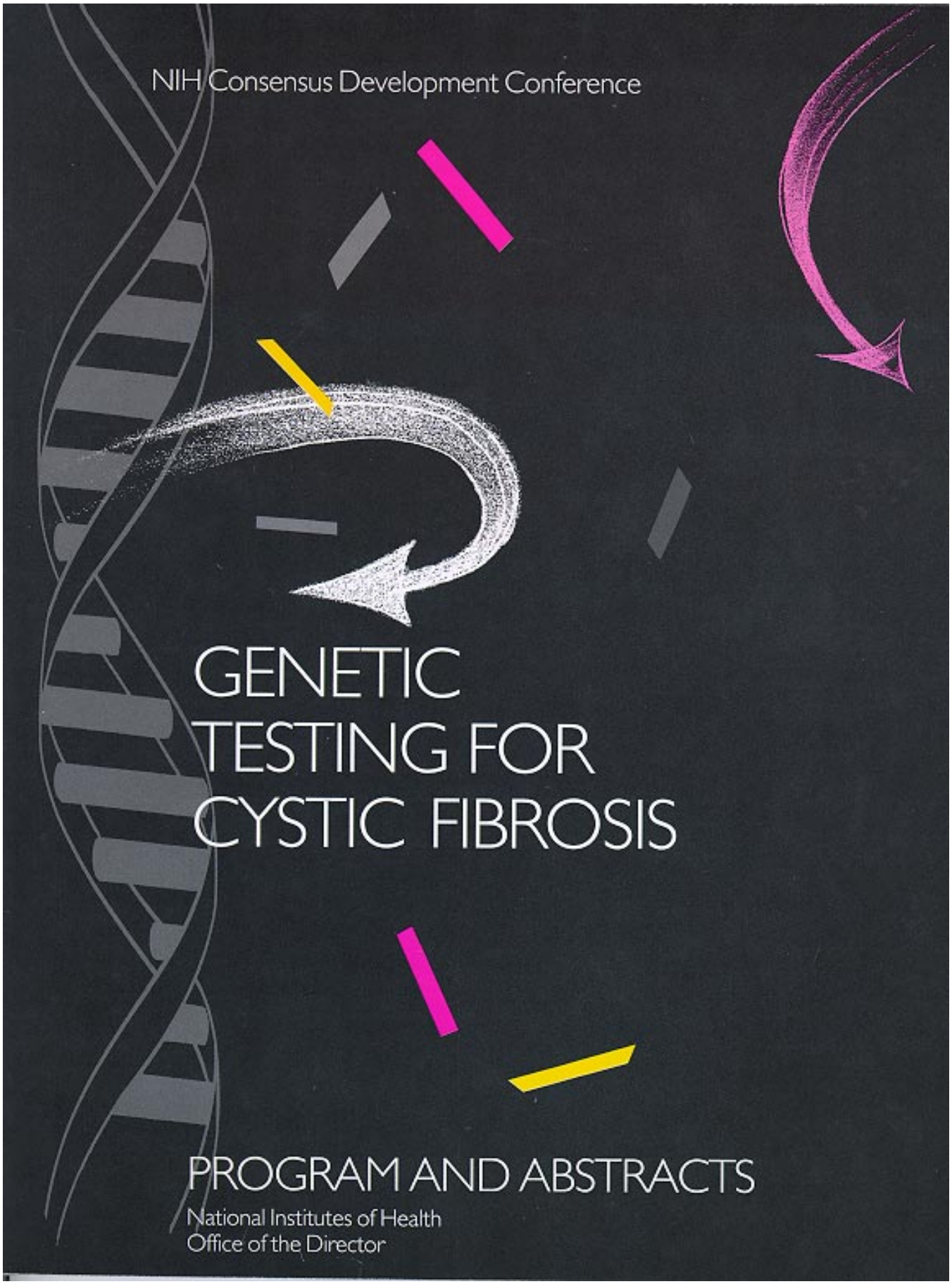
NIH Consensus Development Conference



GENETIC TESTING FOR CYSTIC FIBROSIS

PROGRAM AND ABSTRACTS

National Institutes of Health
Office of the Director

NIH Consensus Development Conference on Genetic Testing for Cystic Fibrosis

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NIH Consensus Development Conference
April 14–16, 1997

Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Sponsored by the National Human Genome Research Institute and the NIH Office of Medical Applications of Research; co-sponsored by the Agency for Health Care Policy and Research; Centers for Disease Control and Prevention; National Institute of Child Health and Human Development; National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Mental Health; National Institute of Nursing Research; NIH Office of Rare Diseases; and NIH Office of Research on Women's Health.

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Introduction to the NIH Consensus Development Conference on Genetic Testing for Cystic Fibrosis

When the gene for cystic fibrosis (CF) was discovered in 1989, a great deal of attention was given to the implications of this discovery for widespread testing for CF mutations. At the time, scientists, health care providers, and the public urged that research be carried out to examine knowledge and attitudes about, interest in, and demand for CF testing; the effectiveness of educational interventions; optimal informed consent procedures; laboratory issues associated with carrying out such tests; costs and benefits of testing; and possible deleterious effects associated with this testing. They suggested that alternative delivery mechanisms should be explored and called for Federal funds to carry out such research. Since that time, new research has yielded a large body of data on these and other issues.

This conference will bring 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 1 1/2 days of presentations and audience discussion, an independent, non-Federal consensus panel will weigh the scientific evidence and write a draft statement that it will present to the audience on the third day. The consensus statement will address the following 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?

On the final day of the meeting, the conference and panel chairperson, R. Rodney Howell, M.D., Professor and Chairman, Department of Pediatrics, School of Medicine, University of Miami, will read the draft statement to the conference audience and invite comments and questions. A press conference will follow to allow the panel and chairperson to respond to questions from media representatives.

GENERAL INFORMATION

Conference sessions will be held in the Natcher Conference Center (Building 45), NIH, 9000 Rockville Pike, Bethesda, Maryland. Sessions will run from 8:30 a.m. to 5:30 p.m. on Monday,

8:30 a.m. to 12:15 p.m. on Tuesday, and 9 to 11 a.m. on Wednesday. The telephone number for the message center is 301-496-9966.

CAFETERIA

The cafeteria is located on the lobby level and is open daily from 7:00 a.m. to 2:00 p.m.

CONTINUING EDUCATION CREDIT

The purpose of this Consensus Development Conference is to review the current state of knowledge regarding genetic testing for cystic fibrosis, evaluate optimal testing practices, and identify directions for future research.

The conference will (1) present in open, public sessions state-of-the-art information regarding genetic testing for cystic fibrosis, (2) prepare a statement in response to the five specific questions, and (3) inform the biomedical research and clinical practice communities and the general public of the conclusions and recommendations of the panel.

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 a maximum of 14 hours in Category 1 credit toward the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit he/she actually spent in the educational activity.

SPONSORS

The primary sponsors of this conference are the National Human Genome Research Institute and the NIH Office of Medical Applications of Research. The conference is cosponsored by the Agency for Health Care Policy and Research; Centers for Disease Control and Prevention; National Institute of Child Health and Human Development; National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Mental Health; National Institute of Nursing Research; NIH Office of Rare Diseases; and NIH Office of Research on Women's Health. This is the 106th Consensus Development Conference held by the NIH since the establishment of the Consensus Development Program in 1977.

Agenda

Monday, April 14, 1997

8:30 a.m.	Welcome and Introduction	Francis S. Collins, M.D., Ph.D. Director National Human Genome Research Institute National Institutes of Health
8:35 a.m.	Charge to Panel	John H. Ferguson, M.D. Director Office of Medical Applications of Research National Institutes of Health
8:45 a.m.	Conference Issues	R. Rodney Howell, M.D. Conference and Panel Chairperson
	I. Current State of Knowledge Regarding CF	
9:00 a.m.	Cystic Fibrosis in the Post-CFTR Era	Thomas F. Boat, M.D.
9:30 a.m.	Genetic Epidemiology and Genotype/ Phenotype Correlations	Garry R. Cutting, M.D.
10:00 a.m.	Cystic Fibrosis Therapy	Preston W. Campbell, III, M.D.
10:30 a.m.	Newborn Screening	Michael J. Rock, M.D.
10:50 a.m.	Genetic Testing Technologies	Katherine W. Klinger, Ph.D.
11:10 a.m.	Discussion	
12:00 noon	Lunch	
	II. Data on Genetic Testing for CF CF Consortium Studies Presentations	
1:00 p.m.	Carrier Testing Among First, Second, and Third Degree Relatives of CF Patients	James R. Sorenson, Ph.D.
1:15 p.m.	Carrier Testing for Adult Cystic Fibrosis Siblings: The Importance of Not Knowing	Joanna H. Fanos, Ph.D.
1:30 p.m.	Cystic Fibrosis Mutation Screening and Counseling	Wayne W. Grody, M.D., Ph.D.

Monday, April 14, 1997 (continued)

1:45 p.m.	Offering Cystic Fibrosis Carrier Screening to an HMO Population: Utilization, Knowledge, and Factors Influencing the Decision To Be Tested	Barbara A. Bernhardt, M.S.
2:00 p.m.	Efficacy of Education for and Interest in Population-Based Cystic Fibrosis Carrier Screening	John A. Phillips III, M.D.
2:15 p.m.	Prenatal Cystic Fibrosis Carrier Population Screening: Lessons from a Regional Trial	Peter T. Rowley, M.D.
2:30 p.m.	How Much Information About the Risk of Cystic Fibrosis Do Couples Want to Know?	David A. Asch, M.D., M.B.A.
2:45 p.m.	Discussion	
	Other Relevant Studies	
3:15 p.m.	Prenatal Genetic Carrier Screening: Experience With Multiple Option Screening in the Ashkenazi Jewish Population	Christine M. Eng, M.D.
3:30 p.m.	Prenatal Cystic Fibrosis Heterozygote Screening of 5,161 Women in a Large HMO	David R. Witt, M.D.
3:45 p.m.	Prenatal Couple Screening for Cystic Fibrosis in Primary Care Settings	Richard A. Doherty, M.D.
4:00 p.m.	Cystic Fibrosis Carrier Testing in the Population: A U.K. Perspective	Theresa M. Marteau, Ph.D.
4:15 p.m.	Cystic Fibrosis Among Native Americans of the Southwest	Theresa A. Grebe, M.D.
4:30 p.m.	Discussion	
5:30 p.m.	Adjourn	

Tuesday, April 15, 1997

III. Goals of Cystic Fibrosis Testing

Genetic Testing for Cystic Fibrosis: For Whom and at What Cost?

8:30 a.m.	Cost-Effectiveness of Prenatal Carrier Screening for Cystic Fibrosis	Tracy Lieu, M.D., M.P.H.
8:50 a.m.	Prescriptive Decision Modeling for Cystic Fibrosis Screening	David A. Asch, M.D., M.B.A.
9:10 a.m.	Economic Evaluation of Cystic Fibrosis Carrier Population Screening	Peter T. Rowley, M.D.
9:30 a.m.	Discussion	
10:00 a.m.	Making the Case for Offering Cystic Fibrosis Carrier Testing on a Population Basis	Arthur L. Beaudet, M.D.
10:30 a.m.	A Standard of Care for Cystic Fibrosis Carrier Screening: Satisfying Equity and Autonomy	Neil A. Holtzman, M.D., M.P.H.
11:00 a.m.	Normative Issues in Developing Public Policy for Cystic Fibrosis Carrier Testing	Benjamin S. Wilfond, M.D.
11:30 a.m.	Discussion	
12:15 p.m.	Adjournment	

Wednesday, April 16, 1997

9:00 a.m.	Presentation of the Consensus Statement	R. Rodney Howell, M.D. Conference and Panel Chairperson
9:30 a.m.	Discussion	
11:00 a.m.	Panel Meets in Executive Session	
1:00 p.m.	Press Conference	
2:00 p.m.	Adjournment	

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Abstracts

The following abstracts of presentations to the NIH Consensus Development Conference on Genetic Testing for Cystic Fibrosis were furnished by presenters in advance of the conference. This book is designed for the use of panelists and participants in the conference and as a reference document for anyone interested in the conference deliberations. We are grateful to the authors who have summarized their materials and made them available in a timely fashion.

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Cystic Fibrosis in the Post-CFTR Era

Thomas F. Boat, M.D.

Introductory Information

Cystic fibrosis (CF) is often characterized as the most common life-limiting genetic disorder in the Caucasian population. The estimated incidence of this disorder in North American Caucasians is 1:3,300, in African Americans, 1:15,300, and in Asian Americans, 1:32,000. More than 20,000 individuals with CF were recorded by the National Cystic Fibrosis Foundation Registry in 1995. The Registry entered 864 newly diagnosed cases in 1995; this number has not changed substantially since 1991. The median age at diagnosis is 6–8 months. The mean age at diagnosis is 3–4 years. As with the detection of new cases, there has been little change in the age of diagnosis over the last 5 years. This is not unexpected, as population-based neonatal screening has been carried out for a substantial length of time in only two states.

Historical Perspectives

While CF-like disorders were described in the literature going back several hundred years, the CF syndrome was first described as a separate entity by Dr. Dorothy Anderson in 1938. The patients she described had pancreatic insufficiency with growth failure, malnutrition, and suppurative lung disease. In the 1940's, it became clear from the studies of Dr. Sidney Farber that an important pathogenetic mechanism, especially in the lungs, was failure to clear mucus secretions. In this decade, an autosomal recessive inheritance pattern was also noted. In the 1950's, the sweat defect was detected by Dr. Paul DiSant'Agnese, and shortly thereafter the current test for the determination of sweat chloride was described. In the 1960's and 1970's, comprehensive therapy programs—including treatments to enhance lung mucus clearance and control airways infection, and the use of pancreatic enzyme and vitamin supplements, together with prevention by immunization of devastating viral lung infections such as measles and influenza—appreciably increased life span. An understanding of disease pathogenesis was sketchy, at best, until the early 1980's when the ion transport defect in epithelial cells of the lung and sweat glands was described, including inability to secrete chloride in response to CAMP-mediated stimuli and hyperabsorption of sodium from the lumenal surface liquids of airways. In 1989, the gene associated with cystic fibrosis was identified and named the cystic fibrosis transmembrane conductance regulator (CFTR). The structure and function of this gene product, a membrane protein that serves both as a chloride channel and as a regulatory molecule, were uncovered. Even with this knowledge, the pathogenesis of CF lung and other organ system disease is not fully understood. There is not as yet an adequate explanation of the failure to clear CF epithelial secretions, nor is there a clear understanding of the failure of the CF airways to defend themselves against bacterial pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Following the identification of the CFTR gene, a large number of mutations associated with CF were identified and reported. Well over 400, and perhaps more than 500 mutations of the CFTR gene can be considered CF mutations. Fairly quickly, it has become apparent that some of the variability in the

clinical presentation and progression of disease in cystic fibrosis can be attributed to various genotypes, although genotype/phenotype correlations for lung disease are not tight.

Natural History

Cystic fibrosis presents in many different ways and its course is highly variable. Even with treatment, lung disease may have an early onset and then an unrelenting course, leading to death, even within the first years of life. On the other hand, a number of other individuals with cystic fibrosis have had symptom free intervals for a decade or two and have a near normal life span. With the identification of the CFTR gene and its mutations, it has become apparent that there are mild and atypical clinical presentations associated with several CF mutations.

Although the course is variable, there is a typical clinical course that is usually associated with the most common CF allele, DF508. In these cases, the diagnosis is usually made in the first year of life and almost always in the first 3 years of life. There is early onset of obstructive lung disease and superimposed infection. These children usually also present with steatorrhea, failure to thrive, and evidence for malnutrition. With aggressive therapy, most of these children improve remarkably and often have a stable course for months to years. Serial pulmonary function tests, however, show that sometime in the first decade of life or soon thereafter, progressive deterioration of lung disease sets in. Despite ongoing comprehensive therapy, the result is ventilatory failure and cor pulmonale. The mean survival for all CF patients in the United States is now approximately 30 years of age. This number has changed very little over the last 5 years.

Impact of the CF Gene

Some facets of CF have changed since identification of the CFTR gene and its product. However, knowledge of mutations in this gene has had very little impact on the frequency with which the gene is detected in the population as a whole, on the frequency with which new cases are detected, or on the outcome for individual patients, including measures of quality of life and prognosis. An absence of change in these areas is to be expected, because no general screening program has been instituted, and no new therapies based on the recently recognized molecular pathogenesis have been introduced.

Knowledge of CFTR mutations has made some difference concerning diagnosis. Previously, typical pulmonary or gastrointestinal (GI) symptoms, or the diagnosis of CF in a close family member, coupled with the documentation of high sweat chloride values, constituted a diagnosis of CF. Now, a typical clinical presentation, coupled with either the identification of two CF alleles, or epithelial cell dysfunction as documented by elevated potential difference measurements, is sufficient for a diagnosis of CF.

Identification of the mutations in the CFTR gene has had a substantial impact on recognition and understanding of the extent of variability of organ system dysfunction. It has also had a considerable impact on clinical research, in that genetically homogeneous study populations can be identified for assessment of the outcome of interventions. In addition, the identification of CFTR and assignment of function to this molecule has allowed investigators to focus on interventions that might possibly correct

the molecular defect. For example, cloning and characterization of the CFTR gene has also opened the door for consideration of gene transfer therapy.

Questions Related to Genetic Screening for Cystic Fibrosis

1. In view of the fact that new molecular information about CF pathogenesis has not changed the prevalence of the gene, the rate at which new cases are appearing, the therapeutic approach, or the ultimate outcome, is there a need to reevaluate the importance of preventive strategies?

2. In what timeframe is it likely that there will be new, effective lung interventions for CF based on an understanding of molecular pathogenesis?

3. Even if new effective lung therapies are forthcoming, will they influence the course of the disease for those with already established chronic lung disease? In other words, will the impact of effective preventive interventions take 30 or more years to play out if survival is the outcome measure?

4. Are all individuals with CF to be treated similarly in these considerations, or are there "mild genotypes" that can be excluded from screening considerations?

5. Have longevity and quality of life for individuals with CF improved to the point where some or many families see screening as irrelevant?

Genetic Epidemiology and Genotype/Phenotype Correlations

Garry R. Cutting, M.D.

Cystic fibrosis (CF) is one of the more common lethal inherited disorders among Caucasians. CF has also been reported in non-Caucasian populations but the precise incidence is unknown. To address this issue, we have utilized information from the U.S. Cystic Fibrosis Foundation National Patient Registry and from the National Center for Health Statistics to calculate race-specific and ethnic-specific incidences and carrier rates for U.S. populations (Table 1). The expected incidence (1 in 3,300) and calculated carrier rate (1 in 29) in Caucasians is slightly higher than generally quoted (1 in 2,500) but is consistent with results of carrier screening studies.[1,2] CF is a rare disorder in native Africans and native Asians, estimated to occur in less than 1 in 50,000 individuals. The disorder has a higher incidence in African-Americans and Asian-Americans probably as a result of admixture with Caucasian population. Admixture also appears to play a role in the frequency of CF in Native-Americans.

The genetic basis for CF was confirmed by the cloning of the cystic fibrosis transmembrane conductance regulator (CFTR) gene and identification of deleterious mutations in patients with CF. A deletion of three nucleotides causing the omission of the amino acid phenylalanine at codon 508 (DF508) was found to occur on a majority of CFTR genes from patients with CF. The frequency of this mutation varies considerably, depending on the population studied. The frequency of DF508 is highest in Northern Europeans and decreases in frequency in a gradient from Northwest to Southeast Europe.[4] In addition to the DF508 mutation, there are approximately 15–20 other "common" mutations that account for 2 percent to 15 percent of CF alleles depending on the ethnic composition of the patient group studied.[5] Compilation of data reported from laboratories operating in various parts of the United States

TABLE 1. Number of Newly Diagnosed Cases of Cystic Fibrosis in the United States by Race and Ethnicity 1990–1992[3]

	NCHS Total Live Births	CFF† Incident Cases	Expected* Incidence	Calculated Carrier Rate
By race				
Caucasian	3,201,678	824	3,300	29
African-American	673,633	37	15,300	62
Native-American	39,453	3	11,200	53
Asian-American	150,250	4	32,100	90
Total	4,065,014	868	4,000	32
By ethnicity				
Hispanic	643,271	58	9,500	49

†Average of 3-year incident cases as reported to the 1990–1992 CF Foundation National Registry.
*Adjusted by a coefficient of 1.17 to correct for CF patients not followed in CF Foundation Care Centers and therefore not reported to the Registry. The expected incidence is 1 divided by (CFF incident cases x 1.17/NCHS total live births). Carrier rate is based on Hardy-Weinberg calculations. Both expected incidence and carrier rate are rounded.

show that the DF508 mutation accounted for 66 percent of CF alleles while the "common" mutations account for another 13 percent, for a total of 79 percent (Table 2). Beyond the "common" group, there are a few mutations that occur at high frequency in specific populations, probably as a result of founder effect. For example, five mutations account for 97 percent of CF alleles in Ashkenazi Jews.[6] The vast majority of the remaining mutations are exceedingly rare occuring in one or at most, a few CF patients worldwide. Thus, screening tests that include mutations beyond the "common" CF alleles increase detection rates only marginally. Inclusion of mutations known to be frequent to a particular geographic region should optimize detection rates. However, current data suggest that mutation detection rates are unlikely to exceed 85 percent for a diverse population such as the United States.

Mutation screening has also been performed on reasonably large groups of African-American and Hispanic CF patients. Screening of the former group for DF508 and "common" alleles detects just over 50 percent of mutations. However, African-Americans have a subset of eight mutations that account for an additional 23 percent of CF alleles, bringing the combined detection rate to 75 percent. In the Hispanic group, the DF508 frequency is considerably lower than non-Hispanic Caucasians producing an overall detection rate of less than 60 percent. A small study of Pueblo Indians in Southwest United States revealed that a vast majority carry a mutation that is relatively frequent in Southern Europe. It is suspected that this mutation was introduced by a European ancestor. A small number of Asian-Americans have been studied (Table 2). The DF508 mutation in Asian-American patients appeared to be inherited from a Caucasian ancestor in each case. Other mutations identified in this group have not been observed in Caucasian patients.

A number of studies addressing the relationship between genotype and phenotype of CF have been completed. Several generalizations can be made. First, there is a correlation between the severity of pancreatic disease and the degree of elevation of the sweat chloride concentration and specific genotypes.[13,14] The common mutation DF508 and most of the less common CF mutations are associated

TABLE 2. Distribution of CF Mutations Among Racial and Ethnic Groups in the United States

	Number of Chromosomes	ΔF508 Mutation	Common† Caucasian Mutations	Group‡ Specific Mutations	Combined Detection Rate
By race					
Caucasian[7]	8714	5769 (.66)	1086 (.13)	–	.79
African-American[8]	148	71 (.48)	6 (.04)	34 (.23)	.75
Native-American[9]	16	0	4 (.25)	11 (.69)	.94
Asian-American[10,11]	10	3 (.30)	0	–	.30
By ethnicity					
Hispanic[12]	129	59 (.46)	14 (.11)	–	.57

†Caucasian: R117H, 621+1G→T, R334W, R347P, A455E, ΔI507, 1717-1G→A, G542X, S549N, G551D, R553X, R560T, 3849+10kbC→T, W1282X, N1303K.
‡ African-American: 405+3A→C, 444delA, G480C, A559T, 2307insA, 3120+1G→A and S1255X; Native-American: R1162X.

with severe pancreatic exocrine dysfunction (pancreatic insufficiency). Five of the less common mutations are associated with preservation of pancreatic function (pancreatic sufficiency) and detection of one of these mutations in a patient is predictive of less severe pancreatic disease. Intestinal obstruction at birth termed "meconium ileus" is a life threatening complication in approximately 19 percent of CF patients. This feature of the disease also appears to be related to genotype.[3]

Second, the association between genotype and severity of pulmonary disease is not clear. This is problematic because lung disease is the major cause of morbidity in CF, accounting for about 90 percent of deaths in this disorder. One mutation, A455E has been reported to be associated with less severe pancreatic disease, less significant elevations in sweat chloride concentrations and milder pulmonary disease.[15] Several studies have suggested that the level of the CFTR transcript plays a critical role and is correlated with the severity of lung disease.[16,17] This is based on the observation that patients with a different disorder, congenital bilateral absence of the vas deferens (CBAVD), an almost invariable feature in males with CF, also carry mutations in the CFTR gene. Intriguingly, a high proportion of males with CBAVD have a variation in intron 8 of the CFTR gene called 5T that reduces the level of normally spliced CFTR transcript.[18] This variation does not cause CF. Third, it has been suggested that the severity of disease in CF can be influenced by variations in other genes. Studies performed in mice with CF indicate that severity of intestinal disease appears to be modulated by a separate genetic locus.[19] The equivalent locus has been studied in humans and preliminary data suggest it may play a role in modifying both pulmonary and intestinal disease in humans.

In summary, the relationship between genotype and phenotype is relatively straightforward for several features of the disease. However, this relationship is quite complicated for the life-limiting manifestation of CF, progressive obstructive pulmonary disease.

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Cystic Fibrosis Therapy

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Conventional Therapy

The treatment of cystic fibrosis (CF) is directed toward alleviation of symptoms and correction of organ dysfunction.[1,2] Although the sweat gland, intestine, liver, sinuses, uterine cervix, and vas deferens are affected, the epithelial dysfunction in the pancreas and lung results in the most clinically significant problems. The pancreas is affected in 85 percent of patients and results in malnutrition if the exocrine pancreatic insufficiency is not treated. In the lung, altered airway secretions lead to airway obstruction, chronic infection, and inflammation. The resulting lung destruction accounts for more than 90 percent of fatalities. The cornerstones of conventional treatment have been pancreatic enzyme and vitamin replacement, nutritional supplements, airway clearance techniques, and antibiotics for the treatment of pulmonary infections. Aggressive use of conventional therapy for CF has resulted in an increase in the median survival from 14 years in 1969 to 30 years in 1995.

Anti-inflammatory Therapy

Based on recent data indicating that airway inflammation is present in CF patients during infancy, attention has been focused on the inflammatory response in the lung. The massive influx of neutrophils into the airways impairs opsonophagocytosis and perpetuates inflammation by the release of proteases and oxidants. Blunting the inflammatory response using alternate-day corticosteroid therapy slows the progression of lung disease but is associated with significant adverse effects.[3] Ibuprofen given in high doses to CF patients with mild lung disease also slows the progression of lung disease but without an increase in adverse effects.[4] Inhaled antiproteases are also being evaluated to determine their potential to reverse airway inflammation in CF.[5,6]

Enzyme Therapy for Airway Secretions

The abnormal viscosity of airway secretions is due in part to the presence of neutrophil degradation products, of which the most important are DNA and filamentous actin. Another strategy to slow lung destruction in CF is to use inhaled enzymes to cleave these neutrophil-derived products. For example, the efficacy and safety of inhaled recombinant human deoxyribonuclease I (rh DNase I) have been studied in several clinical trials. Once-daily inhalation of rh DNase I for 24 weeks resulted in a 5.8 percent improvement of FEV_1 and a 28 percent reduction in the age-adjusted risk of respiratory exacerbation requiring intravenous antibiotic therapy as compared with placebo.[7] No significant adverse effects were noted. Gelsolin, a filamentous actin severing enzyme, significantly reduces the viscosity of CF sputum *in vitro*, but clinical trials have not been reported.

Potential Therapies To Restore CFTR Function

Since the identification of the CF gene in 1989, an exponential increase in our understanding of the structure and function of the protein product called the cystic fibrosis transmembrane conductance regulator (CFTR) has occurred. CFTR is a cAMP-activated chloride channel that may also stimulate other chloride channels and inhibit sodium absorption by sodium channels. This new knowledge has suggested potential new therapies directed at the basic defect, including gene therapy, restoration of electrolyte transport, and activation of mutant CFTR. Gene therapy seems well suited to CF because it is a single gene defect, only small amounts of functional CFTR are necessary to protect the lung against disease, complementary DNA (cDNA) for CFTR has been successfully cloned and transferred into cultured CF epithelial cells correcting the chloride channel defect, and the airway is easily accessible by inhalation therapy. Three different vector systems for delivering the CFTR cDNA to CF airways—modified adenovirus (AV), adeno-associated virus (AAV), and liposomes—have been examined in Phase I trials. To date, these trials suggest that CFTR cDNA can be transduced into airway-lining cells, but with very limited efficiency or resulting functional expression.[8] The current focus of these efforts is aimed at developing a vector that results in long-term expression of CFTR without evoking an inflammatory response.

Another strategy, restoration of electrolyte transport in the airway, is based on the hypothesis that the airway epithelial cell's sodium absorption is excessive and chloride secretion is blocked. For example, inhaled agents that have been evaluated are the sodium channel blocker amiloride and uridine triphosphate (UTP), which activates alternative chloride channels.[9]

Finally, the pharmacologic activation of mutant CFTR protein is a very promising area of CF research. Pharmacologic agents are used either to enable intracellular processing and insertion of the protein into the apical membrane or to "upregulate" its activity.[10–12]

Human Beta-Defensin

It was recently shown that common CF bacterial pathogens were killed when added to normal airway epithelia, but not CF epithelia *in vitro*.[13] Natural bactericidal activity was present in both normal and CF epithelia, but this activity was inhibited on CF epithelia because of a high extracellular NaCl concentration. This defect in bacterial killing was corrected on CF epithelia when the NaCl concentration of extracellular fluid was reduced. These data provide a potential link between the physiological hallmark of CF (defective chloride transepithelial transport) and the clinical hallmark of this disease (persistent endobronchial infection). The factor responsible for this innate immunity has recently been identified as human beta-defensin-1.[14] This small peptide has salt-dependent antimicrobial activity. These exciting data may set the stage for new strategies for the prevention or treatment of lung infections in CF patients.

Summary

Survival in CF has improved dramatically over the last several decades using more aggressive but fairly conventional therapy. The more recent development of anti-inflammatory therapy and agents that reduce mucous viscosity suggest that additional improvement is possible. Promising new strategies for correcting or circumventing the basic defect have evolved from our improved understanding of the basic defect in CF. Cautious optimism exists within the CF community that a significant advance in therapy will occur, but its imminence can not be guaranteed.

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Newborn Screening

Michael J. Rock, M.D.

Although cystic fibrosis (CF) is the most common, potentially lethal disease in Caucasians, there is often a delay between the onset of symptoms and definitive diagnosis. In 1995, there were 864 new diagnoses of CF in the United States, with a mean age at diagnosis of 4.5 years and a median age at diagnosis of 8 months. For all of the patients in the CF Foundation Patient Registry, the mean and median ages at diagnosis are 2.9 years and 6 months, respectively.[1] Retrospective observations have suggested that an earlier diagnosis and initiation of therapy results in an improved prognosis and course of the disease. In 1970, Shwachman observed that children diagnosed prior to symptoms or with mild symptoms had improved survival compared with those diagnosed during hospitalization.[2] In 1977, Orenstein published the results of a 7-year study of 16 sibling pairs. The younger siblings had significantly better chest x-ray scores, total clinical scores, residual volumes, and lower RV/TLC ratios.[3] To critically examine the feasibility of neonatal screening for CF, a task force was convened by the CF Foundation in 1983.[4] The task force concluded that extensive research was needed with regard to neonatal screening. Issues that must be addressed prior to implementing mass screening included:

- Determine the value of early treatment on prognosis.
- Determine the reliability and validity of the screening method.
- Determine the benefits and risks of early detection.
- Define the incidence and preventability of stigmatization in families with false-positive and true-positive tests.
- Determine cost-effectiveness.
- Determine availability of competent counseling for families with false-negative, false-positive, and true-positive results.

In 1979, Crossley described the elevation of trypsinogen in infants with CF as measured from a dried blood spot.[5] This is a convenient specimen in that a Guthrie card (dried blood spot on filter paper) for newborn screening of other diseases such as phenylketonuria and congenital hypothyroidism is collected on all infants in the United States and developed countries.

Previous newborn screening programs for CF utilized a repeat sampling method. If the neonatal trypsinogen result was above the decision value, then a second specimen was obtained from the baby at 2–8 weeks of age for analysis of trypsinogen. A definitive diagnostic sweat test was obtained from the infant if the trypsinogen value of the second specimen was also above the decision value. Newborn screening programs that have used this repeat sampling approach have used a lower cutoff value for the second specimen to account for the expected decline in trypsinogen level with age.[6]

In Wisconsin, a randomized study of newborn screening for CF was conducted from April 1985 to June 1994. In addition to examining the medical benefits and risks of neonatal screening, there has also been a rigorous examination of false positives, false negatives, sensitivity, positive predictive value, and the age-related decline of trypsinogen values. With the repeat sampling approach, we have found a

sensitivity of 87 percent, a specificity of 99.9 percent, and a positive predictive value of 12.5 percent.[7] More importantly, children with CF can have trypsinogen values decrease at 4–10 weeks of age into a range in which there is overlap with values from children without CF.[8] In other words, we have not been able to distinguish CF infants from the false-positive infants based on a second blood specimen (the repeat sampling approach).

The discovery of the CF gene in 1989[9] and the most common mutation, the DF508, have given us the opportunity to develop newborn screening into a two-tier test. The first tier is measurement of trypsinogen; if that value is above the cutoff, then DNA analysis is performed on the same dried blood spot for the DF508 mutation. This two-tier technique was utilized from July 1991 through June 1994 in the screened half of the population in the Wisconsin study. Using this trypsinogen/DNA method, the sensitivity improved to 95.2 percent, the specificity remained at 99.9 percent and the positive predictive value improved to 15.2 percent.[10] The major advantage of this two-tier protocol is that the number of families that must be contacted for sweat testing is reduced.

Beginning in July 1994, the state of Wisconsin added CF neonatal screening to the panel of newborn screening tests. This pilot project continues while we await the final data analysis of the randomized study. Five categories of reports are issued to the primary care physician:

1. A normal, low level of trypsinogen.

2. Trypsinogen level between the 94 and 99.8 percentiles, followed by DNA analysis resulting in no DF508 alleles detected. This is a second category of negative report.

3. Trypsinogen level greater than the 99.8 percentile and no DF508 alleles detected. This report specifies that "This trypsinogen level may be indicative of cystic fibrosis." Sweat testing is recommended if there are symptoms of CF or a positive family history.

4. Trypsinogen level greater than the 94th percentile and one DF508 allele. This report states that CF is possible and a sweat test is recommended at 4 weeks of age.

5. Trypsinogen level greater than the 94th percentile and two DF508 alleles. This is a definite CF report, and a confirmatory sweat test is recommended.

In the latter two categories, the primary care physician is advised that sweat testing should be carried out in a Cystic Fibrosis Foundation-certified center that is experienced in sweat testing of infants. Despite this recommendation, we have found that a substantial number of infants are receiving sweat tests outside of CF Centers. In a geographically large State such as Wisconsin, some of the population is several hundred miles away from a CF Center and families are unwilling to drive that distance. In the first 2 years of this pilot project, 18 different laboratories in Wisconsin or near the State border have performed sweat tests as a result of newborn screening. Three of these laboratories are CF Centers (Madison, Milwaukee, and Minneapolis). In patients who do not have CF but who have one copy of the DF508 allele (normal heterozygote carriers), 199 infants had sweat tests in CF Centers and 71 infants had sweat tests outside of CF Centers.[11] (One laboratory that measured sweat osmolality was excluded from this analysis.) We are currently working on a sweat testing quality assurance (QA) program to establish that laboratories are performing this difficult test satisfactorily.

In this pilot project, the trypsinogen cutoff level has been decreased to the 94th percentile in an effort to avoid missed cases of CF. However, this lower cutoff level generates a larger number of infants who are heterozygote carriers. Future research will need to determine the optimal trypsinogen cutoff level. Research will also need to determine the cost-effectiveness of adding other mutations to the second tier of the newborn screen.[12]

An unavoidable outcome of two-tier CF newborn screening is identification of infants who are heterozygote carriers. This information is of no known value to the infant until he/she reaches reproductive age.[13] However, because we have identified the infant as a carrier, at least one of the parents must be a heterozygote carrier, and therefore genetic counseling is warranted. Although this genetic counseling is occurring in the CF Centers, we do not know of the quality or occurrence of genetic counseling in those sites outside of CF Centers that are performing sweat tests. In addition to the sweat testing QA program, we are also working on ensuring that proper genetic counseling is occurring in non-CF Centers. Other large geographic States that are considering CF newborn screening should take into account the issue of sweat testing quality and genetic counseling of heterozygote carriers.

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Genetic Testing Technologies

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Over the last several years, there has been a significant increase in the number of identified, cloned, and characterized genes responsible for inherited diseases in humans. As the number of disease-associated sequences has increased, the number of mutations identified within the genes has likewise increased. In some genes, only one or a few mutations are specifically responsible for the disease phenotype (e.g., sickle cell anemia).[1] However, in most disease genes, many different causative mutations exist. This is certainly the case with cystic fibrosis (CF). Delta F508 is the most common mutation within many affected patient populations, and is present in about 70 percent of Caucasian CF carriers. However, more than 400 additional mutations have been described (Cystic Fibrosis Genetic Analysis Consortium), as well as significant ethnic variations in the frequency of DF508. While most of these mutations occur in a small fraction of families, some occur at frequencies in the 1–3 percent range.

In March 1990, the consensus at the National Institutes of Health (NIH) Workshop on Population Screening for the Cystic Fibrosis Gene concluded that, among other criteria, a mutation detection rate of 90–95 percent was required before routine screening could be offered. Addressing this issue in 1992, the Office of Technology Assessment[2] correctly noted that properly performed DNA-based mutation tests for CF were accurate and specific, but could leave ambiguity because the tests could not detect sufficient mutations to reach a 90+ percent detection rate in the general population. Furthermore, at the time it was thought impractical to develop a 170 mutation test.[2]

In the interval since 1992, it has been recognized that extensive mutation heterogeneity appears to be the general case in human genetic disorders, requiring efficient methods of mutation analysis not only to confirm that a candidate gene truly represents the disease gene, but also to build mutation databases and provide clinical diagnostic assays. Accordingly, a wide variety of mutation detection technologies have been developed, as summarized in Figure 1.[3,4] These techniques have varying degrees of suitability for routine diagnostic use. The first group, designed to scan for mutations within a gene, includes single-strand conformational polymorphism (SSCP),[5] denaturing gradient-gel electrophoresis (DGGE),[6] heteroduplex analysis (HET),[7] chemical cleavage analysis (CCM),[8] ribonuclease cleavage (RNAase),[9] and direct sequencing of the target.[10] These procedures are highly informative, but can be tedious and are poorly compatible with high throughput and low cost. In the second group, more direct methods of mutation analysis have been developed such as allele-specific amplification (ASA),[11] oligonucleotide ligation assay (OLA),[12] primer extension,[13] artificial introduction of restriction sites (AIRS),[14] allele-specific oligonucleotide hybridization (ASO),[15] and variations of these procedures. Together with robotics, these methods for direct mutation analysis have helped in reducing cost and increasing throughput when only a limited number of mutations need to be analyzed. The "chip" technology, or Sequencing by Hybridization (SBH), involves the hybridization of a single labeled target to a dense panel of oligonucleotides arrayed on a solid support.[16–21] Recently, a prototype array analysis was used to detect mutations in exon 11 of BRCA1.[22] Although a number of technical issues must be addressed before arrays can be routinely applied to clinical diagnostics, this approach is an extremely appealing solution for large multiplex mutation analysis.[23] However, as with the reverse dot blot procedure, each sample analysis is performed independently.

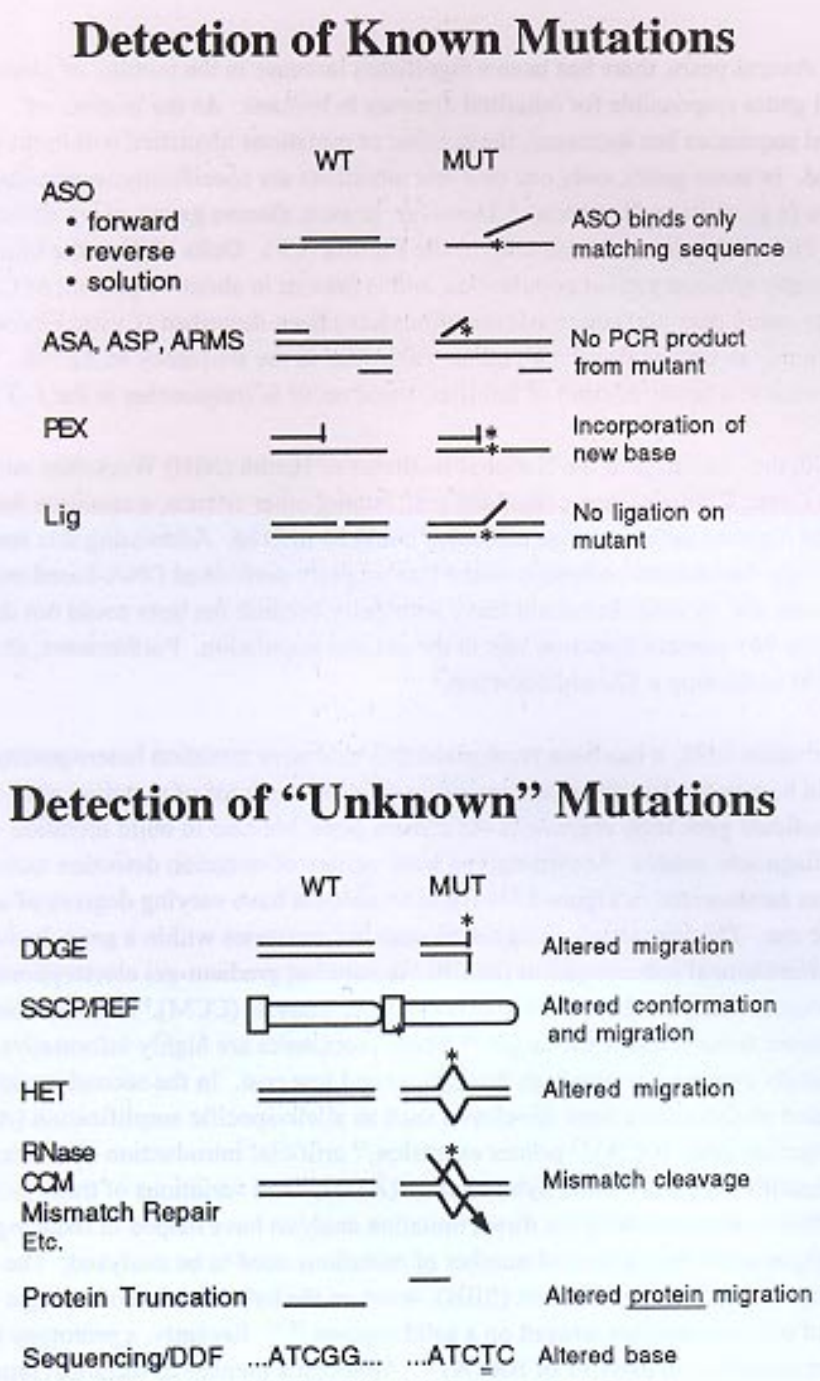
Detection of Known Mutations
WT
MUT
ASO
• forward
• reverse
• solution
ASO binds only matching sequence
ASA, ASP, ARMS
No PCR product from mutant
PEX
Incorporation of new base
Lig
No ligation on mutant
Detection of "Unknown" Mutations
WT
MUT
DDGE
Altered migration
SSCP/REF
Altered conformation and migration
HET
Altered migration
RNase
CCM
Mismatch Repair
Etc.
Mismatch cleavage
Protein Truncation
Altered protein migration
Sequencing/DDF
...ATCGG...
...ATCTC
Altered base

Figure 1

Recently, we developed a methodology that combines high sample throughput and direct detection of a large number of sequence variants.[24] The Multiplex Allele-Specific Diagnostic Assay (MASDA) has the capacity to cost-effectively analyze large numbers of samples (>500) for a large number of mutations (>100) in a single assay. Target DNA is immobilized to the solid support, and interrogated in a combinatorial fashion with a complex pool of ASOs. During the hybridization, the ASO(s) corresponding to a specific mutation(s) present in a given sample is hybrid-selected from the pool of probes by the target DNA. Sequence-specific band patterns associated with the bound ASOs are generated by chemical or enzymatic sequencing, readily identifying the mutation or mutations present in the sample. A schematic diagram of the MASDA technology and an example of the MASDA readout are shown in Figures 2 and 3. By retaining the forward dot blot format, we can simultaneously analyze large numbers of samples (>500) for a large number of mutations (>100). This high throughput parallel multiple sample analysis and parallel multiplex mutation detection process permits increased mutation detection with negligible increased cost.

Because many CF mutations are relatively rare, what is the effect of increasing the number of mutations analyzed in a CF assay? We designed an expanded CF assay to analyze 70 CF mutations in a MASDA format. These sequence variations were selected to include the most frequently detected mutations within a CF patient population, mutations identified in specific ethnic populations, and additional point mutations that lead to premature translation termination. Included in these 70 mutations are 32 mutations routinely analyzed in our DNA laboratory. In the course of assay validation studies, we tested samples from 713 patients previously found to be negative for at least one CF allele in the 32 mutation CF test in the 70 mutation MASDA assay. Additional mutations were detected in 20 of these patients. One mutation was detected in five unrelated individuals, one was detected in two unrelated individuals, with the remainder single observations. Our standard 32 mutation assay has a circa 90 percent detection rate. As anticipated, increasing the assay to 70 mutations increased the detection rate by a small increment. However, this increased mutation detection was achieved with negligible increased cost. Because we have included nearly 200 mutations in model studies, additional mutations could be included in the assay, if desired.

The ability to cost-effectively test large numbers of patient samples for large numbers of mutations is a key one for genetic testing. With techniques such as MASDA, microarrays, and mutation scanning available or under development, this ability is at hand. However, high-quality tests with high specificity and sensitivity are only one component of genetic testing. The laboratory component must be delivered in the context of ethical, legal, and social issues such as counseling, education, confidentiality, and so on.

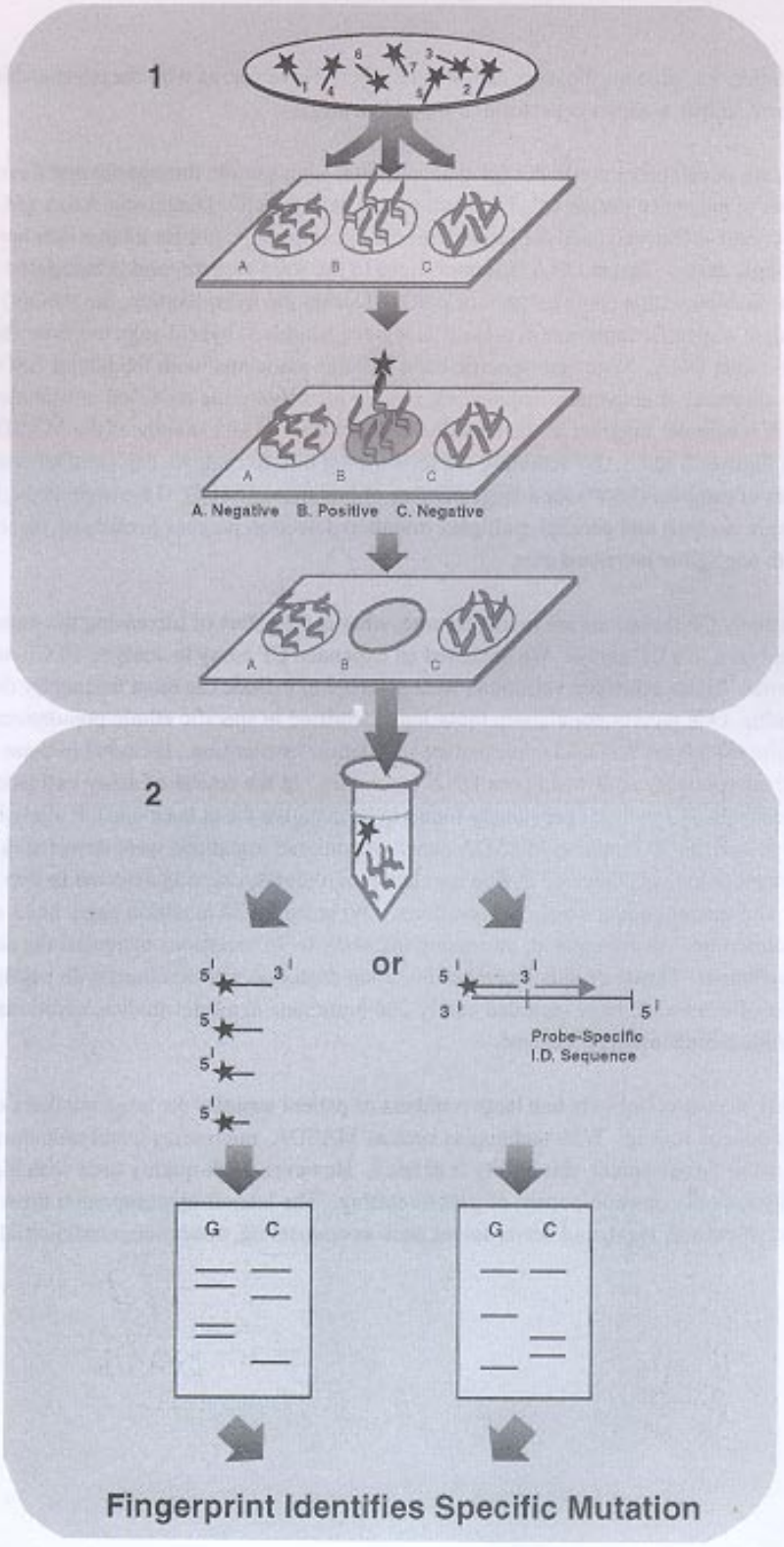
1
A
B
C
A. Negative B. Positive C. Negative
2
or
5'
3'
Probe-Specific
I.D. Sequence
G C
G C
Fingerprint Identifies Specific Mutation

Figure 2

Specific Mutation Identification by Enzymatic Fingerprinting

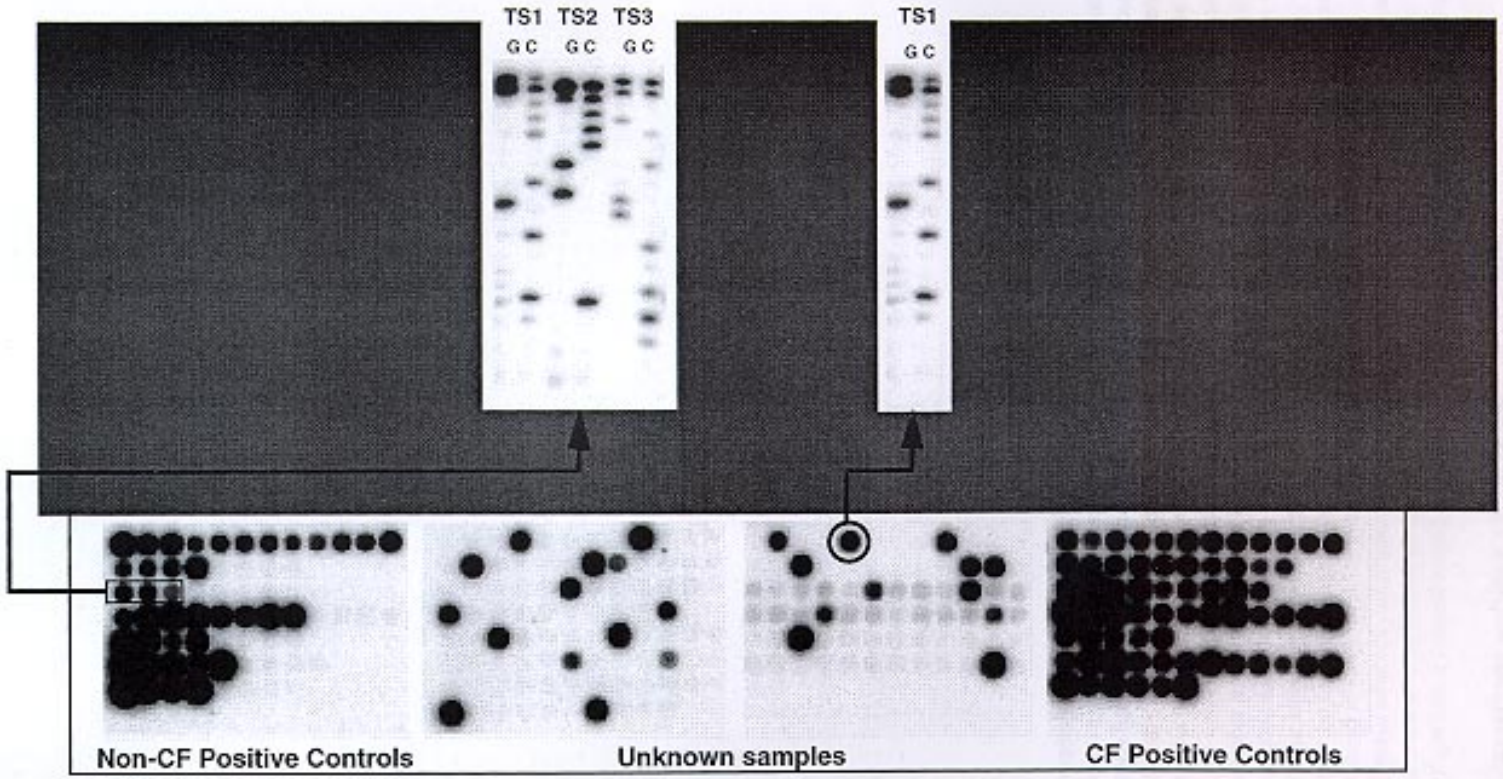

Figure 3

Figures 2 and 3. Schematic Representation of MASDA Procedure

In Phase 1 (panel 1), the probe corresponding to a specific mutation (one probe sequence per mutation interrogated) is hybrid-selected from the pool of probes by the target DNA on a dot blot. In this diagram, seven different probes and three different patient samples (multiplexes A, B, and C) are depicted, whereas in the MASDA assay >100 probes are routinely used to interrogate >500 patient samples in each assay. Each dot represents the multiplex amplification performed on one patient DNA for one disease gene only. Unhybridized probes are washed away, and mutation-positive patient samples are located by the presence of the labeled probe. The second phase of the assay (panel 2) reveals the identity of the probe, and therefore the specific mutation present in the patient DNA. The dot from each positive sample is excised, and the probe eluted off the membrane disc. The identity of the probe is revealed by one of two methods: directly by chemical cleavage sequencing, or indirectly by using the probe as a primer in a cycle sequencing reaction. In the latter case a pool of templates is used where only one template has a region complementary to the eluted probe, and therefore downstream sequencing of the probe-specific identifier (I.D.) sequence reveals the identity of the probe. With limited sequencing of “C” and “g” residues only, the fingerprints obtained on sequencing gels are compared to a known database of sequences, the probe is identified, and consequently unequivocal mutation identity is assigned.

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Carrier Testing Among First, Second, and Third Degree Relatives of Cystic Fibrosis Patients

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L. Silverman, Ph.D., G. Koch, Ph.D., and G. Fernald, M.D.

Specific Aims: To assess the level of acceptance of cystic fibrosis (CF) carrier testing among relatives of patients with CF and to compare the effectiveness of home-based and clinic-based CF carrier education and testing for this population.

Subject recruitment: 109 (53.7 percent) of 203 patients or their parents, being followed at a large southeastern CF clinic, provided contact information on relatives.

Population. 514 first, second, and third degree relatives of these CF patients.

Subject inclusion/exclusion criteria. Residency in North Carolina, South Carolina, Virginia, West Virginia, and Tennessee; 18 years of age or older; not pregnant; English language; regular access to a telephone; informed consent.

Mutation testing: DF508, G542X, G551D, R553X, W1282X, N1303K.

Conditions: No billing to subjects. Saliva sample. Home-based education provided by pamphlet, clinic education by a genetic counselor.

Design: Randomized controlled trial with longitudinal followup.

Methods: Questionnaires, standardized psychological scales, telephone interviews.

Analyses: Clustered bivariate and clustered logistic regression.

Subject Acceptance of CF Carrier Testing

Of 514 relatives offered free CF carrier education, testing, and genetic counseling, 299 (58 percent) accepted. Significantly more (67 percent) of those offered education and testing in their homes accepted than did those offered education and testing in a genetic counseling clinic (45 percent). A total of 120 (40 percent) tested positive, with 90 percent having the DF508 mutation. Overall predictors of acceptance of carrier testing included higher education, higher income, being female, and perceived higher risks of having a child with CF or who carries the CF gene. Within the limits of this study, the data suggest that when CF carrier testing is offered free of charge, including education and testing in the home, and employs a saliva-based sampling method, overall acceptance of carrier testing is just under 60 percent among at-risk relatives. Also, convenience makes a difference in acceptance of CF carrier testing.

Comparative Effectiveness of Home/Clinic Education and Testing

To assess the comparative effectiveness of the home and clinic-based education and testing arrangements, subjects were compared on knowledge of CF, anxiety (STAI) positive and negative affect (PANAS), and satisfaction with education and testing. No statistically significant differences between the home and clinic groups were noted on measures of CF knowledge, anxiety, and positive and negative affect, either while waiting for test results or within a few weeks after learning test results. At both measurement points, subjects who received home education and testing reported the testing was more convenient, but also reported they received somewhat less information than they would have liked and were somewhat more likely to be confused by the testing, although their levels of CF knowledge was comparable to those seen by a genetic counselor. These data suggest that home-based CF carrier education and testing, for populations similar to that seen in this study, may warrant further consideration and research as one approach to facilitating access to CF carrier testing.

Sharing of Positive Test Results

The study protocol included several safeguards to protect the confidentiality of subjects' test results. Subjects were informed in the consent process that they would be the only ones told their test results and that their test results would not become part of any medical record or be shared with their physicians, unless they requested so in writing. The consent process informed subjects that there was some nonquantifiable risk that either or both insurers or employers might discriminate against people with a positive test result. Finally, subjects were informed that the study was covered by a Federal writ of confidentiality. With these safeguards in place and subjects informed of them, we were interested in subjects' sharing of test results within and outside the family. A subsample (N = 76) of subjects who tested positive for the CF gene in their family returned a one-year questionnaire. Subjects were asked if they had told relatives and nonfamily members that their CF carrier test result was positive. There was considerable sharing of the decision to be tested as well as test results within families. For example, 79 percent of the subjects reported that other family members tested shared the results of their test. Twenty-five percent of the subjects reported knowing that some of their relatives had decided not to be tested. In terms of sharing of test results outside the family, 68 percent reported that they had told at least one friend and 55 percent reported telling at least one co-worker. Thirty percent reported telling a health worker. Thirty percent reported that at least one other person had asked them about their test result, most often another family member. Just over 72 percent of the subjects reported that there were other people whom they would not tell their test result, including insurance agents, employers, and certain other family members. Subjects reported most of the sharing of test results occurred within a month or two of learning test results. These data suggest that a majority of subjects who tested positive selectively shared their test results both inside and outside the family.

Carrier-by-Noncarrier Couples

The study identified a total of 120 carriers. Of these, 92 had spouses or partners. Fifty-seven of these accepted carrier testing, with five carrier-by-carrier couples identified. These five couples were removed from the study and provided traditional genetic counseling. One of the concerns about CF carrier testing is that it may contribute to reproductive uncertainty among carrier-by-"noncarrier" couples because not all mutations can be detected, leaving a residue of uncertainty for couples. In our study this uncertainty would be about the spouse's or partner's "real" carrier status, and hence possible uncertainty about what to do reproductively. To examine this issue we assessed the knowledge, psychological status, and reproductive plans of our 52 carrier-by-noncarrier couples.

Both relatives and their spouses showed slightly elevated anxiety, as measured by the Speilberger STAI instrument, while waiting for the partner's test results, although the scores were not outside the normal range. By our 6-month followup, both groups had somewhat lower anxiety scores, again within the normal range. In addition, relatives had normal positive and negative affect scores, both while waiting for the results of their partner's test and again, 6 months later. At entry into the study, only 2 percent of the relatives could accurately report their risk of being a carrier, and most rated their partner's risk as low. At our 6-month followup, relatives and spouses or other partners were asked to give an estimate of their risk of having a child who was a carrier or had CF. The majority of spouses and partners at 6 months reported that their risk for having a child who was a carrier was medium to high, but their risk for having a child affected with CF was low. Only 32 percent of the 52 carrier-by-noncarrier couples accepted our offer of followup genetic counseling. Finally, for 31 relatives on whom we had reproductive plans at enrollment in the study and again 6 months later, there was no shift to reproductive uncertainty. Six months after learning their own and their spouse's carrier status, fully 97 percent reported the same reproductive plan that they had reported before knowing the carrier status of either. In sum, in this sample of carriers, very few of whom knew their risk at entry into the study, and of noncarrier partners, most of whom viewed their risk as low, we did not find that the carrier testing engendered significant anxiety or negative affect, nor was it associated with an increase in reproductive uncertainty.

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Carrier Testing for Adult Cystic Fibrosis Siblings: The Importance of Not Knowing

Joanna H. Fanos, Ph.D., and John P. Johnson, M.D.

Introduction

Research prior to the identification of the cystic fibrosis (CF) gene demonstrated long-lasting misunderstandings regarding carrier risks in siblings.[1–4] Early experience thus far with direct cystic fibrosis transmembrane conductance regulator (CFTR) testing indicates low utilization rates among adult CF siblings. Therefore, our study was designed to (1) assess levels of understanding of test results and of medical aspects and genetics of CF and (2) identify factors motivating or interfering with the pursuit of carrier testing in adult CF siblings.

Eighty-four individuals, including 54 CF siblings and 30 spouses, drawn from Children's Hospital, Oakland, CA, and Children's Hospital, Boston, MA, were interviewed for about an hour, and qualitative material was coded on various themes. Anxiety and depression scales were administered. Questions were also read to siblings and their spouses concerning their knowledge of CF genetics.[5,6]

Results

Anxiety and Depression

Anxiety levels were above those of a random normative sample of community adults, as were depression levels. The scores on the anxiety and depression scales were positively correlated with each other. There were no significant gender differences on the anxiety and depression scales.

Levels of Understanding of Test Results

Of the 45 tested siblings, the 33 siblings tested at Children's Hospital, Oakland, were questioned as to their testing.[5] Their actual results were the following: 36 percent were carriers of DF508, 21 percent were carriers of another identified mutation, 30 percent were negative for the sibling's mutations (noncarriers), and 12 percent were given intermediate carrier risk status. For these latter individuals, mutation analysis was negative, but information was not available regarding which mutations were present in their families.

These results were compared with the participants' own statements concerning their genetic status following testing. One 21-year-old sibling, tested 2 years ago, still had not been told her results by her parents (she is a carrier). Three siblings (9 percent) were not accurate in reporting their carrier status following testing. One sibling incorrectly reported that he had received ambiguous results from testing, when in fact he was an identified DF508 carrier. Two young men who believed they were not carriers had ambiguous results according to the testing. Only one spouse was identified as a carrier, of DF508, and he knew it. Three of the 18 tested spouses incorrectly recalled their carrier status. Two identified as noncarriers believed that they were carriers. One spouse reported he had not been tested although he had indeed been tested and found not to be a carrier. These errors appeared not to be associated with any one referral source or testing site, or method of notification of testing results (e.g., letter sent directly to participant as opposed to referring physician).

Knowledge

The questionnaire yielded some problematic areas.[5] Many CF siblings and their spouses believe the incidence of CF in the general population to be approximately twice its actual rate, perhaps because of the saliency of their experience with CF. On the other hand, almost half of the CF siblings indicated that the carrier frequency is 1 in 40 or less. Similarly, about half of the spouses underestimated carrier frequency. While only 2 percent of the CF siblings believed that all CF genetic defects can now be detected, 29 percent of spouses were incorrect, underestimating the true ambiguity of the results. Of siblings, 17 percent, and of spouses, 21 percent erroneously assumed that if both parents are negative for the DF508 defect, they can't have a child with CF.

Carrier Status and Anxiety over Health

CF siblings face the impact of genetic illness without the support of genetic counseling and develop many mistaken beliefs surrounding carrier status in the absence of reliable information.[5] Thirty percent of siblings and 13 percent of spouses believed that carrier status implies health difficulties. Eleven percent of the siblings hoped that they were carriers. Increased feelings of guilt were significantly related to the belief that carrier status implies health problems and to a wish to be a carrier. Nine percent of siblings had had their child tested for carrier status, and 55 percent were planning to before the child reaches 18 years.

Barriers to Testing

Participants' attitudes toward testing were influenced by individual and family dynamics. Structural and psychological barriers to the seeking of testing were identified:[6] (1) Siblings encountered difficulty in obtaining information concerning availability of testing; (2) parental guilt and blame prevents parents from discussing genetic issues with the sibling; (3) siblings rarely discuss testing with each other; (4) the CF patient or parent often has difficulty with the implications of the sibling seeking carrier testing; (5) family and individual myths about carrier status influence the sibling's decision to seek testing; (6) statistical odds have lost meaning in families where the rare has already occurred; (7) the sibling fears loss of interpersonal desirability; and (8) carrier status can serve an important function in binding guilt.

A surprising finding was that 15 percent of siblings either hoped that they were carriers or felt guilty that they were not. The psychological function of not knowing one's carrier status can be helpful in mitigating feelings of guilt. If one assumes that one is a carrier, one shares the burden of the illness to some extent. Remaining unaware of carrier status serves significant psychological functions for some individuals at risk.

Recommendations

Based on our studies, we make the following recommendations for practice and research in this area:

- *The family needs support from the time of diagnosis of CF.* Siblings struggle with the psychosocial impact of a genetic burden outside the genetic counseling system. Somehow, genetic information must be made accessible to family members, perhaps by closer integration of genetics and CF clinics. Siblings need educational support to understand and normalize carrier status.

- *Geneticists must take into account underlying psychological factors shaping both the search for and the interpretation of genetic results.* Our findings in CF siblings suggest that remaining unaware of carrier status serves significant psychological functions for some individuals at risk. Psychological support for negative as well as positive findings should be provided. The challenge for the genetic counselor is to assess the individual's knowledge and disposition toward CF and to take this into account in discussing the risks and benefits of genetic testing.

- *Research on the impact of genetic testing of children and adolescents should be undertaken.*[7,8] Long-term followup of prenatal testing and screening should be undertaken to determine whether results of carrier status are given to children, and how they handle the information. There are many potential dilemmas in deciding whether to test a child or adolescent for genetic status. If parents choose not to test, the risk is difficulty in later integrating such information into the self- concept. If parents test and do not tell results, the risk is creating a climate of family secrecy. If parents test and tell results, the risk is robbing the child of the autonomy of his or her own later decision.

Conclusion

Perhaps the question of whether to test is not the real question. A more important question may be how to provide unaffected individuals in at-risk families with appropriate counseling. Provision of psychosocial services to these families will enable siblings to encounter genetic testing, if necessary, supported with the best possible resources.

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Cystic Fibrosis Mutation Screening and Counseling

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As the most common lethal autosomal recessive disorder in North America, cystic fibrosis (CF) is an obvious candidate for general population carrier screening. While the identification of the causative gene made detection of asymptomatic carriers possible, the extreme heterogeneity of its mutations has limited the sensitivity of the available DNA screening tests and called into question their utility when applied to patients with no family history of the disease.

As part of the consortium of studies sponsored by the National Center for Human Genome Research, we sought to examine the technical feasibility, patient acceptance and understanding, and psychosocial impact of large-scale CF carrier screening in an ethnically diverse pregnant population with no family history of the disorder. Our Southern California target population is among the most ethnically diverse in the United States and includes large numbers of minority groups, such as Hispanic Americans, which hitherto had not been studied extensively for either their allele frequencies of CF mutations or their response to screening and counseling. Multiple approaches to pre- and post-test counseling were compared for their effectiveness. Attitudes about genetic screening—and CF screening in particular— and the impact of positive and negative results on those tested, were compared among the different groups and different health care delivery milieus.

A total of 4,739 pregnant women attending prenatal clinics located in both an academic medical center and a large HMO were invited in person to participate. Of this group, 3,543 received CF instruction and knowledge and mood assessments and 3,192 (along with the mates of those testing positive) underwent DNA testing for the six most common CF mutations (DF508, G542X, G551D, R553X, W1282X, and N1303K), using a PCR-based reverse dot blot method kindly provided by Roche Molecular Systems. For specimen collection, we employed gentle scraping of the buccal mucosa with a single standard Pap-smear type cytobrush. We produced both a brochure and an 8-minute videotape (English and Spanish versions) describing the nature and incidence of CF, its anticipated prognosis in the coming years, and the advantages and imperfections of the currently available DNA screening method. The CF carrier frequencies and relative test sensitivities in various ethnic populations are described in the brochure and shown graphically in the video. A series of questionnaires assessing clinical knowledge of CF, mood state, and health belief perceptions relevant to genetic screening were administered before and after the instruction sessions and after receiving results of the DNA test.

Overall participation rates (ranging from 53 percent at the HMO to 77 percent at the academic center) and consent rates for DNA testing after CF instruction (more than 98 percent) were quite high, exceeding those of most other American studies. The PCR-based screening method worked efficiently on large numbers of samples, and 55 carriers and one at-risk couple were identified. Understanding of residual risk, anxiety levels, and overall satisfaction with the program was acceptable across all ethnic groups. Across all subject groups, baseline knowledge of the genetics of CF (recessive inheritance, ethnic differences, etc.) was poorer than knowledge of the disorder's clinical features. Delivery of instruction in the manner described above appeared to be both efficient and effective, with correct-answer scores in both categories increasing by 30–100 percent between the pre- and post-instruction knowledge assess-

ments. In a subset of subjects carefully matched for age, ethnicity, socioeconomic status, and educational level, there were no significant differences in test scores between those receiving instruction by video and those using the brochure. By the end of testing, only 7 percent of subjects completing all questionnaires evinced inadequate understanding of the residual risk inherent in a negative DNA test result.

In followup questionnaires, the vast majority of subjects (more than 98 percent) expressed a high degree of satisfaction with the screening program and results reporting. In general, there does not appear to have been any increase in anxiety levels evoked by either the CF educational intervention or the DNA testing. Similarly, we have detected no significant residual change in anxiety levels nor evidence of stigmatization or discrimination among those testing positive, although the numbers involved in the latter group are small and the followup period still limited. While this group, as expected, showed concern while awaiting partners' test results, the vast majority (97 percent) were reassured by their partners' negative outcome and remained emotionally unaffected for the duration of the pregnancy. Although we do keep the testing confidential, most subjects stated little concern about other people, such as family members, friends, or physicians, knowing their test results; indeed, all of our interviewed positives had confided in their relatives and physicians. However, 30 percent of negatives and 5 percent of positives said they would refuse testing if results were to be given to their health insurance carriers.

One striking aspect of our findings has been the relatively high level of interest in CF screening. Our proportion of decliners was quite small relative to some of the other studies in the consortium, and 38 percent of those subjects indicated to us that it was the questionnaires, not the DNA test, that dissuaded them from participating. This was borne out by the even higher participation rates observed (92 percent) when we introduced a streamlined protocol with a greatly reduced questionnaire component. There are a number of attributes of our approach that may account for these high consent rates. First, the specimen collection technique was noninvasive and painless; subject responses uniformly indicated great appeal for this aspect and some aversion to tests requiring phlebotomy. Second, the DNA test was offered free of charge; our responses to questioning revealed an aversion to testing at costs above $25. Third, our subjects were approached in person by one of our genetic counselors, project coordinators, or trained assistants in the respective clinics, rather than by mail, posted notices, or through contact with primary care providers. Even though this first contact was noncoercive and verbalized nothing about CF other than the invitation to participate in a research project to evaluate a new method of screening, we believe it served to humanize the encounter and to pique more interest than a mass mailing to which the subject or provider must take the initiative to respond. Finally, there was our strategy of predominantly targeting pregnant women in prenatal clinics. As others have noted in past programs, we believe this population is among those most predisposed to be receptive and motivated toward genetic screening.

In summary, our approach to CF screening in this study has resulted in relatively high uptake in an ethnically diverse western U.S. population, with generally satisfactory understanding of the subtleties of the genetics and test results and no adverse psychosocial consequences detected thus far. Although we remain concerned about the small minority of subjects who continue to misunderstand the residual risk inherent in a negative test result, this proportion may represent a practical minimum given the diversity of educational levels in our country. In general, our experience with the use of modern DNA technologies and ancillary counseling modalities indicates that multiplex population screening for such molecularly heterogeneous genetic traits need not overwhelm either laboratory or genetic counseling resources. Indeed, these results suggest that a larger CF carrier screening program could be initiated using this model, and would especially seem to justify offering it routinely to such high-risk ethnic groups as non-

Jewish Caucasians of northern European descent and Ashkenazi Jews. Such findings should help us to formulate a national policy for application of the powerful yet still imperfect molecular genetic techniques available for detection of CF mutations, and may serve as a guide for delivery of DNA-based population screening for other common genetic disorders and cancer predispositions in the future.

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Offering Cystic Fibrosis Carrier Screening to an HMO Population: Utilization, Knowledge, and Factors Influencing the Decision To Be Tested

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Goals of the Study

This study measured (1) the effect on utilization by enrollees in an HMO of two different approaches to offering cystic fibrosis (CF) carrier screening; (2) the effect of each approach on knowledge of CF and CF carrier screening; and (3) factors influencing the decision to have carrier testing.

Methods

Approach 1

A letter from HMO physicians invited adult enrollees of reproductive age to participate in a study in which CF carrier testing would be offered at no charge. The letter emphasized that the study was not encouraging people to have the test. A brief fact sheet on CF and carrier testing was enclosed. Those who mailed back a form expressing interest in CF carrier testing were telephoned to schedule an appointment to attend a 45-minute group educational session conducted by a genetic counselor at the HMO site at a convenient time (including evenings or weekends). The session was conducted by a genetic counselor who briefly described CF and salient issues of carrier testing (including its 85 percent sensitivity), showed a videotape, distributed a brochure on CF carrier testing, and answered questions. Toward the end of the session, saliva samples were collected from those who were interested in having the carrier test. The carrier test was performed only after participants mailed back a consent form.

Approach 2

Adult enrollees of reproductive age at HMO sites different from those used in Approach 1 who had made a nonacute visit, either for themselves or their children, were asked by a study team counselor to read a letter from HMO physicians, similar to that used in Approach 1, inviting participation in the study. Those who were interested were given the CF brochure to read while they were waiting to see the physician. They also had the opportunity to ask the counselor questions. Before they left the site, those who were interested in testing (again at no charge) left a saliva sample. The same procedure as in Approach 1 was used for consent.

Questions on demographic characteristics, knowledge of CF and CF carrier testing, and concerns and attitudes regarding CF testing were asked by written questionnaire at the time of initial contact. When subjects who had given a saliva specimen were considering whether or not to consent to the test, they completed another written questionnaire containing knowledge and attitude questions and instruments for measuring tolerance for ambiguity (TFA) and tolerance for test uncertainty (TTU).[1] This same questionnaire was given to study participants in both approaches who indicated that they were not interested in having the CF test but who were planning to have children. True/false and multiple choice were used for the knowledge questions and Likert scales for many of the attitudinal questions.[2]

CF carrier tests were performed on buccal cells using a reverse dot-blot format with probes for six mutations that were estimated to account for about 85 percent of CF mutations in Caucasians.

Results

Forty-two percent of enrollees responded to the initial letter in Approach 1 and 78.5 percent in Approach 2 (Figure 1). Very few of the respondents were pregnant. In Approach 1, respondents had higher educational attainment and were more likely to be female than nonrespondents. Compared with respondents in Approach 2, those in Approach 1 were more likely to be college graduates (50.2 percent vs. 25.8 percent) and planning to have children (56.6 percent vs. 44.7 percent) and were less likely to be female (58.8 percent vs. 73.2 percent) and married (42.1 percent vs. 70.2 percent). As shown in Figure 1, only 3.7 percent of those contacted consented to the test in Approach 1, compared with 23.6 percent in Approach 2.

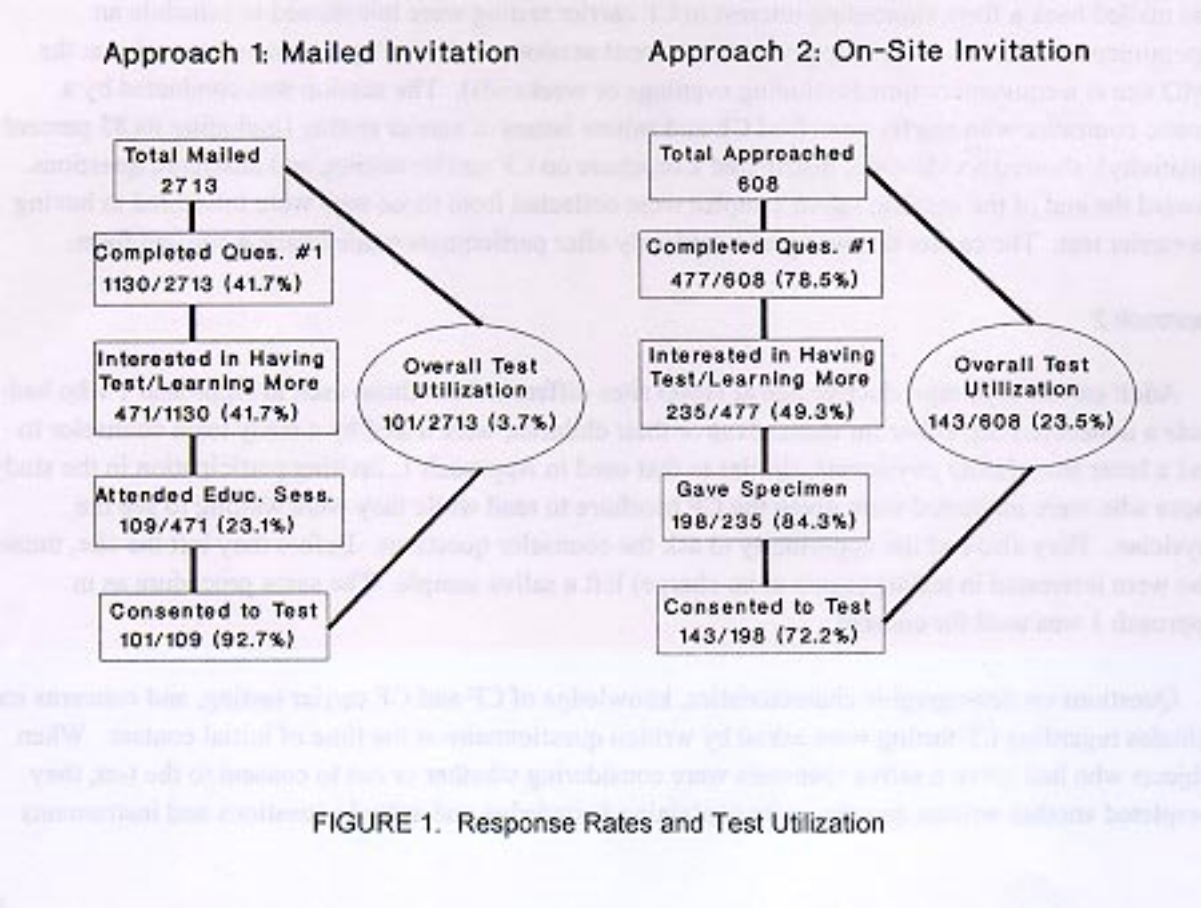

FIGURE 1. Response Rates and Test Utilization

FIGURE 1. Response Rates and Test Utilization

Changes in knowledge between the time of initial contact and consent, stratified by level of education, are shown in Figure 2 for those having the test. Regardless of their level of education, consenters in Approach 1 had significant gains in knowledge, with all three groups having mean knowledge scores of 92 percent or higher. In Approach 2, only those with a high school education or less had a significant improvement in knowledge (from 58 percent to 68 percent). Those with more education had higher initial knowledge scores (68 percent and 82 percent), but their final scores were only 2–3 percent higher.

Among enrollees planning to have children, we analyzed factors influencing the decision to have testing by comparing those who consented to the test with those who said they were not interested in testing. In multiple logistic regression analyses for Approach 1, TTU (O.R.=3.8), perceived likelihood of being a carrier (O.R.=3.1), and fear of stigma associated with CF carrier testing (O.R.=0.4) were significantly associated with the decision to have the test. In Approach 2, only TTU (O.R.=3.7) and fear of stigma (O.R.=0.4) were significantly associated. Likelihood of choosing abortion for CF and the perceived burden of an affected child with CF were not associated with the decision to have the test in either approach.

Discussion

Approach 1 attracted a small and highly educated group to the educational session. Attendees were not representative of HMO enrollees. Those attending the session may have had greater interest in CF or been more committed to research. Approach 2 attracted a more representative group of HMO enrollees. Utilization of testing was more than six times higher than in Approach 1. However, the educational intervention in Approach 2, giving the brochure and answering questions, was not nearly as successful as the face-to-face multifaceted educational program of Approach 1. The knowledge deficiencies of Approach 2 consenters cast doubt on whether they were adequately informed.

People who would take a hypothetical test regardless of imperfect sensitivity and or positive predictive value (those with high TTU) were almost four times more likely to consent to CF testing than people who would not take a test if it were imperfect. We have confirmed the importance of TTU in an additional study.[3,4] TTU is not significantly correlated with TFA and may reflect receptiveness to using new medical technologies as well as desire for empathic physicians.

Summary and Conclusion

People are more likely to decide to have CF carrier screening if it is offered conveniently, without taking extra time. When offered conveniently, subjects had little improvement in knowledge after reading an educational brochure and having the opportunity to ask questions, except for those with less than a high school education. Many of these individuals will have insufficient knowledge to ensure that their consent to testing is truly informed. Tolerance for test uncertainty proved to be the most important factor in people's decision to have the test. In view of its importance, information on test sensitivity should be included in educational material.

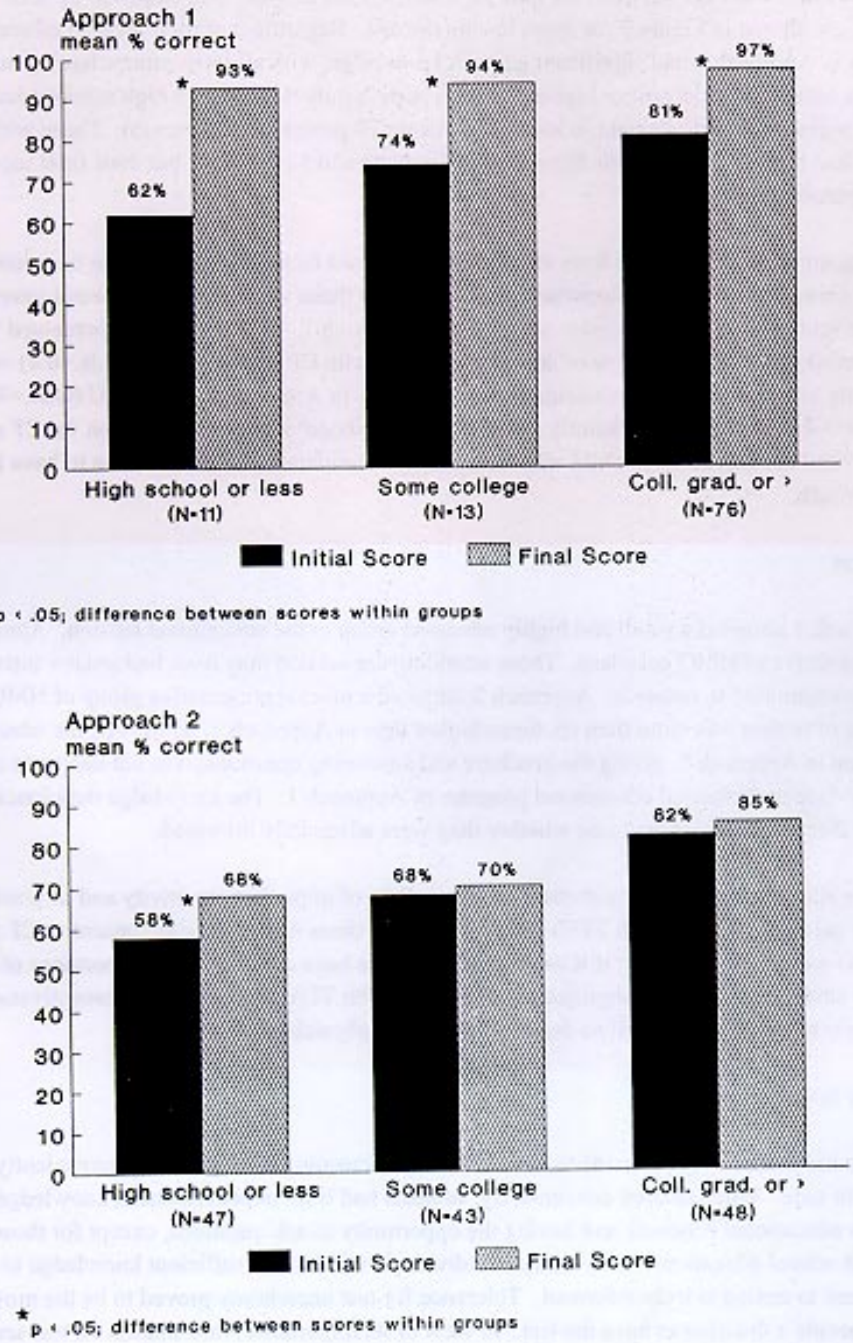

FIGURE 2. Knowledge Scores of Subjects Consenting to CF Carrier Test by Education

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Efficacy of Education for and Interest in Population-Based Cystic Fibrosis Carrier Screening

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We carried out three studies on cystic fibrosis (CF) carrier screening at Vanderbilt University. In the first two, we determined the efficacy of written and video materials in educating people about CF and CF carrier screening without face-to-face counseling.[1] In the third, we determined the demand of non-pregnant adults in stable relationships for free CF carrier screening in numerous clinical and nonclinical settings.[2]

We performed two studies to determine the efficacy of written and video materials in educating people about CF and carrier screening without face-to-face counseling. In the first study, participants were randomized to receive written or video materials and asked to respond to a brief questionnaire. Subjects were eligible for inclusion in the first study only if they were (1) in steady relationships with partners who would also participate, (2) at least 18 years old, and (3) not pregnant (n=238). Those who accepted free CF screening and were not demonstrable carriers were sent a letter with their results and asked to complete another questionnaire.[1] In the second study, subjects were parents seeking well child care in a university clinic (n=108). The main outcome measures were their ability to answer questions correctly about (1) the health status of CF carriers and people with CF, (2) the possibility of false negative test results, and (3) for those who had screening, the implications of their own test results. In these studies we found that written and video educational materials were equally effective in conveying information (see Figure 1). Subjects answered an average of 86 percent of questions correctly after receiving written or video educational interventions. Subjects with less formal education answered fewer questions correctly, e.g., 60 percent of those with less than a high school education had adequate knowledge of the health consequences of having CF or being a carrier compared with 94 percent or more of college graduates. Of subjects who proceeded with CF carrier screening, most answered questions correctly after they received their screening results. In couples where neither partner was a demonstrable carrier, 88 percent knew their own and their partner's test results, and 90 percent indicated that their risk of having a child with CF was not zero. Our data indicate that written and video educational materials can be used without face-to-face counseling to inform most people about carrier screening and their test results, but these materials may be less effective for those with lower educational backgrounds.[1]

We carried out a third study to determine the demand for free CF carrier screening. In this study we used signs and letters to offer free screening to nonpregnant adults in stable relationships who attended numerous clinical and nonclinical sites in Nashville, TN. We found that of the thousands who were eligible, only 179 (less than 1 percent) elected to be tested.[2] To understand this observation, we used questionnaires to assess individuals' attitudes about genetic testing in general and CF carrier screening in particular (n=873). Although greater than 90 percent of participants thought that genetic testing should at least be available, many expressed conflicting views about both genetic testing in general and CF carrier screening in particular. Most respondents said that the views of their partners and physicians were important in their decisionmaking, and most believed that these others favored genetic testing.

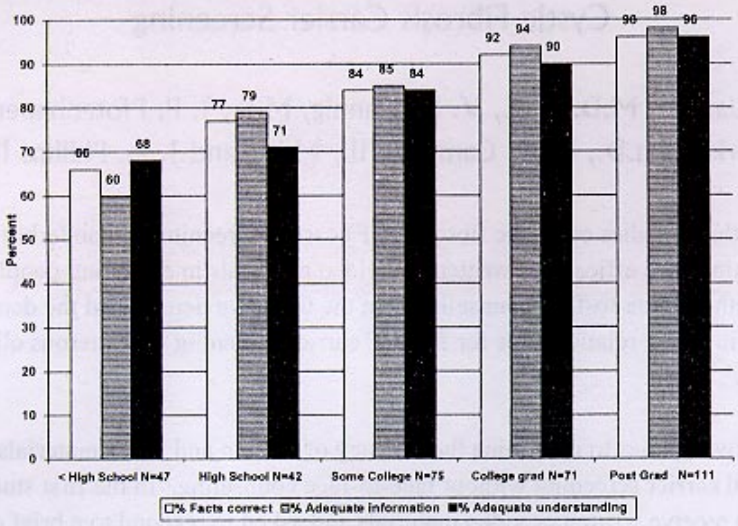

FIGURE 1. Efficacy of Educational Materials and Relationship to Educational Background

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Yet more than two-thirds indicated that factors including insurability, being "at risk," what they would need to learn, their opinions on abortion, and their religious beliefs were important in their decisionmaking as well (see Figure 2). These factors appeared to mitigate against their having CF carrier screening. In particular, one-third feared that CF carriers would lose their health insurance, and one-quarter said that they would have been more interested had they been able to provide DNA by buccal swab rather than by finger stick. Our data showed (1) a low level of use of free CF carrier screening by nonpregnant couples when it was not offered in person by health professionals and (2) concerns about a variety of factors, opinions, and beliefs were related to their declining CF carrier testing.[2] Based on these data we (1) conclude that it is possible to convey sufficient information about CF carrier screening to enable individuals to make informed decisions about whether to proceed with screening using written or video materials but (2) question whether sufficient interest exists in the general population to warrant the routine offering of carrier screening to nonpregnant individuals who do not have a family history of CF.[1,2]

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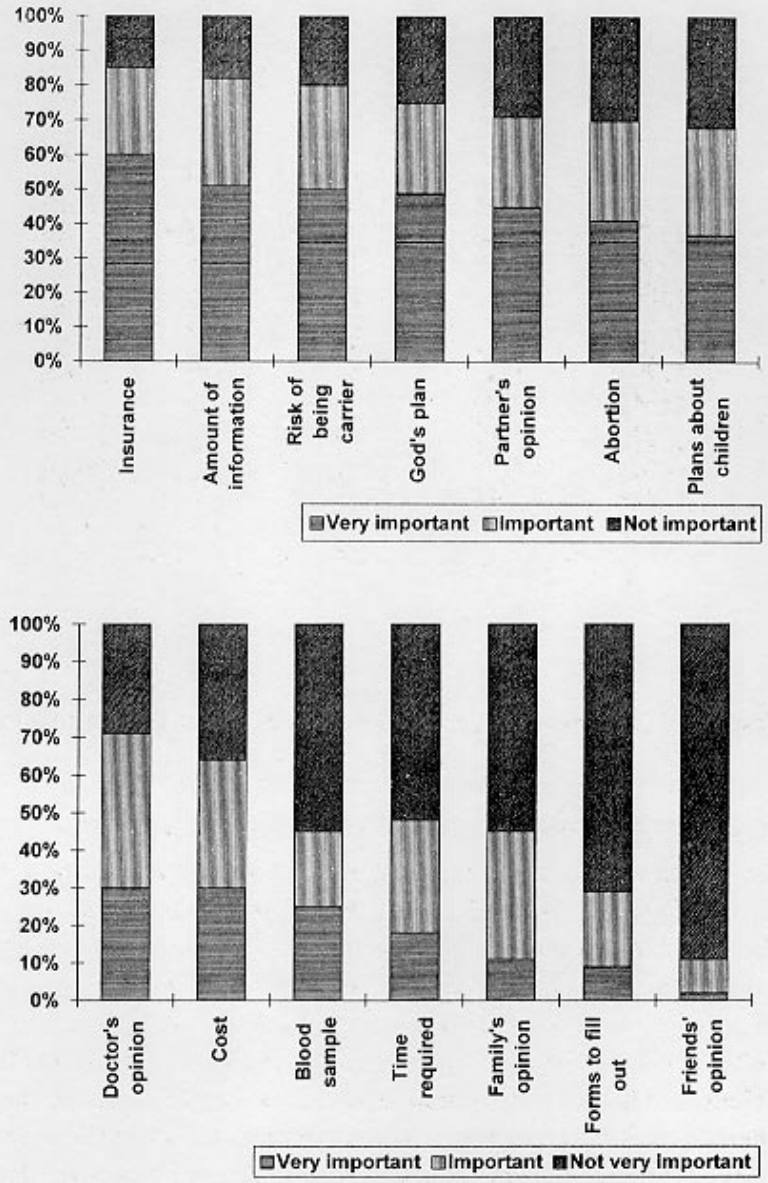

FIGURE 2. Importance of Factors in Decisionmaking Regarding CF Carrier Screening

FIGURE 2. Importance of Factors in Decisionmaking Regarding CF Carrier Screening

Prenatal Cystic Fibrosis Carrier Population Screening: Lessons from a Regional Trial

Peter T. Rowley, M.D., Starlene Loader, and Jeffrey Levenkron, Ph.D.

Design of the Study

We have conducted a clinical trial to asssess the clinical utility of cystic fibrosis (CF) carrier population screening. Our trial differed from other trials in several regards. First, we chose to study provider receptivity as well as patient receptivity; we chose the prenatal care provider as the provider most likely to offer such screening in practice. Second, the offer of screening was made by the primary care provider rather than by research staff, to better simulate the practice setting. Third, participation was offered to all prenatal care providers in the region to minimize bias in provider participation. Fourth, both testing and genetic counseling of carriers were offered free in an attempt to minimize economic bias in patient participation.

Receptivity of Providers

To enlist providers, we presented a description of the trial to the obstetrical staffs of the five Rochester, NY, hospitals having delivery services. Of the 124 prenatal care providers (111 obstetricians and 13 family practitioners) having delivery privileges at the five hospitals, 81 (65 percent) attended one of our presentations; the others were invited to participate by mail. We explained that testing, counseling, and patient educational materials would all be provided free of charge. Of the 79 providers completing an attitude questionnaire, 68 (86 percent) stated that they were willing to offer carrier screening to all their patients. After visiting participating physicians' offices to orient their staff, we reached two additional conclusions. First, some providers were more resistant to offering screening to nonpregnant patients than to pregnant patients, not because they believe that the timing is less appropriate, but because nonpregnant patients do not routinely receive an advance mailing, have phlebotomy, or return for followup. Second, in considering whether to offer CF carrier screening to their patients, prenatal care providers were more concerned about the time required to answer patients' questions if they screened and about their legal liability if they did not screen than about some of the issues that troubled the project staff, such as imperfect test sensitivity, false reassurance of those testing negative, or discrimination against those testing positive. Our experience raised concerns about the willingness and capability of prenatal care providers to translate advances in molecular medicine into prenatal screening services.[1]

Receptivity of Patients

The acceptance rate among pregnant women was approximately 57 percent. The most common reasons for accepting screening were to obtain reassurance (50.7 percent) and to avoid having a child with CF (27.8 percent). The most common reasons for declining screening were the intention not to terminate a pregnancy for CF (32.4 percent) and belief that the chance of having a CF child was very low (32.2 percent). Compared with decliners, acceptors were more likely to have no previous children, to regard having a child with CF as more serious, to believe themselves more susceptible to having such a child, to know more about CF, and to terminate a pregnancy if the fetus were shown to have CF. Acceptors also more strongly supported offering CF screening to women of reproductive age. Together, these six factors permitted a correct classification regarding CF carrier test acceptance of 77.5 percent of all subjects. For those who were pregnant, the most influential of these factors was a more accepting attitude toward abortion. As an indication for abortion, women ranked CF between mild and moderate degrees of

mental retardation.

Of 4,879 women on whom results were obtained, 124 were found to be carriers. Of these 124 carriers, 106 partners were tested. Of the five at-risk couples, four requested prenatal diagnosis and one requested neonatal diagnosis. All five offspring proved to be heterozygotes. No woman found to be a carrier whose partner tested negative requested prenatal diagnosis. Most of the adverse outcomes predicted for CF carrier testing in the general population were not observed in this study. The most serious failure was the providers' failure to make clear to patients the meaning of a negative test result; only 45 percent of those testing negative understood that they could still have a child with CF. This misconception probably could have been avoided if providers had given results in writing as well as orally.[2] See Figure 1 on the next page.

Carrier Knowledge and Anxiety

Carriers' mean score for knowledge about CF rose significantly from 51.1 ± 20.7 percent correct before counseling to 84 ± 12.4 percent after counseling. At 1-year followup, although the score had fallen slightly (77.4 ± 13.2 percent), it was still significantly higher than before counseling.

Anxiety about having a child with CF significantly declined from 25.8 ± 8.0 *SD* immediately after counseling to 18.9 ± 7.8 at 1 year.

Carrier Followup

Of the 124 carriers detected, 1-year followup information was obtained for 100. Eighty-three percent believed they benefited from testing, 83 percent would make the same decision to be tested again, and 79 percent would recommend testing to a friend. Fifteen percent of carriers regretted having been tested; all these women had been pregnant when tested, felt considerable anxiety when told they were carriers, and had partners testing negative. Although the partner's result relieved their anxiety, their anxiety may have seemed needless in retrospect.

Conclusions

We conclude that, for most women, CF carrier screening accomplished its purpose: 92 percent of carriers detected came for counseling, 80 percent of these had their partners tested, and, if their partners were also carriers, 80 percent of these couples chose prenatal diagnosis. The major undesirable outcome was that many women testing negative did not understand that a negative result did not exclude being a carrier. But even this undesirable outcome could have been avoided by greater attention to patient education by the primary care provider.[3]

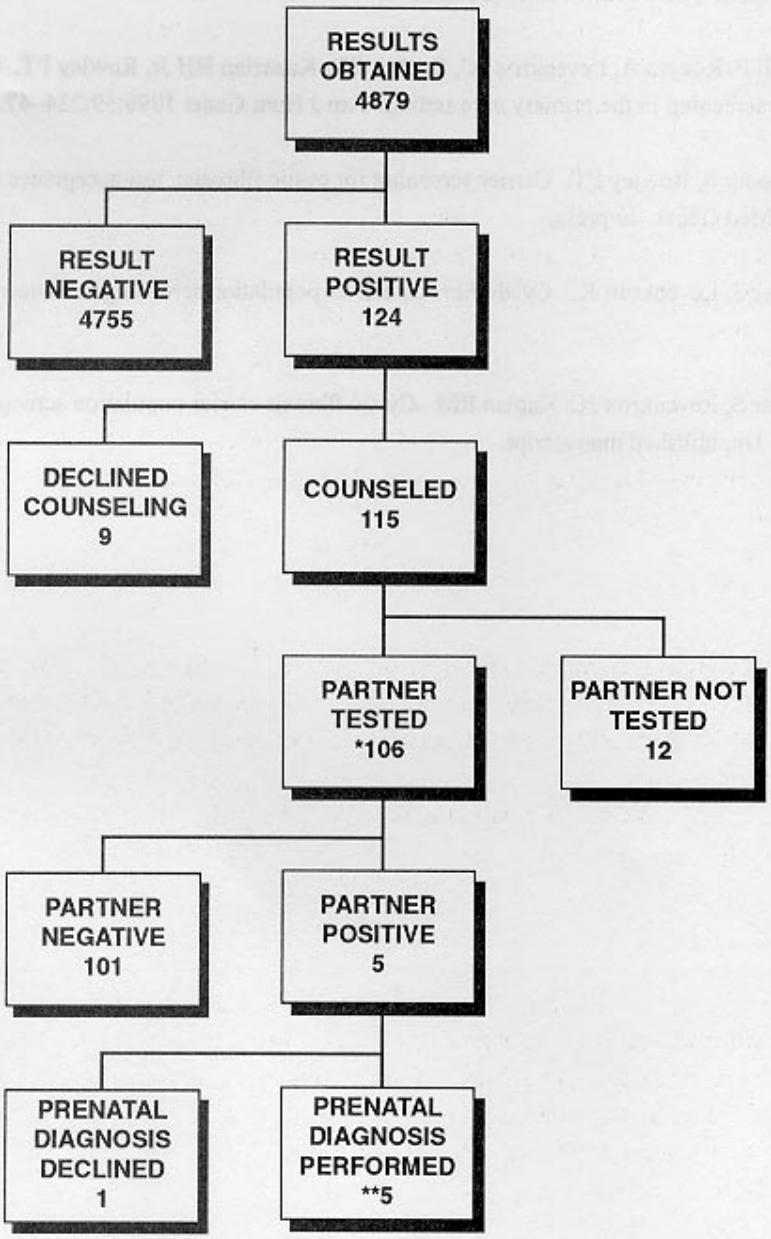

FIGURE 1. CF Carrier Screening Results

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Prenatal Genetic Carrier Screening: Experience With Multiple Option Screening in the Ashkenazi Jewish Population

Christine M. Eng, M.D.

Background and Objectives

Rapid progress in gene discovery, accelerated by the Human Genome Project, has dramatically increased our diagnostic capabilities for carrier screening and prenatal testing for genetic diseases. The Ashkenazi Jewish population provides the unique opportunity to evaluate simultaneous prenatal carrier screening for several genetic disorders (i.e., multiple option prenatal screening), since about one in eight individuals is a carrier for Tay-Sachs disease (TSD), Type 1 Gaucher disease (GD), or cystic fibrosis (CF), disorders in which carrier detectability is 95–99 percent. Experience with TSD carrier screening established that this ethnic group would be an ideal population in which to evaluate a pilot program for carrier screening designed to do the following: (1) identify issues related to disease-specific differences in severity, life expectancy, and availability of treatment; (2) evaluate educational models; and (3) assess patient attitudes toward the three diseases. Therefore, an educational, counseling, and carrier testing program designed to screen for these three disorders—which differ in detectability, severity, and availability of effective therapy—was evaluated.

Study Design and Methods

Educational materials were developed for each disease. Focus groups composed of potential screenees were used to assess and optimize the educational materials and information presented at a group genetic counseling session. Prospective screenees received educational materials by mail that described the major manifestations, treatment, and inheritance of each disease. Prior to testing, potential screenees received genetic counseling, gave informed consent, chose tests, and completed pre- and post-education questionnaires that assessed knowledge, attitudes toward genetic testing, and disease testing preferences. The reproductive attitudes and the potential psychosocial consequences of carrier identification were investigated. Carrier testing for CF was performed by analysis of five mutations DF508, W1282X, G542X, N1303K, and 3849+10kbC_T), which detected approximately 96 percent of Ashkenazi Jewish carriers.

Results

Demographics and Test Acceptance

Individuals were enrolled as couples, and testing was performed simultaneously on both partners. The mean age of participants was 33 years and most (89 percent) had college and/or postgraduate education. Seventy-five percent of the couples had first-trimester pregnancies. Of the 2,824 Ashkenazi Jewish participants, 100 percent chose testing for TSD and 97 percent also chose testing for CF.

Identification of Carriers and At-Risk Couples

The frequency of detected CF carriers in this population was 1 in 25. The distribution of mutations was 47 percent, 39 percent, 8 percent, 5 percent, and 1 percent for DF508, W1282X, G542X, N1303K, and 3849+10kbC_T, respectively. Of the six at-risk CF pregnancies, three were predicted to be affected and these couples elected termination; two were predicted to be carriers and one was predicted to be unaffected, and all three continued. One CF carrier couple who previously terminated an affected fetus had a second pregnancy monitored that was predicted to be unaffected.

Pre- and Post-Education Knowledge

The baseline knowledge, impact of education and counseling, and attitudes affecting disease test selection were compared among the participants for the three diseases. Pre- and post-education questionnaires revealed that screenees initially knew little about the diseases, but acquired disease information and mastered genetic concepts. Before learning of the screening program, 83 percent and 88 percent of individuals were aware of TSD and CF, respectively, but only 24 percent were aware of GD, the most prevalent Jewish genetic disease. Despite familiarity with two of these disorders, they had little knowledge about these diseases. Nine disease-specific questions concerning clinical manifestations and carrier frequencies of the three diseases were assessed as a single scale (Cronbach a = 0.86) that had a mean score on the pre-education questionnaire of 3.2. After receiving written educational materials and attending a genetic counseling session, the level of knowledge increased to a mean score of 7.3 ($p < 0.0005$). In addition, baseline knowledge of each disease differed significantly according to prior familiarity, but the educational intervention was effective in raising knowledge to essentially equal levels for all three disorders. In both pre- and post-education responses, knowledge of TSD exceeded that for CF, which exceeded that for GD ($p < 0.001$). Those who attained a higher level of knowledge were less likely to have misconceptions regarding the implications and accuracy of carrier tests. More knowledgeable screenees were less concerned if their spouse were identified as a carrier (Pearson's $r = -0.10$; $p = 0.009$), less likely to experience decreased self-esteem if identified as a carrier ($r = -0.19$; $p<0.0005$), and less likely to worry about their own health if identified as a carrier ($r = -0.35$; $p<0.0005$). Also, those who attained a higher level of knowledge were less likely to feel reassured by a negative result from a carrier test with a 50–65 percent mutation detectability ($r = -0.11$; $p<0.004$).

Attitudes Toward Genetic Testing

Participants felt that screening for the three disorders was important and indicated a strong desire for knowledge about the genetic characteristics of themselves, their partners, and their children, and a strong desire for genetic testing for other disorders, especially if recommended by their physician or if the disease were severe. Women considered testing for the three genetic disorders somewhat more important than did men ($p = 0.0002$). Pre- and post-conception individuals were equally interested in learning their carrier status for these recessive conditions. The potential psychosocial consequences of carrier identification were explored; 60 percent of individuals indicated that they were "likely or very likely" to want to speak to an expert about personal feelings if they were found to be a carrier of any of the three disorders.

Factors Affecting Disease Choice

Participants understood the concept of disease severity and differentiated among neurodegenerative TSD, moderately severe CF, and treatable GD as demonstrated by their attitudes toward reproductive decisionmaking. Statistically significant differences were found for questions regarding reproductive decisions involving each of these disorders. If prenatal diagnosis indicated that a fetus were affected, the attitudes toward termination differed significantly among the disorders. On a 1 to 5 scale (1 strongly favoring and 5 strongly opposing termination of an affected pregnancy), the mean responses were
1.36, 1.68, and 2.43 for TSD, CF, and GD, respectively ($p < 0.0005$).

Conclusions

Among couples being screened for TSD, additional testing for CF and other Jewish genetic diseases was well accepted and useful in reproductive decisionmaking. Seeking information for more informed reproductive decisions, Ashkenazi Jewish couples readily accepted carrier testing for three diseases that varied in detectability, severity, and treatability. Education and genetic counseling increased understanding and retention of genetic concepts and disease-related facts, and minimized test-related anxiety. Although the couples sought screening for all available diseases, attitudes toward termination of affected fetuses were influenced by disease severity and treatability. The lessons learned from this pilot program should prove instructive to the further development and evaluation of carrier screening programs in this and other populations.

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Prenatal Cystic Fibrosis Heterozygote Screening of 5,161 Women in a Large HMO

David R. Witt, M.D.

Introduction

In 1989, the discovery of the cystic fibrosis transmembrane conductance regulator (CFTR) gene enabled the relatively simple identification of the majority of cystic fibrosis (CF) heterozygotes. However, a moratorium on general population screening was enacted due to concerns over a variety of educational, counseling, laboratory, and logistical issues not previously encountered in other forms of genetic testing. The Kaiser Permanente study[1] was developed to examine these issues in a population of pregnant women and their partners, and to assess the feasibility and value of CF heterozygote screening in an HMO setting. To accomplish this, the evaluation included the level of interest among eligible patients, the effectiveness of prescreening education, attitudes toward the screening process, psychological effects, and utilization of prenatal diagnosis and its outcomes. The heterozygote identification rate and frequency of specific CFTR mutations were also assessed.

Study Design

Enrollment/Eligibility

Patient enrollment occurred at 13 medical facilities in the Kaiser Permanente Medical Care Program (KPMCP) of Northern California between December 1991 and September 1992. Eligibility criteria included Caucasian (non-Hispanic) or Hispanic ethnicity in a pregnant woman or her partner, gestational age $\leq$ 16 weeks, and no family history of CF. CF heterozygote screening was offered to women during a single, group prenatal class routinely used to educate women about prenatal care. Written informed consent was obtained after pretest education. Options included refusing participation in the study, carrier testing with completion of survey instruments (consenters), or completion of survey instruments only without carrier testing (decliners). Blood specimens were obtained at the time of routine phlebotomy for prenatal care. Testing of the male partner was subsequently offered only if a woman was identified as a carrier. Prior to initiating the screening study, an additional group of women attending similar prenatal classes completed survey instruments (controls).

Pretest Education

A videotape narrated in English at a fifth-grade comprehension level was viewed by women in the class in order to provide essential information about CF and carrier screening that would be used to make a decision regarding testing.

Posttest Counseling

Risk assessments were based on a carrier frequency of 1 in 25 and a test sensitivity of 85 percent. Women without an identifiable CFTR mutation received a letter informing them of a decrease in their carrier risk from 1/25 to 1/165 and in their risk for an affected fetus from 1/2,500 to 1/16,500. Women identified as carriers were contacted by telephone by a genetic counselor, and they and their partner were offered genetic counseling and testing of the male partner through an office appointment. The partner's test result was provided at a second counseling visit 2 weeks later. Couples in which the partner did not have an identifiable CFTR mutation were given a revised risk of 1/660 (intermediate risk) of having an affected fetus. Couples in which the partner was identified as a CF carrier were given a 1/4 risk (high risk) and were offered prenatal diagnosis (as were female carriers whose male partners refused testing or were unavailable).

Survey Instruments and Semistructured Interviews

A variety of survey instruments were administered to several groups of subjects at specific intervals during the screening process including post-delivery for longitudinal assessment. This included a sociodemographic questionnaire (SQ), a knowledge questionnaire (KQ), the brief symptom inventory (BSI), an opinion survey (OS), and semistructured interviews (SSI).

CFTR Mutation Analysis

Participant specimens were randomly assigned to one of two testing laboratories. Lab group A (39 percent of total) was screened for the 6 most common mutations and lab group B (71 percent of total) was screened for 12 mutations, including an additional 6 less common alleles.

Results

A total of 6,617 eligible women were offered participation. There were 5,161 consenters (78 percent), 947 decliners (14 percent), and 509 who refused all participation (8 percent). Among consenters, 72 percent were Caucasian, 20 percent Hispanic, and 7 percent Mixed.

Sociodemographics

A majority of subjects were ages 21–34 years, were Caucasian, spoke English as a first language, were relatively well educated, worked full or part time, had moderately high annual incomes, were Catholic or Protestant, and were married. Decliners were somewhat more likely to be of lower socioeconomic status.

Pretest Education

The KQ results show that subjects who viewed the videotape (consenters and decliners) scored significantly higher (average of 3 more questions correct out of 10) than those who did not view it (controls).

Psychological Symptoms

Mean levels of psychological symptoms as measured by the BSI in all subjects, regardless of time of assessment and carrier test result, were low and similar to those reported for healthy populations.[2]

Attitudes and Decisionmaking Factors

For consenters, the major factors that led to a decision to be tested included a desire to know whether they were a CF carrier, the ease of testing, the hope that the test would be reassuring, and the value of knowing the fetal status for future management or pregnancy intervention. For decliners, the major factors that led to a decision not to be tested included a belief that their risk for having an affected baby was very low, a belief that the test result would not alter their attitude toward the pregnancy, and a desire to avoid being worried about the test result. Regardless of CF carrier test result, a large majority of women expressed satisfaction with their decision to be tested and endorsed the opinions that carrier testing was useful despite its insensitivity and that prior knowledge of an affected baby would be helpful. Among carriers, 46 percent said they would consider termination of an affected fetus, and 20 percent were neutral; among women testing negative, 30 percent would consider termination and 24 percent were neutral. Most women in both groups rejected the notion that they would feel stigmatized by being identified as a carrier. Data from the SSI's obtained after delivery demonstrated a high level of retention about the test result and its meaning. The vast majority of identified carriers felt genetic counseling sessions were informative and emotionally helpful, and would recommend testing to other women. Twenty of the 142 identified maternal heterozygotes did not attend counseling because of inability to contact them (2), miscarriage (7), and refusal of further participation (11).

Molecular

A total of 142 heterozygotes (including one compound heterozygote) were identified. The carrier identification rates for lab groups A and B were statistically similar and, for ease of presentation, are combined. The identification rate in Caucasians was 1/29. This was significantly higher than the 1/105 rate in Hispanics. The distribution of specific CFTR mutations was remarkable for the unexpected high incidence of R117H (16 percent of all carriers in lab group B). Ninety-five percent of eligible male partners underwent testing; seven heterozygotes were identified. All seven high-risk couples, and two women whose male partners were not tested, chose to have prenatal diagnosis. One couple had a second pregnancy during the course of the study. CFTR mutation analysis is unavailable for two pregnancies because of miscarriage. The fetal results include three normal, four heterozygotes, and one twin pregnancy concordant for F508 homozygosity. None of the pregnancies were terminated. Family history information obtained from one of the high-risk couples led to the diagnosis of CF in their two living young children. The compound heterozygote identified through screening was evaluated and found to be normal.

Conclusions

1. There was a high acceptance rate of screening (78 percent). Factors that potentially contributed to this included the following: testing in the context of an ongoing pregnancy, when couples are very concerned about potential problems in their future children and frequent contact occurs with the

health care system and intervention is optimum; incorporation of pretest education into an existing class that did not require attending a separate appointment; absence of an additional phlebotomy; and free testing.

2. Pretest education by videotape alone appeared to be sufficient for most people to make an informed decision concerning screening. Advantages of this method include a uniform, nondirective presentation of essential information in an engaging format with minimal personnel requirements.

3. Levels of psychological distress—whether measured in women waiting for test results, in women informed of their carrier status prior to partner testing, or in intermediate-risk couples in which the partner was not identified as a carrier—were not increased relative to women declining testing and were comparable to the normal population.

4. Test insensitivity was not perceived as undermining the value of the test.

5. Face-to-face genetic counseling served as an important adjunct for education and emotional support of identified carriers but did not appear necessary for women prior to receiving test results or for those who received negative results.

6. Sequential testing of couples, in which a male partner is tested only if a woman is identified as a carrier, is an effective approach to large-scale screening, particularly if the goal is identification of high-risk couples rather than individual carriers or intermediate-risk couples for whom further risk reduction is not realistic. This approach reduces laboratory costs approximately by half.

7. The data on approximately 1,000 Hispanic women demonstrate a CF heterozygote identification rate significantly lower than in non-Hispanic Caucasians, consistent with smaller data sets previously available.[3,4]

8. The frequency of R117H in identified carriers represents a 16-fold increase over that seen in CF Consortium data.[5] This suggests that R117H, a so-called "mild" mutation, may be more prevalent in the healthy general population than predicted based on the frequency in clinically diagnosed CF patients, particularly if the more efficient variable poly T region (7T) is present, as was demonstrated in a related study using our patients.[6] The higher frequency of R117H and perhaps other so-called "mild" CFTR mutations should be anticipated as a potential consequence of general population screening.

9. Similarly, identification of an asymptomatic compound heterozygote in a screened subject and, indirectly, identification of two affected living children in a screened couple indicate additional benefits, as well as problems, that should be anticipated as a potential consequence of general population screening.

10. This study had the advantages of a relatively well-educated population and utilized a preexisting prenatal care network and medical genetics program that may not be representative of population screening in other settings.

11. A cost analysis was not done directly through this study but was addressed as an adjunct to an independent Kaiser Permanente study and will be presented separately.[7]

Commentary

I believe that large-scale, sequential, prenatal population screening for CF heterozygotes is an acceptable method for identifying couples at risk for affected fetuses. Many of the concerns noted previously regarding potential adverse outcomes resulting from broad-based CF testing have been minimized. Other factors, particularly economic issues, require careful assessment. However, the current recommendations regarding limitation of CF testing to only those with a known family history seem unnecessarily restrictive. CF testing could be extended to individuals without a known family history provided that appropriate and sufficient nondirective pretest education and post-test counseling can be assured, informed consent is obtained for participation, laboratory support is available, testing is available at a reasonable cost, and sufficient funding can be allocated to pay for this.

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Prenatal Couple Screening for Cystic Fibrosis in Primary Care Settings

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Introduction

When cystic fibrosis (CF) testing is performed outside of pregnancy, identifying and counseling heterozygous carriers are commonly considered to be the final goals of testing.1,2 By contrast, the goal of prenatal screening for CF is to identify, as efficiently as possible, couples at risk for having a fetus with CF (both parents with an identifiable CF mutation). It is neither financially nor technically feasible to test for a large number of mutations. Approximately 10 mutations cause 81 percent of CF in North American Caucasians, and 66 percent (0.81 ¥ 0.81) of all couples with a CF fetus would be identifiable. Such couples could avail themselves of genetic counseling, prenatal diagnosis, or other reproductive options. In 1991, Wald described an innovative design for identifying these couples.3 In that design, the couple is the screening unit, and the screening testing is defined as positive only when both parents carry one of the CF mutations being tested for. When the couple is screen positive (approximately 1 in 1,000 couples), the risk of the fetus having CF is 25 percent, and definitive prenatal diagnosis can be offered to all of these screen positive couples. A second approach for screening the general pregnancy population begins by offering carrier testing to the woman. This policy identifies 81 percent of CF mutations; 1 in 30 pregnant women are positive and are offered counseling. Subsequently, the woman's partner is offered counseling and testing. This sequential (or two-step) approach requires that counseling be offered to all women identified as CF carriers, even though their collective risk for having an affected pregnancy is nearly the same as the background risk. In 29 of 30 such couples, definitive prenatal diagnosis is not possible.4 In a large pilot project in a centralized care setting in Europe, sequential carrier detection was compared with couple screening in a pregnancy population receiving routine prenatal care.4–6 Both were found acceptable, but couple screening was preferred. It has been suggested that, in the United States, couple screening might not be acceptable.7

Pilot Study in Maine

We examined the efficacy and acceptability of the couple model for CF screening in a pregnancy population in Maine receiving prenatal care in decentralized primary care settings.8 After women received educational material, had questions answered, and provided consent, buccal cells were collected and sent to our laboratory. Informational and buccal cell sampling materials were taken home to their partners. Testing was initiated only after receipt of samples from both the pregnant woman and her partner. The woman's sample was tested first. If it was negative, the partner's sample was not tested, and the couple's result was reported as screen negative. If one of the seven CF alleles was identified in the woman's sample, her partner's sample was tested. If his sample tested negative, the couple's result was reported as screen negative. Only when a woman and her partner both had an identifiable CF mutation was the test reported as screen positive.

Sixty-nine of 74 physicians approached agreed to make couple screening available at no cost. Sixty-four physicians actually contributed study subjects. During the 16-month recruitment period, 1,770 women and 1,682 (95 percent) of their partners submitted samples. Testing was successfully completed in 1,645 of these couples (98 percent). The median gestational age was 10.7 weeks; 95 percent were

obtained before 16.6 weeks. Only one couple had a screen positive result, and they decided, following counseling, to have diagnostic testing. A fetus homozygous for DF508 was identified, and the couple chose to terminate the pregnancy.

To determine the response to couple screening by health providers, participating physicians were surveyed by questionnaire and key office staff by telephone. Thirty-three physicians from 23 practices estimated that office staff spent 5–10 minutes in direct contact with the patient; nearly all (31/33) felt this to be acceptable. The office staff's average estimate was 5 minutes. On a scale of 1 to 5 (with 5 being the most positive) physicians reported that their patients were satisfied with CF screening (mean: 4.2), and reported that they and their office staff felt good about providing such screening (4.4) (Table 1). Compared with alpha-fetoprotein (AFP) testing, physicians felt that patients were less anxious (1.6) and that couple screening is important (3.2). Office staff responded similarly.

To determine the response to couple screening by participating women, standardized telephone surveys were administered by a single, experienced genetic counselor to randomly selected women where: (1) both partners submitted samples (n=60), and (2) only the woman submitted a sample (n=19). Interview time was between 5 and 10 minutes at 6–12 months after testing. Sixty-seven of the 79 women surveyed said that they would choose to have the testing performed again in a future pregnancy, six were undecided, and six said they would not choose to have the testing again. Seventy-five would recommend the test to others, three were undecided, and one said that she would not recommend the test to others. Only 3 of the 19 male partners actually refused to submit samples; the others either forgot to send a sample or waited until the pregnancy was too far advanced (after 20 weeks' gestation). The women were interested in CF testing (4.4) and found the office staff response (4.7) and the informed consent procedure (4.5) helpful (Table 2). There were no differences in responses between those who completed the testing and those who did not. Those who completed testing were not especially nervous or anxious (2.6) and were not very worried before receiving the results (2.2).

TABLE 1. CF Pilot Project: Survey Responses by 33 Physicians and 35 Key Office Staff[8]

Survey Question	Physician Response		Office Staff Response	
	N	*Mean Response Score**	*N*	*Mean Response Score**
How satisfied are your patients with CF testing?	32	4.22	33	4.48
How does the physician feel about providing CF testing?	31	4.45	33	4.48
How does the staff feel about providing CF testing?	32	4.41	36	4.47
Compared to AFP testing:				
How anxious are patients prior to test results?	32	1.56	35	1.51
How anxious are patients after results are provided?	32	1.50	34	1.21
How important is couple screening for CF?	31	3.18	36	2.75

* All answers were given on a scale of 1–5, with 5 being the most positive response.

TABLE 2. Results of the Telephone Survey of Women Study Subjects[8]				
Survey Question	Partner Submitted Buccal Sample		Partner Did Not Submit Buccal Sample	
	N	*Mean Response Score**	*N*	*Mean Response Score**
How interested were you in CF testing?	60	4.38	19	4.47
Was the informed consent helpful?	53	4.53	19	4.68
Were office staff explanations helpful?	58	4.69	18	4.56
How willing was your partner to participate?	60	4.95	19	4.84
How easy was the sampling process?	60	4.90	19	4.89
Were the results reassuring to you?	58	4.64	0	NA
I felt very nervous or anxious about the testing.	60	2.63	0	NA
I was very worried before receiving results.	57	1.19	0	NA
Any type of screening makes me nervous.	60	2.83	0	NA

*All answers were given on a scale of 1–5, with 5 being the most positive response. NA = not applicable.

This pilot project in Maine found that physicians, office staff, and nearly all women were satisfied with the screening process. It was concluded that couple screening for CF is feasible and acceptable in decentralized primary care settings.

Fee-for-Service Prenatal Couple Screening in Maine

On the basis of these results, a statewide Demonstration Project was organized, in conjunction with the three largest third-party payors, to evaluate prenatal CF screening as a fee-for-service sequence. During the past two years, 1,119 couples submitted samples. Testing for 33 was canceled due to inadequate specimens, advanced gestational age, or family history of CF. A final success rate of 98.5 percent was achieved after repeat buccal samples were tested for 37 couples. No screen positive couples were identified. Practical issues about the adequacy of cheekbrush sampling (often at home and sent by mail), the logistics of pairing patient and partner samples obtained separately, and the ability to obtain repeat samples have been resolved. Prenatal CF screening has been successfully integrated into routine practice in Maine's decentralized primary care setting.

Comparison of Prenatal CF Screening With Prenatal Screening for Other Fetal Disorders

Three critical characteristics—the detection rate, the false positive rate, and the odds of being affected given a positive result (OAPR)—help to evaluate the performance of a screening test. Prenatal screening is routinely performed for Down syndrome (using either maternal age of 35 and older, or a combination of maternal age and multiple serum markers) and for spina bifida (using AFP measurements).9 The detection rate possible for CF (66 percent) is higher than for any of these (35 percent, 60 percent, and 60 percent, respectively, for Down syndrome using maternal age, Down syndrome using multiple markers, and spina bifida) (Table 3). To achieve this detection, CF screening requires the fewest counseling and invasive procedures (1 per 1,000 couples screened). This compares

TABLE 3. Comparison of Prenatal Screening for CF with Other Prenatal Screening Tests[10]				
Fetal Disorder	Screening Method	Detection Rate (%)	Women Offered Amniocentesis (%)[a]	Amniocenteses to Identify Affected Fetus[b]
Down Syndrome	Maternal age ≥ 35 years	35	9	141
	AFP, hCG, uE3 and maternal age in all pregnant women [c]	60	4	41
Spina Bifida	Maternal Serum AFP	60[d]	2	34
Cystic Fibrosis	CF testing in pregnant couples	66[e]	0.1	4

[a] Roughly equivalent to the false positive rate (in the case of CF screening, defined as pregnancies where both parents are carriers, but the fetus has either one or no identifiable copies of CF mutant alleles).
[b] Based on second trimester prevalence.
[c] AFP: alpha-fetoprotein; HCG: human chorionic gonadotropin; uE3: unconjugated estriol.
[d] Includes the 20 percent of closed spina bifida lesions that are not detectable by AFP screening.
[e] Estimated detection rate in North America populations if the testing panel includes eight common mutations.

favorably with the 90, 40 and 20 per 1,000 required for the tests mentioned above. The birth prevalence for the three disorders are 1 in 850, 1 in 1,000 and 1 in 2,500, respectively. When maternal age of 35 years or older is used to screen for fetal Down syndrome, one affected fetus is identified for every 141 pregnancies undergoing amniocentesis (OAPR of 1:140). When multiple markers are used, the OAPR is 1:40. Prenatal screening for spina bifida yields an OAPR of 1:33. For CF, one affected fetus is identified for every four pregnancies undergoing amniocentesis (OAPR 1:3). Prenatal screening for CF is associated with the lowest false positive rate, the highest detection rate, and the highest probability of an affected fetus being present in pregnancies offered amniocentesis.

Published Intervention Trials of Prenatal Screening for CF

Ten trials of prenatal screening for CF completed in Europe and the United States have provided insights into the suitability of screening policies (one-step versus two-step), acceptability of testing to patients and health care providers, cost, uptake of diagnostic testing, and decisions about termination versus continuation of affected pregnancies.10 Six studies reported results of two-step screening (sequential carrier testing): two in the United States and four in Europe (Table 4). A total of 23,730 women were initially tested; 24 screen positive couples were identified; 23 couples chose diagnostic testing. Five affected fetuses were identified; four couples chose to terminate their pregnancies. Four studies reported results of one-step screening (couple-based): one in the United States and three in Europe. A total of 15,342 couples were tested, 19 screen positive couples were identified; 17 couples chose diagnostic testing. Seven affected fetuses were identified, and all of these couples chose to terminate their pregnancies. Collectively, 39,072 pregnancies have been screened; 43 high-risk couples have been identified, 40 of whom (93 percent) chose diagnostic testing. Twelve fetuses affected with CF were detected; 11 couples chose to terminate their pregnancies. Although only three studies have been reported from the United States, the data appear consistent with larger studies performed in the United Kingdom and Denmark. Close similarity is known to exist between the United States and the

TABLE 4. Prenatal Screening for Fetal CF: A Summary of Two-Step and One-Step Studies[10]					
Study	Number of Subjects	Number of Positive Couples	Number Choosing Diagnostic Studies	Number With Affected Fetus	Number Opting for Termination
Two-Step Protocol					
Denmark, 1993[11]	6,599	3	3	1	1
US-California, 1996[12]	5,161	7	7	1	0
UK-Edinburgh, 1994[4,6]	4,978	7	7	2	2
US-New York, 1996[13]	4,879	5	4	0	—
UK-Aberdeen, 1995[14]	1,475	1	1	0	—
Germany, 1994[15]	638	1	1	1	1
One-Step Protocol					
UK-Edinburgh, 1996[5,6]	12,566	17	15	6	6
US-Maine, 1996[8]	1,645	1	1	1	1
UK-London, 1995[16]	810	0	—	—	—
UK-Aberdeen, 1995[14]	321	1	1	0	—
TOTALS	39,072	43	40	12	11

United Kingdom as regards pregnant women's participation and decisionmaking in existing prenatal screening programs.17 The three pilot studies in the United States have contributed detailed information about physician and patient receptivity to prenatal screening for CF, and also about other aspects of program management. Although two used a two-step protocol (sequential carrier testing), and one used a one-step protocol (couple-based screening), all studies found a high level of acceptability and satisfaction. Given the documentation of efficacy now available, it appears reasonable to encourage larger-scale trials of prenatal screening for CF in the United States to gain further insight into all aspects of program design and patient management and to determine whether such screening might be feasible as part of routine prenatal care.

Couple Versus Two-Step CF Screening Policies

One issue involves the desirability of making individuals aware of their carrier status. The two-step (or sequential) policy calls for all screened women to be informed and counseled if they are found to be carriers. If the sequential model had been applied to the Maine study population, 51, rather than 1, of the screened women would have been identified as having a positive screening test and would have required genetic counseling (the expected ratio is 30:1). The available partners of these women would then have been offered counseling and testing as well, but only one of the partners actually carried an identifiable CF mutation. The remaining 50 couples would have been counseled that an increased risk (approximately 1 chance in 525) remained for their baby to have CF. For these couples, however, no definitive prenatal diagnostic testing would have been possible. Anxiety resulting from this unresolvable situation, combined with the anxiety frequently documented among carrier test positive women while awaiting their partners' results, has led obstetricians in one study of the sequential model to require that a nurse trained in genetics be available on an ongoing basis.5 The classification of all carriers as screen positive in the sequential model would have increased the false positive rate from 0.1 percent to 3.2 percent, but would not have increased detection of homozygous fetuses.

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Cystic Fibrosis Carrier Testing in the Population: A U.K. Perspective

Theresa M. Marteau, Ph.D.

The period since the cloning of the main mutation for cystic fibrosis (CF) has been characterized first, by excitement, and second, by caution about the insensitivity of a screening test. Then followed a series of research projects, mainly in the United Kingdom and the United States, the results of which led to a third phase, characterized by uncertainty about the implications of the results of pilot programs for widespread services.

This paper will review the results of U.K. programs of CF carrier testing to address the following issues:

1. Demand for CF carrier testing
2. Understanding of test results among those tested
3. Behavioral, emotional, and cognitive consequences of testing

Finally, this paper considers possible reasons why the results of these research projects have not led to a clear consensus on the value (or otherwise) of widespread screening programs. Details of much of the research referred to below can be found in a recent literature review.1

1. Demand for CF Carrier Testing

When the major mutation for the CF gene was discovered in 1989, it was assumed that there would be great demand for carrier testing. Public surveys confirmed this. Contrary to such expressions of interest, however, there has been relatively little interest in screening in the general population of the United Kingdom. Two factors have been important in determining uptake rates of CF testing: the population to which testing is offered, and the way in which it is offered (Table 1). A similar pattern has emerged in U.S. studies.

Uptake rates are higher among pregnant women than in general population samples. Methods of offering testing have been systematically investigated only in general population samples. These results show that uptake of the test is highest when offered face-to-face in a health care setting and when there is no need for a return visit. It is lowest when offered by letter. The extent to which decisions about tests offered in these different ways were informed was not assessed in the U.K. studies.

The pattern of results has raised an as-yet-unanswered question concerning the extent to which higher uptake rates reflect interest by the public ("demand pull") or enthusiasm from health professionals for high uptake ("supply push").

- Further research is needed to assess the understanding of testing and the effect on understanding and uptake of varying the methods of offering testing, particularly in pregnant populations.

TABLE 1. Uptake Rates for Carrier Testing for Cystic Fibrosis: United Kingdom vs. United States			
Population	Method	Uptake	Country
Nonpregnancy adult			
Primary	letter	4%	US[2]
		10%	UK[3]
	face-to-face	25%	UK[3]
	face-to-face/same-day testing	24%	US[2]
		66%	UK[4]
		70%	UK[3]
Pregnant women			
Primary care	face-to-face/same-day testing	95%	UK[5]
Hospital	face-to-face/same-day testing	57%	US[6]
		78%	US[7]
		70%	UK[8]
		70%	UK[9]

2. Understanding of Test Results

Understanding of test results immediately after testing has generally been found to be good. For example, in one study more than 90 percent of those receiving negative results on CF carrier testing understood that they had a residual chance of being carriers.3 Three-year followup of those tested in six U.K. CF screening programs revealed a significant decrement in understanding of results.10 At that time, 50 percent of those who had received negative test results erroneously believed that their results meant that they were at no risk at all of being carriers. Sixteen percent of carriers erroneously believed that their results meant that they were probably, but not definitely, carriers. Inaccurate recall for carriers as well as screen negatives is selective, with the direction tending toward reduced risk. It may, therefore, reflect a well-documented phenomenon of threat minimization.11 This study lacked the power to determine whether recall was associated with subsequent reproductive decisions.

- These results do not suggest that initial post-test counseling was ineffective. Rather, they point to the need for more research to (a) develop a better understanding of the cognitive and emotional processes that underlie inaccurate recall and (b) determine the impact of inaccurate recall on subsequent reproductive decisions.

3. Behavioral, Emotional, and Cognitive Consequences of Testing

Reproductive Decisions

The majority of carrier couples detected during population-based screening programs in the United Kingdom elect to proceed to prenatal diagnosis, and all of those with a positive diagnosis of CF have thus far been reported to elect to terminate the affected pregnancies.1 The use of prenatal diagnosis and the rates of termination of affected pregnancies are higher in the general population than among those who have a family history of CF.12,13 This difference may reflect a difference in perception of the disease according to personal experience and to counseling that the people receive. The effect of these and other factors on decisions about termination of pregnancies affected by CF and other conditions has been very little researched.

- Observational studies are needed to determine what information is given to parents and how they make decisions following the diagnosis of a fetus affected by CF.

Emotional and Cognitive Outcomes

Carriers detected during population-based CF testing program experienced brief but marked rises in general levels of anxiety or distress.1 After 3 months this was no longer evident and by 3 years anxiety levels continued to be within normal ranges.10 Before screening programs were established, concerns were expressed that, because those obtaining a negative result could not be given complete assurance that they did not carry a CF mutation, receiving such a result might lead to uncertainty and anxiety. There is no evidence from any of the studies that this has happened. In fact, the main problem resulting from negative test results is that of false reassurance, as described above.

Several studies have documented gender differences in responses to CF testing, with testing having a greater impact on women.14,15 Among carriers, women respond more negatively than do men; among screen negatives, women respond more positively than do men.

- More research is needed to understand gender differences in response to genetic testing and other forms of health risk assessment.

Conclusion

There is uncertainty in the United Kingdom and seemingly in the United States about how best to proceed with CF carrier testing. Several factors have contributed to this. First, public demand for such testing is not strong. Second, there was no formal consensus in the United Kingdom on the objectives of CF carrier testing before research was commissioned, thus making the results of research studies difficult to evaluate. In particular, no operational definition of informed reproductive decisionmaking was made in any of the studies. Therefore, it is not known how this is most effectively and efficiently achieved. A better understanding of the uncertainty engendered by the results of CF carrier screening research is likely to provide important lessons for the future commissioning of studies to evaluate other genetic screening programs.

Acknowledgments

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Cystic Fibrosis Among Native Americans of the Southwest

Theresa A. Grebe, M.D.

Although cystic fibrosis (CF) has long been recognized as the most common lethal, autosomal recessive disease among Caucasians, it has been virtually unknown among Southwest Native American populations. In 1992, my collaborators and I did clinical and molecular analyses of the only known cases of CF in several populations of Native Americans of the Southwest: the Pueblo and Navajo.[1] These two groups of Native Americans are genetically distinct. The Pueblo are thought to be descended from the Anasazi, whose presence as an agricultural society in the Southwest has been traced through archeological evidence back to 10,000 B.C.[2,3] The Pueblo live in separate communities (also called pueblos) scattered throughout New Mexico. The Navajo, however, are descended from the Athabascan people, who were thought to have migrated south from northwestern Canada around 1200 A.D.[3] The principal Navajo reservation extends over 24,000 square miles in northeastern Arizona, southeastern Utah, and northwestern New Mexico. In this original study, six of the patients were from the Zuni pueblo, a geographically isolated group. With a population of 9,500 in 1992, the incidence of CF in this pueblo (1 in 1,580) was greater than that of any group studied to date.

Patients were identified by contacting the CF centers serving the southwestern United States and by survey of all Indian Health Service hospitals of these states. The centers are located in Albuquerque, Phoenix, and San Diego. At the time of this study, 11 Pueblo patients and 1 Navajo patient were identified. A 13th patient was also identified, a female from the Jemez pueblo. She was not included in the mutation analysis, as she was the sibling of one of the male patients. As of this writing, two of the original patients (both Zuni) have died, five new patients have been diagnosed, and one of these (Zuni) has also died. The diagnosis of CF was made on the basis of an elevated sweat-chloride concentration of >70 mmol/liter. All patients were examined by a pediatric pulmonologist and were diagnosed as either pancreatic sufficient (PS) or pancreatic insufficient (PI) (Table 1). Measurements of height, weight, and head circumference were determined in all patients.

Standard PCR amplification of DNA extracted from blood was used in conjunction with direct mutation analysis and haplotype analysis. DF508, N1303K, and G542X were analyzed by standard dot blot analysis, and W1282Y, G551D, and R553X were analyzed by restriction enzyme digestion and gel electrophoresis. Haplotypes were determined using the extragenic polymorphic markers/enzyme pairs Xv2c/*Taq*I and KM19/*Pst*I.

Patient phenotypes varied widely, from mild, in the patients from Jemez pueblo, to severe, in the patients from Zuni pueblo. The most consistent phenotype was found among the Zuni, who were, with the exception of one patient, pancreatic insufficient, and had severe disease. Results of pulmonary function testing, including forced vital capacity and forced expiratory flow, revealed no consistent correlations in patients over 5 years of age. An incidental finding in four of the six original Zuni patients was the presence of microcephaly (head circumference less than the second percentile for age), which is not part of the typical CF phenotype (Table 1). These patients were developmentally normal, and no

TABLE 1. Summary of Clinical and Genetic Data: Native American CF Patients

Patient (sex/age)	Tribe (individual pueblo)	PS/PI	Weight (percentile)	Height (percentile)	Head Circum-ference (percentile)	Haplotype	Genotype
021-1 (M/l year)	Pueblo (Zuni)	PI	20	10	5	CC	R1162X/R1162X
022-1 (F/9 years 6 mo)	Pueblo (Zuni)	PI	7.5	20	10	CC	R1162X/R1162X
023-1 (M/5 years 6 mo)	Pueblo (Zuni)	PI	75	50	<2	CC	R1162X/R1162X
024-1 (F/4 years I mo)	Pueblo (Zuni)	PI	40	10	<2	CC	R1162X/R1162X
028-1 (F/10 mo)	Pueblo (Zuni)	PI	7.7	5	<2	CC	R1162X/R1162X
029-1 (F/22 years)	Pueblo (Zuni)	PS	2	17.5	<2	AC	R1162X/3849+10kbC→T
006-1 (F/15 years 8 mo)	Pueblo (Jemez)	PS	85	45		AC	D648W3849+10kbC→T
007-1 (M/13 years I I mo)	Pueblo (Jemez)	PS	>95	80		AA	Not analyzed
008-1 (F/6 years 6 mo)	Pueblo (Santo Domingo)	PS	>95	>95		AB	G542X/3849+10kbC→T
012-1 (M/32 years)	Pueblo (Zia)	PI	2	2		AA	Not analyzed
030-1 (F/26 years)	Pueblo (Jemez)	PI	7.5	17.5		AA	Not analyzed
004-1 (F/10 years)	Navajo	PI	2	2		AA	Not analyzed
031-1 (M/3 years-died)*	Pueblo (Zuni)	PI	50	25	25		Not analyzed
033-1 (F/31 years)*	Pueblo (Jemez)		<5	15			Not analyzed
034-1 (M/9 years)*	Pueblo (Laguna)		7	7			Not analyzed
035-1 (F/11 years)*	Pueblo (Acoma)		1.5	35			Not analyzed
036-1 (F/2 wks)*	Pueblo (Zuni)						Not analyzed

*These are recently identified cases not included in the original study; therefore, these data are incomplete.
PS = pancreatic sufficient; PI = pancreatic insufficient.

other cause for microcephaly was found. The mutation analyses revealed no copies of DF508, G551D, R553X, N1303K, or W1282X. One patient (008-1) carried a copy of G542X. Affected individuals had either haplotype AA, AC, or CC, except the one carrying the G542X mutation, who had haplotype AB.

This survey revealed that CF occurs commonly among the Pueblo, with an incidence of 1 in 3,970 (population 43,674; Bureau of Indian Affairs, 1990), and 1 in 1,580 in the Zunis, whose population is 9,500. The single Navajo patient, however, represents the only known case of CF in the Navajo population of 186,000. The high incidence of CF in the Pueblo is not secondary to intermarriage with Spanish or northern European settlers, as evidenced by the complete absence of DF508, as well as by the absence of the B haplotype on any except one of the chromosomes. The B haplotype has the highest CF association in Caucasians; the A and C haplotypes, in contrast, have the lowest. Consanguinity was also eliminated as a cause through pedigree analysis. In the Zuni, the high frequency of CF is probably secondary to a typical founder effect from the geographic isolation of this population. We speculated that a single mutation was responsible for CF in these individuals.

Subsequent to this initial investigation, DNA from eight of the original patients was further studied by Mercier et al.[4] They analyzed the entire coding sequence of the cystic fibrosis transmembrane conductance regulator (CFTR) gene using a combination of denaturing gradient gel electrophoresis

(DGGE) and DNA sequencing. They determined the genotype of these eight patients and identified four different mutations among them, including one novel mutation. Using intragenic microsatellites, they also compared the haplotypes of those chromosomes with those of other populations.

The systematic screening of exon 19 via DGGE revealed a common altered pattern of migration for five patients, indicating a probable homozygous allele. This was identified by DNA sequencing to be the R1162X mutation. A sixth patient carried only one copy of this mutation. The second mutation, (3849+10kbCKT), was found on three chromosomes. The third mutation, G542X, was found on a single chromosome.

The fourth mutation was a missense change in exon 13. DGGE, followed by direct DNA sequencing, revealed a nucleotide change at position 2075, an AKT, resulting in a valine instead of an aspartic acid at amino acid 648: D648V. This change was found on only 1 of the 16 CF chromosomes analyzed and has not been previously reported in Caucasian chromosomes to date.

To characterize the genetic backgrounds associated with the R1162X mutations, the authors used both intra- and extragenic markers. Using the extragenic markers XV2c and KMI9, they showed the R1162X mutation to be carried on the C haplotype. This corresponds with that of the Italian population. Using three microsatellite-dinucleotide-repeats, a CA/GT repeat in intron 8 and a TA repeat and CA repeat both in intron 17b, they identified a common haplotype (17-31-13 being the number of repeats in these three systems) bearing this mutation in 11 CF chromosomes of the Zuni patients. Using the same markers, haplotypes were determined for the three chromosomes carrying the 3849+10kbCKT. All three were found on a 16-17-19 type. This haplotype differed from that of three Caucasian chromosomes bearing the same mutation (17-31-13).

These authors hypothesized that because the R1162X mutation is found on a single haplotype on all 11 chromosomes in the Zuni, identity by descent is most likely, in agreement with our hypothesis. Although the three chromosomes carrying the 3849+10kbCKT mutation are all on the A haplotype in these populations, this mutation has been found on different haplotypes in Caucasians. This suggests a recurrent mutation in a hot spot of the CFTR gene. Because this mutation is present in three different Pueblos, however, a single allele may be segregating in these Native American populations.

The results of these two studies show that CF is indeed a common disorder among the Native Americans of the Southwest. It is particularly frequent among the Zuni, who have one of the highest disease incidences reported to date. The phenotype among the Zuni is fairly consistent and severe, leading to a serious health impact on this population. Neither prenatal nor newborn screening for CF are currently being practiced in these communities, although the clinical threshold for diagnostic testing is quite low. The Zuni people are interested in the comments and recommendations of the consensus panel.

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Cost-Effectiveness of Prenatal Carrier Screening for Cystic Fibrosis

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Objective

This study's objective was to evaluate the economic consequences of routinely offering cystic fibrosis (CF) carrier screening to pregnant white women under 35 years of age.

Methods

Decision analysis was used to evaluate the health outcomes and medical costs of a screening program from the health care payer's perspective. Probabilities were taken from the literature; cost data were based on consultations with laboratory and hospital administrators. This analysis has been updated from the 1994 paper to include new information: a higher cost of care for CF, an improved test sensitivity, and a lower discount rate. Sensitivity analysis was performed for key assumptions.

Results

If the test acceptance rate were 78 percent and the screening test identified 90 percent of carriers, a prenatal CF carrier screening program would identify slightly more than half of the high-risk pregnancies in the population. For a cohort of 100,000 pregnant women, the program would cost $8.4 million. If the proportion of couples choosing abortion were 30 percent and the annual cost of medical care for CF were $41,693, the program would save $4.6 million in averted costs of medical care for CF, for a net cost of $3.8 million. Even after subtracting the savings in averted medical care for CF, the net cost per high-risk pregnancy identified would be $29,000; the net cost per unwanted CF birth averted would be $490,000.

Results were sensitive to the cost and the sensitivity of the screening test. They were also highly sensitive to were also highly sensitive to the proportion of CF pregnancies in which termination was chosen, between 10 and 50 percent. An alternative analysis conducted from the long-term perspective of a large health care provider suggested that CF screening might result in net savings.

Conclusions

A prenatal CF carrier screening program would not result in net savings for the general population under current assumptions. However, it may be justified if the benefit of the early information provided to expectant parents is judged worth the cost.

Implications for Consensus Panel

General population screening of pregnant women for CF mutations would enable some families to anticipate or avert CF births, but at a relatively high short-term cost. In the long-term, most of this cost might be recouped, or net cost savings might result, depending on the proportion of parents who chose termination of CF pregnancies. For future research and policy on genetic testing, economic models

should be initiated early and updated as key information becomes available. Studies are needed on how patients and the general population value relevant nonfinancial outcomes such as the psychological value of advance identification of a CF pregnancy.

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Carrier Screening for Cystic Fibrosis: Costs and Clinical Outcomes

David A. Asch, M.D., M.B.A.

Population-based cystic fibrosis (CF) carrier screening is controversial, in part because genetic screening in the setting of reproductive planning raises important social and ethical issues,[1] and also because even very good tests perform poorly when applied to low prevalence conditions. Furthermore, the application of CF carrier screening is not limited to a single clinical strategy. Many plausible strategies may be constructed using different decision rules for proceeding to further testing or deciding whether to continue a pregnancy.[2,3] In turn, each strategy yields different clinical and economic outcomes. Thus, the clinical question is not only whether widespread CF carrier screening should be done but also how it should be done.

My colleagues and I used a decision analytic model to define the clinical and economic outcomes expected from several plausible population CF carrier screening strategies. Each clinical strategy evaluated was composed of a plausible arrangement of the following component tests.

Standard Mutation Analysis

Most centers that screen for CF mutations employ a battery of tests targeted at about 5–10 common mutations that in aggregate represent approximately 85 percent of CF alleles (e.g., DF508, G542X, G551D, R553X, N1303K, W1282X, DI507). Members of a couple are screened in parallel or in series. For example, in one parallel strategy, both partners undergo standard screening and the couple proceeds to prenatal diagnosis with amniocentesis if both partners are found to screen positive. In one sequential strategy, one partner is screened first, the second partner is screened only if the first screens positive, and the couple proceeds to prenatal diagnosis only if both are positive. As an alternative to simple sequential and parallel strategies, we also consider the "couple-screening" strategy proposed by Wald.[4] DNA samples are collected from both partners (as in parallel strategies), but testing is performed sequentially and results are reported at the level of the couple. For example, couples in which the first partner tests positive and the second partner tests negative are designated "screen negative."

Expanded Mutation Analysis

Although standard mutation batteries will identify most carriers who can be identified, one might screen for another 20–30 mutations beyond the standard panel. We investigated strategies that use this expanded analysis at the time of the initial screen. In addition, we considered "mixed" strategies that use the expanded analysis only after one parent screens positive on the standard battery—for example, when one and only one partner in a couple screens negative in parallel testing, or when the first partner screens positive in sequential testing. In addition to the alternative of not screening, we investigated 15 unique ways of performing population CF carrier screening. These strategies are listed in Table 1. Several representative tree branches are shown in Figures 1 and 2. All branches end in one of six clinical outcomes that reflect the alternatives of delivery, miscarriage, or abortion and whether the fetus or child is or is not affected with CF.

TABLE 1. List of Clinical Strategies Evaluated			
Parental Sequence	DNA Test Battery	Additional Tests if One and Only One Parent Tests Positive	Strategy
No Screening			A
Parallel	Standard	None	B
		MIE	C
	Expanded	None	D
		MIE	E
	Mixed[a]	None	F
		MIE	G
Sequential	Standard	None	H
		None[c]	I
		MIE	J
	Expanded	None	K
		None[c]	L
		MIE	M
	Mixed[b]	None	N
		None[c]	O
		MIE	P

MIE = 3D microvillar intestinal enzyme analysis.

[a] If one and only one partner is negative with the standard battery, rescreen that partner with the expanded battery.

[b] If the first partner is positive, screen the second partner with the expanded battery.

[c] DNA samples are collected from both parents, but testing is performed sequentially. If both parents screen positive, the *couple* is told they are positive. Otherwise, the *couple* is told they are negative.

Probability estimates used in the model were obtained by surveying the literature and consulting experts in obstetrics, genetics, and prenatal diagnosis.

Costs and Resource Use

The base-case analysis is based on costs rather than charges. Cost estimates used in the model are in 1995 dollars. Direct medical costs are included, as are indirect costs, including time lost from work, transportation costs, and the like. Costs were measured from three different perspectives: patient, payer, and society.

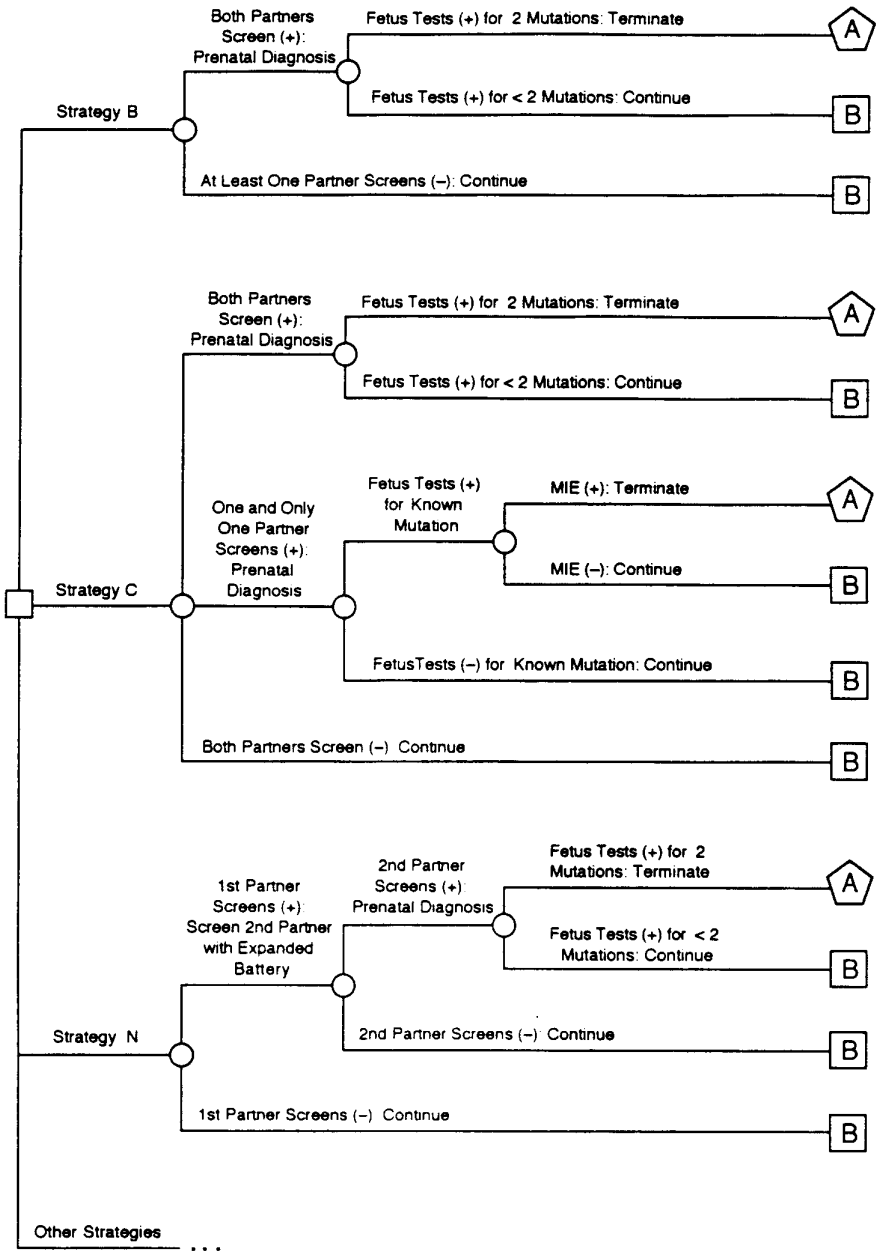

FIGURE 1. Three sample clinical strategies (B, C, and N from Table 1) expressed as a decision tree. The tree is read from left to right. The square node indicates a choice to be made among strategies. The round nodes indicate outcomes that result from chance. Each branch ends on a letter indicating a subtree, shown in Figure 2. MIE =3D Microvillar intestinal enzyme analysis. For an explanation of the three strategies, see Table 1.

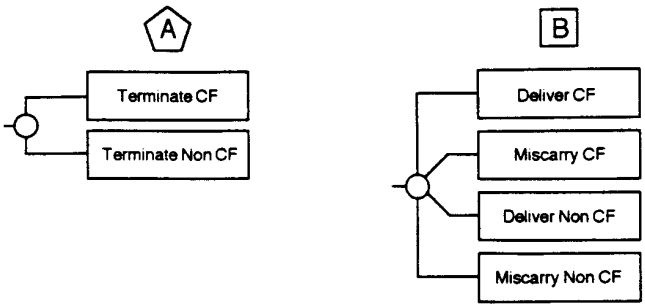

FIGURE 2. Two subtrees for Figure 1. Each pregnancy can either be terminated (subtree A) or continued (subtree B). If it is terminated, it might have led to the birth of a child with CF or without CF. If it is continued, it might lead to a miscarriage or to delivery, and in either case might be affected with CF or not.

Clinical Outcomes

Each strategy was evaluated according to its overall cost and the distribution of a hypothetical cohort of 500,000 pregnancies among six clinical outcomes: (1) delivery of a child without CF; (2) delivery of a child with CF; (3) termination of a pregnancy that, if delivered, would have resulted in the birth of a child without CF; (4) termination of a pregnancy that, if delivered, would have resulted in the birth of a child with CF; (5) spontaneous miscarriage of a pregnancy that, if delivered, would have resulted in the birth of a child without CF; (6) miscarriage of a pregnancy that, if delivered, would have resulted in the birth of a child with CF.

Results

Table 2 reports the base-case analysis for all 16 screening strategies applied to a cohort of 500,000 single gestation pregnancies. The table shows the number of pregnancies falling into each of the six clinical outcomes, the total cost from a societal perspective, and a summary cost-effectiveness measure presented as the cost per CF birth avoided relative to the no-screening alternative (strategy A). Compared with no screening, strategy N has the lowest cost per CF birth avoided. In this sequential strategy, the first partner is tested with the standard battery. The second partner is tested with the expanded battery if and only if the first partner's screen is positive. If the second partner is also positive, prenatal diagnosis is performed. This strategy identifies 75 percent of anticipated CF births at a cost of $367,000 each. This figure assumes that couples who identify a pregnancy at risk will choose to have prenatal diagnosis and termination of affected pregnancies. The cost per CF birth identified is approximately half this figure when couples plan two children. The relative ranking of the various strategies is insensitive to the assumptions in the model, but the cost-effectiveness of each strategy depends critically upon two factors. The cost-effectiveness of carrier screening is significantly reduced if couples decide not to terminate affected pregnancies. The cost-effectiveness of carrier screening is

TABLE 2. Base-Case Analysis for 16 Alternative CF Carrier Screening Strategies

	CF			Non CF					
Strategy	Births	Abortions	Mis-carriages	Births	Abortions	Mis-carriages	CF Births Avoided (rel. to A)	Total Cost	Cost Per CF Birth Avoided (rel. to A)
A	195	0	5	487,305	0	12,495	0	$1,530,313,000	—
B	57	142	1	487,302	0	12,498	138	$1,623,710,000	$676,000
C	8	191	0	486,787	340	12,673	187	$1,641,185,000	$594,000
D	40	159	1	487,300	0	12,499	155	$1,674,352,000	$930,000
E	6	194	0	486,737	358	12,705	189	$1,694,522,000	$867,000
F	39	160	1	487,300	0	12,499	156	$1,627,544,000	$625,000
G	8	192	0	486,789	338	12,673	187	$1,647,277,000	$626,000
H	57	142	1	487,302	0	12,498	138	$1,582,937,000	$381,000
I	57	142	1	487,302	0	12,498	138	$1,606,318,000	$550,000
J	33	166	1	487,044	170	12,586	162	$1,593,161,000	$387,000
K	40	159	1	487,300	0	12,499	155	$1,609,657,000	$512,000
L	40	159	1	487,300	0	12,499	155	$1,632,701,000	$661,000
M	23	177	1	487,019	179	12,602	172	$1,621,475,000	$530,000
N	49	150	1	487,301	0	12,499	146	$1,583,972,000	$367,000
O	49	150	1	487,301	0	12,499	146	$1,607,352,000	$527,000
P	32	167	1	487,045	169	12,586	163	$1,593,807,000	$391,000

The figures represent the results of a strategy applied to a cohort of 500,000 pregnancies. Strategies are defined in Table 1.

that the cost-effectiveness of CF carrier screening depends greatly on couples' reproductive plans. CF carrier screening is most cost-effective when it is performed sequentially, when the information is used for more than one pregnancy, and when the intention of the couple is to identify and terminate affected pregnancies.

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Economic Evaluation of Cystic Fibrosis Carrier Population Screening

Peter T. Rowley, M.D., Starlene Loader, and Robert M. Kaplan, Ph.D.

Questions about the cost and effectiveness of medical care have attracted considerable attention to medical outcomes research. In 1993, the Department of Health and Human Services appointed a multidisciplinary group of methodologists to recommend standardized strategies for the evaluation of health care. The panel's report, released in 1996,[1] suggested that standardized outcome analysis be conducted to evaluate the cost-effectiveness of medical services and screening tests. These analyses require preference-weighted measures of health-related quality of life. Cost-utility methods that consider years of life produced or quality adjusted life years (QALYs) may suggest different policies than do human capital methods that value benefit in monetary terms. In this project, we evaluated the cost-effectiveness of carrier screening for cystic fibrosis (CF) using both human capital and cost-utility methods.

The cloning of the cystic fibrosis transmembrane conductance regulator (CFTR) gene has made averting the unwanted birth of offspring with CF technically possible. Two large trials designed to determine the consequences of offering CF carrier testing to pregnant women—one in northern California[2] and the other in New York State[3,4]—have provided some evidence of its feasibility in the United States. Therefore, we have undertaken an economic evaluation of such screening.[5] For this analysis, the costs we used were estimates of national averages, but the probabilities in terms of patient preferences were derived from the Rochester clinical trial.[6]

The care of a child with CF entails both direct medical costs (estimated at $10,000 per year) and indirect (i.e., parental caregiving) costs (estimated at $9,005 per year). If the average life span is 28 years, the lifetime costs are thus $532,134. Discounting at 5 percent reduces this amount to $283,136 in today's dollars.

The cost of averting the birth of a single unwanted child with CF through prenatal carrier screening of the population at large was calculated to be $961,427. If the discounted savings in medical care costs averted ($283,136) is subtracted, the net cost of screening per CF birth averted is $678,291. Thus we estimate that only 29 percent of the total cost of population screening is recovered in terms of savings of discounted medical costs for the care of children with CF whose birth is likely to be averted by screening.

The above calculation assumes that a pregnancy terminated for CF is not replaced. In fact, it is likely that a couple who terminates a pregnancy for CF will conceive again and use prenatal diagnosis again. Such replacement does not greatly add to the cost of screening because at-risk couples constitute such a small fraction of all couples. However, if one calculates benefit in terms of the total number of years of life expected for the family unit (the "human capital" approach), replacement makes an important difference; that is, the total number of years of life expected for the family is higher when the test is offered than when it is not offered because the replacing pregnancy is more likely than not to produce a healthy child.

A disease's toll is not only the cost of care but also the burden of suffering the disease imposes. Thus the benefits of disease prevention should also account for the prevention of this suffering. To

estimate the burden of having a child with CF, we asked members of families containing a child with CF to evaluate the quality of their lives using the time-trade-off method. Compared with a value of 1.0 for perfect health, the estimates derived for quality of life were 0.90 for the mother, 0.95 for the father, and 0.70 for the affected child. These values permit converting expected life years to QALYs. This quality adjustment had the effect of further increasing the preference of offering testing over not offering testing.

Our analyses proved to be very sensitive to the cost of the screening test. Test cost is likely to decrease in the future becaue of improved technology. To a lesser degree, our analyses were sensitive to the cost of offering the test, to its sensitivity, and to the probability of a carrier's partner being tested, of the at-risk couple using prenatal diagnosis, and of the at-risk couple terminating the pregnancy if the fetus is affected. Factors having little effect are the cost of care of a CF child and the costs of carrier counseling, of abortion, and of a normal delivery.

A different method of evaluating health services is to ask individuals how much they would be willing to pay for a service. Even though the test was offered free of charge, all the women tested in the Rochester study were asked how much they would be willing to pay for the test once the test had been explained. Seventy-seven percent said $0–$25, far below the present test cost. However, to some extent, this low valuation may represent a lack of familiarity with the costs of medical laboratory tests, rather than a lack of interest in learning one's CF carrier status.

In the Rochester trial, even with free testing and counseling, screening provided very incomplete coverage of the population. The probability that a fetus with CF carried by a woman in our region during the period of study would have been detected in our trial can be calculated as the following product:

The proportion of providers offering screening = 30 %

– the proportion of pregnant women offered screening who accepted it = 57%

– the probability of a carrier being detected by the test used = 75%

– the proportion of pregnant carrier women having their partners tested = 93%

– the proportion of at-risk couples who accepted prenatal diagnosis = 80%

= 8.5%.

Thus only about 1 in 12 CF fetuses would have been detected.

The above analysis identifies three factors principally responsible for the low fetal detection rate, viz. provider reluctance to offer the test, test insensitivity, and patients choosing not to be tested. Provider reluctance to offer the test, the most important single factor, was the most surprising, especially because testing and counseling were provided free of charge. The second factor, test sensitivity, has since improved; commercial testing is now available for 70 mutations with 90 percent sensitivity, albeit at a higher cost. However, insofar as our 57 percent patient acceptance rate was based on understanding the significance of the test being offered, one cannot wish it were higher. The leading reason women gave for declining testing was they would not terminate a pregnancy even if the fetus had CF. The foremost purpose of prenatal screening is not to reduce the incidence of genetic disease but to fulfill couples' reproductive goals.

Because screening generates a net cost, rather than a net saving, how does its cost compare with that for other health care services? Under the base case assumption, screening costs $24,881 per QALY. If the cost of the test should fall to $20, the cost per QALY would be only $8595; advancing technology makes a reduction in test cost likely, especially if test volume rises. Costs between $20,000 and $100,000 per QALY are commonly regarded as reasonable health expenditures. Thus expending health care dollars on population carrier screening of pregnant women for CF may be a reasonable investment of health care resources.[7]

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Making the Case for Offering Cystic Fibrosis Carrier Testing on a Population Basis

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The basic facts regarding the genetics and reproductive counseling issues surrounding population-based carrier screening for cystic fibrosis (CF) were obvious prior to the cloning of the gene, and many geneticists, CF caretakers, ethicists, and others held significant prior opinions regarding the desirability of such screening. In many instances, divergent opinions remain unchanged and are little affected by activities such as pilot studies.

With the cloning of the CF gene, certain technical issues became clear, such as the frequency of various mutations and the feasibility of achieving various levels of sensitivity for detecting carriers (i.e., percent detection of carriers by mutation analysis). Various laboratories test for from 6 to more than 60 mutations with testing for 20–30 being typical to achieve around 90 percent detection of carriers in most populations. A detection rate of 90 percent translates to an 81 percent detection of couples at risk for bearing a child with CF. The specificity of mutation testing is close to 100 percent (i.e., individuals with well-defined pathologic mutations are CF carriers).

What follows is a series of observations and opinions reflecting major biases of the author. First, CF remains a burdensome disorder with major morbidity and mortality, and the future of treatment is uncertain, with either a virtual cure or serious setbacks due to drug-resistant bacteria both being possibilities. Second, most or all families would prefer to have healthy children rather than children with CF, if there were an ethically acceptable and cost-effective ability to achieve that end. Third, a major determinant affecting attitudes regarding CF screening is differences of opinion regarding the use of selective termination of pregnancy as an avoidance strategy; if there were a cure for CF that could be implemented only during the second trimester, no consensus conference would be needed and screening would be universal. Fourth, the inability to identify 100 percent of at-risk couples is not a relevant argument against the option of identifying the great majority of couples at risk. Fifth, cost will be a major impediment to screening, but individuals and health care providers can consider this factor in deciding whether to opt for testing. Finally, given the above views, individual autonomy should outweigh paternalism, and educational materials should be developed and made available on a population basis to allow individuals to select between two moderately presented positions to accept or decline screening.

Pilot studies and major screening programs around the world have provided significant data. Although testing prior to conception is theoretically preferable and should be encouraged, a major proportion of testing is likely to occur during a pregnancy for the current generation. In studies, acceptance of screening in the population varies widely from extremely low to extremely high. Opting for testing is greater when there is an ongoing pregnancy, when testing is convenient, and when testing does not involve out-of-pocket costs. Identifying one partner as a carrier with the other partner untested during a pregnancy is an anxiety-provoking situation requiring counselor time. Testing of partners simultaneously eliminates this occurrence. Large numbers of couples have one partner identified as a carrier and the other partner with a negative test. This equates to about a 1:960 chance of a CF birth and does not elicit major anxiety; these couples could be dealt with through written and video counseling, and their education supplemented by telephone access to a counselor.

If population-based testing is to be offered as an option, it would be desirable to identify the maximum number of interested carrier couples for the least cost and to maximize the sensitivity for detection of carrier couples. Encouraging the testing of relatives of known carriers (cascade testing) is an attractive option, recognizing that a positive family history of an affected individual or of a carrier identified by screening is of equal significance. For couples where one partner is a carrier, an attractive option is more intensive testing of the partner with the negative test result, by testing for a larger number of mutations or even sequencing all coding regions of the gene as technology improves. Modest improvements in technology are likely to increase the detection rate and decrease the cost as high-throughput strategies and DNA chip-based methods become more widespread. If 95 percent detection of carriers could be achieved, 90 percent of at-risk couples could be identified and couples with one positive test and one negative test would have a 1:1920 chance of having a child with CF. If carrier testing becomes widespread, in future generations the offspring of couples who had undergone carrier testing would preferentially seek testing if either parent were identified as a carrier, and testing would be more likely to occur prior to conception. This already occurs for Tay Sachs testing in the Jewish population. If the cost and technology for preimplantation diagnosis became more favorable, a larger proportion of couples might opt for carrier testing. If a therapeutic breakthrough occurred, a smaller proportion of couples would opt for testing.

Given the broad range of opinions and the personal aspects of reproductive choices, an attractive plan would be to develop written, video, and other educational materials contrasting the issues in favor of screening and the issues against screening. I would advocate providing this information on a population basis, encouraging individuals and couples to identify with one or the other position. Based on precedent with other reproductive options, it appears unjustified to fail to inform the population of the availability of carrier testing for CF.

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A Standard of Care for Cystic Fibrosis Carrier Screening: Satisfying Equity and Autonomy

Neil A. Holtzman, M.D., M.P.H.

Equity for people wanting to avoid the conception or birth of a child with cystic fibrosis (CF) would be achieved by offering CF carrier testing on a populationwide basis and ensuring access. This might reduce equity for society as a whole, however. If high utilization of CF carrier screening increased short-term health care costs, insurance premiums could go up and fewer people would be insured. Alternatively, health insurers could decide to forgo covering some other service in order to contain costs; equity for those benefiting from that service would be reduced.

Sometimes, satisfying the principle of autonomy contributes to societal equity. Acting autonomously, so few people might be interested in CF carrier screening that health care costs would not rise sufficiently to increase insurance premiums or displace other covered services. Eliciting individual preferences for nonessential interventions for many diseases might reveal that not all consumers will choose all of them or even those that providers believe to be most promising. In this paper, I will answer three questions bearing on autonomy and equity: (1) How can autonomy be assured in providing CF carrier screening? (2) How great is interest in CF carrier testing? (3) What factors influence health insurers' coverage decisions? I will conclude by presenting a standard of care for CF carrier testing.

Autonomy

To act autonomously, people must be given sufficient information to make rational decisions in accordance with their values and concerns. The first step is finding out what people deem important. In developing educational material for CF carrier screening, we first asked consumers to rate the importance of several different questions. The three most important were, "What are my chances of being a carrier?," "What is the cystic fibrosis carrier test?," and "What are my chances of having a child with CF?"[1] In designing an educational brochure for our pilot study, we answered these questions more or less in order of importance to consumers.[2] From our pilot study, we learned additional factors that were important. The most powerful predictor of people's decision to have the test was their tolerance for test uncertainty; that is, those who would take a hypothetical (non-CF) test even if it had false negative and/or false positive results were almost four times more likely to decide to have the CF carrier test than those who would not take a test that gave erroneous results.[3,4] In our educational brochure, we indicated that the CF carrier test detects about 85 percent of carriers among Caucasians.

To reach an autonomous decision about CF carrier testing, people also need to know if the outlook of the disease is likely to change. Prognosis of CF has improved markedly. Clinical trials of gene therapy are under way. Having an effective treatment might, as in the case of phenylketonuria, reduce interest in carrier screening. To decide autonomously on CF carrier screening, potential parents need to be told how current research could improve the outlook of children born soon with CF and of the families of those children.

Interest in CF Carrier Screening

CF Consortium and other studies suggest that interest in CF carrier testing is low among nonpregnant populations and higher among pregnant women, but still not universal.[5] In many of the Consortium studies, people were not charged for the test. If they had to pay, interest might have been lower. Higher acceptance rates among both nonpregnant and pregnant women are observed when the offer of testing is least intrusive and most convenient. Unfortunately, this often means less opportunity to present information to permit autonomous decisions. Given the opportunity to exercise their autonomy, people increasingly may decide that carrier screening, prenatal diagnosis, and pregnancy termination are inappropriate.

Health Care Coverage

Schoonmaker et al.[6] have examined the factors that influence private health insurers in making hypothetical coverage decisions regarding CF. Thirty-nine percent of insurance decisionmakers said they would cover carrier screening of all pregnant women. If the sensitivity of testing increased from 85 percent to 100 percent, if the cost fell from $40 to $5, if the American College of Obstetricians and Gynecologists endorsed testing, and if consumer and provider demand for the test increased, coverage increased to 60–65 percent. Insurance decisionmakers are not much less interested in finding ways of improving treatment for CF than they are in carrier screening. Twenty-seven percent of decisionmakers said they would cover the medical costs of a clinical trial of gene therapy in asymptomatic children with CF. Coverage increased to about 50 percent if the trial was in symptomatic adults, or could be done in an outpatient department, and to 75 percent when only one dose of gene therapy proved effective. Thus, lower costs are major determinants of coverage, but so are evidence of effectiveness and professional endorsement.

What Should the Standard of Care Be for CF Carrier Testing?

The responsiveness of health insurers to professional endorsement of new technologies makes the conclusions of this consensus panel extremely important. I propose the following standards:

– CF carrier screening should be offered to people of reproductive age, *provided* that a full description of the benefits, risks, and implications of carrier testing, as well as of the progress that has been made in the treatment of CF, precedes or accompanies the offering.

– Offering should be accomplished in as nondirective a manner as possible with a combination of written, visual, and personal (face-to-face) approaches.

– Signed informed consent for CF screening, or refusal, should be obtained.

Three other conditions must be met to satisfy the standard of autonomy. They should be included in policy statements. First, as long as there is evidence that truly informed consent has been obtained, providers should not be liable if a person or couple has a child with CF after declining carrier testing. As evidence of being truly informed, the score on a brief quiz on CF carrier testing should be part of documentation of refusal (as well as consent). When low scores raise doubt about how well informed the person is, the provider should document that additional educational efforts were made before accepting the person's decision. Second, the care of children born with CF whose parents declined to be screened should be reimbursed or paid for to the same extent as other chronic illnesses for which carrier screening or prenatal diagnosis is not an option. Without such coverage, people, particularly those with limited means, may decide that they have no choice but to avoid the conception or birth of a child with CF.

Third, research to discover means of preventing the devastating effects of CF in those born with it should receive high priority in order to reduce reliance on avoidance options.

If these polices are implemented, carrier testing by the most sensitive methods in quality-assured laboratories should be reimbursed. A more difficult question is whether screening should be targeted to pregnant women and their partners. They are in a sense a vulnerable population, expecting and wanting a healthy baby and having limited time to make decisions. Offering carrier testing in pregnancy may not give women sufficient time to appraise the benefits and risks of carrier testing and how it fits with their own values. Although largely due to the inconvenience of testing at a time when it is not urgent, the lower acceptance rates of CF carrier testing in nonpregnant people planning to have children may also reflect that well-informed people, who are under little pressure to make a decision, conclude that testing is not appropriate. Whether this is the case is an urgent question for research.

At a time when prenatal testing is becoming possible for a widening array of adult-onset diseases, or merely *risk* of such diseases, a society that claims to value diversity needs to consider the extent to which eugenic approaches should be encouraged. Such consideration is germane to CF carrier screening. Survival of people with CF extends well into adulthood. The outlook for children born with CF today may be considerably better yet. One way of encouraging consideration at the individual level is to let people decide on carrier testing under circumstances in which they are fully informed and not under pressure to decide quickly—that is, before pregnancy. (This also provides more options and was the initial approach taken for Tay-Sachs carrier screening.) Offering screening to nonpregnant, child-planning people satisfies equity for CF. Offered under conditions that permit autonomous decisionmaking, it may not have high uptake and may not, therefore, diminish societal equity. Ideally, people should be asked to choose which among competing health care interventions they would like to cover, and that should determine what is covered and what is not.

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Normative Issues in Developing Public Policy for Cystic Fibrosis Carrier Testing

Benjamin S. Wilfond, M.D.

The central policy question before this panel is whether there should be routine testing for cystic fibrosis (CF) carrier status in the general population. Health policy decisions about genetic testing are the result of clinical, sociopolitical, and ethical considerations. These considerations can be evaluated by viewing them through two complementary models: the extemporaneous model and the evidentiary model.[1] Each model describes a mechanism by which new clinical interventions become routine. While most health policy decisions reflect features of both models, examining the implications of each model can be useful in understanding the basis of public health policy decisions about new interventions.

The Extemporaneous Model

The extemporaneous model is descriptive and acknowledges the role of the various stakeholders advocating for their interests. These stakeholders may include the general public, patients, advocacy groups, clinicians, researchers, insurers, state health departments, and biotechnology companies. In the extemporaneous model, these forces interact to determine the standard of care on the basis of who can most effectively advocate for their particular position. The decision to begin phenylketonuria testing in the early 1960's, without clear evidence of clinical benefit at the time, is an illustrative example, as was the decision by the American College of Obstetricians and Gynecologists (ACOG) to recommend maternal serum alpha tetoprotein (MSAFP) testing in 1985, on the basis of potential legal liability for its memberships.[2] Those who predicted that CF carrier testing was inevitable in the early 1990's may have been relying on such a model.[3]

The Evidentiary Model

The evidentiary model is prescriptive, and refers to an explicit approach to health policy decisions. The first point of this model is that empirical data are necessary prior to a health policy decision. There has been an emerging interest in making health policy decisions on the basis of empirical evidence. In fact, this is precisely what has been happening in the United States regarding CF carrier testing.[4]

However, the thrust of this model is that while adequate empirical evidence is necessary, it is insufficient because of normative assessments that must also be completed. Normative assessments refer to decisions about the value of the intervention. Such decisions about value cannot be determined quantitatively but require considered ethical judgments about what is good.

Yet there is no clear agreement about the nature of the good in our pluralistic society.[5] The evidentiary model suggests that such decisions be made procedurally with a process that involves public representation. The standard of care can be determined by this process. Since the evidentiary model still involves advocacy by interested parties, it may not seem too different from the extemporaneous approach. But, it is distinguished by the explicit attention to empirical data and the normative evaluations as the substantive focus of the process.

If we consider this panel as reflecting this evidentiary model, it implies that conclusions of the panel cannot be based solely on quantitative assessment of the data. Instead, it requires a consideration of the underlying normative assumptions of the studies themselves, as well as the normative issues of the

decisions about population carrier testing for CF. This panel has heard and read most of the empirical data. I would like to focus on the normative issues that the panel must also consider.

Normative Issues

The success of genetic testing for CF carriers must be measured in relation to its goals. It is popular to articulate the goal as improved reproductive decisionmaking, and not as a reduction in births of affected individuals.[6] This emphasizes the importance of autonomy in reproductive decisionmaking. This also may serve to distinguish this goal from those goals with a more overt eugenic connotation.

Yet in this context, reproductive choice may only be a euphemism for abortion. Public policy related to reproductive genetic testing requires some expectation that people will avoid the birth of a child with the condition. For example, a program that is successful in informing people about CF carrier status but does not result in a decrease in the number of births of children with CF or otherwise save money associated with CF care, is not likely to be considered a high priority in a health care system with many unmet needs.

Therefore, serious consideration of a policy decision supporting population testing for CF is premised on an assumption that it is ethically appropriate to terminate a fetus with CF. The issue is not the policy question of whether abortion should be permissible, but rather the personal ethical issue of whether this is a good reason for abortion. Public support is less likely for a testing program related to a condition for which most people would agree that a decision to abort would be morally suspect. To illustrate this, we can note the controversy over sex selection, or imagine the detectability of a genetic marker linked to aptitude in math. Even if there were consensus that people should be allowed to abort a fetus for any reason, some might be troubled by people who would choose abortion because their child may never be able to balance a checkbook. There would be little interest in promoting testing to identify fetuses with this problem. At the very least, this is because, while society might permit abortion for this reason, it may not wish to socially encourage or financially support this reason. This is the primary normative question before the panel. Is CF the type of condition for which abortion should be implicitly promoted by a recommendation of population testing?

The empirical data that have been presented demonstrate a range in interest in carrier testing, prenatal diagnosis, and abortion. This, in part, may reflect the variation of these research participants' normative stance on this issue, but it may also be related to elements of the study design. People are more interested in testing if it is convenient or presented by a physician, or if there is an existing pregnancy.[7] These data are important to consider in marketing, if one were interested in maximizing the uptake of testing. Yet, it is difficult to interpret the normative meaning of the decisions made by subjects in the studies, as these decisions are partially based on the information provided. Different studies emphasize different aspects of CF in the informational materials.[8] Some brochures have highlighted the medical risks of CF, while others focused on the voluntary nature of the decision about testing. The variation of the informational materials may reflect different answers to the following normative question. While people with CF, as a group, have shorter life spans, is the experience of life with CF so unpleasant, per se, that people with CF, their families, and society would be better if such pregnancies were terminated?

A related normative issue is how much information should be presented during the informed consent process. For example, should people be told about the potential for insurance or employment discrimination? None of the studies reported such problems. But this is still a potential issue and its acknowledgment will discourage some from being tested.[9] This question can be resolved by considering whether a reasonable person would wish to know about the potential for discrimination.[10] This normative

question may also be influenced by the decisionmaker's stance about the goals of testing. In other words, an emphasis on the risks of testing may reflect an assumption that testing should not be promoted, and on the other hand, an emphasis on the benefits may reflect an assumption that testing should be done.

Policy Implications of the Normative Meaning of CF Carrier Testing

Once the questions about the normative meaning of CF carrier testing and its goals are addressed, it allows policies, materials, and programs to be assessed within that context. As a clinician who cares for people with CF, I have met individuals who are doctors, and artists, as well as drug dealers, who believe that CF, per se, is not the defining characteristic of their being. It seems misguided that the value of these persons' lives should be based on the presence or absence of a disease such as cystic fibrosis. Thus, I find it difficult to implicitly, let alone explicitly, promote population testing that could send such messages. The policy implications of this answer can still acknowledge the importance of reproductive autonomy.

I still support the personal ethical decision to avoid bearing a child with CF that is made by those who choose carrier testing, prenatal diagnosis, and abortion. Whether it is 5, 25, or 75 percent of the public who hold this view, their views should be accounted for in any policy decision. This is because, even with advances in the treatment, CF poses at least the same qualitative burden as does an unwanted pregnancy.[11] And some proportion of the population will answer the normative question in the direction of testing, and abortion. The policy question is not just whether testing should be available for those who desire it but to the extent that routine offering of CF carrier testing itself could be received as a message that having CF is qualitatively different from the usual burdens and stresses of human existence,[12] should it be offered?

While offering usually refers to the provision of a service, it can also refer to the provision of information. This distinction is subtle. There is a middle ground that would allow those who are interested in CF carrier testing to become informed and make this choice, without having to develop a policy that would endorse population CF testing with its potential eugenic implications.[8] People could be informed about the availability of CF carrier testing within the context of a checklist with brief descriptions of the diseases for which tests are available, rather than by a specific brochure for CF, as part of a routine provision of CF testing. Such an approach may be less likely to influence the level of population interest in CF testing, but it would be a way of informing those people who wish to specifically avoid the birth of a child with CF. The effectiveness of such an approach in providing information without such messages about the value of CF individuals being received has not been empirically tested.

Yet, this approach would be consistent with the less controversial policy to inform people with a family history of CF about the availability of carrier testing. Why is this policy less controversial? One reason cited is the sensitivity of the test.[13] However, test sensitivity is rarely the critical characteristic. Consider the problems of confusion, stigmatization, and discrimination with testing for sickle cell carriers with 100 percent sensitivity. A second distinction is the increased risk. Whether the risk is l:4 or l:30, it is not clear if this is the relevant difference, given the difficulties of the public in interpreting probabilities.[14] A more important difference may be that the acknowledged desire to avoid having a child with CF is less likely to be motivated from an effective marketing position but is instead based on the perceived challenges of the family member with CF. A checklist of testable genetic diseases would allow those people who have an independent desire to avoid a child with CF, whether at l:4 or 1:30 risk of being a carrier, to utilize this technology. Particularly because of the increasing number of conditions that can be detected prenatally, such an approach may serve as an ideal way to inform the public about a range of conditions, and yet send a more muted message about the conditional value of children. CF may be one of first diseases for which such policy questions must be answered, but it will certainly not be the last.

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