Chapter 10

Cystic Fibrosis Carrier Screening in the United Kingdom

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Three pilot projects to explore the implications of population screening for cystic fibrosis (CF) carriers are under way in the United Kingdom, funded by the Cystic Fibrosis Research Trust (CF Trust), a private, nonprofit philanthropic organization. The goals of the programs, which began in 1990, are to identify the most appropriate populations for screening, evaluate various test protocols and techniques, arid understand the psychosocial consequences of carrier identification. In addition to pilot programs supported by the CF Trust, at least two other ongoing CF carrier screening pilots are supported by private and various research funds.

This chapter discusses the structure of CF carrier screening programs in the United Kingdom-the most extensive, comprehensive, and advanced pilots currently under way. It analyzes the strategies being used and reports on results recorded to date—both of which could bear on how CF carrier screening is approached in the United States, This chapter is based, in part, on interviews conducted by OTA during June 1991 visits with pilot project staff and staff of the Medical Research Council (MRC).

GENETIC SERVICES IN THE UNITED KINGDOM

Through the British National Health Service (NHS), all citizens receive medical care. Individuals self-assign themselves to a general practitioner (GP) within close geographic proximity. Private, for-pay medical care is also available to those willing and able to pay. Through the NHS, the British government informs GPs of new tests and medical practices, although some believe that such information does not always get communicated in a timely fashion (12). As in the United States, GPs are likely to learn about new developments in diagnosis and therapy through continuing education.

The British health care and legal systems have protected medical professionals from malpractice suits because there is no contingency fee arrangement as in the United States. Moreover, in general, patients can only sue for actual cost. Because health care is free, the actual costs are likely to be low.

In the United Kingdom, individuals are usually referred to a genetics unit by their GP, who is responsible for primary health care screening and prevention and is the usual means by which individuals are introduced to the need for genetic information. Family plarming and prenatal clinics are also sources of genetics information. Ideally, when a woman tests positive for pregnancy, she is booked with a hospital prenatal clinic for management of her pregnancy, where she may receive relevant genetic information. The provision of routine genetic counseling is increasingly offered through primary care. Unusual or difficult cases are referred to a genetics specialty unit.

Medical genetics is a rapidly developing specialty that has been widely introduced in the United Kingdom. Population screening and prenatal diagnosis have been available for groups at risk for Tay-Sachs disease and thalassemias. Genetics services routinely deliver neonatal screening for phenylketonuria and congenital hypothyroidism, maternal serum alpha-fetoprotein screening, and fetal karyotyping in women of advanced maternal age (12,18). A national network of regional genetic services exists but is currently threatened by recent governmental changes in the NHS (2,10,12).

Cystic *Fibrosis in the United Kingdom*

In Great Britain, about 300 babies a year are born with CF. The average annual cost of treating someone with CF is estimated to be £5,000 (20) to f 10,000 (6). The Caucasian population in South East England has undergone extensive genetic analysis for CF carrier status (8,9), and the frequency of the DF508 mutation in this part of England has been variously reported at a minimum of 70 percent in adult CF populations (21),71.5 percent (8,9), and 80 percent (27). In the Scottish population, DF508 represents about 71 percent of all CF mutations (15,22). (See app. A for international distribution of mutation frequencies.)

Buccal mouthwashes are increasingly used as the source of DNA for screening in the United Kingdom. The mouthwash technique is inexpensive and considered safe, and the DNA can be extracted rapidly and reliably in sufficient quantity for amplification by polymerase chain reaction (PCR; ch. 4). Welsh investigators have compared mouthwash, bucca1 scrapes, and finger pricks as the methods for sample

collection, and determined that the mouthwash is the most desirable in terms of patient acceptability, successful DNA extraction, and cost (12). Among pregnant women, blood-already being drawn for other diagnostic tests—is used rather than mouthwash.

With births numbering 700,000 annually, an estimated 1.4 million screening assays would have to be performed if all couples were screened prenatally. About 56,000 carriers would be detected from this cohort, requiring counseling and the option of prenatal diagnosis. The identification of 56,000 carriers annually would overwhelm the 157 full-time doctors and clinical coworkers in clinical genetics centers in the United Kingdom, excluding laboratory scientists (10). One survey of health professionals showed that approximately 75 percent of both GPs and family planning clinic staff thought that the introduction of CF carrier screening was appropriate; less than 10 percent opposed it (27).

In addition to staffing difficulties, it is widely acknowledged in Britain (as it is in the United States) that there are serious deficiencies in the teaching of clinical genetics in medical schools, which makes experts reluctant to rely on primary care doctors to provide genetics advice (13). In contrast to the United States, genetic counseling in Britain is most frequently offered by M.D. and Ph.D. clinicians. Counselors trained at the level of a master's degree are rare; nurses trained in genetics are more common. As a result, genetic services tend to be provided through highly specialized, highly trained individuals. A survey of health visitors (the U.K. equivalent of a U.S. visiting nurse) showed that while generic health visitors (i.e., those not working in genetics) had a reasonable knowledge of the more obvious aspects of genetic services, there were a number of areas about which they were unsure. Furthermore, they viewed their own knowledge of genetics as poor (7).

The Role of the Medical Research Council in Cystic Fibrosis Carrier Screening

The MRC is a public agency of the British Government. "The MRC has a long history of supporting research of direct relevance to health services, in addition to, and often built around, the biomedical and clinical research that forms the bulk of its work' (16). Much of the MRC's health services research is conducted by its units (comparable to the intramural programs of the U.S. National Institutes of Health). In 1981, the MRC established a Health Services Research Panel (HSRP) as an advisory body to the Council's Boards and Grants Committees. In 1986, the HSRP was reconstituted as a committee, the Health Services Research Committee (HSRC), with powers to promote the development of health services research and to make funding recommendations (16). In general, HSRC concentrates on: research into the effectiveness and efficiency of health services in implementing medical knowledge to improve health; and needs for which effective medical interventions exist or could be developed in the future. Design and delivery of health services is integral to the research interests of the HSRC; thus CF carrier screening projects fall squarely within its domain (24).

Involvement of the MRC with CF began in 1989 when it received outline proposals for CF carrier screening pilot studies. At the same time, the CF Trust invited applications for pilot studies. The outlines and the proposals funded by the CF Trust had a broad focus, whereas the MRC was interested in studies that would address the costs, benefits, disbenefits, and acceptability of screening programs. The MRC, therefore, convened a workshop for geneticists and social scientists to discuss the research questions raised by CF carrier screening (24). After the workshop, pilot proposals were considered. Based on the conclusions of the workshop, the MRC placed a high priority on studies to:

- evaluate the objectives of screening programs (e.g., identify carriers to reduce birth incidence, aid reproductive choice, or provide information);
- address the acceptability and participation rate of carrier screening for different target groups and in different settings;
- compare screened and nonscreened groups;
- clarify what information should be provided about carrier screening to the general public and to individuals or couples to whom screening might be offered, and evaluate ways of presenting that information;
- assess anxiety specific to carrier screening in addition to general anxiety levels;
- measure short- and long-term outcomes of carrier status identification;
- follow up couples at low risk who subsequently produce an affected child; and

- measure the costs of providing a screening program (17).

In addition to the preceding research issues, the MRC considers the cost-effectiveness of screening programs an important factor and encourages researchers to address this issue (24). This could prove difficult: Because of the way the NHS operates, cost accounting has always been elusive. Few providers of genetic services would likely document evidence of beneficial outcome, workload, or costs for each of the districts they serve and would have difficulty assigning a figure to the cost of tests.

The MRC currently supports two projects. A pilot study at St, Mary's Hospital Medical School will produce a videotape for CF carriers and monitor and evaluate the use of the videotape (£19,000). An evaluation of carrier screening for CF in couples at the Human Genetics Unit in Edinburgh also receives MRC funds (£97,000) (3,24). Some staff working on the pilot projects finded by the CF Trust also receive money through the ''Genetic Approach to Human Health" project. Through this project, the MRC aims to encourage more applications for studies of the health services research issues associated with carrier screening.

THE CYSTIC FIBROSIS RESEARCH TRUST PILOT PROGRAMS

The CF Trust, analogous to the Cystic Fibrosis Foundation in the United States, funds research related to improved diagnosis, understanding, and treatment of the disorder. The CF Trust has been the lead organization in the United Kingdom's investigation of carrier screening programs. Acknowledging the complexity of a national screening program, the CF Trust sought advice from an expert panel, the MRC, and the Department of Health before deciding to fund three pilot projects for evaluation of heterozy - gote screening. The three sites to receive funds were:

- University of Wales College of Medicine, Cardiff, Wales, for 3 years, f 197,540;
- University of Edinburgh, Western General Hospital, Edinburgh, Scotland, for 3 years, £197,540; and
- Guys Hospital, London, England, for 2 years, f 177,775.

In addition to performing their own tests, all three pilots are simultaneously using Cellmark Diagnostics' amplification refractory mutation system (ARMS) multiplex kit. The ARMS multiplex assays DF508, 621+1 G---›T, G551D, and G542X, with a sensitivity of 83 percent. Cellmark is not yet charging for the use of the kits because it has not yet been licensed to do so.

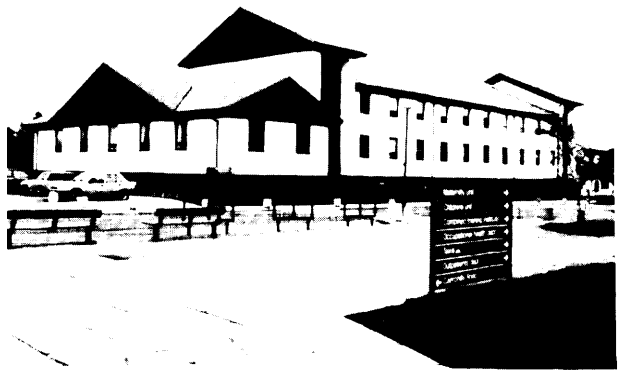


Photo credit: Peter Harper, University of Wales College of Medicine

Institute of Medical Genetics, University of Wales College of Medicine, Cardiff, Wales.

University Hospital of Wales, Cardiff, Wales

The 3-year pilot project under way at the Institute of Medical Genetics, University Hospital of Wales in Cardiff has the following aims:

- evaluate the attitudes of GPs and primary care staff to CF carrier screening;
- evaluate the feasibility of screening for CF carriers in general practices;
- evaluate clients' interest in and reactions to CF carrier screening;
- develop accurate, informative, and acceptable educational material for the public and health professionals; and
- consider the possibility of a pilot prenatal carrier screening project.

In addition to these clinical objectives, the Cardiff group has established an effective PCR multiplex system to test for the major CF mutations. The Institute of Medical Genetics of the University Hospital of Wales is not a basic CF research group, but a comprehensive genetics center. As a result, the clinic assumes the need for well-prepared GPs in order to make new screening programs work (1 1). Much of the first year of this pilot was spent evaluating attitudes about screening in urban and rural/industrial mining-town general practices. Al-

though geneticists view CF as a relatively common genetic disorder, GPs do not; the Cardiff pilot group did not want to mistakenly assume that GPs would give the necessary time to ensure a successful screening program. In addition, the pilot coordinator has been working with health professionals such as nurses and midwives to educate them about CF carrier screening and prepare them for questions that may arise.

Opportunistic screening refers to the practice of approaching individuals either in person or via brochure while they are waiting for appointments for other reasons at either their GP or family planning clinic. Screening is offered opportunistically to all individual adults between the ages of 16 and 45 who are registered with two general practices in Wales (each approximately 1,500 individuals). The Welsh plan for screening and followup of individuals is depicted in figure 10-1.

Prenatal screening is not offered at this time, but will be offered in 1993, the third year of the pilot. Known CF families have been contacted, and family testing has been completed for that group. Screening of couples is under consideration (box 1O-A). This project, if implemented, will offer CF carrier screening to all couples (but not individuals) in a separate general practice (approximately 1,000 individuals) who are in the reproductive age group and are planning a pregnancy (figure 10-2). The attitudes of participating couples will be evaluated. This protocol, as with all protocols, must be approved by the Ethical Committee of the Division of Child Health of the University Hospital of Wales.

Mouthwashes are used for collection of DNA. The Cardiff multiplex tests for DF508, DI507, G551D, R553X, and 621+1 G---›T, providing 81.5 percent sensitivity. As with the other two pilots, Cellmark's ARMS is run concurrently, with a sensitivity of 83 percent.

The project is designed to compare the differences of participation in screening following invitation by letter, opportunistic invitation, and self-referred requests for screening. In addition, socioeconomic variables will be compared, including social class, age, sex, and marital status. As with the London and Edinburgh pilots, the Cardiff pilot will also evaluate the psychological sequelae to screening for CF. Participants will be asked to complete questionnaires at a minimum of three junctures: prior to screening, after being told of their carrier status, and at a 3-month followup. The questionnaires will evaluate perceived health through the perceived health measure (14), a shortened State of Anxiety Inventory (23), a reproductive intentions questionnaire, and a knowledge-of-CF questionnaire. Box 1O-B describes the protocol.

Those who choose not to be screened will be contacted to determine their reasons for refusing screening. Finally, the Cardiff team will calculate the costs and time implications of screening for general practices and laboratory staff.

Western General Hospital, Edinburgh, Scotland

The CF pilot at Western General Hospital in Edinburgh, Scotland is modeled after existing ß-thalassemia and Tay-Sachs programs offered through prenatal clinics in the United Kingdom. The long-term goal is to introduce prepregnancy CF carrier screening. The philosophy of this pilot is markedly different from that of the other two CF Trust pilots and the program at St. Mary's Hospital in London. The pilot director believes that CF mutation analysis should first be offered to individuals with the most limited choices (i.e., women who are pregnant) while simultaneously initiating screening in the broader preconception population (3). This philosophy is based on the assumption that pregnant couples coming through prenatal clinics are more motivated, more in need of this type of information, and more likely to make immediate use of the information provided through screening (4).

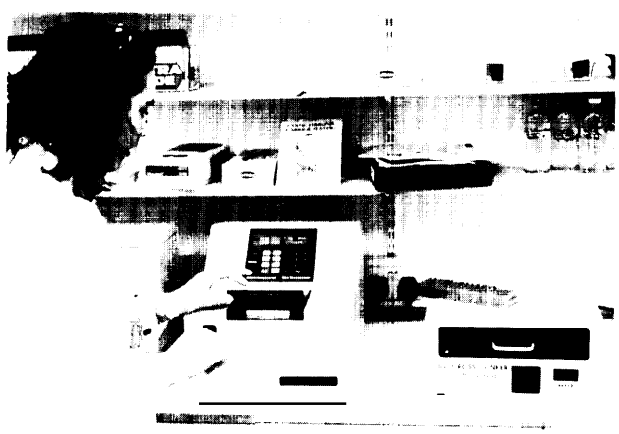
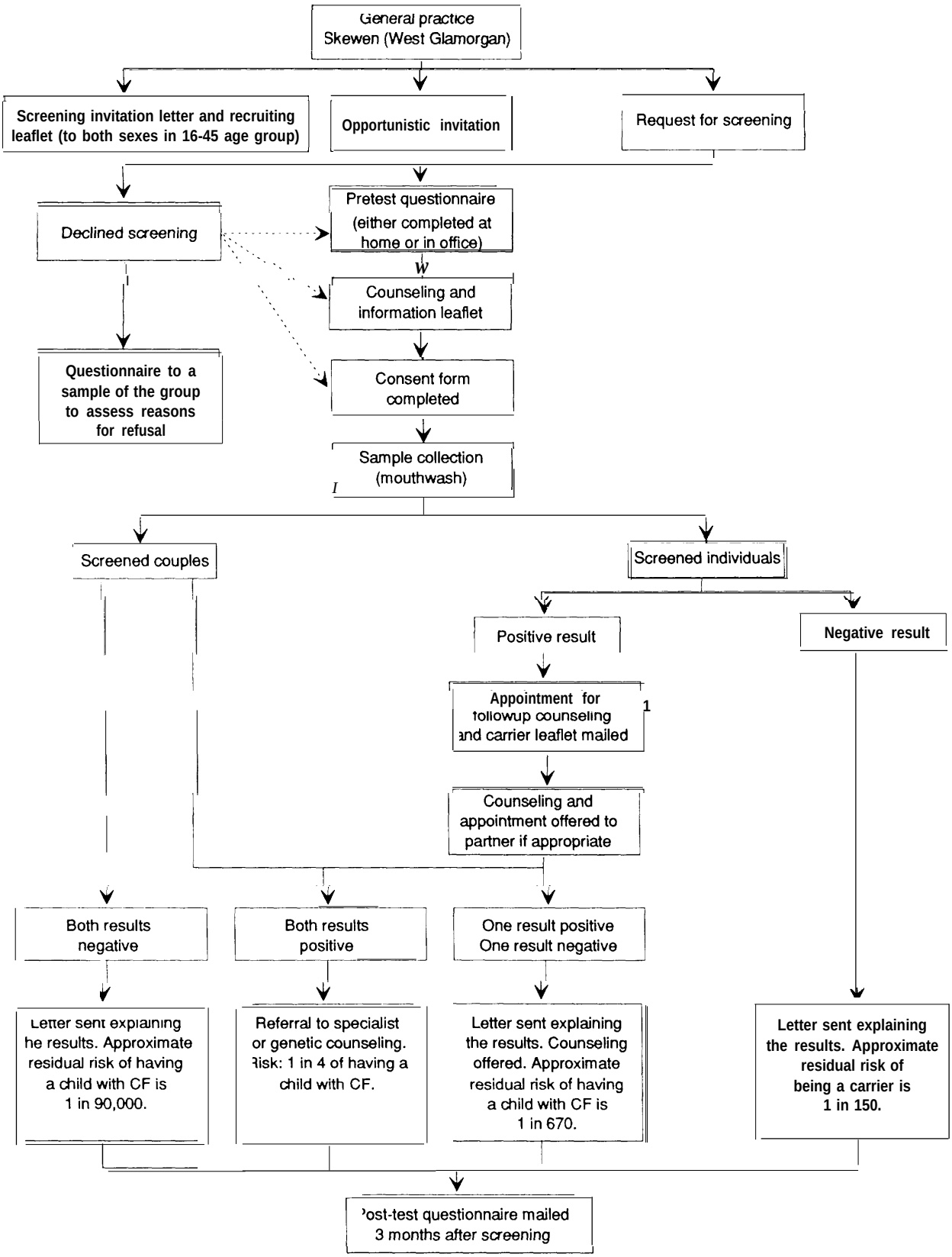


Photo credit: David J.H. Brock, University of Edinburgh

CF mutation analysis of samples in a laboratory at Western General Hospital, University of Edinburgh, Edinburgh, Scotland.

Figure 10-1—Plan for Screening and Followup in West Glamorgan, Wales (Individuals)



SOURCE: P. Harper, University of Wales College of Medicine, Cardiff, Wales, personal communication, 1991.

Box 10-A—The Couples Approach to Carrier Screening

One approach currently used in London and under consideration elsewhere in the United Kingdom is the ''couples' protocol for carrier screening. This protocol aims to identify high risk couples (both partners are carriers, thereby each pregnancy has a 1 in 4 risk of having an affected child). Using this protocol, couples are screened as a unit and receive their results as either high or low risk of producing an affected child Individual carrier status is not discussed Even if the geneticist determines that one of the members of the couple is a carrier (a +/- couple), that couple is grouped with negative-screening couples (-/-) in terms of risk. (See figure 10-2 for protocol.)

Several medical geneticists in the United Kingdom are disturbed by this approach as it involves a failure to disclose known information. At a meeting convened by the Medical Research Council in May 1991, participants considered the concept of blind testing. If test results could not be attributed to an individual but rather the couple, then, the group concluded information was not being concealed and the protocol could be considered ethically acceptable.

Approximately 3 percent of couples will test +/-, and their risk of producing an affected child is 1 in 600. This compares to the lower risk group of -/- couples, whose chances of producing an affected child are 1 in 50,000. The residual risk to the first group presents ethical dilemmas currently being sorted out in the United Kingdom.

Proponents of this approach feel it is more economical and reduces the anxiety associated with knowing one's carrier status. In addition, both partners are screened simultaneously. If the woman is pregnant, the amount of time needed to identify a couple at risk is reduced.

Just how to obtain informed consent in this process remains a problem, although proponents claim that if the contractual agreement is to identify only high risk couples, then those who find such an approach disturbing could opt out. In addition, the implications for liability should a couple deemed 'low risk' give birth to a child with cystic fibrosis have not been addressed.

SOURCE: Office of Technology Assessment, 1992.

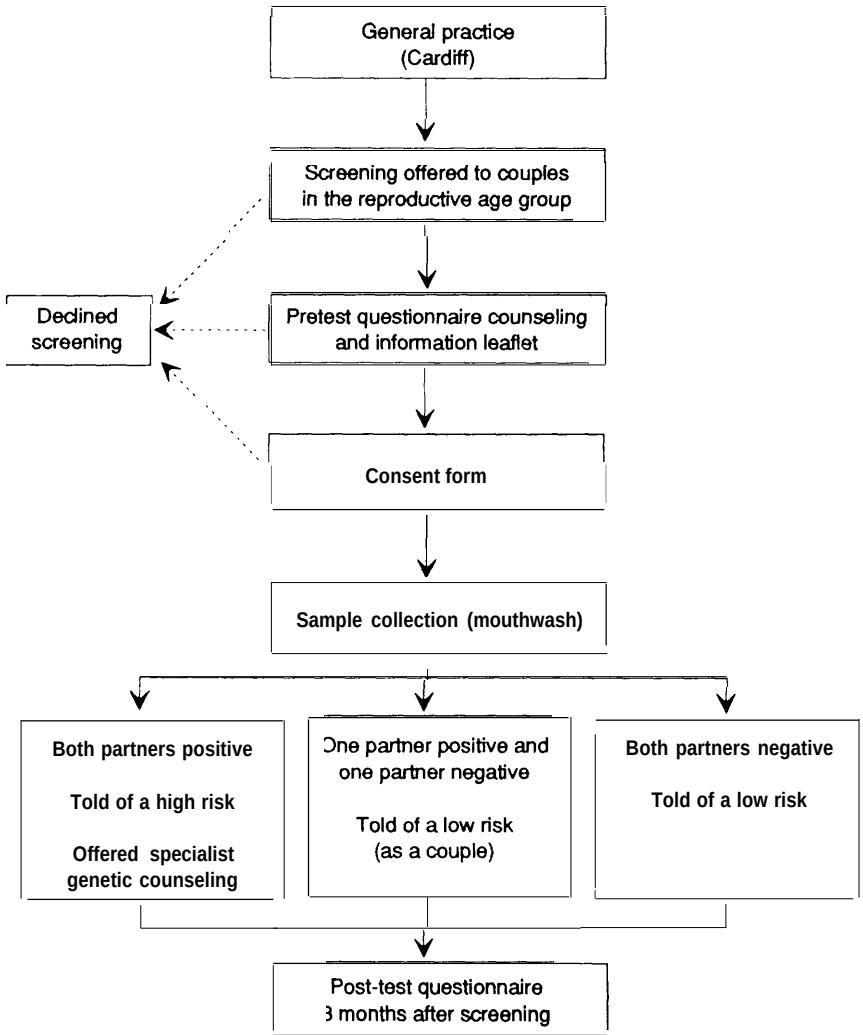
When a woman is booked for her frost appointment through a family planning service, she also receives a CF carrier screening 'booklet. Upon her arrival at the clinic, a genetic nurse or midwife (who has been previously trained to handle CF questions) asks her if she wants to be screened. Women who are late in their pregnancy (beyond 16 weeks' gestation) are excluded, as are those with no partners, since prenatal screening is most informative using results from both parents, The goal of the program is to reach at least 80 percent of patients coming through a major maternity hospital with the aim to expand to two other hospitals in the near future. In addition to the prenatal program, the Edinburgh pilot study is going back to CF families and offering the test. Offering screening to school-age individuals has been explored but not initiated. In a study of 14- to 16-year-old school children in Edinburgh, investigators found a positive attitude to carrier screening for CF and to the offer of prenatal tests of those couples shown both to be carriers (5).

The Edinburgh pilot employs a two-step model, first screening the pregnant woman for carrier status using assays for three mutations (DF508, G551D, and G542X, providing a predictive value of 85 percent in the population) and then testing her partner for 15 mutations if she is diagnosed as a carrier (evaluating 12 more mutations provides a predictive value of 92 percent in the population). The Edinburgh laboratory is currently running 50 to 60 samples a week and running the ARMS test kit simultaneously. By December 1991, more than 2,000 samples had been run, detecting 74 carriers (table 10-1).

Like the other pilot programs, Edinburgh is devoting considerable effort to examining the acceptability of offering the test, in this case prenatally. Maternal and parental anxiety is the focus of the assessments—in specific, determining to what extent offering the test to pregnant women raises anxiety in preconception and prenatal populations. Consulting psychologists and psychiatrists are developing a survey instrument that will measure anxiety, self-esteem, and perceptions of stigma in those screened.

As noted earlier, the program received funds in January 1992 from the MRC to carry out a separate

Figure 10-2—Plan for Screening in a Cardiff, Wales General Practice (Couples)



SOURCE: P. Harper, University of Wales College of Medicine, Cardiff, Wales, personal communication, 1991.

Box 10-B---Cardiff Protocol for Evaluating Psychological Sequelae

Step I

Participants are invited either through the mail or directly through their general practitioner. Prior to screening they are asked to complete the perceived health measure questionnaire and the State of Anxiety Inventory. Immediately prior to counseling, they are asked to complete the reproductive intentions questionnaire and the knowledge-of-CF questionnaire.

Step 2

Within 1 week of notification of their carrier status, all participants are asked to complete the questiomaires again.

Step 3

Three months after screening, participants are again sent all the questionnaires.

SOURCE: P. Harper, Institute of Medical Genetics, University Hospital of Wales, Cadiff, personal communication 1991.

Table 10-1—Results of the Edinburgh Pilot Program (as of December 1991)

Number of women approached.	2,780
Ineligible for screening	
late gestation.	245
abnormal pregnancy.	50
no partner.	31
other.	35
Total.	361 (13 percent)
Eligible for screening.	2,419 (87 percent)
Declined screening.	331 (12 percent)
Screened.	2,088 (75 percent of all; 86 percent of eligible)
Carrier women.	74
Carrier partners.	3
Carrier frequency found.	1 in 28
Carder frequency expected.	1 in 30

SOURCE: D.J.H. Brock, Western General Hospital, Edinburgh, Scotland, personal communication, 1991.

trial of couples screening in another maternity hospital in Scotland.

Guy's Hospital, London, England

Guy's Hospital in London offers CF carrier screening to adults of reproductive age (18 to 45 years old) through a general practice. Screening prenatally is not the goal of the program. The philosophy of this pilot is to introduce screening through the GP so that after the pilot programs expire, screening can be run by the GPs.

The predictive value of the test when used in the Guy's population is approximately 80 percent using the four mutations detected with the Cellmark ARMS kit. Through mid-1991, approximately 200 samples had been run at a rate of 10 to 20 per week (l).

As with the Cardiff and Edinburgh pilot programs, participants are asked to complete the psychological questiomaires (which were developed in collaboration with a Guy's psychologist). At the end of the pilot programs, all three groups will compare results.

OTHER PILOT PROGRAMS IN THE UNITED KINGDOM

In addition to the pilot programs funded by the CF Trust, two other programs-funded privately or by a variety of public and private funding mechanisms—have also begun to evaluate the implications of population carrier screening for CF. The most active non-CF-Trust program in the United Kingdom is at St. Mary's Hospital Medical School, Imperial College, London. The St. Mary's program is similar to those in Cardiff and at Guy's Hospital, focusing on screening nonpregnant adults of reproductive age.

Another program, funded entirely through private sources, is at St. Bartholomew's Hospital (Bart's) in London. The Bart's program is unique, in that it offers only couples screening. In fact, the director of the Bart's program has been the most outspoken advocate in the United Kingdom of the couples screening approach (box 1O-A) (4). Pilots are also under way in Italy, Denmark (box 1O-C), and Austria (table 10-2).

St. Mary's Hospital Medical School, London

The pilot study operated out of St. Mary's Hospital Medical School in London is evaluating preconception CF carrier screening of males and females of reproductive age through three GPs and three family planning clinics (figure 10-3). This genetic service opted to offer the test to nonpregnant individuals of reproductive age, because the director believes screening this population maximizes reproductive choice and autonomy.

Box 10-C-Carrier Screening in Denmark

The carrier frequency for the DF508 mutation is nearly 88 percent in Denmark. This makes screening simpler because of the higher sensitivity of the test. This factor, combined with a national health program, made the introduction of CF carrier screening more feasible. Using national health service funds, carrier screening is offered to all pregnant women seen at an out patient clinic at the Rigshospitalet in Copenhagen, as well as to families of CF patients. Blood samples are drawn and tested for the presence of the DF508 mutation. Among 3,664 women tested as of September 1991,91 were found to be carriers of the DF508 mutation (1 in 40). When the partners of these women were tested, only one was found to also be a carrier of the DF508 mutation. Prenatal diagnosis revealed that the fetus was homozygous for DF508 and the pregnancy was terminated. In addition, prenatal diagnosis was performed on an additional 42 fetuses. Of these, 24 were found to be carriers (heterozygotes) for the DF508 mutation.

SOURCE: M. Schwartz and N.J. Brandt, Rigshospitale, Copenhagen,. Denmark personal communication, 1991.

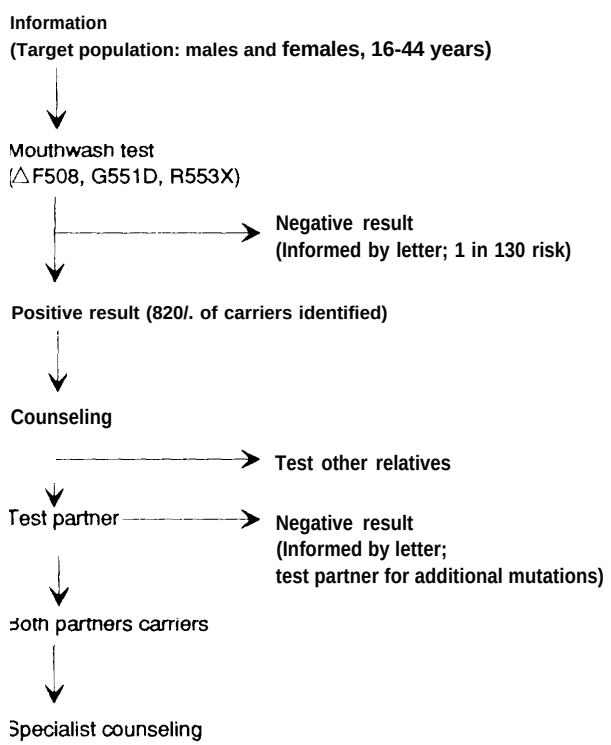
Table 10-2—International Cystic Fibrosis Carrier Screening Pilot Programs

Country	institution	Target population
Austria	University of Vienna	Newborns
Denmark	Rigshospitalet	Prenatal
England	St. Mary's	Adult preconception
	Guy's	Adult preconception
	St. Bartholomew's	Adult preconception
Italy	University of Padua	Newborns
Wales	University of Wales College of Medicine	Adult preconception
Scotland	University of Edinburgh	Prenatal

SOURCE: Office of Technology Assessment, 1992.

Using mouthwash samples, the St. Mary's group is presently looking for the DF508, G551D, and R553X mutations, which together should detect 82 percent of the CF carriers in their population. Through mid-1991, St. Mary's had screened about 1,600 individuals at the rate of approximately 50 samples a week. Rough estimates of the cost of screening run about £1.75 per sample for laboratory costs alone. Estimating total costs, however, is difficult as some laboratory staff are paid out of a research grant, and others are paid through the NHS.

Figure 10-3—Carrier Screening in Primary Care (St. Mary's Hospital)



SOURCE: R. Williamson, St. Mary's Hospital, London, England, personal communication, 1991.

Counseling is not a major cost as it is, for the most part, carried out by GPs or practice nurses who are already employed by the NHS (28). Because the tests are part of a research protocol, for which the laboratory does not charge, they do not pay PCR royalties.

One approach used by this group is opportunistic screening. The St. Mary's group has found that approximately 66 percent of individuals approached through their GP eventually request screening, while 87 percent of individuals in the family planning clinics request the test (25,28). Another approach being tested by this pilot group involves solicitation by invitation letter. Individuals receive a letter offering the test on Saturday mornings at their GP's office. The response rate of this method approximates 10 percent (25).

With both approaches, each person is given a leaflet that explains the test. Those who opt for screening are told about the limited sensitivity of the assay. The results are sent through the mail. The letter to those screening negative reemphasizes the sensitivity of the test, informs the individual that his or her risk of being a carrier has been reduced to 1 in 130, and offers screening for partners or spouses. Carriers are invited to attend a counseling session where risks are explained and the testing of partners or relatives is discussed. The partners of identified carriers are screened for several additional mutations, which brings the detection rate up to around 86 percent (26,29).

Participants in this screening program were asked how they thought their future reproductive plans might be affected if both they and their partners were found to be carriers. For those with no experience with CF, 38 percent felt they might choose not to have children, 78 percent would request prenatal diagnosis should they become pregnant, and 16 percent would not consider terminating an affected pregnancy. For those who had a relative or knew someone with CF, 45 percent felt they might choose not to have children, 82 percent would opt for prenatal diagnosis in pregnancy, and 20 percent would not consider terminating an affected pregnancy (25).

This study has also begun offering screening at selected work sites, such as police barracks or the Royal Mail, There are also plans to mail the mouthwash kits to the homes of relatives of carriers.

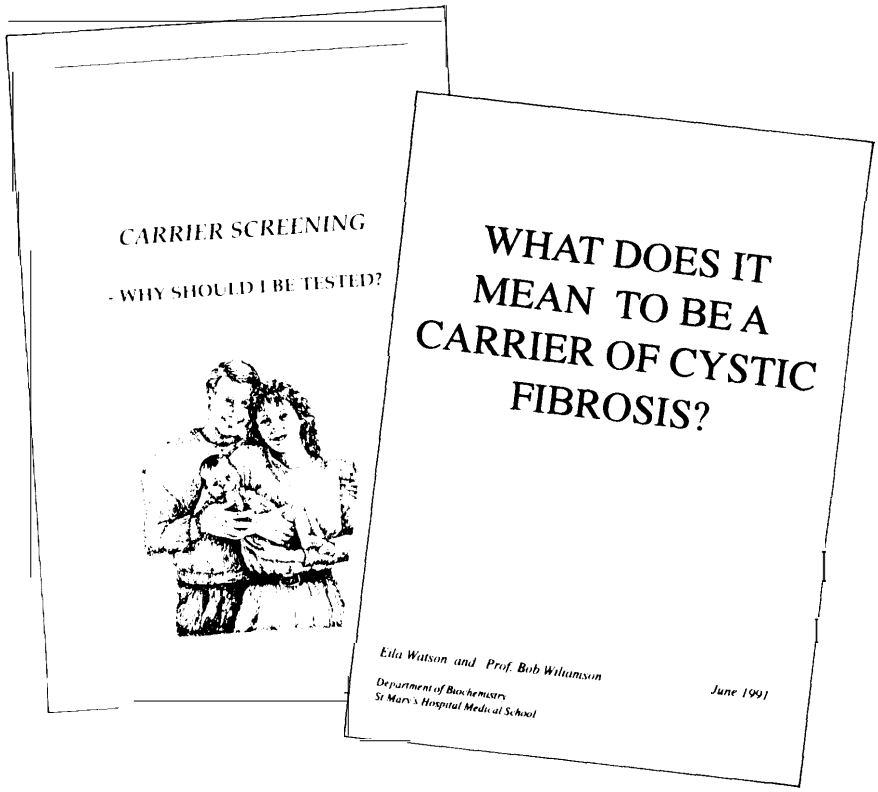


Photo credit: Robert Williamson, St. Mary's Hospital

Sample educational materials used by the CF carrier screening pilot study at St. Mary's Hospital Medical School in London, England.

PROSPECTUS

The future of broad population carrier screening for CF in the United Kingdom is yet to be decided. Many interviewees were skeptical that widescale screening will be pursued by the NHS once the pilot programs are completed. Moreover, even if the NHS takes up carrier screening, there is no guarantee that it would last. It is generally easier to retract programs in the United Kingdom than in the United States.

As in the United States, there is speculation about whether the necessary infrastructure exists to proceed with broad based screening. In the United Kingdom, it will be necessary to provide:

- information to the population;
- a system for collecting samples from a cohort of the population at some point before reproduction, and delivering the samples to the laboratory;
- a network of diagnostic laboratories with a quality control system;
- a system for reporting the results to doctors and the people concerned;
- an information storage and retrieval system;
- information and counseling for carriers;
- adequate expert centers for counseling couples at risk and providing prenatal diagnosis; and
- a system for monitoring the service (18).

There is a general consensus in the United Kingdom that newborn screening would be an inefficient approach to reducing the incidence of CF. One of four carrier couples would already have an affected child before being identfied as carriers, and an additional 25 percent would not be identified because their child had inherited neither CF mutation. Ensuring that this information follows the carrier child into adulthood is also problematic (27). Legal, ethical, and logistical problems also make school-based screening programs difficult to implement in the United Kingdom (4).

There remains some disagreement as to whether prenatal CF carrier screening unduly raises maternal

anxiety in the approximately 24 of 25 women who will test negative. Proponents of prenatal screening feel that pregnant couples are most in need of and most likely to use this information. Furthermore, the infrastructure already exists for working with these individuals. Those opposed to prenatal screening feel that it raises anxiety at an already anxious time and leaves little time for reflection (18,27). People of this view tend to believe that screening should be offered preconceptionally, when carrier couples will have a maximum range of reproductive options. Carrier screening offered when pregnancy is known has the advantage of a captive population, but the disadvantage of limited time for screening and decisionmaking, as well as eliminating the option of avoiding conception if both partners are carriers. The pilot studies will help clarify some of these issues as they encompass both prenatal and preconception populations.

If the pilots are successful and the NHS embraces the notion of a widescale screening program, the laboratory service would be provided by centralized regional DNA laboratories run by the NHS. One area in which the United Kingdom lags behind the United States is in the area of quality control and assurance. Lacking regulatory agencies comparable to the U.S. Health Care Financing Administration and the U.S. Food and Drug Administration, laboratories need only voluntarily comply with quality standards.

In the late 1980s, the European Concerted Action on Cystic Fibrosis was formed for the purposes of data coordination, information exchange, and establishment of international standards of quality control (table 10-3). Organized out of St. Mary's Medical School in London, the consortium supplies every participating laboratory with oligonucleotides for CF analysis in exchange for data. The group interacts with the Genetic Analysis Consortium in North America, but does not consider itself a '' Euro-equivalent,' in that it is not primarily a research group, but a clinical assistance group. A newsletter published six times a year serves as a point of exchange for information about ongoing work and technical advances.

Coded samples and a list of mutations to be tested were distributed in June 1991 to 35 voluntary hospital-based research groups. A database program for the collection of mutation and patient data is available through the European Concerted Action on Cystic Fibrosis (19). The program will allow laboratories to computerize their records and analyze data according to mutations, clinical details, and ethnic groups. Each of the pilot projects is participating in this quality control exercise. The MRC is seeking additional information regarding quality control and assurance.

Table 10-3—Members of the European Concerted Action on Cystic Fibrosis (as of February 1991)

Australia	New Zealand
Austria	Northern Ireland
Belgium	Norway
Bulgaria	Poland
Cuba	Portugal
Czechoslovakia (former)	Republic of Ireland
Denmark	Scotland
England	South Africa
Finland	Spain
France	Sweden
Germany	Switzerland
Greece	USSR (former)
Israel	Wales
Italy	Yugoslavia (former)
The Netherlands	

SOURCE: R. Williamson, St. Mary's Hospital Medical School, London, England, personal communication, 1991.

Establishing the infrastructure necessary for CF carrier screening, if it is done, could lay the ground work for other forms of genetic screening in the future. Current reform of the NHS might well be the best predictor of the future of genetic screening programs in the United Kingdom. Under the new reforms, health authorities will assess the health needs of their resident populations and then negotiate contracts to purchase the services that they expect will achieve the most improvements in health (10). With the reforms, hospitals can function outside health authority control as ''self-governing hospital trusts,' and it is not yet clear how specialized, preventive, genetic services will be administered under this new plan. They may be deemed too costly. Results of the pilot programs in the United Kingdom will provide valuable information on the ability of primary care providers to assist in screening, the acceptability by the public of screening, and the most appropriate population for screening.

SUMMARY AND CONCLUSIONS

The private CF Trust is largely responsible for the existence of CF carrier screening pilot projects in the United Kingdom. Were the availability of government funding the determinant of pilot project initiation, it is uncertain any pilots would exist. Results of pilot studies in the United Kingdom will

be directly relevant to consideration of population screening in the United States because of similar concerns about the appropriate target population, levels of anxiety, and the role of primary care providers. Although the latter concern is of a different nature in the United Kingdom because of the role of the general practitioner and the National Health Service retain, the ability of GPs to participate in screening in the United Kingdom will be of significant interest in the United States.

The role of the British GP as the likely first point of contact for CF carrier screening makes preconceptional carrier screening of adults more easily achieved than in the United States, where primary care physicians are less likely to refer individuals for screening in the absence of a positive family history. Targeting GPs as important collaborators and resources in CF carrier screening is done by nearly every British pilot program. GPs are actively recruited to participate in the development and implementation of screening.

Prenatal clinics provide another population easily targeted for screening. Yet there is no consensus on the appropriateness of targeting pregnant women for CF carrier screening. Only the Edinburgh pilot project is actively recruiting pregnant women. Concerns about raising anxiety in pregnant women and the logistical restrictions to offering first, rather than second, trimester prenatal diagnosis, are the impetus for screening programs airned at preconceptional individuals. Anxiety levels are being followed by the CF Trust pilot projects and the results of these analyses should shed light on the validity of those concerns.

Debate over couples screening has focused on the ethics of not informing carriers of their status in couples in which one partner is a CF carrier and the other has a negative test result (an informing practice that would be considered legally and ethically dangerous in the United States). In addition, those opposed to the concept of couples screening fmd the treatment of individuals as reproductive units unsettling, given the possibility of nonpaternity or new partners in the future. Unlike the United States, the British medical community does not operate under the fear of malpractice or litigation. Because the British pay for their health care indirectly, through taxation, they do not view themselves as consumers or buyers of services.

While screening cost is a major consideration in the United States, it is viewed differently in the United Kingdom, as the total cost is likely to be borne by the NHS. New programs, such as routine CF carrier screening, must compete with other desirable projects for available funds. In addition, services are more centralized, lowering overall costs. Reform of the NHS, however, will likely alter the manner in which genetic services are offered and made available.

Except for samples from pregnant women, investigators in the United Kingdom rely on mouthwash for their DNA extractions. This approach, seldom used in the United States, is thought to be as effective for DNA extraction as other sources and is less costly. In addition, investigators feel that the use of this noninvasive procedure contributes to higher rates of participation in screening programs. Quality control and assurance, currently conducted on an informal basis throughout the United Kingdom, would have to be addressed.

The British health care system is significantly different from that found in the United States. The existence of preliminary carrier screening pilot projects in no way commits the system to sustain the programs. It is generally easier in the United Kingdom than in the United States to retract policies or cease offering services if they are deemed unnecessary or inappropriate. Results of the pilot programs in the United Kingdom will provide valuable information on the ability of primary care providers to assist in screening, the acceptability of screening by the public, and the most appropriate population for genetic carrier screening.

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