10/7/97**Genetic Testing for Cystic Fibrosis Consensus Development Conference Follow up Workshop**

October 15-16, 1997
Pooks Hill Marriott, Bethesda, Maryland

AGENDA

October 15, 1997

1:00 Welcome and Introductions

Francis Collins, M.D., Director, National Human Genome Research Institute (NHGRI)
Nancy Press, Ph.D., Co-chair, University of California, Los Angeles
Michael Mennuti, M.D., Co-chair, University of Pennsylvania Medical Center

1:15 Background to the Research Initiative
Elizabeth Thomson, M.S., R.N., ELSI Research Program, NHGRI

1:25 Consensus Development Conference Process
John Ferguson, M.D., Director, Office of Medical Applications of Research, NIH

1:35 Consensus Recommendations
R. Rodney Howell, M.D., University of Miami

2:00 Introduction to the Panel Presentations and Initial Organizational Responses to the Recommendations--Michael Mennuti, M.D.

2:15 Implications of Recommendations for Couples in the Prenatal Period Panel
Facilitator: Nancy Press, Ph.D.
Panel: Nancy Press, Ph.D., University of California, Los Angeles
Ellen Wright Clayton, M.D., J.D., Vanderbilt University Medical Center
David R. Witt, M.D., Kaiser Permanente Medical Group

2:45 Discussion

3:15 Break

3:30 Education, Counseling and Informed Consent Issues Panel Presentation
Facilitator: Nancy Press, Ph.D.
Panel: James R. Sorenson, Ph.D., University of North Carolina

Benjamin S. Wilfond, M.D., University of Arizona Health Science Center
Barbara A. Bernhardt, M.S., Johns Hopkins University School of Medicine
Joanna H. Fanos, Ph.D., California Pacific Medical Center Research Institute
Suzanne Tomlinson, J.D., CF Consumer

4:30 Discussion

5:30 Adjourn

<u>October 16, 1997</u>

8:00 Variations in Penetrance & Prevalence and Implications for Various Populations
Facilitator: Michael Mennuti, M.D.
Panel: Muin Khoury, MD., Ph.D., Centers for Disease Control and Prevention
Garry R. Cutting, M.D., Johns Hopkins University School of Medicine
Christine M. Eng, M.D., Mount Sinai School of Medicine
Charmaine Royale, Ph.D. National Human Genome Research Institute

8:45 Testing Strategies & Fiscal Implications
Facilitator: Michael Mennuti, M.D.
Panel: Peter T. Rowley, M.D. University of Rochester School of Medicine
David A. Asch, M.D., M.B.A., University of Pennsylvania Medical Center
Michael Watson, Ph.D., Washington University School of Medicine

9:25 Discussion

9:45 Break

10:00 Implications of Recommendations for Primary Care Providers
Facilitator: Michael Mennuti, M.D.

10:15 Organization Responses and Discussion

11:15 Working Group Session
Provider Challenges
Consumer Needs

12:30 Working Lunch
Progress Reports and Discussion Between Working Groups

1:30 Working Group Session (continued)

3:00 Break

3:15 Presentation of Working Group Recommendations and Discussion

4:45 Next Steps
Michael Mennuti, M.D.
Nancy Press, Ph.D.

5:00 Adjourn

Genetic Testing for Cystic Fibrosis Consensus Development Conference
Follow up Workshop

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ANNOTATED PRELIMINARY AGENDA

October 15, 1997

1:00 Welcome and Introductions

Francis Collins
Nancy Press
Michael Mennuti

1:20 Background to the research initiative
Elizabeth Thomson

1:40
Consensus Development Conference process
John Ferguson

1:55 Consensus Recommendations
Rod Howell

2:15 Introduction to the Panel Presentations and Initial Organizational Responses to the Recommendations--Michael Mennuti

2:30 Implications of recommendations for couples in the prenatal period
Panel Presentation and Discussion--Nancy Press (facilitator)
Nancy Press (structural factors)
Ellen Wright Clayton (demand)
David Witt (managed care implications)
TBA (implications for various populations)

3:15
Discussion

3:45
Break

4:15
Education, Counseling and Informed Consent Issues
Panel Presentation and Discussion--Nancy Press (facilitator)
Jim Sorenson (how patients learn)
Ben Wilfond (existing CF ed. materials)
Barbara Bernhardt (informed consent)
Joanna Fanos (implications for the family)
Suzanne Tomlinson (implications for adults with CF)

5:00
Discussion

5:30
Adjourn

October 16, 1997

8:00
Implementation Issues in GeneticTesting for CF

8:00
Variations in Penetrance & Prevalance and Their Implications for Various Populations
Garry Cutting--tentative (Overview)
Christine Eng (Implications for specific populations)
TBA (Historical perspectives and implications for specific populations)

8:35
Testing Strategies & Fiscal Implications
Peter Rowley (Summary of research)
David Asch (Cost/Benefit analysis)
TBA (Insurance Industry Perspectives)
Muin Khoury (Public Health Implications)

Discussion

9:40
Implications of recommendations for primary care providers
Michael Mennuti (facilitator)
Dr. Mennuti will coordinate this session which will include comments from primary care group representatives (5 minutes each) and a discussion/presentation on some of the key issues that will need to be considered. Dr. Mennuti will end the session with a charge to the working groups.

9:55
Organization Responses

10:15 Break

10:30
Organization Responses (continued)

10:40
Discussion

11:00
Working Group Session
Provider Challenges
Consumer Needs

12:00
Working Lunch (Progress Reports and Discussion with both working groups)

1:30
Working Group Sessions (continued)

3:00 Presentation of Working Group Recommendations and Discussion

4:45 Next Steps
Michael Mennuti
Nancy Press

5:00 Adjourn

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(one page description)

Followup Workshop Exploring the Recommendations of the Consensus Development Conference on Genetic Testing for Cystic Fibrosis

Background: An NIH Consensus Development Conference on Genetic Testing for Cystic Fibrosis was held on April 14-16 of this year. After weeks of preparation, two days of scientific presentations and intense deliberations, an independent, non-governmental consensus panel recommended that genetic testing should be offered to "adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal testing." (Consensus Statement enclosed). The panel did not recommend offering the test to the general population or to newborn infants. In recognition of the fact that this is the first time

that a recommendation has been made to offer genetic testing for CF to a large number of individuals in the prenatal period, the panel concluded that, "It is essential that the offering of CF carrier testing be phased in over a period of time in order to ensure that adequate education and appropriate genetic testing and counseling services are available to all persons being tested."

These recommendations mark a distinct departure from previous recommendations made by genetic and health professional organizations and will require careful consideration. To facilitate this process, the National Human Genome Research Institute, the NIH Office of Rare Diseases, the Agency for Health Care Policy and Research and the Centers for Disease Control and Prevention in collaboration with a number of other NIH institutes and health professional organizations, will hold a workshop October 15-16, 1997, in Bethesda, Maryland.

Purpose: The purpose of this meeting will be to bring together representatives of relevant health care and genetic organizations, researchers and consumers to examine the recommendations from the Consensus Development Conference on Genetic Testing for Cystic Fibrosis. Participants will come prepared (on behalf of their organization) to discuss the implications of these recommendations for their members' future clinical practice and will communicate the outcomes of this meeting back to their organizations. It is hoped that as a result of this meeting, organizations will be better able to develop appropriate and consistent guidance concerning if, when, and how these recommendations should be implemented.

Dates: October 15 (1pm to 6pm)
October 16 (8am to 5pm)

Structure: The first few hours of the meeting will be devoted to a discussion of the NIH Consensus Development process and the recommendations made by the panel. The remainder of the meeting will focus on the implications of these recommendations for health care providers and consumers. It is anticipated that two working groups will be formed to examine the feasibility and possible development of specific educational and practice guidance related to the recommendations. The outcomes of the working group deliberations will then be presented to the entire group for discussion and further refinement.

Co-chairs:
Michael Mennuti, M.D., Department of Obstetrics and Gynecology,
University of Pennsylvania Medical Center
Nancy Press, Ph.D., Department of Psychiatry and Biobehavioral Sciences
University of California, Los Angeles

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Human Genome
Research Institute
38 Library Drive MSC 6050
Bethesda, MD 20892-6050
Ethical, Legal, and Social Implications
Research Program
Building 38A, Room 617

October 6, 1997

Kathy Hudson, Ph.D.
Director, Office of Policy Coordination
National Human Genome Research Institute
National Institutes of Health
Building 31, Room 4B09
Bethesda, Maryland 20892

Dear Dr. ~~Hudson~~ Kathy:

We are pleased that you will be attending the October 15 and 16, 1997 Followup Workshop to the Genetic Testing for Cystic Fibrosis Consensus Development Conference. The meeting will be held at the Pooks Hill Marriott in Bethesda, Maryland and will begin at 1pm on October 15 and conclude at 5pm on October 16.

The first few hours of the meeting will be devoted to a discussion of the NIH Consensus Development process and the recommendations made by the panel. The remainder of the meeting will focus on a series of panel discussions on the implications of these recommendations for health care providers and consumers. Following these discussions, on the morning October 16, we will divide into two working groups looking at: 1) Provider Challenges and 2) Consumer Needs. (A table summarizing the issues that each of these groups will address is attached.) The deliberations of these working groups will then be presented and discussed in a final session on the afternoon of October 16. (A copy of the workshop agenda is enclosed).

In preparation for the meeting, I have enclosed a copy of the complete statement of the Consensus Development panel, a copy of the program and abstract book for the Consensus Conference, and the conference bibliography. While the Consensus Development Conference will not be a focus of this workshop, this background information will be helpful as we consider the Consensus Panel's recommendations.

If you have questions or would like to discuss the meeting further, please call me or Joy Boyer at 301-402-4997.

Sincerely,

Elizabeth J. Thomson

Elizabeth Thomson, M.S., R.N.
Program Director, Clinical Genetics Research
ELSI Research Program
Enclosures

Ground Transportation Information:

Using the Metrorail System

The Metrorail System is clean, reliable, and safe. It operates from 5:30 a.m. to 12:00 midnight Monday through Friday and 8:00 a.m. to 12:00 midnight on Saturdays and Sundays. Each passenger must buy a farecard to travel in the system. Guides for buying a farecard are posted on the vending machines in each station.

- **From Washington National Airport to the Bethesda Marriott**
  Board the Metrorail Yellow Line to Gallery Place at the airport. Transfer at the Gallery Place Station to the Red Line to Shady Grove. Exit at the Medical Center Station and take the escalator to the street level. The Marriott Shuttle departs from the Medical Center Station every half hour beginning at 6:00 a.m. Travel time is approximately 45 minutes.

- **From Dulles International Airport to the Bethesda Marriott**
  Take a Washington Flyer van from the airport to the West Falls Church/Orange Line Metrorail Station. Board the train heading toward New Carrollton and transfer at Metro Center to the Red Line to Shady Grove. Exit at the Medical Center Station and take the escalator to the street level. The Marriott shuttle departs from the Medical Center Station every half hour beginning at 6:00 a.m. Travel time is approximately 1 hour.

- **From Union Station to the Bethesda Marriott**
  Take the Metrorail Red Line to Shady Grove. Exit at Medical Center Station and take the escalator to the street level. The Marriott shuttle departs from the Medical Center Station every half hour beginning at 6:00 a.m. Travel time is approximately 35 minutes.

Each Metrorail car features a complete color-coded map. Station attendants on duty at each station can provide additional information on request.

Airport Shuttles

From Washington National, Dulles International, and Baltimore-Washington International (BWI)
You may use Montgomery Airport Shuttle by making reservations at least one day in advance. Call 1-800-590-0000 or 301-590-0000 to make a reservation. The cost is $19 one way from National or Dulles Airport and $25 each way from BWI Airport.

From Baltimore-Washington Airport
You may use Airport Connection by reserving at least 2 days in advance. Call 301-441-2345 to make a reservation. The cost is $25 each way and takes approximately 50 minutes.

Taxi Service

From Washington National and Dulles International Airports
The taxi fare is approximately $35 from National, and $45 from BWI and Dulles.

By Automobile

South Bound
I-95 South to I-495 (Silver Spring). Follow I-495 West 9 miles to Exit 34 (Bethesda). Follow signs for Route 355 South (Washington/Bethesda) right hand lane. Turn left at traffic light. Turn right at light onto Pooks Hill Road. The hotel is on the right.

North Bound
I-95 North to I-495 (Fairfax/Frederick). Follow I-495 20 miles. Take Exit 34 (Wisconsin Avenue). At the first light turn right onto Pooks Hill Road. The hotel is on the right.

National Airport
Take the George Washington Parkway North 12 miles to the Capital Beltway (I-495). Take I-495 to Maryland 7.5 miles to Exit 34 (Wisconsin Avenue). At the first light turn right onto Pooks Hill Road. The hotel is on the right.

Dulles Airport
Take the Dulles Access Road 13 miles to I-495. Take I-495 to Maryland 10 miles to Exit 34 (Wisconsin Avenue). At the first light turn right onto Pooks Hill Road. The hotel is on the right.

BWI
See Southbound directions above.

Issues to be Addressed by the Working Groups

A major component of this Workshop are the Working Groups which are scheduled to meet for most of the meeting's second day. Below is an initial list of the topics that the Working Groups will examine. It is hoped that by the end of the two-day meeting, we will have recommendations in most of these areas. On some topics it is expected that these recommendations will comprise suggestions for implementation. On others, the recommendations may be for short-term, targeted follow-up research.

Provider Challenges	Consumer Needs
Central Issues: *To consider the continuum from "making tests available" to "offering tests." What is ideal? What is practicable? How can structural factors which shape consumer demand for testing be dealt with to enhance autonomous and informed decision-making?*	**Central Issues:** *What are the goals of prenatal testing? Is there agreement on these goals? Are there obstacles in the way of complete openness in educating potential test consumers about those goals and, if so, how might they be overcome?*
1. Challenges and solutions in implementing informed consent and educational protocols.	1. What should educational materials look like? What should the informed consent process look like?
2. Educational needs for providers	2. Educational needs for consumers
3. Cost effectiveness/cost utility issues	3. Cost effectiveness/cost utility issues
4. What services need to be covered in a CF screening program? (e.g. follow-up testing, genetic counseling) Who is going to pay for these services?	4. How can consumers be protected from risks of insurance and employment discrimination based on their decisions in regard to CF screening?
5. Should tests be offered in all populations? Test offering protocols (e.g. pregnant women versus couples) (disentangling issues of science and fairness)	5. Should tests be offered in all populations? Test offering protocols (e.g. pregnant women versus couples) (disentangling issues of science and fairness)
6. On-going quality assurance issues in population-based CF screening	6. On-going quality assurance issues in population-based CF screening

10/7/97

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5:30 Adjourn

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8:45 Testing Strategies & Fiscal Implications
Facilitator: Michael Mennuti, M.D.
Panel: Peter T. Rowley, M.D. University of Rochester School of Medicine
David A. Asch, M.D., M.B.A., University of Pennsylvania Medical Center
Michael Watson, Ph.D., Washington University School of Medicine
Insurance Industry Perspective -- TBA

9:25 Discussion

9:45 Break

10:00 Implications of Recommendations for Primary Care Providers
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Michael Mennuti, M.D.
Nancy Press, Ph.D.

5:00 Adjourn

IN PRESS

6/3/97 3:00 p.m.

NATIONAL INSTITUTES OF HEALTH

CONSENSUS DEVELOPMENT CONFERENCE STATEMENT

GENETIC TESTING FOR CYSTIC FIBROSIS

April 14–16, 1997

NIH Consensus Statements are prepared by a nonadvocate, non-Federal panel of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Abstract

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

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

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

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

Conclusions. Genetic testing for CF should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal testing. The panel does not recommend offering CF genetic testing to the general population or newborn infants. The panel advocates active research to develop improved treatments for people with CF and continued investigation into the understanding of the pathophysiology of the disease. Comprehensive educational programs targeted to health care professionals and the public should be developed using input from people living with CF and their families and from people from diverse racial and ethnic groups. Additionally, genetic counseling services must be accurate and provide balanced information to afford individuals the opportunity to make autonomous decisions. Every attempt should be made to protect individual

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

Introduction

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

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

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

1. What is the current state of knowledge regarding natural history, epidemiology, genotype-phenotype correlations, treatment, and genetic testing of cystic fibrosis in various populations?

2. 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?

3. 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?

4. What are the optimal practices for cystic fibrosis genetic testing (setting, timing, and the practices of education, consent, and counseling)?

5. What should be the future directions for research relevant to genetic testing for cystic fibrosis and, more broadly, for research and health policies related to genetic testing?

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

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

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

Natural History

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

Severity of lung disease is the key to the quality of and length of life. Ninety percent of persons who have CF die from pulmonary complications. Pulmonary function tests, especially forced expiratory volume (FEV_1), are predictive of mortality: when the FEV_1 is ≤ 30 percent, mortality is 50 percent in 2 years. Poor prognosis is related to respiratory complications before 1 year of age, malnutrition, and denial of the condition. Better prognosis is indicated from mild symptoms at diagnosis, pancreatic sufficiency, and atypical presentation. There are suggestions in the literature that early diagnosis and treatment may result in improved growth of young children; however, data are limited about whether early treatment decreases morbidity as measured by hospitalizations and pulmonary function tests and, ultimately, mortality rates.

Treatment

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

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

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

Epidemiology

Incidence

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

CF Mutation Analysis

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

TABLE 1

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

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

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

The proportion of detectable mutations is an important indicator of the utility of a population-screening program. Combining detection of the ΔF508 with other mutations common to specific ethnic groups, it appears that there are several populations for which 90–95 percent sensitivity can now be achieved with the current technology: Ashkenazi Jews, Celtic Bretons, French Canadians from Quebec, and some Native Americans. In Caucasians in the United States, it is feasible to approach 90 percent sensitivity at the current time. The detection rate in African-Americans is about 75 percent. Despite the relatively high incidence in Hispanics, the detectable alleles account for only 57 percent of the CF mutations in this group. The promise appears to be weak in Asian-Americans, at 30 percent sensitivity. Because the remaining mutations are rare, expanding the panel of screened mutations is expected to achieve only marginal gains in sensitivity.

Genotype-Phenotype Correlations

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

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

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

Genetic Testing in Various Populations

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

programs, all testing has been free of charge. Direct provider recruitment has proven more effective than less personal approaches.

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

Knowledge and Attitudes Toward Cystic Fibrosis and Genetic Testing

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

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

Public Interest and Demand

Notwithstanding the limits of public understanding of genetics and genetically related diseases, prospective parents have enormous interest in the health and well-being of children to be. In an Office of Technology Assessment survey of a decade ago, 83 percent of Americans said they would take a genetic test before having children, if it would tell them whether their children would likely inherit a fatal genetic disease. Many genetic counselors and nurse geneticists report that they are frequently asked about DNA-based CF tests. However, studies have shown that interest in CF genetic testing is limited in the general population, and that agreement to participate in genetic education and testing procedures occurs primarily among pregnant women and persons with positive family histories.

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

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

Risks

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

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

Impact and Effectiveness

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

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

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

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

Cost

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

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

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

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

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

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

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

3. <u>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?</u>

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

1. *Individuals with a family history of CF and partners of those with CF should be offered genetic testing.* As a group, individuals with a family history have relatively high

frequencies of mutations in the CFTR gene. Members of this group have increased awareness of their risk of being carriers, as well as increased familiarity with the disease and its impact on the family. Testing can be helpful with regard to reproductive decisionmaking and informative regarding family health.

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

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

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

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

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

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

4. <u>What Are the Optimal Practices for Cystic Fibrosis Genetic Testing (Setting, Timing, and the Practices of Education, Consent, and Counseling)?</u>

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

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

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

Timing for Testing Depends on Targeted Group

- In adults with a positive family history of CF, genetic testing should be provided at any time requested.

- Newborn siblings of patients with CF as well as other siblings who exhibit atypical symptoms should be tested. However, testing of minors for the purpose of identifying carrier status is not recommended.

- Carrier detection in pregnant couples with a family history of CF should be provided in an expeditious manner. Similarly, the request by a couple with known carrier status for prenatal diagnosis must be addressed promptly to facilitate access to all needed services so as to provide an optimal opportunity to make an informed decision.

- Couples in the prenatal population (i.e., those not in a high-risk group) should be offered the opportunity for carrier detection as early as possible to provide them time to consider the full range of informed reproductive decisions.

- The rationale for offering testing to couples currently planning a pregnancy is predicated on timely provision of balanced, accurate information about CF, including natural history of the disease, relative frequency in different ethnic and racial groups, variability of disease manifestation, and availability of highly sensitive and specific tests to determine carrier status.

- Although most males who have CF are sterile, partners of persons with CF should be tested on request for carrier status. The highest practical level of sensitivity of the DNA test should be used to maximize detection of at-risk couples.

Education

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

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

Educating patients and families can be accomplished by utilizing a wide variety of printed materials and media, including videos and interactive on-line systems. At present, information

content is presented in a variable manner. It is recommended that effort be directed to develop model information that highlights the positive as well as the negative aspects of living with CF, using input from people living with the disease, their families, and members from diverse racial/ethnic groups.

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

Informed Consent

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

Counseling

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

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

Nondiscrimination

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

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

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

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

- As treatment options and screening technologies change, what are the impacts on medical costs, ancillary costs, and quality of life associated with CF? What are the cost-effective approaches to treatment and screening in different settings?
- What is the actual incidence of discrimination and stigmatization with respect to carriers, persons with genetic disorders, and their families? How does fear or anticipation of discrimination impact decisionmaking by some persons with identified genetic disorders?
- What is the most effective mechanism to educate health professionals about the current state of genetic disorders, genetic testing, and management of genetic disorders?
- What are effective educational strategies to educate the public and specific populations about genetics and genetic testing?
- What are patients' expectations of pretest education, genetic reproductive risk counseling, genetic evaluations, and transmittal of test results?
- Do early diagnosis and treatment of newborn infants with CF modify the morbidity as indicated by pulmonary function tests, maturation status, rates of infection, hospitalization, and mortality rates?
- A variety of screening strategies have been used in various studies (e.g., sequential versus couple screening). A systematic literature review should be undertaken, and, if warranted, a randomized controlled trial should be initiated to assess the relative merits of these strategies.
- Certain specific mutations appear to result in limited phenotypes, such as CBAVD. A goal of future research should be to continue to identify additional mutations, modifier genes, and environmental factors, and correlate these with the phenotype.
- Because CF is characterized by multiple mutations of the CFTR gene, this disease would be the prototype for the assessment of multiple methodologies to define numerous allelic mutations of a large gene.
- The optimal system for delivery of genetic services in rural and nonacademic settings should be studied.
- What are long-term effects of pregnancy termination or continuation on high-risk couples?

Conclusions and Recommendations

- Active research should continue on improved treatments for people with CF, enhanced molecular diagnosis of CF, and better understanding of the pathophysiology of CF.
- Over the past two decades, aggressive management of the pulmonary manifestations of CF and new treatment modalities have resulted in much longer survival.
- More than 90 percent of CF mutations can be identified in certain populations. Although generally good correlations exist between certain CF mutations and pancreatic status, it is known that CF mutations are not robust predictors of severity of disease and longevity.
- The goal of genetic testing is to provide individuals with information that will permit them to make informed decisions.
- CF genetic testing should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal testing.
- Comprehensive educational programs are recommended, utilizing a variety of media, for health care professionals and the public.
- Counseling services must be accurate and provide balanced information to afford individuals the opportunity to make autonomous decisions. Every attempt should be made to protect individual rights and genetic and medical privacy rights and to prevent discrimination and stigmatization.
- Access to genetic testing in the prenatal setting enhances the ability of couples to make reproductive choices, as shown by their interest in and use of the information they gain. The cost is reasonable in relation to the benefits obtained.
- Offering CF genetic testing to the general population or to newborn infants is not recommended.
- Genetic testing for many additional conditions will be available in the future. Some of the principles considered for CF genetic testing might well have broader application.
- It is essential that the offering of CF carrier testing be phased in over a period of time in order to ensure that adequate education and appropriate genetic testing and counseling services are available to all persons being tested.

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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., ΔF508, G542X, G551D, R553X, N1303K, W1282X, ΔI507). 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

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.

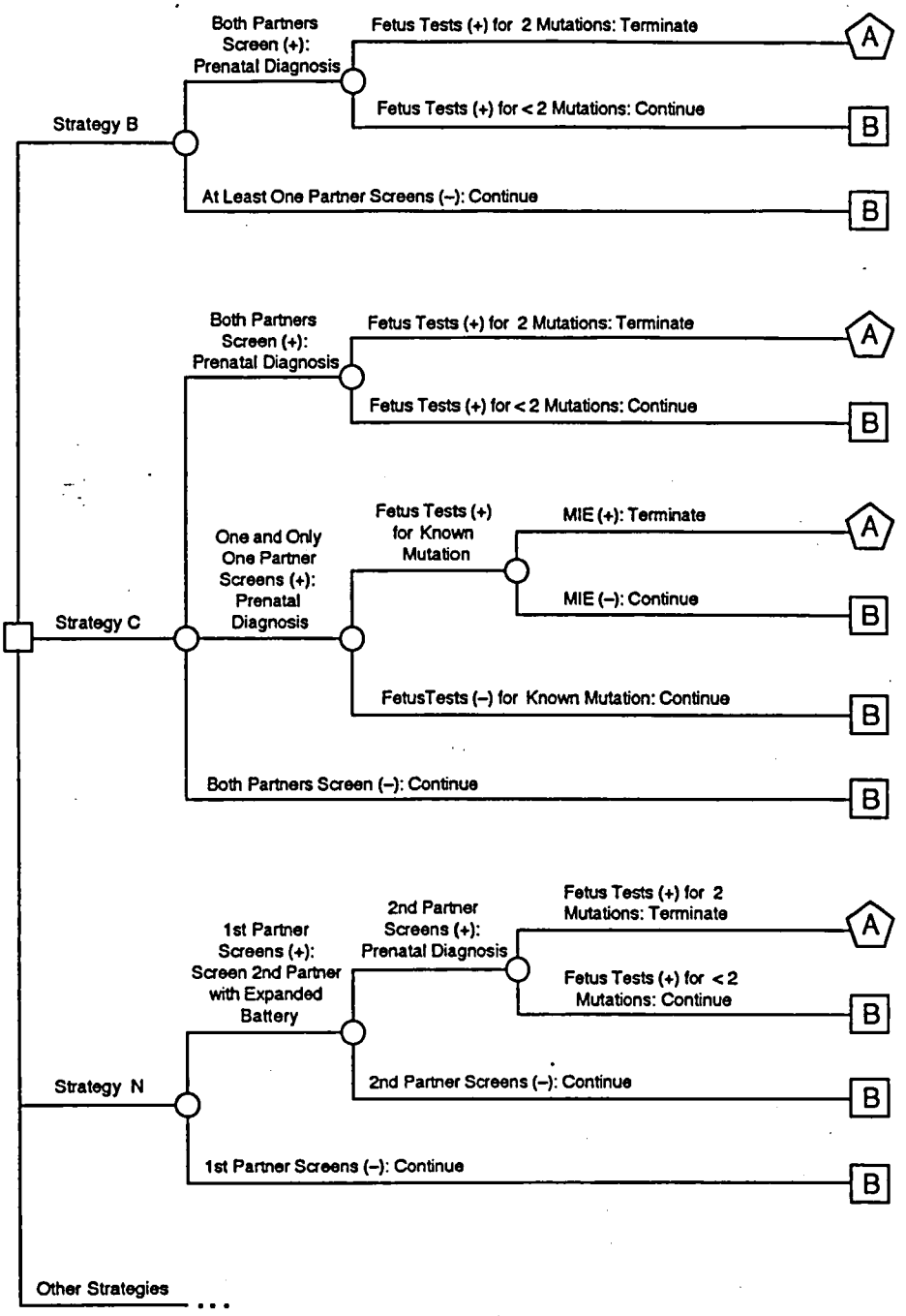

FIGURE 1. Three sample clinical strategies (B, C, and N from Table 1) expressed as a decision tree. The tree is read from left to right. The square node indicates a choice to be made among strategies. The round nodes indicate outcomes that result from chance. Each branch ends on a letter indicating a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

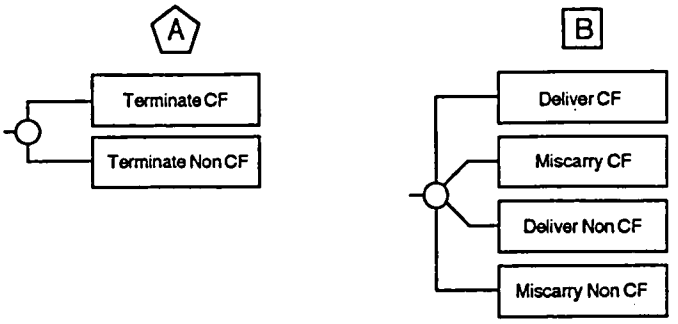

FIGURE 2. Two subtrees for Figure 1. Each pregnancy can either be terminated (subtree A) or continued (subtree B). If it is terminated, it might have led to the birth of a child with CF or without CF. If it is continued, it might lead to a miscarriage or to delivery, and in either case might be affected 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

Strategy	CF			Non CF			CF Births Avoided (rel. to A)	Total Cost	Cost Per CF Birth Avoided (rel. to A)
	Births	Abortions	Mis-carriages	Births	Abortions	Mis-carriages			
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.

significantly increased if couples plan two or more pregnancies. A central conclusion of this analysis is 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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