is awaiting a heart-lung transplant, one had a successful transplant about 2 years before this study, UK.
2. Country Report from Denmark

H. Clausen

Key Persons Interviewed in the Danish Study:

H.W. Tybkjaer, manager of the Danish CF-Association, Viborg. The CF-Association has supported the start of the Danish pilot study on CF-carrier screening and is following the study.

P. Riis, professor, MD, the Central Scientific-Ethical Committee. The committee has approved of the start of the Danish pilot study.

C. Koch, MD, chief physician at the CF-centre, Rigshospitalet (State Hospital), Copenhagen.

N.J. Brandt, MD, metabolic laboratory, department of clinical genetics, Rigshospitalet, Copenhagen. N.J. Brandt is the initiator of the Danish pilot study on CF-carrier screening.

M. Schwartz, biochemist, PhD, metabolic laboratory, department of clinical genetics, Rigshospitalet, Copenhagen. M. Schwartz is the initiator of the Danish pilot study on CF-carrier screening in collaboration with N.J. Brandt. She is in charge of the analyses.

J. Moeller, President of the Federation of Disablement Organisations (DSI).

O. Jensen, PhD, High school principal, member of the Danish Council of Ethics.
The Danish Council of Ethics advises the parliament and the Minister of Health on all legal and ethical issues concerning new biomedical techniques.

L. de Neergaard, MD, the National Board of Health. The National Board of Health is just now considering new guidelines for PD to pregnant women.

Jytte and Bent Nielsen, a family with a CF-child, who has chosen not to make use of PD.

Kirsten and Soeren Nielsen, a family with a CF-child, who have chosen to make use of PD.

The selection of key persons is strategic rather than representative. The Danish key persons all have influenced the decision process concerning a Danish pilot study on CF-carrier screening or decisions in health policy concerning carrier screening for CF.

To document the views of the key persons in the study, semi-structured oral interviews and document analysis were used. The issues covered by the interviews were: Decision processes in relation to the pilot study. Preliminary results from the pilot study on CF-carrier screening. Preferred target population. The role of primary health-care providers in screening. Demands for genetic counselling in relation to screening. Protection of privacy and individual autonomy. Ethical issues in relation to carrier testing. Policies of the health care system concerning CF-screening, etc. The interviews focused on the particular roles of the key person in relation to an ongoing pilot study of CF-carrier screening in Denmark. The selection of key persons has been made in collaboration with the consultants of the study and the researchers in the other countries. The interviews lasted between 45 - 90 minutes. Interviews were tape recorded and transcribed later.

Health Services in Denmark

Denmark has a population of 5.15 million. Politically and administratively Denmark is governed on three levels: at state, county and municipal level. The country is divided in 14 counties (+ Copenhagen and Frederiksberg) and 276 municipalities. The state lays down legislation and bylaws under which the various activities of the health services are carried out and undertakes supervision and control through the National Board of Health. The National Board of Health advises the parliament (Folketinget) and the Minister of Health on all medical matters. The county councils provide hospital services, and the National Health Insurance Scheme is responsible for the curative health services carried out by doctors, dentists, etc. working in pri-
vate practices. The Danish health services operate on three main levels. The primary health services are built on GP's services, which are based on the family-doctor principle. The GPs operate in private practices and undertake examination and treatment of patients, and also refer patients to practising specialists or hospitals. The primary sector also includes dentists, retail chemists, physiotherapists etc. working in private practices. Services are paid by the National Health Insurance Scheme, which guarantees free medical treatment by the general practitioner. The services are financed through taxes and rates (for some services such as dental services). The National Health Insurance Scheme also covers part of the expenses for drugs and medicine.

The secondary level consists of somatic and psychiatric hospitals. Each county must provide services to meet the requirements of the county. The municipalities are responsible for the tertiary level. The municipalities provide nursing homes, home help services, school medical and dental services etc.

The Danish health services are free of charge with equal access for everybody. The counties and the municipalities have the main economic responsibility. But their expenditure is partly reimbursed by block grants from the state. The National Health Insurance Scheme was nationalised in 1973. Hospital services are free of charge for all patients and are financed through taxes. The majority of hospitals are publicly owned (a few private hospitals are subsidised by public funds). The state runs a university hospital, Rigshospitalet, in Copenhagen, where the CF-carrier-screening is carried out.

PD in Denmark

The utilisation of prenatal diagnoses in Denmark is high. Between 65% and 85% of all pregnant women over 35 years make use of the offer. The highest utilisation is found in Copenhagen and Northern Zealand, and the lowest in Western Jutland. In 1990, 7 539 prenatal diagnoses were made. (This number does not include the number of ultra-sound scans, however.) Of these 5 631 were amniocenteses, while 1 908 were chorionic villi biopsies. This means that PD was made at approximately 12% of all births. The number of amniocenteses has been fairly stable since 1984, whereas the number of CVS has been increasing. Provoked abortions were carried out in 114 cases after the finding of abnormalities. This corresponds to 1.51% of the analyses made. Most prenatal diagnoses are made on the indication of high maternal age (≥55%), previous child with chromosomal aberration or another reason that can cause a chromosomal disease, 17%. The number of analyses for metabolic diseases amounts to 7% of the prenatal diagnoses. An increasing number of women have PD because they fear that something is wrong with the child. At the moment there is no
political wish to extend the access to PD, e.g. through an extension of the age limit for PD.

Abortion in Denmark

From 1939 legal abortion was permitted when certain medical, ethical, and eugenic conditions were present. In 1973, after recurrent public debates, the Danish parliament introduced legal abortion for all women until the end of the 12th week of pregnancy. After the end of the 12th week of pregnancy abortion is still permitted, when special conditions are present. One of the special indications is the genetic indication. The frequency of abortions in Denmark must be evaluated in relation to the size of the population and the birth-rate. In 1990 the Danish total number of births was 63,433. The number of provoked abortions was 20,589. (The number of spontaneous abortions is estimated to 13-15,000.) Compared to other Scandinavian and Western European countries this number of abortions is high. 97-98% of the provoked abortions were made before the end of the 12th week of pregnancy, while 434 abortions were made after the end of the 12th week of pregnancy. This corresponds to approximately 2% of all abortions. 114 abortions were made because of genetic indication.

CF in Denmark

CF is the most common autosomal, recessive inherited disease in Denmark. Today there are 330 living patients with CF in Denmark. The frequency of CF is 1:4,760. Approximately 3% of the population are healthy carriers.

Prognosis, Treatment and Control:
Earlier, most patients died before the age of five. But during the last 30 years the prognosis has improved considerably and is still improving. During the period from 1945 to 1959 the 10-year survival was 9%, from 1960 to 1969 it was 44%, and from 1970 to 1981 it increased to 75%. From 1981 to 1992 it has increased further, but topical figures are not yet available (4).

The improved survival is due to early diagnosis of the disease, effective substitution treatment of the pancreas symptoms, and especially effective treatment and prophylaxis of the lung infections. In 1975 the treatment of Pseudomonas aeruginosa was changed from on demand antibiotic treatment to regular hospitalisations for a fortnight every third month. This has improved the survival of patients with Pseudomonas aeruginosa considerably. During the period from 1976 to 1980 the 5-year survival from the start of the infection increased from 58% to 82%, and in 1988 it
was 94%. The 10-year survival after the start of the Pseudomonas-infection was 91% in 1988. During recent years heart-lung transplantation have been carried out for patients with poor lung function. Until now only three Danish patients have had heart-lung transplantations (abroad).

**Ch. Koch** gives the following short status of the situation in Denmark: There are 330 patients with CF in Denmark. Of these 240 to 250 are treated at the CF-centre in Copenhagen. The rest - apart from very few - are treated at the CF-centre in Aarhus. We have today an average life-expectancy of 30 years for CF-patients. The life-expectancy has been prolonged from 20 to 30 years during the last 10 years. But the prognosis varies much depending on the severeness of CF and on the time of the beginning of the treatment. Now about 98% of the patients are treated at one of the two Danish CF-centres. A Danish study (5) showed that the survival of patients treated at the CF-centre compared to patients treated at other hospitals was significantly higher. The 10-year survival for patients treated at the CF-centre was 88% in 1981, whereas only 52% of the patients treated at other hospitals became 10 years old. The probability for reaching the age of 20 was 61% for patients treated at the CF-centre, whereas it was 14% for patients treated at other hospitals.

**Reproductive Behaviour in Families with a CF-Child**

Earlier, the birth of a child with CF often had the effect that the parents ceased to have children or chose an abortion in case of another pregnancy. After the introduction of PD the number of families having more children after the birth of a child with CF has increased (6). A study at the CF-centre in Copenhagen showed that 83% of the parents of children born with CF between 1948 and 1975 ceased to have children (7) after the birth of the CF-child. During the period from 1976 to 1989 only 76% ceased to have children after the birth of a child with CF.

The study also showed that most families wanted PD even if they did not necessarily use this information for an abortion if the fetus had CF. It was found that 90% of the families accepted PD whereas 10% said no. Of the 90% who accepted PD, 10% chose to carry through the pregnancy even if the test showed that the child had CF. The number of abortions in these families has also been reduced after the introduction of PD. Earlier they aborted also healthy fetuses because of lack of information.

**Ch. Koch** and **N.J. Brandt** say about PD in families with a CF-child:

**Ch. Koch**: Now that you can offer PD to families with a CF-child, several families make use of this offer - in order to have more children - without CF. Earlier they
dared not have more children. It is my impression that now they dare, because they can have PD. However, there are a few families with a CF-child, who do not want PD. And some want PD, but want the child, no matter what the answer is. So we have families with all views. For the living patients it is of course a sensitive subject when it is suddenly personified for them that he/she should have been an abortion, or that this is what society is working at. Some are very offended. Then you must try to explain them that the reason is that you do not want others to be born with CF. My own opinion is that if the parents can live with an abortion, I recommend this. But it must agree with their attitude to abortion. If a family have asked directly for my advice, I have recommended abortion, but I have always emphasised that they must choose in accordance with their own conviction. I have never put pressure on a family to make it choose an abortion. I say this, because the child is the one to live with the disease, and the family are the ones to take care of it. It is ethically complex: On the one hand you kill a fetus by choosing abortion. It is becoming a human being. On the other hand you cannot change the fact that it must live with CF, and I know that it can be hard to live with CF.

N.J. Brandt says: Generally, I think it is a great responsibility to choose to have a child with CF. But I do understand the doubts about abortion - especially for women it is a difficult decision. Women do not scamp this - even if we have free abortion in Denmark.

When you ask women, who ask for PD, what they will do if the fetus is severely handicapped, 99% say that they want an abortion. But there are exceptions. A few women want information and certainty - without choosing abortion. For the researchers starting the carrier screening there is a direct line from PD in families with a CF-child to carrier screening in non-risk families. As almost all CF-families ask for PD in order to avoid having another child with CF. They look at the carrier screening as a way to prevent families from have their first child with CF.

**PD in Families with a CF-Child:**

*Two examples*

For the people carrying an inherited disease, the questions about PD are personal and concrete. Today the majority of the families with a CF-child request PD at a new pregnancy. But a few families say no to this offer. As a part of this investigation interviews have been made with two families, who have acted differently as to PD.

Bent and Jytte Nielsen (17) belong to the families choosing not to make use of PD. Their first child was born with CF. So they knew that they had a 25% risk of having
another child with the disease at their next pregnancy, they chose not to make use of PD (18). Jytte Nielsen says about this decision: It should not be a sort of sorting out. We would not take part in this - to scrap human beings in this way. We found this very unpleasant. We wanted another child, and it did not have to be a "prize baby". We quite agreed, and none of us had to persuade the other one.

*Have you had religious considerations as to abortion?* No, we haven't. We are quite ordinary members of the Danish national church going to church on Christmas Eve. Perhaps not even then. None of our kids has been baptised. We are also for free abortion. People should decide for themselves. The family had another child with CF in their second pregnancy. When Jytte Nielsen got pregnant the third time, the pregnancy was not planned. They thought it was enough with two children, who also were ill. It was a very great dilemma, and we discussed it a lot. I think I (J.N.) was the one to say no. I was not sure whether I could go through an abortion, because after all I wanted to have the child. I would always have blamed myself that I had chosen the abortion because of the disease and not because I did not want more children. The family had a healthy baby.

The crux of the family's reasons for rejecting PD was not - as it is in some cases - religious values. But ideas about PD being a form of choice of consumption or quality control: Today you can choose much more - whether you want children, and when you want them. You get used to being able to choose everything, I think. If we are only going to have two children, they must preferably be - if not the best - at any rate as faultless as possible. And then if you are suddenly told that they might be sick, do we have room for them?

I think that the reason why we did not feel a pressure is that we had made up our minds before we came to the doctors. If you are saying: "I don't want that", the doctors are not trying to press you. But if we had been doubting, and I had said, "I do not know what to do" - without knowing anything about the disease - I think I would also have chosen an abortion.

The other family Soeren and Kirsten Nielsen have three children. Their first child was born with CF. She was born approximately at the time when it became possible to make PD for CF. They chose to make use of PD at three later pregnancies.

We did not doubt that we would make use of PD. Actually it was a great relief for us that this possibility appeared and became available to us.

*If this possibility had not been available?* I have not thought of that. We were quite sure that we would use it. At the first pregnancy (after Hanne's birth) the test showed that the fetus had CF. So we chose not to have this baby. We had decided before the
test was made. But it certainly was a disappointment that the fetus had CF. But the decision that it should be an abortion, if the fetus had CF, had been taken. We thought there was no reason to take the test, if you did not want to use it.

Did you agree? We quite agreed. There was no doubt in our minds.

Did you discuss it with anybody before you made up your minds? Did you seek advice? I am a doctor myself. We knew about the methods and possibilities. We had no doubts at all. We knew the disease from our elder daughter. We were the ones to live with the decision. As to the ethical question about abortion or not, we thought this was for us to decide. Others should not make this decision for us. Kirsten Nielsen continues, I knew nothing of CF before we had our first child. But if somebody had explained to me what it would imply, I am sure I would have chosen an abortion. I also think I would have approved of carrier screening, if I had been asked. I don't think you can put such a burden (a life with CF) on to another human being, if it can be avoided. I don't think you can burden another human being with that disease. If it is possible, I think it should be avoided. If I had another child with CF, I think this child could have blamed me for the disease. As to the first child, I didn't know I was a carrier.

Have you had any reactions after the abortion? Any doubts? No. But it must be admitted that later on I have had two healthy children. If I had aborted three times, I might have looked differently at it. The first time of the pregnancy, until the test has been taken, is a hard time. But it is a relief to receive the result. At our next pregnancy we had the test made again and were told that our fetus was a carrier - and as such not ill. We chose to have this one.

How will you explain to your eldest daughter that you can choose abortion of fetuses with CF? And how will she, who has CF, perceive it? K.N.: We have thought of this. Certainly she would have preferred to be without her disease. I don't think she likes her disease. She has said that she wished she was born without it. We try to separate it by saying, that we would not have been without her, but we would like to have been without her disease. I think she understands. S.N.: She thinks life is very hard with that disease, and she identifies many of her problems with it. She would prefer to be like everybody else.

K.N.: I don't think it should be glorified to have a sick or handicapped child, as some people do. Of course you must try to get the best out of the situation. But I don't think you should seek out this sort of situations. S.N.: I think you should listen to families with a CF-child. They know what kind of disease it is. I don't mean that you should force people to take the test; but they should have the choice.
Mutation for CF in Denmark

Several mutations have been shown to cause CF. The most frequent mutation has been shown to be ΔF508. ΔF508 makes up about 88% of all mutations in Denmark, about 80% in the Netherlands, whereas in Eastern Europe it only makes up about 46% of the mutations (8). By testing 285 patients M. Schwartz has identified the following mutations in Denmark (9): 285 examined persons: 570 chromosomes; ΔF508 positive 500 (88%), ΔF508 negative 70 (12%): G551D = 1, G5542X = 4, 621+1Gt = 2, N1303K = 4, unknown = 59 (10%).

Couples who both are heterozygote carriers for CF, have earlier been identified at the birth of a child with CF. But after the ΔF508 mutation has been found, it has become possible to identify most of the carriers. Because of the high frequency of ΔF508 the possibilities for screening for CF are especially favourable in Denmark.

A Pilot Study of Carrier Screening for CF

In 1990 the department of clinical genetics, Rigshospitalet, started a pilot study on carrier screening for CF of 10 000 pregnant women. The study is made by chief physician, N.J. Brandt, M. Schwartz, and Dr. F. Skovby, MD (10). The carrier screening for CF at Rigshospitalet consists of the following steps:

I. The carrier test is offered to two groups of pregnant women: (1) Women who are referred to the hospital for PD (most often because of advanced maternal age). (2) Women attending the obstetric out-patient clinic for routine prenatal care. The women receive written information about CF and about the carrier test together with the letter about her appointment at the clinic. The test is made on a blood sample taken in connection with other routine examinations.

II. After approximately a week the woman is informed of the result of the test by letter. If the test shows that the woman is not a carrier, she will be informed of this and will also be told that her risk of having a child with CF is very limited. However, if the test shows that the women is a carrier, she is informed by letter and phone about the results. She is although offered to have her partner tested as soon as possible.

III. The woman's partner is tested for ΔF508 and other mutations known in Denmark. After about a week he is informed of the result of the test. If the test shows that he is not a carrier, the couple will be informed by phone that the risk of having a child with CF is very low, but not zero. However, does the test show that
the husband is a carrier, the couple will receive further genetic counselling and be informed about the possibility of prenatal diagnosis.

IV. If the couple requests PD, and if the fetus has CF, they are informed about the possibility of abortion.

As it is only possible to screen for about 90% of the mutations, a woman identified as a carrier, with a partner who is ΔF508 negative, will still have a certain - though very small - risk of having a child with CF. Correspondingly a woman, who is ΔF508 negative, and whose husband is not tested, will also have a very small risk of having a child with CF. The aim of the study is to examine the psychological and ethical problems caused by the carrier screening. A questionnaire is sent to the participating women/families after the test asking them about their previous knowledge of inherited diseases/CF, their evaluation of the information, their reactions to participating, their attitude to PD and abortion, and as to carriers, their reactions to realising that they are carriers. Furthermore it is examined whether the women understand that the carrier test does not give absolute certainty.

The Results of the Carrier Screening Study

From June 1990 to June 1992 (when the carrier screening was stopped) 6,599 women were tested. 172 women were found to be heterozygote carriers of ΔF508. All but 10 of their partners were tested. Three men were found to be heterozygote carriers of ΔF508. No partners were found to be heterozygote carriers for any of the five other mutations. All three couples requested PD. This was done on CVS on cells already obtained for other reasons (since all three women came from group (1)). One fetus was found to be homozygous for ΔF508. This couple chose to terminate the pregnancy. The two other pregnancies were continued since the fetuses were found to be heterozygous for ΔF508. The results are summarised below:
CF-Screening Results:

<table>
<thead>
<tr>
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<th>Persons tested</th>
<th>N / ∆F508</th>
<th>∆F508 / ∆F508</th>
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</thead>
<tbody>
<tr>
<td>Women</td>
<td>6 599</td>
<td>172</td>
<td>0</td>
</tr>
<tr>
<td>Partners</td>
<td>162</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fetuses</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

In group (1) more than 98% accepted the test, and in group (2) more than 80% did. The average time from taking the blood sample to the mailing the first answer was 6 days. The time from testing the partner until delivering the final answer for the couple was 11 days (M. Schwartz, personal communication).

The Counselling of Heterozygote Carriers for CF

Women identified as heterozygote carriers for CF are informed about this by letter and on the phone by M. Schwartz or N.J. Brandt. During this communication it is pointed out that carriers are not ill, and that the women's fetus' and other children are not ill even if they might be carriers.

N.J. Brandt says: All women get worried. A few are really shocked. Most of them tell us that the result worries them very much. But it is a great relief, when they receive the result of their husband's test.

Most people do not realise how close it is, in spite of the fact that one out of 34 is a carrier. But this is the expected unfortunate side effect of this. M. Schwartz says: Generally the women say that they know nothing about CF - perhaps very little. It is quite clear that there is a need for an improved biology teaching in the Danish primary and secondary school.

The counselling of the couple with the affected fetus was given by N.J. Brandt: I contacted their family doctor when we knew the result of the PD. He contacted the couple and asked them to come and see me. He also asked them, what they would do if the fetus was ill. Of course they guessed that something was wrong and insisted on being informed. And so they were. When they came to see me, they had already decided to have an abortion as soon as possible, and they did not want to hear more about the disease. They did not want to speak to a doctor at the CF-centre. I had arranged with Ch. Koch at the CF-centre that they should speak with him about the consequences of having a child with CF and about the treatment, and also he should tell them that it is possible to live with it, but it requires an intensive treatment. Ch. Koch adds as follows: At first it might be enough for couples where both are carriers to speak with a geneticist. In the first place they must only decide whether
they want PD. But if the fetus appears to have CF, it is important that they speak with a geneticist as well as a CF-doctor. Does the family choose to have the child, they will get in contact with us at the CF-centre.

Do the families also have the opportunity to speak with a family with a CF-child? That kind of contacts, which are very important, are normally established through the CF-Association. When a family has a CF-child, they are told about the association. They get a brochure and are encouraged to contact it. The association is often able to arrange a contact with families nearby.

The Decision-Making Process

For the researchers starting the carrier screening in non-risk families there is a direct line from their experience with PD in families with a CF-child to the idea of carrier screening of non-risk families. They point out that almost all CF-families ask for PD, and they find it natural to use the carrier screening as an extension of this in order to prevent that families have their first child with CF. N.J. Brandt and M. Schwartz say as follows about the start of the study:

M. Schwartz: Already before the localisation of the CF-gene we had decided to start carrier screening when the gene was found. So we were ready to begin when it happened. This was before the mutation (ΔF508) was found, and before we knew that Denmark was in a special situation having a high frequency of this mutation. When we had examined the CF-families and had found that the frequency of the mutation was so high, it became still more important of course. We also knew that almost all families with a CF-child ask for PD if they want more children, and that they choose to have an abortion if the fetus appears to have CF. On this background I found it natural that you do not have to have your first child with CF if it can be avoided.

N.J. Brandt: The moment the gene was found, I said ”Now we must start the carrier screening program as soon as possible.” I didn't really discuss it with anybody, because our experience with PD in families with a CF-child was so good. So I found that the rest of the population should be offered a carrier test so that they could avoid having a child with CF. So we applied to the Scientific-Ethical Committee for permission to start. It was recommended, but our application was also sent to the Central Scientific-Ethical Committee on ground of principle.
The Scientific-Ethical Committee

The Scientific-Ethical Committee system is primarily a control system which secures that the scientific-ethical rules of the Helsinki II declaration are observed before the start of experiments with human beings. The study on carrier screening for CF was sent to the regional Scientific-Ethical Committee in 1990 for approval. The committee system found the study most valuable, and as the research group also complied with the wishes for further information, the study was found to be in agreement with Helsinki II and could be started. However, the regional Scientific-Ethical Committee found the study a principal case and forwarded it to the Central Scientific-Ethical Committee for a discussion. The committee decided to approve the study, but not until the patient information had been improved, and the research group had explained how quickly the tested persons would receive the result. P. Riis adds: This was a case of research in a sensitive area. Can you make a carrier screening without having a negative attitude to persons with CF and other handicaps? Handicapped persons must never feel that the fact that you try to diminish the number of handicaps and diseases, means that handicapped persons are of less value.

Which role did the recommendation of the study by the patient association play? The study on CF would probably have been approved anyway. But it made an impression that the patient association approved of the study. I have participated in a meeting for politicians together with the manager for the CF-Association, H. Tybkjaer, where the patient association expressed its approval of the study, and I think this made an impression. It made an impression that she emphasised that the organisation wanted this research, if only it was voluntary and under ethical control. Many politicians have the opinion that it are only scientists who want to ”potter about things” for the sake of science.

M. Schwartz gives the following information about the approval in the Scientific-Ethical Committee: The letter of information about the carrier screening as well as the letter of reply to the carriers were reformulated several times before the Scientific-Ethical Committee approved of them. We should have emphasised more clearly that you are not ill because you are a carrier. It is important to explain to them that they are not ill, and that their child or older children are not ill. Also the explanation of the certainty of the test was reformulated.
The Statement of the CF-Association on the Carrier Screening Study

In connection with the approval of the study by the Scientific-Ethical Committee N.J. Brandt asked the Danish CF-Association for a statement on the study. The CF-Association stated as follows:

We understand that there are plans to examine the mutations resulting in CF in the Danish population, and that it will then be possible to identify carriers and to offer PD. We have been hoping for many years that these possibilities could be within reach. However, we shall take the opportunity to emphasise our wish that pregnant women will be offered tests that can detect the risk of CF. This is necessary if risk families shall have the possibility to decide by themselves after counselling whether they want to give birth to a CF-child or not. In recent years, when the possibility of PD in families with known CF-patients has improved, we have learned how this has been taken in by the families, and we notice that an increasing number of relatives to CF-patients contact us for information about PD. Therefore, we are very grateful that also pregnant women outside the already known risk groups will now be able to benefit from this offer.

Interview with the CF-Association

As part of this study H. Tybkjaer, manager of the Danish CF-Association, was interviewed. In the interview the organisation had the opportunity to amplify their views on the introduction of carrier screening of non-risk families. H. Tybkjaer says: The population as a whole must decide whether screening for CF shall be introduced - not us as risk families. As an organisation representing risk families we are not able to decide whether a general screening should be introduced. This is the opinion of opponents in our organisation as well as of supporters. But the organisation thinks that the study that is now carried out at Rigshospitalet, can tell us how the population will receive the screening. In our organisation it is crucial that the test is voluntary. You must decide for yourself whether you want the test.

How is the attitude of the CF-families to PD? In a study made at the end of 1989 we saw that the majority of the families approved of PD, whereas 10% said no to have the test at all. Among the 90% of families, who were in favour of PD, 10% chose to carry through the pregnancy, even if the test showed that the child had CF. We have to respect that some persons do not approve of abortion. But even if they are against it, they do not think that PD and carrier screening should not be available. But each family must decide for itself whether they want it nor not. There are a few adult patient members in our organisation who think that screening should not be introduced, as they feel that this affects their own right to live. I do not agree in this view.
You do not want to eliminate the persons, but only the disease. You have to distinguish between yourself and your handicap/disease.

*Does the organisation have an opinion on how to organise a screening?* The organisation does not have an opinion on what is optimal. We hope that the screening study at Rigshospitalet will give an answer. If you want fast results by screening, it must be offered to pregnant women. Later you might offer it to younger people. Young people will need a broad information about the test. If you want to include all pregnant women, the GP must inform them about the test and perhaps refer them to a maternity ward to have the test taken. The testing must be adapted to other services offered to pregnant women in the health system. You must start when pregnant women get in contact with the health system. We have some hesitations regarding the counselling in connection with a general carrier screening. Generally we prefer specialists in our organisation, and the level of knowledge among GPs is not so good that they could advise the patients. We doubt whether it will be possible to organise a sufficiently qualified counselling in connection with a general carrier screening of the population. Information and training of GPs will be necessary if they are to advise the patients. I think that doctors who have specialised in genetics, know genetic counselling better. We do not like the idea of GPs being in charge of testing and counselling. If a general carrier screening will be established, it is important that there is a comprehensive counselling implying: (1) Genetic counselling, (2) counselling on treatment and remedial measures for patients and families, (3) Opportunity for contact with families with a CF-child.

*Some opponents of screening maintain that you put a certain pressure on pregnant women by offering the test to this group?* We are of the opinion that the fastest way to achieve results in a pilot study is by offering the screening to pregnant women. And as far as we know, practical and economical concerns are one of the reasons for choosing pregnant women as a target group in this study. A thorough psycho-social examination in connection with the screening could answer the question whether this target group is appropriate.

*How does the CF-Association think the screening should be financed?* We think that the state should finance the carrier screening. In principle we are of the opinion that these services should be free of charge. We are not satisfied to learn that relatives of known carriers cannot have a guarantee for the payment for a carrier test from the county. The National Health Insurance Scheme does not pay for this. It will also be necessary to inform the population thoroughly about the possibilities opened by gene technology. This applies to the primary as well as the secondary school. The organisation is working to diffuse knowledge of CF, and we take any opportunity to tell about the disease. But it is hard work to diffuse knowledge of a disease that is so rare and unknown. Nevertheless we in the Danish CF-organisation think that we
have a responsibility to help to inform about the positive things the development of gene technology has resulted in for CF-families. CF has become a sort of model for the handling of the new gene technological possibilities in connection with a serious, inherited disease. And if we do not help to inform about the possibilities, insufficient, wrong or negative information will rebound on our families and limit their possibilities.

The Danish Council of Ethics

In 1987 the Danish parliament decided to set up the Danish Council of Ethics. The council advises the Danish parliament and the Minister of Health on legal and ethical matters concerning the new biomedical technique and promote public debate on these subjects.

The Council of Ethics is obliged to make a statement to the Minister of Health about the access to new diagnostic techniques to detect genetic defects or diseases in fertilised human ova, embryos and fetuses. The statement must include suggestions to rules for the access to this technique. In accordance with this the Danish Council of Ethics made a statement in 1990 to the Minister of Health on PD and the consequences of applying new diagnostic techniques to detect inborn defects and diseases (12).

It is the opinion of the Council that any change in access to PD should only take place after a public debate and a political decision. By an essential change is meant: 1. an extension or reduction of the type of PD, 2. an extension or reduction of risk groups. The Council regards screening of all pregnant women as an essential extension of access to PD. A statement from the majority of the Council says: The majority of the Council is against setting up positive or negative lists. Here the woman's/couple's right to self-determination carries the greatest weight. This self-determination also implies that nobody can be forced to have PD and abortion irrespective of the extent of the handicap. A minority of the Council finds: That some day society will be forced to delimit what questions can be asked at PD, and what gives the right to free abortion. This minority advocates for a positive list to be set up. The disagreement is first and foremost due to a different weighing of parents' right to self-determination against the rights of the human worth of the fetus in situations where these two are in conflict. It is the opinion of the minority that parents' right to self-determination is not the only thing to decide what questions can be asked, and what gives access to abortion after PD.
O. Jensen, who belongs to the minority, says: The fundamental ethical problem of abortion is that you deprive another human being of its right to live. That is the fundamental ethical problem. You must hold on to the fact that a human being has a fate. I don't think that you should prevent that human beings have children with certain diseases at any prize. You really have to consider how serious it is. If a couple shares the fate that they must adopt a child, I cannot see that this should be so terrible. Or maybe choose a donor if they have the strength to do that. You could also offer a carrier screening before people get pregnant. Then they could choose adoption and avoid an abortion. Generally, I am very sceptical about carrier screenings. What will the mere fear that the fetus could be ill result in? O. Jensen considers the CF-screening a step in the direction where pregnancy will be regarded as a sickness.

The study on carrier screening has called the attention of the Danish Council of Ethics to the fact that often new methods are tested in research before they are used permanently in the health service. Thus the Council of Ethics has suggested that they are heard before scientific studies are started, because experiments can set up a precedent and contain fundamental problems that should be discussed before the start. This has brought the Danish Council of Ethics in conflict with the scientific-ethical committee system, who thinks that this will limit the freedom of research.

The Administrative-Political Level: The National Board of Health

For the time being the National Board of Health is considering whether the access to PD should be extended or changed. An expert group under the National Board of Health is trying to get an overview of the groups, who are today having their fetuses examined, and the possibilities available because of the new medical technology in this area. L. de Neergaard, the National Board of Health says: The National Board of Health is preparing a revision of its guidelines on PD from 1981. We have asked 6-7 experts to make a recommendation to the National Board of Health concerning the access to PD in the future - preferably including alternatives. It is our intention to submit this for discussion to wider circles (other professions within the health services, administrators), before a final recommendation is submitted to central and local health authorities, relevant scientific societies, organisations, associations and so on. It should primarily discuss which groups should have which offers and when.

Is there a political wish to extend the access to PD? No, I don't think so. But the Minister of Health is very interested in the subject and has no fixed opinion on it. But there is no general wish to extend the access to PD. We hope to be able to allocate our resources in this area so that it will have the greatest effect. I have no clear picture of where we will end. We find it rather confusing. We think that information is of immense importance. And it would be best if it is given before the
woman gets pregnant. This will involve the GP. The next step will be when the woman gets pregnant and contacts the health services. Besides, I trust that the woman/couple is able to handle this difficult situation and the serious choice, if they receive a good information in a correct way. But it will probably be a problem to get a sufficient number of qualified counsellors.

Would you venture a guess on whether screening for CF will be given to everybody in this country? L.N.: I don't think it will be now. I don't think we are ready yet. But we can be moved.

The Danish Council of Ethics has expressed a certain reservation to the screening of non-risk groups - also in relation to the CF-study. We certainly share this reservation to screening. Screenings must be considered very carefully in each single case. It is necessary to make quite clear that it is an informed choice. It is also necessary with a qualified counselling. But the National Board of Health will not withhold the possibility of avoiding to have a sick or handicapped child from women. The crucial thing is how to handle it without creating a lot of unnecessary fear and anxiety. The National Board of Health has not decided whether you should offer carrier screening for CF.

The Relation between the Danish Council of Ethics and the Scientific-Ethical Committees

There is a conflict between the Danish Council of Ethics and the scientific-ethical committees, principally as well as in relation to the study on CF-carrier screening. In a decentral system with freedom of research you may want to test things that the politicians have not yet considered or permitted. Therefore, it will often be the scientific-ethical committees who first meet new initiatives in science. Experimental studies open up for problems where no rules and legislation exist. This could mean that new experiments create an expectation of new possibilities before the politicians have considered them. In this way experiments can anticipate decisions that have not been taken politically. This brings up the question when and how decisions are made in a decentral political system as the Danish one. These problems are discussed in the interviews with P. Riis, with L. de Neergaard and with O. Jensen.

P. Riis says: There is no formal linkage between the scientific-ethical committees and Council of Ethics. The Danish Council of Ethics advises the parliamentary Committee of Ethics. They take care of the political issues and discuss them. The scientific-ethical committees administer the scientific-ethical rules in accordance with the Helsinki-II declaration. But some of the members of the Council of Ethics want to look over the shoulder of the scientific-ethical committees. They want to be
at the level, where the studies are approved, because that is where you first meet new ideas. They want to be able to raise a public debate and somehow block up studies. They do not say that this is their intention. But if they want to raise a political debate, and want the parliament to consider it politically, then they will get into a position where they can stop a research study. This is against the freedom of research. In Denmark we have artistic and scientific freedom, if we observe the Danish laws. I think there must be a clear division of work, meaning that the Council of Ethics takes care of general problems, and the scientific-ethical committees take care of the scientific studies.

In a decentral system as the Danish one the researchers open up for problems via experimental studies before the politicians have considered them. You could claim that in this way they act as if the political decision had already been taken. When are decisions made in a decentral political system? P.R.: If you want a community with extensive decentralisation, you will see some initiatives within art and science, which - in accordance with Danish legislation - the parliament and politicians have to decide on secondarily. In this case the politicians must have the courage to say that we cannot approve of this or that - in the long run. They must not be influenced by the fact that something has been made as an experiment. They are the ones to decide what can be accepted, even if experiments have already been made. If we change this, we will get a centralistic political direction of research, which will have very negative effects. But some politicians have (in relation to other studies) been very worried by the fact that the scientific-ethical committees have approved of studies long before they became a public matter that the politicians should decide on. O. Jensen says: I think the Scientific-Ethical Committee should have submitted this study (the study on carrier screening) to the Danish Council of Ethics, because it might create norms. The Danish Council of Ethics shall draw the big lines. It is not the single researcher who shall draw them. It must take place by a public decision.

L. de Neergaard says about the relation between the Danish Council of Ethics and the scientific-ethical committees: The Danish Council of Ethics sets itself up as a judge. I don't think it is. It is fine that it gives statements on various questions if this is understood as an input to the system. But I don't think that the Council has the competence to set itself up as a judge.

Do researchers by experiments open up for problems, hereby taking a later decision for granted? L.N.: Researchers do indeed open up for decision by their experiments. They start something because they have got something on their brains - and sometimes we get a national problem because they have created expectations of new services. I think that researchers must have an obligation to consider the costs of an experiment, if it shall be continued, as well as the consequences for patients and the system itself. They must have an obligation to inform their system about the consequences. The hospital administrations have been too slow to find out what experi-
ments can result in. We must have a system where the hospital administrations consider whether they want a certain experiment, which consequences it will have, and so on. In this way you would not be able to start a very interesting study and have it brought to a level where it is suddenly impossible to stop it. All the experiments we make today, have organisational and economic consequences - and many involve ethical problems.

The Organisation of CF-Carrier Screening

The interviewed key persons have been asked to consider how a carrier screening should be organised in the future. Their answers reflect their views on abortion, their views on the possibilities of including everybody, and their evaluation of the practical and ethical problems.

M. Schwartz says: I still find it reasonable to offer this test. Whether it should be given to pregnant women, I don't know. If you offer the test to people before they get pregnant, I don't think it will be effective. You will not get a sufficient number of people. Probably people would also forget the result or forget to ask their partners. In this way we would have to test some people several times. My fundamental attitude is that I find it reasonable to do it. The most important thing is that the centres in charge of the genetic counselling, are capable. If they are not, you will only create anxiety, and in this case it is no use. There is no doubt that people get upset and anxious. We can see this from our questionnaires. If our counselling of the carriers is good enough, you will be able to explain to them that they are not ill, and that their children are not ill. But if this counselling is missing, it will be insufficient.

N.J. Brandt has this opinion: Just now I am for the introduction of a general screening. But when we have collected all results, I might find it too expensive, or that there have been too many problems. I might also end up in between saying neither yes nor no. I might doubt that the population has benefited from it, all things considered. It is a rare disease. Only 12-14 patients are diagnosed a year. Many pregnant women will be anxious realising that they are carriers, and their partners must be examined. It is a burden on these people. And of course there is a limit to the number of women you can disturb to prevent the birth of 12-14 children with CF. It will also require resources, if a carrier screening shall be offered to everybody. For the time being we are understaffed with regard to persons trained to give genetic counselling. It will be necessary to train doctors or midwives to counsel the women, if the test is to be given to the whole population. But it must be possible to establish training courses. When the investigation is finished, and we have to consider whether it shall continue, the National Board of Health must decide if they will grant money for it.
Do you put a certain pressure on the women by offering the test when they are pregnant? N.J.B.: It is certainly easier to make pregnant women agree to all sorts of examinations concerning their children. But it would be meaningless to test babies, as they will forget the results before they grow up. They must be old enough to understand what it is all about, and they will not understand this till they have passed puberty. It might also be a problem to get in contact with them. If we had a general screening, the test could be taken by the general practitioner at the pregnant woman's first visit. She could get a written information and decide whether she wanted the test. If so, the blood test could be taken. This would be the easiest way. But it could also take place when the woman comes for control at the obstetric ward. Some women come rather late to these wards, however.

P. Riis, the Central Scientific-ethical Committee, has the following opinion: You could give it to younger people. But would it be possible to get hold of them? It is probably quite pragmatic: When do the health services get in contact with them? When are they motivated? How would it affect a young woman to know that she was a carrier? Would she feel she was carrying a little time-bomb, which would complicate her choice of a partner? The scientific-ethical committees demand that your are 18 years old. As to CF I think that I would recommend my daughters to take the test, if we had a general screening. I would tell them that it might cause some anxiety; but on the other hand I know how life is for a person with severe CF, who is waiting for a lung transplantation.

The screening causes anxiety in women identified as carriers. They will be anxious until their partners have been tested. How do you balance this against the fact that only a few are helped by the carrier screening by being identified as risk couples? P.R.: There is no formula according to which you can compare these women's anxiety to the burdens of a few families and a child being born with CF. Prevalence, the seriousness of the disease, and the time of waiting are the most essential matters. This must be balanced against the fact that you make some persons anxious. You have to balance this and to examine it in the study. It is very important for us that it is voluntary to take the test.

Ch. Koch says about a potential carrier screening: The CF-centre has no opinion on the optimal way of organising a screening. But, I am pretty sure that you will not be able to reach everybody if the test is offered to women, who are not pregnant. You do not think of the fact that you can have a child with CF, before you make a family or have children. I have no objections to the way this has been approached.
Screening and PD in Norway and Sweden

In Norway and Sweden the attitude to introduction of new prenatal diagnostic techniques is more restrictive than in Denmark. In September 1989 an expert committee under the Swedish Ministry of Justice issued a report on PD: Den gravida kvinnan og fostret - tv individer (The pregnant woman and her fetus - two individuals (14). The report finds that general screenings should not be allowed, as they might be regarded as routine search for aberrations. The report also finds that general screenings are of limited value. New type of screening should be evaluated separately. In Norway the Ethical Committee under the Norwegian Ministry for Social Affairs has recommended not to introduce screening for CF. It writes among other things (15), a general carrier screening might give the impression that CF is a disease that should be eliminated. The Committee maintains that the screening will cause increased anxiety and fear - and require considerable economic resources.

Cost-Benefit Analyses

Health economists and politicians ask which forms of PD will have the greatest effect as to the prevention of diseases. How do we prevent most possible diseases and handicaps for the smallest possible amount of money? Here the cost-benefit analyses get into the picture. The interviewed key persons have been asked whether cost-benefit considerations should be included as a reason for the introduction of a carrier screening for CF.

N.J. Brandt replies: It is often sufficient to prove that it will not be more expensive for society to introduce screening.

P. Riis says: I think this should not play any role. I am a little ashamed myself that cost-benefit analyses played a role, when the Act of PD was introduced in 1970 - I myself took part in the introduction of this act. I think you must ensure that there is never pressure on people so that they are forced to choose a screening, because if they don't, they themselves or in their capacity of citizens will cause expenses in connection with the birth of a handicapped or sick child. However, it is a question whether CF-screening shall be introduced on the basis of a consideration of consequences, because it has to compete with other screenings, vaccinations, and other prophylactic measures. So it is a problem how to help the greatest number of people. If we are only able to help a few compared to the costs of money and anxiety, this money could be spent better in other ways. Then we shall have to choose what is best for the population. I can also see great problems in the ethics of allocation, i.e. problems regarding the access to future progress.
H. Clausen has this opinion: My job as a leader of the CF-centre in Copenhagen is not to spare society of expenses by introducing a carrier screening. My job is to guarantee the best possible treatment of the CF-patients already born. Therefore, the cost of the treatment of CF-patients must not be crucial when you decide whether to introduce carrier screening and PD for CF.

J. Moeller says: The attitude of DSI is that the costs for the health services - including potential costs for carrier screening - is a public matter. We are against user-payment in health services - also when it concerns carrier screening. But we have realised that we have to take part in the discussion on priority in health services.

L. de Neergaard says about cost benefit considerations: It must be a part of everything we do. But there might be ethical aspects of greater importance. We cannot avoid the discussion about priority.

A Comparison of Costs of Patient Treatment and Carrier Screening

Below follows a calculation of the annual costs of the treatment of CF-patients of 3, 12, and 20 years. The calculation includes costs of inhalation preparations, antibiotic cures (6 pr. year of each 14 days), pancreas, transportation to ambulant controls, social security, and costs in connection with hospitalisations for intravenous Pseudomonas-treatment (for a 20-year-old) (note 1).

This calculation does not include grants for a pedagogical support in kindergarten (to give medicine and PEP-treatment). The partial wage compensation for the mother of a three-year-old patient is estimated to 12 hours a week, and it is calculated that this will be decreased to only a few hours for a twelve-year-old patient. A twenty-year-old patient is receiving an education and disablement grant that covers the expenses for books and transportation. The calculation does not include the effect of a possible lower working frequency among adult patients, costs of social pension due to early retirement for reasons of ill-health, the effect of a shorter duration of life on taxable incomes, costs of a potential housing grant, and perhaps a grant for a car in accordance with the Social Security Act. Further, the calculation does not include costs of hospitalisation in connection with ambulant
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<th>Patient of 3 years</th>
<th>Patient of 12 years</th>
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<tr>
<td>PEP-mask and pump (one-for-all cost: DKr 4 429)</td>
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<td><strong>Inhalation preparations:</strong></td>
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<td>salt water, venoline, colimycin</td>
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<td>Pancreas: Pancreon Forte</td>
<td>296 460</td>
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<td><strong>Antibiotic cures:</strong></td>
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<td>Fucidin, Diclocil, Abbocitin, Calcipin, etc.</td>
<td>13 861</td>
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<td><strong>Social security:</strong></td>
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<td>Extra costs for food</td>
<td>4 200</td>
<td>4 200</td>
<td>7 240</td>
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<td>Extra costs for laundry, clothes, telephone, etc.</td>
<td>5 400</td>
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<td>Costs of transport to ambulant controls</td>
<td>3 600</td>
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<td>Partial wage compensation</td>
<td>48 000</td>
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<td>Hospitalisation for intravenous Pseudomonas-treatment 49 days in bed, each DKr. 4 600</td>
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<td>225 400</td>
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<td>Disablement grant and educational costs</td>
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<td>36 000</td>
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<td>Antibiotics, etc.</td>
<td>-</td>
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<td>74 186</td>
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<td><strong>Total costs</strong></td>
<td>439 525</td>
<td>413 221</td>
<td>734 447</td>
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controls (laboratory costs, wages, etc.). In general the calculation of costs will probably in some cases be considerably higher than in this calculation. The key variables in a calculation of the cost-effectiveness of a screening of the whole population are: 1. the cost of treatment of patients; 2. the cost of testing; 3. the sensitivity of the test; 3. the participation rate; 4. the screening approach (two stage approach). The costs of a screening test including counselling has been calculated to 300 Danish Kroner per test (16). Thus a test of all pregnant women will cost 18 million Danish Kroner a year: 1. 12%-15% of all women are infertile or choose not to conceive; 2. 82% participation among pregnant women; 3. 90% sensitivity of the test; 4. two-stage screening approach; 5. 95 - 100% of affected fetuses are aborted.

A screening of all pregnant women (and the partners of heterozygote women) with a test with a detection rate of 90% will identify 81% of all at-risk couples. Since not all women will take the test, the actual number will be lower. In the Danish study 82% of the women accepted the test. As a great deal of women have more children, it will in a number of years be sufficient to test only the primiparous women. This will decrease the number of tests to between 30 000 and 40 000 (it will also reduce the number of affected fetuses found by screening). Besides, the price of the test will have fallen (9), and it will be possible to reduce it further by automatisation of the process. Thus the cost of 18 million Danish crowns for a general screening has been set rather high. This screening would identify approximately 9 CF-fetuses a year. For the first four years a screening of the whole population would increase the expenses in the health care system. But after the 5th year the amount of money saved on treatment would be greater than the amount of money spent on screening. This difference would increase over the years. Conclusion: The calculation of the costs of the treatment of CF-patients and of the costs of a screening can be compared - without making a proper cost-benefit analysis. This calculation can be made on the basis of the cost of the treatment of a CF-patient with an average duration of life of 30 years. If you anticipate that a general screening will be able to prevent birth of 9 fetuses with CF every year, it appears from the calculation, that the costs of a screening do not exceed the costs that will disappear as a result of smaller costs of treatment.

Though this calculation contains much uncertainty (concerning the number of persons who will take the test, the actual costs of the screening and the cost in relation to treatment, etc.), the inevitable conclusion is that from an economic point of view the advantages exceed the costs. But as already mentioned, economic considerations are not the only aspect of the health-policy decisions.
Social Regulation of Screening and PD

Social regulation of access to PD is about whether PD should be kept within certain limits. Who shall decide about the access? The parents? Society? Shall a positive list lay down the rules? Shall there be limits as to which diseases and handicaps should give access to PD and abortion, and those that do not. The interviewed key persons express very different views on these issues.

J. Moeller says: DSI has no official attitude to PD. Even if the handicap or disease is a common denominator, the handicap itself must be considered before you decide on the way of helping the group. Some of our organisations take up the attitude that it is our task to attend to the interests of the handicapped persons. In my opinion they do, in this way, avoid the problems raised by PD. DSI must of course respect that the CF-Association recommended the carrier-screening for CF. You must assume that they do this on the basis of their experience with the disease. Many people will consider it an advantage that they will not give birth to a child suffering from a disease or a handicap involving a reduced quality of life. On the other hand an extensive use of PD will change the general attitude to handicap. One could imagine that a couple, who have been told that their expected child has a handicap or a disease, would also be told that they have to bear the costs themselves, because society has now given them the possibility to choose abortion. The next step would be to connect this with economy. I think that the information in connection with PD is insufficient. The couple are very alone in this situation because they are facing specialists, who know a lot about very limited areas. I think that parents should have the possibility to speak with somebody who have themselves gone through this situation, and who know the disease - for example a family with a child carrying the disease. My personal attitude is that I find it too easy to leave this decision to the individual couple. I think society has a responsibility. The couple needs to lean on something. Society must have an opinion and take a responsibility. So the politicians must decide, where the limits shall be as to what we should test for.

Is it a positive list you advocate for? In my opinion some handicaps are so severe that the possibilities of having life with quality are few. Perhaps we ought to examine for these handicaps. You should not examine the rest. For instance I think that many people with Down's syndrome have good lives. That is one of the handicaps you should not examine for, in my opinion. But you do this today, you know. If the National League for the Mentally Retarded (LEV) (for which J. Moeller is a director) was asked to consider a screening for Down's syndrome to the population, the organisation would probably leave the decision to the individual couples. I think that the reason for this is, that we as an organisation do not have the courage to do anything else. So I think that society ought to decide by setting up a list of handicaps for which you will offer a prenatal test. If these decisions were
taken subsequent to a public debate, I think that neither Down's syndrome nor CF would appear on this list. Without a positive list I think that people will ask for an abortion because of quite unimportant things, such as colour-blindness etc. You should not approve this. But it is a risk, if you leave it to the individual couple. However, these issues are so difficult, and I think that most organisations would not be able to come to an agreement. I myself have a religious basis for my attitude to life. But not all members of LEV think like that. They are just as different as the rest of the population. My attitude is that I cannot at all accept this. As a population we are a whole with a certain composition. If you start to pick out some components, the remaining ones will be different. Our variety influences the whole. If you take something out, what remains will be different. I am very concerned about this.

P. Riis has the following opinion of positive lists: As a citizen I am against a positive list. Also legally it is problematic to build many specifications into a law. This might have the result that after a few years it is useless, because development has moved in another direction than expected. Laws must be general and fundamental. In my opinion there is a continuum of functional disorders from the quite unimportant ones as colour-blindness to very severe disorders. It is not possible to put these disorders into a general formula. I think you should start with the very severe diseases. Some families manage Down syndrome, others don't. It will be a political matter where to draw the line. We did not feel that the CF-study opened up quite freely for this sort of activity. A graduated system must of course be regulated. It will require a competent, reliable, and independent judgement function placed in an advisory committee under the National Board of Health.

Can this imply that criteria will slip gradually? P.R.: The slippery slope has been discussed a lot. A great number of decisions involving estimates has to be taken in the health care system. If this happened behind closed doors and without an open debate, it would lead to problems. M. Schwartz is in agreement with P. Riis: I am very much against that (= positive lists). You might be able to agree on some diseases being tested for; but you would very slowly reach a grey zone of diseases not included or not thought of.

O. Jensen says: I cannot agree that ethical decisions lies solely with the individual couple. I think that a society must have an opinion. It is pitiful if a society only dares to have the attitude that everything is good enough as long as you do not bother others. This is a kind of liberalistic bargain. Some day society has to set up a positive list. We will agree on some extremes. I don't think that minor sufferings should give access to abortion. There will also be a grey zone for which you cannot legislate. In my opinion such a disease as CF would be within this zone. Here the individual couple should decide. If I myself had to advice a couple, whose fetus had CF, I would tell them that it was not right to choose an abortion, but that they had to
live with it as their destiny. I would hope that I myself would be able to live with it. But I do understand the families with a CF-child, who choose abortion. It certainly involves troubles. I don't think either that the fact that you are close to a case, gives you a bigger right to express yourself (such as patient families). You can be so close to something that you are not able to see the long-term perspective. This also applies to the doctors, who far too often take the patients' point of view.

**L. de Neergaard** says: We have no official attitude to this. But personally I don't think it is a good idea with a positive list. There are too many nuances. We might agree on some extremes, but there would certainly be a broad grey zone. And before the list has been finished, it will be out of date.

The Danish CF-Association is against a positive list. **H. Tybkjaer** says: We are against a positive list laying down rules as to for what you can and may test, because we fear that in this way society will be able to eradicate certain serious diseases causing great expenses. You might risk that an economic responsibility will be imposed on the people choosing to have children with these diseases, because they could have been avoided by screening. Thus a screening is no longer voluntary. This will result in less understanding and solidarity with the human beings born with the diseases mentioned on the positive list. In Denmark we have free abortion, and I cannot tell the difference between wanting abortion because of a serious disease in the child and just not wanting the child. There is an agreement in the Danish CF-Association that a couple/the mother are the only ones, within the limits of law, who are qualified to make a decision during pregnancy on PD and abortion. The parents should have an unlimited right to make an informed choice.

**Decisions in Health Policy**

In June 1992 the pilot study on carrier screening for CF was stopped after testing of approximately 7 000 women. For the researchers starting the carrier screening there is a direct line from their experience with PD in families with a CF-child to the idea of carrier screening of non-risk families. They look at the carrier screening as an extension of PD (to CF-families) in order to prevent that families have their first child with CF. With the exception of **O. Jensen** most of the key-persons interviewed in this study accept the idea of testing pregnant women. The reasons are primarily pragmatic. It is easy to get in touch with this group and it is important that the test is offered to everybody. The test, however, should be voluntary. The carrier test could be offered by the general practitioner at the woman's first visit during her pregnancy. There is a need to establish and strengthen counselling services to women, men and couples identified as heterozygote carriers. The test should be free.
of charge and paid as part of the hospital services or the services paid by the National Health Insurance Scheme.

Cost-benefit considerations should play no role or only a minor role as an argument for setting up a carrier screening service. Yet L. de Neergaard says: It must be a part of everything we do. But there might be ethical aspects of greater importance.

However, one must remember that the fundamental value of CF-carrier screening lies not in its potential for saving money but in its potential for providing information about reproductive decisions. No one can place a value on having information.

In the Danish study it was apparent that the closer you got to the administrative and political level the more important the cost benefit considerations became.

The National Board of Health is preparing a revision of its guidelines about PD. No decisions have yet been taken, but screening for CF seems to have low priority. But L. de Neergaard adds the following: "The National Board of Health will not withhold the possibility of avoiding to have a sick or handicapped child from women. The crucial thing is how to handle it without creating a lot of unnecessary fear and anxiety. The National Board of Health has not decided whether you should offer carrier screening for CF.’” It is important to note, that there is no political wish to extend the access to PD in Denmark. At least 80% of all women accepted the screening test in the pilot study.

In the public debate about genetic screening and PD there is what I would call an "anti-screening-anti-abortion-lobby”. Some of the members of the Danish Council of Ethics belong to this group. They are against any use of any genetic screening, advocate strict public control through positive or negative lists and restrictions in access to abortion in connection with genetic screening and PD.

When the results of the pilot study have been assessed, politicians must discuss and decide whether carrier screening for CF should be made an offer for the whole population. How this decision will turn out, we can only guess at the moment. But one could ask whether the political decision will at all be influenced by the scientific results of the pilot study? It is well established that health policy decisions are only to some extent influenced by research results. Other factors influence the decisions as well as decisions are influenced by the public attention to a health problem, by PR-work, topics raised by the media, etc. The fact that new or better treatment is still improving the life expectancy of CF-patients and the fact, that gene therapy may be within reach may also influence the decision. General screening for a genetic disease, that does no longer result in early death for all patients, involves
ethical problems. However, CF is still a very severe disease. Patients are still threatened by shorter duration of life. In my opinion this justifies an introduction of a general carrier screening for CF. If the test is voluntary, and the counselling of carriers is easily accessible and qualified, the inconveniences of a carrier screening could be avoided. There is, however, no formula according to which we can compare the anxiety caused in some women by the screening to the burdens of a few families and a child being born with CF.
Note

(1) Nurse Annelise Hansen and Dr. Christian Koch, Rigshospitalet, Social worker Else Marie Bjoernsen, Centre for Small Handicap Groups, and Hanne Tybkjaer assisted in procuring the necessary information for the analysis.

References

5. Ibid. (4).
6. PD became an offer to families with a CF-child from 1981 as amniocentesis and from 1987 as chorionic villus biopsy.
9. Personal communication with Marianne Schwartz.
10. Ibid. (8).
12. Ibid. (8).
15. Here cited according to (2).
17. The names of the families have been change to secure anonymity.
3. Country Report from Germany

I. Nippert

Key Persons Interviewed in the F.R.G. Study:

K. Bachmann, professor, MD, chairman of the Scientific Council of the Federal Board of Physicians (Vorsitzender des Wissenschaftlichen Beirates der Bundesärztekammer), Münster/Köln, F.R.G.

E. Bulmahn, MdB, member of the Federal Parliament (Mitglied des Bundestages), Bonn, F.R.G.

W.M. Catenhusen, MdB, member of the Federal Parliament (Mitglied des Bundestages), at that time chairman of the Committee for Research, Technology and Technology Assessment of the German Federal Parliament (Vorsitzender des Ausschusses für Forschung, Technologie und Technikfolgenabschätzung im Deutschen Bundestag), Bonn, F.R.G.

Ch. Coutelle, molecular geneticist, professor, PhD, department of biochemistry and molecular genetics, St. Mary's Hospital Medical School, London-Paddington, UK, at that time Max-Delbrück-Centrum für molekulare Medizin, Berlin-Buch, F.R.G.

H. v.d. Hardt, paediatrician, professor, MD, head of the department of paediatrics, Medizinische Hochschule Hannover, head of the Cystic Fibrosis centre Hannover, F.R.G.

W. Holzgreve, obstetrician, professor, MD, head of the Universitäts-Frauenklinik, Kantonsspital, Basel, Switzerland, at that time head of the department of prenatal medicine, Westfälische Wilhelms-Universität Münster, F.R.G.
U. Jung, geneticist, paediatrician, MD, 2nd paediatric clinic department of human genetics, Städtisches Klinikum Berlin-Buch, F.R.G.

D. Kaiser, paediatrician, professor, MD, chairman of the German Cystic Fibrosis association, Städtisches Krankenhaus Pforzheim, F.R.G.

A. Kersting-Wilmsmeyer (†), Nebel, Amrum, at that time representative of the CF-patient group in the German CF-Association, F.R.G.

S. Kruip, member of the Board of the German Cystic Fibrosis Association (Vorstandsmitglied des Mukoviszidose e.V.), Reichenberg, F.R.G.

H. Mehl, representative of the parent group in the German Cystic Fibrosis association, Winnenden, F.R.G.

E. Passarge, geneticist, professor, MD, head of the department of human genetics, Universität Gesamthochschule Essen, at that time chairman of the German Society of Human Genetics (Deutsche Gesellschaft für Humangenetik e.V.), F.R.G.

P. Propping, geneticist, professor, MD, head of the department of human genetics, Rheinische Friedrich-Wilhelms-Universität Bonn, F.R.G.

A. Statz, MD, MR, Federal Ministry of Health (Bundesministerium für Gesundheit), Bonn, F.R.G.

B. Tümmler, paediatrician, MD, PhD, department of biophysical chemistry, Medizinische Hochschule Hannover, F.R.G.

W. Vogel, professor, MD, head of the department of clinical genetics, Universität Ulm, at that time chairman of the Professional Board of the Geneticists, (Berufsverband Medizinische Genetik e.V.), Ulm, F.R.G.

H.P. Wolff, professor, MD, chairman of the standing subcommittee "Biomedical Ethics and Technology Assessment", Scientific Council of the Federal Board of Physicians (Vorsitzender des Ständigen Arbeitskreises "Biomedizinische Ethik und Technologiefolgenabschätzung” beim Wissenschaftlichen Beirat der Bundesärztekammer), Köln, F.R.G.
**Health Care Infrastructure**

At the moment the major challenges facing Germany's health care system are:

a) the rising costs, 8.1% of the Gross Domestic Product was spent in 1989 on health care (a new cost containment law "Gesundheitsstrukturgesetz" was enacted in January 1993) and

b) as a consequence of its recent unification the transformation of East Germany's national health service into a social insurance plan modelled on that of West Germany.

West Germany's health care system is a blend of government mandated financing by employers and employees combined with a private provision of care by physicians, controlled hospital expenditures and administration by not for profit insurance organisations. These insurance organisations, known as sickness funds, establish and collect the contributions of employers and employees. The sickness funds turn this revenue over to regional associations of ambulatory care physicians that reimburse doctors for their services on the basis of a negotiated fee schedule ($\approx$74 000 ambulatory care physicians belong to regional associations).
The Federal Republic of Germany (F.R.G.) currently has a population of about 81 million. In West Germany about 90% of the population are covered by the health insurance funds ('sickness funds') and about 8% by private health insurance (42 private commercial insurance companies exist at the moment), 0.4% are not insured and the rest has other insurance coverage. The sickness funds are organised on the basis of geography (Ortskrankenkassen), occupation (Betriebskrankenkassen), trade (Innungskrankenkassen) and income. Depending on the member's economic status, he or she is either a voluntary member of a health insurance fund or must join on a mandatory basis.

There are 1,169 autonomous insurance funds in West Germany. Although each fund is expected to be fiscally autonomous, its financial matters are supervised at the level of each Bundesland ('Land' or state). Overall supervision rests with the Federal Government's Ministry of Health. Since each sickness fund must operate within statutory guidelines which prescribe, among other things, the benefit package that must be offered to the insured under statutory health insurance, the funds are actually fairly similar to one another.

The health insurance funds' over-all scheme provides full coverage for all medically necessary services, including ambulatory and in-patient care, prescribed drugs, medical appliances, dental care, etc. The patient is free to choose his/her physician, no money passes between the patients covered by the sickness funds and their physician. In most instances patients therefore, have no idea how much their treatment costs, except for a small cost sharing amounts paid for some services.

Germany's social insurance model, originating in the last century, was substantially restored after World War II. In the process the medical profession won a dominant role for solo office based physicians of ambulatory care prohibiting industrial or public health doctors from treating patients and discouraging the use of physician's assistants and the creation of group practice.

Usually, West German physicians work entirely either in private practice or in a hospital. The dichotomy between ambulatory and in-patient practice is statutory and strictly enforced, and has a number of peculiar consequences. First, most hospitals are prohibited from operating out-patient departments, because the provision of ambulatory care is the preserve of physicians in private practice. Hospitals may intrude on this monopoly only if they are affiliated with a medical school and their out-patient clinic serves a teaching function. Second, a private physician sending a patient to a hospital loses both medical and economic control over the patient during the latter's hospital stay.
Infrastructure of Genetic Service Provision

After World War II in Germany human genetics was totally discredited by its use in the service of the Nazi state. Human genetics as a scientific discipline not only had a very doubtful reputation but was in a very fragmented state. It was scarcely represented in medical school curricula. Even as late as 1959 only four departments of human genetics existed in the F.R.G. Today there are 55 genetic counselling centres (Tab. 1) in the F.R.G. (including the former GDR), primarily located at medical schools. These centres were mainly established in the mid 1970s, when amniocenteses was implemented in prenatal care via genetic service provision. To have the states (Länder) step in and to fund an out-patient medical service such as genetic counselling and prenatal diagnosis at their medical schools is unusual in the F.R.G. health care system in which out-patient services are typically delivered by private practitioners. But because of the scarcity of special skills required when genetic services started in the early seventies, and the fact that in those days there was likely to be little profit to the practitioners, there was no alternative but to implement genetic services and prenatal diagnosis at university level.

Today this structure causes conflicts between practitioners who offer genetic services and genetic centres who want to keep their level of quality performance. As each practitioner is allowed to offer genetic services and to employ for diagnosis private laboratories, the quality control issue and the provision of adequate counselling in terms of the understanding and psychological health of the patients that are offered the services, raises concern among geneticists. Although recently medical genetics has been acknowledged as a medical speciality by the German Board of Physicians (Deutscher Ärztetag), this medical speciality still has to be enacted on state level.

| Table 1: Clinical genetic services in Germany in 1992 (genetic counselling and/or diagnostics) |
|---------------------------------|-----------------|-----------------|
|                                 | West | East |
| Departments at universities     | 27   | 9    |
| Departments at other hospitals, State Health Offices | 8    | 11   |
| Private offices/laboratories    | >30  | ?    |
| Total                           | >68  | 20   |


Considering the current number of practising board certified human geneticists (based on the membership list of the Professional Board of Human Geneticists this
number is estimated to be \( \approx 250 \), it is obvious that there is not enough professional genetic counselling capacity to deal with a swell of CF-carrier screening cases, i.e. to provide adequate pre- and post-test counselling. Routine CF-carrier screening would strain the present genetic counselling service system in the F.R.G. There are 17 laboratories that provide CF-diagnosis services scattered all over Germany. Most of them are at university level and funded by the state. There exists an unknown number of private laboratories, probably a very small number.

**Clinical Aspects of Cystic Fibrosis: Pathology, Diagnosis and Prognosis**

CF is the most common, life shortening autosomal recessive disorder in Germany. Today, it is estimated that more than 4 800 patients with CF live in West Germany. CF affects the respiratory, gastric intestinal, and reproductive organs and the sweat glands. The disorder is present at birth in affected persons but the symptoms may vary among individuals considerably. This leads sometimes to diagnostic difficulties. In Germany (the following data are based on reports provided by Prof. Dr. H.-G. Posselt, Frankfurt for West Germany and are not including the former GDR) approximately 53% of the CF-patients are diagnosed within the first 6 months, 78% of the CF-diagnoses have occurred by age of 3 and almost all are detected by age of 10. Although some individual do not develop symptoms until later in adolescence or even adulthood. CF puts great strain on the digestive and respiratory organs and the severity of respiratory conditions resulting in lung damage affect survival. Due to improved symptomatic treatment, survival data for individuals change rapidly. Median age at death has increased over the past decades. In 1987 the mean age at death was for all deceased patients 16.7 years, for males 18.4 years, for females 15.6 years. In 1991 the mean age at death was for all patients 19.34 years, for males being higher (20.15 years) than for females (19.3 years). (In the former GDR median age at death is 15.7 years).

The goal of CF-treatment is to maintain a stable condition for long periods of time and to allow affected individuals to lead relatively normal lives. General therapy includes home treatment combined with hospital stays as needed. The number of necessary hospital stays varies with the individual and ranges from 1 to more than 3 stays in a year. Today treating CF has become increasingly specialised. Currently 52 CF clinical centres (CF-ambulances) are delivering care to more than 2 000 patients. These centres play a large role in advancing CF-treatment and care in the F.R.G. Characteristically, the average age of the patients is increasing. In 1983 it was 11.1 years, today it is 13.3 years and the percentage of adults patients has increased from 16.7% in 1983 to 31.9% in 1992. (In the former GDR the percentage of adult patients is 19%). Advances in therapies and comprehensive approaches in care have contributed to a longer life span. Although there are no data available about the
current average life expectancy, the latest data stemming from 1984 document an average life expectancy of 24 years, it is estimated that today life expectancy has increased to 28 years. Today, people with CF can pursue college or university education (5% of all adult females are enrolled at universities; 9.8% of all adult males), or maintain professional careers (43% of adult females; 44% of adult males), can live on their own (43% of all adult females; 26% of all adults males) some marry (Tab. 2) and some even have children, have their own family.

<table>
<thead>
<tr>
<th>Table 2: Marital Status of Adult CF-Patients (n = 777 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n=400</td>
</tr>
<tr>
<td>Single</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Divorced</td>
</tr>
<tr>
<td>Missing information</td>
</tr>
</tbody>
</table>

Source: CF VII 91, Posselt, Frankfurt

Epidemiology of Cystic Fibrosis and Cystic Fibrosis Mutations

4% of the population are suspected to be carriers of a CF-mutation (≈ 3 mill. people). The prevalence of CF at life birth is ≈ 1:2 500. The most common mutation, ΔF508 can be identified in 73.2% of all CF-carriers (Tab. 3). The next most common mutations identify 8.2% of all cases, 17.1% of actual carriers can't be detected at the moment. The prevalence of ΔF508 is lower in East Germany where 62% of the carriers have this mutation.
Table 3: The Distribution of CF-Mutation in the West-German Population

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Exon</th>
<th>Hannover</th>
<th>Berlin</th>
<th>Göttingen</th>
<th>Overall</th>
<th>Non ΔF508</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>ΔF508</td>
<td>10</td>
<td>412</td>
<td>73.6</td>
<td>275</td>
<td>71.2</td>
<td>251</td>
</tr>
<tr>
<td>R347P</td>
<td>7</td>
<td>5</td>
<td>0.9</td>
<td>7</td>
<td>1.8</td>
<td>5</td>
</tr>
<tr>
<td>G542X</td>
<td>11</td>
<td>5</td>
<td>0.9</td>
<td>5</td>
<td>1.3</td>
<td>5</td>
</tr>
<tr>
<td>G551X</td>
<td>11</td>
<td>7</td>
<td>1.3</td>
<td>5</td>
<td>1.3</td>
<td>5</td>
</tr>
<tr>
<td>R553X</td>
<td>11</td>
<td>12</td>
<td>2.1</td>
<td>10</td>
<td>2.6</td>
<td>12</td>
</tr>
<tr>
<td>N1303</td>
<td>21</td>
<td>7</td>
<td>1.3</td>
<td>5</td>
<td>1.3</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>18</td>
<td>3.2</td>
<td>2</td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>94</td>
<td>16.8</td>
<td>77</td>
<td>19.9</td>
<td>48</td>
</tr>
<tr>
<td>Non ΔF508 overall</td>
<td>148</td>
<td>26.4</td>
<td>111</td>
<td>28.8</td>
<td>85</td>
<td>25.3</td>
</tr>
<tr>
<td>CF-Chrom. overall</td>
<td>560</td>
<td>386</td>
<td>336</td>
<td>1282</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Cystic Fibrosis Carrier Screening - Policy Issues in the F.R.G.
Health Care Provider's Views and Actions

Health care providers interviewed for this study represent 3 different professional backgrounds: 1. Medical geneticists and molecular biologists; 2. Paediatricians; 3. Obstetricians. They were chosen either because of their formal position as chairman of a scientific or professional organisation, subcommittee or board; as heads of departments of human genetics, as heads of CF-centres or prenatal centres or as specialists in CF-research. We expected them to present different views on CF-carrier screening, influenced by their different professional backgrounds. All health care providers interviewed agreed on one issue: persons at risk (i.e. with the family history of CF) should have access to CF-testing together with the option of PD. But no agreement was found whether the same test should be offered to persons at average risk (Tab. 4).
Table 4: Should the option to undergo CF-carrier screening be available in our health care system: a) through a screening program, b) on a strictly individual basis (“only those who ask for it should get it after pre-test counselling”) or c) should not be available at all?

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Organisation of Geneticists (Deutsche Gesell-schaft für Humangenetik)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Professional Board of Geneticists (Berufsverband Medizinische Genetik)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Federal Board of Physicians' Scientific Council's standing subcommittee &quot;Biomedical Ethics and Technology Assessment&quot; (Ständiger Arbeitskreis &quot;Biomedizinische Ethik und Technologiefolgenabschätzung&quot; beim Wissenschaftlichen Beirat der Bundesärztekammer)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Geneticist, Berlin-Buch</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geneticists, Göttingen</td>
<td></td>
<td></td>
<td>(X) active information of the population at reproductive age</td>
</tr>
<tr>
<td>Paediatrician, Hannover</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatrician, Hannover</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatrician, Pforzheim, Chairman, CF-Association (Deutsche Gesellschaft zur Bekämpfung der Mukoviszidose)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Obstetrician, Münster</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrician, Freiburg</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrician, Dachau</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Member of the Federal Parliament</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Member of the Federal Parliament</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Government health administrator</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents from CF-Association (Deutsche Gesellschaft zur Bekämpfung der Mukoviszidose)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CF-patient group from CF-Association (Deutsche Gesellschaft zur Bekämpfung der Mukoviszidose)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CF-parents asked in DFG-study</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There is broad consensus among the interviewed health care providers that CF-carrier screening should be available in Germany on a strictly individual base and should not be actively offered and no screening programs should be started at the
moment or in the near future. Two dissenting groups can be identified among geneticists: one group located in East Germany, the other one in West Germany who are in favour of assessing CF-carrier screening and who started small scale pilot projects to evaluate their screening approach (s. below). The chairman of the German CF-Association, a paediatrician, and head of a CF-centre, is opposed against any kind of carrier screening. However, in a recent survey (supported by ESLA) on the attitudes towards prenatal screening, German geneticists were asked whether they would like to see CF-screening available for all pregnant women. The majority (56.4%; Tab. 5) said that testing should only be available for women at high risk, but more than a third (38.3%) opted for CF-screening being offered to all pregnant women, a small minority (5.3%) stated, that CF-screening/testing should not be offered at all.

<table>
<thead>
<tr>
<th>Condition</th>
<th>For all pregnant women</th>
<th>For women at high risk</th>
<th>Should NOT be available at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>38.3</td>
<td>56.4</td>
<td>5.3</td>
</tr>
</tbody>
</table>

n = 140, response rate 60%

Source: "Attitudes of consumers and health professionals toward prenatal screening and people with disabilities", EC-ESLA-Program funded study, Th. Marteau, PhD, London, UK, I. Nippert, PhD, Münster, Germany.

This survey reflects what was found by interviewing key-geneticists in Germany: The majority is in favour of a “low key” restrictive approach towards CF-carrier screening, but there are dissenting views and policies favouring CF-screening. The conflicting views over routine CF-carrier screening reflect different objectives in genetic service provision in health care in Germany, balancing individual rights and interests versus broader community interests. The majority of health care providers interviewed in this study explicitly opposes that reducing the prevalence of CF among life births is an important public health goal (Tab. 6). From their point of view a formal positive CF-carrier screening public health policy, via active screening programs harbours the potential of eugenics and should not be pursued.
Table 6: Is lowering the prevalence of CF among live birth from your (professional) point of view an important public health goal?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not sure whether the disease is severe enough to justify special preventive action on a population basis (rather not)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geneticists:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essen</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Berlin-Buch</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Göttingen*</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ulm</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>München</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bonn</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hannover</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Freiburg</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Münster</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Paediatricians</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Obstetricians</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Government health administrator official</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Members of parliament</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*active provision of information and reproductive options is the major goal*

Especially the paediatricians but also the obstetricians interviewed argued that the improving mortality rates among CF-patients did not justify the implementation of a routine CF-carrier screening program into prenatal care. This view is opposed by a group of molecular geneticists and genetic counsellors in East Germany, Berlin-Buch) who state: "The seriousness and relatively high incidence of this disease validate the introduction of a heterozygote tests" (Gille, Grade, Coutelle. A pooling strategy for heterozygote screening of the ΔF508 Cystic Fibrosis mutation. Human Genetics, p. 289-291, 1991). In an interview led with Coutelle and Jung both assert that the tests are sensitive enough for current use: "We have a ΔF508 prevalence of about 62%, we can detect now approximately 40% of all pregnancies at risk for CF."
So why should this test not be offered?” (Coutelle). This group advocates to inform pregnant women about the availability of the test, to give them the opportunity to make informed decisions about their reproductive future and to explore the implications of CF-carrier screening by a pilot study (s. below). This group assumes that individual interests (to obtain reproductive options) and public interests could be brought in accordance. Proponents of a low key approach to CF-carrier screening (located in West Germany) and advocates of heterozygote screening (located in East Germany) both acted rather quickly soon after the CF-gene was identified in 1989. At that time there still existed two different German states. In 1990 the West German geneticists' professional and scientific associations issued policy statements (Medizinische Genetik, Bd. 2/3: p. 6-7, 1. Jahrg. 1990) The statements concur on several points: 1. CF-carrier screening should be offered only on a purely voluntary base. 2. CF-carrier screening should not become standard of care in pregnancy. 3. Pregnant women should not become the target population of CF-carrier screening. 4. CF-screening should be an optional service that should be provided only, if, after extensive pre-test counselling where the ambiguity of test results and its possible consequences have been explained in detail, the counsellee is still interested.

In December 1990 the Scientific Council of the Federal Board of Physicians (Wissenschaftlicher Beirat der Bundesärztekammer) established a subcommittee to develop a ”memorandum on genetic screening”. Instrumental for setting up this subcommittee where the recommendations of human geneticists, that is was time for action and that a policy statement was needed (interview and personal communication P. Propping/Bonn; G. Wolff/Freiburg; K. Bachmann/Münster).

For this report the Federal Board of Physicians' standing subcommittee ”Biomedical Ethics and Technology Assessment” (Ständiger Arbeitskreis ”Biomedizinische Ethik und Technologiefolgenabschätzung” beim Wissenschaftlichen Beirat der Bundesärztekammer), as well as the Commission for Ethics and Public Relations of the German Society of Human Genetics (Kommission für Öffentlichkeitsarbeit und Ethische Fragen der Deutschen Gesellschaft für Humangenetik), and the chairman of the Professional Board of Medical Genetics (Berufsverband Medizinische Genetik) were asked to provide the key-points of their policies towards the provision of CF-carrier screening in Germany.
I. Nippert

Statement of the Scientific Council of the Federal Board of Physicians’ standing subcommittee ”Biomedical Ethics and Technology Assessment” (Ständiger Arbeitskreis ”Biomedizinische Ethik und Technologiefolgenabschätzung” beim Wissenschaftlichen Beirat der Bundesärztekammer):

The implementation of a voluntary population based carrier screening program is not considered desirable nor is lowering the incidence of CF among live birth explicitly asked for (not seen as a public health goal). But rapid advances in instrumentation to automate DNA-diagnosis and the spin off from technologies, from DNA-research as well as pressure from laboratory industries will inevitably create increased demand for CF-carrier screening. Therefore, the following requests should be realised:

- Each genetic diagnosis has to be offered exclusively with genetic counselling.

- Counselling capacities need to be enlarged. The recruitment of non-medical professions should be supported.

- Safeguarding voluntarism should be the guiding principle of genetic services. Legal action is called upon by the physicians to prohibit Third Parties to have access to test results.

- Predictive genetic tests should not be implemented as standard of care. They should be performed on request only on an individual base. Individual autonomy in decision making should be a guiding principle.

Statement of the Professional Board of Geneticists (Berufsverband Medizinische Genetik):

The availability of CF-carrier screening creates problems because it harbours the potential for eugenic effects. The board acknowledges that CF-carrier screening can't be denied to those who ask for it. CF-carrier screening should not be implemented as standard of care, especially not into the existing pregnancy programs. It is not a test that should be considered a basic health care procedure. It should be available mainly for persons with a family history of CF. The following issues regarding CF-carrier screening are regarded as essentials:

- Safeguarding voluntarism.
- Public education. No test should be offered without thorough information about its consequences.

- No target population (pregnant women), minors should understand the implication of the test.

- Quality assurance. Only those with special board certification should be reimbursed by sickness funds.

- A pilot project is needed to address potential adverse outcomes.

Statement of the Ethics Committee of the Scientific Organisation of Human Genetics (Kommission für Öffentlichkeitsarbeit und Ethische Fragen der Deutschen Gesellschaft für Humangenetik):

A CF-carrier screening program is neither desirable nor necessary but because the test is available there is need for action in the following areas:

- Public education in DNA-diagnosis.

- Safeguarding voluntarism in the provision of services.

- Ensuring laboratory competence, quality assurance of the test, maintaining high quality standards of counselling.

- No screening of minors.

- Access for all who ask for CF-mutation analysis to high quality counselling and diagnosis services.

- A pilot project is needed to address potential adverse outcomes.

It is evident that the policy statements of the three organisations serve several purposes:

a) to dampen any initial drive to start CF-screening immediately, to ensure that CF-carrier screening although technically feasible, is not offered routinely by primary care physicians by articulating current consensus on practice recommendations,
I. Nippert

b) to enhance the awareness among the medical community about the complex problems inherent in CF-carrier screening, especially its unknown and not assessed adverse social effects,

c) to protect the primary care physician from legal liability to offer the test to persons with average risk.

So far just one very small pilot project to assess opportunistic CF-carrier screening options has been started in West Germany (s. below) and it remains to be seen whether the policy recommendations will affect physicians' practice. At the moment there is no evidence that CF-carrier screening will enter a medical practice the same way as it has happened with the triple test. This test was taken up immediately by a large number of primary care obstetricians as soon as it became available although the obstetricians' own scientific obstetric societies did not recommended it as a routine test (Moratorium zum Triple-Screening fetaler Chromosomenaberrationen aus mütterlichem Serum, Medizinische Genetik, p. 2, 1. Jahrg. 1992). The three obstetricians that were asked in this study, and were chosen because they are inventors and promoters of prenatal screening services in Germany as well as representatives of professional organisations, clearly stated, that for the time being CF-carrier screening was not considered to be a test that should be offered as standard of care to pregnant women at average risk (Tab. 5/8) In contrast to their colleagues in West Germany, geneticists in East Germany (then still GDR) were in favour of developing a CF-carrier screening program and started in late 1989 talks with their Ministry of Health to implement a nation wide pilot program on screening pregnant women for ΔF508 mutation in the activities of the ministry's 5 years health plan (1990-1995). According to Ch. Coutelle, with the exception of one opponent, Prof. Pelz, paediatrician and clinical geneticist, Universität Rostock, there was general consensus among this colleagues that a pilot program should be started. The Ministry of Health consented to include a pilot program in its 5 years plan but made it clear that its final decision to implement CF-carrier screening on a population base would depend on cost-effectiveness considerations. Due to the reunification in 1990 this plan was never realised. In unified Germany the East German scheme to screen pregnant women for ΔF508 mutation failed to gain grants, was rejected by peer review and was met with open opposition both by West German geneticist and the German CF-Association. Nevertheless a small scale pilot program was started in 1990 in Berlin-Buch (s. below).
Concerns Stated by Health Care Providers

The overall concern stated by medical geneticists is that CF-carrier screening will be offered by primary care physicians who are either concerned about liability or driven by economic interests before an adequate infrastructure to meet genetic counselling needs is developed and evaluated, before the potential for discrimination and stigmatisation is assessed, before standards of quality assurance for DNA diagnostic services are established. Medical geneticists referred to a history of concern about the delivery of genetic information especially in prenatal care (i.e. pre-test counselling prior to amniocentesis). They question whether primary care physicians can be ideal providers of CF-screening services especially of genetic counselling because of lack of adequate training (teaching clinical genetics is underrepresented in the German medical school curricula) and lack of adequate reimbursement for counselling by the sickness funds. Ideally, primary care physicians should refer interested patients to genetic counselling centres or to board certified human genetics in private practice but it is evident that the current small number of medical geneticists would not be able to handle a dramatic increase in counselling cases. Due to the inadequate genetic counselling infrastructure to provide high quality services, to enable a wider population to make informed reproductive choices, restraint in informing individuals at average risk on a routine base about the availability of the test is recommended by geneticists. Further concerns are that pregnant women are likely to become a target population for CF-carrier screening because of the advantage of a "captive" population/market (92% of all pregnant women in West Germany have seen a physician until ≤ 16th week of pregnancy according to the perinatal follow-up study of the Ärztekammer und Kassenärztliche Vereinigung Westfalen-Lippe, Perinatologische Arbeitsgemeinschaft, Geburtshilfestatistik 1990).

This would leave little time for reflection for the women, all adverse psychosocial outcomes of CF-carrier screening would fall disproportionally on women, and it would relate CF-carrier screening too close to abortion.

Paediatricians were mostly concerned about the negative impact CF-carrier screening would have on the perception of CF in the society, that biased information exaggerating the negative aspects of CF to justify screening, may enforce negative stereotypes about diseases genetic in origin and may encourage eugenic orientations. A minority among the interviewed health care providers stated concerns that failing to inform people now, including pregnant women, denies people the right to make autonomous reproductive choices. This view was only found among geneticists. None of the representatives of the other health care professions interviewed in this study expressed this view, nor stated interest in advocating, promoting or supporting a population based CF-carrier screening program at this time.
Views of Health Care Politicians

Interviewed were two members of the Federal Parliament of Germany (Deutscher Bundestag), who were chosen because of their expertise in policy issues in human genome research and their promotion of technology assessment in this area, and one representative of the federal government's health administration, who supported the funding of research to promote and to evaluate the implementation of chorionic villi sampling in prenatal care. It becomes clear from their statements that

a) CF-carrier screening is not on the priority list of services considered to be absolutely worthwhile to be implemented into the German health care system

b) it is acknowledged that CF-carrier screening can't be prohibited and will become available within a certain time frame

c) the possibility is acknowledged that individual autonomy in deciding whether or not to be tested might be overridden if adequate counselling is not available.

The three express their concern that the time available for discussion on how the new genetic tests should be used in the best interest of society is compressed due to the rapid developments in this field and the pressure to use the techniques.

Member of the Federal Parliament (Mitglied des Bundestages, MdB), Head of the Committee for Research, Technology and Technology Assessment of the German Federal Parliament (Vorsitzender des Ausschusses für Forschung, Technologie und Technikfolgenabschätzung im Deutschen Bundestag):

"Of course I don't think a voluntary population based carrier screening program is a necessity or desirable, considering the current problems we face politically in health care. But because of the rapid technical development in this area, the availability of the test - and because of the attitude of the German population - it will probably come, inevitably... CF-carrier screening should always be embedded in pre-test education and pre-test counselling as well as in post-test counselling. It should be absolutely voluntary and people should be sensitive about the consequence that will arise if it is implemented as standard of care into our health care system and the costs are covered by the sickness funds. Then it will be offered routinely and although the test is still considered voluntary it will be used more or less automatically... I would prefer if those who offer the counselling were completely independent institutionally from those who perform the test..."
Government Administrator from the Federal Ministry of Health (Bundesministerium für Gesundheit):

"I don't consider a population based CF-carrier screening program desirable and not at all a necessity and I am not even sure whether it will come inevitably. We on our part would very likely not make any 'propaganda' for it, we would not make it an issue for action, let's say fund the implementation (like chorionic villus sampling) of such a program. There are more imminent problems at the moment that have a far higher priority politically, for instance environmental pollution and its impact upon health: I am not sure whether the implicit consequences of such a screening program, its close connection with the abortion issue qualifies it as a desirable preventive option in the overall context of our health care system. And besides, the disability organisations would not like it... If it is promoted by the physicians then we ought to be able to answer the question how a genetic screening program should look like to become ethically acceptable... I for myself would prefer that the test could be obtained individually. I don't see how we can prohibit it but pre-test and post-test counselling should be connected with the test... We need the informed patient."

Member of the Federal Parliament (Mitglied des Bundestages, MdB), with Special Interest in Human Genome Analysis:

"CF-carrier screening will come inevitably. I don't like it but we can't prohibit it. I think the most interest in promoting the test lies with the pharmaceutical industries, that is logical. And I think people will start asking for it. Personally because of the low risk to get a child with CF, I think we should NOT expect the obstetricians to inform the pregnant women about the availability of the test on a routine base. The test should not become standard of care, it should only be performed – if, let's say, prospective parents explicitly ask for it. Then the test should be offered in connection with pre-test and post-test counselling so that the parents will understand it properly. The test and the counselling should only be provided by specialists (human geneticists)."
Views of the German Cystic Fibrosis Association

The German CF-Association divorces itself from any research into CF-carrier screening, its representative from the parents', the adult patients’ and the physicians’ groups unanimously oppose the prospect of CF-carrier screening. Consequently they oppose pilot programs to explore the implications and psycho-social consequences of CF-carrier screening as "the first step in the wrong direction" (v.d. Hardt, Tümmler, Kaiser). In 1990 the CF-Association published a policy statement with the following key-points: 1. The association rejects CF-carrier screening, 2. CF-testing should be available for persons with a family history of CF. 3. CF-testing should be covered by the sickness funds on the condition that the test has to be provided in conjunction with genetic counselling. 4. No new-born screening at the time being. 5. If CF is diagnosed prenatally, the choice for abortion rests exclusively with the parents after comprehensive genetic counselling and information about CF has been provided, PD of CF does not warrant automatically abortion.

Especially the adult patients’ group organised within the CF-Association voices its opposition against CF-carrier screening. This group questions whether the knowledge about the potential of CF in one's offspring is in the best interest of society. They assume that a push and pull effect will lead to widespread use of the test, they fear discrimination of those who refuse the test, stigmatisation of patients ("CF is worse than to be born"), that public attitudes towards patients and their parents might change negatively and that this could lead to undesirable social consequences such as less solidarity and compassion for the disabled and could foster new eugenics. At the international workshop that was held during the study, Copenhagen, November, 19-20, 1992, the representative of the German CF-Association for the workshop, A. Kersting-Wilmsmeyer (†), gave the following policy statement on behalf of the association:

"As you perhaps know, in Germany a population-screening-program is unanimously rejected, not only by the afflicted patients of Cystic Fibrosis, but also by their parents, their treating doctors and by the majority of human genetic researchers. As a young adult afflicted by CF and a member of the working group "living with CF" (a group that represents the interests of German CF-adults) and having been member of the executive board of the German CF-Association, I want to give you an idea, why we reject a population screening on a wider scale: 1. One can live with CF. The treatment of CF has improved so much, that more and more patients not only reach adulthood but even succeed in living in a state of health that makes life worth living. 2. Children born today have a great chance to benefit early enough of medicines and forms of therapy which in near future will be available thanks to the discovery of the genetic defect. So these children may be able to live quite a normal life. 3. We see our disease as a challenge, which may influence our lives in a positive way, for
example towards a greater sensibility for the discriminated and towards a deeper sense of life. Many of us feel their lives to be more conscious and desirable than their non-handicapped fellowmen. 4. If there exists a general population screening, a mother of an afflicted unborn child cannot really come to a free decision of her own for or against her child. Even if the screening is voluntary, it will be expected to make use of it. Parents who are both carriers will be expected to order a prenatal diagnosis, and in case of an affected embryo they will be urged to interrupt pregnancy. A self assured mother, assisted by her husband and her friends, who is well informed about CF and who knows patients with CF, may be able to come to a free and responsible decision. But think of the reality: The normal citizen never has heard of CF, nor does he know someone who lives with CF. When mothers get informed about screening on a sheet of paper which contains only five sentences about CF (as was done by the pilot program in Edinburgh), they cannot decide freely. 5. CF is only the beginning! We fear that human genetics will avoid many further so-called diseases of men, as soon as prenatal genes testing is generally accepted. We want to stop such development at the beginning, thinking of our bad experiences with eugenics during the Third Reich in Germany. 6. We cannot accept that parents without deep knowledge and experience about the CF will be forced to decide, whether an unborn child shall live with this disease or not. I want to ask you: How can you decide that a human being afflicted with CF does not want to live and should be better not born? How do you measure the value and sense of life? Don't you think that living with trouble and knowing one's own limitations means having a much more intensive life than that of careless so-called non-handicapped people? We therefore, demand: Gene testing only if personally wanted, no advertising and as a precondition in any case a human genetic consultation!"

**Attitudes in the General Population**

There are hardly any empirical information available about the attitudes of the general population towards the option of CF-carrier screening, or attitudes toward PD of CF-affected fetuses and abortion. Two studies conducted in 1992/93 are investigating consumers and geneticists attitudes towards prenatal screening and subsequent abortion. One study included pregnant women from the general population, the other one included women that underwent PD (Tab. 7).
Table 7: How would you personally respond if you and your partner were expecting a child with CF

<table>
<thead>
<tr>
<th></th>
<th>I would probably have an abortion</th>
<th>I would not have an abortion, but it should be available for others</th>
<th>I would not have an abortion and it should not be available for others</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population*</td>
<td>39.4%</td>
<td>42.4%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Pregnant women*</td>
<td>49.3%</td>
<td>43.7%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Pregnant women with PD and subsequent negative test result**</td>
<td>50.0%</td>
<td>37.3%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Geneticists*</td>
<td>56.2%</td>
<td>41.5%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Sources: * "Attitudes of consumers and health professionals toward prenatal screening and people with disabilities”, EC-ESLA-Program funded study, Th. Marteau, PhD, London, UK, I. Nippert, PhD, Münster, Germany. ** "Impact of prenatal diagnosis upon women”, DFG funded Study 1991-1993, I. Nippert, PhD, Münster, Germany.

These studies show remarkably little differences among the attitudes of geneticists and pregnant women, the majority is in favour of abortion. The general public is less in favour of abortion than the other three groups. But even in this group the majority would tolerate the abortion of CF-affected fetuses (the majority of the general public are members of the catholic church). As there is no much difference between the attitudes of geneticists who are very well informed about CF and those groups that know little to nothing about CF, these data seem to support N. Holtzman’s hypothesis: ”When fully educated and informed, most people will probably accept carrier screening, prenatal diagnosis, and the abortion of fetuses who are destined to develop a severe disease in infancy or childhood.” (Statement made at the study's workshop, Copenhagen op.cit.; s. also N. Holtzman "Proceed with Caution”, Johns Hopkins University Press, Baltimore, p. 229, 1989). This assumption is also supported by preliminary findings of the above mentioned DFG study on pregnant women. The majority of couples (n=11/12) with a family history of CF who attended genetic counselling prior to PD in 1992 at the department of human genetics, Westfälische Wilhelms-Universität Münster, stated that they would be in favour of CF-carrier screening for persons at average risk. This attitude somewhat contrasts the attitude of the parents’ group with in the German CF-Association.
Table 8: Do you consider population based CF-carrier screening as ...  

<table>
<thead>
<tr>
<th></th>
<th>Desirable and necessary</th>
<th>neither desirable nor necessary but probably inevitable</th>
<th>should NOT be offered to persons with an aver-age risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>From a geneticist's point of view:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chairman of the German Society of Human Genetics (personal view)</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ethic's Committee of the same organisation (published statement)</td>
<td>-</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Berlin-Buch:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Head of the dep. of biochemistry and molecular genetics, Max-Delbrück-Centrum für molekulare Medizin</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>- 2nd paediatric clinic, department of human genetics, Städtisches Klinikum Berlin-Buch</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Göttingen (2 geneticists):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Head of the department of human genetics</td>
<td>(X)</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>- Geneticist (MD), department of human genetics</td>
<td>(X)</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Geneticists who were serving in the stand. subcommittee &quot;Biomed. Ethics and Technology Assessment&quot; of the Scientific Council of the Fed. Board of Physic. (from Bonn, Hannover, Freibur)</td>
<td>no</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>From a paediatrician's/obstetrician’s point of view:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head of the department of paediatrics, head of the CF-centre, Städt. Krkh. Pforzheim, chairman of the German CF-Association</td>
<td>no</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Head of the department of paediatrics and head of the CF-centre, Medizinische Hochschule Hannover</td>
<td>no</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Head of the department of prenatal medicine, Westfälische Wilhelms-Universität Münster</td>
<td>no</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Honorary president of the Professional Board of the Obstetricians (Ehrenpräsident des Berufsverbandes der Frauenärzte)</td>
<td>no</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Obstetrician in private practice, Freiburg</td>
<td>no</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Chairman of the Scientific Council of the Federal Board of Physicians (Vorsitzender des Wissenschaftlichen Beirates der Bundesärztekammer)</td>
<td>-</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>From a health care politician's/government health official's point of view:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Members of the Fed. Parl. (Mitglieder des Bundestages, MdB)</td>
<td>no</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Government health official (Bundesministerium für Gesundheit)</td>
<td>no</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Parents from CF-Association</td>
<td>no</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>CF-patients from CF-Association</td>
<td>no</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>CF-parents asked in DFG-study</td>
<td>X</td>
<td>-</td>
<td>-</td>
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</table>
Current Screening Efforts

Two small scale pilot projects, using different strategies and target populations are currently conducted in Germany. One study in Berlin-Buch, East Germany, offers CF-screening to pregnant women, the other in Göttingen, West Germany, offers opportunistic screening to all persons of reproductive age who seek an appointment for any reason at the Göttingen genetic counselling centre. Both studies are not funded by research grants. The study in Berlin-Buch is the remainder of what was originally planned as a nation-wide pilot program in the former GDR. Both studies are underway because individual human geneticists decided to go ahead and they have the means via other resources to do so. Both pilot projects provided a preliminary results for this report:


Aim of this limited pilot study is to investigate the possibility to perform a heterozygote screening test for CF by PCR-based detection of the ΔF508 mutation in the CFTR gene. In particular we are investigating the acceptability of such tests by pregnant women, the logistics of organisation, improvements to laboratory methods, the psychological effects of a positive test on the women and their partners and ethical aspects of such tests. The study is performed by a laboratory of molecular human genetics and a counselling centre for human genetics in collaboration with three local clinics of obstetrics. Pregnant women attending the obstetrics clinic before the 10th week of gestation are informed by a leaflet about CF and the possibility of this test and are offered further information by an appointment with a consultant human geneticist. Participation is completely voluntary and has to be confirmed by written consent. The preparation of genomic DNA is performed from 5 ml whole blood or more recently from a spot of blood dried onto filter paper. After amplification of exon 10 the ΔF508-mutation is detected by polyacrylamide gel electrophoresis. The frequency of this mutation is 62% in our population. From July 1990 to December 1992 593 pregnant women were offered this test of which 16 turned out to be heterozygote for the ΔF508-mutation. None of the approached women took the offer of a personal consultation and only one woman refused to be tested. All 16 heterozygotes and their partners were invited to a consultation with the genetic counsellor in our team. They were informed in this consultation about the test result and its implications. A second test involving the partner and including the analysis of the two next frequent mutations in our population was offered. All 16 couples took these tests and none of the
partners was shown to be heterozygote for the tested mutations. The results of the second test were also discussed with the couple in a second consultation. The consultations showed minimal to no knowledge about genetic disease and in particular about Cystic Fibrosis. The detection of heterozygosity in the pregnant female caused initially strong anxiety in 9 cases. This could, however, be dissolved in all cases by an extended consultation and 8 couples were very co-operative in handling the risk information. The residual risk of missing a rare mutation in the male partner was tolerated well by all probands. Our preliminary data show so far that the idea of testing for CF is generally accepted by most pregnant women and that the anxiety caused by positive test results can be controlled by professional genetic counselling that, we are convinced, is an absolute requirement for any genetic screening.

From the Göttingen pilot study, F. Laccone reports: "Since August 1991, we offer to people attending our institute for genetic counselling, information about CF and the possibility of having a test for carrier status. At first, we test for ∆F508, and if one of the couple is heterozygous for ∆F508 mutation, we screen for the next frequent mutations in the CFTR gene. We don't make a distinction between pregnant and non pregnant women. During the course of the study, we changed the method of informing the patients as follows: 1. We gave information about CF as a

<table>
<thead>
<tr>
<th>Table 9: Time period 25.5.1992 - 4.11.1992</th>
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</thead>
<tbody>
<tr>
<td><strong>Department of human genetics,</strong></td>
</tr>
<tr>
<td><strong>Georg-August-Universität Göttingen</strong></td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Patients actively informed via questionnaire</td>
</tr>
<tr>
<td>Patients who did not return the questionnaire</td>
</tr>
<tr>
<td>Patients who returned questionnaire</td>
</tr>
<tr>
<td>Patients who stated that they did not want to be counselled or receive further information</td>
</tr>
<tr>
<td>Patients who stated that they wish to be screened prior to pre-test counselling</td>
</tr>
<tr>
<td>Patients who stated that they were undecided prior to pre-test counselling whether to be screened or not</td>
</tr>
<tr>
<td>Patients who underwent screening after pre-test counselling</td>
</tr>
</tbody>
</table>
matter of routine during the course of counselling. 2. We asked the people if they would like to have some information about CF. 3. We made a leaflet about the symptoms and genetics of CF. The patients were requested to read the leaflet and to fill in a short questionnaire before counselling. The questionnaire contained 6 questions, which should help us to find out the attitude of our patients towards the initiative. If the patients were interested in more information, the counsellor was glad to give some. Our results show that the acceptance of a test for CF changed according to the approach used to inform the patients. By the first approach (19.08.1991 until 28.09.1991) 22.5% of the people underwent the test by the second (29.09.1991 until 24.05.1992) 12.3% and by the third (from 25.05.1992 until 04.11.1992) almost 15.5% of the patients underwent the test: (s. Tab. 9).

The studies indicate that if CF-carrier screening is offered opportunistically there seem to be much less interested individuals than in prenatal care. But experience of the past with offering tests to the prenatal population clearly show that pregnant women are more likely to comply with testing, for what reason so ever, and it is questionable whether the high compliance (99.8%) in the Berlin-Buch study indicates a general interest in and acceptance of CF-carrier screening by pregnant women.

<table>
<thead>
<tr>
<th>Location</th>
<th>Target population</th>
<th>Approach</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max-Delbrück-Centrum für molekulare Medizin, Berlin-Buch, 2nd paediatric clinic department of human genetics, Städtisches Klinikum, Berlin-Buch (East Germany)</td>
<td>pregnant women, before 10th week of gestation</td>
<td>woman is screened for ΔF508 with sequential screening for ΔF508 + R553X + G551D of partner if woman is positive</td>
<td>as of July 1992 638 women had accepted, 20 carriers had been found, 1 affected pregnancy found and subsequently aborted</td>
</tr>
<tr>
<td>Department of human genetics, Georg-August-Universität Göttingen (West Germany)</td>
<td>information about the availability of the test is actively offered to all persons of reproductive age who seek an appointment for any reason at the genetic counselling centre</td>
<td>consenting persons are screened for ΔF508 screening of partner is offered for ΔF508 + ? mutations if person is positive</td>
<td>since August 1991. As of November 1992 968 persons had been informed, 150 had consented to be screened; demand can be increased or decreased depending whether or not the test is offered opportunistically during genetic counselling</td>
</tr>
<tr>
<td>Other departments of human genetics like Freiburg, Hannover, Münster, Stuttgart (all West Germany)</td>
<td>no target population, no active information</td>
<td>those who ask for it without family history are counselled and subsequently offered the test if they wish to be screened</td>
<td>as of November 1992 none in Freiburg, 2 in Hannover, 2 in Münster, at least 2 in Stuttgart, have been screened</td>
</tr>
</tbody>
</table>
I. Nippert

Table 10 shows the actual CF-carrier screening provision in Germany in 1992. Apart from the two places where the pilot studies are run, there are several departments of human genetics who offer CF-carrier screening to those who explicitly ask for the service. These departments provide extensive pre- and post-test counselling. So far only very few people have asked for the test. These fragmented approaches towards CF-carrier screening are typical for the implementation of new techniques into the German health care system. The German medical profession enjoys a substantial amount of professional autonomy in deciding which new services and new techniques they want to be available. There is little national health care planning and it is not unusual at all in the German health care system that "innovative" health care providers begin to offer services, even in spite of their professional organisation’s recommendations.

Summary and Conclusion

The major factors that affect the current state of CF-carrier screening, the provision of services, and the existing policies towards the implementation of CF-screening services into the German health care system are the following: The underlying health care infrastructure which is characterised by a substantial degree of clinical autonomy enjoyed by the medical profession. It is the medical profession who decides which new techniques are considered to be medically feasible and necessary. (The fees and which medical speciality is allowed to offer the techniques is regulated among the regional associations of the sickness funds physicians and the sickness funds.) Medical geneticists are until now the key actors in the process of policy shaping regarding the introduction and diffusion process of CF-carrier screening within and outside the medical profession in Germany. Medical geneticists are the solo gate openers for the introduction of CF-carrier screening services (no other medical speciality i.e. paediatricians or obstetricians are seeking collaboration at the moment to support or initiate a carrier screening program). Government's role is characterised by two aspects: Government will not fund the diffusion process of CF-carrier screening and maintains that most of the problems indicated by the medical geneticists should be solved and managed within the medical profession with the exception of two issues for which legislative action is considered. These are regulations regarding insurance (private health insurance, life insurance), and screening at the workplace.

At the moment it seems that the policies shaped by the medical geneticists’ professional and scientific organisations have gained recognition for the time being among the majority of health care providers - though not among all of them - as well as among politicians and health administration. It is agreed upon that persons with a family history of CF should obtain CF-carrier testing (general consensus), that
reducing the prevalence of CF among life births via population based voluntary CF-
carrier screening programs is not regarded as a public health goal, CF-carrier
screening should not be implemented as standard of care into the health care service.
People with unknown risk of conceiving a child with CF should not be routinely
informed about the availability of mutation analysis by the medical profession. Screening pregnant women is not recommended.

Contrary to other genetic screening programs (i.e. screening for chromosomal
aberrations, MSAFP-screening, triple test) the prenatal population will probably not
be the entry point for CF-carrier screening in Germany for the next years.

**Concerns that Predominate the Discussion**

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</tr>
</thead>
<tbody>
<tr>
<td>Commercialisation, market pressures will drive widespread use</td>
<td>X X X</td>
<td>X X X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Adequacy of quality assurance for DNA diagnostic facilities</td>
<td>X X X</td>
<td>X</td>
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<tr>
<td>Current number of genetic specialists/ counsellors can't handle the swell of CF-carrier cases</td>
<td>X X X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Use of genetic information by third parties (life insurance etc.)</td>
<td></td>
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<td>X</td>
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<tr>
<td>Abortion of CF as a preventive option</td>
<td>X X X</td>
<td>no</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Eugenic effects”</td>
<td></td>
<td>X</td>
<td>no</td>
<td>X X</td>
<td>(?)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Social coercion to use the test and to prevent the birth of an affected child</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Less money available for CF-therapy research</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pressure exerted by sickness funds to use the test and to prevent the birth of an affected child</td>
<td></td>
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</table>

*Human Genetics. ** Medical Genetics

*It is agreed upon that the implementation of CF-carrier screening represents policy problems that go far beyond the implications for CF-carrier screening, and that the*
main problem today is how appropriately controllable is the evolution of standards of practice by the medical profession as new powerful diagnostic tests rapidly become available by the new genetics. Use of these tests in health care raises questions that go far beyond medicine and affects society on multiple levels. Shown below is a summary of the concerns of the key-persons interviewed (Tab. 11).

**Prospects for the Future**

Two different scenarios are likely for Germany to happen:

- The information about the availability of CF-carrier screening will trickle down from the better informed segment of society to the broader population leading to a steady increase in demand for CF-carrier screening and probably other diseases such as Fragile X, in the next decade.

- Or, successful liability suits brought forward by parents to whom a child with CF is born, implying a duty to inform pregnant women about the availability of the test, will spur the offer of CF-screening (and other DNA diagnosable diseases) in prenatal care.
4. Country Report from the Netherlands

P.G. Frets, M.F. Niermeijer, D.J.J. Halley, H. Galjaard

Cystic Fibrosis in the Netherlands

CF is the most common autosomal recessive disorder in the Netherlands, 1:30 is a carrier. At present there are about 1 000 CF-patients in the Netherlands. Most of the diagnoses for CF are made before the age of 2 years. The survival rate has improved over the years. In 1985 one-third of the CF-patients were 15 years or older and in 1990 this was the case for half the CF-patients. The mean life-expectancy of a Dutch CF-patient rose from 24 in 1985 to 28.5 years of age in 1990 (National CF-registry, department of medical genetics at the University of Groningen). Most paediatric CF-patients frequently visit their paediatrician at the regional hospital and are evaluated periodically at one of the specialised CF-treatment units, mostly at university paediatric departments. For adult CF-patients management is given at pulmonary and internal medicine departments of university hospitals and a few of the larger regional hospitals.

CF-Carrier Testing

At present 12 CF-mutations or polymorphisms have been identified in the majority (85%) of Dutch CF-patients. These include ΔF508, R553X, 1717-1 G→T, W1282X/R1283 M, F508C(S12512 N), G542X, ΔI507, G550X, G551D, 621+1 G→H, N1303 K, 1677del, C524X, V520F, S549I, S549N. Nowadays in the Netherlands CF-carrier testing is only offered to relatives of CF-patients and the relatives' partners. Between 1988 and 1991 at the department of clinical genetics in Rotterdam DNA-analysis for CF was performed in 1 297 persons of whom 130 were carrier, and 80 prenatal diagnosis were carried out. There are no epidemiological data on the proportion of relatives of CF-patients who requested CF-carrier testing and genetic counselling. No CF-carrier screening pilot projects are running in the Netherlands nor are there any commercial labs which offer CF-carrier testing, since DNA-testing
for genetic diseases is limited to clinical genetic services. In theory, physicians might send blood samples to foreign commercial labs.

**Health Care in the Netherlands**

In the Netherlands, with a population of 15 million people, 9% of the gross domestic product is spent on health care.

The level and framework of health care provisions are controlled by the government and the council of health insurers, a body combining the health insurance executive board and private health insurance companies. Decisions regarding health care provisions must be approved by the Ministry of Welfare, Health and Cultural Affairs. Legal restrictions to unlimited growth of new and expensive treatment and health care costs are regulated in the law of special hospital services. This act allows the Minister of Health to restrict certain activities such as heart, liver or lung transplantation but also clinical genetic services (Galjaard, 1991). Advice about new technological developments which might be of importance in health care is provided by an independent organisation, the Health Council. On genetics, the Health Council issued reports on Organisation of Genetic Services (1977), the Ethical Aspects of Cytogenetics (1980) and Technological Development and Social Aspects of Modern Genetics (1989). The health policy goal is a balanced growth of regionally available genetic services. The seven clinical genetic centres are associated with university hospitals and provide pre- and postnatal chromosome studies, diagnosis of metabolic disease and prenatal diagnosis by DNA methodology, and genetic counselling (Galjaard, 1989). The capacity of genetic services is regulated and influenced by 1) the Hospital Provision Act which regulates the numbers of genetic centres and 2) the General Law on Special Health Care Costs. Clinical genetics centres are paid for by a scheme under this General Law on Special Health Care Costs. There is free access when the indication for the investigation is approved by the health insurer. Access is equal for patients insured through the sickness funds (70% of the population) or those having private insurance. By 1989, the annual case load of clinical genetic services were ca. 6 500 postnatal cytogenetic studies, ca. 5 000 metabolic diagnosis, metabolite and enzyme studies, ca. 2 700 DNA-analyses, ca. 7 000 prenatal diagnoses, and 2 500 cases of complex genetic counselling\(^1\) in the Netherlands (Galjaard, 1991). One or two decades ago the majority of the people who sought genetic counselling were parents who already had given birth to one or more affected children. Now, an increasing proportion of counselees (30-50%) do not have any children yet and want genetic counselling because one or more relatives have a congenital disorder or unexplained mental or physical handicap.

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\(^{1}\) excluding cases e.g. for chromosomal abnormalities or advanced maternal age.
Referral for genetic counselling is made by the GP (40%), a medical specialist from a university hospital (30%) or a regional hospital (30%). Only four clinical genetics centres receive a budget for DNA-analysis from the General Law for Special Health Care Costs. DNA-analysis for CF is only performed in Groningen and Rotterdam. There is no specific fee for a CF-carrier test because DNA-analysis is paid out of a special budget for DNA-analysis. It is freely available for all patients, relatives and their partners but does not include population-screening.

Organisational Aspects

Implementation of CF-carrier screening would need approval by the government. As the law now stands mandatory screening would certainly not be allowed. A new law limiting population screening to serious diseases for which cure or treatment is available will be introduced in the near future. In the Netherlands an extensive debate has been going on for many years about population screening for neural tube defect in pregnant women. Some health policy-makers and representatives of the parent and patient support groups are in favour of introducing this screening program. The Health Council has recommended to carry out experimental studies to evaluate pilot-screening program. However, the majority of the politicians has rejected, and still rejects, population screening for neural tube defect in pregnant women. The Dutch association for clinical genetics prepares a position paper on CF-carrier screening. Moreover, a Dutch Health Council committee on genetic population screening has started recently. Other important organisations in public debate on health issues including clinical genetics are the parent and patient support groups. In the Netherlands these organisations are run by volunteers with only marginal support from the Ministry of Health. In contrast to other countries, most have no regular or professionally organised fund-raising activities, and they have no research budget to organise research in their particular field. In the Netherlands there is a federation of at least 30 patient support groups for different genetic disorders (called the VSOP: Vereniging van Samenwerkende Ouder-en Patientenorganisatie); one of these is the large and very well organised Dutch Foundation for CF. The latter did not present a statement on CF-carrier screening yet. However, the VSOP is very active to profile patients' and parents' views on screening e.g. for neural tube defect in pregnancy. Their general attitude is to promote the availability of diagnostic techniques for carrier-detection or diagnosis during pregnancy upon individual request, after information is provided by their own physician. In this way, "population screening" is transformed into personal health care and their associated individual choices.
The aim of the comparative evaluation of CF-carrier screening development in Northern Europe was to identify factors influencing decisions by key-persons on CF-carrier screening (=CFCS). For the Dutch study 12 key-persons were interviewed using the protocol for the international study on attitudes towards CFCS. These key-persons belong to 3 groups:

**Representatives of the patient support groups (=RPSG):**

- a CF-patient and committee member of the Dutch Foundation for CF
- a parent of a CF-child, functioning as a contact person for parents of a CF-child and committee member of the Dutch Foundation for CF
- the chairman of the Dutch Federation of Patient Support Groups (VSOP)
- Health policy makers (=HPM)
- a health policy advisor, advising the Ministry of Health e.g. on genetics and general population screening
- a health policy decisionmaker, important advisor on population screening projects at the Ministry of Health
- head of a university department of technology assessment
- an academic expert in legal aspects of genetics
- the chairperson of the parliamentary Standing Committee for Health
- Professionals/Others (=P/O)
- a paediatrician with longstanding experience in management of CF-patients
- CF-researcher, involved in DNA analysis of CF
- a journalist experienced in the field of genetics
- a representative of the Dutch Royal College of Physicians

All interviews were recorded on audio tape and lasted between 45-90 minutes. The selection of the key persons was made because of their influence on an eventual decision-making process in implementing CFCS, based upon their various professional and social backgrounds. The interviews addressed the following issues: desirability and feasibility of CFCS in the near and remote future, possible obstacles to the implementation of CFCS, methods to implement CFCS, the need for public and professional education concerning CF and CFCS, financial issues involved in CFCS, confidentiality of data obtained in CFCS and its quality control. To evaluate the perceptions towards screening for other genetic diseases, the option for screening for carrier status of hemoglobinopathies, relevant to immigrant groups in the Dutch population, was addressed as well. The answers to the key-questions, as formulated in the international protocol, are given in Table 1-5 for the interviewees from the different categories. All interviewees participated anonymously.
Results and Discussion

Desirability and Feasibility of CFCS and Possible Obstacles

More than half the respondents said that implementation of CFCS was desirable in the near future (Tab. 1).

Table 1: Dutch interview study on attitude towards CFCS: Desirability of CFCS in near future?

<table>
<thead>
<tr>
<th></th>
<th>RPSG</th>
<th>HPM</th>
<th>P/O</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Doubt</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

RPSG = Representatives of the patient support groups
HPM = Health policy makers
P/O = Professionals or others

Those in favour of implementing CFCS said that it should be voluntary, and information on the test should allow the option to refuse participation. Moreover, one RPSG stressed that a CF-carrier should be protected against problems with obtaining health insurance and one RPSG proposed that the population screening should be extended to a greater number of genetic diseases.

Objections against CFCS were based on the following reasons:

1. the existing political resistance

   *This resistance has 2 aspects:*

   - CF is an untreatable disease which may lead to a feeling of helplessness. That indicates that the improved prognosis of CF remains unrecognised. It was argued, moreover, that increased knowledge on health should be questioned when it concerns disorders which cannot be prevented totally. This knowledge might lead to feelings of powerlessness and doom-mongering.

   - Prenatal diagnosis is, by some, not considered as an option of (secondary) prevention when this is to be offered to carrier couples. They fear that CFCS creates the dilemma of abortion. Withholding CFCS might avoid this dilemma. The principal goal of freedom of information and autonomous choice for carrier couples is apparently less important in this view. The political resistance against
abortion among these groups does not seem to reflect the view of the majority of the general Dutch public.

2. The psychological consequences of CF-carrier status are unknown.

3. The limitations of the test may be too difficult to explain to people in the general population, i.e. testing negative for the frequent mutations does not completely exclude the chance of being a carrier but reduces it from 1:30 to \( \pm 1:200 \).

4. Possible insurance problems for CF-carriers due to persistent misunderstanding that this might be harmful for the individual despite the recessive nature of the mutation in a carrier.

5. It is unknown whether CFCS is a priority health care issue for the general population.

6. Anxiety of social pressure to take the test.

The 5 respondents who said that CFCS was not desirable in the near future but only in the remote future indicated certain conditions for its implementation. One HPM and 1 P/O argued that implementing CFCS should become dependent on the treatability of CF. Another HPM felt that a public discussion was necessary to establish whether (a) CFCS is a priority health care issue and (b) on the ways in which CFCS should be offered. One HPM stressed that future implementation of CFCS depends upon 3 conditions: (a) The optimisation of the test to identify all carriers. (b) Insight into the psychological consequences of the test. (c) Outcome of the evaluation of the educational programs. One P/O indicated that implementation of CFCS would be dependent upon its proven cost effectiveness. The feasibility of CFCS was also discussed. Only 3 of the 12 respondents thought that CFCS would be feasible in the near future (Tab. 2). Nonfeasibility was mainly attributed to the

<table>
<thead>
<tr>
<th>Table 2: Dutch interview study on attitude towards CFCS: Feasibility of CFCS in near future?</th>
</tr>
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<tbody>
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<td>-------</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Don't know</td>
</tr>
</tbody>
</table>

For abbreviations, see legend Tab. 1
existing political resistance against CFCS.

A majority was positive about the feasibility of CFCS in the remote future depending upon the following factors:

- change in political climate in respect to the existing political resistance
- positive experiences in other countries
- availability of sufficient laboratory and genetic counselling facilities

Interestingly, a number of potential obstacles were considered less relevant for not introducing CFCS: the present impossibility to detect all mutations, the variability of CF in its manifestation, and the potential improving options of CF-treatment. Seven respondents disagreed with the statement that CFCS might reduce resources for treatment of CF because there would be fewer patients. Two were afraid of that possibility, three did not know.

Methods and Strategies for Implementation

Rather than actively offering CF-screening to the entire population - or a subgroup - by general public information, the alternative approach of offering CFCS ”low profile” was discussed. This approach entails that people would be informed e.g. by their GP or through public education about the possibility of CFCS and could ask for the carrier test themselves e.g. their GP. This alternative was favoured by 5 respondents, 3 of them were P/O’s (Tab. 3).

Table 3: Dutch interview study on attitude towards CFCS: Offering CFCS ”low profile” by GP or through the public media and subsequent request to their own GP

<table>
<thead>
<tr>
<th></th>
<th>RPSG</th>
<th>HPM</th>
<th>P/O</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
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<tr>
<td>No</td>
<td>1</td>
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<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
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For abbreviations, see legend Tab. 1

The principal difference between the ”low profile-approach” and actively offering CFCS is that a personal effort to get CF-carrier testing has to be made instead of reacting to an institutionalised offer made by the health services. Discussions on the various possible strategies for offering CFCS when it would be implemented showed that there was no specific majority preference (Tab. 4). Four respondents
preferred prenatal screening, two of those were HPM and 2 P/O. Three favoured new-born screening of whom two belonged to the patient support groups. Three respondents believed that the development of family planning clinics, not functioning as such in the Netherlands, would be most suitable for CFCS.

Table 4: Dutch interview study on attitude towards CFCS: Preferred strategies for CFCS

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
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<td>New-born</td>
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<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Schools</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Primary health</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal screening:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>early in pregnancy</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>No preference</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

For abbreviations, see legend Tab. 1

The reported advantages of new-born screening were based on practical considerations, like easiness to incorporate in PKU-screening. The objections were that carrier-babies would be burdened with this knowledge when they grow up. Moreover, incorporating CFCS in the PKU program, which is aimed at treatment of identified PKU cases, would add a totally different aspect to the screening, being the detection of healthy carriers. Screening children in schools at 16 years of age has the advantage that these children may be receptive to the information and easy to motivate for the test. In addition, when both future partners are informed that they are carrier, they have a maximum of freedom of choice concerning reproductive options. Proponents of this approach did not expect stigmatisation of carriers. The main objections against screening in schools were that carrier-stigmatisation might influence dating behaviour and partner choice. Other reservations concerned possible peer group pressure to take the test, possible limitations in obtaining insurance for CF-carriers and doubts about the children's receptiveness to information that may become relevant only many years later. The advantages reported for screening in primary health care were that only well informed and really motivated individuals will ask testing before pregnancy, allowing freedom of reproductive choice when both partners were carriers. The main disadvantages mentioned were that a potential majority of people would be missed, because people in reproductive age rarely visit their GP according to 1 HPM. This, however, is not confirmed by recent Dutch data (CBS, 1991). Moreover, standardised education about the test by the GP would become difficult to realise. The arguments in favour
of screening early in pregnancy were that it addresses the most relevant and easy-to-reach group. Arguments against prenatal screening were that abortion was the only available option to prevent the birth of a CF-child and that pregnancy is a too sensitive period in life. The majority of the respondents felt that either the GP or a nurse with experience in CF would be best suited to inform about the test. Those who were tested negative could be notified by letter. The GP should inform carriers. When both partners are carrier the couple has to be referred to a clinical genetics centre.

The Need for Public and Professional Education

Knowledge about CF in the general public and in professionals was generally viewed as insufficient. Education of the general public might be most effectively given through the mass media like TV/radio, in women's magazines, in schools and through leaflets in GP-waiting rooms, pharmacies etc. One HPM opposed to public education altogether because of the general fear of medicalisation of society: ”There are already so many medical educational programs on TV which cause a lot of problems. It is important that people know what is possible but it is not good when this leads to an obligation to use medical facilities. The psychological consequences of offering CFCS are questionable. I think it creates commotion in the general public.” One P/O was opposed to public education and only wished individual education about CF-carrier testing of pregnant women given by the gynaecologist or midwife. In that view public education is held as extremely expensive, with people misinterpreting information and making them worried. Most respondents said that education of professionals must be provided during university training, postgraduate courses and through publications in scientific journals. They expect a beneficial influence of a future law requiring regular examinations for recertification of physicians. The government was given the task to stimulate and provide financial support for public and professional education.

Financial Aspects

Most respondents indicated that CFCS should be financed through a national plan regulated by the General Law on Special Health Care Costs. A minority said that the expenses should be covered by national and private health insurance. Only 2 respondents felt that a small personal contribution might be required from those wishing the test, showing their motivation in this way.
Confidentiality of Data Obtained in CFCS and its Quality Control

Half the respondents (n=7) preferred central storage of the test results but in a system separate from other hospital data, like the computer system of clinical genetics centres. Three respondents preferred storage in the files of GP's. One P/O felt that only the tested individuals needed to be informed of their test result and 1 did not know. Methods generally indicated for privacy protection included a separate computer registry (n=7) or specific legal protection necessitating installation of new laws providing this protection (n=4). Most respondents felt that the actual systems of quality control of laboratory systems and genetic counselling in clinical genetics centres are sufficient for future purposes.

Offering Carrier-Screening for CF and Haemoglobinopathies to Immigrant-Groups

The majority (n=10) thought that CFCS should also be offered to immigrants living in the Netherlands although the test can identify ± 55% of the CF-carriers (± 700 000 - 800 000 people). The question was posed of offering haemoglobinopathy-carrier-screening to immigrants living in the Netherlands, originating from African or Mediterranean countries. These populations in the Netherlands probably have a carrier frequency of 1:10 (Spit et al., 1992).

Table 5: Dutch interview study on attitude towards CFCS: Desirability of implementing haemoglobinopathy-carrier screening for immigrants in the Netherlands?

<table>
<thead>
<tr>
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<th>RPSG</th>
<th>HPM</th>
<th>P/O</th>
<th>Total</th>
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<tbody>
<tr>
<td>Yes</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Cost-effective?</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

For abbreviations, see legend Tab. 1

More than half (n=7) was positive about offering carrier screening for haemoglobinopathies to immigrant-groups, 2 said that it had to be cost effective, 1 HPM wanted to wait for the results of a study in progress and 1 P/O said that he did not know enough about these disorders but that screening for this high-risk-group had to be taken in consideration. One HPM was opposed because these disorders were not treatable (like PKU).
Conclusions

The following conclusions can be drawn from this interview study in 12 Dutch key-
persons:

1. In the Netherlands, screening for the carrier status for CF and other genetic
disorders is unlikely to be implemented in the near future because of 2 reasons:

- influential health policy makers are opposed or doubtful about it because CF
cannot be treated. It may create commotion in the general public and raises the
dilemma of choices for carrier couples preparing for or going through a
pregnancy.

- a new law limiting population screening to serious diseases for which cure or
treatment is available will be introduced. At present prenatal diagnosis is
offered to a (sub)group of the general population under very special
circumstances e.g. through individual health care to pregnant women over 35
years. From the latter perspective, 1 HPM claimed that offering CFCS through
individual health care might be allowed. CFCS might also be allowed when
offered BEFORE pregnancy to avoid the question of abortion as the only option
for carrier couples to avoid the unwanted birth of a CF-child. The majority of
the respondents foresee that CFCS will be introduced at a later stage, also
dependent on experiences elsewhere. However, it is foreseen that the political
climate in respect to population screening will become more restrictive in the
near future.

2. There is no consensus on the best timing of CFCS; interestingly, some
representatives of the patient support groups have no principal objections
against neonatal carrier detection.

3. Public and professional education about CF and CFCS is considered essential
by most respondents.

4. CFCS - if implemented - should be financed through a national plan for special
health care costs, and not through health insurance.

5. Privacy of the persons to be screened is important and to be protected by either
storage in a separate computer system and/or covered by legal protection. From
these results, the general impression on the future of CFCS is that one wants to
"proceed with caution", with more active impetus from the side of patient
support groups and more reluctance from the policy-makers. The latter mainly try to obviate the potential problems about the abortion issue which might be perceived as a greater problem by the policy-makers than it possibly is in the view of the general public. The utilisation of prenatal diagnosis in the general public in case of advanced maternal age to detect chromosomal abnormalities has increased from 6% in 1976, to 20% in 1980 to, 60% in 1990 (Galjaard, 1991; Brandenburg et al., 1992). Other data indicate that 15% of the population would refuse abortion in a pregnancy for any indication, including severe fetal abnormality (Thomassen-Brepols, 1985). This study shows the relatively time-consuming nature of developmental processes in health policy making. Within western societies there are still major differences in the organisation of health care, attitudes towards genetic testing, fetal diagnosis and abortion (Galjaard, 1990). These differences may give clues for developing future strategies for screening for genetic disorders and congenital anomalies in this part of Europe.
Acknowledgements

This study was financed by the EC-Human Genome Analysis. The investigators are very thankful for the full co-operation given by the participants in this study.

References

5. Country Report from the United Kingdom

M. Modell

Key Persons Interviewed in the UK Study:

M. Bobrow, geneticist, professor, MD, department of medical genetics, Addenbrooke’s Hospital, University of Cambridge, at that time Clinical Research Unit, division of medical and molecular genetics, United Medical and Dental School of Guy's and St. Thomas Hospital, Guy's Hospital, London. Professor of human genetics. Head of the genetics team which formed one ‘arm’ of the team of collaborators for the study of screening in primary care in a large London general practice.

D.J.H. Brock, professor, MD, human genetics Unit, the University of Edinburgh, Western General Hospital, Edinburgh. Professor of biochemistry. Head of the team which conducted the trial of screening for carriers of CF in Edinburgh ante natal clinics.

A. Clarke, geneticist, MD, regional medical genetics Service for Wales, University Hospital of Wales, Cardiff. Consultant clinical geneticist. Has a particular interest in ethical aspects of genetic screening.

R. Dinwiddie, MD, consultant paediatrician, Hospital for Sick Children. Head Respiratory Unit. In charge of the CF clinic.

Dave, Louise, Mark and Pat. Four adults who suffer from CF. One is awaiting a heart-lung transplant, one had a successful transplant about 2 years ago.
M. Modell

**M. Goodchild**, physician, MD, CF-Unit, University Hospital of Wales. Responsible for the care of CF-patients.

**H. Harris** (Wife of Rodney), general practitioner (GP) in the north of England, Manchester, UK. Conducting a study of screening for carriers of CF amongst women who first report a pregnancy to their GP.

**R. Harris**, geneticist, em. professor, MD, department of medical genetics, St. Mary's Hospital, Manchester, UK. Professor of medical genetics, chairman of a confidential enquiry into counselling for genetic disorders. Particularly interested in the organisation of clinical and laboratory genetic services in the UK.

**A. Hunt**, MD, Genetic Interest Group (G.I.G.), c/o institute of molecular medicine, Radcliffe Hospital, University of Oxford. Chairwoman of GIG, which is an umbrella group of more than 60 voluntary organisations for patients with genetic disorders.

**I.A.F. Lister Cheese**, MD, Department of Health (DoH), Wellington House, London. Senior medical officer. Principally responsible for genetics and child health, works in the maternal and child health division of the DoH.

**Y. Payne**, regional medical genetics Service for Wales, Project Co-ordinator, University Hospital of Wales, Cardiff. Research worker on the pilot project examining the feasibility of screening for carriers of CF in Welsh general practices.

**J.A. Raeburn**, professor, MD, Interdisciplinary centre for medical genetics, University of Nottingham, City Hospital, Nottingham. Professor of medical genetics. Particularly interested in the education of teenagers genetics.

**A.K. Webb**, MD, Monsall Hospital, Manchester. Consultant chest physician. In charge of a unit for the management of adult patients with CF.

**R. Williamson**, professor, PhD, Murdock Institute, Parkville, Melbourne, Australia, at that time department of biochemistry an molecular genetics, St. Mary's Hospital Medical School, Imperial College, London, UK. Professor of biochemistry, molecular biologist. Has pioneered much of the basic scientific work in this field, has a grant of about 1 million pounds to study gene therapy for CF.

*Statements in the text that are based on the views of one of the people interviewed, are followed by the initials of that person.*
Introduction

On reading this report, I realise that I have tried to answer the questions: what section of the population should be screened for the CF gene? when should they be screened? and where? I have made the assumption that in the UK, screening for congenital and genetic diseases leading to prenatal diagnosis (PD) and possible termination of pregnancy, is accepted, well-established and does not raise unresolved ethical issues. There is no national ethics committee in the UK. When scientific advance leads to potential ethical and moral dilemmas, the Government tends to set up an “ad hoc” committee of eminent people who try and resolve conflicts, and produce recommendations which are often embodied in (usually liberal) legislation. A recent example is the Committee on the Ethics of Gene Therapy chaired by Sir Cecil Clothier the former health service “ombudsman”. It's report recommend the use of gene therapy subject to strict safeguards. PD for Down Syndrome started in the early 1960s. The UK and Hungary are the two European countries with the highest incidence of neural tube defect (NTD); measurement of alpha-fetoprotein in maternal serum as a marker for NTD has been established for more than two decades. Population screening of ethnic minorities, to detect carriers of haemoglobin disorders began in association with PD for these conditions by fetal blood sampling in the mid 70s. Routine fetal anomaly scanning at around 19 weeks’ gestation is gradually becoming more widespread and efficient. There have been several instances of parents of affected children suing health authorities, because they were not informed of their risk during pregnancy, or because of an error in the PD. The novelty of the possibility of CF-screening is only that it potentially involves the whole population in the UK. At the moment it is possible to easily detect about 85% of CF-mutations. This means that only 72% of couples at risk of an affected child can be identified. Thus the DNA test, whilst 100% specific, is only moderately sensitive. Partly because of this the prospect of general population screening is being approached very cautiously.1

The organisation of the National Health Service (NHS)2

Health care for the population of the UK (around 55 million) is provided by the NHS. This cost around £29 billion in 1990. In 1989 the country spent about 6% of its gross domestic product on health - a smaller proportion than many other Northern European countries or the USA. Though private spending on health has increased during the last decade, it still only accounts for about 15% of total expenditure. About 80% of the cost of the NHS is drawn from general taxation and 15% from individual NHS (national insurance) contributions. The remainder comes from charges to patients, e. g. part of the costs of adult dental treatment and drugs. Most young and middle aged adults pay about £4 towards the cost of each
prescribed drug. Patients suffering from diseases such as diabetes and hypothyroidism are exempt. The fact that this does not apply to young adults with CF unless they also have diabetes caused much annoyance to the CF-patients interviewed. The state covers most of their medical costs, except for some items of equipment such as nebulisers.

The Structure of the NHS in England (Figure 1, at the end)²

Apart from the homeless in inner cities, nearly everybody is registered with a general practitioner (GP) and around 30 000 GPs cover the UK. A patient may consult the GP for anything they consider relevant. The GP is also known as the "Family Doctor" as entire nuclear families are encouraged to register with one practice. Not infrequently, more than one member of a family are included in a single consultation. Many individuals are registered with the same practice for several decades, though a significant proportion of the population living in an inner city frequently change their address. The GP acts as the ‘gate keeper’ for hospitals, referring people when appropriate: however, there is also access to the secondary care system via the accident and emergency departments of the larger hospitals. The structure of general practice is very variable, but in 1986 50% of family practitioners were working in groups of 3 or more, many as part of a "primary care team” including administrative staff, practice nurses, health visitors (who specialise in surveillance and the prevention of illness in young families), district nurses and sometimes midwives. In the future many practice teams will include specialist nurses and counsellors. An age/sex register is an essential tool for enabling the practice to provide such services. At present, many general practices have either a manual or computerised age/sex register, and there many others working towards it. It contains the name, sex and age of each patient, their address, and the date on which they registered with the practice. The register is used as a data-base for screening procedures, and also as an aide-memoir, e.g. for ensuring immunisation of all the babies registered with the practice. A rapidly increasing number of practices have computers to hold the age/sex register, store details of patients’ medical histories, and issue recall reminders. They will eventually be linked with (a) the local hospital computer for results of investigations (b) the screening and immunisation records of Health Authorities and (c) the Family Health Service Authorities (FHSAs), so that they can gather local health statistics. When fully established, this system will be ideal for storing results of genetic screening tests. The NHS is in the midst of the most radical reorganisation since its inception in 1948. This began 2 years ago. The fundamental concept at the heart of the changes is that of the ‘internal market’. Medical care will still, with a few exemptions, be free at the point of use. Formerly regions and districts were given money that was supposed to cover the services they currently provided. This was often insufficient
as the NHS, like other public services, is cost limited and under-funded. That basis is gradually changing, and in future a District’s funding will depend on the size of its population adjusted for certain demographic and social factors. There is now a division between the ‘purchasing’ and ‘providing’ role of the NHS. A few services are still provided by the regions but generally the DHAs are given money by the regions to purchase health services on behalf of their population. The hospitals and some community services are the ‘providers’ and compete to get ‘contracts’ from the DHA, and some large general practices, to provide services. If they cannot get the contract they will have to cease to provide that particular portion of medical care. One reason for a hospital not being awarded a contract is that it charges too much for the services it provides. Costs in London are about 20% higher than in other parts of the country; thus some of the larger teaching hospitals are losing business to cheaper units outside the capital. The aim of the changes is to make the NHS more efficient and improve quality by introducing competition. The danger is that health care will become fragmented by being provided by a large number of competing units. Also DHAs will consider some services as too expensive to purchase. Many of the people interviewed were concerned that services for people with genetic diseases would fall into this category because the conditions are individually rare, and the cost of treating affected individual high. Until recently hospital consultants were a more powerful and prestigious part of the medical establishment than GPs. That is gradually changing. GPs are closer to the "consumers" than are hospital doctors, and their patterns of referral for secondary care have a profound influence on which services are bought from which hospital. Their opinion is being sort, and they are being wooed by other sections of the health service in an unprecedented manner.

The Organisation of Genetic Services in the UK\(^3\)

The organisation of the genetic services in the United Kingdom is basically satisfactory. Clinical genetics is a hospital speciality closely associated with academic units, but with little extension into the community. It is based on the 14 regions in England that each serve 2-5 mill. people. There is at least one consultant geneticist in each of 13 regions and in general when specialist genetic counselling is needed it is available; however, there are gaps in certain parts of the country. The Clinical Genetics Society and the Royal College of Physicians’ recommendation that there should be two consultants per million would require an extra 77 consultant geneticist posts (RH). Two of the main features of the service are, firstly, that the work is done by a team, in which genetic nurses and social workers collaborate with the clinicians; secondly the clinical and laboratory side work closely together.
What will be the main effect of the NHS changes on genetic services?

Many of the interviewees were concerned that the changes would have a detrimental effect by reducing and fragmenting the service. Though the governmental documents on which the changes are based highlight the importance of preventive care they do not mention genetics (RH). There is no certainty that genetic services will continue to be organised as a collaborative grouping within each region. Already in a few areas the responsibility for purchasing genetic services has been devolved to the 14 or so districts in the region. A major market component is being introduced, and the anxiety is that the managers in the District Health Authorities or large general practices who are responsible for buying health care from hospitals, will not judge genetics to be a priority. There was an anxiety that this would apply particularly to rare disorders, which are often expensive to treat. There are fears that CF care might be affected as there are only about 30 affected individuals in each District (≥ 6 000 patients with CF in the UK). Concerns were expressed that some genetic centres would close because they would not secure enough ”contracts” to be financially viable. If the NHS does not continue to provide a comprehensive service private laboratories will pick up the lucrative diagnostic work, but they will not provide essential counselling, interpretation of results or training for health care workers. There may be central direction from the Department of Health with memoranda to Districts setting out the importance of, and need for, genetic services. This may lead to these services being purchased on behalf of the local population. Geneticists, like GPs, look after families whose members are likely to live in several different districts. Services for their care and surveillance need to be organised at a regional level. The adult CF-patients interviewed were generally positive about NHS treatment they had received, but all four were fearful that it would deteriorate as a result of the reorganisation. The present situation is very uncertain, with providers of genetic services competing with other specialities for limited resources at a time of economic decline. It is unlikely to be clarified in the near future.

Diagnosis and Management of CF

CF patients are usually cared for by paediatricians until their mid-teens when responsibility for their management is transferred to an adult physician, often a specialist in respiratory diseases. Individual physicians have considerable autonomy in the management of patients. There are no national guidelines which have to be applied. There was general support for specialised CF-units (RW, KW, L-C), though they do not all provide an equally high standard of care. Some interviewees felt that care could be shared with the local district general hospital and the general practitioner if he was interested and knowledgeable. The annual costs of treating an
adult patient is very variable. It was an average of £8 241 in 1989-90 in one unit at Monsall Hospital in Manchester\(^4\). The cost of drugs accounted for 57% of this. However, patients who were given intravenous antibiotics on the ward every three months, cost about £13 501-£5 000 more than the average.

**The Role of the Voluntary Organisations**

The people interviewed considered that voluntary organisations are a crucial element in the present and future management of CF in the UK. They are an essential source of social and psychological support for patients and their families. They provide members with up-to-date information about advances in treatment and the state financial benefits that can be claimed. They have an important role in educating the general public, health professionals and the government about CF. It was recognised that tension could arise within an organisation over apparently conflicting obligations namely to represent the interests of its members, and to put forward an objective view on a proposal- for example, the pros and cons of screening.

The CF Research Trust is a main voluntary organisation for CF in the UK. It increases public awareness, raises money and funds research into the disease. For example, it has provided most of the funds (£600 000) for the projects evaluating CF-carrier screening. The Trust also finances some of the care within the NHS. Whilst this is recognised as essential to keep some of the services going (RH, MG), there is unease in case this funding should be used as an excuse not to provide, for example, NHS salaries for essential personnel such as physiotherapists and specialist nurses. Concern was also expressed, firstly that the CF Trust was committed to expenditure on services that it could not sustain, and secondly that financing posts that are the responsibility of the NHS would diminish the Trust's ability to fund research. The Genetic Interest Group has a particularly important role for families of patients with rare diseases, who otherwise would feel isolated, with nobody to represent them (L-C).
Screening for Carriers of CF

Introduction

The carrier frequency of CF is about 4.3% in the United Kingdom. This means that about 1 in 550 couples have a 1 in 4 risk of producing an affected child in each pregnancy. After the cloning of the CF-gene in 1989 it became possible to detect the commonest mutations by simple DNA methods. In the UK this means that about 85% of carriers can be easily identified from a mouth wash. ΔF508 accounts for 72-75% in different parts of the country. Watson et al. 1992 suggest that 75-80% of CF-alleles are the ΔF508 mutation. G551D and G542X are the next most common, each accounting for about 5% of mutations (DB). The main objective of screening for carriers of a recessively inherent disease is to identify carrier couples, and inform them of their risk of having an affected child so that they can avoid this if they so wish. There is general acceptance of PD in the UK and this was reflected in the views of the interviewees. With the exception of two of the adult CF-patients none was against termination of pregnancy for CF in principle. This may be less acceptable in the future as improved management leads to a better quality of life and extended life expectancy (MG).

The timing and setting for offering a new test need careful judgement. Apart from thalassaemia screening in parts of Southern Europe, carrier detection has usually been left until the ante natal period. Though screening at this stage is concentrated on couples most immediately at risk and is efficient, it has a number of disadvantages. By the time both members of a couple are found to be carriers, it may be too late for PD in the presenting pregnancy - or at least in the first trimester. Some couples find the prospect of a second trimester termination unacceptable. Identification of a serious genetic risk in pregnancy forces couples to make important decisions quickly and it can be difficult to make a cool, objective assessment. Also ante natal screening reinforces the erroneous belief that only women are likely to have genetic problems. However, it is an efficient approach to screening. Population screening before pregnancy resolves these problems but creates new ones, even if it is restricted to people of reproductive age. It aims to identify potential abnormalities in people who often consider themselves fit and well, so theoretically might damage a person’s healthy self image, and lead to a fear of stigmatisation. Population screening before pregnancy is unlikely to be systematic as many individuals (particularly those without partners) will not bother to be tested because they perceive testing as irrelevant at that particular stage of their lives. In addition others, especially if they screened “negative”, may forget their result by the time it becomes relevant to themselves.
An 85% detection of CF-mutations means that the overt carrier frequency is reduced to 3.6% of the general population, leading to the detection of, on average, one carrier for every 28 people tested. Also, one would need to test 28 partners of carriers in order to identify an ‘at risk’ couple. The carrier rate is lower in most ethnic minorities and many carriers will not have partners. Thus it is likely that over 1 000 people of reproductive age would have to be tested to identify a vulnerable couple. By contrast Mennie et al 1992 reported that one carrier couple was found for approximately every 800 pregnant women tested.

The usual follow up when a genetic abnormality is found is to do family studies to find and counsel other carriers (“cascade screening”). Parents, sibling and offspring of a carrier have a 1 in 2 chance of also being carriers. If the parent who carries the CF-gene can be identified that indicates the side of the extended family where the mutated gene would be found. If screening is to be carried out in the community, the organisation of general practice in the United Kingdom seems ideal for this type of family study. Neonatal screening is another possibility and will be a tempting prospect to health authorities, as dried blood spots are already collected from all new-born infants. However, there will be a number of problems if this is used as the main CF-screening strategy for identifying families at risk of CF. It could lead to timely identification of only 1/2 parents "at risk", as 1 in 4 of their children will not be carriers and a quarter will have the disease. The parents of affected children are likely to be particularly upset because they where not discovered to be carriers in time to be offered PD.

Genetic screening raises ethical questions apart from those associated with abortion, the one that currently gives rise to concern is a proposal for "efficient” CF-carrier screening that has won some professional support in the UK (though not from the people I interviewed)6. This approach, which has been piloted in some places, was proposed in order to limit costs, especially those associated with counselling of single carriers, whilst still identifying as many “at risk” couples as possible. For this system of "couple screening":- 1. Pregnant women are informed of the availability of testing and asked to provide mouthwash samples from themselves and their partner. The test is done only if both partners provide a sample. 2. Only couples where both are shown to be carriers are considered as "screened positive", since only they can be offered PD. All others are considered as "screened negative" and informed accordingly. 3. The counselling required for the few at-risk couples detected is absorbed into the existing genetic counselling service.

With this strategy, costs are limited almost to those of laboratory testing; there is no need for a public education campaign, or training health workers in counselling carriers. However, in denying the right of each member of the couple to full information about their carrier status, it treats two people as if they were one. This
means, for example that cascade screening will not be an option for couples who
‘screen negative’ though one member is in fact a carrier (RH).

Screening for carriers of CF - views of people interviewed

There was a consensus amongst the people interviewed that screening should be
offered to the partners and relatives of families where one of its members had CF.
There was more disagreement about the desirability of general population screening.
The views ranged from the enthusiastic (RW) to the very cautious (AC, YP). Many
of the people interviewed were reserving judgement until the results of the trials had
been published. One concern expressed was that if people are tested immediately
after pre-test counselling they will not have had time for a considered decision
whether they wish to be screened or not. The next section summarises the views of
the people interviewed, on desirability, timing and place of CF-screening.

Martin Bobrow: The country as a whole is agnostic about genetic screening and it
is important to get it right. Other recessively inherited conditions may get tagged
onto a CF-screening program. At the moment the test only identifies about 85% of
carriers. It is important but time consuming to convey that information to people be-
fore they are tested. Antenatal screening is efficient, but there must be a system
which ensures that people who do not want to be screened can opt out. Primary care
would be my preferred place of screening, if it proved feasible. I am quite relaxed
about screening older school children as long as it is associated with proper teaching
of biology. However, in 10 years time CF-screening is likely to be very patchy.

David Brock: The case has been made from the trial projects that screening is
acceptable and can be made to work. I am in favour of the ‘backstop’ (antenatal)
first approach. However, when we have reasonable coverage from antenatal clinics
we should screen from primary care, so that one day the majority of women will
come to the antenatal clinic having been screened. That would be the ideal
situation.

Adult CF-patients:
Dave: I would like to see genetic screening available to all people for all genetic
disorders that can be tested for. It would be common sense to have screening
available for a couple thinking of having children.
Mark: They should first try and screen the relatives of a CF-person. There should
be a follow-up scheme of counselling for the identified carriers. You need to let
people know what they let themselves in for by having the test. There should be
literature available.
Louise: Screening should be available for relatives. If you are to have screening you need the counselling, you can't do that with the whole population. If a couple has been screened and found to be carriers, but still go ahead and have a baby, they should accept that child whether or not it has CF.

Pat: I think that the whole population should be screened for CF. Many people do not necessarily know they are carriers even though they are related to an affected person. You can't say it is right or wrong to have children with CF. People have different reasons for having, or not having children. You would not eradicate the disease even if genetic screening was available.

Angus Clarke: Our experience is that the average general practitioner does not have the time and funding to devote much effort to screening. Screening should be done on the basis of maximum information and appropriate counselling. There is a psychological cost in identifying healthy people as carriers. High quality population screening is not realistic.

Dr. Robert Dinwiddie: The optimum time for screening is before pregnancy, at family planning clinics or when giving pre-conception advice. That is the time when interest is most focussed on having a baby.

Hillary Harris: I feel that general practice is the best place to screen from. We know our patients and we can pitch our counselling at the right level. General practice is a very familiar setting for patients, and much less threatening than a hospital environment. In Manchester in the past year we have set up a pilot study in my own practice of 4500 patients. In the pre-pilot year of 1990 about 96% of pregnant women first consulted about their pregnancy before 14 weeks of pregnancy- average gestation time about 8 weeks. We then looked at the interval of time between the booking in general practice, and when they were seen in the ante natal clinic, a delay of about 4-6 weeks, often at the beginning of the second trimester. We have set up a study to carry out CF-carrier screening at the first diagnosis of pregnancy.

Rodney Harris: Most surveys show that people who see themselves at risk, because of a family history of CF, seize upon the offer to be screened. Indeed in our region, most people related to a definite case of CF will be offered screening. However, if you go out to the general population you find very mixed views because for most genetic disorders, the attitude to PD and termination of pregnancy is coloured by experience. If you have seen a close relative in misery and dying you are much more likely to be keen on genetic procedures. Thus the reaction of members of the general population without such experience depends upon their knowledge, understanding and education. To the clinical geneticists preventive medicine must always be secondary to giving people free individual choice. However, when you consider the
current life expectancy and quality of life of most people with CF one feels that preventive medicine has a lot to offer. The real aim of genetics is to find better means of treatment, but failing that population screening giving people the option of avoiding births of affected children must be a good thing.

**Ann Hunt:** What you can offer, and the uptake of screening depends a lot on the pool of knowledge and information in the community. People have a personal responsibility, in the same way as knowing about safe sex, to know their own genetic status. Most people would want to know, if they realised the implications. Theoretically one would want to offer screening before pregnancy, but it becomes more relevant when people get into a more long-term relationship. Midteens is a disastrous age to screen; there is too much going on emotionally. It should be offered antenatally if it has not been offered at an earlier stage.

**Ian Lister Cheese:** Policy development in this area will be guided by the results of evaluative pilot studies which are now being carried out. If the results of screening offer significant benefits, and in this instance this seems likely, then it is a development that we should consider for the NHS:

Perhaps ideally we should know our carrier status in respect of severely disabling disorders before contemplating reproduction.

On the other hand if one took the pragmatic view that couples most want to know their risks when a woman is pregnant, that might lead to approaches that are more feasible. There is already in place a system of antenatal care that could be used to organise the necessary investigations and counselling. I imagine that will be the obvious way forward. The practical advantages would be countered a bit by the adverse consequences of late diagnosis. But is might be something that could be done without a great deal of additional resources. Neonatal screening using Guthrie blood spots is another existing mechanism that might be used. Neonatal screening will be attractive to service providers because arrangements are already in place to collect blood specimens from all newborn infants. Where the results offer the prospect of a beneficial intervention to the child this should raise no difficulties: but detection of carrier states may carry no immediate benefit, and this raises ethical problems.

**Vivette Payne:** I do not think the pilot studies are answering questions on the psychological cost of screening in enough detail, because a much longer follow-up is needed. I am sceptical, that the present time, whether population screening will be put into practice in the short term. Further evaluation is also needed of educational and counselling issues.
Sandy Raeburn: We should start by looking for carriers in families of CF-patients. I have contacted 2 clinics with about 120 patients between them. I was surprised that under 30 relatives have been referred for screening. I suspect that organising cascade screening through local CF-groups would be successful. I am in favour of more education for teenagers in genetics. Testing could then be offered to the older adolescents. This should not be done at the same time as the educative session, otherwise the young people are likely to feel under peer pressure to be tested, and to divulge the result to the rest of the group.

Kevin Webb: I have no strong views. We screen siblings and partners of patients because they ask us to do so. We haven't had many problems, I presume that is because the partners tend not to be carriers. The demand from families for screening has not been as high as I would have thought. About 5 or 6 requests a year, out of our 120-130 patients. We don't push it; we don't say would you like your brothers and sisters screened?

Robert Williamson: Everyone aged 16-45 should be offered CF-screening through general practices. Autonomy should be respected and individuals rather than couples should be tested. A small amount of counselling, possibly by practice nurses is required before screening. If there were systematic cascade screening you would perhaps have to initially test 40% of the population to then go on to identify 90% of carriers in the population by studying their relatives. We asked for the views on screening of 250 parents and close relatives of CF-children. They all favoured screening being freely available, about 70% would consider termination of an affected pregnancy, and 30% would not.

Audit of Screening Programs

Most people interviewed felt that the desired outcome was an informed population, made up of individuals who where free to decide whether to be screened or not. It will be important to assess whether the minimum amount of essential information has been absorbed- a) that carriers are healthy, b) there are reproductive implications only if your partner is also a carrier; and c) there are false negatives. The proportion of a population who take up an offer of screening is relevant, especially when programs in different parts of the country are compared. Carriers should be aware of the implications and be free to choose from a range of reproductive options. The number of birth of babies with CF may fall following screening, but that would be a measure of population coverage, not of the quality of the screening program (L-C). However, realistically, if in an area where there had been intensive screening for over 10 years there was no fall in birth of CF-children, people would ask if screening had been worth the effort. In other words, a national screening program
might be accompanied by subtle pressures to terminate an affected pregnancy in order to save NHS resources (MB). Fears were expressed that if parents succumbed to such pressure, they could very much regret their decision in future years, when the treatment and prognosis of CF had significantly improved. A confidential enquiry into counselling for genetic disorders was set-up by the Royal College of Physicians of London, with support from the Department of Health in February 1992. Rodney Harris is the chairman. The steering committee made up of eminent people in the field, selected 7 disorders including some where PD is important, and others like adult cancers where early diagnosis can reasonably be expected to lead to better treatment and life expectancy. The aim of the enquiry is to ascertain whether the needs of patients, who suffer from genetic disorders, and their families, are being met. For each disease they have selected a number of rare events. In the case of thalassaemia, all births of children with the disease since 1986 are ascertained, and the circumstances surrounding the birth identified. For CF, they are looking at families where a second child with the disease has been born. A confidential questionnaire is sent to the consultant involved, who is asked to examine the records of the patient to assess whether the parents were adequately counselled after the birth of the first affected child. The aim is to ascertain whether the second affected child was born as a consequence of an informed choice or not. It is hoped that, following the Enquiry’s report, there will be an improvement in the quality of care of these patients.

Counselling

There was agreement that, until we have an informed population, detailed pre-test counselling is desirable. This is usually possible at the present time with the existing research studies, but face to face pre-test counselling of relatives of known carriers is difficult if they live in a part of the country where there is no easy access to genetic services. These people have to be satisfied with written information passed on, plus perhaps a talk from the relative who was originally tested. In addition, they may only come forward to be screened some time after they have received the invitation- when they perceive testing as relevant to themselves. There was agreement also that, if screening becomes more widespread, it would be unrealistic for newly identified carriers to be counselled by the staff of a clinical genetics unit. Most felt that the appropriate counsellor would be a member of the primary care team (perhaps a nurse or health visitor rather than the GP): or a midwife if screening took place in the ante natal clinic. A leaflet giving information is essential. Ideally this should be sent to the individual to study before the counselling session. Counselling ‘at risk’ couples is more complex and generally should be done by someone who could give an objective picture of what it means to suffer from CF. However, in David Brock’s study these couples were counselled by
the consultant obstetrician, who then decided whether to refer the couple to someone else or not.

**Pilot Studies of Screening for CF in the UK**

All new screening procedures need careful evaluation. The CF Research Trust funded three projects to evaluate the practicality and acceptability of screening for carriers of CF from ante natal clinics, family planning clinics and general practices. Another study of screening from primary care was funded by one of the London Regional Health Authorities and the Medical Research Council (RW). Below is a summary of 3 of the 4 projects. Professor Peter Harper’s study of screening in Cardiff general practices and ante natal clinics has not yet been completed. In all the studies mouthwash samples were tested for the 4-6 commonest mutations.

**Prenatal Screening for CF**

4 348 pregnant women attending an Edinburgh maternity hospital were offered screening. They were first given a leaflet that described the project and emphasised that a negative test reduces, but does not eliminate the risk of an affected child. Women were asked if they had read the leaflet and wished to join the trial by the midwife responsible for booking. Those who did not understand the project were counselled by a genetics nurse who also counselled the carriers detected. PD was discussed with at risk couples by a consultant obstetrician.

All women in the trial were asked to complete a 12 item general health questionnaire before the test. Carriers completed one at the time they were given their test result, at the time of their partner’s test result and 6 weeks later.

All 4 at risk couples opted for PD. There was one affected fetus; that pregnancy was terminated. As one would expect there was evidence of some increase in stress when carriers got their result which disappeared when the partners result was negative.
**Delivery of Prenatal Screening:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women offered screening</td>
<td>4,348</td>
</tr>
<tr>
<td>Declined offer (most against termination)</td>
<td>609 (14%)</td>
</tr>
<tr>
<td>Not eligible (&gt;18 weeks gestation-430; abnormal pregnancy, usually blighted ovum-73; partner not available-56)</td>
<td>574 (13%)</td>
</tr>
<tr>
<td>Total screened</td>
<td>3,165 (73%)</td>
</tr>
<tr>
<td>No. of carriers</td>
<td>111 (3.5%)</td>
</tr>
<tr>
<td>Partners screened</td>
<td>110</td>
</tr>
<tr>
<td>At risk couples identified</td>
<td>4</td>
</tr>
</tbody>
</table>

**Comment**

Though 84% of eligible women agreed to the testing the actual screening rate was 73%. A 73% screening rate, coupled with a detection rate of 85% of CF-alleles in the UK, means that one would expect to identify around 53% of carriers (0.73x0.85x0.85). If a test for the CF-gene became part of the routine prenatal service, would this increase the uptake rate? If so, would this be because of inadequate counselling? Who should counsel at risk couples identified during the antenatal period? Will obstetricians know enough about the clinical picture of CF to offer nondirective counselling?

**Screening for Carriers of CF through Primary Care Services**

The initial paper reported on carrier testing of about 1,000 people attending two general practices and four family planning clinics in South Eastern England. Individuals aged 16-44 were approached when they attended the practice or clinic for a consultation. Before the test each possible participant was given a leaflet describing the project and was spoken to by the researcher. She described the range of severity of CF, mentioning the increasing life expectancy. The uptake of screening was 66% in general practice and 87% in family planning clinics. By 1992, 3,176 participants had been tested and 100 carriers identified. The effect of screening ‘positive’ was assessed by means of questionnaires completed pre-test, after notification of the result, 2 weeks after post-result counselling and 6 months later. These contained the Spielberger state/trait anxiety inventory.
Response to a Positive Result:

<table>
<thead>
<tr>
<th></th>
<th>Initial (n=88)</th>
<th>2 weeks (n=88)</th>
<th>6 months (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surprised</td>
<td>67%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slightly anxious</td>
<td>25%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Worried</td>
<td>22%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Not worried</td>
<td>32%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Less worried</td>
<td></td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td></td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>More worried</td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Depressed</td>
<td>7%</td>
<td></td>
<td>1.5%</td>
</tr>
<tr>
<td>Indifferent</td>
<td>8%</td>
<td></td>
<td>15%</td>
</tr>
</tbody>
</table>

**Comment**

The authors conclude that post-test counselling of carriers is essential and helps to allay initial anxiety. There did not appear to be adverse psychological effects after screening. Two thirds of carriers would consider PD, and one third termination of an affected pregnancy. However, there were a lot of ‘don’t knows’. Observing carrier couples’ actual behaviour in pregnancy will produce more valid answers to these questions than asking hypothetical questions.

**Evaluation of Different Methods of Screening for Carriers of CF in a Primary Care setting**

Carrier testing by mouth-wash was offered in seven different ways to the 5 529 individuals aged 18-45 registered with an inner London general practice, and also to close relatives of the identified carriers. The names, addresses and dates of birth of patients aged 18-45 were identified from the practice’s age/sex register. All staff members of the practice received training sessions on the incidence and symptoms of the disease, the carrier frequency, and the implications of being a carrier and given a brief outline of the study design. Two booklets were produced, a) the ‘screening booklet’ outlined the project, and explained why it was important to know one's carrier status when thinking of having children. It emphasised that being a carrier does not affect one's health and that the test could identify only 85% of carriers. b) The booklet for identified carriers explained the reproductive risks, and invited the individual to arrange for his/her partner to be tested. Three questionnaires were also produced to ascertain peoples’ reaction to being tested and receiving the result, their knowledge of the genetics of CF and their perception of their state of health. The first was administered just before the test was carried out.
and the second shortly after the result had been received. The third, was completed three months later, and included questions on reproductive plans.

Types of Approach

Letter-(Beginning)

In February 1991, 1,000 names of people of the selected age group were randomly selected and divided into two groups of 500. The first group were sent only a letter of invitation to be screened. The second group were sent the same letter and in addition the screening booklet.

Two weeks after the letters were sent, opportunistic screening began.

Passive Opportunistic

Patients aged 18-45 were given the screening booklet by a receptionist when they came into the health centre with an appointment to see their GP. They were told that if, after reading the booklet, they wanted more information or wished to be screened, a member of the research team was on hand.

Active Opportunistic

Patients were approached directly by a member of the research team as they reported to the reception desk. They were handed a booklet and told briefly what it meant to be a carrier of the CF-gene. On most occasions screening was available while they waited to see their GP, but sometimes they were told they would have to come back another day.

Letter-End

The same letter of invitation as in letter 1991 (but not booklet), was sent to all 2,953 patients on the data base who had not been previously approached in other ways. The group who received the 1992 letter included all those who had not been to the practice since the onset of the study. It was therefore, likely to contain a large number of people who attended the surgery reluctantly or who had moved away, but were still on the practice register.
All patients who requested screening completed the first questionnaire and were then seen by the research nurse. She spent on average ten minutes with each person discussing the test and the implications of the result. A mouth-wash was collected using a 4% sucrose solution. This was analysed for 5 mutations (ΔF508, G551D, G542X, 621+1G and W1282X). The result was received usually about three weeks after the test. Letters, which clearly stated that the test could not identify all carriers were sent to the participants together with the second questionnaire. In addition carriers received the carrier booklet and an appointment for further counselling. They were invited to bring their partner and/or other family members to be screened.

Results

28 carriers were identified in the main study (2.9%), 9 male and 19 female. Though there was an initial increase in anxiety when they received their result, this had largely dissipated 3 months later.

Following table shows the uptake rate for each method of approach.

<table>
<thead>
<tr>
<th>Method of Approach</th>
<th>No. approach</th>
<th>Screened no. uptake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter-beginning</td>
<td>502</td>
<td>59 (12)</td>
</tr>
<tr>
<td>Letter + booklet</td>
<td>496</td>
<td>47 ( 9)</td>
</tr>
<tr>
<td>Letter-end</td>
<td>2953</td>
<td>128 ( 4)</td>
</tr>
<tr>
<td>Passive opportunistic</td>
<td>471</td>
<td>81 (17)</td>
</tr>
<tr>
<td>Active opportunistic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- test now</td>
<td>649</td>
<td>453 (70)</td>
</tr>
<tr>
<td>Active opportunistic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- return visit</td>
<td>88</td>
<td>22 (25)</td>
</tr>
</tbody>
</table>

In addition a GP, health visitor or practice nurse invited 179 patients to be screened when they came to register with the practice or during selected consultations i.e. reported a pregnancy to the GP; attended the practice ante natal clinic before 14 weeks gestation (11/13 screened); consulted the practice nurse or GP for contraceptive advice, preconception care or cervical smears; attended the child health clinic. 76 (42%) were screened but the health professional often did not offer screening when relevant and the research team could not identify all the eligible patients in this group. A further 191 patients were invited by other approaches.

637/2 772 (23%) women and 320/2 428 (12%) men accepted the offer of screening. Thus about twice as many women as men requested the test except where they had
been actively approached by a research worker, when men seemed slightly more inclined to come forward. There was strong self selection by educational level: About half of those tested had a postgraduate degree or some sort of professional training. This was much higher than the average for the practice population, 80% live in localities where there is a high level of social deprivation. 641 (69%) of the 927 people who received a negative result, returned their third questionnaire. In spite of the booklet and pre-test counselling, 17% thought that a negative result meant that they were definitely not a carrier.

By the end of the study screening had been offered to the partners and/or other family members of the carriers. 15 had partners, and 11 of these were tested - no carrier couples were detected. 14 first degree relatives were screened and 5 carriers were detected. The numbers are small but this is a much higher percentage than the 2.9% carriers found in the total group screened. During the study the research nurse was approached by an individual had a family history of CF and was registered with the other practice in the health centre. She asked if other members of her family could be tested. 20 were tested and 6 carriers were identified, including one carrier couple.

**CF-Carrier Screening at First Diagnosis of Pregnancy in General Practice**

Dr. H. Harris (preliminary results, personal communication) 6 practices with a registered population of 36 000 have been recruited so far. After four months 74% of women attending their booking appointment had been tested (120/162). At least 10 women were not tested because they booked after 14 weeks gestation, which means that at least 79% of those eligible were screened. So far 1 carrier couple have been identified. They had no family history of CF. They chose PD by chorionic villus sampling and the fetus was normal.

This study is addressing the question of whether there should be a gap between counselling and testing to give patients time to reflect on whether they wish to take a test or not.

**Discussion of the Study and Conclusion**

About 70% of individuals who are actively recruited for screening in antenatal clinics or the community agreed to be tested. The percentage is somewhat higher from family planning clinics. In general practice the uptake rate was below 26% unless the test was actively "sold" to patients, and was immediately available or women were approached at the practice/antenatal clinic. We do not know whether
pregnant women would respond more enthusiastically than patients visiting the GP, to just receiving a letter or being handed a leaflet. It is likely that they would be more positive as they would perceive the test as relevant to their particular situation. As mentioned before, many of the people interviewed stressed the importance of pre-test counselling and post-test counselling of carriers. This will be necessary until there is an informed population that does not need it. Such a labour intensive approach to genetic screening is feasible, (a) in ante natal clinics where CF-testing is offered as part of a screening ‘package’ by a midwife counsellor, (b) as part of a research project, or (c) if relatively small numbers of the general population are screened. It is likely that, at the moment in the UK, there is a relatively low level of awareness of CF and the reproductive implications of carrying the gene. Genetic screening of the general population is not practicable and even elective national screening needs to be preceded by a prolonged campaign by the DoH and relevant voluntary organisations such as the CF Research Trust, to increase public awareness of CF and the possibility of its prevention. This will need to involve the media and to include a program for teaching more basic genetics to teenagers in school. This could be focused on conditions that might be later relevant to the young people. The importance of education was stressed several times in the interviews (L-C, SR). Health professionals will require further training at an early stage, i.e. at the undergraduate level; as large numbers of carriers will eventually be identified who will need counselling, often in primary care (RW). The production of high quality simply written information to hand out before screening and to give to carriers is essential. Some form of population screening is likely to be considered for other disorders such as the Fragile X Syndrome in the near future. As we live in a multi-ethnic society any genetic screening should include testing for carriers of haemoglobin disorders and Tay-Sachs disease, common amongst specific ethnic minorities. It will take many years for comprehensive CF-carrier screening to be established in the UK. The recent NHS reforms will add to the difficulties. Initially, as with the early phases of other screening programs, it is likely that enthusiastic individuals will intensively screen in districts dotted around the country. In the early years at least, screening could be organised from several settings. Though ante natal screening will be the most popular, because it is relatively efficient and the structure for collecting specimens is already in place, other sites will include some general practices and health authority family planning clinics. Auditing a new service is essential. The temptation could be to audit purely in terms of number of people tested, or reduction in number of children born with CF as these outcomes are relatively easy to measure. A more valid measure will be the number of ”at risk” couples identified in good time for them to decide what to do when expecting a child. The London and Edinburgh projects are being followed up by an economic appraisal of alternative approaches to screening. However, it will be difficult to extrapolate from the present situation to a future when on the one hand DNA analysis is almost certain to be cheaper, but on the other there may be a request for a
financial contribution from the laboratories using gene technology towards the patent of the gene sequence.

The Role of General Practice in CF-Screening

Unless and until there is an informed population and an established national screening program akin to those for childhood immunisations and cervical smears, including financial inducements to practices, it is unrealistic to expect blanket coverage of the population from general practices. However, practice screening is initially most likely to be offered when it is perceived as directly relevant both by the primary care worker and the person being screened; the most important being when a pregnancy is first reported to the GP. This occurs on average 4 weeks before attendance at the hospital ante natal clinic (HH). Other opportunities for screening are when an individual attends for preconception or family planning advice. Screening may eventually be included as part of the statutory examination of an individual that is offered when an individual registers with a new GP. The figures from the London study confirm, albeit with small numbers, that screening families of known carriers is an efficient method of finding other heterozygotes. 'Cascade' screening will be a vital part of a practice's genetic screening program and the GP must be informed about all carriers, including those identified in ante natal clinics. Some practices already have their records arranged in family groups rather than in alphabetical order. Because of the issue of confidentiality, partners and other members of a family can only be approached via the individual who was discovered to be a carrier. This may create some administrative problems; for example it is likely that some relatives will be registered at a different practice. Another problem mentioned before, is that it will be difficult to offer pre- and post-test counselling to relatives who live in parts of the country where there is no screening program. A short video may be useful in this situation (RW). Even if the appropriate literature is available, explaining genetic concepts to individuals is not easy and is time consuming. Whilst all members of a primary care team who come into contact with potential parents should be able to give basic genetic information, it may be helpful for the larger practices to arrange for one member, perhaps a practice nurse or community midwife or health visitor to get extra training in basic genetic counselling. He/she will then be able to accept intra-practice referrals. Practices will also be involved in identifying relatives of carriers detected elsewhere.
In Conclusion

The prognosis of CF is getting better, but it is unlikely that, in the foreseeable future, the management will improve sufficiently to invalidate a preventative approach to the disease. Also carrier testing is now available, relatively simple and as with other medical advances, gradually more and more people are going to demand it. However, the introduction of screening for carriers will be complicated and needs careful preparation. The population is as yet relatively uninformed, and that means it is difficult to assess whether they wish to be tested or not. Not all CF-mutations can be identified, and further long term studies are needed to discover whether people who have been tested remember the full implication of a positive or negative result. Another important question is whether fully informed carriers use the information to extend the reproductive options. At the present time we are not sure enough of the effects of screening to encourage testing of school age children or individuals in their place of work. With these provisos our attitude should be positive and my guess is that, within the next 10 or 15 years, national genetic screening will become established in the UK, with testing targeted at times that the individual (and health professional) will perceive as relevant to their live situation. However, it is unlikely that pre-test counselling will be as comprehensive as those working in the field would wish.
STRUCTURE OF THE NHS IN ENGLAND

SECRETARY OF STATE FOR HEALTH
(Member of the Cabinet and responsible to Parliament)

DEPARTMENT OF HEALTH (DOH)
Includes junior ministers and over 5,000 civil servants. Makes policies, issues advice and guidance to health authorities and health professionals, allocates resources and monitors performance of the NHS

SPECIAL HEALTH AUTHORITIES
A few NHS services such as some London postgraduate hospitals

NHS TRUSTS
"Self governing units", mainly hospitals, steadily growing section of the NHS

14 REGIONAL HEALTH AUTHORITIES (RHA)
They cover the whole country, serving populations of 2-5 million people, allocates money to DHAs and FHSAs

189 DISTRICT HEALTH AUTHORITIES (DHA)
Serves Populations of 90,000 - 800,000. Several connected to each RHA. Manages hospitals that are not NHS Trusts

90 FAMILY HEALTH SERVICE AUTHORITIES (FHSA)
Manages the services provided by general practitioners (GPs) dentists, chemists and opticians. Pays these health professionals

27,000 GPs in England with an average of 1,900 patients each. Many work in groups of 3-5 doctors which are part of a primary care team

The interest of the "consumer" are represented by COMMUNITY HEALTH COUNCILS, usually one to each DHA
References

6. Summary

I. Nippert

This report illustrates the development towards the introduction of CF-carrier screening into clinical practice in Denmark, Germany, the Netherlands, and the United Kingdom since the identification of CF-gene in 1989. In all these countries CF is the most common autosomal recessive disorder. The prevalence of ΔF508 mutation ranges from 73-88%.

In three countries, Denmark, Germany and the United Kingdom, immediate action was taken in late 1989 to get pilot studies started. In his report Hans Clausen quotes Marianne Schwartz: "Already before the localisation of the CF-gene we had decided to start carrier screening when the gene was found. So we were ready to begin when it happened" (p. 22) and N.J. Brandt: "The moment the gene was found, I said 'Now we must start a carrier screening program as soon as possible.'" (p. 22). In Britain, the CF-Trust pioneered and advertised in December 1989 in NATURE for researchers to request money for research grants and subsequently set up 3 pilot studies. In East Germany, a nation wide pilot program scheme was incorporated 1989 in the 5 years health plan of the Ministry of Health of the GDR for 1990-1995 (due to the unification that plan never materialised).

Between 1990-1991 at least 8-9 pilot studies were started: 1 in Denmark, 5-6 in the United Kingdom and 2 in Germany. 3 different target populations and 3 different kind of approaches are evaluated. There are 4 projects: 1 in Berlin-Buch, 1 in Copenhagen, 1 in Edinburgh and 1 in North England that approach pregnant women through ante natal clinics or the GP; there are 2 projects in London that are offering preconceptional CF-carrier screening to males and females of reproductive age through GPs and family planning clinics, 1 "couples" approach to carrier screening in London, couples are screened as a unit, individual carriers status is not addressed, 2 pilot projects offer CF-screening through departments of human genetics, in Edinburgh couples are approached in Göttingen CF-screening is offered to all patients of reproductive age regardless whether they are pregnant or not.

As far as data from the pilot studies were made available for this report they show an uptake of the offer to be screened by pregnant women of 99.8% (!) in East Germany, 80% in Denmark and 73% in the United Kingdom. The recruitment of individuals in general practice, family clinics or genetic counselling centres clearly show, that the uptake rates differ in relation to whether the test is actively offered "on the spot" or not. In London in general practice the uptake rate was below 26% unless the test was actively "sold" (M. Modell, p. 104), it then increased to 70%. In
Göttingen the uptake rate was 22.5% when offered directly during genetic counselling but decreased when people had to return or sent their blood samples in (15.5%). During 1990-1992 more than 15 000 persons have been screened in the four countries altogether. The majority of them being pregnant women in Denmark and the United Kingdom. 7 at risk pregnancies were detected: 3 in Copenhagen, 4 in Edinburgh, all couples underwent PD, 2 affected fetuses were found and aborted (H. Clausen, p. 20; M. Modell, p. 98).

It is interesting to know that the Danish and German pilot studies received no public or private funding. The expenses were/are paid by the Rigshospitalet, by the Max-Delbrück-Centrum für molekulare Medizin and by the department of human genetics in Göttingen. In Britain the CF-Trust is considered to be the “lead organisation in the United Kingdom investigation of carrier screening program” (Office of Technology Assessment, Cystic Fibrosis and DNA Test: Implications of Carrier Screening, Washington, p. 233, August 1992). From the pilot projects run in the UK, three are funded by CF-Trust, one by the Medical Research Council, the other programs are funded by other public or private resources. In the Netherlands no pilot program was started (P. Frets, p. 71) and the Netherlands is the only country of the four investigated, where no person at average risk has been screened so far for carrier status since the CF-gene was detected.

In all 4 countries CF-testing is offered to persons with a known family history of CF on a routine base.

The attitudes between the national CF-Associations differ. The German CF-Association was found to be the only one that opposes CF-carrier screening and its policy statement regarding CF-carrier screening is in striking contrast to those of the Danish CF-Association (p. 24-26) and of the British CF-Trust (the British CF-Trust's carrier screening policy guidelines are: "1. Primary purpose of CF-carrier screening is to provide reproductive options for high risk couples. Allied with this purpose is the expectation that there will be a possible reduction in birth prevalence. 2. Treatment prospects estimated for the next ten years are unlikely to invalidate the concept of carrier screening. 3. Immediate need to define priority groups. 4. Carrier screening is justified despite limited sensitivity. 5. Three groups should be excluded from screening: school age children and scholars, no shop front screening. 6. Two models of screening are acceptable.: ante natal screening of pregnant women and community screening preconceptional screening through the GP or through the family planning clinic.” M. Scott, representative of the British CF-trust, paper given at the study's workshop Copenhagen op.cit.).

The Dutch CF-Association has no official policy statement issued so far, but there seems to be a tendency to accept CF-carrier screening "but not at any price"
I. Nippert

According to H. Weggen, representative of the Dutch CF-Association (paper given at the study's workshop, Copenhagen op.cit.).

Because of the potential magnitude of providing CF-carrier screening to the whole population and its unknown implications there is disagreement found about the desirability of such a program among the key persons interviewed in all countries. It is interesting to compare the groups that voice restraint or opposition on an intra- and inter-country level. In Denmark (p. 26), Germany (p. 61) and the Netherlands (p. 75), those who strictly oppose CF-carrier screening, oppose it either because of the abortion issue related to it and/or because they feel that the proponents of the new technique are pushing and imposing their interests and values upon society, hardly allowing any time for reflection and discussion. The conflict between the Danish council of Ethics and the Scientific Ethical Committee (p. 28) clearly illustrates an ongoing social struggle about who should be involved first hand in the decision of implementing CF-carrier screening into prenatal care in Denmark and it touches in general fundamental issues of social control in the decision making process on how to implement the new genetics in society.

In the Dutch report P. Frets states: "one health policy maker felt that a public discussion was necessary to established whether a) CF-carrier screening is a priority health care issue and b) on the ways CF-carrier screening should be offered.” (p. 76).

Arguments among opponents and proponents in Denmark, Germany and the Netherlands reflect conflicting norms and values. One central conflict is which rights should have priority: Individual rights to be informed and to have access to the test versus society's right to control the implementation process and the access to such services. The proponents of CF-carrier screening stress its potential for providing information, allowing autonomous reproductive decision, giving people the option of avoiding the birth of affected children. Opponents argue that autonomous reproductive choices might be overridden by subtle social coercion and persuasion (i.e. biased information about the severity of the disease, s. p. 61) to use the test and to abort affected fetuses. It remains to be seen whether a more liberal or a more restrictive approach will gain recognition in the future in political decision making, especially in Denmark and the Netherlands where the implementation of CF-carrier screening would need government approval (s. H. Clausen, p. 39; P. Frets, p. 73). In Denmark (since the Danish pilot study was stopped in June 1992) CF-carrier screening is no longer available. Both the Danish and the Dutch report state, that there is no political climate to support CF-carrier screening. For Denmark this was commented by M. Mikkelsen at the study's workshop in Copenhagen: "There is absolutely no climate for screening in this country just now. No CF-screening, no triple test screening, no screening of the fetus by ultrasound. I don’t
think that we will have screening for CF in the near future. It might change with a change in government.” P. Frets reports for the Netherlands: “A majority was positive about the feasibility of CF-carrier screening in the remote future depending on the following factors: change in political climate in respect to the existing political resistance.” (p. 77).

There is a strikingly different situation to be found in the United Kingdom as compared to other countries regarding the political climate and social acceptance of running and funding CF-carrier screening programs to assess CF-screening implementation into the NHS. B. Modell, UK, commented at the workshop on the country reports: "My personal view is that the introduction of genetic screening on a population level actually represents a social change and these things take a long time to enter society. I think the reason for the difference between the UK and the other European countries is the fact that we had earlier experience of population screening for genetic risks simply because we had some more striking genetic risks.” (i.e. neural tube defects, haemoglobinopathies in ethnic minorities from Cyprus, India and West Africa).

In the UK, although “views on CF-carrier screening ranged from the enthusiastic to the more cautious” (M. Modell, p. 93), it is evident that there is consensus among health care providers, especially geneticists, that CF-carrier screening should be made available, and they are acting accordingly. Due to the different pilot program schemes and the different approaches that are evaluated, the United Kingdom probably will be the only country in the near future, that will have sufficient empirical data to base their decision upon on how to proceed. Although one must bear in mind that the NHS is in no way committed to take up the pilot programs, it seems "likely that enthusiastic individuals will intensively screen in districts dotted around the country” (M. Modell, p. 104), including different settings like antenatal clinics, general practice and health authority family planning clinics.

Although it is commonly agreed upon today that the major benefit of CF-carrier screening lies in providing more informed reproductive decision - the objective of lowering the prevalence of CF-births being disavowed by the majority of key persons interviewed - it might become difficult to defend the expenditures for screening programs if these programs would not avert a single case of CF (s. M. Modell, p. 97). A new science on how genetic service provision should be structured within the NHS, what standards of care should be adhered to, is being developed in the UK: Community Genetics (B. Modell, study's workshop Copenhagen op.cit.).
In the Netherlands CF-carrier screening has been met as compared to the other Northern European countries with remarkable restraint. By the end of 1992 neither the Dutch CF-Association nor the Dutch geneticists had made a public statement regarding their policies towards screening.

In Germany, where it is mainly up to the medical profession to decide whether CF-carrier screening will become available or not (no government decision needed), the majority of the key persons interviewed favour a “low key” approach, offering screening only to those who actively ask for it after extensive pre-test counselling. Implementing CF-carrier screening into prenatal care is opposed by the majority of health care providers in Germany in contrast to Denmark and the United Kingdom, where the idea of screening pregnant women is accepted.

The following key factors have been identified to influence the implementation and diffusion process of CF-carrier-screening in Northern Europe:

- **Policies** shaped by the medical geneticists’ professional and scientific organisations

- **”Innovative” geneticists** who actively promote CF-carrier-screening (to be found in: Denmark, Germany and the United Kingdom)

- **Policies of the CF-Associations** (to be found in Denmark, Germany and the United Kingdom)

- **Underlying health care infrastructure.** In countries with a relatively high degree of professional autonomy such as a Germany and the United Kingdom it is more likely that CF-carrier-screening will be first offered by individual efforts of “innovative” geneticists and not by decisions made by health politicians. Whereas in countries with considerable governmental control over health care delivery i. e. Denmark and the Netherlands, this control seems to somehow influence the speed of the implementation process, especially when the technology is debated controversially in the public. (Even when there are “innovative” geneticists to be found in these countries like in Denmark)

Consumers (except CF-associations) seem to have little influence on the implementation process.

Although feared by some key persons interviewed in this study, commercial interests and industry seem to play a surprisingly little role in promoting population based CF-carrier-screening - at least for the moment being.
In this study geneticists and CF-associations have been shown to take a leading role either in the introduction and implementation of CF-carrier-screening (especially in the United Kingdom) or in halting this process down (especially in Germany). However, the implementation process does not follow a simple pattern. Although there seems to be a correlation between the type of health care system and the speed of implementation, some of the emerging characteristics and attitudes towards CF-carrier-screening such as the abortion issue and fear of eugenics are more linked to cultural and historical traits of each country than to features of the health care system.

The issues most consensus was found upon in this study are:

1. CF-testing should be available for persons with known family history of CF.

2. Because the majority of the population is completely uninformed, pre-test and post-test carrier counselling is absolutely necessary to safeguard individual autonomy and choices.

3. No infrastructure available at the moment to ensure high quality genetic counselling to the wider population.

4. Professional education needed.

5. **It will take many years for (comprehensive) CF-carrier screening to be established.**

*I. Nippert, PhD*
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