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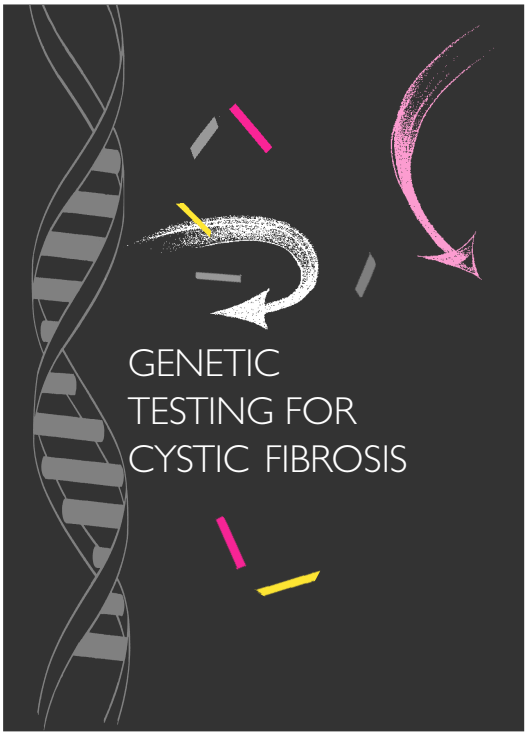

Genetic Testing for Cystic Fibrosis

NATIONAL INSTITUTES OF HEALTH
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This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

National Institutes Of Health
Continuing Medical Education

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Abstract

Objective

To provide health care providers, patients, and the general public with a responsible assessment of the optimal practices for genetic testing for cystic fibrosis (CF).

Participants

A non-Federal, nonadvocate, 14-member panel representing the fields of genetics, obstetrics, internal medicine, nursing, social work, epidemiology, pediatrics, psychiatry, genetic counseling, bioethics, health economics, health services research, law, and the public. In addition, 21 experts from these same fields presented data to the panel and a conference audience of 500.

Evidence

The literature was searched through Medline, and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process

The panel, answering predefined questions, developed its conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference.

Conclusions

Genetic testing for CF should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal testing. The panel does not recommend offering CF genetic testing to the general population or newborn infants. The panel advocates active research to develop improved treatments for people with CF and continued investigation into the understanding of the pathophysiology of the disease. Comprehensive educational programs targeted to health care professionals and the public should be developed using input from people living with CF and their families and from people from diverse racial and ethnic groups. Additionally, genetic counseling services must be accurate and provide balanced information to afford individuals the opportunity to make autonomous decisions. Every attempt should be made to protect individual rights, and genetic and medical privacy rights and to prevent discrimination and stigmatization. It is essential that the offering of CF carrier testing be phased in over a period of time to ensure that adequate education and appropriate genetic testing and counseling services are available to all persons being tested.

Introduction

Genetic testing is available for a variety of diseases and will soon be available for many more. Furthermore, genetic predispositions to common diseases are becoming known and potentially will affect large segments of the population. This consensus conference considered cystic fibrosis (CF), a well-characterized, serious genetic disease for which testing is becoming available, and a series of recommendations for genetic testing in the population is presented. The analysis and recommendations may prove relevant to genetic testing in other situations.

At the beginning of this decade, a test was developed that could identify individuals who carry the genetic mutation associated with CF. Concerned that this test might be inappropriately or prematurely used, several genetic and health professional organizations issued recommendations on its use. These groups considered the circumstances under which the tests should be offered and the populations that would potentially benefit. Almost all their recommendations were against using the test for large-scale, population-based screening until more sensitive tests were developed and until more had been learned about the risks and benefits of genetic testing for individuals and their families. Several statements called for additional support for research on the educational, laboratory, counseling, ethical, and cost-benefit issues associated with the delivery of population-based screening for CF. Since that time, new research has yielded a large body of data on these issues.

This conference brought together research investigators, health care providers, epidemiologists, geneticists, ethicists, and other experts, as well as representatives of the public, to present and discuss the latest data.

Following 1½ days of presentations by experts and audience discussion, an independent, non-Federal consensus panel composed of experts in the fields of genetics, obstetrics, internal medicine, nursing, social work, epidemiology, pediatrics, psychiatry, genetic counseling, bioethics, health economics, health services research, and law and the public weighed the scientific evidence and developed a draft statement in response to the following five key questions:

- What is the current state of knowledge regarding natural history, epidemiology, genotype-phenotype correlations, treatment, and genetic testing of cystic fibrosis in various populations?
- What has been learned about genetic testing for cystic fibrosis regarding (public and health professional) knowledge and attitudes, interest and demand, risks and benefits, effectiveness, cost, and impact?
- Should cystic fibrosis carrier testing be offered to (1) individuals with a family history of cystic fibrosis; (2) adults in the preconception or prenatal period; and/or (3) the general population?
- What are the optimal practices for cystic fibrosis genetic testing (setting, timing, and the practices of education, consent, and counseling)?
- What should be the future directions for research relevant to genetic testing for cystic fibrosis and, more broadly, for research and health policies related to genetic testing?

The primary sponsors of this meeting were the National Human Genome Research Institute and the NIH Office of Medical Applications of Research. The conference was cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases; the National Heart, Lung, and Blood Institute; the National Institute of Child Health and Human Development; the NIH Office of Rare Diseases; the National Institute of Mental Health; the National Institute of Nursing Research; the NIH Office of Research on Women's Health; the Agency for Health Care Policy and Research; and the Centers for Disease Control and Prevention.

What Is the Current State of Knowledge Regarding Natural History, Epidemiology, Genotype-Phenotype Correlations, Treatment, and Genetic Testing of Cystic Fibrosis in Various Populations?

CF is a multisystem genetic disease in which defective chloride transport across membranes causes dehydrated secretions. This leads to tenacious mucus in the lungs, to mucus plugs in the pancreas, and to the characteristically high sweat chloride levels. Intelligence and cognitive function are typically normal. A survey in 1995 reported that 35 percent of young adults with CF worked full-time, and almost 90 percent had completed a high school education. More than 25,000 Americans have CF, with approximately 850 individuals newly diagnosed each year. CF is inherited as an autosomal recessive disorder; the responsible gene, the CF transmembrane conductance regulator (CFTR), was mapped to chromosome 7 and identified in 1989.

Natural History

CF has a highly variable presentation and course. Median age at diagnosis is 6 to 8 months; nearly two-thirds of individuals are diagnosed before 1 year of age. Some individuals have severe pulmonary and/or gastrointestinal disease, whereas others have relatively mild disease with presentation during adolescence and young adulthood. Outcomes range from early death from pulmonary complications to mild atypical disease in the second and third decades and a rare normal length of life. Even though median survival increased from 18 years in 1976 to 30.1 years in 1995, there has been little life-span extension between 1990 and 1995. Survival has improved, thus far, through aggressive management of pulmonary, pancreatic, and intestinal complications. Despite advances in treatment, there is no cure for CF.

Severity of lung disease is the key to the quality of and length of life. Ninety percent of persons who have CF die from pulmonary complications. Pulmonary function tests, especially forced expiratory volume (FEV_1), are predictive of mortality:

when the FEV_1 is 30 percent, mortality is 50 percent in 2 years. Poor prognosis is related to respiratory complications before 1 year of age, malnutrition, and denial of the condition. Better prognosis is indicated from mild symptoms at diagnosis, pancreatic sufficiency, and atypical presentation. There are suggestions in the literature that early diagnosis and treatment may result in improved growth of young children; however, data are limited about whether early treatment decreases morbidity as measured by hospitalizations and pulmonary function tests and, ultimately, mortality rates.

Treatment

The major goals of traditional treatment of CF are to improve pulmonary, gastrointestinal, and pancreatic outcomes. Pulmonary treatment is focused on physical therapy to decrease obstruction of the airways, antibiotics to decrease colonization by *Staphylococcus aureus* and *Pseudomonas aeruginosa,* and nonsteroidal anti-inflammatory drugs to decrease the inflammatory cascade and resulting tissue damage. Gastrointestinal and pancreatic treatments include high protein/high caloric diets, pancreatic enzymes, and fat-soluble vitamins.

New modalities include the use of inhaled DNase, which breaks down the DNA from neutrophils, and pharmacologic modification of ion transport to loosen secretions. Pharmacologic activation of mutant CFTR protein to stimulate chloride channel activity is being investigated. Double lung transplantation extends life but is not curative.

There are new findings regarding human beta defensin-1, a factor responsible for innate immunity. The natural bactericidal activity of human beta defensin-1 is inhibited on CF epithelia because of high extracellular sodium chloride, and correction of the sodium chloride concentration of extracellular fluid holds promise for therapy in CF. Finally, although the feasibility of gene therapy is currently under investigation, this potential "cure" is not anticipated in the near future.

Epidemiology

Incidence

CF is one of the most common genetic diseases in Caucasians, with an incidence of about 1 in 3,300. The disease also has a fairly high incidence among Hispanics, 1 in 9,500. CF is a rare disorder in native Africans and native Asians, estimated to occur in less than 1 in 50,000, but higher incidences are observed in American populations of these ethnic groups (1 in 15,300 and 1 in 32,100, respectively), suggesting Caucasian admixture. Recent surveys of some Native-American populations also indicate high incidences: 1 in 3,970 in the Pueblo people and 1 in 1,580 among the Zuni. These data are summarized in Table 1. The relatively high incidence and concomitant high frequency of carriers motivate the proposal of population-based screening.

CF Mutation Analysis

Since the identification of the gene and the major mutation responsible for CF, more than 600 mutations and DNA sequence variations have been identified in the CFTR gene. The ΔF508 mutation is represented in almost all populations, although its relative frequency varies among different geographic locations. The highest frequency is observed in Caucasian populations, where it accounts for approximately 70 percent of the CF alleles (Table 1).

Table 1

Group	Incidence	Carrier Frequency	% ΔF508	% Common Caucasian Alleles	% Group-Specific Alleles	Sensitivity
Caucasians	1/3,300	1/29	70	13	–	80
Hispanics	1/8–9,000	1/46	46	11	–	57
Ashkenazi Jews		1/29	30	67	–	97
Native Americans	1/3,970 1/1,500		0	25	69	94
African Americans	1/15,300	1/60–65	48	4	23	75
Asian Americans	1/32,100	1/90	30			30

Source: Modified from Cutting GR. Genetic epidemiology and genotype/phenotype correlations. In: Program and abstracts. NIH Consensus Development Conference on Genetic Testing for Cystic Fibrosis, 1997 Apr 14-16, Bethesda, MD.

ΔF508 mutation accounts for large portions of the alleles in other racial or ethnic groups: 48 percent in African Americans, 46 percent in Hispanics, and 30 percent in Asian Americans and Ashkenazi Jews. Some 15 to 20 other "common" mutations account for 2 to 15 percent of CF alleles, depending on the ethnic composition of the patient group studied. Most of the remaining mutations are rare.

The proportion of detectable mutations is an important indicator of the utility of a population-screening program. Combining detection of the ΔF508 with other mutations common to specific ethnic groups, it appears that there are several populations for which 90 to 95 percent sensitivity can now be achieved with the current technology: Ashkenazi Jews, Celtic Bretons, French Canadians from Quebec, and some Native Americans. In Caucasians in the United States, it is feasible to approach 90 percent sensitivity at the current time. The detection rate in African Americans is about 75 percent. Despite the relatively high incidence in Hispanics,

the detectable alleles account for only 57 percent of the CF mutations in this group. The promise appears to be weak in Asian Americans, at 30 percent sensitivity. Because the remaining mutations are rare, expanding the panel of screened mutations is expected to achieve only marginal gains in sensitivity.

Genotype-Phenotype Correlations

The discovery of the gene has enabled evaluation of specific mutations in relation to the observed clinical heterogeneity. The correlation of genotype with phenotype is substantial for pancreatic function; however, identification of the specific CFTR mutation has not been highly predictive of the severity and course of pulmonary disease, which is the major factor affecting patient quality of life and longevity. Furthermore, there is evidence to suggest a role for modifier genes and environmental factors that are as yet unidentified.

Virtually all males with classic CF have congenital bilateral absence of the vas deferens (CBAVD). However, there is a population of otherwise healthy males with CBAVD who have a high frequency of CF mutations. It appears that more than half of these males have one or two specific mutations, which identifies these genotypes as the most common cause of CBAVD. Some women with these genotypes are normal or develop chronic sinusitis or bronchitis as the extent of their morbidity. It is unclear whether such mildly affected individuals can be reliably identified by their genotype.

Thus, it appears that knowledge of the genotype is as yet of limited value in making predictions about the anticipated course of disease in an individual, although research to identify genotypes associated with relatively mild presentation such as CBAVD may prove useful in informed decisionmaking.

Genetic Testing in Various Populations

Genetic testing has been performed for CF carriers in various racial and ethnic groups, mass and focused screening, and different types of organized medical settings. At this time, there is limited spontaneous public request for this testing. Although testing has not met with enthusiasm, there has been little or no group opposition to offering testing to African Americans, Asian Americans, Caucasians, Hispanics, Native Americans, and persons of Jewish ancestry. Most experience has been gained with Caucasians and Ashkenazi Jews, where incidence is highest. Mass screening has resulted in the least response. Pregnant patients appear to be motivated to obtain genetic information. Nonpregnant patients and those with a family history have exhibited only moderate acceptance rates. In the United States, mass screening of newborns has occurred in only two States, Colorado and Wisconsin; otherwise, newborn testing has been limited to those with a family history. The logistics of testing has been successfully implemented in various settings such as HMOs and primary care settings, including fee-for-service settings. With the exception of one fee-for-service setting and the newborn State programs, all testing has been free of charge. Direct provider recruitment has proven more effective than less personal approaches.

What Has Been Learned About Genetic Testing for Cystic Fibrosis Regarding (Public and Health Professional) Knowledge and Attitudes, Interest and Demand, Risks and Benefits, Effectiveness, Cost, and Impact?

Knowledge and Attitudes Toward Cystic Fibrosis and Genetic Testing

As with most genetic diseases, the public's knowledge is very low regarding CF, its genetic basis, and its variable course and prognosis, and understanding of genetic testing is poor. Moreover, among those who have heard of CF, inaccurate impressions often exist because people are generally not familiar with the progress in treating the disease over the past 40 years. Understanding genetic testing for CF involves learning complex concepts such as test sensitivity, carrier status, patterns of inheritance, risk/probability, and genotype-phenotype correlations. These gaps in the public's genetic knowledge suggest that genetic testing programs must include written informed consent and educational and counseling components.

There are only approximately 2,000 genetic professionals nationally, so implementation of widespread genetic testing must rely heavily on primary care providers and prenatal providers. Some research efforts, however, have shown that many office-based physicians are not interested in participating in genetic testing programs involving CF because of lack of familiarity and concerns with unreimbursed time. Medical practitioners need to become more knowledgeable about genetics, genetic testing, and nondirective counseling as genetic tests become more widely available.

Public Interest and Demand

Notwithstanding the limits of public understanding of genetics and genetically related diseases, prospective parents have enormous interest in the health and well-being of children-to-be. In an Office of Technology Assessment survey of a decade ago, 83 percent of Americans said they would take a genetic test before having children if it would tell them whether their

children would be likely to inherit a fatal genetic disease. Many genetic counselors and nurse geneticists report that they are frequently asked about DNA-based CF tests. However, studies have shown that interest in CF genetic testing is limited in the general population and that agreement to participate in genetic education and testing procedures occurs primarily among pregnant women and persons with positive family histories.

In the prenatal testing context, participation rates have varied widely in studies to date because of variability of methods used, with acceptance of offers for testing ranging from about 50 percent to a high of 78 percent in one HMO population. Participation has been affected by factors relating to convenience, education, cost, views regarding abortion, concerns about the low sensitivity of the test, and the manner of presentation of the testing opportunity. Concerns about confidentiality and insurability are often mentioned in the genetic testing context. There also is evidence of reluctance to engage in carrier testing on the psychological grounds of "not wanting to know," as has occurred in studies where some people with positive family histories chose not to participate.

The reasons for interest in prenatal genetic testing are diverse. Some participants in studies have sought information in anticipation of a decision about pregnancy termination in the case of a fetus with CF. Others wished to know only their carrier status, perhaps to make emotional and practical plans for parenting a child with CF.

Risks

Research has assessed initial concerns among providers of genetic services that genetic testing might have adverse psychological consequences, such as anxiety and depression caused by the difficulty of conveying the uncertainties inherent in genetic testing or the challenge of adjusting to identification as a carrier. The research to date has shown such problems to be transitory; the topic, nevertheless, may warrant additional research incorporating comprehensive psychological assessment tools. The risks of misinformation or misunderstanding highlight the need for a high level of competence in conveying

the results and meaning of information derived from genetic testing. Problems retaining complex genetic concepts highlight the need for broad-based public education.

Another concern is the fear that disclosure of genetic test results might affect one's family relationships, employment, educational or other opportunities, or ability to maintain or obtain health insurance. This is a more general problem and needs to be addressed at a broader level to ensure patient access to genetic services and other opportunities without threat of harmful consequences.

Impact and Effectiveness

The effectiveness of genetic testing can be judged in terms of its ability to convey information that patients find useful. The experience to date reports high levels of patient satisfaction after undergoing genetic testing for CF. In the prenatal situation, because of the rarity of the disease, over 99 percent of couples tested receive reassuring information regarding the improbability of having a child with CF.

Several studies have reported significant increases in knowledge of CF among couples who have undergone genetic testing and participated in the educational programs connected with it. Although there was some drop in knowledge after several years, knowledge levels still were higher than in the pretesting period. A decline in understanding has been reported in some research, where a considerable portion of the individuals who were carriers did not retain the meaning of the test results. In some instances, this meant that people incorrectly believed they were no longer at risk for having offspring with CF.

In addition to the educational and psychological benefits of CF testing, the effectiveness of testing can be judged in terms of how the information is used. This is most germane in situations in which a test produced a positive result. Most couples in whom the woman was found to be a carrier chose to have the partner tested as well. The inability of current DNA testing technology to detect all possible mutations and the difficulty in conveying the concept of residual risk temper these positive effects.

Another indicator of impact occurs in the rare instances in which a fetus with CF is identified. In the limited studies to date, most couples with no positive family history in this circumstance choose to terminate the pregnancy. It should be noted that some couples do not undergo final stages of testing because of their intention to continue the pregnancy.

Cost

Assessment of the costs associated with testing, screening, and treatment of CF is challenging because technology and treatment modalities are changing rapidly. Nonetheless, there is general agreement about the magnitude of many of the key cost variables and the likely future direction of change in these costs.

In terms of treatment, options for care for many individuals with CF have expanded over the past decade with implications for the average cost of care. Although the Office of Technology Assessment estimated in 1992, based on 1989 data, that the annual treatment costs were approximately $10,000 per year per individual with CF, current estimates exceed $40,000 per year in direct medical costs and $9,000 per year in ancillary costs. Using a 3 percent discount rate, this implies a net present value of approximately $800,000 for direct and ancillary costs associated with a CF birth.

The technology and cost of DNA diagnostic testing for a CF mutation are changing rapidly. At present, the cost of DNA diagnostic testing for CF is between $50 and $150 per test, testing for between 6 and 72 CF mutations. Rapid progress is being made in cost of testing, however, because of improvements in instrumentation. These costs will likely decline, and the number of mutations screened will quickly increase.

In terms of the cost of prenatal testing, the costs of informed consent procedures, educational and counseling services, associated administrative costs, and so forth must be added to the laboratory testing costs per se. These costs will vary as a function of the level of various educational and counseling services accompanying the testing according to evolving professional standards for genetic testing procedures.

Regarding cost savings from neonatal testing, currently no definitive data demonstrate medical benefit and cost savings associated with population-based neonatal screening. However, there is suggestive evidence that differences in height, weight, and nutrition of youngsters with CF are a function of whether they had neonatal screening and early diagnoses. These may well translate into future health outcomes and treatment savings, but the magnitude of such benefits is not known.

Broader assessment of the costs of a voluntary, broad-based prenatal screening program depends on variables such as the number of individuals deciding to participate in the test, the incidence of CF carriers in the population involved, the testing method (e.g., sequential or couple-based), the proportion of couples with an affected fetus who choose to terminate the pregnancy, and the number of children the couples wish to have. Although assumptions about these variables differed, studies showed that the cost per identified CF fetus averted ranged from $250,000 to $1,250,000 for a Caucasian population of Northern European ancestry. Estimates on the high end of this range come down substantially if one considers couples who plan to have more than one child or if identified carriers inform siblings and other relatives.

A broad educational effort is essential to create a level of genetic literacy in the population and among health care professionals that will allow individuals to utilize genetic and other information in making important life decisions. An estimate of the costs of this effort is not available.

Should Cystic Fibrosis Carrier Testing Be Offered to (1) Individuals With a Family History of Cystic Fibrosis, (2) Adults in the Preconception or Prenatal Period, and/or (3) the General Population?

The first two sections of this report summarized the knowledge base for the recommendations that follow. Objectives for CF testing and reasons for and against testing are different for each population, but in all cases individuals' acceptance of testing must be entirely voluntary. Each population is considered separately.

1. *Individuals with a family history of CF and partners of those with CF should be offered genetic testing.* As a group, individuals with a family history have relatively high frequencies of mutations in the CFTR gene. Members of this group have increased awareness of their risk of being carriers, as well as increased familiarity with the disease and its impact on the family. Testing can be helpful with regard to reproductive decisionmaking and informative with regard to family health.

2. *CF genetic testing should be offered to the prenatal population and couples currently planning a pregnancy, particularly those in high-risk populations.* Data indicate that a significant level of interest in CF testing exists in this group. Because this is a vulnerable population and because of the inherent time constraints, it is particularly important that they receive adequate and balanced information. The information includes, but is not limited to, sensitivity of the test, a description of the range of severity of the disease, and risks. The offer of testing should be made to enable couples who wish to avoid the birth of a child with CF to do so, without influencing those who do not. Care should be taken to ensure that the decision to have testing is completely voluntary.

3. *CF testing for the general population is not advocated.* Given the low incidence and prevalence of CF and the demonstrable lack of interest in the general population, there is little justification for testing.

Routine genetic screening for CF in newborns is not advocated, based on available data. Studies have not provided sufficient evidence that identifying CF patients earlier than the current average age of diagnosis improves outcomes. The panel recommends that studies of CFTR screening in newborns be developed to provide a foundation for assessment of benefits of early therapy.

Education and informed consent. Genetic testing for CF should begin with education concerning CF. It should be clear that the patient has received the material and has had an opportunity for questions to be answered before testing is undertaken. Development of model educational and consent forms for genetic testing, as well as education programs for providers, is encouraged. All persons undergoing genetic testing should give written informed consent for the test, receive culturally sensitive educational materials, and demonstrate an understanding of the test and test results.

It is essential that the offering of CF carrier testing be phased in over a period of time to ensure that adequate education and appropriate genetic testing and counseling services are available to all persons being tested.

Genetic testing and counseling for CF in the populations identified by the panel's recommendations should be eligible for payment by insurers.

What Are the Optimal Practices for Cystic Fibrosis Genetic Testing (Setting, Timing, and the Practices of Education, Consent, and Counseling)?

The goal of genetic testing for CF is to provide individuals with information that will permit them to make informed reproductive and other decisions. Testing is of benefit only if there is access to the necessary comprehensive health services and resources that ensue from case/carrier detection. Components of a testing program should include education, counseling, and the use of medical facilities to improve health outcomes.

The setting must provide access for provision of comprehensive services. Whether it is based in a medical center or in a primary care setting, a professional interdisciplinary team should address the individual's genetic, medical, emotional, and reproductive health needs. The services should not be administered in isolation, but in association with tertiary care centers.

The complexity of DNA diagnostic data and the vast number of mutations in CF mandate sophisticated laboratory capability (or access to it) as an integral component. Laboratories providing molecular diagnostic capability should utilize tests that achieve a mutation detection rate of approximately 90 percent or better for Caucasians or a detection rate for African Americans, Asian Americans, Hispanics, Ashkenazi Jews, Native Americans, and others comparable to that available at present.

Timing for Testing Depends on Targeted Group

- In adults with a positive family history of CF, genetic testing should be provided at any time requested.
- Newborn siblings of patients with CF as well as other siblings who exhibit atypical symptoms should be tested. However, testing of minors for the purpose of identifying carrier status is not recommended.

- Carrier detection in pregnant couples with a family history of CF should be provided in an expeditious manner. Similarly, the request by a couple with known carrier status for prenatal diagnosis must be addressed promptly to facilitate access to all needed services so as to provide an optimal opportunity to make an informed decision.
- Couples in the prenatal population (i.e., those not in a high-risk group) should be offered the opportunity for carrier detection as early as possible to provide them time to consider the full range of informed reproductive decisions.
- The rationale for offering testing to couples currently planning a pregnancy is predicated on timely provision of balanced, accurate information about CF, including natural history of the disease, relative frequency in different ethnic and racial groups, variability of disease manifestation, and availability of highly sensitive and specific tests to determine carrier status.
- Although most males who have CF are sterile, partners of persons with CF should be tested on request for carrier status. The highest practical level of sensitivity of the DNA test should be used to maximize detection of at-risk couples.

Education

Genetic testing should be provided in response to the needs of patients. Thus, programs must provide information relating to genetics in general such as basic inheritance patterns, variable nature of disease expression, risk of occurrence, and diagnostic and therapeutic options. In the case of CF testing programs, balanced information should be presented and regularly updated. The elements that must be included are:

1. Natural history of the disease
2. Range of severity

3. Improvement in survival rates
4. Quality of life for patients and families
5. Full range of therapeutic modalities
6. Reproductive options, including adoption, use of artificial reproductive modalities, and continuation or termination of pregnancy

Educating patients and families can be accomplished by utilizing a wide variety of printed materials and media, including videos and interactive online systems. At present, information content is presented in a variable manner. It is recommended that effort be directed to develop model information that highlights the positive as well as the negative aspects of living with CF, using input from people living with the disease, their families, and members from diverse racial/ethnic groups.

Every attempt should be made to ascertain the level of understanding and cultural background of the person being tested. Followup assessment to determine retention of knowledge is an essential ingredient of any educational program.

Informed Consent

To ensure informed choice, it is imperative that the informed consent process demonstrate that the individual has fully understood the multiple options and implications that ensue from genetic testing. It is also important to ensure that those who decline to be tested do so knowledgeably, although this is typically not documented. Informed consent must include a clear description of the disease, of the limitations of the genetic testing methods, and of the voluntary participation of the individual giving consent. Individuals must be assured that although every effort will be made to ensure the confidentiality of their medical and genetic data, absolute confidentiality cannot be guaranteed.

Counseling

Provision of accurate genetic counseling, particularly when the results are provided to the patient or when the intervention strategies are discussed, is essential. The implications of genetic testing, its limitations and strengths, and the risks of ensuing potential therapies and interventions mandate that individuals knowledgeable in genetics provide these services. The counseling skills required must combine respect for a patient's right to make an autonomous decision with an appropriate level of support to facilitate the decisionmaking process.

Any strategy attempting to provide these services to the public carries with it a responsibility to enhance the educational process for physicians and other health care providers. Rapid changes in the methodology of molecular diagnosis, and therapeutic options that result from them, mandate continuing education and involvement of genetic specialists in the process of translating these developments into practical and beneficial terms. CF centers should make counseling available to minor siblings, who often have a need for information that goes unaddressed.

Nondiscrimination

Pivotal to individual autonomy is the guarantee that genetic data not be used for discrimination with reference to insurability, employment and educational opportunities, and social stigmatization.

Federal and State statutes currently in place to address nondiscriminatory practices against any carrier, person with a genetic disorder, or family member need to be enforced. However, these laws provide limited protection from discriminatory practices. Additional Federal and State statutes are needed to broaden protection from harm based on genetic status from educational, health care, and other organizations that may impact on and restrict immediate and long-term opportunities. Special attention should be given to expanding the understanding and awareness of the legal, insurance, health care, and educational professions about discriminatory practices.

In spite of laws that are put into place to protect people from external discrimination, less visible or more subtle harm may occur. For example, families may perceive differently a member found to be a carrier or found to be affected with a genetic disorder. These families may marginalize or ostracize the identified person. No laws can be passed to provide protection from this practice; however, future research is needed to understand the parameters of this problem and the moderating impact of education and counseling.

What Should Be the Future Directions for Research Relevant to Genetic Testing for Cystic Fibrosis and, More Broadly, for Research and Health Policies Related to Genetic Testing?

- As treatment options and screening technologies change, what are the impacts on medical costs, ancillary costs, and quality of life associated with CF? What are the cost-effective approaches to treatment and screening in different settings?
- What is the actual incidence of discrimination and stigmatization with respect to carriers, persons with genetic disorders, and their families? How does fear or anticipation of discrimination impact decisionmaking by some persons with identified genetic disorders?
- What is the most effective mechanism to educate health professionals about the current state of genetic disorders, genetic testing, and management of genetic disorders?
- What are effective educational strategies to educate the public and specific populations about genetics and genetic testing?
- What are patients' expectations of pretest education, genetic reproductive risk counseling, genetic evaluations, and transmittal of test results?
- Do early diagnosis and treatment of newborn infants with CF modify the morbidity as indicated by pulmonary function tests, maturation status, rates of infection, hospitalization, and mortality rates?
- A variety of screening strategies have been used in various studies (e.g., sequential versus couple screening). A systematic literature review should be undertaken, and, if warranted, a randomized controlled trial should be initiated to assess the relative merits of these strategies.

- Certain specific mutations appear to result in limited phenotypes, such as CBAVD. A goal of future research should be to continue to identify additional mutations, modifier genes, and environmental factors, and correlate these with the phenotype.
- Because CF is characterized by multiple mutations of the CFTR gene, this disease would be the prototype for the assessment of multiple methodologies to define numerous allelic mutations of a large gene.
- The optimal system for delivery of genetic services in rural and nonacademic settings should be studied.
- What are long-term effects of pregnancy termination or continuation on high-risk couples?

Conclusions and Recommendations

- Active research should continue on improved treatments for people with CF, enhanced molecular diagnosis of CF, and better understanding of the pathophysiology of CF.
- Over the past two decades, aggressive management of the pulmonary manifestations of CF and new treatment modalities have resulted in much longer survival.
- More than 90 percent of CF mutations can be identified in certain populations. Although generally good correlations exist between certain CF mutations and pancreatic status, it is known that CF mutations are not robust predictors of severity of disease and longevity.
- The goal of genetic testing is to provide individuals with information that will permit them to make informed decisions.
- CF genetic testing should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal testing.

- Comprehensive educational programs are recommended, utilizing a variety of media, for health care professionals and the public.
- Counseling services must be accurate and provide balanced information to afford individuals the opportunity to make autonomous decisions. Every attempt should be made to protect individual rights and genetic and medical privacy rights and to prevent discrimination and stigmatization.
- Access to genetic testing in the prenatal setting enhances the ability of couples to make reproductive choices, as shown by their interest in and use of the information they gain. The cost is reasonable in relation to the benefits obtained.
- Offering CF genetic testing to the general population or to newborn infants is not recommended.
- Genetic testing for many additional conditions will be available in the future. Some of the principles considered for CF genetic testing might well have broader application.
- It is essential that the offering of CF carrier testing be phased in over a period of time in order to ensure that adequate education and appropriate genetic testing and counseling services are available to all persons being tested.

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Genetic Testing For Cystic Fibrosis

A Continuing Medical Education Activity Sponsored by the National Institutes of Health

OBJECTIVE

The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Genetic Testing for Cystic Fibrosis. The statement provides state-of-the-art information regarding the appropriate use of genetic testing for cystic fibrosis, and presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. Upon completing this educational activity, the reader should possess a clear working clinical knowledge of the state of the art regarding this topic.

ACCREDITATION

The National Institutes of Health is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The National Institutes of Health designates this continuing medical education activity for 1 credit hour in Category I of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

EXPIRATION

This form must be completed and **postmarked by October 31, 1998**, for eligibility to receive continuing medical education credit for this continuing medical education activity. The expiration date for this test may be extended beyond October 31, 1998. Beginning November 1, 1998, please check the NIH Consensus Development Program Web site (http://consensus.nih.gov) or call the NIH Office of Medical Applications of Research at 301-496-1144 for information regarding an extended expiration date for this continuing medical education activity.

INSTRUCTIONS

The consensus statement contains the correct answers to the following 11 questions. Select your answer(s) to each question and write the corresponding letter(s) in the answer space provided. Mail the completed test by the expiration date shown above to the address at the end of this test. You will receive notification of your test results within 2 to 3 weeks. If you have successfully completed the test (8 or more correct answers), you will receive a certificate for 1 hour of continuing education credit along with your test results. Photocopies of this form are acceptable. There is no fee for participating in this continuing education activity.

National Institutes Of Health
Continuing Medical Education

1. Cystic fibrosis is:
(You must indicate all that are true.)

   a. an autosomal recessive genetic disorder
   b. a condition affecting 25,000 Americans
   c. diagnosed in 850 individuals each year
   d. a disorder that affects many organ systems

   ANSWER(S) _____

2. The gene for cystic fibrosis:
(You must indicate all that are true.)

   a. was discovered in 1989
   b. is on chromosome 7
   c. is called the cystic fibrosis transmembrane conductance regulator (CFTR)
   d. has hundreds of mutations that result in the development of disease

   ANSWER(S) _____

3. Cystic fibrosis:
(You must indicate all that are true.)

   a. is usually diagnosed in an infant within the first month after birth
   b. rarely leads to death before age 40
   c. can result in severe pulmonary and/or gastrointestinal disease or it may result in a very mild disease
   d. can be cured by gene therapy

   ANSWER(S) _____

4. The key to the quality and length of life in cystic fibrosis is:

   a. early growth and development in the normal range
   b. severity of lung disease
   c. pancreatic sufficiency
   d. frequency of hospitalizations

   ANSWER _____

5. The frequency of mutations in the CFTR gene is:
(You must indicate all that are true.)

   a. similar across all populations
   b. about 1 in 30 Caucasians
   c. much higher in Asian Americans than in Caucasians
   d. more frequent now than in the 1950s

   ANSWER(S) _____

6. There are more than 600 mutations that have been identified in the CFTR gene.

   a. true
   b. false

   ANSWER _____

7. CFTR mutations:
   (You must indicate all that are true.)

   a. if present, can be detected in almost everyone who is tested
   b. are more frequent in Caucasians than in African Americans
   c. are more likely to be identified in Hispanic populations than in Caucasian populations
   d. have never been found to be present in a double dose in people who are healthy

   ANSWER(S) _____

8. Education about genetic testing for cystic fibrosis can be accomplished by:
   (You must indicate all that are true.)

   a. individual counseling
   b. group counseling
   c. written materials such as brochures
   d. videotape

   ANSWER(S) _____

9. Interest in genetic testing for cystic fibrosis:
   (You must indicate all that are true.)

   a. is increased in the general population
   b. is increased in the pregnant population
   c. is increased in individuals with a family history of cystic fibrosis
   d. none of the above

   ANSWER(S) _____

10. Potential risks associated with genetic testing for cystic fibrosis are:
    (You must indicate all that are true.)

    a. misunderstanding of the meaning of test results
    b. difficulty in retaining complex genetic information
    c. stigmatization and discrimination in insurance and employment
    d. none of the above

    ANSWER(S) _____

11. Genetic testing for cystic fibrosis should be:
(You must indicate all that are true.)

a. completely voluntary
b. offered to pregnant women
c. offered to every teenager
d. offered to anyone who has a family history of cystic fibrosis

ANSWER(S) _____

Your response to the following two questions is optional and will have no effect on the grading results of this test.

Was the objective of this continuing education activity clearly stated?

a. not at all
b. very little
c. somewhat
d. considerably
e. completely

ANSWER _____

Did the activity planners provide the necessary information to meet the stated goals and objectives?

a. not at all
b. very little
c. somewhat
d. considerably
e. completely

ANSWER _____

_____
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