

# The Introduction of Cystic Fibrosis Carrier Screening into Clinical Practice: Policy Considerations

BENJAMIN S. WILFOND and  
NORMAN FOST

*University of Arizona Health Sciences Center  
University of Wisconsin Medical School*

SINCE THE IDENTIFICATION OF THE GENE ASSOCIATED with cystic fibrosis (CF) (Rommens et al. 1989; Riordan et al. 1989; Kerem et al. 1989), interest in general population CF carrier screening has been growing (Kolata 1990; Schulman et al. 1990; Brock 1990). Screening has the potential to allow individuals to make more informed reproductive decisions and to increase the choices available to them for avoiding the birth of a child with CF while offering society the potential public health benefit of a reduced incidence of individuals with CF. With the anticipated expansion of genetic knowledge resulting from the Human Genome Initiative (McKusick 1989), the experience of providing CF screening to the general population may become a model for developing new genetic tests and subsequently integrating them into clinical medical practice. More important, the potential magnitude of CF carrier testing in the reproductive-aged population gives this issue immediate relevance.

Soon after the CF gene mutation sequence was published, several biotechnology companies offered this service to physicians. However, enthusiasm for screening has been tempered by two policy statements, one issued by the American Society of Human Genetics (ASHG) (Caskey

et al. 1990) in November 1989, and the other by the National Institutes of Health (NIH) during a workshop on population screening for the CF gene held in March 1990, both recommending a moratorium on routine screening. The statements concur on several key points:

1. Routine screening should be delayed until pilot studies are completed, as "there is little experience in the delivery of such complex information to large populations" (Caskey et al. 1990). The complexity of the information derives from the ambiguity of negative test results and the variable prognosis for CF, complicating the education and counseling process, which would be formidable for a large population even with a simpler test.
2. If the test had a greater detection rate, then it might be appropriate to consider mass population screening. The NIH workshop report recommends that "screening could be offered to all persons of reproductive age if a 95 [percent] level of carrier detection were achieved," but only if additional conditions were met.
3. "Carrier testing should be offered couples in which either partner has a close relative affected with CF." (National Institutes of Health 1990)
4. The "optimal setting for carrier testing is through primary health care providers." (National Institutes of Health 1990)

Although these recommendations have dampened the initial drive for screening while articulating the current consensus on practice recommendations, they have not been analyzed in detail. Our purpose in this article is to review critically the ASHG and the NIH workshop recommendations, to evaluate some of the legal and ethical issues that will influence physicians' screening practices for cystic fibrosis, and to propose guidelines for their screening practices to primary care physicians and genetics services providers.

## Clinical Background

Cystic fibrosis is one of the most common significant autosomal recessive diseases affecting the white population. The median life expectancy of about 28 years has been steadily rising for more than two decades (Cystic Fibrosis Foundation 1991). The median survival of patients born in 1990 has been estimated to be 40 years, based on an observed decline in

infant mortality of CF patients (Elborn, Shale, and Britton 1991). Current investigational therapies, such as DNase (Aitken et al. 1992), offer the potential for even longer survival. Patients are variably affected, some dying in infancy from meconium ileus, a neonatal intestinal obstruction, some severely disabled with chronic obstructive pulmonary disease (COPD) as children, whereas others are rarely hospitalized, play competitive sports, and may not even develop symptoms until adulthood. However, most people with CF develop moderate lung disease by late adolescence or early adulthood.

The CF incidence in whites ranges from 1 in 1,700 to 1 in 6,500 in various populations, but is generally estimated to be 1 in 2,500 live births (Boat, Welsh, and Beaudet 1989). Assuming this incidence, approximately 1 in 25 white individuals (4 percent) are heterozygotes— asymptomatic carriers with a 1 in 4 chance of having a child with CF if their partners are also carriers. Recent newborn screening data from Colorado and Wisconsin suggest that the incidence of CF in whites may be in the range of from 1 in 3,000 to 1 in 3,500 (Hammond et al. 1991; Gregg et al. 1992). The Cystic Fibrosis Patient Registry estimates the incidence to be 1 in 3,400 in whites and 1 in 15,000 in blacks, with a corresponding carrier frequency of 1 in 30 for whites and 1 in 62 for blacks (Stacey FitzSimmons, Cystic Fibrosis Foundation, 1991: personal communication). Risk calculations in this article will be based on the most current data.

Cystic fibrosis results from mutations in a gene mapped to chromosome 7 that codes for a protein, the cystic fibrosis transmembrane conductance regulator (CFTR), which facilitates chloride transport (Anderson et al. 1991). In the United States, the most common CFTR mutation,  $\Delta F508$ , a three-base pair deletion, has been found on approximately 75 percent of chromosomes from CF patients (Lemna et al. 1990). Over 175 additional mutations have been identified, most of them rare, but analysis of from four to seven of the most common mutations, using polymerase chain reaction (PCR) amplification and gel electrophoresis, could increase the carrier detection rate in the U.S. population to about 85 percent (Beaudet 1990). With this detection rate, 72 percent ( $85 \times 85$ ) of at-risk couples will be identifiable. For varying ethnic and geographic groups, different mutations occur more commonly (Tsui and Buchwald 1991), which may require individualizing the testing protocol. Although the charge for the test is currently between \$150 and \$200, if screening is done on a mass scale, and with improved technology, the charge may

be reduced to a range of from \$30 to \$50 (Katherine Klinger, Integrated Genetics, Inc., 1990: personal communication).

### Deferment of Population Screening Until Pilot Studies Demonstrate Its Safety and Effectiveness

The ASHG and the NIH workshop statements advocate that mass CF carrier-screening programs should only be implemented after pilot studies are completed. Pilot studies prior to mass genetic testing have been recommended by reports from the Hastings Center (Lappé, Gustafson, and Roblin 1972), the National Academy of Sciences (1975), and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1983). The rationale for pilot testing is that previous experiences with genetic testing have demonstrated serious problems such as confusion, stigmatization, and discrimination when no comprehensive infrastructure was in place to provide education, informed consent, and counseling (Leonard, Chase, and Childs 1972; Kaback and Zeiger 1973; Childs et al. 1976a; Zeesman et al. 1984; Stamatoyannopoulos 1974; Whitten 1973; Reilly 1977; Berlfein 1990; Billings et al. 1992). The primary purpose of pilot studies is to establish effective educational methods, to determine interest in testing, to evaluate the influence of test results on reproductive behavior, and to document the occurrence of adverse psychological and social effects.

Support for pilot studies of CF carrier screening has been articulated in the medical literature by ethicists, geneticists, obstetricians, pediatricians, and pulmonologists (Wilfond and Fost 1990; Beaudet, 1990; Gilbert 1990; Elias, Annas, and Simpson 1991; Kerem and Lynch 1991). Recently, the American Medical Association (1991) adopted a report affirming the same position, as did the American College of Obstetrics and Gynecology (1991). As a result of the professional consensus for pilot studies, the NIH Ethical, Legal, and Social Implications Program of the National Center for Human Genome Research funded seven pilot programs for CF screening in October 1991 (National Center for Human Genome Research 1991).

However, many individuals with a commercial interest suggest that mass screening should be instituted without prior pilot studies. In 1989,

Keith Brown, president of Gene Screen, a biotechnology company that markets the test, suggested that pilot studies were not reasonable and that mass screening was inevitable: "to [expect us to] wait until we get 99 percent of the mutations and a national program is defined in 2½ years, that's kind of dreaming. The genetics community is thinking about how to make it happen ideally. Forget it, that game is already lost" (Roberts 1990b). Others believe the potential benefits of testing sufficiently outweigh the possible risks and suggest that empirical verification of benefit is not necessary. For example, Schulman et al. (1990), writing for the Genetics and IVF [In Vitro Fertilization] Institute, a private laboratory and clinic in Virginia, argue that it is "neither necessary nor desirable to delay access to a test now capable of detecting the large majority of CF carriers and families [and that the] benefits to the general public must take priority over possible perturbations within the healthcare delivery system (expanded education and counseling efforts) if CF screenings were implemented without delay."

The central ethical dilemma is how to balance the benefit to persons who may wish to avoid the birth of a child with CF against the potential harm that would result from the confusion, stigmatization, and discrimination associated with testing. Although the rationale for pilot studies prior to population testing is based on the duty to avoid harm, it does not mean that interventions must carry no risks because this requirement would preclude most medical care. Rather, risks are expected to have at least the potential of compensating benefits; in this case, that patients have sufficient information to allow an informed choice. The problem with Schulman's argument is that weighing the potential benefits and harms of mass screening cannot be performed without the empirical evidence from pilot studies.

Brock (1990), who runs a pilot screening program in Scotland, puts forth a different argument in favor of screening, focusing on the autonomy of the patient. He asks "whether we have the right to withhold, largely because of our own unresolved worries about the capacity to provide adequate counseling, screening from those who request it." He implies that patients' requests for testing should outweigh paternalistic actions to withhold testing. However, such paternalism is consistent with long-standing policies that limit the use of experimental drugs and devices unless there has been institutional review and patient consent after being informed about the experimental nature of the medical intervention (Levine 1986). There is no clear obligation to provide experi-

mental interventions to persons who request them. However, what is actually experimental in CF carrier testing is not the test itself, but the mechanism to provide the test to large groups of people.

The mechanism to provide education, consent, and counseling should be evaluated because these activities will determine the balance between benefits and harms. Before deciding whether the benefits of screening are worth the risks, potential screenees must be educated so they can make a preliminary judgement about their reproductive options. In CF carrier testing, the major benefit is the opportunity to avoid the birth of an affected child, but this benefit disappears if test results would not affect a couple's reproductive plans. Unless the person identified another potential benefit, there would be no reason to conduct the test. Other benefits of testing would include reassurance that a fetus does not have CF or emotional preparation for the birth of an affected child. The knowledge of an affected fetus may offer families the following practical benefits:

1. arranging for adequate medical insurance
2. providing for perinatal assessment
3. moving closer to a CF center that provides medical care
4. moving closer to family or other support networks
5. changing employment for the purpose of providing home care

Whether such potential benefits will be sufficient motivators to obtain testing is unknown.

In deciding whether to be tested, an individual would also need accurate, balanced information about the medical aspects of cystic fibrosis and, in order to comprehend their reproductive options, about the potential risks of being identified as a carrier and the implications of a negative test. Using current standards, such informed consent may require one to two hours of a genetic counselor's time (Barbara Bowles Biesecker, University of Michigan, 1990: personal communication). The use of alternative delivery systems, including pamphlets, videos, computers, or group sessions, will reduce personnel time, but these, too, need to be studied. The results of the NIH-funded pilot studies, which may not be available for at least two years, may not answer these questions sufficiently. Further studies may be required before population testing can be adequately assessed.

## The Limited Relevance of the Detection Rate

Both documents cite the limited sensitivity of the tests as a major impediment to mass screening. Several biotechnology companies also acknowledge this factor, but their opinions vary as to what degree of sensitivity would justify mass screening. One commercial brochure states: "We would like the test to detect at least 90 [percent] of CF carriers before advising routine screening" (Gene Screen 1990b). Others claim that, at 75 percent, the necessary threshold had been reached (Kolata 1990). In fact, as early as February 1990, the Genetics and IVF Institute began offering prenatal  $\Delta F508$  screening of fetuses to all white couples undergoing amniocentesis or chorionic villus sampling (CVS) (Bick et al. 1990).

The NIH workshop noted the 95 percent threshold because of a concern for couples in which one partner is a carrier while the other has a negative test (table 1). Approximately 5 percent (1 in 18) of the couples

TABLE 1  
Cystic Fibrosis Carrier Testing—Chances After Mutation Analysis<sup>a</sup>

Percent of cystic fibrosis mutations detectable	Chance of being a carrier risk for person after a negative test	Chance of cystic fibrosis in offspring		
		One partner tested	Both partners tested	
		Negative	Both negative	One positive/ one negative
0	1 in 30	1 in 3,400	1 in 3,400	1 in 3,400
55	1 in 66	1 in 7,900	1 in 17,400	1 in 264
75	1 in 118	1 in 14,200	1 in 55,700	1 in 472
85	1 in 196	1 in 23,500	1 in 154,000	1 in 784
90	1 in 294	1 in 35,300	1 in 346,000	1 in 1,180
95	1 in 587	1 in 70,400	1 in 1,380,000	1 in 2,350
96	1 in 838	1 in 101,000	1 in 2,810,000	1 in 3,350

<sup>a</sup> Calculations described in Lemna et al. (1990). The chance of being a carrier (assuming an incidence of 1 in 3,400) after a negative test (assuming a detection rate  $[d]$ ) is obtained by calculating the joint probability that a person is a carrier and has a negative test ( $.033 \times [1 - d]$ ) divided by the sum of the joint probabilities that a person is a carrier and has a negative test plus that of a person being a noncarrier and having a negative test ( $.967 \times 1$ ).

in the general population would fall into this category (table 2). These couples cannot be reassured that they are not at risk. The complexities associated with an imperfect CF test will be difficult to convey and understand, as evidenced by this confusing excerpt from the consent form of one commercial company:

Due to the present inability to detect all CYSTIC FIBROSIS CARRIERS, if I am a carrier of the cystic fibrosis gene, and if the other parent of any child I may have is also a carrier of the cystic fibrosis gene, and if either of us are [sic] not detected to be carriers of the CYSTIC FIBROSIS GENE using the test presently available, then a child born to us may be affected with CYSTIC FIBROSIS. (Gene Screen 1990a)

The challenge for education and consent posed by these complexities has been a deterrent to mass screening. Ten-Kate (1990) has argued that once the detection rate is greater than 95 percent, the major barrier to mass population screening will have been removed because the risk to couples with only one detected carrier of having a child with CF will be no greater than the a priori risk in the general population (table 1). Although an improved detection rate is necessary, it is not sufficient, as indicated in the NIH workshop statement:

These difficulties would be substantially reduced if testing could detect at least 90 to 95 percent of carriers. There is a consensus that population-based screening for carriers could be offered to all persons of reproductive age if a 95 percent level of carrier detection were achieved. The offering of population-based screening would still require that substantial educational and counselling guidelines be satisfied. (National Institutes of Health 1990)

However, the NIH workshop statement has been misrepresented by at least one commercial company, whose brochure implies that a 90 percent detection rate would be sufficient:

The members of that workshop also suggested that testing of individuals with no family history of the disease should not begin until, among other things, the test could detect "at least 90-95 [percent] of carriers." *This new CF carrier test satisfies that requirement for Caucasians of northern European ancestry.*

For those individuals who are found not to carry any of these ten mutations, the negative results will, in effect, reduce their chance of



being a CF carrier to only about 1 in 250. Thus, this new test may be of interest to ANYONE who has not yet completed their reproductive plans. (Collaborative Research 1991) (emphasis in original)

The brochure creates the impression that the NIH workshop would endorse screening for "anyone" because 90 percent of carriers are detectable. However, the consensus was 95 percent, not 90 percent. More important, the counseling and educational guidelines for population testing have not been sufficiently developed because the necessary research is still in progress.

### *Concern About Persistent Uncertainty*

Although a higher detection rate will simplify the information, a detection rate of 95 percent is not sufficient justification for mass screening. It is still possible that families with one positive and one negative test will be left with uncertainty and a sense of increased risk. Basic concepts of probability and risk are not easily understood. A study of middle-class, pregnant women found that 25 percent interpreted a 1 in 1,000 chance to mean 10 percent or greater (Chase, Fadden, and Holtzman 1986). People also tend to translate uncertainty into a binary form that focuses on the numerator of one, projecting from it that the event either will occur or not (Lippman-Hand and Fraser 1979). Even though the majority of couples is not at risk of having a child with CF, some might alter their reproductive plans (including the abortion of healthy fetuses) because they are confused about the impression of risk created by testing results.

Even with a 95 percent rate, as a result of the testing process, a couple with one positive test may falsely *perceive* their risk for having an affected child to be higher than before testing. Without testing, the couple may have given little thought to CF, unaware of the baseline risk. The process of carrier testing may heighten a couple's concern about CF, causing anxiety or irrational changes in reproductive plans, particularly if genetic counseling is inadequate. For example, although few couples' reproductive plans are influenced by the theoretical 2 percent risk of serious congenital problems (Marden, Smith, and McDonald 1964), a couple that was informed about a "test" result showing a 2 percent chance of their child having a major birth defect may become anxious or change their reproductive plans. An effective, research-based

counseling program for avoiding these problems and the practical ability to provide such a system are necessary criteria for population testing.

### *The Need for an Effective Infrastructure*

Even with 100 percent sensitivity, an effective program to provide education, consent, and counseling is still necessary. This lesson was demonstrated by the experience of the sickle cell screening programs of the early 1970s (Reilly 1977; Whitten 1973; Hsia 1980; Culliton 1972). Even though the sickle cell tests had a specificity and sensitivity of virtually 100 percent, the early programs generally did not adequately provide for education. Misunderstanding about the difference between being a sickle cell carrier and having the disease, sickle cell anemia, led to persons being stigmatized and experiencing discrimination in their access to employment and ability to obtain life insurance.

In contrast, Kaback and Zeiger (1973) established an effective pre-testing education program for the voluntary Tay-Sachs screening program piloted in the Baltimore and Washington Jewish community in the early 1970s. In addition to informed consent, Kaback emphasized community support and multimedia educational information; more than one year was devoted to educating the community before the first person was tested. The program was well received by the community and there was an effective transfer of information with minimal adverse psychological effects (Childs et al. 1976a,b). This program differed from the sickle cell program in that there were no racial issues involved in the screening, prenatal diagnosis was available, and the population was better educated.

Public education will be important in shaping attitudes toward genetic disorders and genetic testing to avoid stigmatization. Genetic counseling is necessary, but not sufficient, to prevent problems of stigmatization. A study of the long-term effects of a screening program for Tay-Sachs disease among high school students in Montreal revealed that, eight years later, 19 percent of carriers still attached some anxiety to being a carrier (Zeesman et al. 1984). A seven-year follow-up study of the sickle cell carrier screening program in Orchomenos, Greece (Stamatoyannopoulos 1974) revealed that 34 percent of couples perceived the trait as a mild disease. Twenty percent of these families felt that sickle cell trait meant a restriction of freedom and a risk of social stigmatization. Frequently, carrier status was concealed at the time of

marriage arrangements, and engagements between carriers and unaffected individuals were broken once carrier status was disclosed. Furthermore, the study found no reduction in sickle cell births. However, experiences with heterozygote detection for other diseases have fared better than those with sickle cell anemia. For example, screening for  $\beta$ -thalassemia in Sardinia resulted in a decline in incidence from 1 in 250 to 1 in 1,200 (Cao, Rosatelli, and Galanello 1991).

Genetic counseling for CF will require extensive explanation about CF and the potential risks associated with screening, particularly the possibility of insurance or employment discrimination (Billings et al. 1992). Medical insurers may attempt to coerce reproductive decisions. For example, a Los Angeles couple who already had a child with CF was informed that their health maintenance organization (HMO) would cover either prenatal diagnosis or the medical care of an affected child, but not both (Berlfein 1990). The fetus was diagnosed with CF and the couple elected to continue the pregnancy. The HMO told the family that they would not cover the medical expenses of the child. When challenged, the HMO reversed its decision, but the case demonstrates the potential for coercion. Potential screenees will at least need to be aware of these risks before they consent to testing. Recently, Wisconsin enacted legislation to prevent medical insurers either from requiring individuals to reveal whether a genetic test has been obtained, and, if so, the results, or from requesting genetic tests as a condition of coverage or in order to set rates.<sup>1</sup> The impact of this legislation is unclear, as the subsequent regulations are still being developed.

Given the complexities of genetic counseling for CF carrier testing, the development of an effective mass population screening program will be challenging because of its potential to screen the entire childbearing population. Pilot studies will be needed to determine the amount of personnel time required and whether there are sufficient resources to provide effective counseling. Even if ten minutes of direct personnel time were devoted to prescreening consent and education, an annual screening program for three million couples (an estimate of the potential magnitude if screening was provided to 75 percent of the four million women who become pregnant annually [U.S. Bureau of the Census 1990]) would require at least 638,000 hours (table 2). Counseling provided by the approximately 1,000 certified clinical geneticists and genetic

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<sup>1</sup> Wis. Stat. §631.89.

TABLE 2  
Genetic Counseling Hours for 3 Million Couples

Carrier status	Frequency (%) <sup>a</sup>	Total couples	Minutes per couple	Hours
No carriers	94.47	2,834,100	10	472,400
One carrier	5.45	163,500	60	163,500
Two carriers	.08	2,400	60	2,400
Total	—	—	—	638,300

<sup>a</sup> Calculated given a carrier frequency  $q = .033$  and detection rate  $d = .85$ ;  $(1 - dq)^2 + 2dq(1 - dq) + (dq)^2 = 1$ .

counselors (American Board of Medical Genetics 1990) would require each provider to spend 16 weeks every year on CF testing. Therefore, a mass screening program would require a tremendous increase in trained personnel to achieve only a minimum standard of consent and counseling. The only current alternative is to assign this very complex counseling task to persons not trained in genetics or genetic counseling, and unlikely to be informed about the rapidly changing complexities of CF testing. Alternative mechanisms for counseling, including multimedia resources (such as interactive computers and video), community-based programs, and improved training of primary care providers, especially nurses, need to be developed and assessed.

### *Cost-Effectiveness Considerations*

Even if a safe and effective delivery infrastructure were developed, policy makers will need to look carefully at the program costs per case of CF prevented. Commonly the public health goal of reducing disease as the *raison d'être* of genetic counseling is disavowed; the purpose instead is generally described as one of allowing more informed reproductive decisions by individuals (President's Commission 1983). Policy makers must consider whether it would be a fair or prudent use of resources to spend money on this arguably discretionary program at a time when approximately 33 million Americans are without basic health insurance (U.S. Bureau of the Census 1990). It is not enough to point out that most of the money for screening would be spent in the private sector because this does not address the question of whether such services should be

available to Medicaid recipients or persons with no third-party coverage. Moreover, dollars spent for CF screening are unavailable for other social needs. If costs incurred through population screening did not avert a single case of cystic fibrosis, it would be difficult to defend the expenditure for the sole benefit of providing more informed decisions. Evidence that testing does result in the reduction of disease, and at what cost, will be needed before funding of such a program could be justified from a public health perspective.

The impact of a screening program on the incidence of CF is uncertain, but preliminary evidence suggests that many people may not be interested in undergoing testing, prenatal diagnosis, or aborting a fetus with CF. CF differs from many other diseases for which there is interest in prenatal diagnosis because the severity of symptoms in a particular individual is unpredictable, there is the potential for survival into middle age, and normal intelligence is preserved. In a survey of parents of children with CF, Wertz et al. (1991) found that only 20 percent indicated a willingness to abort a fetus with CF, compared with 79 percent of this group who indicated a willingness to abort a pregnancy to save the mother's life, 75 percent for rape, and 58 percent for severe mental retardation. In another study, 214 pregnant women in the general population were surveyed after reading educational materials on CF. Although 98 percent believed carrier testing should be available, only 84 percent would have taken the test prior to pregnancy. If found to be at risk, 67 percent would be interested in prenatal diagnosis, whereas only 29 percent indicated a willingness to abort an affected fetus (Botkin and Alegmagno 1992).

If these preliminary findings reflect actual practices, the direct costs to avoid one CF birth could be close to 2.4 million dollars and might involve screening as many as 27,000 couples (table 3). An accurate cost-effective analysis will require further empiric assessment of behaviors. However, there may be less test-seeking behavior than these studies suggest because responses in questionnaires do not always translate to behavior. For example, although approximately 70 percent of at-risk people for Huntington disease indicated an interest in being tested, when the test was offered fewer than 15 percent actually responded (Quaid, Brandt, and Folstein 1987). In fact, in one of the few reports of CF testing, from a self-paying CF screening program, only 43 percent of CVS patients and 19 percent of amniocentesis patients agreed also to have their fetus tested for CF (Maddalana et al. 1991).

TABLE 3  
 Cost of General Population CF Carrier Testing to Avoid One CF Birth<sup>a</sup>

	Number of families	Services	Costs (\$)
Total couples approached	27,010	Education and consent @ \$10	270,100
Couples tested (.8)	21,607	Testing and counseling @ \$100	2,160,700
Couples at risk (.033 × .85) <sup>2</sup>	17	Counseling @ \$100	1,700
Prenatal diagnosis (.7)	12	CVS and CF testing @ \$1,200	14,400
Affected fetuses (.25)	3	Counseling @ \$100	300
Abortions (.33)	1	Abortion @ \$2,000	2,000
		Total	\$2,449,200

<sup>a</sup> Based on estimates of utilization (Wertz et al. 1991; Botkin and Alegmagno 1992) and direct costs (Garber and Fenerty 1991).  
 Abbreviation: CVS, chorionic villus sampling.

## The Role of Primary Health Care Providers

The NIH workshop (1990) statement concluded that the "optimal setting for carrier testing is through primary health care providers." Involvement of primary care providers is attractive for mass population genetic testing because of the apparent logistical advantage of using a large personnel reservoir. However, the primary care setting may not be ideal for population carrier screening. Primary health care providers may not have the time, information, training, experience, or interest to provide this service well.

Physicians may not be sufficiently informed about the genetic testing and reproductive counseling to provide the necessary information. For example, a study involving pediatricians found that 54 percent could not accurately state the risk of phenylketonuria (PKU) in a neonate with a moderately elevated test result (Holtzman 1978). In another study, Holtzman (1989) found that only 22 percent of a sample of obstetricians could describe the recommended clinical course of action following an elevated maternal serum alpha fetoprotein (MSAFP). Some respondents may have recommended abortion instead of first repeating the test or obtaining sonography, as recommended by the American College of Obstetrics and Gynecology (1986).

The NIH workshop (1990) statement on CF states: "Providers of

screening services have an obligation to ensure [that] adequate education and counseling are included in the program." The National Academy of Sciences report (1975) recommended that a comprehensive program include an ongoing assessment of patients' comprehension of information. Such standards would be difficult for most primary care providers to fulfill. It is not clear whether primary care providers will be able or willing to spend the time for education, consent, test interpretation, counseling, and assessment that is necessary in a CF screening program. However, it may be feasible to train primary care nurses, perhaps under the supervision of genetic counselors, to provide at least such services as prescreening education and consent.

Some primary care settings may pose additional problems. For example, prenatal visits appear to be an efficient setting for population CF carrier testing. However, the NIH workshop (1990) concluded that, ideally, population screening should be done prior to conception so that patients could avail themselves of preconception alternatives such as adoption or artificial insemination, and decisions would not be complicated by the urgency and emotional burden of an existing pregnancy.

Carrier screening during pregnancy is also likely initially to involve testing only women, which is not desirable for several reasons. First, any adverse effects of carrier identification would fall disproportionately on women. Second, testing both partners together would reduce the anxiety associated with the time delay in obtaining the partner's results after the woman has a positive test. Finally, the test results of the partner would greatly alter the risk assessment. For example, at an 85 percent detection rate, a person with a negative test has an apparent risk of 1 in 23,500 of having a child with CF (table 1). If the partner was negative, the risk would be reduced to 1 in 154,000; if the partner was positive, the risk would be 1 in 784. Testing the partner is desirable because these results could alter the apparent risk by close to 200-fold.

## Relevance of a Family History of CF

The ASHG and the NIH workshop statements acknowledged that people with a family history of CF should be offered testing. Testing of family members has been available since the late 1980s, using linkage analysis (Beaudet et al. 1989). Combining this with mutation analysis could allow carrier testing of blood relatives to be informative at close to

100 percent, provided that a proband's chromosomes were available. The chance of a relative of a CF patient being a carrier is 67 percent for a sibling, 50 percent in an aunt or uncle, 33 percent in a niece or nephew, and 25 percent in a first cousin. Relatives of identified carriers are also at increased risk.

Testing a population whose a priori chance of being a carrier is higher will result in proportionately fewer false positives for a given specificity, increasing the positive predictive value of the test (Wilfond and Fost 1990). Although the specificity of mutation analysis is unknown, false positives should be uncommon. However, laboratory or clerical errors will still cause a low proportion of false positive results and even this will become a finite number if screening is done on a mass scale.

The potential benefits of testing individuals with a positive family history are greater than for the general population. Some may already be anxious about their uncertain carrier status. Couples may otherwise have chosen not to bear children. High-risk couples with negative results could be reassured; the knowledge may allow some to bear children without fear. A couple found to be at a one in four risk prior to conception would be able to apply that knowledge to a full range of reproductive options. These families should be easier to counsel than the general population, as they are more likely to be familiar with the clinical course of CF and the associated burden of care. However, because more than 85 percent of CF patients are born to families without a prior family history (Kaback et al. 1984), testing this high-risk population is not likely to result in substantial reduction in CF incidence.

A screening program directed toward relatives of CF patients would limit the size and cost of the program. Cystic fibrosis centers could facilitate such a program by informing their patients that carrier testing is available for interested family members. Interested persons could be referred to genetic counseling programs, or counseled directly in centers that have genetic counselors or other clinicians competent in genetic counseling. Physicians and other health professionals in the CF centers would be able to play a substantial role in providing education and counseling. The CF Foundation could establish criteria for quality control of the test, as is currently done for the diagnostic test for CF known as the "sweat test" (Cystic Fibrosis Foundation 1990). The resources for counseling and quality control of testing even within such a limited program remain to be organized, but an infrastructure using existing resources has a greater potential of being developed to meet these needs.



## Legal Influences on Physician Practices

The ASHG and NIH workshop recommendations have influenced physician practices with the result that population screening has not yet become widespread (Kolata 1990; Roberts 1990a). However, other factors may influence practices.

1. Practices will be shaped by the policy statements of other relevant professional organizations, including the American Medical Association (1991), American Academy of Pediatrics, American College of Obstetrics and Gynecology (1991), Cystic Fibrosis Foundation, College of American Pathologists, and the National Society of Genetic Counselors.
2. Physicians' practices themselves will influence the practices of others. If the majority of physicians begin testing, it will push other physicians to do so. Similarly, if physicians do not offer testing, then screening is less likely to become a standard of care.
3. Entrepreneurial interests may drive screening practices. Biotechnology companies have been promoting screening and physicians and genetic counselors may have financial incentives for offering routine CF testing, especially if they are employed by, or have financial interests in, biotechnology companies or private testing laboratories. (Kolata 1990; Bick et al. 1990)
4. Physicians' perceptions of legal liability may be an impetus for screening.

We turn now to this last concern and provide a legal and ethical analysis of physicians' duties to offer carrier testing to their patients.

Although the ASHG and NIH workshop statements advise against population screening, perceptions of legal liability may influence physician practices. Brown, of Gene Screen, has described these legal pressures.

Cosmo or Redbook runs an article that will educate a lot of women about the test. It will educate a lot of lawyers, too. And the first lawsuit against someone who didn't offer the test will get a lot of attention . . . and once one company starts to offer it, it will be very difficult for others to hold back. (Roberts 1990b)

The implied message is that a physician who does not offer the test may be liable if a child is born with CF.

Over the last 20 years, court decisions have defined physicians' duties and parents' and children's ability to collect damages following the birth of a child with handicaps (Coplan 1985). Such cases have been labeled "wrongful birth" (parents' claim for cost of care and damages) and "wrongful life" (children's claim for compensation). Whether physicians will be found liable for not offering CF carrier testing to a patient has not yet been determined. The following conceptual analysis of this question centers on the meaning of *offer* to define the variety of legal and ethical duties involved.

### *Offering Screening*

The ASHG and NIH workshop statements use the term *offer* to describe the provision of screening services. Offering a service implies that the patient has considerable discretion in making the choice. It usually distinguishes services that are, on the one hand, *not discussed* because they are not within the range of acceptable alternatives from those at the other end of the continuum that are specifically *recommended* more strongly than if they were discretionary activities. Where a service falls along this continuum depends, in part, on a subjective assessment of the potential benefits and harms of the action. For example, consider the question of whether a surgeon should *offer* exploratory abdominal surgery. This is typically *not discussed* for an otherwise healthy young child with chronic symptoms suggestive of psychosomatic abdominal pain. However, such surgery may be strongly *recommended* for the child with an apparent appendicitis. In neither example would the surgery be offered.

Thus, offering is generally used to signify an optional service that will be provided if the patient is interested. The ASHG and NIH workshop statements, which state that CF screening should not be offered to the general population, posit that the service should not be provided at this time because there have not been pilot studies demonstrating safety and efficacy. Therefore, one might conclude that it is not necessary to discuss CF testing with patients. This would be consistent with the experimental status of testing programs. However, in addition to designating a stance toward *providing* a service, offering may also mean *informing* the patient about the availability of a service. The decision to inform a patient about a test may hinge on different criteria from those used for deciding whether to provide the test. Thus, offering is ambiguous be-

cause it fails to distinguish between the duties of providing information and providing a service. This distinction is important in understanding a physician's legal duties.

### *Providing Information*

The legal duties that have evolved in the wrongful birth cases focus on the provision of information. In a New Jersey case, *Berman v. Allan*,<sup>2</sup> a cause of action for "wrongful birth" was recognized when the parents of a child with Down syndrome filed a claim against the physician for failing to inform the 38-year-old mother that amniocentesis was available. In a California case, *Turpin v. Sortini*,<sup>3</sup> an audiologist did not diagnose a genetic form of deafness, resulting in a second child being born with the same condition. The court held the audiologist was negligent in failing to advise the parents of the hereditary nature, and that the family could recover for medical expenses necessary to treat the disorder. Cystic fibrosis was the subject of a case in New Jersey, *Schroeder v. Perkel*,<sup>4</sup> where the diagnosis of CF in a child was delayed until the mother was eight months pregnant with a second child who had CF. The court held the physicians liable for the medical expenses of the second child.

These cases point to the duty of the physician to disclose information that the patient might find material for making reproductive decisions. Instead of wrongful life and wrongful birth, Capron (1980) suggests that the term "wrongful nondisclosure" better captures the breach of duty by the provider. Robertson (1990) has argued that there may be a legal duty to inform patients in the general population that CF testing is available. He based his argument on a standard for informed consent that has evolved since the 1972 ruling in Washington, D.C., in *Canterbury v. Spence*,<sup>5</sup> which involved a patient who was not informed about the potential risks of a laminectomy. In *Canterbury*, the standard that was articulated suggests that determining what information must be presented should be based on information a reasonable person would find material, and not on the usual practices of physicians. Robertson also points to the Washington decision of *Helling v. Carey*<sup>6</sup> (involving

<sup>2</sup> 404 N.J. A.2d 8. (1979).

<sup>3</sup> 643 Cal. P.2d 954 (1982).

<sup>4</sup> 432 N.J. A.2d 834 (1981).

<sup>5</sup> 464 F2d 772 (D.C. cir.) cert. denied, 409 US 1064 (1972).

<sup>6</sup> 83 Wash. 519, P.2d 981 (1974).

a physician who failed to diagnose glaucoma in a 30-year-old patient because it was not the professional standard to screen patients under the age of 40) to suggest the possibility of courts making an independent determination of the standard of care that could differ with the assessment of the NIH workshop and the ASHG. Unlike CF testing, however, glaucoma testing is inexpensive and carries a low risk.

Robertson concludes that because some members of the general population will have an authentic interest in obtaining more information regarding their carrier status, there may be a legal duty to inform patients that the test is available, particularly in the one-third of the states that have adopted the more patient-centered standard of what a *reasonable patient* might want to know (Faden and Beauchamp 1986). However, the majority of states relies on a community standard of information that *physicians usually* disclose, supporting the view that there is no legal duty to inform patients about testing because most physicians do not routinely inform patients about CF testing and because policy statements from the NIH and ASHG advise against routine screening in the general population. The decision in *Munro v. Regents of the University of California*<sup>7</sup> supports this position. This case involved a non-Jewish couple who had a child with Tay-Sachs disease and claimed that the geneticists who provided counseling for advanced maternal age should have informed them about Tay-Sachs disease and testing so they could have made a more informed decision. The court held there was no duty to disclose because Tay-Sachs testing was not routinely provided to members of the general population. This legal position would also imply that there is no duty to inform patients about experimental alternatives that are not standard practice.

Although the legal analysis generally does not indicate a clear obligation to inform patients, there may still be an ethical obligation to inform patients about CF testing. As Robertson (1990) has pointed out, a reasonable person may wish to know about an existing test to detect CF carriers. People who have been anxious about CF (perhaps as a result of knowing a person with CF) may be very interested in testing. Withholding this information would infringe on their autonomy to make an informed decision. Whether the autonomy argument is sufficient justification for a duty of disclosure requires it to be balanced with the potential harms of testing, as we will elaborate in a later section.

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<sup>7</sup> 263 Cal. Rptr. 878 (Cal. app.2 Dist. 1989).

### *Providing the Test*

A duty of disclosure, if it exists, does not necessarily imply a duty to *provide* the test. Before the test is actually provided, it will also be necessary to educate the patients about the benefits and risks of the test. Without this additional information, the patient cannot make a fully informed decision to be tested. In fact, a provider may be liable for providing the test without sufficient education, consent, and counseling: he or she may offer incorrect information or might omit important information. One example of potential liability might be a couple with one detected carrier who decided that the partner should be surgically sterilized because they did not understand the information about degree of risk or severity of the disease; another might be a carrier who was not informed about the risk of losing employment or insurance, and then encountered these problems.

Andrews has argued that providing the test would require a further duty to provide *understandable* information about the risks and benefits of the test: "since the main service a health professional performs in genetic counseling is not treatment, but the provision of information, there is also the possibility the health care provider could be held liable if he or she conveys accurate information in such a way that the couple does not understand it . . . [or even] if the information might have been understood by a reasonable person, but is clearly not understood by that particular couple" (Andrews 1987). This position may set too high a standard, but the provider should give information that is, at least, capable of being understood by the patient. Andrews suggests that a personalized, written summary of the counseling session might enhance patient understanding and offer some legal protection against claims of inadequate information.

### Guidelines for Primary Care Physicians

Physicians could fulfill the potential legal and ethical duty to inform all patients about test availability without necessarily being prepared to provide testing. However, they must recognize the potential for this information to influence behavior, depending on what information is given and how it is framed and delivered (Lippman and Wilfond 1992). Although the goal of disclosure should be to provide nondirective infor-

mation, how the information is presented may motivate people to be tested. For example, Goodman and Goodman (1982) have commented that some of the brochures used in Tay-Sachs screening programs successfully promoted screening because they generated anxiety. Private companies with financial interests in promoting screening are also likely to present information in a potentially misleading fashion. A brochure from the Genetics and IVF Institute states: "Could I have a child with CF? The answer is probably yes. Almost any couple is at risk for having children with CF" (Genetics and IVF Institute 1991). In fact, fewer than 1 in 900 couples are at risk, but information presented in this way may be a strong motivation for screening.

Decisions to be tested for CF may also be influenced by how information about the disease is presented. An illustration of the possible impact of an arguably biased presentation is provided by the following excerpt from a consent form used in a pilot study from Denmark:

Cystic fibrosis is a serious disease that causes a marked tendency to pneumonia and a reduced function of the pancreas. Today, the disease is incurable and, if untreated, it leads to death in childhood as a result of increasing damage to the lung tissue. A very intensive life-long treatment of the lung disease now enables many patients to reach adulthood, but many still risk acquiring some degree of lung disablement at an early stage. At present, most patients are hospitalized every three months for two weeks of intensive treatment of infections; they also are treated daily for several hours in their homes. (Brandt and Schwartz 1990)

Not surprisingly, more than 90 percent of clients who read this description accepted testing. Consider the difference in a client's reaction to the following alternative hypothetical version:

CF is an inherited disease which used to be fatal, but now half of all patients will live into their fourth decade. CF does not affect intelligence; many people with CF go to college, enter professional occupations, get married, and have children. CF affects the respiratory and digestive systems, but symptoms can be controlled by taking enzyme capsules to help digestion, as well as antibiotics to fight off lung infections. Average life expectancy is steadily increasing, with rapidly advancing research producing the potential for better controls in the near future, and perhaps even a cure.

Both descriptions provide accurate, but limited, information. The second version, if read and understood, would almost certainly lead to a

lower interest in testing than the Danish model. The point is not that either description is better, but only that the information sent by the counselor and the way it is sent, or more important, the way it is received by the client, will have a profound impact on what reproductive decisions are made.

Therefore, CF testing will need to be presented in a balanced fashion. If, once informed, patients then want to learn more about the test, they could be referred to a genetics counseling program. A proposal for a more balanced disclosure follows:

There is now a blood test to identify carriers of the cystic fibrosis gene. Carriers are healthy but may be at risk for having a child with CF. CF occurs in about 1 in 3,400 births, but it is more likely to happen if there is a history of CF in your family. People with CF have chronic lung disease, but normal intelligence, and usually live into early adulthood. Testing is done in conjunction with genetic counseling, which may require one to two hours of your time before you would be in a position to know whether you would want to be tested. If you are interested in hearing more about this, please let your doctor know.

One argument for mentioning CF testing to all white patients, not just those with a family history, is because CF is a relatively common genetic disease in that population. However, what counts as common is arbitrary. Because the CF carrier frequency in blacks is close to half that of whites, some might suggest that blacks also be tested. Others might claim that CF is a relatively infrequent occurrence, even in whites. These potentially conflicting interpretations suggest that the frequency of the disease is not itself the central issue, but one of several that must be considered.

As physicians become more oriented to initiating discussions about reproductive health issues with their patients, information about CF testing, and genetic testing in general, should be discussed with patients along with such issues as family planning and contraception. However, there are over a hundred conditions for which carrier detection and prenatal diagnosis are potentially available (Elias and Annas 1987) and the Human Genome Initiative will increase this number. Primary care physicians are not likely to have the time to inquire about a family history, ethnic background, or interest in testing for each of these diseases. The patient's genuine interest in being informed of available tests could be supported by a checklist to be completed in the physician's waiting room and reviewed during the visit. The checklist might include a list of

genetic diseases with brief descriptions, as well as a list of symptoms suggestive of genetic disease. If the patient is interested in further testing, the primary care practitioner could provide it if he or she is prepared also to provide genetics counseling; if not, the patient could be referred to a genetics counselor. This approach has been implemented in family planning clinics in New England (Lea, Gardiner, and Guttacher 1992).

### Guidelines for Geneticists and Genetic Counselors

Geneticists and genetic counselors are more likely to have the time and training to provide the education, consent, and counseling needed for CF screening. However, because providing CF testing to all genetics clients who are seen for other reasons would place a great strain on these counseling programs, an additional hour might be required for each visit. Like primary care physicians, clinicians could acknowledge the availability of the CF test during a visit by asking patients to review a checklist and arranging an additional appointment for those interested in further testing. A generic list of testable genetic disorders may be less likely to raise anxiety about CF than a brochure specifically about CF. Persons interested in CF testing should be informed that the test is not yet routine, and may not be covered by insurance. Finally, the patient should be aware that prescreening counseling, ideally for both partners, is necessary, and this may take up to an hour. Unless the interest in CF testing exceeds the resources of a particular genetics clinic, counseling and testing should be provided to anyone who requests it. It is possible that referrals from primary care physicians and interest among existing genetics counseling clients still could exceed the resources of a particular clinic, in which case the clinic might consider giving priority to patients who have a relative with a CF mutation.

The distinction between informing and providing draws attention to the ethical obligation to inform patients about the test. Although this distinction is valuable in determining the extent of a physician's obligation toward patients, it may be lost on other practicing clinicians whose manner of informing may motivate patients to be tested, but who do not provide adequate education, consent, and counseling. Geneticists' practice of informing patients about CF testing might result in other less qualified practitioners informing, offering, and providing testing to



their patients. This might result in de facto mass testing with a great potential to cause harm. Thus a geneticist's decision of whether to inform patients about CF testing must not only include an evaluation of his or her obligation to promote the autonomy of the patient at hand, but must also account for the social consequences of this action on other patients, who may be harmed by an unevaluated mass testing program. Because providing specific information about CF is more likely than mentioning CF as one of many potentially available tests to result in the rapid diffusion of testing, we recommend that genetics providers meet their ethical obligation to inform patients by providing a generic checklist.

## Conclusion

The ASHG and NIH workshop reports concluded that mass population CF screening should be deferred until pilot studies demonstrating effective mechanisms for delivery of these services are completed. The NIH statement emphasized the importance of a 95 percent detection rate in deciding whether population screening should be initiated. We have argued that a high detection rate is not the central issue. It is a necessary, but not sufficient, reason for population screening. Even with 100 percent detection of carriers, the personnel and logistical resources needed to meet education and counseling needs must be developed and evaluated. Furthermore, policy makers must determine whether the goals of a population program — prevention of CF or informed reproductive decision making — warrant public funding or private reimbursement preferentially over other urgent health care needs of the American public.

Primary care physicians may not be the ideal providers of mass population carrier screening programs. Alternative mechanisms of community-organized programs with trained providers and multimedia educational resources should be developed and evaluated. There is no clear legal duty for primary care physicians to provide patients who have no family history with direct access to the test. Primary care physicians who are concerned about liability may discharge their ethical and legal duty by *informing* patients that CF carrier testing is available. *Providing* testing requires adherence to strict standards of education and consent. This should include information about CF, reproductive options, the meaning of a negative test, and the risks of testing. Providers may be liable if information is not communicated accurately or clearly. Therefore, pri-

mary care physicians who are not equipped to provide such services should refer interested patients to qualified genetics counseling programs. Ideally, geneticists and genetics counselors should inform patients about the availability of CF carrier testing. However, because this might result in de facto mass testing, as the distinction between informing and providing is easily blurred, geneticists should exercise restraint in informing patients about CF testing except in the context of a general description of potentially available tests.

In response to the ASHG and NIH workshop statements, most physicians have not provided CF screening to patients. Biotechnology companies have backed off from initial marketing positions. The NIH has funded pilot studies. In one to two years, we will have more data from which to develop a rational screening policy for CF. The initial experience with CF carrier testing indicates that it is possible to learn from past mistakes. This is encouraging, in light of the anticipated mapping and sequencing of the human genome, which will continue to raise the question of whether or not to screen.

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*Address correspondence to:* Benjamin S. Wilfond, MD, Department of Pediatrics, University of Arizona Health Sciences Center, 1501 N. Campbell Ave, Tucson, AZ 85724.