Chapter 6

Education and Counseling

Contents

Boxes

Figures

Tables

Major questions raised by the implementation of routine CF carrier screening include:

- Can pretest education and post-test counseling adequately inform participants and prevent harm?
- What is the role of public education as a source of pretest information?
- Who should be offered screening and in what setting?
- Can confidentiality be assured?
- Is quality assurance possible?

The answers to these questions will surface as time passes and the results of several pilot projects in the United Kingdom (ch. 10) and the United States become available. How education for cystic fibrosis (CF) carrier screening is conducted will likely serve as a prototype for screening for other autosomal recessive disorders. This chapter examines the educational and counseling issues that will need addressing as CF carrier screening becomes more widespread, as well as the roles of various health professionals.

There are no mandatory genetic screening programs of adult populations in the United States. In this regard, OTA finds it highly unlikely that CF carrier screening will set a precedent. In a 1991 OTA survey of 431 genetic counselors and nurses in genetics, 99 percent of those who responded said CF carrier screening should be voluntary (71). Thus, this chapter assumes voluntary screening and examines factors in delivering CF carrier screening to a large group of Americans. Topics discussed are: the complexity of pretest education and post-test counseling for CF carrier status; the capacity of the professional clinical genetics community to assume the primary role in the provision of counseling; the most appropriate sites, facilities, and resources for screening; and contributions to be made by CF carrier screening pilot projects.

THE NEED FOR SUFFICIENT AND APPROPRIATE EDUCATION AND COUNSELING

For some individuals, even considering whether to undergo genetic screening or testing constitutes a potential life crisis because of the possible outcomes. If the results are positive, the crisis is exacerbated. How results affect an individual has much to do with the person's own frame of reference, but also with the implications of the condition and its prognosis.

Psychological issues permeate every aspect of genetic consultation. Information received can be ego-threatening, or even life-threatening, as individuals find they are '' flawed,' ''imperfect, ' ' 'defective.' ''inadequate, ' or ''abnormal, ' and could potentially transmit these "flaws" to their progeny (37). How the information is obtained, communicated, retained, and eventually used by the person being tested or screened involves a "series of complex, multidimensional processes with major rational and nonrational components" (37).

Beyond the intrapsychic consequences of receiving genetic information are the potential impacts on family. Genetic information affects not only the individual, but also the partner, parents, grandparents, siblings, and children of the individual being tested or screened. Social and psychological stress, as well as future financial and emotional burdens, can strain family functioning (61).

The psychological impact of a positive diagnosis varies with its severity, treatability, and potential for different families to react uniquely to similar situations. Support, counseling, and followup can assist individuals and their families in coping with positive test results. The knowledge and skills of a properly trained counselor can help the individual understand the diagnosis, risk, prognosis, and relevant preventive and therapeutic measures, and also aid in communicating important information to other family members. When these goals are accomplished, genetic counseling is usually perceived as a valuable experience by the counselee and the professional (50).

Pretest Education

In routine genetic counseling, **the** genetics professional elicits the reasons for testing or screening and discusses the implications of possible outcomes. The counselor prepares the individual for both positive and negative test results. It is also the time

Photo credit: Peter T. Rowley, University of Rochester School of Medicine

Educational materials, such as this pamphlet developed at the University of Rochester School of Medicine, Rochester, NY, can be useful for pretest education.

to discuss risk reduction strategies, if relevant, and the nature and severity of the disorder for which the test is being done. Counseling for CF carrier screening, if conducted in the typical genetic services setting, is no different from routine counseling for other disorders for which tests have less-than-perfect sensitivity.

Most studies of genetic counseling have focused on cases where the client already has an affected child or relative and is familiar with the disorder. Experience with Tay-Sachs, sickle cell anemia, and ß-thalassemia screening provides some information about the effects of education prior to screening people with no previous family history of the condition for which they are being screened (app. B). Clearly, without pretest education—and in some cases even after such education—misperceptions can be great. Pretest education is imperative in cases where there has been no family history-i. e., screening.

Understanding Risk

One task of the genetics professional is to communicate risks to the client-a job not easily performed (31). A decision to be screened or tested will be influenced by a person's perception of the chance that the test will be positive, The interpretation of numerical risk varies depending on:

- prior perception of the magnitude of the risk,
- anxiety of the client at time of test,
- familiarity with the outcome (whether there is an affected relative or fiend),
- how treatable the condition is, and
- belief that the outcome with which the individual is familiar is representative of all such outcomes (34).

Cultural differences need to be understood, as they also influence interpretation of risk (46).

The perception of risk is a more important determinant of decisionmaking than the actual risk. The way risks are posed can influence the client's choices. When confronted with the risk of genetic disease in their offspring and when making reproductive decisions, people tend to place greater weight on their ability to cope with a disabled or fatally ill child than on precise numerical risks. For some couples, for example, a risk of 10 percent could be perceived no differently from a risk of 50 percent if they believe that they cannot cope with the situation. In prenatal counseling, regardless of actual risk, parents might perceive the chance of occurrence as either O or 100 percent-it either will or will

not happen. By processing risks in this way, individuals simplify probabilistic information and shift their focus to the implications of being at risk and the potential impact of what could occur (40).

In addition to subjective factors that influence the interpretation of risk, many individuals have difficulty understanding risk in arithmetic terms. Comprehension of the concepts of probability and risk influence a clients understanding of the information provided by genetic tests. In a Maryland study of 190 predominantly Caucasian, middle-class women, over one-fifth thought that ''1 out of 1,000' meant 10 percent, and 6 percent thought it meant greater than 10 percent (12). In addition, interpretation of risks varies according to whether they are presented as a single figure or in comparison to a variety of genetic risks (65).

Even for individuals who are familiar with a disease because they have an affected family member, comprehending risks can be elusive. In a study of 190 subjects from 100 families with a family member with adult polycystic kidney disease (APKD) —a kidney disease inherited in an autosomal dominant fashion (each child of an affected individual has a 50 percent chance of inheriting the disease)---most tested poorly on questions reflecting their knowledge of the genetics of APKD. Twenty-nine percent had a genetic knowledge score considered good or excellent, while 46 percent had poor or absent knowledge (30).

How risks are framed also influences understanding and choices (45). Deciding to have a genetic test can be different if the risk is presented as a 25 percent chance of having an affected child rather than a 75 percent chance of having an unaffected child (31). Risk perceptions vary among individuals and among counselees and counselors: Patients tend to interpret the same level of numerical risk as lower than do geneticists (79).

Presenting risks in personal terms can improve the chance that the information will be understood. For example, one genetics center that conducts routine carrier screening for hemoglobinopathies in at-risk populations uses a videotaped drama to present information about screening during pregnancy and has demonstrated effective and lasting transmission of information (41). Videos of patients are particularly useful in demonstrating the gestalt of a condition, its natural history at various ages, and variability among affected individuals (4).

A recent survey of public attitudes regarding genetic tests revealed that belief in the technology's accuracy is one of the strongest predictors of favorable attitudes toward its use (66). Thus, an individual's decision to undergo screening or testing is likely influenced by the manner in which the accuracy of the test is presented. Even under the best circumstances, however, counseling might not be satisfactory. In a survey of 1,369 counseling cases at 47 clinics-after counseling sessions that typically lasted 45 to 60 minutes—both the counselor and the patient were aware of what topic the other party had most wanted to discuss in only 26 percent of the sessions. In almost half the sessions, neither party ever became aware of what the other had most wanted to discuss (80). Many of the undesirable psychological effects of screening might be avoided or reduced by careful attention to patients' needs at each stage of the screening process.

Maternal serum alpha-fetoprotein (MSAFP) screening is instructive in this regard. Women who are notified that their MSAFP test is abnormally low or high must await further testing, either through ultrasound or amniocentesis, to rule out the possibility of a fetus with Down syndrome or a neural tube defect, but a small percentage of neural tube defects will still be missed (box 6-A). *(This* situation parallels that of a pregnant woman who finds she is a carrier for CF and must sometimes await the results of her partner's test and subsequent fetal tests.) The mental anguish and apprehension that women encounter when faced with the prospect of having a child with a condition such as Down Syndrome is well documented (20,69). Although increased anxiety among women might persist until a definite chromosomal diagnosis by amniocentesis rules out the condition, initial anxiety can be reduced by comprehensive genetic counseling (36).

The importance of informed consent, careful presentation of counseling, and confidentiality have long been recognized as essential components of genetic testing and screening (29). Geneticists, perhaps more than any other medical specialists, have advocated a nondirective approach to counseling and have a strong commitment to patient autonomy (6). Further, a history of concern exists about genetic information being delivered by health professionals used to a more directive approach (13). This concern has been played out in the debate over MSAFP and is a factor in the reluctance of the clinical genetics community to rush toward wide-

Box 6-A—Maternal Serum Alpha-Fetoprotein Screening

Alpha-fetoprotein (AFP) is a glycoprotein that is synthesized first by the embryonic yolk sac and later by the fetal gastrointestinal tract and liver. Its concentration in fetal serum is 150 times that found in amniotic fluid; an even smaller amount enters maternal blood, most likely through the placenta. Although its function in the fetus is unclear, the association of an abnormally increased AFP concentration in maternal serum with a variety of fetal abnormalities and adverse pregnancy outcomes has been known for 20 years. Elevated maternal serum AFP (MSAFP) can indicate an open neural tube defect (NTD) or an abdominal wall defect in the fetus. Abnormally low MSAFP levels are associated with fetal chromosomal abnormalities such as Down syndrome.

As with some other screening tests, the incidence of false positive MSAFP tests is high, and about 4 to 5 percent of women have abnormally high initial MSAFP values. More than half these women will have abnormal results when tests are repeated and will need to be assessed by ultrasonography. Because MSAFP levels must be correlated precisely with gestational age and the number of fetuses, ultrasonography provides an explanation for the elevated MSAFP in about half these women because of either incorrect dating of the last menstrual period or multifetal gestation. Thus, 1 to 2 percent of all women screened will be candidates for diagnostic amniocentesis to assess the AFP concentration of their amniotic fluid, and about 1 in 10 will ultimately be found to have a fetus with a NTD.

At the other end of the curve, another 5 percent of all women screened will have abnormally low MSAFP. Ultrasound eliminates half of these women from further evaluation because of inaccurate gestational dating, and the other half will be advised to undergo amniocentesis for karyotyping; 1 in 40 will have a chromosomally abnormal fetus.

Because of the number of false results at both ends of MSAFP screening, the cost-effectiveness of universal screening was debated widely during the early years of the assay's development. Moreover, there was heightened concern about the possibility that the test could fall into the hands of practitioners not familiar with the complexities of the required followup. Of further concern was the reproducibility of results with the available assay kits, as well as the lack of standardized controls for the specific population studies. In 1978, the U.S. Food and Drug Administration (FDA) was on the verge of releasing AFP test kit reagents on a totally unrestricted basis. The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) formed a task force on the issue that concluded:

> There is no precedent in the United States for a mass disease detection program that requires the coordination of so many disparate elements of the health care system as in APP screening. Maternal serum AFP screening should be implemented initially only where it can be done within a coordinated system of care which contains the requisite resources and facilities to provide proper safeguards and potential for follow through.

AAP and the American Society of Human Genetics (ASHG) asked FDA to restrict MSAFP testing to programs that can provide qualified personnel and equipment, rather than making the test available to every pregnant woman regardless of capability for followup. In 1983, the FDA adopted unrestricted regulations approving MSAFP test kits, making expanded use of the test possible.

A properly designed MSAFP program demands public education, assurance of quality laboratory work accurate interpretation of test results, and public health tracking to assure appropriate followup and testing of positive results. Misinterpretation or improper followup could result in either the unwanted birth of a seriously impaired child or the termination of a healthy fetus. MSAFP screening also depends on the availability of ancillary services (counseling, ultrasound, amniocentesis) for further diagnostic evaluation, particularly in underserved areas. At the time the test kit was introduced, there was concern that sufficiently equipped facilities and trained personnel were not yet available to handle the large number of potential cases.

In 1986, ACOG recommended to physicians that MSAFP screening be offered to all women, and, at least legally, such screening became the de facto standard of care. In the same year, ASHG developed a policy statement detailing the conditions necessary to provide for appropriate use of this test. Today, numerous MSAFP screening programs operate in the United States. By its very nature, MSAFP screening is the kind of program that lends itself to a State or regional public health approach since there is no clearly definable high-risk group. It is standard practice to refer women with positive test results to specialized diagnostic centers for confirmation. It is unclear, however, whether the counseling needs of this high-anxiety group are being met.

SOURCE: Office of Technology Assessment, based on G.C. Cunningham and L.C. Gilstrap, "Maternal Serum Alpha-Fetoprotein Screening," New *England Journal of Medicine 325:55-57,* 1991; and G.C. Cunningham and K.W. Kizer, ''Maternal Serum Alpha-Fetoprotein Screening Activities of State Health Agencies: A Survey," *American Journal of Human Genetics 47:899-903,* 1990.

spread screening for any disease. Nearly 82 percent of the respondents surveyed by OTA said the human genetics community should be the primary organizer of CF carrier screening programs. Also mentioned were State or local health departments (59 percent) and primary care givers (27 percent). Over 89 percent felt CF population screening should be provided in genetics centers, but 59 percent felt that carrier screening could also be provided in the primary care setting or organized, community-wide programs (54 percent). Concern about the sometimes difficult nature of communicating risk information regarding CF (as described in the following section)---even for experienced genetic centers—has led some in the clinical genetics community to warn against rapid movement to routine CF carrier screening (5).

THE SCENARIO FOR CYSTIC FIBROSIS COUNSELING

As mentioned earlier, while the CF mutation assay poses probabilistic uncertainties, similar circumstances exist for other tests, such as MSAFP. Education and counseling for CF carrier screening need not be viewed in a vacuum.

OTA's survey found genetic counselors and nurses in genetics estimate that, on average, 1 hour is needed to obtain a three-generational family history and to discuss carrier assays and recurrence risks, regardless of family history (71). The majority (70 percent) of genetic counselors and nurses in genetics surveyed by OTA feel that widespread screening should be withheld until a sensitivity of 95 percent or more is attained (71). This section focuses on some common scenarios likely to be encountered in routine CF carrier screening.

A Priori Risks

Before providing DNA analysis for CF carrier status, it is important to understand and explain to the client his or her a priori risk-that is, an individual's risk prior to any test result. Two factors significantly influence an individual's a priori risk of being a CF carrier: ethnicity and presence or absence of a family history of CF. In the case of a positive history, an individual's chance of being a carrier depends on his or her relationship to the individual with CF. With a negative family history for CF, an individual's ethnic background is most important in defining a priori risk. Table 6-1 presents the a priori probabilities of carrier status for individuals with negative and positive family histories of CF.

Table 6-l—A Priori Carrier Risks for Cystic Fibrosis

Negative family history	
Caucasian	1 in 25 (4%)
African American	1 in 60 to 65 (1.5 to 1.7%)
Asian American	1 in 150 (0.7%)
Hispanic American	1 in 46 (2.2%)
Positive family history	
Parent of child with CF	1 in 1 (1 OO°/.)
Sibling with CF	2 in 3 (670/f)
Aunt or uncle with CF[a]	1 in 3 (33°/0)
First cousin with CF	1 in 4 (25%)
Niece/nephew with CF[a]	1 in 2 (50%)

[a] Consanguineous.

SOURCE: Office of Technology Assessment, 1992.

Prior to any CF carrier screening, patient prescreening education is imperative. It is important potential screenees understand information regarding a priori risk, types of tests available, and uncertainties in risk assessment based on screening results.

Testing To Determine Risks for Relatives of Affected Individuals

Currently, it is accepted practice to offer CF carrier tests to individuals who have a positive family history of CF (71). OTA's survey of genetic counselors and nurses revealed 86 percent of respondents' clinics have policies stating CF carrier tests should be routinely offered to individuals with a positive family history of CF but not to those with a negative family history.

OTA's finding that clinics' policies offer CF carrier assays to those with positive family histories is not surprising. An unaffected sibling of an individual with CF has a 2 in 3 likelihood of being a CF carrier. A consanguineous uncle or aunt of an individual with CF has a 1 in 2 likelihood of being a carrier. A first cousin of an individual with CF has a 1 in 4 likelihood of being a carrier (table 6-l).

In families where CF is due to the DF508 or another common mutation, carrier tests are relatively straightforward. If an undescribed CF mutation is involved, however, carrier detection might not be possible via direct mutational analysis. In these cases, indirect methods must be used, and there is a possibility that several family members will require analysis to arrive at an answer regarding carrier status. For at-risk families (those with a consanguineous relative who has or had CF), the use

Table 6-2—Adjusted Carrier Risks After Negative Test Results at Various Detection Rates

Relationship of affected	a priori	Percent detection 75	80	85	90	95
Sibling	67%	34%	29%	23%	17%	9%
Niece or Nephew[a]	50%	20%	17%	13%	9%	5%
Aunt or Uncle[a]	33%	11%	9%	7%	5%	2%
First cousin	25%	8%	6%	5%	3%	1%

consanguineous.

SOURCE: Office of Technology Assessment, 1992.

of restriction fragment length polymorphism analysis in conjunction with direct detection of DF508 and other CF mutations can improve the tests' sensitivity to nearly 100 percent (ch. 4). The individual whose test reveals a CF mutation is definitely a carrier (the test is 100 percent predictive). However, if no mutation is found (a negative test), carrier status cannot be ruled out. Thus, CF tests, at best, can provide a definitive positive answer. At worst, they alter or modify the assessment of individuals' or couples' risk from their a priori risk. CF mutation analysis does not alter the actual risk, it merely reduces the uncertainty about what that actual risk is.

CF mutation analysis can adjust the assessment of risk downward: Table 6-2 displays how those risks are adjusted after analysis at several test sensitivities. As the sensitivity improves, the uncertainty—i.e., possibility of a false negative result-diminishes. For example, without any testing, a sibling of an individual with CF has an a priori risk of 2 in 3, or 67 percent, of being a carrier. If the sibling is tested for CF carrier status using a test that is 85 percent sensitive and is found to be negative, the adjusted risk of being a carrier is 23 percent. At 90 percent sensitivity, the carrier risk drops to 17 percent.

Screening To Determine Risks of Those With No Family History

To date, most genetic counselors do not offer unsolicited CF mutation assays to individuals with a negative family history (71). The American Society of Human Genetics (ASHG) and a workshop of the National Institutes of Health (NIH) published policy documents in 1990 discouraging CF carrier screening (1 1,53); a 1992 ASHG statement reaffims that position (50). OTA's survey found 21 percent of respondents felt that CF carrier tests should be offered to individuals with no family history of CF.

Table 6-3-Potential for Detecting Couples at Risk for a Child With Cystic Fibrosis

Percent of cystic fibrosis mutations detectable	Percent of carrier couples detectable
75	56.3
85	72.3
90	81.0
95	90.3

SOURCE: W.K. Lemna, G.L. Feldman, B.-S. Kerem, et al., "Mutation Analysis for Heterozygote Detection and the Prenatal Diagnosis of Cystic Fibrosis," New *England Journal of* Medicine 322:291 - 296, 1990.

CF mutation analysis can, however, yield information about the carrier status or risk for individuals who have no family history of CF. In the recent past, the sensitivity of the carrier test was limited to the frequency of the DF508 mutation. Today, however, most commercial and university laboratories examine DF508 and 6 to 12 additional mutations. Taken together, these mutations comprise 85 to 90 percent of CF mutations in U.S. Caucasians (95 percent in Ashkenazic Jews). Counselors report an almost even split between commercial and university-based laboratories as the facility performing their CF mutation assays (45 percent and 48 percent, respectively) (71).

As with individuals who have affected relatives, determining risks in persons with no family history of CF also depends on test sensitivity. At 85 percent test sensitivity, about 72 percent (0.85 x 0.85) of at-risk couples will be identified. As the sensitivity of the assay improves, a greater proportion of +/+ couples can be identified (table 6-3). Simlarly, at 85 percent sensitivity, the probability that a couple from the general population would bear a child with CF is reduced from 1 in 2,500 to about 1 in 16,100 if one partner is screened and found to be negative; risk is reduced to 1 in 103,700 if both have negative test results. In roughly 7 percent of couples screened for CF mutations, one partner will be found to carry a mutation and the other will not (+/-). Such couples constitute the most difficult counseling situation because, assuming 85 to 90 percent sensitivity, the risk of having an affected child remains 1 in 644 (table 6-4). Computerized programs have been developed to incorporate factors such as a priori risk and mutation frequency when determining risk. In addition, a "slash sheet, ' or pedigree flow chart,

Table 6-4--Cystic Fibrosis-Related Risks After Mutation Analysis for Carrier Status[a]

Percent of cystic fibrosis mutations detectable	Risk of cystic fibrosis in offspring: Carrier risk for person with negative test	One screened; negative result	One parent positive, one parent negative	Both parents negative
0	1 in 25	1 in 2,500	NA[b]	1 in 2,500
75	1 in 97	1 in 9,700	1 in 388	1 in 37,600
85	1 in 161	1 in 16,100	1 in 644	1 in 103,700
90	1 in 241	1 in 24,100	1 in 964	1 in 232,300
95	1 in 481	1 in 48,100	1 in 1,924	1 in 925,400

a Assumes earner frequency of 1 in 25.
b NA = Not applicable.

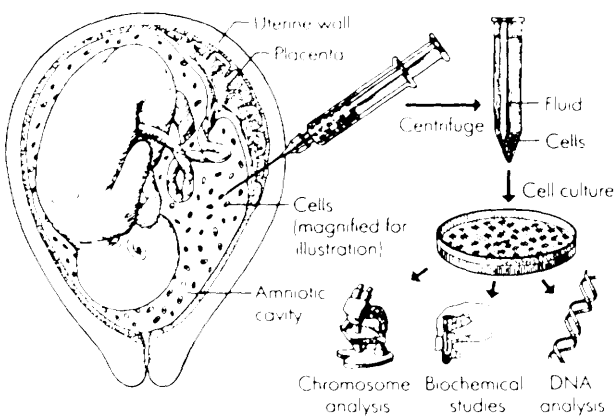
SOURCE: Office of Technology Assessment, based on W.K. Lemna, G.L. Feldman, B.-S. Kerem, et al., "Mutation Analysis for Heterozygote Detection and the Prenatal Diagnosis of Cystic Fibrosis," *New England Journal of Medicine* 322:291-296, 1990.

was developed to assist in the estimation of risk (21). The value of either of these tools in the clinical setting is yet to be determined.

Prenatal Diagnosis of Cystic Fibrosis

In addition to CF carrier screening of adults, prenatal diagnosis of CF can be performed. The type of test used to establish carrier status of the parents determines the DNA protocol for the fetus. The choice of technique to obtain a sample for DNA analysis involves consideration of timing, procedural risk, access to procedures, cost, and the presence or absence of other indications for prenatal diagnosis. Cells can be obtained via chorionic villus sampling (CVS) (performed at 9 to 12 weeks of pregnancy), amniocentesis (performed at 16 to 18 weeks), or through percutaneous umbilical blood sampling, also called cordocentesis (performed at 20 weeks). When CF mutation analysis is unavailable or inconclusive, microvillar intestinal enzyme levels can sometimes be measured in the amniotic fluid at 17 to 18 weeks, but this method suffers from a high false-positive and false-negative rate,

A new, experimental procedure, called blastomere analysis before implantation, or BABI, has been used to diagnose the CF status of an in vitro fertilized embryo before implanting it in the woman's uterus. The technique involves extracting a single cell from an embryo at about the eight-cell stage and analyzing its CF mutation status. Recently, an



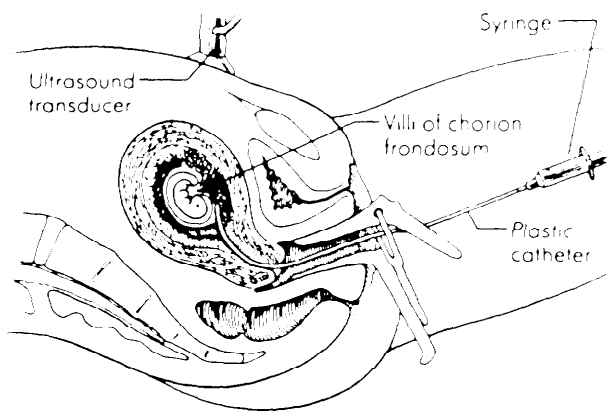


Photo credit: National Institute of *Genera/* Medical Sciences

Left: Amniocentesis—the most widely used technique for prenatal diagnosis, generally at 16 to 18 weeks of a pregnancy. Cells shed **by** the developing fetus are extracted from a sample of amniotic fluid that has been withdrawn from the expectant mother's uterus by a hypodermic needle. The cells are cultured and then can be analyzed for chromosomal defects, such as Down syndrome. DNA analysis can also be performed (e. g., for CF mutation status).

Right: Chorionic villus sampling-a method of prenatal diagnosis that provides results as early as the 9th week of pregnancy. Fetal cells from the chorionic villi (protrusions of a membrane called the chorion that surrounds the fetus during its early development) are suctioned out through the uterine cervix and their DNA is analyzed. Preliminary results of this process can be obtained within a day.

unaffected baby that had been tested with BABI was born to a couple in Lxmdon at risk for CF (70).

For some families, prenatal diagnosis for CF is inconclusive. As in screening for carrier status, couples receive test results that yield percentages rather than certainties (54). There is speculation that this ''restructuring of uncertainty' versus a' yes/no answer' will be confusing to individuals and cause undue stress; pilot studies to examine levels of anxiety in test populations before and after screening are under way. Assessments of anxiety levels of participants in other carrier screening programs are limited in what they offer to CF carrier screening because the levels of test uncertainty are not as great. Women offered hemoglobinopathy carrier screening, for example, were found to manifest appropriate levels of concern rather than undue anxiety, but the test results were less ambiguous because the test is more sensitive (59).

Informing Relatives and Inductive Screening

In any type of genetic screening, a real possibility exists that test results will affect other family members. In the usual genetic counseling setting, the person being screened (the proband) is routinely advised of risks to other family members. If, for example, an individual is found to be a carrier for an autosomal recessive disorder such as CF, the genetics professional informs the client that siblings also each have a 50 percent chance of being carriers. In most cases, the suggestion is made that the individual contact his or her siblings, and that they consult with their personal physician or come to the same clinic. The genetics professional does not usually confirm that the proband has informed relevant family members due to limits of confidentiality in the counselor-client relationship. Some argue that genetics providers should be legally permitted to disclose such relevant information to relatives at risk (76).

As discussed in chapter 5, breaching confidentiality to disclose medical information to relatives raises legal and ethical issues. Not all families are emotionally and psychologically secure, Sibling relationships could impede full disclosure. Sharing highly personal medical information that involves reproductive and health futures can cause personal embarrassment or emotional stress for family members.

From the point of view of identifying the largest number of carriers by screening the fewest number of individuals, however, encouraging carriers to notify relatives provides economic and pragmatic benefits. Encouraging known carriers to refer siblings and first cousins for testing can detect a larger percentage of at-risk couples. This approach, also known as ''inductive screening, '' improves the efficiency of screening by 10 to 15 percent (15). Testing those known to be at higher risk because of family history is more effective than screening those with unknown risk. In reality, complex psychological factors enter when family members of individuals with CF contemplate screening, and it cannot be assumed that all will want to be tested (63).

OTA's 1991 survey of genetic counselors and nurse geneticists revealed that most families who have a child with CF are not routinely seen in genetics service settings, and few counselors have routine contact with CF families (71). For inductive screening to work, those providing health care and counseling to CF families will have to actively participate in referrals of relatives to genetics centers. Less than 10 percent of respondents reported contacting previously identified CF families regarding the availability of CF mutation analysis.

Post-Test Counseling

When attending a genetics clinic for reasons other than prenatal genetic screening, people typically come because they have or had an affected relative, usually a child. These individuals tend to be aware of the disorder, and the affected relative, rather than a test, serves as the indicator of potential disease for other offspring. As the number of genetic tests administered to healthy individuals with no apparent family history of genetic disease increases, genetics providers might need to spend more time describing the disorder to those with positive results.

Results are best reported in person, by the same person who provided the pretest education—although this is not always possible or practical (16). If the test results are positive, prior contact might have alerted the professional as to who else should be informed, whose help might be needed on behalf of the client (e.g., for emotional support), and important information about the client's lifestyle and family (as well as financial and insurance information).

Followup counseling and support are also strongly advised for persons with positive results. News of a positive result can impede a person's ability to receive information on both emotional and practical levels. Faced with positive results, most individuals are unable to act until they overcome the shock and possible denial that their fate or their children's fate could suddenly shift in a negative direction. People's perceptions of their own health can worsen, for example, as occurred for some when they were made aware of their carrier status for Tay-Sachs disease (42,43); such anxiety can be prolonged (83). Knowledge of carrier status can also have an impact on reproductive intentions or behavior, including decisions relating to marriage or choice of marriage partner (49,68).

Even in the best of all worlds, where consistent counseling has been provided throughout the process, the effectiveness of counseling is sometimes questionable. An analysis of nine studies on counseling published since 1970 concluded, "many parents of children with a genetic disorder have an inadequate understanding of the genetic implications of the disease, even after one or more genetic counseling sessions' (23). One survey found that more than half of the 87 percent of people who came to a genetic counseling center with inaccurate knowledge of risk were still misinformed after counseling (67). It is not clear whether they were incrementally better informed,

The task of communicating genetic information is formidable. Genetic counseling programs continually try to improve the process (74). A major impediment to satisfactory genetic counseling has been a profound lack of understanding of basic genetics by almost everyone in the general public. Anyone administering tests necessarily takes on the role of educator as well as practitioner.

The Need for Better Public Education

Whether CF carrier screening programs are offered to prenatal or preconception populations, public education efforts aimed at better understanding of genetic conditions and inheritance will be increasingly essential. The need for better scientific literacy has been a topic of great concern in recent years. Even by the 12th grade, fewer than half of students can use data in tables or graphs (72). A recent survey of 1,006 Americans regarding attitudes about genetic testing revealed that fewer than half were able to correctly answer 4 of 5 technical questions regarding genetic testing (66).

Photo credit: University of South Carolina School of Medicine

Genetic consultations can require longer office-visit time because of the need for gathering detailed information about the client and for followup counseling and support. This genetic counselor is discussing the client's chromosome profile with her.

Most counselors and nurses responding to the OTA survey, however, indicated they spend little to no time on general public education in schools and communities (71). Thus, most people will rely on their primary care provider for preliminary genetic information. Survey respondents indicated that they think primary care providers and public health departments should play an active role in educating the public about DNA tests for CF carrier status (71).

Public education programs for genetic diseases have been nearly nonexistent since the programs established under the National Genetic Diseases Act (Public Law 94-278) were phased out in 1981. In terms of public education, the National Science Foundation has supported a teacher training program in genetics for school teachers in Kansas, but there is no similar program through NSF at the national level (14). In the Kansas program, lead teachers were trained to teach peer teachers in genetics. Teachers who participated in the program showed a 3-fold increase in genetics instruction at the high-school level and a 22-fold increase at the elementary school level (28). More recently, a project to prepare 50 selected science teachers per year for 3 years to become State resource teachers in human genetics received funds though the Department of Energy's Ethical, Legal, and Social Issues Program. Nevertheless, fewer than half the Nation's elementary

schools and about one-third of high schools make science education a curriculum priority (72).

The importance of a period of community education before the implementation of genetics programs has been demonstrated in sickle cell and Tay-Sachs screening programs in the United States, and in thalassemia screening programs in Sardinia and Cyprus (app. B). More public awareness about genetic diseases and tests could result in less time needed for individual counseling. Experiences with ß-thalassernia carrier screening in Sardinia and Cyprus demonstrate the impact of public education. Aggressive public education campaigns orchestrated in these countries placed information on the disease and carrier screening on television and in large department stores and factories, marriage registry offices, general practitioners' offices, and family planning clinics. In Sardinia, the birth rate of thalassemia-affected newborns fell from 1 in 250 to 1 in *1,200* (10). In Cyprus, genetics is taught in school and screening is encouraged before marriage. As a result, the time needed for counseling has decreased as public education has increased (2).

In an ideal world, better education in the schools would make individuals more aware of genetic risks before they are confronted with genetic screening programs. And if pregnant women are informed, they might initiate genetics discussion with their obstetricians rather than waiting to be informed (8).

STRATEGIES FOR SCREENING VARIOUS POPULATIONS

Two key considerations in deciding how best to implement routine CF carrier screening are the clinical settings in which it will take place and the target populations. Delineation of a target group (or groups) determines other elements such as location, educational approach and tools, time, format, types of counseling, facilities, and publicity.

The NIH statement on CF carrier screening emphasized the importance of preconceptional screening (53). Most pilot projects in the United Kingdom are directed at preconceptional populations (ch. 10). Pilot studies under way in the United States are both prenatal and preconceptional (see following section). One program in Canada targets high school students (35).

Newborn Screening

Numerous newborn screening programs exist for genetic disorders such as sickle cell anemia and phenylketonuria. These are programs intended to screen for the presence of disease, although some can also detect the carrier status of the newborn. Wisconsin has performed statewide neonatal screening for CF disease since 1985, using the immunoreactive trypsin assay. Primary care physicians have been cooperative in referring screened patients to designated CF centers (47). But even newborn screening for CF disease is not without controversy. Evidence of heightened anxiety and disrupted maternal-infant bonding have been reported in cases of false-positive diagnoses (7).

For at least two reasons, many believe that newborn screening is an inappropriate and inefficient mechanism for carrier detection. First, newborns determined to be carriers must be tracked through their reproductive years to ensure they are aware of their carrier status. Second, detection of newborn carriers might unnecessarily raise the anxiety level of parents. Thus, newborn screening for CF carrier status is not generally viewed as acceptable (48). OTA's survey of genetic counselors and nurses bears this out; a minority of respondents (33 percent) felt the newborn population would be an appropriate target group for widespread CF carrier screening (71).

Adolescent Preconceptional Screening

Some geneticists advocate screening at the high-school level (35). A recent nationwide survey of American attitudes about, and knowledge of, genetic tests showed better knowledge and more positive attitudes in younger populations (66). Studies of pregnant women known to be carriers of a hemoglobinopathy gene have shown that age is a predictor of postcounseling knowledge-younger women (and adolescents as young as 12 years old) are more likely to understand genetic information (41). While not routinely done in the United States, high-school screening programs have been conducted in Canada for some time (app. B). For any disease where screening is done in childhood or adolescence, however, the benefits of such screening, including savings in inconvenience, resources, and anxiety, must be balanced against the potential problems, such as the possibility that an adolescent will be falsely assigned to a low-risk group because of poor

test sensitivity (thereby obviating further screening), or the possibility of psychosocial harm to the child as a result of identified carrier status (29).

Adolescents were not considered to be an appropriate target by the genetic counselors and nurses surveyed by OTA (71). Less than 18 percent felt individuals ages 13 to 18 years should be screened. Only 6 percent felt that children ages 2 through 12 years should be screened.

Adults—Preconceptional or Prenatal?

Current debate surrounding CF carrier screening focuses on whether the goals are best accomplished by targeting preconceptional adults or pregnant women. These approaches are not necessarily mutually exclusive. Many feel, however, that receipt of troubling information during pregnancy is not desirable, and that it would be better for individuals to know their risks before getting pregnant (39). Others argue that individuals not facing a pregnancy are not motivated to seek or use information on their carrier status, but will wait until they are either planning a family or starting a family before viewing such information as useful (9).

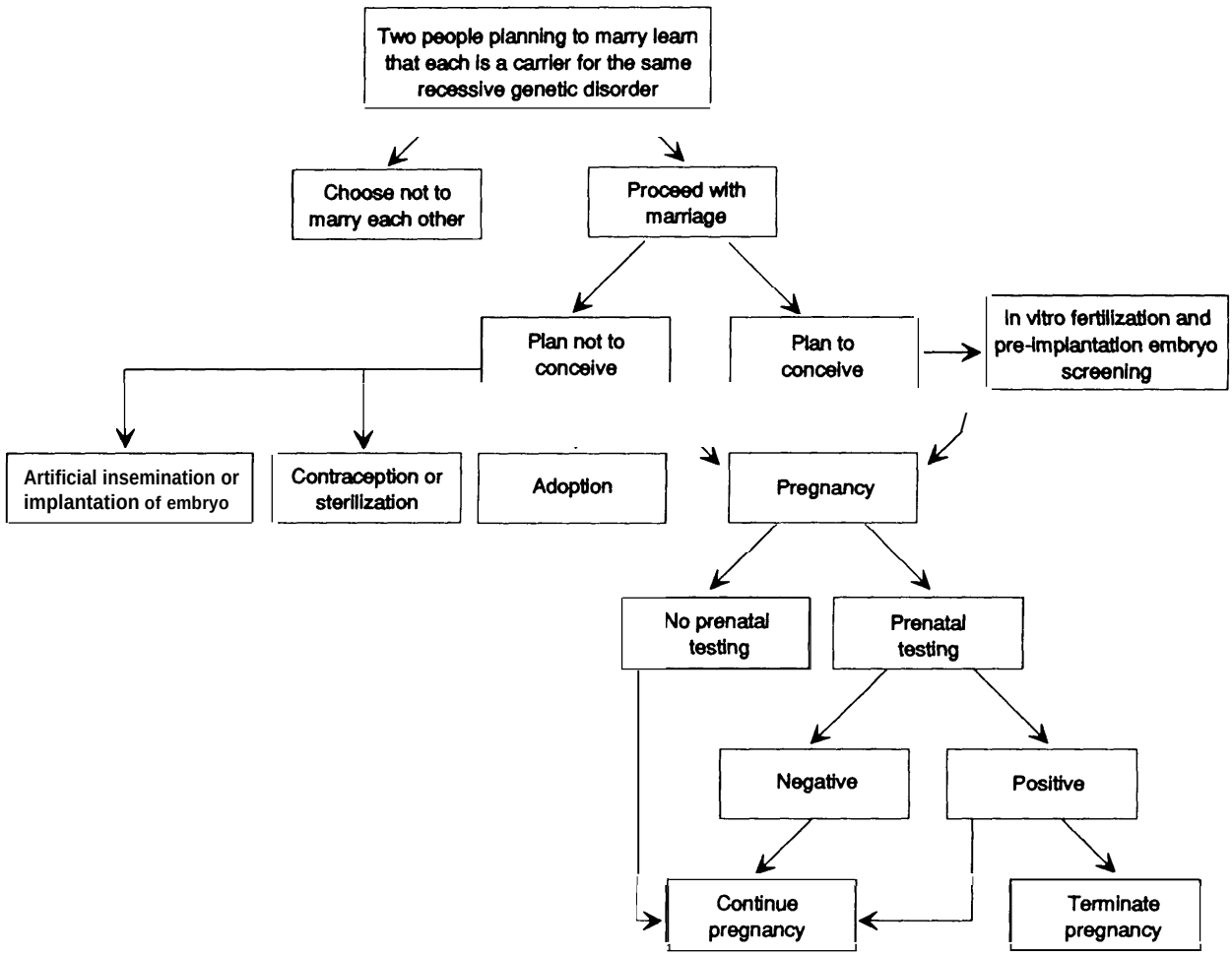
CF carrier screening offered as part of primary health care rather than prenatal care is likely to encourage preconceptional CF carrier screening. For most individuals, however, the first real opportunity for carrier screening takes place post-conception (22). It could well be that the primary responsibility for providing CF carrier screening will reside with the obstetrician, as has happened with MSAFP screening. Sixty-six percent of respondents to OTA's survey identified pregnant women or couples as the appropriate target population for CF carrier screening. Yet 88 percent generally identified adults in their reproductive years as the appropriate target group (71). While most respondents state that the *ideal* population to target for carrier screening is the preconceptional adult (71), in reality, the first target population is likely to be the prenatal population because it has been the traditional entry point into genetic services for many people.

Pregnant women often have established a relationship with an obstetrician/gynecologist or prenatal clinic staff, who can provide information about CF carrier screening. Ideally, individuals should receive potentially emotionally loaded information when they have the most latitude for reproductive choice (figure 6- 1). Women in the early stages of pregnancy have the choice to continue the pregnancy or electively terminate it; attitudes regarding abortion of CF-affected fetuses indicate that prenatal screening would only modestly reduce the incidence of CF, as many couples with CF-affected children speculate that they would not elect termination of an affected fetus (1,77,78). Studies of pregnant women screened for hemoglobinopathy carrier status have shown little evidence that screening raised anxiety (41). Pregnant women with fetuses at risk for hemoglobinopathies are highly receptive to genetic information (60) because they seek reassurance that fetuses are not affected.

The increasing availability of genetic tests might shift genetic services from specialized clinics, where they are now usually located, to primary care settings. This is likely to be especially true for tests for disorders like CF. First, the possibility exists for the clinical genetics community to become overwhelmed by the volume of tests and counseling. If this occurs, genetic specialists will need to rely on primary care providers and community and public health institutions to bear some of the workload, Two examples of public health models are State-sponsored MSAFP screening in California and newborn screening programs for hemoglobinopathies and phenylketonuria. Second, some aspects of medical genetics—specifically routine screening of those with no family history of genetic disease—could increasingly be considered less of a medical specialty (tertiary care) and more a part of primary care. Thus, genetics education must reach primary caregivers, yet the average 4-year medical school curriculum includes only 21.6 hours of genetics instruction (57). Third, placing CF carrier screening within the realm of obstetric care might decrease out-of-pocket expenses to the client. As part of routine care, insurers might be more likely to reimburse CF carrier screening in the prenatal population.

Overall, then, if carrier screening is to become routine, it is likely that it will be offered as part of family plarming or reproductive health, and the medical specialty most likely to offer the test will be obstetrics-a prospect some genetic specialists find unsettling. Experience with MSAFP has shown that despite the development of practice guidelines, obstetricians often perform tests on pregnant women without obtaining their consent (31). In addition, obstetricians who do not screen for certain genetic conditions in individuals at high risk could be at risk

Figure 6-1---Decisionmaking in Premarital Carrier Screening



SOURCE: Office of Technology Assessment, based on F. Cohen, C/Mea/ *Genetics in Nursing Practice* (Philadelphia, PA: Lippincott, 1984).

for malpractice or wrongful birth suits (64). This perceived tension—lack of informed consent coupled with pressure to screen—leads many in the clinical genetics community to express concern about premature widespread CF carrier screening before adequate professional education is in place. With regard to CF carrier screening, concern exists that layers of uncertainty will inhibit informed consent and that, ultimately, more harm than good might be done.

The sickle cell and Tay-Sachs carrier screening programs provide valuable information on the importance of prescreening education, understanding the culture and values of the population being screened, and optimizing the setting in which screening occurs. Mistakes were made and lessons learned (app. B). While CF carrier screening also involves identification of carriers and high-risk couples, it differs from these experiences because of the sensitivity of the test and the larger number of couples at risk. There is little experience in the delivery of such complex information to large populations (11). Initial experiences with MSAFP screening revealed some confusion and concern on the part of patients because of a high false positive rate, limited test sensitivity, and apparent lack of understanding within the obstetrics community about the screening procedure (box 6-A).

PROFESSIONAL CAPACITY

As mentioned earlier, OTA reserves the term ***genetic counselor*** to specifically describe master' s-level individuals certified as genetic counselors by the American Board of Medical Genetics (ABMG)

Photo credit: Diane Baker

Genetic counseling prepares the individual for both positive and negative test results.

(or board-eligible) because legal distinctions in licensing and third-party reimbursement exist among the different types of practitioners. OTA uses the term ***genetic counseling*** generically to refer to the information delivery process that is performed by genetic specialists, including physicians, Ph.D. clinical geneticists, genetic counselors, nurses, and social workers. overall, approximately 630 individuals from the range of types of training are certified by the ABMG to perform genetic counseling. (The exams are given every 3 years so many practitioners are board-eligible but have not yet taken or passed the exam.)

At issue in considering widespread carrier screening for CF is whether there are enough adequately trained health professionals to handle the volume of tests. One study estimated that a minimum of 651,000 counseling hours would be required annually if their maximum estimate of 6 to 8 million preconceptional couples are screened for CF carrier status (81). Considering the current number of board-certified genetic counselors practicing in the United States today, this translates to 17 weeks per year from each genetic counselor to serve CF-related clients (81). On the other hand, one estimate suggests the supply of genetic specialists could absorb routine carrier screening for CF, sickle cell anemia, hemophilia, and Duchenne muscular dystrophy, assuming that obstetricians or other primary care physicians perform the screening on pregnant women, with referral of those with positive results to genetics professionals (31).

The counselors and nurses surveyed by OTA estimate that pretest counseling for CF carrier status, regardless of family history, would take, on average, 1 hour (71). It is unclear to what extent increased demand for CF carrier screening would strain the current system. Current estimates undercount the number of health care professionals who practice genetic counseling and assume that counseling would always be provided in a clinical genetics setting by board-certified or board-eligible counselors. Such estimates also ignore the role that aggressive public education can play in improving pretest knowledge (2,10). Improvements in public education could result in dramatically less time required in formal counseling as could reliance on health professionals not formally trained in genetics.

The following section addresses the traditional roles played by master 's-level genetic counselors and presents nontraditional sources as possible options for handling an increasing caseload.

Master' s-Level Counselors

The master' s-level genetic counselor is a relatively new addition to the health care system. In 1971, 10 graduates of the first such program entered the workforce; in 1979, the National Society of Genetic Counselors (NSGC) was incorporated as a professional organization. Today, there are approximately 1,000 master' s-level genetic counselors practicing in the United States.

Master' s-level genetic counselors receive specialized multidisciplinary training and experience to prepare them for counseling related to a wide variety of genetic disorders and birth defects. They are typically graduates from a 2-year master's degree program, during which time they receive didactic course work in the principles and application of human genetics, clinical and medical genetics, genetic laboratory methods, and interviewing and counseling. Genetic counselors are also trained in social, ethical, legal, and cultural issues relating to genetic diseases, principles of public health and health care delivery systems, and education for the lay and professional community (73). Over the past 20 years, master' s-level graduate programs in genetic counseling have increased to 15; combined,

they produce approximately 75 graduates each year (54).

Genetic counselors receive a minimum of 400 hours of supervised clinical training in at least three clinical settings, including a general genetics clinic, a prenatal diagnosis clinic, and a speciality disease clinic. Until 1992, graduates were eligible to sit for the certification examination in genetic counseling by the ABMG, but the continuing certification of these individuals by this body is unclear. In the past, counselors were required to submit their credentials and a logbook of 50 cases obtained in a clinically accredited training site before taking the exam (54). Genetic counselors typically work in university medical centers or private hospitals in metropolitan areas, and tend to be female, Caucasian, and married (71). The mean gross salary in 1990 was $33,879 (56). The majority are board-certified or board-eligible by the ABMG and have been in clinical practice for at least 6 years (71).

Training support for master' s-level genetic counselors has been minimal. No financia1 support is supplied by the U.S. Department of Health and Human Services (DHHS) for the training of genetic counselors or for improving genetics education in medical schools (31). Through support to the Council of Regional Networks for Genetic Services (CORN), the DHHS Bureau of Maternal and Child Health and Resources Development provides support for some continuing professional education programs for physicians and postdoctoral students, but not for master' s-level counselors.

As the profession has developed, master' s-level counselors have begun to consider taking the role of trainer of other health professionals. This role with respect to "single-gene counselors, " discussed in the following section, could serve as an example of how an increase in CF-related counseling could be handled.

Non- Master' s-Level Counselors

In some clinical settings, a role has been created for a non-master' s-level individual to meet the demand for patient education related to one diagnostic category of disease. In other settings, such individuals assist genetic counselors in overcoming cultural, linguistic, geographic, or economic barriers: The OTA survey of genetic counselors and nurses in genetics, for example, revealed that only 14 percent were fluent in a language other than English (71). Individuals who assist genetic counselors, often called ''single-gene counselors, ' or "non-master' s-level counselors, ' do not have the same training as master' s-level genetic counselors and have not been eligible for ABMG certification. With the growth of genetic services and increasing demands on the time and resources of traditionally trained counselors, use of these individuals has raised debate.

Advocates of single-gene counselors cite the current shortage of genetic counselors-the NSGC maintains a jobs hotline, and has consistently over the last 3 years posted at least 35 unfilled positions at a given time. Single-gene counselors could also improve the quality of service in underserved, culturally diverse populations that are disproportionately affected by a particular genetic disease (54).

Those opposed to single-gene counselors express concern about what they view as a lack of genetics training. Some view them as a possible threat to the professional status of genetic counselors. There is also concern about whether single-gene counselors have a broad enough view of clinical genetics to identify complex and obscure risks of other genetic disorders in their patients. Since taking a family history often exposes previously unknown or undiagnosed genetic disorders or predispositions, individuals who focus on one category of disease might not recognize the need to further investigate peripheral information.

An NSGC task force has recommended that the society:

- acknowledge the current and predicted personnel needs for genetic counselors as well as the shortage of master' s-level genetic counselors;
- recognize the existing use of non-master' s-level counselors and the benefits they offer;
- educate the NSGC membership regarding the potential use of these individuals;
- support the use of non-master' s-level counselors in specific settings where genetic counselors can be involved in training, evaluating, and supervising these individuals; and
- establish a committee to collaborate with other organizations.

Genetic counselors have been involved in developing and conducting training programs as well as supervising hemoglobin trait counselors in several

States. Programs in California and Massachusetts, for example, employ non-master' s-level professionals to conduct genetic counseling for sickle cell disease (26).

Other Health Professionals

Integration of other health professionals, such as nurses, nurse practitioners, social workers, dietitians, psychologists, and physicians, into the existing genetics network will supplement the skills of the traditional genetic counselor. Similarly, the involvement of other health care professionals will be important to increasing public awareness and education. If CF carrier screening were to become routine, clinical geneticists would have to become more involved in the delivery of community (public health) genetic services, the education and training of other health care professionals, and public education.

Nurses in Genetics

There are nearly 2 million registered professional nurses in the United States, many involved in maternal and child health nursing. These professionals provide a unique potential to contribute to the effective deliver-y of genetic services. Efforts are under way to encourage the incorporation of clinical genetics into the curricula of schools of nursing at both the graduate and undergraduate level (32). The need for better genetics education in nursing stems from the recognition that genetics is generally within the realm of tertiary care; thus, genetic specialists are not always in the position to screen every individual needing genetics referral (32). That is, individuals who need genetic services must first be identified by the primary health care professional, and in some settings—such as community, occupational, or school health—nurses are the only link with the health care system (27). Thus, nurses can assist in the identification, education and counseling, and followup of patients (25,32). Yet while nurses can be a valuable part of genetic services, to date they are a largely untapped resource (27).

Opportunities for clinical genetics experience in nursing programs vary. Genetics is generally a part of the nursing school curriculum, but again, variability exists among programs (27). Four of the 200 universities in the United States that offer graduate degrees in nursing have established programs providing a master' s-level genetics major (27). A small number of nurses, particularly those in maternal *and* child health nursing, have focused on genetics in order to sit for the genetic counseling examination given by the ABMG (27,33). There are over 100 nurses who are employed in genetics, according to the International Society of Nurses in Genetics. Governmental support of genetics education for nurses has been through the Health Resources and Services Administration, Bureau of Health Care Delivery and Assistance, Division of Maternal and Child Health (26).

Social Workers and Public Health Professionals

Social workers can play an important role in genetic services delivery, particularly in undeserved communities. Nevertheless, only 9 of almost 100 accredited social work graduate programs in the United States offer special courses on genetic topics (28).

Similarly, public education in genetics requires increased commitment at the public health level. This requires educating public health professionals about pertinent issues related to medical genetics and changing the attitudes and staffing patterns of key State agencies (17,18). Yet a survey of curricula at member schools of the Association of Schools of Public Health indicated a decrease in the number of schools offering human genetics as a major area of study (28). Few schools of public health offer genetics as part of their curriculum, and in none is it required (62).

THE FEDERAL ROLE IN DECIDING THESE ISSUES

In 1990, NIH convened a consensus workshop on ''Population Screening for the Cystic Fibrosis Gene. ' Participants concluded that tests should be offered to all individuals and couples with a family history of CF. However, the group did not recommend population-based screening for individuals and couples with a negative family history, because:

- With a sensitivity [at the time] of 70 to 75 percent, only half of the couples at risk can be identified.
- The frequency of the disease and the different mutations vary according to racial and ethnic background, so that important laboratory and counseling modifications would be required in different populations,

- There are substantial limitations on the ability to educate people regarding the use of an imperfect test.
- Without more definitive tests, about 1 in 15 couple---those in which one partner has a positive test and the other has a negative test—would be left at increased risk (approximately 1 in 500) of bearing a child with CF (53).

The workshop concluded that these difficulties would be substantially reduced if the test were improved to 90 to 95 percent accuracy. Population-based CF carrier screening was considered appropriate if a 95 percent level of carrier detection were achieved. Additional screening guidelines were developed, including:

- Screening should be voluntary and confidentiality assured.
- Informed consent must be obtained via pretest education.
- Providers of screening have an obligation to provide adequate education and counseling.
- Quality control of all aspects of laboratory testing, including systematic proficiency testing, is required and should be implemented as soon as possible.
- There should be equal access to counseling.

The NIH group felt that legislative action regarding CF carrier screening was not required unless it became evident that individuals identified as carriers were suffering from discrimination, either through employment or insurance. It described the most appropriate group for population-based carrier screening as individuals of reproductive age, preferably preconception. Furthermore, the NIH group agreed that the optimal setting for carrier screening is through primary health care providers or via community-based screening. It concluded that newborn or childhood screening would be inappropriate. The NIH statement stressed the importance of providing nondirective genetic counseling for individuals determined to be carriers. Finally, the group called on the Federal Government to fund pilot projects to investigate research questions in the delivery of population-based screening. The pilots were envisioned to address the effectiveness of educational materials, the level of use of screening, laboratory aspects, counseling issues, costs, and beneficial and deleterious effects of screening (53).

NIH Clinical Assessments

Responding to increasing calls for a Federal initiative to evaluate population carrier screening (58), the Ethical, Legal, and Social Issues Working Group of the National Center for Human Genome Research (NCHGR) hosted a workshop in September 1990 to discuss an appropriate role for NIH. This workshop concurred with earlier statements that clinical evaluations of alternative approaches to genetic education, testing, and counseling were needed to establish the professional practices that should govern widespread CF carrier screening. In stressing the importance of setting professional standards as early as possible, CF mutation analysis was viewed as a prototype for future DNA-based genetic tests.

In January 1991, NCHGR, the National Institute of Child Health and Human Development (NICHD) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invited a group of consultants to advise NIH on the appropriate issues to be addressed through pilot studies. They arrived at six Questions:

- What are the levels of understanding of, and interest in, CF carrier screening among different patient populations?
- What are the optimum forms and levels of pretest education for different patient populations?
- What are the accuracy and cost effectiveness of various types of tests?
- What are the best approaches to post-test counseling, in terms of patient understanding and psychological health?
- What are the optimum settings for providing CF carrier screening services?
- What record-keeping and reporting policies best protect against breaches of confidentiality, stigmatization, and discrimination?

The consultants recommended that NIH develop a consortium of multiple studies, each addressing some subset of the overall agenda. Such an approach would allow for standardization across the participating groups in terms of evaluation measures and tools, cost accounting, laboratory quality control, and human subjects protection. It was also recommended that NIH provide support to underwrite the current laboratory costs of the assay during these

clinical studies, to improve access to the pilots by all interested persons.

In April 1991, NCHGR, the National Center for Nursing Research, NICHD, and NIDDK issued a request for applications (RFA) for clinical evaluations related to CF carrier screening. The grant competition was open to nonprofit and for-profit organizations, including universities, public health departments, and voluntary organizations. The award period is for up to 3 years, and is renewable.

Originally, the RFA specifically excluded laboratory costs of the assays as eligible for grant support, since they were considered part of the clinical care of the individuals involved in the studies. Applicants were urged to obtain additional institutional and corporate support for these costs. (After the grants were awarded, the exclusion of test cost was rescinded for those studies involving subjects without a family history of CF.) Another requirement was that minorities and women were to be sufficiently represented in study populations.

In September 1991, NIH awarded eight grants to seven research teams around the country (box 6-B). A consortium approach to the pilot projects has been adopted: Grantees meet in workshops to coordinate and share information. "The underlying goal of these studies is to help determine whether CF mutation analysis should remain focused on members of families already known to be at risk, or whether it is feasible to offer the test more widely in an ethically acceptable manner" (52).

For fiscal year 1993, NCHGR announced that it intends to collaborate with the National Cancer Institute to begin pilot projects to help health care

Box 6-B-Clinical Studies of Testing, Education, and Counseling for Cystic Fibrosis Mutations, National Institutes of Health

In October 1991, three components of the National Institutes of Health-the National Center for Human Genome Research, the National Institute of Child Health and Human Development and the National Center for Nursing Research-launched a 3-year research initiative to optimize parameters for educating and counseling individuals who want to& screened for CF mutations. The research teams supported under this initiative coordinate their efforts. Where appropriate, some features of the research, such as evaluation measures and tools, cost assessment, laboratory quality control procedures, and human subjects protections have been standardized across sites. U.S. research teams at seven sites will conduct eight studies:

University ***of*** *North* ***Carolina, Chapel Hill, NC, "An Evaluation of Testing and Counseling for CF Carriers" ($2.31,916). C1ose relatives*** of CF patients will receive pretest education either from a pamphlet in a private physician's office or in a traditional genetic counseling setting. The investigators will also assess the effectiveness of a pre-genetic-counseling video for CF carrier screening clients. Both before and after receiving the results of CF carrier tests, subjects will be assessed to determine genetic and medical knowledge, psychological status, and selected health behaviors.

Children's Hospita[Oakland Research Institute, Oakland, CA, "Perception of Carrier Status by Cystic Fibrosis Siblings" ($73,196). By interviewing the adult siblings of (CF patients and the (CF siblings' spouses, the investigators will identify factors motivating or interfering with the pursuit of CF carrier testing in siblings, and assess their spouses' level of interest in screening. In addition to examining interest in testing, this study aims to assess the levels of understanding of test results and knowledge of medical aspects of CF, as well as to assess psychological functioning of CF siblings and spouses following testing.

Vanderbilt University, Nashville, TN, "Cystic Fibrosis Screening: An Alternative Paradigm" ($206,513). This study aims to determine the feasibility of a (CF carrier screening program that incorporates pre- and post-test education for people with negative screening tests and provides personal counseling primarily for those who test positive for CF carrier status. Written and video materials will be developed. The investigators will examine various settings for provision of carrier screening, determine the factors that affect a couple's decision whether or not to be screened for CF carrier status, and determine general acceptance of population screening.

University ***of*** *Rochester, Rochester, NY, "Testing* ***and Counseling for Cystic Fibrosis Mutation" ($274 ,110). CF*** carrier tests will be offered to women of reproductive age to determine what proportion desire it, what proportion of women who are tested adequately comprehend the significance of the results, and what proportion of partners

(Continued on next page)

Box 6-B---Clinical Studies of Testing, Education, and Counseling for Cystic Fibrosis Mutations, National Institutes of Health-Continued

of the screened women decide to be screened themselves. Anxiety, lack of comprehension, requests for prenatal diagnosis despite low risk, and the costs of the program will be assessed.

UCLA School of Medicine, Los Angeles, CA, "Cystic Fibrosis Mutations Screening and Counseling" ($179,067). Women of reproductive *age* and the partners of those who test positive will be screened. The target population includes large numbers of Hispanic and Asian Americans, two groups that have not been studied extensively for either their CF mutation frequencies or their response to screening and counseling. Pre- and post-test questionnaires will be used to determine level of understanding of CF, predictors of consent to screening, and emotional responses to implications of the test results in the various ethnic and socioeconomic subgroups. Strategies of pre- and post-test counseling will be compared for their effectiveness.

Johns Hopkins University, Baltimore, MD, "Ethical and Policy Issues in Cystic Fibrosis Screening" ($314,449). This project focuses on families and individuals receiving care from a health maintenance organization. It seeks to determine the level of interest in learning more about CF and factors that distinguish those who are interested in participating in a CF education program from those who are not. The focus consists of three elements: education of the study population, determination of the characteristics that distinguish those who agree to have the CF carrier test from those who decide not to be screened, and comparison of the responses of individuals identified as CF carriers and those identified as probable noncarriers, with emphasis on the extent to which these responses are influenced by marital status, or carrier status of the partner. All participants who test positive for CF carrier status and a sample of those who test negative will be followed for 1 year.

University of Pennsylvania, Philadephia, PA, "Prescriptive Decision Modeling for Cystic Fibrosis Screening" ($197,634 and $180,201). Decision theory and economic techniques will be used to model decisionmaking about CF carrier screening that addresses the following issues: who should be offered carrier screening and the best method for screening couples; the best course and sequence of further screening and treatment following initial results; rescreening individuals who have been screened in the past for CF mutations as more mutations are uncovered; the anticipated impact of future technologic innovation on CF carrier screening and treatment; tradeoffs between monetary and nonmonetary effects that the alternative answers to these questions imply; and differences in responses of various groups (i.e., patients, health care providers, and insurance companies, which have varying financial, psychological, and moral perspectives).

In addition, a team will conduct a clinical study, *How Much Information About the Risk of Cystic Fibrosis Do Coup/es Want?,* to complement the theoretical work. This project will analyze the decisionmaking processes of preconceptional and prenatal couples who are offered CF carrier screening one partner at a time, and, in the event of a negative result for the first partner, whether or not the couple chooses to have the second partner screened. The appropriate timing of CF carrier screening, as well as the amount that should be performed, will be investigated.

SOURCE: National Center for Human Genome Research, National Institutes of Health, October 1991.

professionals understand the best way to educate and deliver genetic tests to patients who ask for them, specifically genetic tests related to colon and breast cancer (75).

Funding for Genetic Services

Recent Federal support for genetic services, and thus salaries, has been minimal. Prior to 1981, genetic programs could apply through their State for funds under the National Genetic Diseases Act. The Omnibus Reconciliation Act of 1981 (Public Law 97-35) replaced the National Genetic Diseases Act and amended Title V of the Social Security Act to create the Maternal and Child Health (MCH) Block Grant (ch. *2).* This resulted in a drastic reduction of direct Federal support for genetic services not related to newborn screening (38). States that had received Federal support in the past now had to rely on the discretion of their State agencies and compete with other public health initiatives for diminishing dollars.

In fiscal year 1990, Federal and State funds for genetic services other than newborn screening totaled about $34 million, of which the Federal share was approximately $12 million (table 6-5). Other sources of finds that States used for genetic services

Table 6-5-Total Funding **for Genetic Services by** State, **Fiscal Year 1990**[a]

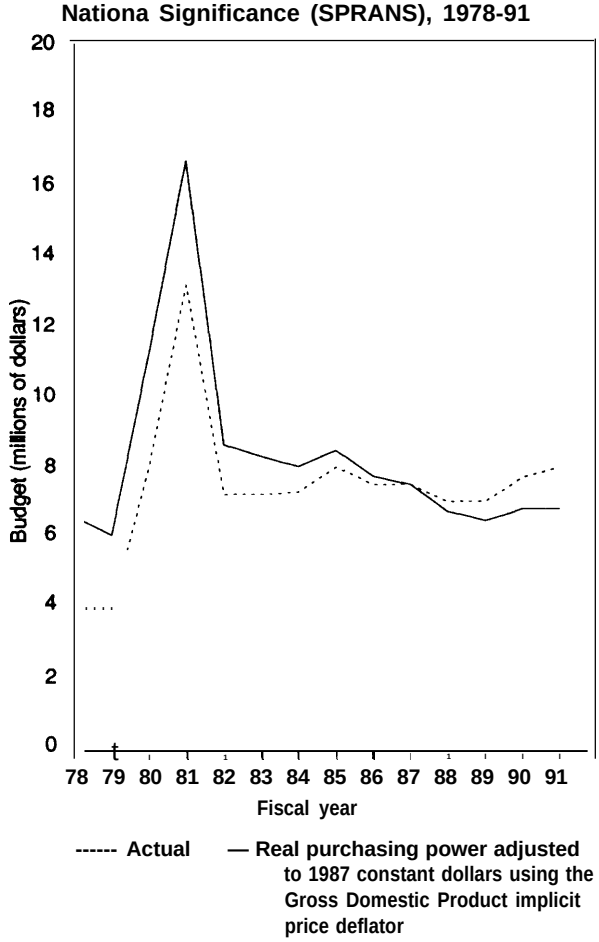
State	Total funds	Maternal and Child Health block grant	Other Federal	State	Other
AL	$ 228,000	*$24,000*	0	$60,000	$144,000[b,c]
AK	103,000	103,000		0	NA
AZ	524,600	0	$218,600	306,000	NA
AR	984,200	0	0	574,60@	409,600[b]
CA	16,673,300	0	470,200	2,163,800	14,039,300[e]
CO	403,000	0	0	27,000	376,000[f]
CT	371,400	0	0	371,400	NA
DE	145,800	0	0	145,800	NA
DC	481,200	40,000	220,700	220,500	NA
FL	1,070,300	0	0	1,070,300	NA
GA	1,567,000	162,700	0	1,404,300	NA
HI	318,900	102,000	216,900	0	NA
ID	246,900	123,400	0	0	123,500[b]
IL	292,000	262,800		0	29,200[f]
IN	843,100	254,200	0	149,300	439,600[c,g]
IA	935,000	0	o	860,200	74,800[b]
KS	50,000	0	0	50,000	NA
KY	291,000	171,700	0	0	119,300[b,g]
LA	388,600	0	0	388,600	NA
ME	293,400	60,000	0	233,400	NA
MD	798,300	400,300	0	398,000	NA
MA	716,100	0	632,500	83,600	NA
MI	725,000	0	0	100,000	625,000[f]
MN	256,400	51,900	135,800	68,700	NA
MS	333,300	0	173,300	0	160,000[f]
MO	1,617,000	180,000	0	1,437,000	NA
MT	423,400	0	59,400	0	364,000[h]
NE	202,000	167,700	0	34,300	NA
NV	582,100	54,400	80,000	217,500	230,200[e,g]
NH	152,300	38,100	0	91,400	22,800[b]
NJ	500,700	197,200	160,700	142,800	NA
NM	635,400	31,000	0	604,400	NA
NY	26,654,200	1,755,300	849,800	1,260,000	22,789,100[b,c,e,g]
NC	2,152,900	344,500	0	1,808,400	NA
ND	99,900	15,000	0	0	84,900[g]
OH	3,558,500	282,200	0	1,552,400	1,723,900[b,e,g]
OK	386,400	236,400	150,000	0	NA
OR	599,000	35,200	0	121,500	442,300[b]
PA	779,800	649,000	130,800	0	NA
PR	107,500	0	0	25,000	82,500[e,g]
RI	1,355,000	0	155,000	1,200,000	NA
SC	300,000	0	0	0	300,000[g]
SD	112,600	64,200	0	48,400	NA
TN	2,332,900	291,600	0	1,808,000	233,300[b,j]
TX	4,311,900	415,600	201,800	2,300,000	1,394,500[b,c,e,g]
UT	197,000	197,000	0	0	NA
VT	235,000	103,700	0	99,400	31,900[b,c,e]
VA	755,000	513,400	0	241,600	NA
WA	1,300,000	650,000	0	0	650,000[b,c,e,g]
WV	375,000	155,000	0	0	220,000[e,g]
WI	540,300	47,300	0	0	493,000[e,g]
WY	125.000	0	125,000	0	NA
TOTAL	$79,430,600	$8,179,800	$3,980,500	$21,667,600	$45,602,700

[a]Excluding newborn screening..
[b]Funds derived from third-party reimbursement.
[c]Funds derived from grants and contracts.
[d]Funds derived from a one-time grant of 18 months.
[e]Funds derived from provider service charges.
[f]Funds derived from newborn screening fee.
[g]Funds derived from provider in-kind services.
[h]Funds derived from surcharge to health insurers.
[i]Funds reported are for an integrated, tertiary care program that includes a genetic service component.
[j]Funds derived from mental health and mental retardation funds.
NA = Not available.
SOURCE: F.J. Meaney, "CORN Report on Funding of State Genetic Services Programs in the United States, 1990," contract document prepared for the U.S. Congress, Office of Technology Assessment, April 1992.

include provider-in-kind services, third-party reimbursement, and user fees. These funding mechanisms provided an additional ***$45.6*** million for at least 26 States (44).

Support for education, training, and services of rnaster's-level genetic counselors and other genetics personnel also comes chiefly through the MCH block grant and has declined precipitously. MCH genetics laboratory training grants totaled just under $1 million in 1991 **spread among *9* States** through Special Projects of Regional and National Signifi cance (SPRANS) monies, down from $2.6 million in 1981. In real purchasing power, this decrease represents a decline of about 76 percent. Total SPRANS funding, not just that devoted to training, but to provide seed money for services, education, and technical assistance demonstration projects has also declined in real purchasing power since 1981 (figure 6-2). In addition to Federal funding, at least 25 States devote State monies to education, technical assistance, and training (table 6-6) (44).

Figure 6-2-Federal Support of Genetic Services Through the Special Projects of Regional and Nationa Significance (SPRANS), 1978-91



SOURCE: Office of Technology Assessment, based on E. Duffy, Maternal and Child Health Bureau, U.S. Department of Health and Human Services, Rockville, MD, personal communication, February 1992.

RESULTS OF NONFEDERAL PILOTS

In the absence of federally sponsored pilot projects to evaluate CF carrier screening, several public and private institutions began to systematically screen subsets of the population-pregnant women and their partners, preconceptional teenagers and adults, and fetuses. While most are collecting data on the incidence of carrier status and mutation frequencies, some are also following psychosocial issues, such as levels of anxiety and retention of information. The various populations targeted for screening and the strategies used reflect the lack of consensus on the best approach to CF carrier screening. Some of these privately funded pilot projects are described in the following section. Because most were initiated at least one year before

Table 6-6-Funding for Genetics Education, Technical Assistance, and Training, Fiscal Year 1990[a]

State	Funding level	Percent of total[b]
AR	$14,000	13.1
DE	6,800	4.7
GA	20,400	1.3
HI	10,200	3.2
ID	19,000	7.7
IL	29,200	10.0
IA	467,500	50.0
LA	16,900	4.4
MD	98,000	12.3
MA	372,900	52.1
MI	320,000	44.1
MS	166,700	50.0
MO	80,800	5.0
NV	27,400	7.8
NM	195,200	30.7
NC	215,300	10.0
OK	19,500	5.0
OR	221,500	37.0
SD	69,800	62.0
TN	58,300	2.5
UT	14,800	7.5
WA	260,000	20.0
WV	33,400	8.9
WI	216,400	40.0
WY	10,000	8.0

a Figures not available for States not listed.
b Calculated as a percentage of genetic services funding (excluding newborn screening) from State, Federal, and other sources.

SOURCE: F.J. Meaney, "CORN Report on Funding of State Genetic Services Programs in the United States, 1990," contract document prepared for the U.S. Congress, Office of Technology Assessment, April 1992.

the NIH studies commenced, these efforts have more data.

Baylor College of Medicine: Prenatal and Preconceptional Carrier Screening of Couples

From 1990 through 1991, Baylor College of Medicine (Houston, TX) processed more than 1,800 samples for CF carrier screening and testing, using six mutations at 84.5 percent sensitivity. Baylor employs a two-step approach. First, both partners are concurrently screened for DF508+5. Anxiety of pregnant women who test positive and must wait for the results of their partner's test is reduced if both samples are processed simultaneously, rather than sequentially. Second, partners of identified carriers are subsequently analyzed for 12 additional mutations at no extra charge (24).

The original Baylor population was a mix of prenatal and preconceptional couples, many related to affected individuals. Of the high-risk group, 64 at-risk pregnancies were diagnosed. Of these 64, 14 affected fetuses were found; half of the pregnancies were electively terminated. Sixteen carrier fetuses were identified. Of those couples found to be +/-, no pregnancies were terminated and there did not appear to be undue anxiety. None of these +/-couples requested prenatal fetal diagnosis, Six couples in 1991 were identified as +/+ prior to conception (24).

Starting in September 1991, screening has been offered to all couples of reproductive age who have contact for any reason with Baylor's genetic services. Again, couples are screened, rather than individuals, at a charge of $100 per couple. Identified carriers are encouraged to refer their relatives for testing.

Cornell University Medical College: Prenatal Carrier Screening

Since April 1990, Cornell University Medical College has offered CF carrier screening to couples with a negative family history for CF who are enrolled in the prenatal diagnosis program (primarily for advanced maternal age). In 1992, screening has been extended to all couples of reproductive age coming to the genetic service, whether or not pregnancy is involved.

Initially, one partner was screened for DF508 mutation only; the W1282X mutation was added later because 30 percent of the Cornell couples are Ashkenazic Jews. If the partner is positive, followup testing of the other partner is done using six mutations. More than 500 couples have been screened to date using mouth rinse specimens. At a charge of $100 per couple, about 33 percent choose to participate. Those who choose to participate cite an interest in learning about the health of the fetus. Those who choose not to participate primarily cite a perceived low carrier risk and the fact that the patient's referring physicians had not specifically recommended the test.

All those who participate in the screening are informed (and in followup questionnaires, acknowledge) that the assays will miss some at-risk couples. Virtually all agree that the screening should continue and not be slowed until a greater proportion of CF carriers can be detected, or limited to those ethnic groups in which the detection rates are the highest (19).

Genetics & IVF Institute: Elective Fetal Screening

The Genetics & IVF Institute (Fairfax, VA) is a clinical and Laboratory facility that provides integrated outpatient services in the areas of human genetics and infertility. In 1990, the Institute began offering CF carrier screening of fetal samples to an unselected Caucasian population undergoing amniocentesis or CVS primarily for advanced maternal age.

As of August 1991,4,782 consecutive Caucasian patients undergoing a prenatal procedure were offered concurrent CF carrier screening of their fetal sample, on a self-paying basis. Initially, screening only detected DF508, but for some time has included DF508 and six other mutations. Of 3,013 CVS patients, 1,327 (44 percent) elected screening. Of 1,769 amniocentesis patients, 370 (20.9 percent) chose CF carrier screening. Three carrier fetuses were found in patients with a family history of CF, and 48 carrier fetuses, including a set of twins, were found in patients with a negative family history. Of these 50 couples, 12 declined further testing. In one couple requesting further testing, both partners were found to be DF508 carriers. In the other couples who had further testing, only one partner in each carried a mutation; all carried the DF508 mutation except for one who carried the G542X mutation. No couples chose to terminate the pregnancy based on these results.

Patients are called by a counselor or physician after delivery of the baby to determine the pregnancy outcome and apparent health of the child, to determine if a sweat test was performed, and to discuss retrospective attitudes toward CF carrier screening (63).

Roche Biomedical Laboratories: Prenatal Couples Screening

Roche Diagnostic Genetics, a national, full-service commercial genetics laboratory, launched a nationwide collaborative research study of CF carrier screening in July 1991. Using a reverse dot blot/ploymerase chain reaction method (ch. 4), Roche intends to screen 20,000 couples in the United States. Originally intended to last 6 months, participation has been less than expected, so the study has been expanded to 1 year. Assays are performed on bucca1 cell samples obtained at home using a buccal brush, collected in tubes, and mailed to Roche Biomedical Laboratories (Research Triangle Park, NC). Roche believes the ideal patients are those who are 15 to 16 weeks pregnant and are undergoing MSAFP screening. The sample can be collected as early as the first prenatal visit, week 8 of the pregnancy. This 'captive" population, believe Roche officials, is more likely to volunteer as research participants (3). A solicitation letter was sent to 100 obstetricians around the country introducing the program.

Roche employs the two-step approach, although samples will be collected simultaneously for both partners. The woman's sample will be screened first for DF508, G551D, G542X, and R553X. These mutations collectively account for about 85 percent of all CF mutations, according to Roche. If the woman's sample tests negative for these mutations, analysis is not performed on her partner's sample. The couple is then informed that they are at diminished risk. If the woman tests positive for one of the four mutations, then her partner's sample is tested for the same four mutations. If his sample is negative, the couple is told they are at reduced risk, and the woman is informed that she is a carrier. If the sample is positive, the couple is referred to a genetic counselor and advised of opportunities for prenatal diagnosis.

Roche officials believe this approach avoids undue anxiety on the part of a pregnant woman found to be positive. Roche reports that this approach will detect 72 percent of at-risk couples and 85 percent of carrier females. As of the fall of 1991, the subscription rate was 50 percent. There are no plans to offer the screen to preconception individuals (3).

Hypothetically, if Roche screens 20,000 Caucasian couples, and assuming a carrier frequency of 1 in 25, some 800 women will be identiled as carriers. If the partners of all 800 women are tested, 32 men will be found to be carriers. Thus, out of 20,000 couples, at a detection rate of 72 percent, 23 at-risk pregnancies will be identified. Because Roche will not screen the male samples unless the female sample is positive, however, the opportunity to identify 768 male carriers is lost.

McGill University: High School Carrier Screening

In Montreal, Canada, carrier screening for genetic diseases, such as Tay-Sachs, is a common practice in some high schools. In May 1990, nine students and four biology teachers at four schools in the Montreal area conducted a pilot study of attitudes in persons tested for the DF508 mutation. Forty percent of the nearly 600 students invited to participate in the project did so. Of these, two carriers were found. The carriers and their families were interviewed and found to hold positive views about their new awareness. Additional family members have been tested at their own request. Followup questionnaires showed that participants who received negative test results were found to be reasonably well informed about the CF clinical phenotype, its inheritance, and its distribution. Most understood that a negative test did not rule out carrier status and were satisfied they had taken the test (35).

Permanence Medical Group, Inc. —Vivigen— Integrated Genetics: Carrier Screening of Pregnant Women

In November 1991, the Kaiser Permanence Health Care System of Northern California undertook screening of 5,000 pregnant Caucasian and Hispanic women—with a negative family history only-for CF carrier status. The analysis and cost of running the samples is equally divided between Vivigen, Inc. (Santa Fe, NM) and Integrated Genetics (Frarningham, MA). The samples are screened for six mutations, at a sensitivity of about 85 percent.

Women are screened first. If positive, their partner's specimen is obtained and tested for 12 mutations.

Kaiser has developed an informational videotape that is being tested on control and experimental groups to determine its adequacy for educational use. In addition, several psychosocial survey instruments are being used to assess patients' understanding of the progression and genetics of CF both before and after screening.

The pilot program will end after 5,000 samples have been analyzed. At that time, Kaiser Permanence will make a decision as to how to proceed with general screening for members of its health plan. As of March 1992, 78 percent of women offered CF mutation analysis elected it (82).

SUMMARY AND CONCLUSIONS

The prospect of a highly sensitive, inexpensive assay for CF carrier status is not far into the future. As the sensitivity approximates 90 percent[1] for the general population, demand for carrier screening is likely to increase as the medical profession concomitantly recognizes its increasing duty to inform patients about the availability of the information. The ambiguous nature of the information, however, requires that the consequences of screening be fully understood.

Public education can go a long way toward preparing individuals for the decision of whether and when to be screened. However, public education campaigns related to family planning issues, such as CF carrier screening, are unlikely to be sponsored by the Federal Government. Thus, the clinical genetics community will have to work with allied health professionals and educators in designing and delivering information regarding CF carrier screening and, for that matter, other genetic tests to come.

In addition, the clinical genetics community will need to train other health care providers to help bear the educational burden as CF and other genetic tests become widely used. This expansion must maintain the nondirective philosophy of traditional genetic counseling. The Federal Government, through more support for training and genetic services, could facilitate this effort.

Because the current genetics infrastructure is built around the concept of entry into genetic services during the prenatal period or following the birth of an affected child, adults involved in a pregnancy will likely be the frost population to undergo routine CF carrier screening—this despite recognition that preconceptional screening is considered by most to be the optimal situation. Although adolescent screening programs appear to be successful in Canada, they are as yet unproven in the United States. At *this* time, widespread newborn CF carrier screening is unlikely.

Privately funded pilot studies have contributed groundbreaking and timely data about test sensitivity, target population, participant education, and patient response. As well, the Federal Government, through its clinical assessments of CF carrier screening, is playing an important role in examining the factors important to widespread carrier screening. The lessons of the past, from Tay-Sachs, sickle cell, and MSAFP screening programs, are instructive for ***the*** future.

CHAPTER 6 REFERENCES

1. Al-Jader, L. N., Goodchild, M. C., Ryley, H, C., et al., "Attitudes of Parents of Cystic Fibrosis Children Towards Neonatal Screening and Antenatal Diagnosis," *Clinical Genetics* 38:460-465, *1990.*
2. Angastiniotis, M., Cyprus Thalassaemia Centre, Archbishop Makarios III Hospital, Nicosia, Cyprus, "Development of Genetics Services From Disease Oriented National Genetics Programs,' presentation at **the 8th** International Congress **of** Human Genetics, Washington, DC, October 1991.
3. Barathur, R., Roche Biomedical Laboratories, Research Triangle Park, NC, personal communication, September 1991.
4. Benkendorf, J.L., and Bodurtha, J. M., "Human Genetics Education Videoshare: Round One, ' *American Journal of Human Genetics* 44:611-615, *1989.*
5. Biesecker, L., Bowles-Biesecker, B., Collins, F., et al., "General Population Screening for Cystic Fibrosis Is Premature, ' *American Journal of Human Genetics* 50:439, *1992.*
6. Botkin, J. R., ''Prenatal Screening: Professional Standards and the Limits of Parental Choice, ' *Obstetrics and Gynecology* 75:875-880, *1990.*
7. Bowling, F., Cleghorn, G., Chester, A., et al., "Neonatal Screening for Cystic Fibrosis," *Archives of Disease in Childhood* 63:196-198,1988.
8. Bowman, J.E. "Invited Editorial: Prenatal Screening for Hemoglobinopathies,'' *American* ***Journal*** *of Human Genetics* 48:433-438, *1991.*

[1] As noted previously, dF508+6- 12 detects 85 to 90 percent of CF carriers in the general population but 95 percent in Ashkenazic Jews.

9. Brock, D. J., "Cystic Fibrosis," *Antenatal and Neonatal Screening,* N.J. Wald (cd.) (New York, NY: Oxford University Press, 1984).
10. Cao, A., "A Disease Oriented National Health Service," *American Journal of Human Genetics* 49(Supp.):31, *1991.*
11. Caskey, C. T., Kaback, M. M., and Beaudet, A.L., "The American Society of Human Genetics Statement on Cystic Fibrosis,' *American Journal of Human Genetics* 46:393, *1990.*
12. Chase, G. A., Faden, R. R., Holtzman, N.A., et al., "Assessment of Risk by Pregnant Women: Implications for Genetic Counseling and Education,' *Social Biology* 33:57-64, *1986.*
13. Clarke, A., "Is Non-Directive Genetic Counseling Possible?," *Lancet* 338:998-1001, 1991.
14. Collins, D. L., University of Kansas Medical Center, Kansas City, KS, personal communication, September **1991.**
15. Cox, T. K., and Chakravarti, A., "Detection of Cystic Fibrosis Gene Carriers: Comparison of Two Screening Strategies by Simulations, *American Journal of Human Genetics* 49(Supp.):327, *1991.*
16. Crisis Counseling and HIV Antibody Testing, Report from the First Interdisciplinary Conference on Human Imrnunodeficiency Virus Antibody Testing and Counseling, sponsored by Sarah Lawrence College and Memorial Sloan-Kettering Cancer Center, Nov. 17, 1987.
17. Cunningham, G, C., and Kizer, K. W., "Maternal Serum Alpha-Fetoprotein Screening Activities of State Health Agencies: A Survey," *American Journal of Human Genetics* 47:899-903, *1990.*
18. Davis, J, G., "Invited Editorial: State-Sponsored Maternal Serum Alpha-Fetoprotein Activities: Current Issues in Genetics and Public Health, *American Journal of Human Genetics* 47:896-898,1990.
19. Davis, J. G., New York Hospital, Cornell University Medical College, personal communication, March 1992.
20. Earley, K. J., Blanco, J. D., Prien, S., et al. "Patient Attitudes Toward Testing for Maternal Serum Alpha-Fetoprotein Values When Results Are False-Positive or True-Negative, ' *Southern Medical Journal* 84: *439442, 1991.*
21. Edwards, J. H., and Miciak, A., "The Slash Sheet: A Simple Procedure for Risk Analysis in Cystic Fibrosis,' *American Journal of Human Genetics* 47: *1024-1028, 1990.*
22. Elias, S. E., Annas, G. J., and Simpson, J. L., "Carrier Screening for Cystic Fibrosis: Implications for Obstetrics and Gynecologic Practice, ' *American Journal of Obstetrics and Gynecology* 164:1077-1083, *1991.*
23. Evers-Kiebooms, G., and van den Berghe, H., "Impact of Genetic Counseling: A Review of Published Follow-Up Studies," *Clinical Genetics* 15:465-474, 1987.
24. Fernbach, S. D., Baylor College of Medicine, Houston, TX, personal communication, December 1991.
25. Fibison, W. J., "The Nursing Role in the Delivery of Genetic Services," Issues in Health *Care of* Women 4:1-15, 1983.
26. Fine, B.A., Northwestern University Medical School, Chicago, IL, personal communication, September 1991.
27. Forsman, I., "Education of Nurses in Genetics," *American Journal of Human Genetics* 43:552-558, *1988.*
28. Friedman, J. M., and Blitzer, M., ''ASHG/NSGC Activities Related to Education: Workshop on Human Genetics Education," *American Journal of Human* Genetics 49:1127-1128, 1991.
29. Harper, P. S., and Clarke, A., "Viewpoint: Should We Test Children For 'Adult' Genetic Diseases?," *Lancet* 335:1205-1206, 1990.
30. Hodgkinson, K. A., Kerzin-Storrar, L., Watters, E.A., et al., "Adult Polycystic Kidney Disease: Knowledge, Experience, and Attitudes to Prenatal Diagnosis,' *Journal of Medical Genetics* 27:552-558, *1990.*
31. Holtzman, N. A., *Proceed With Caution: Predicting Genetic Risks in the Recombinant DNA Era* (Baltimore, MD: The Johns Hopkins University Press, 1989).
32. Jones, S, L., "Decision Making in Clinical Genetics: Ethical Implications for Perinatal Practice, ' *Journal of Perinatal and Neonatal Nursing 111-23, 1988.*
33. Jones, S. L., Genetics & IVF Institute, Fairfax, VA, personal communication, December 1991.
34. Kahneman, D., and Tversky, A., "ThePsychologyof Preference, ' *Scientific American* 246:160-171, *1982.*
35. Kaplan, F., Clew, C., and Scriver, C.R., "Cystic Fibrosis Carrier Screening by DNA Analysis: A Pilot Study of Attitudes Among Participants," *American Journal of Human Genetics* 49:240-243,1991.
36. Keenan, K. L., Basso, D., Goldkrand, J., et al., ''Low Level of Maternal Serum Alpha-Fetoprotein: Its Associated Anxiety and the Effects of Genetic Counseling," *American Journal of Obstetrics and Gynecology* 164:54-56, *1991.*
37. Kessler, S. (cd.), *Genetic Counseling: Psychological Dimensions (New* York, NY: Academic Press, Inc., 1979).
38. Lin-Fu, J. S., Genetic Services Branch, Maternal and Child Health Bureau, U.S. Department of Health and Human Services, Rockville, MD, personnal communication, April 1992.
39. Lipkin, M., Fisher, L., Rowley, P. T., et al., "Genetic Counseling of Asymptomatic Carriers in a Primary Care Setting, " *Annals of Internal Medicine 105:* 115-123, 1986.

40. Lippman-Hand, A., and Fraser,F.C.,''Genetic Counseling—The Postcounseling Period: Parents' Perceptions of Uncertainty, " *American Journal of Medical Genetics* 4:51-71, *1979.*
41. Loader, S., Sutera, C. J., Walden, M., et al., "Prenatal Screening for Hemoglobinopathies. II. Evaluation of Counseling, ' *American Journal of Human Genetics* 48:447-451, *1991.*
42. Marteau, T.M.., "The Impact of Prenatal Screening and Diagnostic Testing Upon the Cognition, Emotions, and Behaviour of Pregnant Women, ' *Journal of Psychosomatic Research* 33:7-16, *1989.*
43. Marteau, TM., ''Reducing the Psychological Costs,' *British Medical Journal* 301:26-28, *1990.*
44. Meaney, F. J., "CORN Report on Funding of State Genetic Services Programs in the United States, 1990," contract document prepared for the U.S. Congress, Office of Technology Assessment, April 1992.
45. McNeil, B. J., Pauker, S, G., Sex, H. C., et al., ''On the Elicitation of Preferences for Alternative Therapies, New *England Journal of Medicine* 306:1259-1262, *1982.*
46. Miller, S. R., and Schwartz, R. H., "Attitudes Toward Genetic Testing of Amish, Mennonite, and Hutterite Families With Cystic Fibrosis, *American Journal of Public Health* 82:236-242,1992.
47. Mischler, E., et al., "Progress Report: Neonatal Screening for Cystic Fibrosis in Wisconsin, " *Wisconsin Medical Journal* 88: *14-18, 1989.*
48. Modell, B., ''Cystic Fibrosis Screening and Community Genetics, '' *Journal of Medical Genetics 27:475-479, 1990.*
49. Modell, B., Ward, R. H., and Fairweather, D. V., "Effect of Introducing Antenatal Diagnosis on Reproductive Behavior of Families at Risk for Thalassemia Major, ' *British Medical Journal 280;1347-1350, 1980.*
50. *Nance,* W. E., ''Statement of the American Society of Human Genetics on Cystic Fibrosis Carrier Screening,' in press, 1992.
51. Nance, W. E., Rose, S. P., Conneally, P. M., et al., "Opportunities for Genetic Counseling Through Institutional Ascertainment of Affected Probands," *Genetic Counseling,* F. de la Cruz and H.A. Lubs (eds.) (New York, NY: Raven Press, 1977).
52. National Center for Human Genome Research, press release, ''NIH Collaboration Launches Research on Education and Counseling Related to Genetic Tests,' Oct. 8, 1991, Bethesda, MD.
53. National Institutes of Health, Workshop on Population Screening for the Cystic Fibrosis Gene, ''Statement From the National Institutes of Health Workshop on Population Screening for the Cystic Fibrosis Gene, " New I *England Journal of Medicine 323:70-71, 1990.*
54. National Society of Genetic Counselors, Wallingford, PA, personal communication, June, 1991.
55. National Society of Genetic Counselors Cystic Fibrosis Ad Hoc Committee, *Genetic Testing for Cystic Fibrosis: A Handbook for Professionals* (Wallingford, PA: National Society of Genetic Counselors, 1990).
56. *Perspectives in Genetic Counseling* 12:6, spring 1990.
57. Riccardi, V. M., and Schmickel, R. D., "Human Genetics as a Component of Medical School Curricula: A Report to the American Society of Human Genetics, ' *American Journal of Human Genetics* 42:639-643, *1988.*
58. Roberts, L., "Cystic Fibrosis Pilot Projects Go Begging, " *Science* 250:1076-1077, *1990.*
59. Rowley, P.T., Loader, S., Sutera, C. J., "Do Pregnant Women Benefit From Hemoglobinopathy Carrier Detection?,' *Annals of the New York Academy of Sciences* 565:152-160, *1989.*
60. Rowley, P. T., Loader, S., Sutera, C. J., et al., "Prenatal Screening for Hemoglobinopathies. I. A Prospective Regional Trial," *American Journal of Human Genetics* 48:439-446, *1991.*
61. Schild, S., "Psychological Issues in Genetic Counseling of Phenylketonuria, ' *Genetic Counseling; Psychological Dimensions, S.* Kessler (cd.) (New York, NY: Academic Press, 1979).
62. Schull, W. J., and Hanis, C. L., "Genetics and Public Health in the 1990s," *Annual Review of Public Health* 11:105-125, 1990.
63. Schulman, J. D., Genetics & IVF Institute, Fairfax, VA, personal communication, March 1992.
64. Shaw, M. W., ''Conditional Prospective Rights of the Fetus," *Journal of Legal Medicine* 5:63-1 *15,* 1984.
65. Shiloh, S., and Sagi, M., "Effect of Framing on the Perception of Genetic Recurrence Risks,' *American Journal of Medical Genetics* 33:130-135, *1989.*
66. Singer, E., "Public Attitudes Toward Genetic Testing, '' in *Population Research and Policy Review* 10:235-255, *1991.*
67. Sorenson, J. R., Levy, H. L., Mangione, T. W., et al., "Parental Response to Repeat Testing of Infants With 'False-Positive' Results in a Newborn Screening Program, ' *Pediatrics* 73:183-187, *1984.*
68. Sujansky, E., Kreutzer, S. B., Johnson, A. M., et al., "Attitudes of At Risk and Affected Individuals Regarding Presymptomatic Testing for Autosomal Dominant Polycystic Kidney Disease, " *American Journal of Medical Genetics* 35:510-515,1990.
69. Tabor, A., Norgaard-Pedersen, B., and Jacobsen, J. C., ''Low Maternal Serum AFP and Down Syndrome, " *Lancet* 2(8395):161-162, 1984.
70. Thompson, L., "Cell Test Before Implant Helps Ensure Healthy 'Test-Tube' Baby, " *Washington Post,* Apr. 27, 1992.

71. U.S. Congress, Office of Technology Assessment, *Cystic Fibrosis and Genetic Screening: Policies, Practices and Attitudes of Genetic Counselors—Results of a Survey, OTA-BP-BA-97* (Washington, DC: U.S. Government Printing Office, forthcoming 1992).
72. U.S. Department of Education, *1990 Science Report Card, National Assessment of Educational Progress* (Washington, DC: U.S. Government Printing Office, 1992).
73. Walker, A. P., Scott, J. A., Biesecker, B. B., et al., ''Report of the 1989 Asilomar Meeting on Education in Genetic Counseling, *American Journal of Human Genetics* 46:1223-1230, *1990.*
74. Waples, C. M., Buswell, B. E., Martz, J. C., et al., "Resources for Genetic Disorders,' *Genetics Applications: A Health Perspective* (Lawrence, KS: Learner Managed Designs, 1988).
75. Watson, J. D., testimony before the House Appropriations Committee, Subcommittee on Labor—Health and Human Services-Education, Mar. 25, 1992.
76. Wertz, D. C., and Fletcher, J. C., "Attitudes of Genetic Counselors: A Multinational Survey, ' *American Journal of Human Genetics* 42:592-600, *1988.*
77. Wertz, D. C., Janes, S. R., Rosenfeld, J. M., et al., "Attitudes Toward the Prenatal Diagnosis of Cystic Fibrosis: Factors in Decision Making Among Affected Families," *American Journal of Human Genetics* 50:1077-1085, *1992.*
78. Wertz, D. C., Rosenfeld, J. M., Janes, S.R., et al., "Attitudes Toward Abortion Among Parents of Children With Cystic Fibrosis," *American Journal of Public Health 81:992-996,* 1991.
79. Wertz, D. C., Sorenson, J. R., and Heeren, T. C., ''Clients Interpretation of Risks Provided in Genetic Counseling, *American Journal of Human Genetics* 39:253-264, *1986.*
80. Wertz, D. C., Sorenson, J. R., and Heeren, T.C., "Communication in Health Professional-Lay Encounters: How Often Does Each Party Know What the Other Wants to Discuss?," *Information and Behavior,* vol. 2, B.D. Ruben (cd.) (New Brunswick, NJ: Transaction Books, 1988).
81. Wilfond, B. S., and Fost, N., "The Cystic Fibrosis Gene: Medical and Social Implications for Heterozygote Detection, " *Journal of the American Medical Association* 263:2777-2783, *1990.*
82. Witt, D., Kaiser Permanence Medical Group, San Jose, CA, personal communication, March 1992.
83, Zeesman, S., Clew, C. L., Cartier, L., et al., "A Private View of Heterozygosity: Eight Year Follow-up Study on Carriers of the Tay-Sachs Gene Detected by High School Screening in Montreal," *American Journal of Medical Genetics* 18:769-778,1984.