CYSTIC FIBROSIS HETEROZYGOTE DETECTION: THE INTRODUCTION OF GENETIC TESTING INTO CLINICAL PRACTICE

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Summary

Recent discoveries involving the gene associated with CF have created the potential for a mass genetic screening program which offers the possibility of substantial benefit to individuals and society that would be of unprecedented complexity and cost.
Within months of the identification of the CF gene, two policy statements offered recommendations for the clinical use of this technology for CF heterozygote detection. The American Society of Human Genetics in November 1989 and a National Institutes of Health Workshop in March 1990 issued reports on cystic fibrosis population screening, recommending that routine screening not be instituted at this time. Despite these recommendations, some physicians have begun to provide this test for patients in the general population. This report examines the guidance offered by these policy statements and provides specific recommendations for individual physicians, professional organizations, and public health policymakers. The following recommendations are made:

Mass population screening should be deferred until pilot studies are completed that demonstrate effective mechanisms for delivery of these services.

2. Even with 100% detection, the personnel and logistical resources needed to meet education and counseling needs must be developed and evaluated.

3. Physicians who provide clinical services or conduct clinical investigation of screening should avoid the perception and reality of conflict-of-interest by distancing

themselves from a financial interests in companies which offer CF testing, or profit-oriented laboratories in their own institutions.

4. Policymakers will need to 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.

5. Primary care physicians may not be the ideal providers for mass population carrier screening programs. Alternative mechanisms of community-organized programs with trained providers and multimedia educational resources should be developed and evaluated.

6. Population screening pilot studies should target reproductive-age couples prior to conception. Neonatal heterozygote detection will further complicate the process and is not a sufficient reason on its own for CF newborn screening.

7. Regulation to ensure quality control in the laboratories offering the screening will be necessary.

8. Physicians may discharge their legal and ethical duty by informing patients that CF carrier testing is available. Interested patients, ideally, should be referred to qualified

genetic counselors prior to testing. There is no clear duty for physicians to offer, recommend, or perform the test in the general population.

9. The provision of testing requires that strict standards of consent be followed. Providers may be liable if information is not successfully communicated or if pertinent information is not provided.

10. Individual genetic counseling programs may have to limit their services to clients with a family history of CF if the demand for general population screening exceeds their available resources.

INTRODUCTION

This paper has been prepared for the NIH-DOE Working Group on Ethical, Legal, and Social Implications of Human Genome Research. The objective has been defined in a letter from Eric Juengst, Ph.D. on August 31, 1990:[1] to identify the professional and social policy questions involved in the introduction of cystic fibrosis (CF) carrier screening into clinical practice. Specifically, we have been charged with addressing three questions: "1) What guidance has been provided to date by relevant policymaking organizations on how best to introduce CF testing into health care; 2) What additional factors will influence the way it is implemented; and 3) What policy needs remain in attempting to improve this situation."[1] A review of cystic fibrosis carrier screening policy can serve as a paradigm to more fully understand the general issues surrounding the development of new genetic tests and their subsequent integration into clinical medical practice. This expansion is expected as one outcome of the Human Genome Initiative. Awareness of the ethical, legal, and social implications of genetic screening are not new and have been thoroughly reviewed over the last fifteen years in a series of reports from the Hastings Center,[2] the National Academy of Science (NAS),[3] and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.[4] However, the current federal research agenda[5] has stimulated a renewed interest in these issues, and the recent discoveries involving the gene associated with CF[6,7,8] have created the potential for a mass genetic screening program which offers the possibility of substantial benefit to individuals and society that would be of unprecedented complexity and cost.

Within months of the identification of the CF gene, two policy statements offered recommendations for the clinical use of this technology for CF heterozygote detection. The American Society of Human Genetics (ASHG) issued a statement in November 1989.[9] The National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health convened a workshop and issued a report on population screening for the cystic fibrosis gene in March 1990.[10] These two statements have served as the foundation for policy discussion in this area. After a review of the medical background, we will provide a detailed analysis of these statements, comment about physicians' potential legal duties, and conclude with recommendations aimed at practicing physicians, professional organizations, and public health policymakers.

MEDICAL BACKGROUND

Cystic fibrosis is the most common, lethal, autosomal, recessive disease affecting the Caucasian population. This disease is presumed to result from an improperly functioning protein, the cystic fibrosis transmembrane regulator (CFTR),[7] that is involved in chloride transport across epithelial membranes. Recurrent pulmonary infections with Pseudomonas aeruginosa result in progressive obstructive lung disease, and pancreatic insufficiency is present in 85% of patients.[11] The median life expectancy is about 27 years and has been steadily rising for more than two decades.[11] Patients are variably affected, some dying in infancy from meconium ileus while others live well into their fourth decade. Some are severely disabled, while others are rarely hospitalized, play competitive sports, and may not even be diagnosed until adulthood.

The incidence of CF in Caucasians is estimated to be 1-in-2500 live births.[11] Approximately 1-in-25 individuals (4%) are heterozygotes. More recent newborn screening data suggests that the incidence of CF may be as low as 1 in 4000 to 1 in 5000,[12,13] with a corresponding carrier frequency of 1 in 33. CF is less common in American blacks and rare in Asians. The most common CF mutation, ΔF_{508}, has been found on 68% of a worldwide sample of 9000 CF chromosomes.[14] The frequency of the non-ΔF_{508} CF gene is equivalent in Caucasian, American black, and Asian populations, suggesting that the increased frequency of CF in whites is due to the ΔF_{508} mutation.[15] The frequency of ΔF_{508} among CF chromosomes from whites varies with different ethnic and geographic populations (see Table 1). Over sixty additional mutations have been identified,[16] most of them rare, but analysis of four to seven of the most common mutations could increase the detection rate in the US population to 85%.[17] With an 85% detection rate, 72% of couples will be identifiable ($.85^2$).

PROFESSIONAL RESPONSE

Soon after the ability to detect CF heterozygotes in the general population was possible, several biotechnology companies began marketing the test to physicians.[18,19] Shortly thereafter, the ASHG and the NIH Workshop statements were drafted. These statements concurred on two key points: 1) patients with a family history of CF should be offered testing, but 2) population screening is not indicated at this time. The NIH Workshop went further to suggest that: 3) population screening could be offered if a 95% detection rate is reached, provided that education and counseling guidelines were satisfied. The NIH Workshop also recommended that: 4) optimally, population testing should be offered by

primary care providers, and that the most appropriate population would be persons of reproductive age prior to conception. These four recommendations will be examined.

Recommendation 1: "Routine population screening should not be instituted at this time."

One of the major arguments against routine screening is that "there is little experience in the delivery of such complex information to large populations."[9] This information is particularly complex in the case of CF because of the ambiguity of negative test results. A person with a negative test can still be a carrier. This ambiguity complicates the education and counseling process, which would be formidable for a large population even with a simpler test. Both documents did suggest that if the test had a greater sensitivity, then it might be appropriate to consider mass population screening. The NIH Workshop report recommended that "screening could be offered to all persons of reproductive age if a 95% level of carrier detection were achieved."[10] This specific requirement of 95% detection will be addressed later in more detail.

Pilot Studies. Both documents advocate that new mass screening programs should only be implemented after pilot studies demonstrate the program's safety and its effectiveness in transferring information. The ASHG and NIH Workshop recommendations against population screening are rooted in widely accepted principles for genetic testing (see Table 2). The abbreviated form of the ASHG and NIH Workshop reports did not allow for a detailed discussion of the importance of pilot studies. We, therefore, think it important to explicate the central importance of a proven effective program infrastructure before widespread screening is underway.

The oldest and most fundamental ethical principle in medicine is primum non nocere--"first do no harm." This duty does not require that interventions have no risks, since such a requirement would preclude most medical care. Rather, the requirement is that risks have at least the potential of compensating benefits. The related principle of volenti nonfit injuriae--"with consent there is no injury"--implies that it is the patient's prerogative to choose whether the benefits outweigh the risks.

In CF carrier testing, the major benefit is the opportunity to change reproductive plans or behavior based on a clear understanding of the benefits and risks of various alternatives (see Table 3). If test results would not affect a couple's reproductive plans, this benefit disappears. Such a person would need to identify another potential benefit, or he/she would have no reason to be tested. For this reason, it is essential for potential screenees to understand and make a preliminary judgement about their reproductive options before making a choice as to whether screening is worth the risks. The desirability of a CF screening program would need to be evaluated on the basis of whether it can successfully communicate meaningful information in a way that will allow informed decision-making. **Empirical data are needed to determine if clients comprehend the information and act upon it in a rational manner, as well as to determine the incidence and severity of adverse effects such as stigmatization or discrimination.**

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In spite of the widely held view that new screening programs should be considered experimental, there is some restlessness among the biotechnology companies who would like

to proceed quickly without pilot studies. Keith Brown, President of GeneScreen, commenting on the need for pilot studies, stated:

> "...to [expect us to] wait until we get 99% of the mutations and a national program is defined in 2 1/2 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."[20]

This lack of regard for health services planning and policy analysis only underscores its importance in determining whether screening should proceed.

There are some who believe that the potential benefits of testing sufficiently outweigh the potential risks that empirical verification of benefit is not necessary. Shulman, et al.[20a] argue that it is "neither necessary or 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 health-care delivery system (expanded education and counseling efforts) if CF screening were implemented without delay." However, whether the expected benefits of mass testing would materialize with limited education and counseling will require empirical verification. Similarly, unless the harm from insufficient education has been documented, it is difficult to even attempt to determine a risk/benefit assessment.

A different argument has been put forth by Brock[20b] who 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 shifts the focus of benefit to the individual patient. Given the ability to provide education and counseling to a single person who requests testing, there may be little reason for a competent practitioner, with sufficient time, not to provide these services. However, it doesn't follow that the ability of the test to benefit an individual patient will translate to similar benefits if *screening* is performed on a large population. Thus, even though under ideal conditions, a person may benefit from being tested, a decision about mass population testing must be assessed by the benefit/costs to the population. Empirical data are needed to determine if clients comprehend the information and act upon it in a rational manner, as well as to determine the incidence and severity of adverse effects such as stigmatization or discrimination.

Soft Regulation. Mass screening for CF carrier detection might become standard practice, even if it is not legislatively mandated, as is done for newborn screening. It could take the form of routine testing in physicians' offices. Therefore, commercial marketing and entrepreneurial interests could drive screening practices as much as public health concerns. Marketing strategies could focus on consumers' interests in having perfect babies, as well as on physicians' fears of legal liability. Brown of GeneScreen has acknowledged these 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."[20] Even if Brown is correct about

public enthusiasm or risks of liability, it is not self-evident that these factors should determine whether physicians should offer testing. Practicing "defensive medicine," balancing the physician's interests with those of his patients, may offer an explanation, but it is not a justification for doing things that may be contrary to the patient's interests. It also may not be in the medical community's long-term interest to succumb to these pressures. If physicians wish to maintain a position of advocacy for their patients for the future, they will need to resist such pressures in the present.

The current policy statements will provide guidance to those physicians who are in a position to offer testing. The statements articulate a consensus of the expert community and serve an important function, to informally regulate physicians' behavior. They also help to establish a standard of care and provide support for the physician who wants to resist pressures to do routine screening. It may be that such proactive soft regulation will forestall the legal pressures. To an extent, the standard of care will be determined by physicians' practices. If physicians screen routinely, then screening will become the professional standard. If they resist legal and consumer pressures, then screening will not become the standard of care. We will return to a more detailed discussion of legal issues.

Recommendation 2: "Screening will be more feasible once the detection rate has reached 95%."

The limited sensitivity of present tests is cited in both documents as a major impediment to mass screening. This factor is acknowledged by several biotechnology companies, but

opinion varies as to which sensitivity would justify mass screening. One brochure suggests that "we would like the test to detect at least 90% of CF carriers before advising routine screening."[21] Some claim that the necessary threshold has already been reached.[22] One might ask: what is the rationale for the 95% threshold?

The central issue in the emphasis of the 95% threshold by the NIH Workshop was a concern for couples in which one partner is negative and the other is positive. This couple cannot be reassured that they are not at risk.[23] At a 75% detection rate,[a] a person with a negative test has a 1-in-100 chance of being a carrier, as 25% (1/4) of carriers will be missed [1/25 x 1/4]. A couple with only one positive test has a 1-in-400 chance of having a child with CF [1 x 1/100 x 1/4] (see Table 4). Prenatal diagnosis may exclude CF in 50% of those fetuses who do not receive the mutation from the known carrier, but the other 50% will be unable to obtain definitive information.

This scenario will occur commonly. Approximately 6% of the general population (1 in 17) would be in this situation.[b] For every couple in which both members are positive (one-in-four risk), there will be approximately 33 couples[c] {1/(1/25 x 3/4)} who will have one partner with a negative test and one with a positive test. In fact, 97% (33/34) of carriers will be in the situation of having a partner with a negative test. Almost all carriers, therefore, would be put into a limbo of uncertain risk, and perhaps, uncertain benefit. The impact of this uncertainly on such couples and how it affects decisions is central to the assessment of a population carrier screening program.

The actual risk of such a couple is either 25% or zero. However, the apparent risk is determined by the detection rate. At 75% detection, the apparent risk is 1 in 396. Although 97% of these couples could never have a child with CF, they may alter their reproductive plans (including the abortion of healthy fetuses) on the basis of this apparent risk. This complex concept will require careful explanation. The consent form with which one commercial laboratory attempted to clarify this problem included the following explanation:

> "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 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."[25]

All that is clear is the potential for confusion. A consumer who reads the patient information brochure from another company might be given the false impression that there is no risk if one partner has a negative test:

> "Does a positive result on the carrier screening mean that your child will be born with CF?...If you are identified as a carrier but your spouse is not, then your child will be either a carrier or unaffected."[26]

The implications for a couple with only one positive test will be difficult for physicians to explain, and for the public to understand. Comprehending simpler genetic tests is difficult

for physicians and the public, as evidenced by the widespread confusion associated with sickle cell testing in the 1970s.[27,28] The public is often unable to understand basic concepts of probability and risk. A study of middle-class, pregnant women found that 25% interpreted a 1-in-1000 chance to mean 10% or greater.[29] Physicians, themselves, are often unfamiliar with genetic tests. Holtzman,[30] in a study of pediatricians' knowledge of PKU testing, found that 54% could not accurately state the risk of PKU in a newborn with a moderately elevated phenylalanine level. In another study[31] of obstetricians' knowledge of maternal serum a-fetoprotein (MSAFP) levels, only 22% could describe the recommended clinical course of action following an elevated level. Some respondents may have recommended abortion, instead of first repeating the test, then performing sonography, followed by amniocentesis, as recommended by the American College of Obstetrics and Gynecology (ACOG).[32]

As the CF gene detection rate approaches 96%, the apparent risk for couples with one carrier detected will approach 1 in 2500 (the apparent risk in the general population). It has been argued that once the detection rate reaches 96%, and a couple's apparent risk will not have increased because of testing, then the major barrier to mass population screening will have been removed.[24] However, even if a 96% detection rate is obtained, there will still be significant issues to be addressed prior to mass population screening.

A) The 95% detection rate will leave many couples with uncertainty and a sense of increased risk.

The ethnic variations in the frequency of the ΔF_{508} mutation[14] (see Table 1) will require individualized risk predictions, which will be difficult to do in a heterogeneous population. A couple with one positive test may falsely perceive their risk of having an unaffected child to be much higher than the general population, although the risk is similar to the apparent risk in the general population (see Table 4). Without testing, the couple may have given little thought to CF, even though there is an apparent risk of 1 in 2500. Similarly, few couples worry about the 2% risk of serious congenital problems.[33] It is unclear how a couple would react to being told that a "test" result suggests there is a 2% chance that their child will have a major birth defect. The process of testing may heighten a couple's concern for CF, that there is still some degree of risk for CF may cause anxiety or irrational changes in reproductive plans, even after several hours of genetic counseling. Second, this couple will be at a relatively high apparent risk compared to other couples in which both partners have negative tests (1 in 1,500,000). Studies are needed to determine if single-carrier couples comprehend their situation and whether they alter their reproductive plans irrationally.

B) Even with 100% detection, it would not follow that population screening should be adopted.

The NIH Workshop acknowledged that an infrastructure to deliver education, consent, and counseling is necessary for the implementation of a population screening program. The importance of pretesting education has been demonstrated in earlier screening programs, even when the tests offered had a specificity and sensitivity of virtually 100%. The sickle cell screening programs of the early 1970s generally did not have adequate provisions for

education.[28,34,35] Misunderstanding between sickle cell carriers and sickle cell anemia led to inappropriate stigmatization and discrimination in access to employment and ability to obtain life insurance.[27,28,35]

An effective pretesting education program was employed by Kaback and colleagues[36] for the voluntary Tay-Sachs screening program piloted in Baltimore and Washington in the early 1970s. They emphasized community support and multimedia educational information, in addition to informed consent; over one year was devoted to educating the community before the first person was tested. Consequently, there was an effective transfer of information with minimal adverse psychological effects.[37,38] The principle to "do no harm" would require that routine screening only be instituted after it was clear that the program would not cause substantial harm. Even with definitive information, the infrastructure to provide the education, consent, and counseling to ensure that this information is successfully transferred to the client is essential.

Informed Consent. If only minimal information is necessary prior to testing, then the infrastructure for screening may be more attainable. Thus, the specific content of the information must be defined. Couples' interest in CF carrier testing will depend in part on what information they receive before testing. Couples will need to be educated about CF, including its inheritance, prognosis, treatment, and costs. People with CF may obtain advanced education, enter an occupation, marry, and bear children. This distinguishes it from most diseases which are prenatally diagnosable, such as Tay-Sachs disease, Down Syndrome, and neural tube defects. However, some CF patients may die in infancy from

meconium ileus, or have frequent hospitalizations. An unbalanced description of the disease may result in a biased decision about screening and reproduction. An illustration of the possible impact of an arguably biased presentation is provided by the following excerpt from a consent form used in Denmark:

> "Cystic fibrosis is a serious disease which causes a marked tendency to pneumonia and a reduced function of the pancreas. Today, the disease is incurable, and untreated it leads to death in childhood due to increasing damage of the lung tissue. By a very intensive lifelong treatment of the lung diseases, it can now be achieved that many patients reach adulthood. But rather many of these patients still risk, at an early stage, to acquire some degree of lung disablement. At present, most of the patients are hospitalized every 3 months for 2 weeks of intensive treatment of infections, and daily they have to use several hours on treatment in their homes. The pancreatic deficiency can be compensated by supplements to the food in the form of enzymes. With age, many of the patients will develop diabetes, which then demands insulin treatment."[39]

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

> "CF is an inherited disease which used to be fatal, but now, close to half of all patients live into their fourth decade. CF does not affect intelligence, and 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. Our 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 importantly, the way it is received by the client, will have a profound impact on what reproductive decisions are made.

Information about the disease will need to be coupled with information about reproductive options. Couples have two decisions to make. First, they must decide whether to be screened. Second, if they are at risk, they need to consider the reproductive options that are available and acceptable (see Table 3). The couple's response to the second issue may influence their response to the first. Although some couples may be uncertain about how they would respond if they were found to be at risk, a couple who would not consider aborting a fetus with CF may have less interest in being screened. Thus, a couple's sense of whether being at risk for CF would alter their reproductive plans will have some bearing on whether they will want to be screened. **Therefore, this information about CF and reproductive options will need to be presented prior to screening.**

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Prior to consenting to screening, the couple would also need to be informed of any potential risks associated with screening. Specifically, they would need to know about the possibility for insurance or employment discriminations, as this problem continues to occur.[40] Carriers could have difficulty obtaining life insurance or have reduced opportunity for employment. Medical insurance companies may attempt to coerce reproductive decisions. For example, a couple from Los Angeles who had a child with CF asked their HMO whether CF prenatal diagnosis would be covered.[41] They were informed that the HMO would cover the test or the medical care of an affected child, but not both. 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 their decision, but the case does demonstrate the potential for coercion.

Carriers may also be stigmatized, either by themselves or others. A study of the long-term effects of a screening program for Tay-Sachs disease among high school students in Montreal revealed that 8 years later, 19% of carriers still attached some anxiety to being a carrier.[42] A seven-year follow-up study of the sickle cell carrier screening program in Orchomenos, Greece[43] revealed that 34% of couples perceived the trait as a mild disease. Twenty percent of families felt that sickle cell trait meant a restriction of freedom and a risk of social stigmatization. Frequently, there was concealment of carrier status at the time of marriage arrangements and there were broken engagements between carriers and unaffected individuals once carrier status was disclosed. The study also found that there was no reduction in sickle cell births. **Pilot studies will be needed to determine the incidence and severity of adverse effects of a CF screening program.**

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The resources for providing education, consent, and counseling have not been developed. Using the current standards for genetic counseling, this information can be expected to require at least two hours of a patient's time with a genetic counselor.[44] The use of alternative delivery systems, including pamphlets, videos, computers, and group sessions, may reduce the time, but still would require considerable resources. If only ten minutes of personnel time was spent in education and counseling before a couple was capable of giving consent, then each of the 950 physician geneticists or genetics counselors[45] in the US would be required to spend 17 weeks a year to operate a screening program for 3 million couples who may be considering the possibility of having children[23] (see Table 5). Existing resources clearly will not be sufficient, resulting in less qualified personnel becoming involved in the process. Pilot studies will be needed to determine whether there are satisfactory alternative delivery mechanisms to meet clients' needs in providing understandable information, as well as to define the necessary time and resources needed.

C) Even if a safe and effective delivery infrastructure were developed, it does not follow that mass screening should be advocated.

The NIH Workshop statement defines the goal of a screening program as allowing people to make informed, reproductive decisions. The attainment of this goal can be measured by whether patients, in fact, become informed, and whether decisions are based on an accurate understanding of this information. This goal places appropriate emphasis on the promotion of individual autonomy in reproductive decisions. Even if this goal is achieved, there are additional considerations.

Public policy decision-makers will need to consider a cost/benefit analysis and consider the program within the context of the equitable allocation of health care resources. The goals of the screening program would need to be defined and the program's efficacy assessed. Policymakers should look carefully at costs of the program per case of CF prevented in determining whether the money is well spent. For example, a pilot study might demonstrate that a mass population screening program with a projected annual cost of one billion dollars[23] would not appreciably reduce the incidence of CF. Policymakers would need to consider whether it would be a fair or prudent use of resources to spend the billion dollars on this arguably discretionary program to improve reproductive decision-making at a time when approximately 33 million Americans are without basic health insurance.[46]

The impact of a screening program on the incidence of CF is uncertain. In a survey of parents of CF patients, 33% indicated that they would prevent the birth of an affected child, and another third were undecided.[47] It is not clear whether couples from the general population would be more or less likely to avoid a CF birth; the interest in this may continue to change as treatment of CF improves.

Based on the current practices of CF patients with respect to prenatal diagnosis and abortion, it could cost as much as 2.2 million dollars in direct costs per case prevented (see Table 6). If the detection rate were 95% and the cost of testing and counseling per couple were only $140, it would still cost one million dollars to avoid one CF birth.[23] One estimate of the cost of CF care is $7500 annually, or $200,000 over a lifetime.[48] Many clinicians believe that this estimate is conservative, that the lifetime cost may be greater than $500,000. **Better**

data are needed to determine the cost of the program per CF birth avoided before policy decisions of this nature can be considered.

Recommendation 3: "Screening is optimally administered through primary health care providers."

The NIH Workshop statement concluded that the "optimal setting for carrier testing is through primary health care providers."[10] Potential settings which are likely to involve primary care physicians are prenatal visits and newborn screening. However, these settings are not ideal for population carrier screening.

Prenatal Visits. Prenatal visits would be a potential entry point for clients in a screening program. Obstetricians are likely to be responsive to the perception of liability if available testing is not offered. For example, soon after the Food and Drug Administration (FDA) released MSAFP test kits, the American College of Obstetricians and Gynecologists (ACOG) Department of Professional Liability recommended that every prenatal patient be advised of the availability of the test, even though its scientific committees recommended that testing be linked with resources for genetic counseling, sonography, and amniocentesis.[49] A disadvantage of prenatal screening is that preconception alternatives such as adoption or artificial insemination would not be available, and prenatal decisions would be complicated by the emotional burden of an existing pregnancy. **The NIH Workshop affirmed that population screening ideally should be done prior to conception.**

Many reproductive-age clients may have little contact with health care providers other than for prenatal care. Prenatal screening may involve the testing of only one partner. At a 75% detection rate, a person with a negative test has an apparent risk of 1 in 10,000 of having a child with CF (see Table 4). The test result of the other partner would greatly alter this assessment. If the other partner were negative, the risk would be reduced to 1 in 40,000; if the partner were positive, the risk would be 1 in 400. The other partner's test result could alter the apparent risk by 100-fold. **A mass screening program would need to test both partners of a couple to obtain the most accurate information.**

Neonatal Carrier Detection. Neonatal carrier detection was favored by 45% of geneticists in an international survey.[50] Carrier detection of newborns is problematic, since they will have little or no direct benefit from this information until they reach reproductive age. However, they still may be subject to stigmatization and discrimination. Since newborn carrier detection offers potential risks with few direct benefits, screening should be approached cautiously. Parental consent prior to newborn screening may not remove these risks, but it would serve to educate families about the implications of being a CF carrier and allow them to decide whether the risks are outweighed by the benefits of early diagnosis of CF. However, considering that education and meaningful consent are difficult to accomplish, even in the best of circumstances, it is not likely that many parents will understand the information presented at the time of the birth of a child.

There are potential indirect benefits to the parents of carriers. The parents will have the knowledge that at least one of them is a carrier and that they, in fact, may be at risk for

having a child with CF. Thus, newborn screening for CF could be an efficient mechanism for identifying parents who are carriers. However, if the goal of the program is to identify parental carriers, it would expose a nonconsenting third party (the newborn) to the risks of carrier detection. Parents could obtain this information directly without exposing their child to these risks.

More importantly, neonatal carrier detection for the purposes of informing parents of their risk will be fraught with the same problems of direct carrier detection. That is, the lack of consent may result in a person being tested without being fully informed, with the subsequent potential for confusion or stigmatization. In 97% of the cases, a newborn carrier will imply that only one parent is a carrier. Thus, the result of an indirect carrier screening program will be that most carriers are left with the dilemma of not knowing with certainty whether the other partner is truly a noncarrier.[d] Additionally, nonpaternity may be disclosed if the parents of the child are tested. This potentially explosive consequence would have to be explained prior to testing if meaningful, informed consent is taken seriously.

The NIH Workshop statement recommended that screening be limited to people of reproductive age; that "newborn screening primarily to detect carriers is inappropriate."[10] This suggests that incidental newborn carrier screening, as a consequence of a newborn screening program to diagnose CF, may be appropriate. With a 75% detection rate, mutation analysis could identify 94% of CF patients.[e] Utilizing mutation analysis as a second tier following a CF screening assay [such as the immunoreactive trypsinogen (IRT) test] may be a feasible approach to improving the sensitivity and positive predictive value of the IRT.[12]

The benefits of early diagnosis and presymptomatic treatment of newborns with CF have not been resolved.[13,51,52] There is some retrospective evidence that screening and presymptomatic diagnosis may improve prognosis,[53,54] but the Cystic Fibrosis Foundation[55] has not recommended screening, until that time when the completion of prospective studies demonstrate the efficacy of screening and early intervention. Such a prospective, randomized, controlled study has been ongoing in Wisconsin, which has not shown any benefits after five years.[56,57] **Until the medical benefits of CF newborn screening are defined, it would be premature and inaccurate to advocate CF newborn screening and to cite CF newborn carrier detection as an <u>additional</u> benefit of newborn screening.** In fact, incidental carrier detection may complicate a newborn screening program due to the need for parental consent. Currently, only three jurisdictions have an explicit consent requirement for newborn screening.[58] **If CF newborn screening is found to have a favorable cost/benefit ratio and if the screening procedure utilizes mutation analysis, then it may be necessary for state newborn screening programs to re-examine the question of informed consent for newborn screening.**

Primary Care Providers. As previously mentioned, primary care providers have difficulty providing counseling for less complex tests such as MSAFP or PKU.[30,31] It is not clear whether primary care providers will be able or willing to spend the time for education, consent, test interpretation, and counseling. The NIH Workshop statement affirms that "providers of screening services have an obligation to ensure that adequate education and counseling are included in the program."[10] The NAS recommended that a comprehensive program include an ongoing assessment of patients' comprehension of information.[3]

Primary care physicians who are unable to provide comprehensive screening services should refer interested patients to genetic counseling programs. Since there are insufficient genetic counselors to meet the demand of a mass population program, alternative mechanisms, including community-based programs and specially trained CF carrier counselors, will need to be developed.

Recommendation 4: "Patients with a family history of CF should be offered testing."

The primary argument in the NIH Workshop document supporting this claim regards the improved accuracy of the test in this population. Combining mutation analysis with linkage analysis, carrier testing would be close to 100% informative, providing that a proband's chromosomes were available.[59,60] Unambiguous test results would simplify the counseling, increase the likelihood that information were understood, and increase the likelihood that patients would be able to make informed, reproductive decisions. This improved sensitivity of the tests would allow patients whose tests are negative to be more certain that they truly are not at risk for having an affected child.

Families in which there is a positive history also have a higher prevalence of carriers than the general population. For a given specificity (1 minus false-positive rate), the positive predictive value (the proportion of people with positive tests who are actually carriers) will be greater. Theoretically, biological specificity should be 100%, but there will be some finite number of laboratory and clerical errors. If the false-positive rate for couples identified to be at a 1-in-4 risk, due to laboratory and clerical errors, were only 1 per 1000

(99.9% specificity), the positive predictive value would be 94% in a select population of CF siblings and their spouses (1 in 37.5 couples are at-risk of both partners being carriers). In the general population, where 1 in 625 couples are at-risk, the positive predictive value would be reduced to 47%.[4] This analysis is based on a hypothetical assumption of a specificity of 99.9% to illustrate the basic epidemiologic principle that even with a high specificity, positive predictive value diminishes with prevalence. Most experts agree that with careful quality control, including the resampling of couples with positive results, the number of false-positive couples should be negligible. However, this analysis does emphasize the importance of regulation in ensuring a high standard of quality testing. Individuals with a positive family history may already be in a heightened state of anxiety regarding their uncertain carrier status. Some of these couples may have otherwise chosen not to bear children. High-risk couples with negative results can be reassured; the knowledge may allow some to bear children without anxiety. The knowledge prior to conception that a couple is at a 1-in-4 risk, would allow that couple a full range of reproductive and lifestyle options (see Table 3).

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, time will still need to be spent discussing the spectrum of severity of CF. These family members may have an idiosyncratic perspective of CF and could perceive CF to be either more or less debilitating than it is for the typical patient.

Finally, such a restriction would limit the magnitude of the screening program to a more manageable number. An important concern with mass population screening is that there are insufficient personnel trained in genetic counseling who are knowledgeable about the rapidly changing facts of CF screening. An annual screening program for three million couples would require each counselor to spend 17 weeks per year on CF testing (see Table 5). However, a program restricted to first-degree relatives would limit the size of the program. Considering that there are an estimated 20,000 CF patients in the US,[61] there would be a potential pool of 200,000 couples if each CF patient would have approximately 10 close relatives (siblings, aunts/uncles, first cousins). It is not certain how many people in this group would seek out testing. For example, if we assume that 25% of these relatives are of reproductive age, if only 15% of these relatives would seek out screening services during a given year, the annual pool would be reduced to 7500 couples (200,000 x .25 x .15). Additionally, the 129 Cystic Fibrosis Centers[62] could participate in 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 to those centers which have genetic counselors or to other clinicians competent to do genetic counseling, who could then assume some of the responsibility for meeting this population's counseling needs. If each CF center could provide counseling for 50 couples a year, the number of couples requiring services directly from genetics programs would be reduced by half. Additionally, the CF centers could establish criteria for quality control of the test, as is currently done for the sweat test.[63]

Offering testing to couples with a family history of CF is more likely to meet widely accepted criteria for an acceptable screening program.[2,3,4] The test would be highly sensitive and have a high positive predictive value. This population has a defined interest in the test and familiarity with the disease. However, even for such a limited program, the resources for counseling and quality control of testing remain to be organized. There is a greater potential that an infrastructure utilizing existing resources could be developed to meet these needs. **It will be necessary for those professional organizations involved with genetic counseling, cystic fibrosis, and laboratory testing to provide leadership and offer recommendations regarding the effective delivery of services to this population.**

Screening of close relatives still would require demonstration of a mechanism capable of providing the effective transfer of information. Informed consent will be no less important for this group. Entrepreneurial interests also may push screening in this population without regard for genuine consent. For example, a patient information brochure refers to this group and implies that testing is recommended and that counseling is only necessary after the test:

> "At this time, the direct DNA test (for the phenylalanine 508 deletion) is recommended by the American Society of Human Genetics for all individuals and/or couples with a family history of cystic fibrosis ... Reproductive decisions based on these tests should only be made after consultation with a genetic counselor or other knowledgeable health care professional."[64]

This statement has misstated the ASHG recommendations, which is that <u>physicians should offer</u> the test. The ASHG does not make any recommendation as to whether <u>family members</u>

should or should not be tested. Furthermore, consulting with a genetic counselor needs to happen before testing, in order for that client to be able to decide for himself whether or not to be tested. Thus, even though the benefits of screening for this select group are more likely attainable, the same principles would need to be adhered to just as would be for an acceptable testing in the general population. **Patients with a family history of CF should be informed about the test and referred to a comprehensive program if interested in more information.**

ADDITIONAL INFLUENCES ON SCREENING

The ASHG and NIH Workshop statements are grounded in the principles of the Hastings Center, NAS, and President's Commission reports. Based on the ethical concerns about protection from harm and respect for autonomy, they recommend that screening only be offered following provisions for education, quality control, informed consent, and counseling which have been demonstrated to minimize adverse effects from confusion, stigmatization, and discrimination and to deliver on intended benefits. The ASHG and NIH Workshop statements offer general advice to primary care physicians that routine screening is not the "standard of care"[9] and should not be routinely offered, but there are already reports of physicians planning to offer routine screening.[22]

Other factors which may influence physician practices include: 1) Entrepreneurial interests, which may drive screening practices. Biotechnology companies are likely to promote screening. Physicians and genetic counselors may also have financial incentives to offer routine CF testing. Many are in the employ of or have financial interests in biotechnology

companies. 2) Physicians' perceptions of legal liability. 3) The development of additional policy statements by other relevant professional organizations, including the American Medical Association, American Academy of Pediatrics, American College of Obstetrics and Gynecology, Cystic Fibrosis Foundation, College of American Pathologists, and the National Society of Genetic Counselors. 4) Physician practices themselves will influence other physician practices. If the majority of physicians begin testing, it will push other physicians to test as well. Similarly, if physicians refuse to offer testing despite entrepreneurial incentives or fears of liability, then screening is less likely to become a standard of care. Therefore, individual physicians can have an important influence on standard medical practices.

We will briefly review the potential influence of entrepreneurial interests and will examine the legal pressures that biotechnology companies are likely to exploit in order to persuade physicians to offer screening to the general population.

Conflicts of Interest

The entrepreneurial interests in CF screening will be significant because of the potential magnitude of mass population CF carrier screening. Currently, the charge for the test is between $100-$200.[18,19] It has been estimated that commercial laboratories might be able to charge as little as $50 per test if testing is done in a high volume.[65] If the 2.4 million newly married couples were the subjects of a mass screening drive and the test and the counseling program cost $200 per person, then this could become a billion dollar annual industry.

Although not all children are born to married couples and not all married couples bear children, this does suggest the magnitude.

The opportunity for profit in a background of little formal guidance or regulation will invite services with inadequate quality control. The reporting of erroneous information could cause significant harm should clients base reproductive decisions on such information. False-negative results may be caused by genetic variation at the site of the polymerase chain reaction primer or the oligonucleotide probe, which has been found to occur in .5% of CF chromosomes.[59,66] False-positive results could occur secondary to sample contamination with previously amplified DNA.[67] The exquisite ability of the polymerase chain reaction to amplify DNA will require that meticulous care be taken to avoid contamination with other sources of ΔF_{508} DNA. Unreliable data may also result from clerical errors, including mislabeled specimens or test results and poor laboratory techniques. **Therefore, the development of regulation to ensure quality control will be necessary.**

Physicians may profit from testing if they are part of a large clinic which decides it is profitable for them to develop their own laboratory. In the Omnibus Budget Reconciliation Act of 1989,[68] Congress placed some restrictions on physicians making direct referrals to clinical laboratories for Medicare patients. Although this would not directly affect physicians who become involved in CF screening, it does acknowledge the underlying conflict of interest for physicians who refer to laboratories in which they have a financial interest. Another source of conflict of interest would be from clinical investigators of screening programs and physicians and others involved in policy decisions. Currently, medical

journals, including JAMA and N Engl J Med, require the disclosure of financial interests of investigators who submit manuscripts.[69] This issue recently has been brought into focus by Healy and colleagues,[70] who are involved in a multicenter trial to evaluate the effect of reduced cholesterol levels and antithrombotic treatment in patients who have undergone coronary artery bypass surgery. The study, involving pharmaceuticals from three major corporations, obviously could benefit or hurt the sale of these products. The investigators voluntarily agreed on guidelines to avoid conflict of interest; specifically, not to buy, sell, or hold stocks in any of the involved companies, and not to serve as paid consultants to these companies while the study is in progress. Healy points out that even the perception of a conflict could undermine the credibility of the study.

Recent congressional hearings chaired by Representative Ted Weiss (D, NY) explored the potential for conflict of interest by clinical investigators,[71] and there is a bill pending which would restrict financial interests of NIH grant recipients.[72] These events demonstrate the emerging concern for this problem. Krimsky has pointed out that academicians who have entrepreneurial ties will not be perceived as being reliable and unbiased in making policy recommendations that are in the public interest.[73] The potential for profit from population CF screening may create similar conflicts or perception of conflicts. **Screening investigators and other experts involved in DNA testing should disclose any financial interests in screening services or laboratories. Investigators and policymakers should consider severing financial ties which could be perceived to be a conflict of interest.**

Physicians and counselors could benefit in a fee-for-service system by charging for genetic counseling services, though genetic counseling services are not always reimbursed adequately.[74,75] Primary care physicians will have fewer incentives to offer the same standard of counseling that is usually provided with genetic counseling. **Thus, financial incentives may work against the development of an effective primary care physician-oriented screening program.**

The ASHG statement was drafted two months after the gene sequence was published and served to temper the enthusiasm of the biotechnology companies. In fact, Vivogen includes the ASHG statement in its physician information materials.[76] However, in its patient information brochure, there are subtle suggestions about population screening, suggesting that testing is possible:

> "... when there is no known family history of CF, but a particularly concerned couple wants to have as much information as possible about their carrier status. Current genetic counseling resources are not yet sufficient to provide for large numbers of these people, but will probably increase over the next few years. It is also hoped that DNA technology will improve so that more direct tests will become available."[77]

Another biotechnology company has advertised that currently, testing should not be offered routinely except to couples anxious about CF, providing they are both white and non-Jewish. They recommend:

"that individual people (children or adults) not be tested now. Couples considering a pregnancy may wish to be tested now, even though the test is imperfect, especially those in two groups:

--People who have a close relative with CF.

--People who are very anxious about CF. We recommend that in this group, only couples who are both white and non-Jewish should consider being tested.[21]

The incidence of CF is no less in Askenazi Jews; however, the ΔF_{508} mutation is only found in 30% of the CF chromosomes in this group.[59] This recommendation implies that the 75% detection rate is sufficient for population testing. The statement about anxiety may create anxiety, as people who read the brochure may wonder if they should be anxious about CF. Marketing and brochures published by biotechnology companies may influence physicians' and patients' decisions about testing. Additionally, the biotechnology companies are likely to capitalize on physicians' concerns about liability for not screening patients.

Legal Duties and Physician Guidelines

Over the last twenty years, court decisions have defined physicians' duties and parents' and children's ability to collect damages following the birth of a child with congenital anomalies.[78] Such cases have been labeled wrongful birth (parent's claim for cost of care and damages) and wrongful life (child's claim for compensation for diminished quality of

life). An unanswered question is whether a physician is likely to be found liable for not offering CF testing to a patient. The ASHG and NIH report address the policy question of whether a physician should offer CF testing. However, offering may mean informing, providing access to testing, or performing the test. A physician may have a hierarchical range of potential legal or ethical duties toward a patient with regard to CF testing: 1) no duty to initiate a discussion of CF testing unless there is a family history; 2) a duty to inform regarding the availability of the test; 3) a duty to provide access to the test (this is the usual meaning of offer); 4) a duty to inform regarding the benefits and risks of being tested; 5) a duty to recommend a specific action; and 6) a duty to perform the test. This final duty includes questions of mandatory and voluntary testing. Voluntary testing could include mechanisms to opt in or to opt out, with varying requirements for written or oral consent.

No duty toward patients. If one accepts the argument that population screening should be delayed until pilot studies are completed, it may appear logical to conclude that there is no moral or legal duty to offer patients CF carrier testing. It could be argued, at the policy level, that physicians should not offer (provide) screening unless it can be provided safely and effectively. However, at the individual level, even if a physician cannot provide adequate testing for a patient, it is possible that another practitioner could provide testing with the sufficient education and counseling. It does not necessarily follow that just because the physician cannot adequately provide the service, himself, that he has no further obligations to the patient. There may be a duty to patients to inform about the availability of testing and to refer interested patients.

To defend the position that there is no further duty toward patients, one might point out that there are clearly insufficient resources to handle the demand created by informing, and then either providing or referring. This might be an argument, at the policy level, for physicians to not offer (provide) or recommend testing, since a large demand would virtually guarantee poor quality service under present conditions. However, being informed about the availability of testing or a referral to a genetic counseling center which provides clinical services would not necessarily create such a demand. In fact, despite national media attention, there does not appear to have been significant demand for CF carrier testing among the general population. More importantly, the disclosure of information is based on the doctrine of informed consent, which states that there is a duty to inform patients about the availability of therapeutic or diagnostic options and alternatives.

The Duty to Inform. Several court decisions have illustrated the scope of the physicians' duties to inform. In the 1979 New Jersey case of Berman v Allan,[79] 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 the California 1982 case of Turpin v Sortini,[80] an audiologist did not diagnose a genetic form of deafness, where a second child was born with the same condition. The court held that 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 the 1981 New Jersey case of Schroeder v Perkel,[81] where cystic fibrosis was not diagnosed in a child until the mother was 8 months

pregnant with a second child with CF. The court held that the physicians were liable for the medical expenses of the second child.

These cases point to the duty of the physician to disclose information which the patient might find material in making reproductive decisions. Instead of wrongful life and wrongful birth, Capron[82] suggests that the term "wrongful nondisclosure" more succinctly captures the breach of duty by the provider. Robertson[83] has argued that there may be a legal duty to inform patients in the general population that CF testing is available. His argument is based on an objective standard for informed consent which has evolved since the 1972 Washington DC decision of Canterbury v Spence.[84] This standard suggests that the determination of what information must be presented is based on what information a reasonable person would find material, not on the basis of the usual practices of physicians. Robertson also points to the 1974 Washington decision of Helling v Carey[85] to suggest that it is possible that courts could make an independent determination of the standard of care which could differ with the assessment of the NIH Workshop and the ASHG. He concludes that since some members of the general population will have an authentic interest in obtaining more information regarding their carrier status, there may be a duty to inform patients that the test is available. However, most states rely on a community standard of that information which physicians usually disclose.[86] A variant of this standard would be to rely on what a reasonable physician would disclose. Only a few states have adopted the more patient-centered standard of what a reasonable patient might want to know. A community-based standard would support that there is no legal duty to inform patients about testing, since most physicians do not routinely inform patients about CF testing and there are policy statements from the NIH

and ASHG advising against routine screening in the general population. However, there may still be an ethical duty to provide this information if a reasonable patient would want to know it.

The duty for routine disclosure of the availability of the test should be distinguished from providing the test. The duty which Robertson argues for is not to provide the test but only to inform about its availability. Unfortunately, this distinction between disclosure and providing is often blurred in clinical practice. This duty to inform may be independent of any duty to offer (provide) testing. An illustration of the distinction between informing and providing occurs in the example of a child with end-stage biliary atresia. The physician should inform parents that one potential therapy is liver transplantation. This is does not imply a duty to provide the transplant.. There are not sufficient resources to provide liver transplants to all babies with biliary atresia. However, it does not follow that just because all patients cannot receive liver transplants, that there is no duty to inform patients about the option. Just as a parent may wish to know about the transplant option, a patient from the general population may have genuine interest in being informed about CF testing. That patient could be referred to a clinical genetics center which would presumably be able to provide these services. On a practical level, the genetics community may not have the resources to meet the demand for testing. Similarly, there may not be sufficient resources to provide a live transplant to the baby with biliary atresia. However the ethical principle which supports providing information to patients is that physicians should disclose that information which a reasonable person would wish to know.

A reasonable person may wish to know that there is a test for CF carrier testing and that such testing is ideally offered through a genetics counseling program or center. Patients can decide for themselves whether testing is sufficiently important to go through the trouble of seeking out a genetics clinic. There may be at least some people who have had prior anxiety about CF (perhaps as a result of direct knowledge about CF) who may be very interested in testing. While such people cannot require their physician to provide a test which he does not have the resources to perform, the physician can at least inform the patient about the test and refer them to an appropriate facility. **The physician may have a legal duty, or at least an ethical duty, to inform patients, with or without a family history of CF, that the test is available. However a duty of disclosure, if it exists, does not necessarily imply a duty to provide, recommend, or even perform the test.**

The Duty to Provide. Andrews[58] has argued that providing the test would also require a further duty of providing understandable information about 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 that the health care provider could be held liable if he or she conveys accurate information in such a way that the couple would 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."[58, p 149] If information is not understood, then it cannot benefit the patient. A second source of liability could be if misinformation is given or if pertinent information is withheld. Some examples that might demonstrate an actionable claim include: 1) a couple with only one detected carrier who chose for the partner to be surgically sterilized because of poorly understood

information or misinformation about the degree of risk or the severity of the disease; and 2) a carrier who subsequently lost employment or insurance who had not been informed about this risk.

The NIH Workshop's linkage of a diagnostic test with a full complement of supportive services is not a new concept. When MSAFP testing became feasible, the American Academy of Pediatrics (AAP) and ACOG recommended that the FDA require the test be offered only in conjunction with the availability of counseling, follow-up diagnostic services, and provisions for quality control of the test.[87] Although this recommendation was not followed, it articulated a standard, expressed again in the NIH Workshop statement, that physicians who offer screening must also provide education and counseling. It is not sufficient to provide education: it is also necessary to provide education that results in the transfer of usable information. Thus, while it may be in a patient's interest to obtain information about CF carrier status, it is not in the interest of the patient to be given incomprehensible information, particularly if this poorly understood information results in irrational altering of reproductive plans, anxiety, stigmatization, or discrimination. Andrews[58] recommends that a personalized written summary sent to the couple that would review the counseling session may be useful in facilitating understanding. Increasingly, such summaries are becoming a standard for genetics counseling services.[44] Thus, a provider could be held liable for not utilizing this technique. The NAS[3] has recommended that screening providers participate in an ongoing evaluation of the effectiveness of information transfer. The failure of a provider to be able to demonstrate the effectiveness of a particular program may also expose him or herself to liability. **Offering the test could create a risk**

of liability if the physician is not able to provide effective education and counseling. The utilization of individualized written summaries, as well as ongoing evaluation of the transfer of information, may be necessary to limit liability.

Guidelines for Primary Care Physicians. The physician could fulfill the legal duty to inform patients about test availability without offering testing. The physician could inquire specifically about a family history of CF and inform patients that the test is available. Although this information may be of interest to any Caucasian patient, it may be of particular interest to patients with a family history. If patients then wanted to learn more about the test, they could be referred to a genetics counseling program. An illustration of the essential elements of a physician 's disclosure to a patient follows:

> "I would like to ask you if there is a history of cystic fibrosis in your family. 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 is rare and only occurs in 1-in-2500 births, but it can happen more frequently if there is a history of CF in your family. Testing is done in conjunction with genetic counseling, which may require two or more hours before you would be in a position to know whether you would want to be tested. Is there a family history of CF?"

It will be a challenge to inform patients that the test is available without generating anxiety about CF. The intention of disclosure is merely to provide nondirective information, rather than to motivate people to be tested. A specific brochure about CF may have the potential to

be more anxiety-provoking (and motivating) than a simple statement during the visit.[88] This will require empirical verification.

The reason to specifically mention CF to Caucasians is because it is the most common genetic disease in that population. However, there are close to a hundred conditions for which carrier detection and prenatal diagnosis are potentially available,[89] and the Human Genome Initiative should increase this number. Primary care physicians do not have the time to inquire orally about a family history or an ethnic background for each of these diseases. The patient's genuine interest in being informed that the tests are available could be supported by a checklist to be completed in the physician's waiting room and subsequently reviewed with the patient during the visit. The checklist would include a list of genetic diseases or symptoms suggestive of genetic disease. People with a family history for a genetic disease or an ethnic background which places them at an increased risk, if interested, could then be referred to a provider who could provide education, consent, and counseling, or encourage them to discuss the matter further with their primary care physician.

Guidelines for Geneticists. Geneticists are more likely to have the time and training to offer CF screening (consent and counseling). However, offering CF testing to all clients who are seen for other reasons would still place a great strain on such programs. An additional 1-2 hours might need to be added to each visit. Geneticists and genetic counselors could acknowledge the availability of the CF test during a visit, in a similar fashion to primary care physicians, by asking them to complete a checklist describing the diseases for which testing is available.

However, it is possible that referrals from primary care physicians and interest among existing genetic counseling clients still could overwhelm the system. Thus, the geneticist may need to confront the issue of limited resources for counseling. Although a physician may wish to provide an individual patient with usable information, an attempt to provide this benefit to a large group may not be successful due to the barriers to education previously described. It should also be clear that the inability to provide usable information does not merely indicate a lack of benefit. In the circumstance of insufficient personnel qualified for counseling, the consequence of a physician attempting to benefit a patient by offering testing may result in harm. In order to provide genuine benefits, the geneticists/genetics counselors may have to limit the potential pool for screening to manageable size. Such a limit might be patients with a family history of CF, for the reasons previously cited.

Limitation of Services. There are precedents for limited access for genetic services. Doctors have limited amniocentesis in various ways, often based on little more than the physician's personal moral views. Some, for example, would not perform the procedure if the patient stated that the results would not change their reproductive plans;[90] others, when it has been requested for the purposes of sex selection, or more commonly, if a woman is below the age of 35.[4] One reason cited for withholding amniocentesis was that the procedure was a scarce resource, which should be reserved for those who will benefit the most. A related argument is that if the benefits are minimal, then the risk/benefit ratio for the individual will be unfavorable. But paternalistic notions are more difficult to defend in an era of increasing emphasis on patient autonomy. People will have different values and preferences and may disagree with the physician about the extent of benefit. The difficult

question is whether there are objective thresholds of risk that must be reached before a patient is informed of the test, and whether there is the threshold below which a physician may withhold a test.

The answer to this questions must be based on the characteristics of the disease, the test, and the availability of personnel and financial resources to do the test. There will be greater interest in detecting serious problems where the knowledge may influence medical or personal choices. In a low incidence population, a positive test is more likely to be a false-positive, since the positive predictive value of the test decreases as the incidence of a disease diminishes. Thus, the same information may offer varying amounts of benefit when obtained under differing circumstances. If the resources were available to provide effective education and counseling, there would be a stronger case for population screening. Empirical data on the general population's interest in testing is needed. This might be difficult to assess since a questionnaire itself could generate interest. The determination of such interest would require a pilot study of a program that included effective education and counseling. Ironically, if there is little interest among the public for CF carrier testing, then the system may be able to accommodate those who are interested. If the interest is great, the program may have to be limited. Such a policy to limit testing to family members would be consistent with the Hastings Center, NAS, and President's Commission reports (see Table 2). **The most compelling reason to arbitrarily limit access would be if there are insufficient resources to handle the demand. In this case, not only may the benefit not materialize, but patients may be harmed. Thus, an individual genetics counseling program, with**

limited resources and with the support of the ASHG and NIH Workshop recommendations, may not offer screening to people without a family history of CF.

RECOMMENDATIONS AND FUTURE POLICY ISSUES

1. Mass population screening should be deferred until pilot studies are completed that demonstrate effective mechanisms for delivery of these services, as measured by: a) an assessment of the effective transfer of information; b) behavioral outcomes; c) correlations between decisions and comprehension of the information; d) cost/benefit analysis; and e) monitoring for adverse effects, including anxiety, confusion, stigmatization, and discrimination.

2. Even with 100% detection, the personnel and logistical resources needed to meet education and counseling needs must be developed and evaluated. A 95% detection rate will make population screening less complicated. However, an ineffective counseling program may adversely affect the 97% of carriers who will have partners who are negative. Many of these couples may still be anxious, suffer from stigmatization, and/or alter reproductive plans irrationally.

3. Physicians and professional organizations should base decisions about clinical practice policies on the desires and interests of the patient. Although a patient may have an interest in the results of the test, a screening program which does not effectively transfer information may not be in the patient's interest.

4. Physicians who provide clinical services and/or conduct clinical investigations of screening should avoid the perception and reality of conflict-of-interest, by distancing themselves from financial interests in companies that offer CF testing, and from profit-oriented laboratories in their own institutions.

5. Policymakers will need to 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.

6. Primary care physicians may not be the ideal providers for mass population carrier screening programs. Alternative mechanisms of community-organized programs with trained providers and multimedia educational resources should be developed and evaluated.

7. Population screening pilot studies should target reproductive-age couples prior to conception. Newborn screening for presymptomatic treatment of CF is of unproven benefit. Neonatal heterozygote detection will further complicate the process and is not a sufficient reason on its own for CF newborn screening.

8. Regulation, to ensure quality control in the laboratories offering the screening, will be necessary.

9. Physicians may discharge their legal and ethical duty by informing patients that CF carrier testing is available. Interested patients, ideally, should be referred to qualified

genetic counselors prior to testing. There is no clear duty for physicians to offer, recommend, or perform the test in the general population.

10. Offering of testing requires that strict standards of consent be followed. This should include information about CF, reproductive options, the meaning of a negative test, and the risks of testing (stigmatization and discrimination). Providers may be liable if information is not successfully communicated or if pertinent information is not provided.

11. Individual genetic counseling programs may have to limit their services to clients with a family history of CF if the demand for general population screening exceeds their available resources. Further development of the existing infrastructure of regional genetic counseling centers and CF centers will be needed to facilitate education, counseling, and quality control of the test, even for the limited population of CF family members.

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Table 1:Distribution of the ΔF_{508} Mutation Among Different Ethnic and Geographic Groups Based on Data Reported to the Cystic Fibrosis Genetic Consortium[14]

Location/(Ethnic Group)_Chromosomes Screened (CF)_Frequency of ΔF_{508}_Investigator (Affiliation)__North American (Caucasian)_439_.76_W Lemna et al—(Baylor)__Minnesota_394_.74_H Orr—(U of Minnesota)__North America_262_.71_K Klinger et al—(Integrated Genetics)__Midwestern US_256_.57_M Iannuzi et al—(U of Michigan)__Baltimore (American blacks)_43_.37_G Cutting et al—(Johns Hopkins)__North America (Askenazi Jews)_33_.30_W Lemna et al—(Baylor)__Texas (Hispanic)_29_.55_S Naylor—(U of Texas, San Antonio)__North America (Hutterite)_20_.35_MP McGovern et al—(Mount Sinai, NY)__North America (Askenazi Jews)_12_.50_MP McGovern et al—(Mount Sinai, NY)__Germany_244_.77_S Bremer et al—(Hannover)__Italy (Southern and Central)_350_.55_M Ferrari et al—(Milan)__Italy (Northern)_218_.40_P Gasparini et al—(Verona)__Spain_466_.51_T Casals et al—(Barcelona)__United Kingdom (Northwestern)_600_.80_MJ Schwarz—(Manchester)__Northern Ireland_204_.54_CA Graham et al—(Belfast)__Denmark_423_.88_M Schwartz—(Copenhagen)__

Table 2: Principles for Genetic Screening—Areas of Consensus[2,3,4]

Principles_Hastings Center_Nat'l Academy of Science_President's Commission_

Goals of Screening

- Improved health in patients with genetic disease
- Informed reproductive decisions
- Alleviating anxiety of family at risk
- Improved health in patients with genetic disease
- Informed reproductive decisions
- Enumeration of genetic disease
- Informed reproductive and personal decisions

Attainability of Goals

- Define goals
- Goals attainable based on pilot studies
- Define goals
- Goals attainable based on pilot studies
- Standardization of projects
- Goals attainable based on pilot studies

Public Involvement in Screening•Supports community participation in education_• Supports public participation

- Supports involvement of medical community
- Supports involvement of medical community

Access to Screening Services•Information and screening available for all

- Priority for high-risk groups
- Priority for high-risk groups
- Priority for high-risk groups

Necessary Test Characteristics•Precise information to minimize misinterpretation_• Acceptable accuracy, validity, sensitivity, and specificity_•Acceptable accuracy, validity, sensitivity, and specificity__Absence of Coercion in Obtaining Services_• Voluntary testing only

- No constraints on childbearing
- Voluntary testing only
- Voluntary testing only—newborn screening mandatory only if:

a) Substantial harm,

b) Voluntary program fails

Informed Consent• Explicit consent is necessary

- Prior to testing: Clients need to know risks and benefits
- Ongoing assessment of effectiveness of consent procedure
- Explicit consent is necessary
- Prior to testing: Clients need to know risks and benefits
- Explicit consent is necessary

Protection of Subjects• Screening is a form of human experimentation_• Screening is a form of human experimentation_• Pilot studies are necessary__Disclosure of Results_•

Full disclosure_● Full disclosure_● Full disclosure__Provision of Counseling_● Non-directive

- Define qualifications
- Ongoing assessment of:
  a) Clients' understanding of information
  b) Effect of information on clients' lives
- Define qualifications
- Ongoing assessment of:
  a) Clients' understanding of information
  b) Effect of information on clients' lives
- Non-directive
- Define qualifications
- Ongoing assessment of:
  a) Clients' understanding of information
  b) Effect of information on clients' lives

Privacy● Information restricted to individual screened_● Information restricted to individual screened_● Information restricted to individual screened__Laboratory Provisions__● Regional Facilities

- Quality Control
- Regional Facilities
- Quality Control

–

able 3: Alternatives for Couples at Risk for Bearing a Child with CF

I. Reproductive Options: A. Taking chances B. Not bearing children C. Taking steps to avoid bearing a child with CF: 1. Adoption 2. Artificial insemination by donor 3. Surrogate mother

II. Options with Prenatal Diagnosis when avoiding birth of affected child:

A. Reassuring if fetus does not have CF
B. Prepare for birth of an affected child:
1. Move close to CF Center for medical care
2. Move close to family or other support network
3. Change employment to have time to provide care
4. Arrange for adequate medical insurance

Table 4: Cystic Fibrosis Carrier Testing—Risks after Mutation Analysis[23]_____Risk of Cystic Fibrosis in Offspring____% of Cystic Fibrosis Mutations Detectable_Carrier Risk

	for Person with Negative Test	
	One Partner Tested	
	Negative	
Both Partners Tested		
	One Positive	
Both Negative	One Negative	

0%_1in2,500_1in2,500_1in2,500__50%_1in55_1in5,660_1in12,300_1in222__75%_1in99_1in10,100_1in39,200_1in396__85%_1in165_1in16,800_1in109,000_1in660__90%_1in246_1in25,100_1in242,000_1in984__95%_1in491_1in50,100_1in964,000_1in1,960__96%_1in613_1in62,600_1in1,500,000_1in2,450__Calculations describd in Lemna et al, N Engl J Med 1990;322:291-6

Table 5: Genetic Counseling Hours for 3 Million Couples[23]

Carrier Status	Frequency	Total Couples	Min/Couple	Total Hours
No Carriers	94.2%	2,826,000	10	472,000
One Carrier	5.7%	171,000	60	171,000
Two Carriers	.1%	3,000	60	3,000

- 950 Certified Counselors
- 680 Hours per Counselor Annually (17 weeks per year)

646,000 Hours of Counseling

Table 6: Cost/Benefit of Cystic Fibrosis Screening[23]

The Lifetime Cost of Medical Care for CF $200,000

Cost of Screening to Avoid One CF Birth

Couples Screened 11,100

At-Risk Couples Detected: $(1/25)^2 \times (3/4)^2$ 10

Couples Receive Prenatal Dx (80%) 8

Affected Fetuses Identified (25%) 2

Pregnancy Terminated (50%) 1

11,100 Couples x $200 $2,220,000

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Center for Human
Genome Research
Bethesda, Maryland 20892

Building 38A, Room 617
(301) 402-0911

CYSTIC FIBROSIS TESTING AND COUNSELING STUDIES CONSORTIUM (CFSC) PLANNING MEETING
NOVEMBER 1 AND 2, 1991
NATIONAL INSTITUTES OF HEALTH
BUILDING 31, CONFERENCE ROOM 6

FINAL AGENDA

NOVEMBER 1, 1991

8:00-8:30 a.m. Arrival & Coffee

8:30-8:45	Welcome & Opening Remarks Set stage for next 1 and 1/2 days (Dr. Juengst)
8:45-10:00	Overview of Projects (10 min. presentation by PI + 5 min. discussion ea.) (Drs. Asch x 2, Fanos, Grody, Holtzman)
10:00-10:15	Break
10:15-11:00	Overview of Projects (continued) (Drs. Phillips, Rowley, Sorenson)
11:00-12:00	Laboratory Standards/Practices (Haig Kazazian, Wayne Grody)
12:00-1:00	Lunch

NOVEMBER 1 (CONT.)

1:00-2:30	Psychosocial Issues and Psychologic Testing (Charles Spielberger, Caryn Lerman)
2:30-2:45	Break
2:45-4:45	Confidentiality and Informed Consent Guidelines (Ellen Wright Clayton, Loretta Kopelman)
4:45-5:15	Discussion
5:15	Adjourn

NOVEMBER 2, 1991

8:00-9:00	Developing and Testing Educational Materials (Polly Hadow, Judy Capra)
9:00-10:00	Ethnocultural Issues (Ora Strickland, Barbara Dixson)
10:00-10:15	Break
10:15-11:15	Cost-effectiveness Issues (David Asch)
11:15-12:00	Discussion
12:00	Adjourn

Resolution from the NCHGR
Program Advisory Committee on the Human Genome

December 3, 1990

Professional practices and public policies established with respect to genetic testing for cystic fibrosis will provide important precedents for the introduction of the new genetic tests that the Human Genome Project is expected to produce.

There has not yet been a systematic evaluation of the questions to which those practices and policies must respond. This includes such questions as 1) how CF testing services should be offered; 2) what educational materials should be developed; 3) how test-related information is to be channeled; 4) how tests will be performed and interpreted; and 5) what the outcomes are for those who avail themselves of testing.

Pilot research projects for CF testing are needed to address such questions in order to develop responsible and beneficial testing services for the public.

As demand for CF testing begins to escalate, there is increasingly limited time available to gather the information necessary to ready genetic services in this area. To effectively influence practice, pilot projects must begin in 1991.

1. The Program Advisory Committee therefore recommends that the NCHGR take a leadership role in developing support for funding of well designed, cost effective pilot research projects to evaluate approaches to the provision of genetic testing for cystic fibrosis carriers.

2. The Program Advisory Committee recommends that the Director of NCHGR discuss this issue with the acting NIH Director to develop plans for coordinating the efforts of the NCHGR with other relevant NIH Institutes, Centers, and Divisions, and other federal agencies.

DRAFT

Working Group on Ethical, Legal, and Social Issues in Human Genome Research
National Center for Human Genome Research and Department of Energy

WORKSHOP ON THE INTRODUCTION OF NEW GENETIC TESTS

Rockville, Maryland
10 September 1990

In 1983, a US presidential commission concluded that

> "Within the next decade screening for cystic fibrosis may be possible. This could be of great benefit. If adequate preparation for its introduction is not made, however, it could also create serious problems... The possible demand for millions - or tens of millions - of tests in a short period of time, and the consequent need for follow-up diagnostic studies and counseling, is daunting in itself. The Commission ... encourages continued attention to this area by government officials, as well as by people knowledgeable about relevant scientific, ethical, social, and legal concerns" [President's Commission, 1983].

The technical capacity foreseen by the President's Commission is nearly upon us. In August 1988, the discovery of the gene causing cystic fibrosis (CF) was announced. Discovery of the gene led quickly to isolation of the protein whose malfunction causes the disease [Kerem, Rommens, Buchanan, et al., 1989; Riordan, Rommens, Kerem, et al., 1989; Rommens, Iannuzzi, Kerem, et al., 1989], and ushered in a new era of hope for children and young people afflicted with the disease. Further understanding of exactly how the disease is caused might lead to new treatments in the next decade. Identifying the gene also raised the prospect of developing a genetic test, at least for some individuals.

The ability to test for cystic fibrosis raises many public policy issues. This is, in large part, because CF is among the most common single gene defects in Caucasian populations. Demand for CF testing may well swamp a system of genetic services already short-handed and underfunded. Because of this, professional practices and public policies established with respect to CF testing will provide important precedents for the introduction of the new genetic tests that the Human Genome Project is expected to produce.

Soon after the cystic fibrosis gene was discovered professional groups warned that any significantly increased testing required that substantial technical and logistical obstacles be overcome. The American Society for Human Genetics issued a statement in November 1989 [Caskey, Kaback and Beaudet, 1990]. A March 1990 consensus development conference convened by the National Institutes of Health concurred [Workshop on Population Screening for the Cystic Fibrosis Gene, 1990]. Wilfond and Fost wrote about the policy issues remaining to be faced in even greater detail in the Journal of the American Medical Association in May 1990 [Wilfond and Fost, 1990].

To analyze the implications of these issues for genome research, the NIH-DOE Working Group on Ethical, Legal, and Social Issues in Human Genome Research convened a workshop on issues involved in the clinical introduction of new genetic tests on 10 September 1990.

The Working Group invited 12 experts from various sectors of genetic services to discuss the technical status of CF testing and to outline the policy issues facing the nation in the near future. The remaining sections of this document summarize discussion at that workshop.

Background

The disease. Cystic fibrosis affects several organ systems, especially the pancreas and lungs. Most symptoms trace to plugging of pancreatic and lung ducts by viscous material, caused by aberrant secretions from nearby tissues. The dysfunction of membrane proteins apparently alters the composition of material secreted into these channels, and the material cannot be cleared.The plugged channels isolate lung spaces which then become fertile ground for infection. The path for secretion of pancreatic enzymes into the intestines is blocked, resulting in poor digestion of fats and other foodstuffs. Diagnosis is usually made in childhood because of recurrent lung infections or digestive problems. The disease was often fatal in childhood until recent years, but survival has now been extended well into the twenties by improved treatment of infections and better management of other common clinical problems.

Clinical variability. The severity of cystic fibrosis varies dramatically from case to case. Some children die even now, despite advances in treatment. Other cases are relatively mild and are not noticed until the teens or even later. This variability makes genetic counseling difficult. The experience of the disease reported by families with affected children reflects this clinical variability.

The molecular defect. Cases of CF studied to date trace the cause to a gene that produces a single protein. This protein appears to be involved in regulating the flux of chloride ions through the cell membrane. There many different ways to disrupt protein function, however, and more than 60 different CF mutations (alterations of DNA) have surfaced in the year since the gene's discovery. The plethora of different mutations may help explain the variations in severity of the disorder. If so, genetic tests may help predict the severity of disease, and the need for increased clinical surveillance.

Genetics of CF. Cystic fibrosis is a **recessive** trait - it is inherited when a child receives defective copies of the CF gene from both parents. Approximately one in twenty-five Caucasians has one such defective CF gene. Such individuals are called **carriers.** Couples are at high risk of having a child with CF only if both parents are carriers (roughly one in six hundred couples). In such couples, the risk of having an affected child is one in four with each pregnancy.

Variable prevalence in different population groups. The prevalence of CF (how many people have it at any given time) differs markedly among different population groups. It is relatively rare in most African and Asian populations studied to date, and much more common among Caucasians, where it affects roughly one of every 2,500 children born. In some populations, especially northern European populations, a single mutation causes the vast majority of cases. In Denmark, for example, 88 percent of cases are caused by a single mutation, called delta-F508. In other regions, however, as few as 30 or 40

percent of CF cases are due to this particular mutation [The Cystic Fibrosis Genetic Analysis Consortium, 1990].

Status of Current Activity in CF Testing

United States

In the United States, individual doctors, usually obstetricians, offer the CF test to their patients. Arthur Beaudet estimated from a series of 500 tests submitted to Houston from around the nation that by testing for the major mutation and the four next most common ones known, 84 percent of carriers are detected.

Michael Kaback made clear at the workshop that in other countries, other forms of screening (among neonates, those getting married, or all those of child-bearing age) might be more practical, but in the United States for the foreseeable future, those first screened will likely be pregnant women. Approximately twenty-four of twenty five tests are negative. When a woman is identified as a carrier, then her spouse (or mate if not married) must also be tested. If both are positive, then they are a high risk couple, and have a one in four risk of having a CF baby with each pregnancy. If the man is negative and the woman positive, the risk is approximately 1 in 600, somewhat higher than the general population. These couples and those at high risk (at one in four risk for each pregnancy) need genetic counseling to explain the risks and to describe CF so that the couples can make an informed choice about whether to seek prenatal testing.

Denmark

Marianne Schwartz reported that in Denmark, 95 percent of CF patients receive their health care from a single hospital, the Rigshospitalet in Copenhagen, where they are seen monthly. This ready access to care, combined with a robust national health program and the high prevalence of a single mutation make introduction of genetic testing for CF desirable. Using national health service funds, the Rigshospitalet now offers CF testing. Early testing has centered on two groups: 1) prenatal and carrier testing among those with

an affected child already, and therefore at one in four risk with each new pregnancy, and 2) carrier testing among those of reproductive age. Among families whose risk is known to be one in four, 80 percent take the test for new pregnancies. Of 50 tests in this group, 12 affected fetuses were detected. Families chose abortion in ten cases and chose not to abort in the other two.

The Rigshospitalet is also offering carrier testing for women of reproductive age, through referral from the obstetrics service. By testing for the delta-F 508 mutation and the next most common one, Schwartz estimated that the Danish group was detecting roughly 90 percent of carriers. Of four hundred women offered the test, all but two took it. This identified 70 couples in which the spouse was tested (to see if he also was a carrier). Three couples at a one in four risk of having a child with CF were discovered. Two fetuses from these couples tested positive for CF, and both were aborted. The Danish group will now be continually evaluating the benefits, costs, and reactions to the CF testing service.

United Kingdom

Robert Williamson reported that in the United Kingdom, there are five pilot studies underway offering CF testing under a variety of circumstances to different populations. By testing for the major mutation and the three next most common ones, he estimated that the British groups are detecting 85 percent of carriers. In surveys of families, 95 percent of CF families wanted the test available, and 90 percent believed abortion should be available to those at high risk of having affected children [put in ref--Eric has it].

The UK pilot programs focus on different test approaches. One tests all single individuals of reproductive age, another tests couples at the time of marriage and couples entering pregnancy, one is offered through general practitioners, and two test during pregnancy and are linked to obstetrical care.

The UK testing pilots are budgeted at $2 per test for a projected 50,000 tests this year. Williamson stressed that costs are much lower than in the United States because the general framework for delivery of

health care provides many of the educational, counseling, and follow-up services that must be separately budgeted in the United States. Katherine Klinger of Integrated Genetics noted that another major cost difference is the high volume of standard samples from a single source, which contrasts markedly with the typical American laboratory that receives different kinds of samples from around the country. Most laboratories in the United States do duplicate tests, print formal reports to the referring physician, and carry significant administrative costs associated with widely disparate reimbursement sources and practices. A CF test generally costs $300 in the United States as a consequence of these technical and logistical differences.

The CF test has proved far more complicated than imagined before the gene was discovered. The fact that many different mutations cause the same disease means that no single DNA-based test is adequate to the task of reliably detecting carriers or affected fetuses. In the future, it may be possible to develop tests that detect many different mutations in a single test; or it may become possible to test the function of the membrane protein directly, so it would not be necessary to sort through genetic differences. Improving the detection of CF is an immediate urgent scientific priority, being pursued in dozens of laboratories around the world.

Even before more sensitive and specific tests become available, however, it is clear that there will be CF testing. The question is how extensive, how good, and how costly such testing will be.

Policy Issues

The NIH-DOE working group on Ethical, Legal, and Social Implications of Human Genome Research identified the following policy issues that need to be considered in preparing for the introduction of new genetic tests like the CF test.

1. Trial testing and screening programs. Both previous policy statements have noted an urgent need for trial testing programs [cite ASHG and Consensus report here]. Such programs are already

underway in other nations. In the United States, however, the situation is much less amenable to study, and the data are spotty. Some doctors offer the CF test, while others do not. A few obstetrics, genetics, and fertility service routinely offer CF testing, while most do not. The severity of illness is highly variable. Religious and family values vary enormously in the United States, reflecting broad cultural, ethnic, and moral pluralism. There is no systematic evaluation of how the services are offered, how the information is channeled, how well tests are being performed and interpreted, or even whether those availing themselves of the test are helped or harmed. There are 3.5 to 4 million births in the United States each year. If even a small fraction of those contemplating pregnancy requested CF testing, the system would be overwhelmed from laboratory testing to genetic counseling. There has been restraint to date among companies offering testing services, doctors, and most genetic clinics. As the general public becomes more aware of the availability of CF and CF testing, however, the demand may escalate. There is a limited time to gather the information necessary to ready genetic services for this demand. **Trial testing programs are urgently needed to anticipate future problems and to make testing efficient, fair, and reliable.**

2. **Assessment of how genetic tests are paid for** by private insurers and prepaid health care providers. Payment for genetic tests varies widely in the United States. In some cases, tests done during pregnancy are reimbursed, but those done to detect carrier status (e. g. , when deciding whether or not to become pregnant) are not. Testing for CF, for example, is not routine, as noted by the public policy statements to date. Some payers reimburse only for services that are "standard care," in which case CF testing is excluded, except in the case of families with an affected child, and thus known to be at high risk. Katherine Klinger notes, however, that most insurers opt to reimburse for the test once educated about its purpose. Her company spends a great deal of time educating payers about the test; without such dedicated efforts, which are not the norm, reimbursement is far less certain. Information on reimbursement practices is needed to devise and to decide among policy options. A distillation of criteria on which reimbursement decisions are now made, and how they are likely to be made in the future would be particularly valuable.

3. Professional education of physicians, genetic counselors, and others who will provide genetic testing services. Medical genetics has until recently been largely an academic specialty concerned mostly with diseases affecting specific populations or rare disorders. An expanding array of new tests like the CF test may well change the complexion of medical genetics, because so many Americans will be directly at risk, and may wish to avail themselves of new genetic tests. Previous policy statements have noted the need to ensure that any testing be performed only where there can be adequate education, counseling, and clinical follow up [cite President's Commission, ASHG statement, and NIH Consensus report]. Barbara Biesecker from the Society of Genetic Counselors, notes that there are only about 800 genetic counselors and 500 board-certified clinical geneticists in the United States, and perhaps another 200 trained individuals offering similar services. They are already strained by current demands, and training is not keeping pace with opportunity. Only 75 new Master' s level genetic counselors are trained each year nationwide. New graduates typically have five or six job offers, and many slots remain unfilled. Yet the anticipated demand for genetic testing has barely begun to be felt. To meet the demand for future genetic services, professional training must be broadened into mainstream medicine and deepened to accommodate the deluge of new information flowing out of molecular genetics.

4. Public education at all levels. Genetic diseases are still largely mysterious to most of the general public. The flurry of publicity surrounding discovery of the CF gene has cast some light on that disease, but general awareness is still quite low. Beyond CF, a general understanding of genetics and genetic factors in health and disease will be increasingly important in the future. The conceptual base of medicine is shifting towards genetics; public knowledge must follow.

5. Laboratory quality control among centers performing genetic tests. For example, at present, only a dozen or so laboratories in the United States offer the CF test. As demand increases, however, this number will increase. With the increased number of testing centers, serious issues about the quality of laboratory services may arise. Given the complexity of testing for the multiple mutations and the state-of-the-art expertise in molecular genetics necessary to perform and interpret the tests, these problems may be even

practices, and greater understanding about how private employers and insurers might use such information. The Working Group identified this topic for future consideration at a public forum.

7. Discrimination against families at genetic risk. The potential for discrimination against those who carry disease-related genes must be further assessed. The workshop discussed a case in which a couple was tested for CF and was found to be at risk. Their child tested positive for CF. A physician then told the couple that their prepaid health care would not cover the infant if they chose not to abort. The decision was reversed by management in the Health Maintenance Organization. Several similar cases have turned up, but in all cases the initial decisions of lower level employees have been reversed. The Working Group believes that the potential for discrimination against CF carriers merits ongoing attention, followed by possible legislative action if abuses are identified.

worse for CF than for previous genetic tests. Quality control standards for genetic tests must be devised, and revised on an ongoing basis as technology improves and knowledge accumulates. A system for checking test accuracy, adequacy of documentation and other factors among different laboratories must be developed.

6. Informed consent and confidentiality of test results. Previous policy statements noted the need for all genetic testing to be voluntary and the results to be held confidential. According to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical Behavioral Research, test results should not be disclosed to third parties without permission of the person tested, unless such disclosure can prevent impending harm to an identified person [President's Commission, 1983]. Tests should thus be administered only when made in response to an educated request by an individual. Results should be reported to the individual, and held confidential in the medical record. There are some ambiguities, however, about how to communicate laboratory results in the American context. Laboratories typically report back to referring physicians. It is then the physicians' responsibility to inform the person tested. In some cases, there is a break in the chain. Some laboratories contact both referring physicians and the person tested, but this can lead to misinterpretation of the result, and in some states disclosure of results to anyone other than the physician is proscribed. The proper referral and notification strategies should be assessed, as part of the trial testing programs noted above.

There is also uncertainty about who now has access to medical records, including genetic data. Whether protections are needed specifically for personal genetic data in medical records and in government files remains an open question. The range of alternatives is much more complicated than simply choosing between mandatory testing or voluntary testing. For an individual seeking private insurance, for example, disclosure of medical records is necessary to obtain the desired insurance. Disclosure of the information may harm the individual, but this may be an unavoidable harm. Moreover, if private insurers learn that individuals are routinely withholding genetic test results from their medical records, then the insurer could consider specifically requesting such tests. This is neither a purely mandatory nor a completely free choice. Sifting through policy alternatives for these and similar cases will require further information about current

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