Thomson, Elizabeth (NHGRI)

From: Thomson, Elizabeth (NHGRI)
Sent: Monday, February 22, 1999 5:19 PM
To: Collins, Francis (NHGRI); Hudson, Kathy (NHGRI); Jordan, Elke (NHGRI)
Cc: Boyer, Joy (NHGRI); Saylor, Susan (NHGRI)
Subject: CF FU

The ACOG/ACMG/NHGRI CF follow up working group met last Thursday. The meeting went well. ACOG has a draft of their practice guidelines, which is virtually the same as it was last meeting. ACMG has drafted guidance about lab issues. The HG Education and Consent Committee has now drafted their educational brochure and consent form and have laid out the thinking behind it and the plan for some field testing. ACOG and ACMG seemed quite impressed with the work the HG group had done and asked if they could draft some "results" brochures for +/+, +/- and -/- results. Although there is interest in the group doing this, I am worried there won't be sufficient time to do them justice. We will see. All three groups are aiming to release this information jointly within the coming six months, I believe.

The commentary that Mike, Nancy and I worked on after the fall meeting (more than a year ago) is FINALLY coming out in the green journal in March. So much for quick turnaround. There is also another paper coming out in April which discusses the lack of adequate MD knowledge and preparation about this topic.

ACMG continued with its mixed messages. While they are moving ahead (begrudgingly) with their part of this guidance, they (Bob Desnick) proposed that this not become the standard of care until there was a "real world" pilot of CF genetic testing (while our research was helpful, it was not real world). The pilot should be carried out.....where else..., but in New York state. As he described it, it sounded like a demonstration project or maybe outcomes research, but he suggested that NIH should fund it (like the big amnio/CVS trials funded by HD). ACOG said that if Bob wanted to write a grant and do this project, fine, but ACOG had no intention of waiting for several more years to release their guidance to OBs. So this concept was basically nixed by the steering committee. Only after the meeting did I learn that ACMG's Board had also nixed this idea. The nixing of this proposal, however, was not communicated by Desnick or Pyeritz in their verbal/written report (but I was given a copy of a letter from Joe Leigh Simpson-who is on ACMG's Board to ACOG in preparation for this meeting. In it, he stated the ACOG should not believe that the ACMG Board supported the pilot project concept. Oh the intrigue.

Gary Cutting was at the and he did present a compelling case for the need to educate some real experts (say one or two folks in each state) who can handle the tough +/+ results. Although there won't be a huge number of them, there will be some and there need to be resource people available to help out. Gary says he will not be able to handle them all himself, as is the case right now. He reports that once or twice a week he gets a call from a couple asking for his help in interpretation of very complicated cases. This usually takes a couple of hours or more and he is very worried about what will happen when there are many more of these calls. We agreed that we need to consider some short courses for geneticists, genetic counselors, obstetricians, nurses, who are willing to learn this and be identified in the materials that are sent out as resource people. We may get a T15 or R25 application to do some of this. We will see.

I will be sending each of you a copy of the materials that I received at the meeting, the draft ACOG and ACMG papers, the Education and Consent materials and plan, and the Joe Leigh letter. Let me know if you have questions or comments.

Elizabeth J. Thomson, M.S., R.N., C.G.C.
Program Director, Ethical, Legal, and Social Implications Research

Cystic Fibrosis Steering Committee

February 18,1999
AGENDA

I. REPORTS

A. Clinical Practice Guideline and Provider Education

B. Patient Education and Informed Consent

C. Laboratory Standards

II. DOCUMENT COORDINATION

A. Publication process
1. Format of final publication - 3 reports combined or issued separately
2. Other supportive documents (eg. videos, pamphlets)
3. Document approval by participating organizations

B. Distribution
1. Organizational newsletter and journal articles
2. Annual meeting presentations
3. Media involvement and assistance
4. Speakers bureau
5. Post-graduate courses
6. Slides and script for Grand Rounds
7. Web-site links
8. Other

III. NEED FOR FUTURE MEETINGS

IV. ADJOURN

CYSTIC FIBROSIS ROSTER
Steering Committee

ACOG

Chair
Michael Mennuti, MD
Dept. of Ob-Gyn
Univ. of Pennsylvania Medical Ctr.
3400 Spruce Street
Philadelphia, PA 19104
Phone (215) 662-3234
Fax (215) 349-5893
e-mail: mmennuti@obgyn.upenn.edu

Sherman Elias, MD
Professor and Head
Department of Ob-Gyn
University of Illinois at Chicago
820 South Wood Street, M/C 808
Chicago, IL 60612
Phone (312) 413-2040
Fax (312) 996-4238
e-mail: selias@uic.edu

Michael Greene, MD
Dept. of Ob-Gyn
Massachusetts General Hospital
32 Fruit Street, FND 430
Boston, MA 02114-2696
Phone (617) 724-9013
Fax (617) 726-4267
e-mail: greene.michael@mgh.harvard.edu

STAFF

Stanley Zinberg, MD
ACOG
Division of Practice Activities
409 12th Street, SW
Washington, DC 20024-2188
Phone (202) 863-2500
Fax (202) 863-4909
e-mail: szinberg@acog.com

Nancy O'Reilly, MHS
ACOG
Division of Practice Activities
409 12th Street, SW
Washington, DC 20024-2188
Phone (202) 863-2557
Fax (202) 494-3993
e-mail: noreilly@acog.com

Patient Education Co-Chair

Nancy Press, PhD
3181 SW Sam Jackson Park Road
CB-669
Portland, OR 97201
Phone (503) 494-8257
Fax (503) 494-4981

James R. Sorenson, PhD
Health Behavior & Education Dept.
School of Public Health
University of North Carolina
Chapel Hill, NC 27599-7400
Phone (919) 966-3761
Fax (919) 966-2921
e-mail: james_sorenson@unc.edu

ACMG

Robert J. Desnick, MD, PhD
Department of Human Genetics
Mt. Sinai School of Medicine
100th St. & 5th Ave.
New York, NY 10029
Phone (212) 659-6700
Fax (212) 360-1809
e-mail: rjdesnick@vaxa.crc.mssm.edu

Lewis B. Holmes, MD
Genetics & Teratology Unit
Massachusetts General Hospital
32 Fruit Street, Warren Bldg. 801
Boston, MA 02114-2696
Phone (617) 726-1742
Fax (617) 724-1911
e-mail: holmes.lewis@mgh.harvard.edu

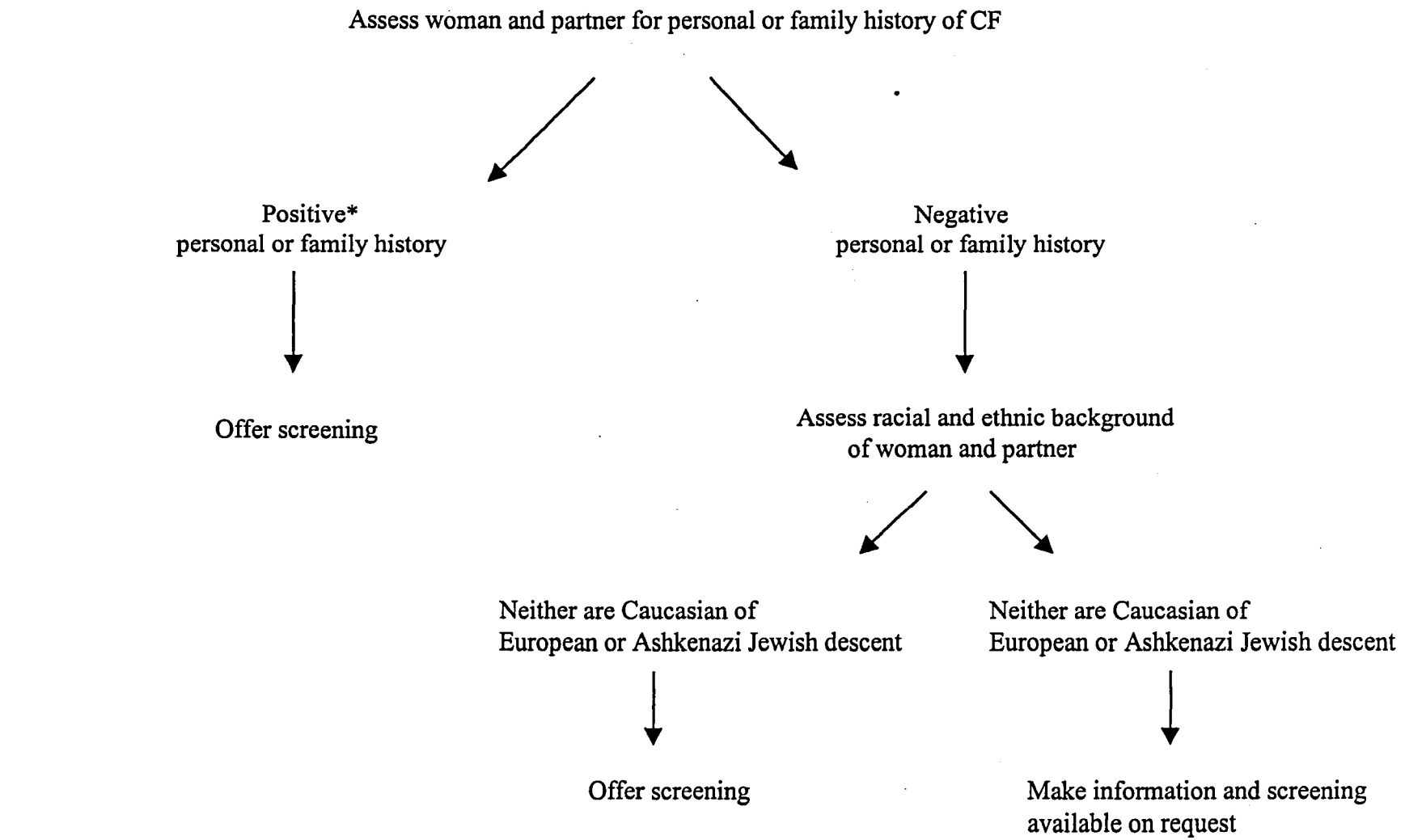
Reed Pyeritz, MD, PhD
Dept. of Human Genetics
Allegheny Univ. of Health Sciences
320 E. North Ave.
Pittsburgh, PA 15212
Phone (412) 359-6388
Fax (412) 359-6488
e-mail: pyeritz@pgh.auhs.edu

NIH

Francis S. Collins, MD, PhD
Director
National Human Genome
Research Institute
31 Center Drive
Bldg. 31, Room 4B09
Bethesda, MD 20892
Phone (301) 496-0844
Fax (301) 402-0837
email: fc23a@nih.gov

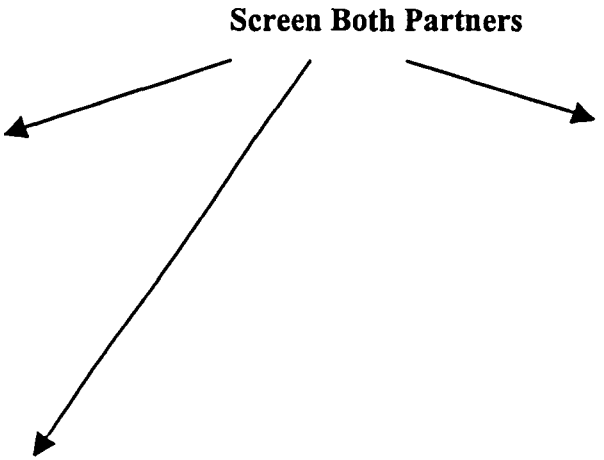
Elizabeth Thomson, MS, RN, CGC
ELSI-Research Program
National Institutes of Health
38 Ubany Drive
Bldg. 38A Rm 617
Bethesda, MD 28902-6050
Phone (301) 402-4997
Fax (301) 402-1950
e-mail:
thomsone@exchange.nih.gov

Implementation of Screening for CF



*consider referral for genetic counseling

Screen Both Partners Simultaneously



Both partners test negative

- Provide results
- Provide estimate of residual risk

One partner tests negative
One partner tests positive*

- Provide results
- Offer screening of negative partner with expanded panel of mutations
- Provide risk estimate for child with CF
- Offer family studies to partner with postive test
- Counsel to inform offspring of carrier risk (1/2 chance) when they reach reproductive age

Both partners test positive*

- Provide results
- provide risk estimate for child with CF (1/4)
- Provide counseling regarding CF severity, variability & treatment
- Provide infroamtion regarding limitations of prediction of phenotype
- Offer prenatal diagnosis
- Discuss future reproductive options (e.g. donor gamete)
- Offer family studies
- Counsel to inform unaffected offspring of carrier risk (2/3 chance)when they reach reproductive age

* consider referral for genetic counseling

Screen Partners Sequentially

Screen one partner first

First partner tests negative

- Provide results
- Provide estimate fo residual risk
- Make screening available to untested partner only on request

First partner tests positive*

- Provide results
- Provide estimate of risk
- Screen untested partner
- Offer family study

Screen untested partner

Second partner tests negative

- Provide results
- Provide estimate of risk

Second partner tests positive*

- Provide results
- Provide risk estimate for child with CF (1/4)
- Provide counseling regarding CF severity, variability & treatment
- Provide infroamtion regarding limitations of prediction of phenotype
- Offer prenatal diagnosis
- Discuss future reproductive options (e.g. donor gamete)
- Offer family studies
- Counsel to inform unaffected offspring of carrier risk (2/3 chance)when they reach reproductive age

Second partner not tested

- Provide results
- Encourage partner testing
- Provide risk estimate for child with CF (e.g. 1/116 if Caucasian)
- Make prenatal diagnosis available
- Counsel to inform unaffected offspring of carrier risk (1/2 chance) when they reach reproductive age

* consider referral for genetic counseling

REPORT OF THE PATIENT EDUCATION COMMITTEE

Presented to the Steering Committee on Cystic Fibrosis Screening
February 18, 1999

I. THE CHARGE OF THE PATIENT EDUCATION COMMITTEE

The Follow-Up Workshop on CF Carrier Testing took as its starting point that the offer of CF screening on a population basis was not currently standard of care and could not become so until many issues of implementation were addressed. Many of those issues concerned fully informed patient education and consent. The Patient Education Committee (PEC) was formed to address those issues. The specific charge of the Patient Education Committee is two-fold: First, to develop and pilot test a model CF carrier testing educational brochure; second, to make recommendations about how to operationalize patient education and informed consent procedures using this brochure.

The PEC is co-chaired by James Sorenson and Nancy Press. Brian Cheuvront is the Project Director, in charge of the production of the model products and responsible for the day to day work of the PEC. To implement its goals, the PEC assembled a Working Group with a variety of expertise, as listed below:

WORKING GROUP	AFFILIATION	EXPERTISE
James Sorenson, Ph.D.	University of North Carolina	Public health, informed consent, patient education. CF researcher; member of CF Consortium
Nancy Press, Ph.D.	Oregon Health Sciences University	Medical anthropologist, prenatal genetics, informed consent
Brian Cheuvront, Ph.D.	Boston University	Patient education. Collaborator of Sorenson as CF researcher
Barbara Bernhardt, M.S.	Johns Hopkins University	Genetic counselor, practice and research experience with patient preferences in informed consent
Ellen Wright Clayton, M.D., J.D.	Vanderbilt University	Pediatrician-attorney, legal and ethical issues in informed consent; member of CF Consortium
Joanna Fanos, Ph.D.	California Pacific Medical Center	Psychologist, seminal work on CF siblings; advisor to CF Consortium
Elena Gates, M.D.	UC, San Francisco	Ob-gyn in practice; long-standing research interest in issues of prenatal genetics
Stanley Grant, M.S.	University of Iowa	Genetic counselor; coordinator of Iowa's MSAFP program
Peter Rowley, M.D.	University of Rochester	Physician, research experience in CF acceptance and cost-effectiveness; member CF Consortium
Suzanne Tomlinson, J.D.	Law practice	CF consumer advocate
Ben Wilfond, M.D.	University of Arizona/NIH	Pediatric pulmonologist with CF pracitce; bioethicist with long-standing interest in prenatal genetics

The PEC has now held two face-to-face meetings, the first in Denver, Colorado on November 29, 1998, the second in Chicago, Illinois, on February 12-13, 1999. In preparation for the first meeting, Sorenson, Press and Cheuvront conducted an exhaustive search of the literature on informed consent and patient education. At the first meeting, an analysis of this literature was presented, a general strategy for working was developed, and specific work tasks were assigned d, In addition to face-to-face meetings, the PEC has had numerous Email and teleconference deliberations. The primary products of our work up to this point are:

- A draft of a model CF Education and Informed Consent brochure
- A plan to operationalize the use of that brochure
- A plan to pilot test the brochure

II. THE PRINCIPLES BEHIND THE PATIENT EDUCATION BROCHURE

The premises which shaped the creation of the brochure are listed below. They rely heavily on the conclusions of the Follow-Up Workshop on CF Carrier Screening and on the resulting article by Mennuti, Thomson, Press (Journal of Obstetrics and Gynecology, forthcoming March 1999).

♦ ***That many of the best efforts at informed consent fail because they take into account only the clinical encounter between provider and patient.*** Thus they ignore the structural factors which shape that encounter itself. One such factor is the patient's belief that any test offered by a physician must be necessary and advantageous. A desire to attend to this structural constraint on fully informed consent led to a discussion in the Follow-Up Workshop on the distinction between "offering" and "making available" a test. The PEC attempted to operationalize this distinction in designing the brochure and the ways it would be used.

♦ ***That the existing patient education materials about CF are generally inadequate and, specifically, present an unbalanced view of CF as a clinical condition.*** With input from physicians experienced in treating individuals with CF, as well as from consumer advocates, and genetic counselors, we crafted what we hope is a more balanced view of the disease condition, the potential familial challenges of the disease, the realities of life with CF, and the current state of treatments.

♦ ***That whether or not to get carrier testing for CF is a decision based on personal values, not a medical decision.*** Since the only way to avoid the birth of a child who will develop CF is to terminate the pregnancy, the PEC concluded that a carrier test decision was based not on medical criteria but rather on personal values. We believe, therefore, that patients should be helped to think through the decision in terms of their values in regard to parenting and abortion, the emotional and financial resources of their family, as well as acceptable levels of risk in pregnancy, etc.

♦ In addition, we realize that severe time constraints in busy obstetrical practices present pragmatic challenges which will only increase as the number of available prenatal tests increase. We considered this issue basic to our work as well.

III. OPERATIONALIZING THESE PRINCIPLES

A. Background on "Offering/Making Available" the test. The PEC belies that the constraints of a busy provider practice can be made to work *with* rather than *against* the need to present testing in a non-directive manner. This can be done by focusing on the distinction between "offering" and "making available" CF carrier testing. Follow-Up workshop participants viewed "offering" the test as more active. Such an offer would typically take place in a face-to-face interaction with the health care provider. Given the faith that most patients put in their physicians and nurses, an "offer" of a test in this context is generally seen by patients as an endorsement of testing on the part of the care provider, whether or not such is intended. On the other hand, it was felt that simply "making available" information could be done through the provision of educational materials (written, by video, or other media). The potential test consumer could be helped to understand what was at stake and led through a decision-making process through these materials. Individuals would then select themselves by an active query of their health care provider about testing.

PEC Recommendations:

(1) In attempting to operationalize this principle, the PEC decided that while we endorsed the idea of a less active "offer" of testing, it was neither possible nor desirable to eliminate the provider from interaction with the patient in regard to her decision about CF carrier testing. We therefore designed a hybrid procedure which begins with the brochure, which we consider adequate preparation for making a CF carrier testing decision. We recommend that this brochure be given to pregnant women <u>before</u> any face-to-face discussion of testing takes place; ideally the brochure would be mailed to the pregnant woman before her prenatal intake visit. This would then be followed by a discussion with the health care provider.

(2) However, by using the brochure , the discussion with the provider will actually take less time for two reasons: First, some women will have eliminated themselves by already deciding that they were not interested in CF testing; second, the provider can use the "reasons to accept and reasons to decline testing" page in the brochure to help women and couples think through their decision and they can use the questions on the tear-out Consent page to rapidly make certain that the patient understands the test she is accepting or declining.

B. How to Decide to Whom Testing is Offered: After much deliberation, the PEC decided consensus was lacking to make a recommendation to target screening along racial/ethnic lines. We also agreed with the point made by Mennuti, Thomson and Press that recommending targeted screening runs a risk for the development of concordant payment policies in which third

party payers would only reimburse for testing if certain criteria for offering screening were met. However, given the variation in test sensitivity among different population groups, we addressed this issue in the brochure in the following way:

(1) We included information on the variable incidence on CF in different racial/ ethnic populations. We did this both through narrative and in tabular form and again raised this issue in the section of the brochure listing reasons for and against testing.

C. Modes of Screening: The PEC made no specific stipulations as to couple versus individual or simultaneous versus sequential testing. We believe that only the individual provider will know what works best in his/her practice setting. We do, however, strongly recommend the following:

PEC Recommendations:

(1) When there is a willing male partner, it is preferable to educate both members of the couple at the same time; we also recommend doing so as early in the pregnancy as possible so that the couple is not rushed at any of the stages of decision-making. However, in reality, women are frequently not accompanied by their partners to early, routine prenatal appointments.

(2) We therefore recommend that testing be done by buccal swab. By sending two buccal swab kits home with the pregnant woman who has decided to be tested, she and her partner can both return samples at the same time.

(3) The laboratory can test the woman's sample first, testing the male partner's only when necessary. However, we recommend that results be given on all samples tested, and couples be told when a male partner's sample was not tested.

The PEC requests further input from both the Physician and the laboratory group in working through the precise protocols that would flow from the above recommendations.

D. Assessing if Education and Informed Consent Has Occurred: Many studies have demonstrated the failure of patient education. Yet, data also indicate that patients are often reluctant to respond in the affirmative to a provider's query "do you have any questions?" For these reasons it was felt that a more creative approach was needed to both insure *and* evaluate patient comprehension. Our recommended approach is outlined below:

PEC Recommendations:

(1) We have used the Informed Consent page in the brochure to try to begin a process which, we hope, the provider will complete. In doing this we wanted to stress that ***patient education*** was the true goal of the brochure, with informed consent a natural,

but secondary, outcome of the educational process.

(2) The informed consent form constitutes the last page of the educational brochure. That page is meant to be perforated so that it can be removed and kept in the patient's chart. However, rather than a legalistic form, this page comprises 5 questions which are the primary "take-home" messages of the booklet. When the patient signs the form, indicating that she accepts or declines CF carrier testing, she is also affirming that she has read, and can answer, these 5 questions.

(3) In addition, the PEC suggests that these 5 points can form the basis for an informed consent discussion with the patient, or the couple, about a testing decision.

IV. CONTENT OF THE EDUCATIONAL BROCHURE

A. Many educational brochures on CF carrier screening already exist. However, it was the opinion of the participants in the Follow-Up Workshop that these existing material failed to accomplish the goals for patient education outlined by the Consensus Development Conference panel. For this reason, the PEC was charged with the creation of a sample educational brochure. A draft of the brochure accompanies this report. Below is a brief description of the purpose of the sections of the brochure. Please note that a question and answer format is used throughout the brochure. The order of sections in the brochure is informed by the work of Bernhardt and Geller which asked women about what they wanted to know about CF screening and in what order they wanted to receive this information.

1. Title and Introduction: The idea that a choice needs to be made about CF carrier screening and that the choice belongs to the woman/ couple is highlighted from the beginning of the brochure. It is also stressed that the reader may have questions and -- implicitly -- has a responsibility to ask for help in addressing those questions. An active stance on the part of the patient is also reinforced by highlighting that the reader should tell the health care provider if she is interested in learning more about CF carrier testing.

2. What is Cystic Fibrosis? Wilfond and Marteau have examined the clinical picture of CF presented in a range of patient information brochures and found those descriptions to be generally inadequate and often unbalanced. The PEC believes that the presentation in the brochure is more balanced. We have based the order of presentation on research regarding which elements of the disease description are likely to be most relevant to prospective parents making prenatal testing decisions. This section only highlights the most crucial features of CF in order to avoid information overload; a later section expands this information for those readers who remain interested in testing.

3. The Purpose of CF Carrier Screening: Most women and couples undergoing

prenatal carrier screening for CF do so for reassurance. Providers, as well as individuals and couples, are expecting the results of the screening to be normal; this is, of course, the statistically most likely outcome. As a consequence, limited time may be spent discussing or considering what are the consequences of, and decisions involved in, a positive test result. The PEC felt that it was important that the educational brochure should help women and couples understand and begin to think through the meaning and decisions involved in carrier testing as early in the process as possible. Thus we placed a frank discussion of the purpose of CF carrier screening near the front of the brochure. We included in those purposes the advantage of having time to prepare emotionally for the birth of a child affected with CF or termination of the pregnancy.

4. The Genetics of CF and the Possibility of Being a Carrier: In two short sections, the brochure attempts to make clear and simple the inheritance of CF. Special attention is paid to the 1 in 4 risk **with each pregnancy** for a dual carrier couple. In addition, a Table is included so that individuals from different ethnic/race backgrounds can compare their risk for CF.

5. Sequelae of a Positive Carrier Test: In several short sections, the reader is walked through what would happen next if she were a carrier and if her partner were a carrier. We also address the issue of residual risk in a negative test and the need to have testing in subsequent pregnancies only if a new partner is involved.

6. More information on CF: Here, toward the end of the brochure, more complete information is given on the symptoms of CF and the health care needs of individuals with CF.

7. The CF Testing Decision: This comprises a parallel list of possible reasons to be tested and not to be tested.

8. Flow Chart: This flow chart summarizes, from the point of view of the woman and couple, the various choices that would b e made, results that might occur, and sequelae of those results.

9. Blank Space for Questions: We have indicated a page where the reader can write down questions they may want to ask their health care provider about any of the information in the booklet. This page is located across from the Consent Page with its 5 questions.

Draft Report 10/14/98

Preconceptional and Prenatal Carrier Screening for Cystic Fibrosis Provider Guidelines

Developed by the Provider Guidelines Working Group

Preconceptional and Prenatal Carrier Screening for Cystic Fibrosis

Physician Guidelines

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive genetic disorder in Caucasian populations. CF is characterized primarily by pulmonary and gastrointestinal manifestations of variable severity. Although there is a wide spectrum of clinical expression, most cases of CF are associated with substantial morbidity and mortality and require lifelong medical care. CF is more common in Caucasians and much less frequent in most other ethnic and racial groups. Since 1989 when the gene responsible for CF was identified, a large number of different mutations in the CF gene have been reported. Testing for these mutations has enabled genetic screening to identify CF carriers. This monograph provides guidelines for implementation of carrier screening for CF in the context of reproductive health care.

Background

Offering screening tests for specific genetic diseases and malformations has become part of obstetrical practice. These tests help the clinician identify pregnancies at increased risk for these disorders and provide information so that couples can make informed reproductive decisions, including whether to have prenatal diagnosis. In general, genetic screening focuses on specific populations at increased risk for a disease based on family history or racial and ethnic background. Examples of genetic screening tests currently offered in obstetrical practice include Tay-Sachs and Canavan screening to individuals of Ashkenazi Jewish descent, sickle cell screening to those of African descent, and thalassemia screening to individuals of Asian and Mediterranean descent. *Genetic screening must always be voluntary and always requires informed consent.*

Incidence of CF

Individually, inherited disorders are rare but collectively they account for one quarter to one third of all major birth defects. CF is the most common autosomal recessive genetic disease among Caucasians, with a frequency of one in 3,300 (Table 1). The frequency of CF in Hispanics is approximately one in 8,000-9,000; in African Americans, one in 15,000; in Asian Americans, one in 32,000; and is low in most other racial or ethnic groups. Limited studies indicate the frequency of CF may be similar to or higher than that of Caucasians in Pueblo (one in 3,970) and Zuni (one in 1,580) Native Americans.

Inheritance of CF

CF is inherited in an autosomal recessive fashion. CF carriers have a mutation in one of their two copies of the CF gene. One-half of the children of CF carriers will also be CF carriers. In general, carriers are healthy individuals and they are not usually aware of their carrier status unless they have an affected relative or offspring. Couples in whom both partners carry a CF mutation have a one in four chance of having an offspring with CF in each pregnancy. When both parents are carriers, two-thirds of the unaffected children will be CF carriers.

In 1989 the gene which causes CF was isolated and localized to chromosome number 7. Since that time over 700 different mutations in the gene have been reported in individuals with CF. The frequency of the specific mutations varies among populations. For example, delta F508, the first CF mutation identified, accounts for 70% of the CF mutations in Caucasians of Northern European descent but only 30% of CF mutations in individuals of Ashkenazi Jewish descent. A different mutation, the W1282X mutation, is more common in Ashkenazi Jews. For Caucasians of Northern European descent, 15 to 20 rarer mutations account for less than half of the remaining detectable CF alleles.

Pathophysiology and Clinical Presentation of CF

The gene product, CF transmembrane conductance regulator (CFTR), was also identified in 1989. The CFTR protein functions as a cAMP-regulated chloride channel in the apical membrane of epithelial cells. Mutations in the gene cause defective chloride transport resulting in high sweat chloride levels and tenacious mucus in the lungs and pancreas which results in the major clinical features of CF.

In the US, approximately 850 individuals are diagnosed with CF each year, nearly two-thirds prior to 1 year of age. Individuals with mild manifestations of CF may not be diagnosed until adulthood. CF is typically a multisystem disease that primarily causes progressive pulmonary disease due to chronic endobronchial inflammation and pulmonary infection. Pancreatic insufficiency and intestinal malabsorption is present in 85% of all affected individuals. Other manifestations include meconium ileus (which occasionally may be identified *in utero* late in pregnancy by means of ultrasonography) and recurrent distal intestinal obstruction in older patients. Chronic sinus disease and nasal polyps, diabetes mellitus, liver disease and pancreatitis can also be observed. Men with CF are infertile due to congenital bilateral absence or atresia of the vas deferens.

Recently, men who have congenital bilateral absence of the vas deferens (CBAVD) but no other clinical manifestations of CF have been found to have a mutation in one or both of their CF genes. In addition, some patients with chronic or idiopathic pancreatitis have also been found to have similar mutations in one or both of their CF genes.

The pulmonary manifestations of CF range from severe progressive chronic lung disease to very mild pulmonary symptoms. Only 15% of individuals with CF have normal pancreatic function. The vast majority of patients with CF die as a result of pulmonary complications. A cure is not

available, but aggressive medical therapy has resulted in increases in survival to a median of approximately 30 years of age and even longer in patients with pancreatic sufficiency.

The diagnosis of CF is considered when one or more of the clinical features are present. A sweat chloride test, often in conjunction with DNA studies, is used to confirm the diagnosis. Management including chest physical therapy, antimicrobial drugs, anti-inflammatory agents, nutritional support, and pancreatic enzyme therapy has resulted in increased survival and quality of life. Individuals with end-stage pulmonary disease may be candidates for lung transplantation. Gene therapy and rectification of the electrolyte transport by various pharmacological means are being actively investigated. However, investigators do not anticipate a cure in the near future.

Carrier Screening for CF

In 1997, a National Institutes of Health Consensus Development Conference recommended that genetic screening to identify carriers of CF should be offered to the following adult populations:

- adults with a positive family history of CF
- partners of individuals with CF
- couples currently planning a pregnancy
- couples seeking prenatal care

Studies have demonstrated that despite a couple's desire to have a healthy child there is limited interest in CF screening prior to pregnancy. Pregnant women and individuals with a positive family history are more likely to be interested in screening although interest, even among this group, was not universal. Many couples who agree to carrier screening do so for reassurance with the expectation that screening will be negative. Studies have demonstrated a high level of patient satisfaction after undergoing carrier screening for CF. Not all couples who are found to be

carriers proceed with prenatal diagnostic testing or termination of an affected pregnancy. Screening should be offered irrespective of how couples intend to use the information.

To whom should carrier screening be offered?

The recommendation to offer carrier screening to Caucasians is based on two factors: frequency of the disease and the detection rate (sensitivity) of the test. Offering CF carrier screening is only recommended for populations in whom there is both a high frequency of carriers and a high detection rate. The frequency of the disease in Caucasians is considered to be relatively high (one in 3300) and the detection rate of screening is 80-85%. In contrast, offering screening is not recommended for African Americans, Hispanics, or Asian Americans in whom the incidence of the disease and the detection rate is lower (Table 1). However, any couple in these racial or ethnic groups who request information about CF screening should have this made available.

CF carrier screening should be offered to: 1) patients with a positive family history of CF; 2) partners of individuals with CF; and 3) couples of Caucasian descent planning a pregnancy or seeking prenatal care.

Individuals with a family history of CF

Individuals with a family history of CF are at higher risk of having children with CF. The risk for being a carrier of a CF mutation depends on the relationship to the affected family member. In eliciting the family history, the practitioner should specifically inquire about CF in family members. Some individuals with a positive family history are familiar with the disease and are also aware of their increased risk of being a carrier. Even those who had genetic testing in the past may benefit from genetic counseling since recent developments may have improved the ability to reassess their carrier status. Genetic referral should be considered when there is a

positive family history, because the interpretation of test results and estimation of risk may be more complex than in the general population.

Partners of individuals with CF

An individual with CF may have either a child who is a carrier of CF or a child affected with the disease depending on the carrier status of the partner. Carrier screening should be offered to partners of individuals with CF. Carrier screening may clarify a couple's risk of having a child with CF and provide them with helpful information for reproductive decision-making. The majority of these individuals are aware of their increased risk for having a child with CF.

Couples planning a pregnancy or seeking prenatal care

Couples who are Caucasian and of European or Askenazi Jewish descent, and who are planning a pregnancy (i.e. those seeking preconception evaluation, or treatment for infertility), or presenting for prenatal care during the first or early second trimester should be considered candidates to whom CF screening may be offered. The ethnicity of the partners should be ascertained at the time of the initial history and used by the practitioner to determine whether the couple is at higher risk for having a child with CF. In many cases, it is necessary to ascertain the ethnic background or origin of their grandparents in order to assess their risk. Any patient in the higher risk groups who is considering CF screening should receive educational information regarding the natural history of the disease, disease prevalence, sensitivity and limitations of carrier screening.

In the event that an individual or couple from a lower risk population requests information about screening for CF, they should be provided with similar information and the limitations of screening should be fully discussed. If they understand this information and request screening, the request should be honored.

When should CF carrier screening be offered?

Ideally, carrier screening should be offered prior to conception to allow couples to consider their reproductive options if they are carriers. However, studies have shown that interest in screening for CF is limited and occurs primarily in persons with a positive family history or among pregnant women. Therefore, most screening will be requested when a patient seeks prenatal care. During pregnancy, screening should be offered during the first trimester or early second trimester to ensure that the couple receives the test results within a time frame that will allow them to consider having prenatal diagnosis if they are both carriers and to have the option of termination of pregnancy in the event that the fetus is affected.

Screening Strategies

Several screening strategies are available. With *concurrent screening* both partners are tested simultaneously. With *sequential screening* one partner is tested and the second partner is only tested if the first partner is identified as a carrier.

Concurrent screening may be preferred when both members of the couple are having screening tests for other disorders (e.g. Tay-Sachs and Canavan disease). Concurrent screening will also more rapidly identify carrier couples when there are time constraints for the selection of the method of prenatal diagnosis (i.e., CVS versus amniocentesis) or when advancing gestation may limit the availability of the option of selective termination of affected pregnancies. Furthermore, concurrent screening more precisely identifies each individual's carrier status and provides the couple with the lowest residual risk of having a child with CF following negative screening. Positive screening results of either partner may be used to identify other relatives at high risk for being carriers. Concurrent screening will identify couples in whom one partner is a carrier but the other does not have a detectable mutation (i.e. positive/negative couples). In this situation

there may be increased anxiety generated because the risk for CF is increased, rather than reduced, but prenatal diagnosis cannot be performed. For example the risk levels for Caucasian Europeans who are identified as a positive/negative couple is intermediate (1 in 564) between that of positive/positive couple (1 in 4) and negative/negative couple (1 in 80,000). See tables 2 and 3.

Since the likelihood that both partners will screen positive is less than 1%, some providers or couples may prefer sequential screening. Using this approach, one partner is screened. The other partner is only screened if the first partner is positive for a mutation in the CF gene. Depending on the gestational age, the delay inherent in the sequential approach to screening may result in a more limited choice of prenatal diagnostic procedures or other reproductive options. When the first partner screened does not have a detectable mutation, the residual risk for having a child with CF, although quite low, is higher than when both partners have had negative screening tests. For example, in a European Caucasian couple in whom one partner tests negative the risk of having a child with CF is reduced to 1 in 16,000 in contrast to the residual risk of 1 in 80,000 if both partners had been tested and were negative. If the woman screens negative, a partner who is a CF carrier will not be identified and carrier screening will not be offered to his extended family. Sequential screening only identifies one-half of the couples in whom one partner is a carrier and a mutation cannot be detected in the other partner. This reduction in the number of positive/negative couples reduces the number of couples in whom anxiety may be generated by determining a risk level which is intermediate between positive/positive and negative/negative.

The optimal screening strategy depends on the couple's perception of their risk and how they plan to use the information. For example, a couple who desires prenatal testing by CVS if both screening test results are positive, may decide to proceed with concurrent testing to ensure that the results are available early in pregnancy and to have the lowest residual risk if both partners

screen negative. In contrast, a couple seeking reassurance may find the reduced risk as a result of one partner testing negative an acceptable outcome.

Screening Process

Pretest counseling and educational material in the form of written material, videos, and/or interactive computer programs should be provided for the patient and, whenever possible, her partner. The information about screening for CF should be provided in a non-directive manner. This information may be ideally provided by trained support staff in the ambulatory practice setting. If the partner does not accompany a woman to her prenatal or preconception visit, educational material should be provided for the partner.

Written, informed consent should be obtained only after the woman and her partner have had an opportunity to review the educational material and receive pretest counseling. Individuals who consent to screening should provide either a blood sample or cheek swab according to the laboratory protocol for screening. When the woman or her partner decline screening, the medical record should reflect that screening was offered and the decision was made not to be screened.

Laboratory testing for CF Carrier Screening

The carrier screening test for CF is performed on DNA which may be extracted from any cells (except gamete), although most laboratories use blood lymphocytes or buccal epithelial cells. The provider should determine the source and quantity of specimen required by the laboratory. The obstetrical provider should supply all of the history and demographic information requested by the laboratory to interpret the results.

It has been recommended that the standard screening tests for CF should encompass ___ mutations which are listed in Table ___. This screening is expected to have a sensitivity of ___

in Caucasians of European descent, and of ___ in Ashkenazi Jews. The sensitivity and residual risk of being a carrier after negative screening for these mutations are provided in Table 1. Laboratory reports should include the results of screening and an interpretation. When screening of one or both partners is positive this interpretation should include an estimation of the risk of having a child with CF and recommendations for any additional testing. When screening is negative on both partners this interpretation should include estimates of the residual risk of the partners being CF carriers and of having a child with CF. When one partner has CF, or is identified as a carrier, testing the other partner for a much larger number of mutations (e.g. ____) may be indicated. A more detailed description of the laboratory standards for CF screening is available at _____.

Counseling Before Screening

Patients should receive information a concise description about the following aspects of CF prior to screening:

- The natural history of CF including the variability, and survival rates
- Current medical therapy
- The carrier frequency
- Inheritance
- Testing options for carrier screening and prenatal diagnosis
- Limitations of testing
- The implications of positive and negative results

Reproductive options that may be discussed with the couple prior to screening include adoption, gamete donor programs, prenatal diagnosis and termination of pregnancy in the event that the test results indicate that the fetus has CF. Patients should understand that screening is voluntary

and that their medical records, including test results, will not be released without expressed written consent. Every effort should be made to ensure confidentiality of the test results.

Screening Limitations

• Screening can not detect all CF mutations. Therefore, **a negative screening test on one or both members of a couple does not exclude the small possibility of an affected offspring**. For example, at a detection rate of 80%, a Caucasian couple with a negative family history having concurrent screening in whom both partners have a negative screening test, the risk of the offspring having CF is lowered from one in 3,000 to one in 80,000 but is not zero (See Table 2). For a similar couple having sequential screening in whom only one partner is screened and that partner is negative, the residual risk is one in 16,356 (See Table 3). The level of this residual risk is dependent on the racial or ethnic group of the patient and on the specific mutations for which testing has been performed, and whether only one or both partners have been screened. (See Tables 2 and 3)

• Following screening, the **estimate of a couple's risk for having a child with CF assumes correctly identified paternity.**

• The **estimate of residual risk only apply when the family history is negative.** The accurate estimation of the carrier risk for individuals with a positive family history requires knowledge of the mutations in the affected family member, and the relationship to the person with CF. Assessment of the risk in individuals with a positive family history may not be straightforward and the couple may benefit from genetic counseling and consultation with a clinician who has special expertise in this area.

• The **estimate of residual risk of having a child with CF applies only to pregnancies conceived as a couple and not with other partners.**

• Although some CF mutations are known to be associated with milder illness, **knowledge of the specific CF mutations cannot be used to predict accurately the severity of the disorder in the offspring.** Couples with an affected fetus should be offered counseling about CF by an individual with special expertise in this area who can provide a general description of the clinical range of severity, treatment, etc.

Interpretation of Results and Post-Test Counseling

Both Patient and Partner Test Negative (Negative-Negative)

In a Caucasian couple of European descent in whom both partners test negative, the residual risk of having a child with CF is one in 80,000. In an Ashkenazi Jewish couple in whom both partners test negative, the residual risk is one in 3.5 million (see Table 2).

Either Patient or Partner Negative and Other Partner Not Screened

When only one partner is screened and he or she has a negative test result the residual risk of having a child with CF is decreased (see table 3). For example, the residual risk is one in 16,000 for a Caucasian couple and one in 108,000 for an Ashkenazi Jewish couple.

Both Partners Tested - One Test Positive, One Test Negative (Positive-Negative)

When a CF mutation is identified in either a patient or her partner it is advisable to request that the partner who is not a carrier be screened with an extended panel of mutations. Although the individual with a CF mutation has a 1 in 2 chance of transmitting the mutation to each of his or her offspring, the likelihood of having an affected child is low because the partner has a negative screening test (Table 2). At a detection rate of 80%, a Caucasian couple in which one partner is positive and the other is negative has a one in 564 risk of having a child with CF. The residual risk for an Ashkenazi Jewish couple when only one partner is screen positive is one in 3736.

There is a possibility that the screening test may identify two CF mutations in a patient or partner with a mild form of the disease. Such individuals should be referred an individual with expertise, or a specialized center for a comprehensive evaluation and counseling. For an

individual with CF, the risk of having a child with CF when the partner is screen negative is one in 280 for a Caucasian couple and one in 1900 for an Ashkenazi Jewish couple.

Prenatal diagnostic testing is not recommended when only one member of the couple is a CF carrier, but the other partner does not have a detectable mutation. In this circumstance the determination that the fetus has inherited one CF mutation, and hence is a CF carrier, is not clinically useful information and would not be an indication to change obstetrical management. or to discuss termination of pregnancy.

Both Patient and Partner Test Positive (Positive-Positive)

When both a patient and her partner test positive for a CF mutation they have a 1 in 4 chance of having a child with CF in each pregnancy. If screening is performed prior to conception, a discussion of the reproductive options for avoiding the risk of conceiving a child with CF include adoption, donor insemination, and donor egg programs. Couples electing donor gamete programs should inquire about the CF carrier status of potential donors. Couples should also be informed that prenatal diagnosis and termination of pregnancy if the fetus is affected with CF will be options if a pregnancy is established without using a donor gamete.

When screening is performed during early pregnancy and both partners are identified as carriers, prenatal diagnosis should be offered.

Patient Positive and Partner Untested

When the woman's screening test is positive and her partner declines or is unavailable for testing, the residual risk of having a child with CF in a Caucasian couple is approximately one in 100 (see Table 3). Testing of the partner should be encouraged to further refine the risk estimate for the pregnancy.

When screening is not performed on the partner, women who are identified as CF carriers should be informed of the availability and limitations of prenatal testing. Prenatal diagnosis can determine whether the fetus has inherited a CF mutation from the mother but may not distinguish between a carrier and an affected fetus. In the event that the fetus inherits the CF mutation identified in the mother, testing for a second mutation from the father may be undertaken by testing for an extended panel of mutations. Such testing may reduce the risk that the fetus has CF, but cannot totally exclude CF in the fetus.

Prenatal Diagnosis of CF

When both partners are identified as carriers of CF mutations during early pregnancy, prenatal diagnosis should be offered. Chorionic villus sampling (CVS) or amniocentesis can be performed at 10-12 weeks or 15-20 weeks of gestation, respectively. Ideally, screening will have been performed prior to 20 weeks of gestation to ensure that prenatal diagnosis can be completed prior to extrauterine fetal viability in the event that they would consider pregnancy termination if the fetus has CF. Some couples who are carriers may elect to have prenatal testing for information only and would not consider termination of a pregnancy in which the fetus is determined to be affected with CF. Other couples may decline further testing even after they are identified as carriers. These decisions should be supported by the clinician.

When a couple requests prenatal diagnosis for CF, testing is performed on amniotic fluid cells or chorionic villus cells for the mutations which have been detected previously by screening tests on the parents. Diagnostic testing for a larger number of mutations on amniotic or chorionic villus cells may be indicated when the woman is a carrier and screening of her partner has not been performed.

If two CF mutations are found in the fetus, the couple should be informed of the results and appropriate non-directive counseling should be provided. Counseling should include discussion of the options of continuation and termination of the pregnancy. An individual able to provide information about the range of clinical severity of CF, management, treatment, prognosis , and the potential for new therapeutic modalities should participate in the counseling. *Counseling should include a discussion of the difficulties in predicting outcome based on the genotype. At the present time, knowledge of the specific CF mutations cannot be used to predict accurately the phenotype or the severity of the pulmonary disease.*

Counseling and Screening of Family Members of CF Carriers

Except in cases of adoption, mis-attributed paternity or new mutations, one of the parents of a CF carrier will also carry the mutation. Since CF is an inherited disease, other close relatives of an individual who carries a CF mutation are at risk for carrying the same mutation. Since there is not a provider/patient relationship with these relatives and because of the need for confidentiality, the provider may not independently contact these relatives. Therefore, women or their partners who are identified as carriers of a CF mutation should be encouraged to discuss this with their family members and written information and other educational materials should be provided for them to use in these discussions. CF carrier screening should be offered to interested relatives, particularly siblings and first cousins who are of reproductive age.

Offspring of carriers have a 50% risk of having inherited a CF mutation from a parent with the mutation. Couples in which a partner is a carrier of a CF mutation should be encouraged to inform their offspring of their risk when they reach reproductive age. Carrier screening is not recommended during infancy, childhood or early adolescence.

Likewise, when a fetus is identified as a CF carrier by prenatal diagnosis, parents should be counseled to inform the offspring, but only when they reach reproductive age.

Summary

CF carrier screening should be offered to patients with a positive family history of CF, partners of individuals with CF and Caucasian couples of European or Ashkenazi Jewish descent planning a pregnancy or seeking prenatal care. Information about CF screening and CF screening testis should be made available to other patients upon their request. Screening may be accomplished prior to conception or during the first or early second trimester.

The clinician should identify couples to whom screening should be offered based on family history and ethnic background during the initial history. Counseling and educational material in the form of written material, videos, and/or interactive computer programs should be provided for the patient and whenever possible, her partner. In the event that her partner does not accompany her to a prenatal or preconception visit, suitable educational material should be provided to the woman to give to her partner. Women and their providers may elect to perform simultaneous or sequential carrier screening for CF. Simultaneous testing is particularly important when there are time constraints for making a decision regarding prenatal diagnosis or the availability of termination of affected pregnancies.

Referral for counseling by a provider with special expertise may be considered when carriers of CF are identified, prior to prenatal diagnosis, or when an affected fetus is identified.

References

Asch, D.A., Patton, J.P. Hershey, J.C., Mennuti, M.T.: Reporting the results of cystic fibrosis carrier screening. Am. J. Obstet. Gynecol. 168:1-6, 1993.

Axworthy, D., Broch, D.J.H., Bobrow, M., Marteau, T.M.: Psychological impact of population-based carrier testing for cystic fibrosis: three year follow-up. Lancet 347:1443-1446, 1996.

Beaudet, A.L.: Invited editorial: carrier screening for cystic fibrosis. Am. J. Hum. Genet. 47:603-605, 1990.

Brock, D.J.H.: Prenatal screening for cystic fibrosis: 5 years' experience reviewed. Lancet 347:148-150, 1996.

Chillon, M., Casals, T., Mercier, B., et al.: Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. N. Eng. J. Med. 332:1475-1480, 1995.

Cohn JA, Friedman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS: Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Eng J Med 339:653-658, 1998.

The Cystic Fibrosis Genotype-Phenotype Consortium: Correlation between genotype and phenotype in patients with cystic fibrosis. N. Eng. J. Med. 329:1308-1313, 1993.

Clayton, E.W., Hannig, V.H., Pfotenhauer, J.P., Parker, R.A., Campbell, P.W. III, Phillips, J.A. III: Lack of interest by nonpregnant couples in population-based cystic fibrosis carrier screening. Am. J. Hum. Genet. 58:617-627, 1996.

Congress of the United States, Office of Technology Assessment. Cystic fibrosis and DNA tests: implications of carrier screening, OTA-BA-532. Washington, DC: U.S. Government Printing Office, August 1992.

Doherty, R.A., Palomaki, G.E., Kloza, E.M., Erickson, J.L., Haddow, J.E.: Couple-based prenatal screening for cystic fibrosis in primary care settings. Prenat. Diag. 16:397-404, 1996.

Durie PR: Pancreatitis and mutations of the cystic fibrosis gene. N Eng J Med 339:687-688,1998.

Genetic Testing for Cystic Fibrosis. NIH Consens Statement 15(4):1-37, Apr 14-16, 1997.

Kerem, E., Corey, M., Kerem, B-S., Rommens, J., Markiewicz, D., Levison, H., Tsui, L-C., and Durie, P.: The relation between genotype and phenotype in cystic fibrosis - analysis of the most common mutation (DF_{508}). N. Eng. J. Med. 323:1517-1522, 1990.

Kiesewetter, S., Macek, M., Jr., Davis, C., Curristin, S.M., Chu, C.-S., Graham, C., Shrimpton, A.E., Cashman, S.M., Tsui, L.-C., Mickle, J., Amos, J., Highsmith, W.E., Shuber, A., Witt, D.R., Crystal, R.G., and Cutting, G.R.: A mutation in CFTR produces different phenotypes depending on chromosomal background. Nature Genetics 5:274-277, 1993.

Lemna, W.K., Feldman, G.L., Kerem Bat-sheva, Fernbach, S.D., Zevkovich, E.P., O'Brien, W.E., Riordan, J.R., Collins, F.S., Tsui, L-C., Beaudet, A.L.: Mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis. N. Eng. J. Med. 322:291-296, 1990.

Levenkron, J.C., Loader, S., Rowley, P.T.: Carrier screening for cystic fibrosis: test acceptance and one year follow-up. Am. J. Med. Genet. (In press).

Loader, S., Caldwell, P., Kozyra, A. Levenkron, J.C., Boehm, C.D., Kazazian, H.H., Jr., Rowley, P.T.: Cystic fibrosis carrier population screening in the primary care setting. Am. J. Hum. Genet. 59:234-247, 1996.

Mennuti, M.T., Thomson, E., Press, N.: Screening for cystic fibrosis: Follow-up workshop to the NIH consensus development conference. Obstet Gynecol (in press)

Mercier, B., Raguenes, O., Estivill, X., Morral, N., Kaplan, G.C., McClure, M., Grebe, T.A., et al.: Complete detection of mutations in cystic fibrosis of Native American origin. Hum. Genet. 94:629-632, 1994.

Ramsey, B.W.: Managemetn of pulmonary disease in patients with cystic fibrosis. N. Eng. J. Med. 335:179-188, 1996.

Rosenfeld, M.A., Collins, F.S.: Gene therapy for cystic fibrosis. Chest 109:241-252, 1996.

Rosenstein, B.J., Zeitlin, P.L.: Cystic fibrosis (seminar). The Lancet 351:277-282, 1998.

Rosenstein, BJ and Cutting, GR: The diagnosis of cystic fibrosis: a consensus statement. J Peds132:589-595, 1998.

Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, Braganza J: Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Eng J Med 339:645-652, 1998.

Welsh, M.J., Tsui, L-C., Boat, T.F., Beaudet, A.L.: Cystic fibrosis. In: The metabolic and molecular basis of inherited disease. 7th ed. New York: McGraw-Hill, pp. 3799-3876, 1995.

Wilfond, B.S., Fost, N.: The cystic fibrosis gene: medical and social implications for heterozygote detection. JAMA 263:2777-2783, 1990.

Witt, D.R., Schaefer, C., Hallam, P., Wi, S., Blumberg, B., Fishbach, A., Holtzman, J., Kornfeld, S., Lee, R., Nemzer, L., Palmer, R.: Cystic fibrosis heterozygote screening in 5,161 pregnant women. Am. J. Hum. Genet. 58:823-835, 1996.

Table 1. Incidence and Carrier Risk for Cystic Fibrosis based on Ethnicity

Group	Incidence	Carrier Risk
Caucasians	1/3300	1/29
Hispanics	1/8-9000	1/46
African Americans	1/15,300	1/62
Asian Americans	1/32,100	1/90

Table 2. Risk of CF in Offspring for Couples Tested

Group	Sensitivity	One Parent Positive One Parent Negative	Both Parents Negative
Caucasian European	0.80	1/564	1/79,524
Caucasian Ashkenzi Jewish	0.97	1/3736	1/3,489,424

Hispanics	0.57	1/424	1/44,944
African Americans	0.75	1/980	1/240,000
Asian Americans	0.30	1/512	1/240,100

Table 3. Risk of CF in Offspring when only One Parent Tested

Group	Sensitivity	One Parent Negative	One Parent Positive
Caucasian European	0.80	1/16,356	1/116
Caucasian Ashkenzi Jewish	0.97	1/108,344	1/116
Hispanics	0.57	1/19,504	1/184
African Americans	0.75	1/60,760	1/248
Asian Americans	0.30	1/46,080	1/360

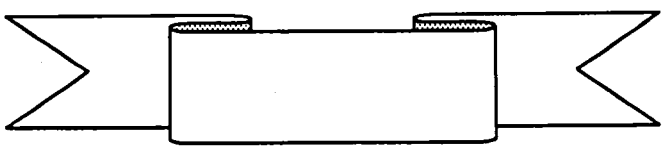
Unresolved ssues for committee discussion

line 30 - written informed consent requirement -- not required for T-S or SCD.

Release of info with written consent -- patients sign blanket permission for insurance companies to be able to obtain records

CYSTIC FIBROSIS CARRIER TESTING DURING PREGNANCY:

THE CHOICE IS YOURS



INSIDE COVER

This brochure was prepared to give you information about cystic fibrosis (CF) and CF carrier testing. Carrier testing is being made available to you on a voluntary basis. You do not have to be tested. Whether or not someone is tested is a personal decision. Before deciding, you should read this brochure so you understand what CF is and what testing is about. On the last page of this brochure, there is space for you to jot down any questions you may have.

If, after reading the brochure, you want to be tested, or simply want to know more about the test, you should tell your health care provider that you are interested in learning more about CF carrier testing.

D R A W I N G .....

What is CYSTIC FIBROSIS

Cystic fibrosis is a disorder which causes problems with breathing and digestion. It is a life-long illness which is usually diagnosed in the first few years of life. The lung problems can be treated with medicine and physical therapy, both at home and in the hospital. However, they become worse over time and more difficult to treat. The digestive problems can usually be treated by taking medicine daily. Cystic fibrosis does not affect intelligence.

It is impossible to know how long a person with CF will live. Some die in childhood, while others live into their 40's or even longer. Although there is no cure for CF, more effective treatments are being developed that may help people to live full, healthy lives.

What is the PURPOSE of Cystic Fibrosis Carrier Testing?

The purpose of CF carrier testing is to see if a couple is at increased risk for giving birth to a child with CF. Cystic fibrosis carrier testing is a laboratory test done on a sample of blood or saliva. If testing shows that the couple *is* at high risk, additional testing can be done to see whether or not the baby will develop CF.

Cystic fibrosis cannot be treated before birth. The purposes of having this information about your developing baby are so you can prepare yourself to care for a child with special healthcare needs, ***or*** so you can terminate the pregnancy.

What CAUSES Cystic Fibrosis?

Cystic fibrosis is a genetic disorder. Genes are nature's blueprint for every living thing. Genes comes in pairs: one set of genes comes from your mother and the other set from your father. Some genes do not function properly because there is a mistake in them. If a gene has a mistake, it is said to be altered or changed.

Everyone has two copies of each gene. If a person has one changed copy of a CF gene, that person is a *carrier* for CF. A *carrier* does not have CF. When a couple, both of whom are carriers, have a child, that child may inherit one changed copy of the gene from each parent. A child with two changed copies of the CF gene will develop CF.

Could I be a CARRIER of Cystic Fibrosis?

Yes. You could be a cystic fibrosis carrier even if no one in your family has CF and even if you already have children without CF. About one in 30 white people (about 3 in 100 or 3%) carries the changed gene. If your family background is not white, your chance of being a carrier is lower. *(See Table)*

If a relative of yours *has* CF, or is known to be a *carrier* of CF, your chances of being a carrier is greater than 1 in 30.

THE CHANCE FOR HAVING A BABY WITH CF

ETHNICITY/ RACE	CHANCE OF BEING A CF CARRIER	CHANCE BOTH PARTNERS ARE CF CARRIERS	CHANCE BABY WILL HAVE CF *IF BOTH PARTNERS ARE CARRIERS*
WHITE	1 in 30	1 in 900	1 in 4
AFRICAN AMERICAN	1 in 62	1 in 3844	1 in 4
HISPANIC	1 in 46	1 in 2116	1 in 4
ASIAN AMERICAN	1 in 90	1 in 8100	1 in 4
ASHKENAZI JEWISH	1 in 29	1 in 841	1 in 4

N Am. varies by tribe

NOTE: If you or a blood relative of yours has CF, or knows they are a carrier, your chance of being a carrier is higher than the numbers presented in the Table.

If the test shows I am a Carrier WHAT SHOULD I DO?

If the test shows that you are a carrier, the next step is to test the baby's father. If the father has a normal test result, it is very unlikely that your baby would develop CF and no further testing is recommended

What if BOTH PARENTS Are Cystic Fibrosis Carriers?

If two people who are both carriers have a child, that child ***may*** have cystic fibrosis. When two carriers have a child together, there is a 1 in 4 chance (25%) with EACH pregnancy that the child will have cystic fibrosis. This is true even if they already have other children without CF.

If CF testing shows both parents are carriers, you might then see a provider for **genetic counseling**. This person could provide you with more information and help you decide if you want to test the baby for CF. This would be done through amniocentesis, a procedure where a needle is used top take fluid from around the baby for testing. If this test shows that the baby will develop CF, you could choose whether to either terminate or continue with the pregnancy.

If my test is normal, COULD I STILL BE A CARRIER?

Yes, because the test is not able to detect all carriers. However, the chance of being a carrier with a normal test result is very low; therefore testing the baby's father is not recommended.

Does the test need to be repeated EACH TIME I GET PREGNANT?

If the test shows you are a crrier, the result is definite and will not change. If you have a new partner for a future pregnancy, however, testing is always recommended to fhre new partner.If you have a new partner for a future pregnancy, testing would be recommended for that new partner.

Is There Anything Else I SHOULD KNOW About Cystic Fibrosis?

What are the Symptoms of Cystic Fibrosis? Cystic Fibrosis causes problems with breathing and digestion. CF can cause thick mucus to collect in the lungs; this leads to breathing problems. Lung problems often become worse and harder to treat over time. Digestive problems make it difficult for children CF toachieve normal height and weight. Almost all men with CF are infertile; some women have difficulty getting pregnant. Cystic fibrosis does not affect intelligence.

What Are theHealth Needs of Children with CF? To treat lung problems, most children with CF need to have physical therapy for about a half hour every day; this helps clear mucus from the lungs. This is something that parents or other family members can do. Sometimes lung infections still develop . They may need to be treated with antibiotics at home or in a hospital. Adoption and new reproductive technologies are available for those who cannot have children of their own. Treatments are costly and may be burdensome without adequate health insurance.

Do All People with CF Have the Same Symptoms? No. Some individuals have far milder symptoms than others and the reasons for this variation are not entirely understood. It is not possible to tell how mild or severe a child's symptoms might be. Still, by adulthood, most people with CF will have some breathing and digestive problems. Today there are many people with CF who are attending school, have careers and fulfilling family lives.

How Do I DECIDE Whether or Not to Have CARRIER TESTING

After learning about CF carrier testing, some people decide to have testing, and others decide against it. The cost of testing is covered by some insurance and not by others. You may want to check with your insurance company before deciding if you want testing.

Listed below are some reasons people give for having or nor having CF testing.

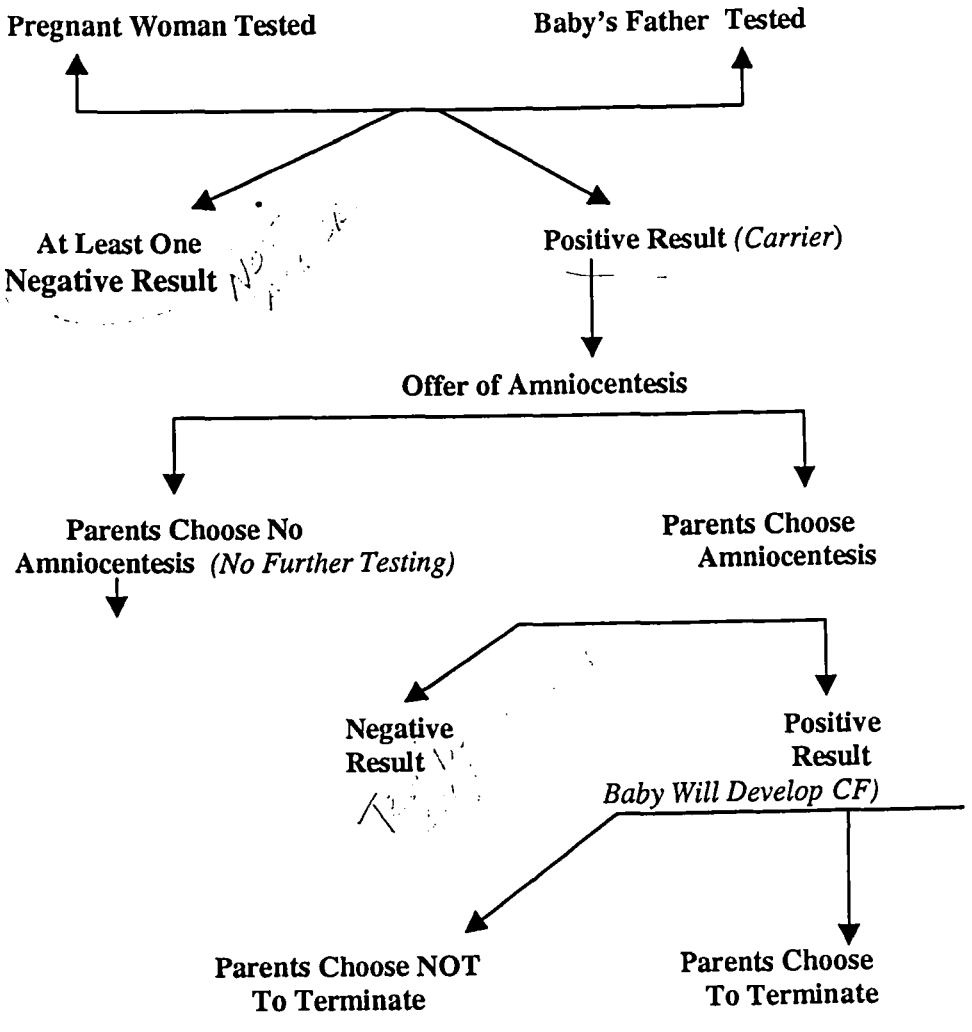
Possible Reasons to be Tested:

- If cystic fibrosis seems like a very serious disorder to you
- If the chance of being a CF carrier seems high to you – especially if a member of yours or your partner's family has CF or is a known carrier
- If you and the baby's father would consider amniocentesis and the option of terminating the pregnancy if you were both found to be carriers
- Because test results are usually reassuring

Possible Reasons NOT to be Tested:

- If cystic fibrosis does not seem like a very serious disorder to you
- If the chance of being a CF carrier seems low to you. This may be especially likely if you are Asian- or African-American.
- If you and the baby's father believe that you would not have amniocentesis or terminate the pregnancy if you were found to be carriers
- Because the test is not perfect and will not identify all carriers.

THIS CHART YOUR CHOICES REGARDING CARRIER TESTING FOR CYSTIC FIBROSIS



QUESTIONS TO ASK MY HEALTH CARE PROVIDER ABOUT CF CARRIER TESTING:

_____

_____

_____

_____

_____

You should be certain you understand the five items listed below. If you are not certain about any of them, please ask your health care provider to explain them further BEFORE signing this form accepting or declining CF carrier testing.

1. ***I understand that the decision to be tested for CF carrier status is completely mine. I realize that it is a personal decision, not medically required.***
2. ***I understand that if I am a carrier, the baby's father must be tested to determine if my developing baby might have CF.***
3. ***I understand that if one parent is a carrier and the other is not, it is possible that the child will develop CF, but that the chance of this is very small.***
4. ***I understand that if both parents are carriers, additional testing must be done to know whether or not the child will develop CF.***
5. ***I understand that if the baby has inherited a changed CF gene from each parent, the only way to avoid the birth of a child with CF is by terminating the pregnancy.***

I have read and understand the information in this brochure and I:

☐ Decline CF carrier testing
☐ Accept CF carrier testing

Signed: _____

IV REMAINING PAMPHLET DEVELOPMENT ACTIVITIES

1. Piloting. The objective of the piloting is to assess the readability and comprehension of the pamphlet. (formative not summative evaluation).

   Patients - First step: N=10, prenatal clinics, full text review
   Second step: Revise pamphlet
   Third step: N=20, prenatal clinics, interviews after reading

   Review by providers: N=10, pamphlets acceptability, fit with practice

   Review by CF Foundation: Appropriateness of CF disease description

2. Final revision, including work with graphic artist.
   We will not address production issues.

V ESTIMATED TIMELINE

We have two ongoing activities: finalization of pamphlet and drafting of Education and Consent Committee 'Report" to the Steering Committee

1. Finalization of Pamphlet could be done in four months June, 1999

2. Preparation of Committee report can be done concomitantly June, 1999

VI ASSISTANCE REQUESTED FROM STEERING COMMITTEE

1. Comments on organization, content, and wording of draft pamphlet

2. Discussion of implementation of pamphlet in various practice settings

3. Some implications of pamphlet content for provider education
   a. Sensitivity/specificity of test
   b. Residual risk
   c. More detail on disease
   d. Testing of relatives

4.What does the Steering Committee expect regarding a report from this committee – a 'stand alone' report, 'part' of a final Steering Committee report, etc. ?

ACMG Working Group on Cystic Fibrosis Screening

RECOMMENDATIONS OF THE LABORATORY STANDARDS COMMITTEE

Wayne Grody, Co-Chair
Garry Cutting, Co-Chair
Bob Desnick (Chair, Accred. of Gen. Srvcs. Cmte.)
Christine Eng
Kathy Klinger
Sue Richards
Mike Watson
George Cunningham, *ex officio*
Reed Pyeritz, *ex officio*
Mike Mennuti, *ex officio*

INTRODUCTION:

[*to be added*]

CONCERNS:

The identification of the cystic fibrosis gene, *CFTR*, in 1989 offered the hope of screening individuals and couples with no family history of the disease in order to alert those unknowingly at risk for producing children with this common disorder and offering them prenatal diagnosis or other reproductive options. After much debate and several pilot screening studies, an NIH Consensus Panel recommended, in 1997 that *CFTR* mutation testing be offered to all pregnant couples and those contemplating pregnancy. However, implementing delivery of mass population screening for cystic fibrosis mutation carriers along these lines remains problematic because of the following circumstances:

- the large number of *CFTR* mutations
- the absence of guidelines for developing appropriate mutation test panels

- the differing prevalence of individual *CFTR* among different populations, based in large part on ethnicity
- the extreme ethnic heterogeneity of the U.S. population
- the increasing admixture occurring among ethnic groups in the U.S.
- the wide clinical variability of the disorder
- the inconsistency of genotype-phenotype correlations for particular mutations
- the fact that not all *CFTR* mutations cause cystic fibrosis
- the changing prognosis of the disease in the face of new and novel therapies
- the documented lack of interest by nonpregnant couples in being screened and consequent limitation of options available to at-risk couples who undergo testing during pregnancy
- the huge anticipated burden that widespread screening would place on existing genetic counseling resources

Nevertheless, we recognize that further delay in implementing the NIH Consensus Conference recommendations risks perpetuating inadequate access to CF carrier testing in the United States. Moreover, the problems with offering CF carrier screening to the general population, while substantial, are of equal order of magnitude to some screening programs already in practice, such as maternal serum multiple marker screening for aneuploidy in the fetus.

While there will be foreseen and unforeseen difficulties, the recommendations of the Laboratory Standards Committee outlined here, in conjunction with those of the other component working groups reporting to the Steering Committee, are designed to ensure that population carrier screening for *CFTR* mutations will be as effective and appropriate as possible.

ISSUE: Target Population

There has been much discussion and debate over which ethnic/racial groups should be offered CF carrier testing in a population screening program. Some feel that screening should be limited to those populations, such as non-Jewish Caucasians and Ashkenazi Jews, in which both the carrier frequency and the detectability of the majority of prevalent mutations are sufficiently high to justify the effort and ensure that the program is efficient and cost-effective for both the clinician and the laboratory. Others feel that the marked and growing ethnic admixture in the United States makes it difficult to readily classify or exclude patients based on ethnic group, and that even attempting to make such ascertainments in a busy clinical setting would place an undue burden on the primary care physician and impair the overall cost-effectiveness of the program. While some of the most successful genetic screening programs, such as that for Tay-Sachs disease, have narrowly targeted particular ethnic groups, there is precedent in the newborn screening field for universal screening without pre-test ascertainment of ethnicity despite wide differences in disease incidence among ethnic/racial groups (e.g., newborn screening for sickle cell disease).

RECOMMENDATION :

1. The Committee appreciates the logic behind both of these positions. As a compromise, **we recommend that CF carrier testing be discussed with non-Jewish Caucasians/Ashkenazi Jews, but all patients should at least be made aware of the availability of testing along with the detectability limits in their respective ethnic/racial groups through brochures or other efficient methods.** In particular, Asian-Americans and Native-Americans without significant Caucasian admixture should be informed of the rarity of the disease and the very low yield of the test in those populations. Testing should be made available to African-Americans, recognizing that only about 50% of at-risk couples will be detected. This approach may require a consent form which recites this information as well as a sign-off for those opting out of testing after reading the brochure. The latter point will be addressed further by the Working Group on Patient

Education and Informed Consent.

2. **While for practical purposes, testing will often occur in the prenatal setting, we recommend that preconception testing be encouraged whenever possible.**

ISSUE: Screening Model -- Couple vs. Sequential

RECOMMENDATION :

Testing should be done using either a sequential or couple-based model, depending on the target population, the nature of the clinical setting, and the appropriate judgement of the practitioner. The sequential model involves first testing one member of the couple (usually the woman), testing the partner only if the first test is positive, and providing full disclosure of test results to both individuals. The couple model described here involves simultaneous collection and testing of specimens from both individuals, with both partners informed of the results at the conclusion of testing. This approach is suggested for Caucasian couples of Northern European descent and also for Ashkenazi Jewish couples, particularly when concurrently testing for other common genetic disorders in that population. The sequential model may be more useful for groups in which the carrier frequency is lower and in situations where obtaining a sample from the partner is impractical. In general, though, the choice of model should be left to the individual center to use whichever method they feel most appropriate or practical.

While we can appreciate some of the theoretical psychosocial and cost advantages of the couple-testing model of Wald (Wald 1991), in which specimens are collected from both individuals at the start and positive-negative couples are reported just like negative-negative couples and treated as such, we do not endorse this approach because of ethical questions surrounding nondisclosure of test results and because it deprives the positive member of the couple of the opportunity of informing his or her relatives of their risk so that they too could be tested.

ISSUE: Core Mutation Panel

RECOMMENDATION :

In part because of the ethnicity considerations discussed above, **we recommend use of a pan-ethnic mutation panel, which should be adopted as a minimum standard by all testing laboratories.** The panel should include all mutations showing an allele frequency of >0.1% in the general U.S. population. The Committee feels that all mutations of this frequency should be included, regardless of whether they have been associated with mild or severe disease or related conditions such as congenital bilateral absence of the vas deferens. The panel should include mutation subsets shown to be sufficiently predominant in certain ethnic groups, such as Ashkenazi Jews and African Americans, so as to raise the yield or sensitivity of testing in those groups to a reasonable level.

Based on these criteria, **the Committee has compiled a list of 32 mutations (Table 1) which represent the obligatory minimum panel to be used for general U.S. population screening.** A recent survey of laboratories participating in the CAP/ACMG molecular genetics proficiency testing program nationwide revealed wide variation in the number and type of mutations offered by individual laboratories, ranging from 1 to 70 (Grody et al. 1998). Adoption of the minimum universal panel recommended here will promote much-needed consistency across the country and establish an acceptable standard of care for CF population carrier screening. Of course, laboratories concentrating exclusively on well-defined ethnic groups with a few prevalent mutations (e.g., Ashkenazi Jews) may utilize a smaller subset of the panel. Conversely, laboratories wishing to supplement this core panel with additional mutations particular to their own uses are free to do so.

ISSUE: Extended Mutation Panel

The question has been raised whether an extended or second-tier mutation test

panel should be offered to couples testing positive-negative with the basic core panel.

RECOMMENDATION :

After careful consideration, the Committee decided that **an extended panel should not be offered routinely** to such couples, since it would have the effect of increasing patients' anxiety, would appear to endorse an alternative mutation panel beyond the basic one defined as standard of care, is likely for the foreseeable future to be available at only a single laboratory, and would provide very low additional yield, leaving such couples with the same level of uncertainty as they had before. It was agreed, however, that the existence of such a panel be made known to couples who request it and be utilized on a case-by-case basis as indicated by the clinical situation.

ISSUE: Quality Assurance

CFTR mutation analysis is a high-complexity laboratory procedure requiring sophisticated molecular biology and human genetics expertise. The advent of population carrier screening for *CFTR* mutations portends adding an extremely high test volume to a procedure of such high complexity and sophistication, a situation unprecedented in the field of laboratory medicine. For this reason it is imperative that such testing be restricted to laboratories possessing the requisite expertise, experience and physical resources.

RECOMMENDATION :

Any laboratory embarking on CF population carrier screening must be able to comply with the stringent quality assurance guidelines specified in the ACMG and CAP checklists and the report of the NIH-DOE Task Force on Genetic Testing, and must participate in the CAP/ACMG quality assurance and proficiency testing programs. Equal attention must be paid to pre- and post-analytic aspects of testing (e.g., appropriateness of test ordering, interpretation, reporting and counseling) as to the

laboratory test itself.

The Committee recognizes that, in the absence of available commercial test kits, the core mutation panel recommended here as standard of care will be difficult for some laboratories accustomed to a smaller panel to set up in-house. It is hoped that our recommendations will lead to some centralization of testing in the most capable centers as well as some impetus for manufacturers to develop kits and reagents with the core panel in mind in order to enhance utilization by additional competent laboratories.

ISSUE: Congenital Bilateral Absence of the Vas Deferens

CFTR mutations R117H and F508C, and sometimes others, along with the 5T variant of the 5T/7T/9T polymorphism within intron 8 of the opposite allele, have been found in a large proportion of otherwise healthy men with infertility due to congenital bilateral absence of the vas deferens; sometimes just the 5T variant and no *CFTR* mutation is found in these individuals. Testing for these mutations and variants in a large population screening program will inevitably produce tricky counseling problems because it will expand the risk ascertainment beyond that for classical CF. While this might be avoided by simply choosing not to screen for these alleles, that choice would be problematic in itself, since the relatively common R117H mutation can also cause classical CF. In addition, a specific F508C test is needed to distinguish it from the more common and serious ΔF508 mutation in some assay methodologies, and detection of the 5T variant (which is found in 5% of the normal population) provides useful prognostic information in relation to the other mutations.

RECOMMENDATION :

The Committee therefore reached the conclusion that **both the R117H and F508C mutations and the 5/7/9T intronic polymorphism must be included in the testing panel, while recognizing that this will have the unwanted effect of screening for male infertility**

as well as CF. Because of the subtle and complicated genetic issues raised, there was general feeling that **detection of one of these unusual mutation combinations in the screening program should be followed by referral to a geneticist for further counseling.** Information about the mutations associated with CBAVD should be included in reports and consent forms.

The Committee is aware of some unpublished data defining a new polymorphism or haplotype in tight linkage disequilibrium with clinical CF-associated vs. CBAVD-associated R117H mutations. If this marker could be incorporated into the test panel, it could potentially obviate the need to test for the 5T polymorphism with its attendant complications, since it would function as a surrogate test for *cis/trans* orientation of R117H (or other relevant mutation) and 5T. This marker will be followed closely and added to the recommended core mutation panel if it proves to be sufficiently informative.

ISSUE: Test Interpretation and Reporting

As is well known, both patients and many primary care professionals are not comfortable dealing with relative risks and non-absolute laboratory test results. It is essential that test reports for negative screens define as accurately as possible, based on current knowledge, the residual risk that the person tested could be a carrier of an untested or unknown mutation. This risk will vary greatly by ethnic group and should be so specified and individualized in the test report.

RECOMMENDATION :

The best current estimates of residual risks for the major ethnic groups after testing negative with the core mutation panel are listed in Table 2 [*to be added*]. For those centers doing concurrent couple screening, the negative/negative (or negative/positive) report must include the residual risk of having a CF child based on the couple's combined test results. For those centers doing sequential testing, a positive

test report on the first partner should include a recommendation that the other partner be tested also.

ISSUE: Referral to a Genetics Center

There was much discussion between our Committee and the Steering Committee regarding whether or not all positive-positive couples should be referred to a geneticist or genetic counselor for further explanation and counseling. Some felt that such referral was necessary to ensure that these couples receive the appropriate amount of accurate information about risks, prognostic factors and range of options available to allow for fully informed decision-making. Others felt that this could be impractical for remote practices which are far from such services, and furthermore felt confident that some obstetricians and other primary care physicians would be competent to perform such counseling themselves and should not be prohibited from doing so.

RECOMMENDATION :

To encompass both points of view, the Committee recommends that **a concise summary of the knowledge and expertise needed relative to CF, human genetics, and the interpretation of CF test results should be provided for the professional providing the counseling. Any primary care provider who does not feel comfortable explaining these concepts to the patients should refer them to a genetics professional.** We expect that most of the essential material can be adapted from that produced by the Patient Education and Informed Consent Committee.

ISSUE: Pilot Program

In making these recommendations, the Committee is concerned that large-scale CF screening of the type we are proposing has never been tried in a real-world setting within

the United States. The several funded pilot projects completed thus far, while useful and instructive, were conducted within the context of research projects and thus were somewhat artificial in their structure. It is possible that they may have failed to reveal certain potential problems and pitfalls that such screening might produce in a true clinical setting of very large scale, much as some adverse drug reactions come to light only after widespread commercial sale as opposed to the more limited Phase III trials conducted for FDA approval.

RECOMMENDATION :

Therefore, **we recommend that a program be established, and ideally federally funded, to evaluate our recommendations in a single large, diverse state (such as New York or California).**

REFERENCES

Grody WW, Desnick RJ, Carpenter NJ, Noll WW. 1998. Diversity of cystic fibrosis mutation screening practices. Am J Hum Genet 62:1252-1254.

Wald NJ. 1991. Couple screening for cystic fibrosis. Lancet 338:1318-1319.

Table 1

RECOMMENDED CORE MUTATION PANEL FOR GENERAL POPULATION CF CARRIER SCREENING

ΔF508	ΔI507	G542X	G551D	W1282X	N1303K
R553X	621+1G-T	R117H	1717-1G→A	A455E	3849+10kbC→T
R1162X	G85E	R334W	R347P	R347H	R560T
2789+5G→A	3659delC	2184delA	S549N	711+1G→T	3120+1G→A*
A559T*	2307insA*	G480C*	405+3A→C*	S1255X*	I506V**
I507V**	F508C**				

*African-American mutations
**CFTR variants/polymorphisms

Table 2

RESIDUAL CARRIER RISKS FOR VARIOUS ETHNIC GROUPS AFTER TESTING NEGATIVE WITH THE CORE MUTATION PANEL

[to be developed]

BAYLOR
COLLEGE OF
MEDICINE

One Baylor Plaza
Houston, Texas 77030-3498

Department of Obstetrics
and Gynecology

Joe Leigh Simpson, M.D.
Ernst W. Bertner Chairman
and Professor

TEL: (713) 798-8360
FAX: (713) 798-8410

Address correspondence to:
6550 Fannin, Suite 729A
Houston, Texas 77030

January 12, 1999

Stanley Zinberg, M.D.
Director of Practice Activities
American College of Ob/Gyn
409 12th Street, SW
Washington, D.C. 20024

Dear Stan:

I have favorable news to report from the American College of Medical Genetics (ACMG) Board of Directors meeting (Coconut Grove, January 7-9).

1. Ob/Gyn Spot on the Medical Genetic RRC. Following up our discussions with Mike Mennuti in Chicago concerning the need for an ACOG member on the Medical Genetics RRC, I contacted other ACMG Board members. These conversations indicated to me sensitivity to our plight and support for ACMG choosing an obstetrician-gynecologist. Thus, I thought it best not to load ACOG's guns (as would a letter from me to you and Ralph). This proved tactically correct, for the Board unanimously agreed to forward the name of Mark Evans as their new representative. An ACMG "spot" for an obstetrician will be more reliable than one from the AMA under any circumstances. Thus, lobbying the AMA should not be pursued, for the issue is solved.

2. Cystic Fibrosis Screening. Bob Desnick presented the attached report on CF Screening. We all agreed up to the final section beginning on p. 8, where Bob with quiet support from Reed Pyretiz proposed a "pilot study" prior to implementing widespread CF screening. Bob sought Board endorsement, which would then be used to "persuade" ACOG and NIH to delay implementation. I insisted on a time line for completing any study and said that longer than perhaps a year or so from now was unacceptable to me. When it became clear that Bob would set no time line (e.g., "applications had to be made, funding secured, results analyzed, etc."), any support he might have generated dissipated. Lynn Fleisher was especially helpful in pointing out current legal jeopardy, but almost everyone else agreed as well. Only Reed and Bob voted for the document with the proposed pilot study. After discussion, I then moved to delete that portion (pages 8 and 9) and insert a sentence urging ongoing "evaluation" once implementation actually begins. This passed unanimously. There thus remains no "wiggle room", and ACOG should not be let to believe the ACMG Board wants any. The Board

is on record as not wishing to delay beyond the reasonable time required to produce educational and other materials. ACOG should feel free to recommend the target date it considers reasonable.

Best regards,

Joe Leigh Simpson, M.D.
Ernst W. Bertner Chairman & Professor
Department of Obstetrics & Gynecology
Professor, Department of Molecular
& Human Genetics

bhs\ltrs\zinberg

Encl.

cc: Michael T. Mennuti, M.D.
Sherman Elias, M.D.
Ralph Hale, M.D.
Michael Greene, M.D.

ACMG Working Group on Cystic Fibrosis Screening

RECOMMENDATIONS OF THE LABORATORY STANDARDS COMMITTEE

Wayne Grody, Co-Chair
Garry Cutting, Co-Chair
Bob Desnick (Chair, Accred. of Gen. Srvcs. Cmte.)
Christine Eng
Kathy Klinger
Sue Richards
Mike Watson
George Cunningham, *ex officio*
Reed Pyeritz, *ex officio*
Mike Mennuti, *ex officio*

The identification of the cystic fibrosis gene, *CFTR*, in 1989 offered the hope of screening individuals and couples with no family history of the disease in order to alert those unknowingly at risk for producing children with this common disorder and offering them prenatal diagnosis or other reproductive options. After much debate and several pilot screening studies, an NIH Consensus Panel recommended in 1997 that *CFTR* mutation testing be offered to all pregnant couples and those contemplating pregnancy. However, implementing delivery of mass population screening for cystic fibrosis mutation carriers along these lines remains problematic because of the following circumstances:

- the large number of *CFTR* mutations
- the absence of guidelines for developing appropriate mutation test panels
- the differing prevalence of individual *CFTR* among different populations, based in large part on ethnicity
- the extreme ethnic heterogeneity of the U.S. population
- the increasing admixture occurring among ethnic groups in the U.S.
- the wide clinical variability of the disorder
- the inconsistency of genotype-phenotype correlations for particular mutations
- the fact that not all *CFTR* mutations cause cystic fibrosis
- the changing prognosis of the disease in the face of new and novel therapies

- the documented lack of interest by nonpregnant couples in being screened and consequent limitation of options available to at-risk couples who undergo testing during pregnancy
- the huge anticipated burden that widespread screening would place on existing genetic counseling resources

Nevertheless, we recognize that further delay in implementing the NIH Consensus Conference recommendations risks perpetuating inadequate access to CF carrier testing in the United States. Moreover, the problems with offering CF carrier screening to the general population, while substantial, are of equal order of magnitude to some screening programs already in practice, such as maternal serum multiple marker screening for aneuploidy in the fetus.

While there will be foreseen and unforeseen difficulties, the recommendations of the Laboratory Standards Committee outlined here, in conjunction with those of the other component working groups reporting to the Steering Committee, are designed to ensure that population carrier screening for *CFTR* mutations will be as effective and appropriate as possible.

Target Population

Testing should be offered to couples of reproductive age. While for practical purposes this will often occur in the prenatal setting, we recommend that preconception testing be encouraged whenever possible.

There has been much discussion and debate over which ethnic/racial groups should be offered CF carrier testing in a population screening program. Some feel that screening should be limited to those populations, such as non-Jewish Caucasians and Ashkenazi Jews, in which both the carrier frequency and the detectability of the majority

of prevalent mutations are sufficiently high so as to justify the effort and ensure that the program is efficient and cost-effective for both the clinician and the laboratory. Others feel that the marked and growing ethnic admixture in the United States makes it difficult to readily classify or exclude patients based on ethnic group, and that even attempting to make such ascertainments in a busy clinical setting would place an undue burden (not to mention liability risk) on the primary care physician and impair the overall cost-effectiveness of the program. While some of the most successful genetic screening programs, such as that for Tay-Sachs disease, have narrowly targeted particular ethnic groups, there is precedent in the newborn screening field for universal screening without pre-test ascertainment of ethnicity despite wide differences in disease incidence among ethnic/racial groups (e.g., newborn screening for sickle cell disease).

The Committee appreciates the logic behind both of these positions. As a compromise, **we recommend that CF carrier testing be discussed with Caucasians/Ashkenazi Jews, but all patients should at least be made aware of the availability of testing along with the detectability limits in their respective ethnic/racial groups through brochures or other efficient methods.** In particular, Asian-Americans and Native-Americans without significant Caucasian admixture should be informed of the rarity of the disease and the very low yield of the test in those populations. This approach may require a consent form which recites this information as well as a sign-off for those opting out of testing after reading the brochure. The latter point will be addressed further by the Working Group on Patient Education and Informed Consent.

Screening Model — Couple vs. Sequential

Testing should be done using either a sequential or couple-based model, depending on the target population, the nature of the clinical setting, and the appropriate judgement of the practitioner. The sequential model involves first testing one member of the couple (usually the woman), testing the partner only if the first test is positive, and providing full disclosure of test results to both individuals. The couple model described

here involves simultaneous collection and testing of specimens from both individuals, with both partners informed of the results at the conclusion of testing. This approach is suggested for Caucasian couples of Northern European descent and also for Ashkenazi Jewish couples, particularly when concurrently testing for other common genetic disorders in that population. The sequential model may be more useful for groups in which the carrier frequency is lower and in situations where obtaining a sample from the partner is impractical. In general, though, the choice of model should be left to the individual center to use whichever method they feel most appropriate or practical.

While we can appreciate some of the theoretical psychosocial and cost advantages of the couple-testing model of Wald (Wald 1991), in which specimens are collected from both individuals at the start and positive-negative couples are reported just like negative-negative couples and treated as such, we prefer not to endorse this approach universally because of ethical questions surrounding nondisclosure of test results and because it deprives the positive member of the couple of the opportunity of informing his or her relatives of their risk so that they too could be tested.

Core Mutation Panel

In part because of the ethnicity considerations discussed above, **we recommend use of a pan-ethnic mutation panel, which should be adopted as a minimum standard by all testing laboratories.** The panel should include all mutations showing an allele frequency of >0.1% in the general U.S. population. The Committee feels that all mutations of this frequency should be included, regardless of whether they have been associated with mild or severe disease or related conditions such as congenital bilateral absence of the vas deferens. The panel must include mutation subsets shown to be sufficiently predominant in certain ethnic groups, such as Ashkenazi Jews and African Americans, so as to raise the yield or sensitivity of testing in those groups to a reasonable level.

Based on these criteria, **the Committee has compiled a list of [__] mutations**

(Table 1) which represent the obligatory minimum panel to be used for general U.S. population screening. A recent survey of laboratories participating in the CAP/ACMG molecular genetics proficiency testing program nationwide revealed wide variation in the number and type of mutations offered by individual laboratories, ranging from 1 to 70 (Grody et al. 1998). Adoption of the minimum universal panel recommended here will promote much-needed consistency across the country and establish an acceptable standard of care for CF population carrier screening. Of course, laboratories concentrating exclusively on well-defined ethnic groups with a few prevalent mutations (e.g., Ashkenazi Jews) may utilize a smaller subset of the panel. Conversely, laboratories wishing to supplement this core panel with additional mutations particular to their own uses are free to do so.

Extended Mutation Panel

The question has been raised whether an extended or second-tier mutation test panel should be offered to couples testing positive-negative with the basic core panel. After much discussion, the Committee decided that **an extended panel should not be offered routinely** to such couples, since it would have the effect of playing into patients' neuroses, would appear to endorse an alternative mutation panel beyond the basic one we will be defining as standard of care, is likely for the foreseeable future to be available at only a single laboratory, and would provide very low additional yield, leaving such couples with the same level of uncertainty as they had before. It was agreed, however, that the existence of such a panel be made known to couples who request it and be utilized on a case-by-case basis as the clinical situation may indicate.

Quality Assurance

CFTR mutation analysis is a high-complexity laboratory procedure requiring sophisticated molecular biology and human genetics expertise. The advent of population

carrier screening for *CFTR* mutations portends adding extremely high test volume (throughput) to a procedure of such high complexity and sophistication, a situation unprecedented in the field of laboratory medicine. For this reason it is imperative that such testing be restricted to laboratories possessing the requisite expertise, experience and physical resources. **Any laboratory embarking on CF population carrier screening must be able to comply with the stringent quality assurance guidelines specified in the ACMG and CAP checklists and the report of the NIH-DOE Task Force on Genetic Testing, and must participate in the CAP/ACMG quality assurance and proficiency testing programs.** Equal attention must be paid to pre- and post-analytic aspects of testing as to the laboratory test itself.

The Committee recognizes that, in the absence of available commercial test kits, the core mutation panel recommended here as standard of care will be difficult for some laboratories accustomed to a smaller panel to set up in-house. It is hoped that our recommendations will lead to some centralization of testing in the most capable centers as well as some impetus for manufacturers to develop kits and reagents with the core panel in mind in order to enhance utilization by additional competent laboratories.

Congenital Bilateral Absence of the Vas Deferens

CFTR mutations R117H and F508C, and sometimes others, along with the 5T variant of the 5T/7T/9T polymorphism within intron 8 of the opposite allele, have been found in a large proportion of otherwise healthy men with infertility due to congenital bilateral absence of the vas deferens; sometimes just the 5T variant and no *CFTR* mutation is found in these individuals. Testing for these mutations and variants in a large population screening program will inevitably produce tricky counseling problems because it will expand the risk ascertainment beyond that for classical CF. While this might be avoided by simply choosing not to screen for these alleles, that choice would be problematic in itself, since the relatively common R117H mutation can also cause classical CF, a specific F508C test is needed to distinguish it from the more common and

serious ΔF508 mutation in some assay methodologies, and detection of the 5T variant (which is found in 5% of the normal population) provides useful prognostic information in relation to the other mutations. The Committee therefore reached the conclusion that **both the R117H and F508C mutations and the 5/7/9T intronic polymorphism must be included in the testing panel, while recognizing that this will have the unwanted effect of screening for male infertility as well as CF.** Because of the subtle and complicated genetic issues raised, there was general feeling that **detection of one of these unusual mutation combinations in the screening program should be followed by referral to a geneticist for further counseling.** Information about the mutations associated with CBAVD may also need to be included in reports and consent forms.

The Committee is aware of some unpublished data defining a new polymorphism or haplotype in tight linkage disequilibrium with clinical CF-associated vs. CBAVD-associated R117H mutations. If this marker could be incorporated into the test panel, it could potentially obviate the need to test for the 5T polymorphism with its attendant complications, since it would function as a surrogate test for *cis/trans* orientation of R117H (or other relevant mutation) and 5T. This marker will be followed closely and added to the recommended core mutation panel if it proves to be sufficiently informative.

Test Interpretation and Reporting

As is well known, both patients and many primary care professionals are not comfortable dealing with relative risks and non-absolute laboratory test results. It is essential that test reports for negative screens define as accurately as possible, based on current knowledge, the residual risk that the person tested could be a carrier of an untested or unknown mutation. This risk will vary greatly by ethnic group and should be so specified and individualized in the test report. The best current estimates of residual risks for the major ethnic groups after testing negative with the core mutation panel are listed in Table 2. For those centers doing concurrent couple screening, the negative/negative (or negative/positive) report must include the residual risk of having

a CF child based on the couple's combined test results. For those centers doing sequential testing, a positive test report on the first partner should include a recommendation that the other partner be tested also.

Referral to a Genetics Center

There was much discussion between our Committee and the Steering Committee regarding whether or not all positive-positive couples should be referred to a geneticist or genetic counselor for further explanation and counseling. Some felt that such referral was necessary to ensure that these couples receive the appropriate amount of accurate information about risks, prognostic factors and range of options available to allow for fully informed decision-making. Others felt that this could be impractical for remote practices which are far from such services, and furthermore felt confident that some obstetricians and other primary care physicians would be competent to perform such counseling themselves and should not be prohibited from doing so. To encompass both points of view, the Committee recommends that **a concise summary of the knowledge and expertise needed relative to CF, human genetics, and the interpretation of CF test results should be provided for the professional providing the counseling. Any primary care provider who does not feel comfortable explaining these concepts to the patients should refer them to a genetics professional.** We expect that most of the essential material can be adapted from that produced by the Patient Education and Informed Consent Committee.

Deleted

Pilot Program

In making these recommendations, the Committee is concerned that large-scale CF screening of the type we are proposing has never been tried in a real-world setting within the United States. The several funded pilot projects completed thus far, while useful and instructive, were conducted within the context of research projects and thus were

somewhat artificial in their structure. It is possible that they may have failed to reveal certain potential problems and pitfalls that such screening might produce in a true clinical setting of very large scale, much as some adverse drug reactions come to light only after widespread commercial sale as opposed to the more limited Phase III trials conducted for FDA approval. Therefore, we recommend that a program be established, and ideally federally funded, to pilot test our recommendations in a single large, diverse state (such as New York or California) before putting them into practice nationwide.

deleted

References

Grody WW, Desnick RJ, Carpenter NJ, Noll WW. 1998. Diversity of cystic fibrosis mutation screening practices. Am J Hum Genet 62:1252-1254.

Wald NJ. 1991. Couple screening for cystic fibrosis. Lancet 338:1318-1319.

Mutation	Validation	Study "A"		Validation	Study "B"
	%	N		%	N
ΔF508	74.50	1117		71.00	242
G542X	2.10	1117		1.20	242
G551D	2.30	1117		1.20	242
W1282X	2.00	1117		0.80	242
3905insT	0.13	764		-	242
N1303K	1.30	1117		1.60	242
3849+10kbC-T	1.00	764		0.80	242
R553X	1.20	1145		1.20	242
621+1G-T	1.10	1117		1.60	242
1717-1G-A	0.54	1117		0.80	242
1078delT	NS	764		-	242
2789+5G-A	1.00	764		1.20	242
3849+4A-G	NS	764		-	242
711+1G-T	0.131	764		-	242
R1162X	0.131	764		-	242
1898+1G-A	ND	-		-	242
R117H	0.89	1117		0.40	242
3659delC	0.262	764		0.70	242
G85E	0.262	764		0.80	242
2184delA	0.393	764		0.80	242
ΔI507	0.18	1117		0.40	242
R347P	0.80	764		-	242
R560T	0.30	764		0.80	242
A455E	NS	788		-	242
R334W	NS	764		-	242
Y122X	NS	764		-	242
S549R(T-G)	ND	-		-	242
Q493X	NS	764		0.80	242
V520F	0.131	764		0.40	242
S549N	0.12	817		-	242
Y1092X	NS	764		-	242
R347H	0.13	764		1.20	242
2183delAA-G	-	-		0.80	242
R1158X	-	-		0.40	242
E560X	-	-		0.40	242

23 with >0.1%

UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
Michael T. Mennuti, M.D.
Professor and Chair

5 Dulles, HUP (215) 662-3234 fax: (215) 349-5893

TO: Stan Zinberg, M.D., Sherman Elias, M.D, Mike Greene, M.D.

FROM: Michael T. Mennuti, M.D.

RE: CF issues

DATE: November 4, 1998

I participated in the Laboratory Committee meeting by speaker phone. We will hear more about it at the next steering committee. I did want to make you aware of a couple of discussion points so that you can look into them or think about them. I hope I have these right --- it is not always easy to hear or interpret the outcome of a meeting of a group of people when you are listening by speaker phone.

1. The Lab group is still not happy with offering screening to a targeted population. Gary Cutting indicated that the addition of a limited number of mutations to the panel would raise the sensitivity in African Americans to a level that is reasonably comparable to Caucasians. Our premise for excluding certain groups from targeted screening had been both low prevalence and low sensitivity. The Lab committee should have the numbers regarding improving the sensitivity in African Americans by time of our next meeting. That being the case, the steering committee will need to revisit the issue of targeted screening.

2. The Lab Committee seemed to feel strongly that we should leave the alternatives of couples versus sequential screening as acceptable alternatives and not state a clear preference for one or the other. The previous draft of the clinical group did this. It pointed out the advantages and disadvantages of both, and cited some examples. At the Steering Committee there was a decision to indicate that couple screening was "preferred" and that sequential screening was an alternative that "might be used" in some settings or for some patients. The document was revised to reflect this change.

In view of the Lab Committee feelings, it seems that we should rediscuss this. On the one hand, I am reluctant to go out with a choice for obstetricians even with clear guidance about how to make the choice. It does complicate an already complicated issue. However, as I have reconsidered this, I think that sequential screening may be the most practical in many populations or obstetrical settings and to depict it as less preferred is probably not wise. This may be particularly true if we do not go with targeted screening.

3. Regarding R117H --- Gary Cutting has new information about a marker that may avoid the need to do the 5T, 9T studies, etc. If I understood this correctly, this is a linked intragenic marker associated with clinical CF in the patients with the R117H mutations. I may have this a little muddled. If my understanding is correct, this marker would potentially more precisely separate the CBAVD (and "at risk for" pancreatitis cases) from classical CF and avoid the need for family studies for phasing. As far as I know this is unpublished and the numbers are small. However, Gary's experience thus far has been that this marker is consistently associated with R117H in the patients who have clinical CF.

Either way we will detect CBAVD and the question arose as to how this would be handled clinically. I didn't think there was much issue for debate. My sense is that the pre-test information would have to explain that a risk for having an infertile male offspring could be detected but that prenatal diagnosis would not be recommended. Presumably the parents would be informed of the results of their studies, unless they specifically asked that this aspect not be disclosed to them. This is my assumption but I think we will need to discuss this. Clinical Committee will need to decide what to include in their documents, once the Laboratory Committee has the information about this marker and makes a decision about including it in the panel or doing it secondarily when one parent has the R117H mutation

4. I was hoping for a fuller discussion about the wording of reports, i.e. interpretations and recommendations. I guess this will be done by a smaller group. I am not sure that they have settled on what will constitute the "panel"

5. They seemed to understand our concerns about not mandating referral to a geneticist, and will accept language that describes the expertise needed for counseling in certain situations.

Finally, I had a follow-up conversation with Gary Cutting, who you may know feels very passionately about these issues. His concern is that we are going from the research mode to a nationwide implementation without some phase-in of our plan that would identify unanticipated problems or pitfalls. It is certainly hard to argue with a "show me" or "phase in" approach. However, the problem is how would this be done and who would do it. As you know there are others who feel just as passionately that it should be done nationwide immediately. Gary's suggestion is to try to identify a single state, such as New York, to implement this first. I am not sure if that can be done or if we have the clout to try to make something like that happen. At any rate, I encouraged Gary to come to the next Steering Committee to discuss this with the full group.

See you at the Boards.

xc: Reed Pyeritz, M.D.
Bob Desnick, M.D., Ph.D.
Francis Collins, M.D.
Elizabeth Tompson, RN, MSN

UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
Michael T. Mennuti, M.D.
Professor and Chair

5 Dulles, HUP (215) 662-3234 fax: (215) 349-5893

TO: Steering Committee on Cystic Fibrosis Screening

FROM: Michael T. Mennuti, M.D.

RE: Revised Draft

DATE: October 19, 1998

Since there will be relatively little time between now and the meeting of the Laboratory Committee, I have summarized my notes from the Steering Committee Meeting and enclosed a revised draft of the Clinical Committee document which incorporates the changes we discussed (will need more work). Since this is the most current draft it should be the one used by the other Committees. Please be sure that copies include the notation "Confidential Draft"

I hope the following notes accurately reflect the many hours of discussion on 10/14.

1. The Steering Committee concurred that we would try to produce a single document. If so, some sections of the document produced by the Clinical Committee may become redundant and/or will have to reference other parts of the document. This will be attended to at a later time when the three components are merged.

2. The Steering Committee reached consensus to target Caucasians provided that screening will be offered "when there is Caucasian ancestry" rather than when one simply identifies one member as Caucasian and it will be offered "when in doubt". This has been incorporated.

3. The Steering Committee also reached consensus to indicate that concurrent screening is preferred, and that sequential screening is an option in individual cases or clinical settings. This has been incorporated as well.

4. The Steering Committee reached consensus that we could not mandate referral to a geneticist or a center. The document reflects the "suggestion" and the need to for counseling by individuals with the expertise etc.

5. There was agreement that the Education and Consent Committee would develop materials for the patients (couples), a packet for a woman to take home to her partner(when he doesn't accompany her), and also a packet for carriers to use to inform their extended families for purposes of cascade screening.

6. The Laboratory Committee agreed to deal with the question of whether an extended panel will be recommended to negative partners of positive/negative couples or for prenatal diagnosis of pregnancies when the mother has a mutation and the father will not be tested. The current draft of the Clinical Committee includes places where an "extended panel" might be referred to if this will be used. Also the algorithms include this.

If the laboratory Committee decides on a single panel ---the text should justify the rationale for not testing for a larger number of mutations, and we will delete reference to an extended panel in the Clinical Committee document.

7. It was agreed that the Laboratory Committee document would need to contain some discussion of R117H and 5T, 9T mutations, etc. --- the potential recommendation for family studies, etc.

8. Some members of the Clinical Committee questioned the necessity for written informed consent since this is not usually used for Tay-Sachs, SCD, etc. There was general agreement that there should be written consent. The Education and Consent Committee will consider a consent/decline form that will be a tear-off of the last page of the information brochure.

9. The Education and Consent Committee will discuss the issue of individual versus group education for consent -- and possible videos etc.

10. The three Committees will develop an integrated work plan with time-lines and submit this to the Steering Committee before the next meeting. One Co-Chair from each will participate in this discussion.

11. We anticipate that the next meeting will be in late January, 1999.

Thanks.

Preconceptional and Prenatal Carrier Screening for Cystic Fibrosis

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive genetic disorder in Caucasian populations. CF is characterized primarily by pulmonary and gastrointestinal manifestations of variable severity. Although there is a wide spectrum of clinical expression, most cases of CF are associated with substantial morbidity and mortality and require lifelong medical care. CF is more common in Caucasians and much less frequent in most other ethnic and racial groups. Since 1989 when the gene responsible for CF was identified, a large number of different mutations in the CF gene have been reported. Testing for these mutations has enabled genetic screening to identify CF carriers. This monograph provides guidelines for the implementation of carrier screening for CF in the context of reproductive health care.

Background

Offering screening tests for specific genetic diseases and malformations has become part of obstetrical practice. These tests help the clinician identify pregnancies at increased risk for these disorders and provide information so that couples can make informed reproductive decisions, including whether to have prenatal diagnosis. In general, genetic screening focuses on specific populations at increased risk for a disease based on family history or racial and ethnic background. Examples of genetic screening tests currently offered in obstetrical practice include Tay-Sachs and Canavan screening to individuals of Ashkenazi Jewish descent, sickle cell screening to those of African descent, and thalassemia screening to individuals of Asian and Mediterranean descent. *Genetic screening must always be voluntary and always requires informed consent.*

Incidence of CF

Individual inherited disorders are rare but collectively they account for one quarter to one third of all major birth defects. CF is the most common autosomal recessive genetic disease among Caucasians, with a frequency of one in 3,300 (Table 1). The frequency of CF in Hispanics is approximately one in 8,000-9,000; in African Americans, one in 15,000; in Asian Americans, one in 32,000; and is low in most other racial or ethnic groups. Limited studies indicate that the frequency of CF may be similar to or higher than that of Caucasians in Pueblo (one in 3,970) and Zuni (one in 1,580) Native Americans.

Inheritance of CF

CF is inherited in an autosomal recessive fashion. CF carriers have a mutation in one of their two copies of the CF gene. One-half of the children of CF carriers will also be CF carriers. In general, carriers are healthy individuals and they are not usually aware of their carrier status unless they have an affected relative or offspring. Couples in whom both partners carry a CF mutation have a one in four chance of having an offspring with CF in each pregnancy. When both parents are carriers, two-thirds of the unaffected children will be CF carriers.

In 1989 the gene which causes CF was isolated and localized to chromosome number 7. Since that time over 750 different mutations in the gene have been reported in individuals with CF. The frequency of the specific mutations varies among populations. For example, delta F508, the first CF mutation identified, accounts for 70% of the CF mutations in Caucasians of Northern European descent but only 30% of CF mutations in individuals of Ashkenazi Jewish descent. A different mutation, the W1282X mutation, is more common in Ashkenazi Jews. For Caucasians of Northern European descent, 15 to 20 rarer mutations account for less than half of the remaining detectable CF alleles.

Pathophysiology and Clinical Presentation of CF

The gene product, CF transmembrane conductance regulator (CFTR), was also identified in 1989. The CFTR protein functions as a cAMP-regulated chloride channel in the apical membrane of epithelial cells. Mutations in the gene cause defective chloride transport resulting in high sweat chloride levels and tenacious mucus in the lungs and pancreas which lead to the major clinical features of CF.

In the US, approximately 850 individuals are diagnosed with CF each year, nearly two-thirds prior to 1 year of age. Individuals with mild manifestations of CF may not be diagnosed until adulthood. CF is typically a multisystem disease that primarily causes progressive pulmonary disease due to chronic endobronchial inflammation and pulmonary infection. Pancreatic insufficiency and intestinal malabsorption is present in 85% of all affected individuals. Other manifestations include meconium ileus (which occasionally may be identified *in utero* late in pregnancy by means of ultrasonography) and recurrent distal intestinal obstruction in older patients. Chronic sinus disease and nasal polyps, diabetes mellitus, liver disease and pancreatitis can also be observed. Men with CF are infertile due to congenital bilateral absence or atresia of the vas deferens.

Recently, men who have congenital bilateral absence of the vas deferens (CBAVD) but no other clinical manifestations of CF have been found to have a mutation in one or both of their CF genes. In addition, some patients with chronic or idiopathic pancreatitis have also been found to have similar mutations in one or both of their CF genes.

The pulmonary manifestations of CF range from severe progressive chronic lung disease to very mild pulmonary symptoms. Only 15% of individuals with CF have normal pancreatic function. The vast majority of patients with CF die as a result of pulmonary complications. A cure is not available, but aggressive medical therapy has resulted in increases in survival

to a median of approximately 30 years of age and much longer in patients with pancreatic sufficiency.

The diagnosis of CF is considered when one or more of the clinical features are present. A sweat chloride test, often in conjunction with DNA studies, is used to confirm the diagnosis. Management often includes chest physical therapy, antimicrobial drugs, anti-inflammatory agents, nutritional support, and pancreatic enzyme therapy, which result in increased survival and quality of life. Individuals with end-stage pulmonary disease may be candidates for lung transplantation. Gene therapy and rectification of the electrolyte transport by various pharmacological means are being actively investigated. However, investigators do not anticipate a cure in the near future.

Carrier Screening for CF

In 1997, a National Institutes of Health Consensus Development Conference recommended that genetic screening to identify carriers of CF should be offered to the following adult populations:

- adults with a positive family history of CF
- partners of individuals with CF
- couples currently planning a pregnancy
- couples seeking prenatal care

Studies have demonstrated that despite a couple's desire to have a healthy child there is limited interest in CF screening prior to pregnancy. Pregnant women and individuals with a positive family history are more likely to be interested in screening although interest, even among this group, was not universal. Many couples who agree to carrier screening do so for reassurance with the expectation that the screening tests will be negative. Studies have

demonstrated a high level of patient satisfaction after undergoing carrier screening for CF. Not all couples who are found to be carriers proceed with prenatal diagnostic testing or termination of an affected pregnancy. How couples intend to use the information should not be a factor in determining whether to offer or perform CF carrier screening.

To whom should carrier screening be offered?

See Fig 1.

Individuals with a family history of CF

Individuals with a family history of CF are at higher risk of having children with CF. The risk for being a carrier of a CF mutation depends on the relationship to the affected family member. In eliciting the family history, the practitioner should specifically inquire about CF in family members. Some individuals with a positive family history are familiar with the disease and are also aware of their increased risk of being a carrier. Even those who had genetic testing in the past may benefit from genetic counseling since recent developments may have improved the ability to reassess their carrier status. Genetic referral should be considered when there is a positive family history, because the interpretation of test results and estimation of risk may be more complex than in the general population.

Partners of individuals with CF

An individual with CF may have either a child who is a carrier of CF or a child affected with the disease depending on the carrier status of the partner. Carrier screening should be offered to partners of individuals with CF. Carrier screening may clarify a couple's risk of having a child with CF and provide them with helpful information for reproductive decision-making. The majority of these individuals are aware of their increased risk for having a child with CF.

Couples planning a pregnancy or seeking prenatal care

CF screening should be offered to couples in whom one or both members have European Caucasian ancestry, and who are planning a pregnancy (i.e. those seeking preconception evaluation, or treatment for infertility), or who are presenting for prenatal care during the first or early second trimester. In contrast to the recommendations of the NIH Consensus Panel, the recommendation to offer carrier screening selectively to Caucasians is based on two factors: frequency of the disease and the detection rate (sensitivity) of the test. Offering CF carrier screening is only recommended for populations in whom there is both a high frequency of carriers and a high detection rate. The frequency of the disease in European Caucasians is considered to be relatively high (one in 3300) and the detection rate of screening is 80% and is even higher among those of Askenazic Jewish descent (97%). In contrast, offering screening is not recommended for African Americans, Hispanics, or Asian Americans in whom the incidence of the disease and the detection rate is lower (Table 1). However, any couple in these racial or ethnic groups who request information about CF screening should have this made available.

The ethnicity of the partners should be ascertained at the time of the initial history and used by the practitioner to determine whether the couple is at higher risk for having a child with CF. In many cases, it is necessary to ascertain the ethnic background or origin of their grandparents in order to assess their risk. At times, the clinician may have difficulty determining whether one or both members of a couples have ancestry which would place them at higher risk. In these cases offering screening is advisable. Any patient in the higher risk groups who is considering CF screening should receive educational information regarding the natural history of the disease, disease prevalence, sensitivity and limitations of carrier screening.

In the event that an individual or couple from a lower risk population requests information about screening for CF, they should be provided with similar information and the limitations of screening based on the frequency of the disease and the sensitivity of the test in the their racial or ethnic group should be fully discussed. If they understand this information and request screening, the request should be honored.

When should CF carrier screening be offered?

Ideally, carrier screening should be offered prior to conception to allow couples to consider their reproductive options if they are carriers. However, studies have shown that interest in screening for CF is limited and occurs primarily in persons with a positive family history or among pregnant women. Therefore, most screening will be requested when a patient seeks prenatal care. During pregnancy, screening should be offered during the first trimester or early second trimester to ensure that the couple receives the test results within a time frame that will allow them to consider having prenatal diagnosis if they are both carriers and to have the option of termination of pregnancy in the event that the fetus is affected.

Screening Strategies

Several strategies may be used when offering CF carrier screening. With *concurrent screening* both partners are tested simultaneously. (Figure 2) With *sequential screening* one partner is tested and the second partner is only tested if the first partner is identified as a carrier. (Figure 3)

Concurrent screening is the preferred strategy, particularly when screening is offered during pregnancy. Concurrent screening will more rapidly identify carrier couples. This may be important when there are time constraints for the selection of the method of prenatal diagnosis (i.e., CVS versus amniocentesis) or when advancing gestation may limit the availability of the option of selective termination of affected pregnancies. Furthermore,

concurrent screening more precisely identifies each individual's carrier status and provides the couple with the lowest residual risk of having a child with CF following negative screening. Positive screening results of either partner may be used to identify other relatives at high risk for being carriers. Concurrent screening for CF is particularly recommended when both members of the couple are having screening tests for other genetic disorders (e.g. Tay-Sachs and Canavan disease).

Concurrent screening will identify couples in whom one partner is a carrier but the other does not have a detectable mutation (i.e. positive/negative couples). In this situation the risk for CF is increased, rather than reduced, but prenatal diagnosis cannot be performed. For example the risk levels for European Caucasians who are identified as a positive/negative couple is intermediate (1 in 564) between that of positive/positive couple (1 in 4) and negative/negative couple (1 in 80,000). See tables 2 and 3. Studies have demonstrated that positive/negative couples do not experience anxiety as a consequence of the results of their screening tests.

Since the likelihood that both partners will screen positive is less than 1%, sequential screening may be preferred by some couples and may be utilized in individual clinical settings. Using this approach, one partner is screened. The other partner is only screened if the first partner is positive for a mutation in the CF gene. Depending on the gestational age, the delay inherent in the sequential approach to screening may result in a more limited choice of prenatal diagnostic procedures or other reproductive options. When the first partner screened does not have a detectable mutation, the residual risk for having a child with CF, although quite low, is higher than when both partners have had negative screening tests. For example, in a European Caucasian couple in whom one partner tests negative the risk of having a child with CF is reduced to 1 in 16,000 in contrast to the residual risk of 1 in 80,000 if both partners had been tested and were negative. If the

woman screens negative, a partner who is a CF carrier will not be identified and carrier screening will not be offered to his extended family. Sequential screening identifies fewer (one-half) of positive/negative couples in whom one partner is a carrier and a mutation cannot be detected in the other partner.

Screening Process

Pretest counseling and educational material in the form of written material, videos, and/or interactive computer programs should be provided for the patient and, whenever possible, her partner. [refer to Education and consent Committee's section of document] The information about screening for CF should be provided in a non-directive manner. This information may be ideally provided by trained support staff in the ambulatory practice setting. If the partner does not accompany a woman to her prenatal or preconception visit, educational material should be provided for the partner.

Written, informed consent should be obtained only after the woman and her partner have had an opportunity to review the educational material and receive pretest counseling. {refer to Education and Consent Committee's section]. When the woman or her partner decline screening, the medical record should reflect that the information was provided, screening was offered and the decision was made not to be screened.

Laboratory testing for CF Carrier Screening

The carrier screening test for CF is performed on DNA which may be extracted from any cells (except gamete), although most laboratories use blood lymphocytes or buccal epithelial cells. The provider should determine the source and quantity of specimen required by the laboratory. The obstetrical provider should supply all of the history and demographic information requested by the laboratory to interpret the results.

It has been recommended that the standard screening tests for CF should encompass the 30 mutations which have a frequency estimated at greater than 0.1% in the US population and are listed in Table ___. This screening is expected to have a sensitivity of ___ in Caucasians of European descent, and of ___ in Ashkenazi Jews. The sensitivity and residual risk of being a carrier after negative screening for these mutations are provided in Table 1. Laboratory reports should include the results of screening and an interpretation. When screening of one or both partners is positive this interpretation should include an estimation of the risk of having a child with CF and recommendations for any additional testing. When screening is negative on both partners this interpretation should include estimates of the residual risk of the partners being CF carriers and of having a child with CF. **[[??? Lab Committee-?** extended panel, if so we would insert this sentence here -- -When one partner has CF, or is identified as a carrier, testing the other partner for a much larger number of mutations (e.g. ____) may be indicated.]] A more detailed description of the laboratory aspect of CF screening is provided on pages ____ .

Counseling Before Screening

To help couple make a decision about whether to have screening for CF, they should receive information which includes a concise description of the following aspects of CF:

- The natural history of CF including the variability, and survival rates
- Current medical therapy
- The carrier frequency
- Inheritance
- Testing options for carrier screening and prenatal diagnosis
- Limitations of testing
- The implications of positive and negative results

The range of reproductive options that may be available to couples who are both carriers should be discussed. For couples having screening prior to conception, these may include adoption, gamete donor programs, prenatal diagnosis and termination or continuation of affected pregnancies . For couples having screening during pregnancy prenatal diagnosis and termination or continuation of affected pregnancies are the options that would be applicable. Patients should understand that screening is voluntary and that their medical records, including test results, will not be released without expressed written consent. Every effort should be made to ensure confidentiality of the test results.

Screening Limitations

• Screening can not detect all CF mutations. Therefore, **a negative screening test on one or both members of a couple does not exclude the small possibility of an affected offspring.** For example, at a detection rate of 80%, a Caucasian couple with a negative family history having concurrent screening in whom both partners have a negative screening test, the risk of the offspring having CF is lowered from one in 3,000 to one in 80,000 but is not zero (See Table 2). For a similar couple having sequential screening in whom only one partner is screened and that partner is negative, the residual risk is one in 16,356 (See Table 3). The level of this residual risk is dependent on the racial or ethnic group of the patient and on the specific mutations for which testing has been performed, and whether only one or both partners have been screened. (See Tables 2 and 3)

• Following screening, the **estimate of a couple's risk for having a child with CF assumes correctly identified paternity.**

• The **estimate of residual risk only apply when the family history is negative.** The accurate estimation of the carrier risk for individuals with a positive family history requires knowledge of the mutations in the affected family member, and the relationship to the person with CF. Assessment of the risk in individuals with a positive family history may not be straightforward and the couple may benefit from genetic counseling and consultation with a clinician who has special expertise in this area.

• The **estimate of residual risk of having a child with CF applies only to pregnancies conceived as a couple and not with other partners.**

• Although some CF mutations are known to be associated with milder illness, **knowledge of the specific CF mutations cannot be used to predict accurately the severity of the disorder in the offspring.** Couples with an affected fetus should be offered counseling about CF by an individual with special expertise in this area who can provide a general description of the clinical range of severity, treatment, etc.

Interpretation of Results and Post-Test Counseling

Both Patient and Partner Test Negative (Negative-Negative)

In a Caucasian couple of European descent in whom both partners test negative, the residual risk of having a child with CF is one in 80,000. In an Ashkenazi Jewish couple in whom both partners test negative, the residual risk is one in 3.5 million (see Table 2).

Either Patient or Partner Negative and Other Partner Not Screened

When only one partner is screened and he or she has a negative test result the residual risk of having a child with CF is decreased (see table 3). For example, the residual risk is one in 16,000 for a Caucasian couple and one in 108,000 for an Ashkenazi Jewish couple.

Both Partners Tested - One Test Positive, One Test Negative (Positive-Negative)

[[???Lab committee --- if an extended panel is going to be considered we would insert this concept here ---When a CF mutation is identified in either a patient or her partner it is advisable to request that the partner who is not a carrier be screened with an extended panel of mutations.]] Although the individual with a CF mutation has a 1 in 2 chance of transmitting the mutation to each of his or her offspring, the likelihood of having an affected child is low because the partner has a negative screening test (Table 2). At a detection rate of 80%, a Caucasian couple in which one partner is positive and the other is negative has a one in 564 risk of having a child with CF. The residual risk for an Ashkenazi Jewish couple when only one partner is screen positive is one in 3736.

There is a very small possibility that the screening test may identify two CF mutations in a patient or partner with a mild form of the disease. Such individuals should be referred to an individual with expertise, or a specialized center for a comprehensive evaluation and counseling for CF. For an individual with CF, the risk of having a child with CF when the partner is screen negative is one in 280 for a Caucasian couple and one in 1900 for an Ashkenazi Jewish couple.

Prenatal diagnostic testing is not recommended when only one member of the couple is a CF carrier, but the other partner does not have a detectable mutation. In this circumstance the determination that the fetus has inherited one CF mutation, and hence is a CF carrier, is not clinically useful information and would not be an indication to change obstetrical management or to discuss termination of pregnancy.

Both Patient and Partner Test Positive (Positive-Positive)

When both a patient and her partner test positive for a CF mutation they have a 1 in 4 chance of having a child with CF in each pregnancy. If screening is performed prior to conception, a discussion of the reproductive options for avoiding the risk of conceiving a child with CF include adoption, donor insemination, and donor egg programs. Couples electing donor gamete programs should inquire about the CF carrier status of potential donors. Couples should also be informed that prenatal diagnosis and termination of pregnancy if the fetus is affected with CF will be options if a pregnancy is established without using a donor gamete.

When screening is performed during early pregnancy and both partners are identified as carriers, prenatal diagnosis should be offered.

Patient Positive and Partner Untested

When the woman's screening test is positive and her partner declines or is unavailable for testing, the residual risk of having a child with CF in a Caucasian couple is approximately one in 100 (see Table 3). Testing of the partner should be encouraged to further refine the risk estimate for the pregnancy.

When screening is not performed on the partner, women who are identified as CF carriers should be informed of the availability and limitations of prenatal testing. Prenatal diagnosis can determine whether the fetus has inherited a CF mutation from the mother but may not distinguish between a carrier and an affected fetus. In the event that the fetus inherits the CF mutation identified in the mother, testing for a second mutation from the father may be undertaken [[????**Lab Committee** -- another place where we had ? of extended panel here --- by testing for an extended panel of mutations]]. Such testing may reduce the risk that the fetus has CF, but cannot totally exclude CF in the fetus.

373

374 **Prenatal Diagnosis of CF**

375 Prenatal diagnosis of CF may be performed on cells obtained by chorionic villus sampling
376 (CVS) or amniocentesis can be performed at 10-12 weeks or 15-20 weeks of gestation,
377 respectively. Ideally, screening will have been performed prior to 20 weeks of gestation to
378 ensure that prenatal diagnosis can be completed prior to extrauterine fetal viability in the
379 event that they would consider pregnancy termination if the fetus has CF. Some couples
380 who are carriers may elect to have prenatal testing for information only and would not
381 consider termination of a pregnancy in which the fetus is determined to be affected with
382 CF. Other couples may decline further testing even after they are identified as carriers.
383 These decisions should be supported by the clinician.

384

385 When a couple requests prenatal diagnosis for CF, testing is performed on amniotic fluid
386 cells or chorionic villus cells for the mutations which have been detected previously by
387 screening tests on the parents. Diagnostic testing for a larger number of mutations on
388 amniotic or chorionic villus cells may be indicated when the woman is a carrier and
389 screening of her partner has not been performed.

390

391 If two CF mutations are found in the fetus, the couple should be informed of the results
392 and appropriate non-directive counseling should be provided. Counseling should include
393 discussion of the options of continuation and termination of the pregnancy. An individual
394 able to provide information about the range of clinical severity of CF, management,
395 treatment, prognosis , and the potential for new therapeutic modalities should participate in
396 the counseling. *Counseling should include a discussion of the difficulties in predicting*
397 *outcome based on the genotype. At the present time, knowledge of the specific CF*
398 *mutations cannot be used to predict accurately the phenotype or the severity of the*
399 *pulmonary disease.*

Counseling and Screening of Family Members of CF Carriers

Except in cases of adoption, mis-attributed paternity or new mutations, one of the parents of a CF carrier will also carry the mutation. Since CF is an inherited disease, other close relatives of an individual who carries a CF mutation are at risk for carrying the same mutation. Since there is not a provider/patient relationship with these relatives and because of the need for confidentiality, the provider may not independently contact these relatives. Therefore, women or their partners who are identified as carriers of a CF mutation should be encouraged to discuss this with their family members and written information and other educational materials should be provided for them to use in these discussions. CF carrier screening should be offered to interested relatives, particularly siblings and first cousins who are of reproductive age.

Offspring of carriers have a 50% risk of having inherited a CF mutation from a parent with the mutation. Couples in which a partner is a carrier of a CF mutation should be encouraged to inform their offspring of their risk when they reach reproductive age. Carrier screening is not recommended during infancy, childhood or early adolescence. Likewise, when a fetus is identified as a CF carrier by prenatal diagnosis, parents should be counseled to inform the offspring, but only when they reach reproductive age.

Summary

CF carrier screening should be offered to patients with a positive family history of CF, partners of individuals with CF and Caucasian couples of European or Ashkenazi Jewish descent planning a pregnancy or seeking prenatal care. Information about CF screening and CF screening testis should be made available to other patients upon their request.

Screening may be accomplished prior to conception or during the first or early second trimester.

The clinician should identify couples to whom screening should be offered based on family history and ethnic background during the initial history. Counseling and educational material in the form of written material, videos, and/or interactive computer programs should be provided for the patient and whenever possible, her partner. In the event that her partner does not accompany her to a prenatal or preconception visit, suitable educational material should be provided to the woman to give to her partner. Simulataneous, i.e. concurrent, screening of women and their partners is preferred. However, women and their providers may elect sequential carrier screening for CF based on individual circumstances. Simultaneous testing is particularly important when there are time constraints for making a decision regarding prenatal diagnosis or the availability of termination of affected pregnancies.

Referral for counseling by a provider with special expertise may be considered when carriers of CF are identified, prior to prenatal diagnosis, or when an affected fetus is identified.

References

Asch, D.A., Patton, J.P. Hershey, J.C., Mennuti, M.T.: Reporting the results of cystic fibrosis carrier screening. Am. J. Obstet. Gynecol. 168:1-6, 1993.

Axworthy, D., Broch, D.J.H., Bobrow, M., Marteau, T.M.: Psychological impact of population-based carrier testing for cystic fibrosis: three year follow-up. Lancet 347:1443-1446, 1996.

Beaudet, A.L.: Invited editorial: carrier screening for cystic fibrosis. Am. J. Hum. Genet. 47:603-605, 1990.

Brock, D.J.H.: Prenatal screening for cystic fibrosis: 5 years' experience reviewed. Lancet 347:148-150, 1996.

Chillon, M., Casals, T., Mercier, B., et al.: Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. N. Eng. J. Med. 332:1475-1480, 1995.

Cohn JA, Friedman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS: Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Eng J Med 339:653-658, 1998.

The Cystic Fibrosis Genotype-Phenotype Consortium: Corrleation between genotype and phenotype in patients with cystic fibrosis. N. Eng. J. Med. 329:1308-1313, 1993.

Clayton, E.W., Hannig, V.H., Pfotenhauer, J.P., Parker, R.A., Campbell, P.W. III, Phillips, J.A. III: Lack of interest by nonpregnant couples in population-based cystic fibrosis carrier screening. Am. J. Hum. Genet. 58:617-627, 1996.

Congress of the United States, Office of Technology Assessment. Cystic fibrosis and DNA tests: implications of carrier screening, OTA-BA-532. Washington, DC: U.S. Government Printing Office, August 1992.

Doherty, R.A., Palomaki, G.E., Kloza, E.M., Erickson, J.L., Haddow, J.E.: Couple-based prenatal screening for cystic fibrosis in primary care settings. Prenat. Diag. 16:397-404, 1996.

Durie PR: Pancreatitis and mutations of the cystic fibrosis gene. N Eng J Med 339:687-688,1998.

Genetic Testing for Cystic Fibrosis. NIH Consens Statement 15(4):1-37, Apr 14-16, 1997.

Kerem, E., Corey, M., Kerem, B-S., Rommens, J., Markiewicz, D., Levison, H., Tsui, L-C., and Durie, P.: The relation between genotype and phenotype in cystic fibrosis - analysis of the most common mutation (DF_{508}). N. Eng. J. Med. 323:1517-1522, 1990.

Kiesewetter, S., Macek, M., Jr., Davis, C., Curristin, S.M., Chu, C.-S., Graham, C., Shrimpton, A.E., Cashman, S.M., Tsui, L.-C., Mickle, J., Amos, J., Highsmith, W.E., Shuber, A., Witt, D.R., Crystal, R.G., and Cutting, G.R.: A mutation in CFTR produces different phenotypes depending on chromosomal background. Nature Genetics 5:274-277, 1993.

Lemna, W.K., Feldman, G.L., Kerem Bat-sheva, Fernbach, S.D., Zevkovich, E.P., O'Brien, W.E., Riordan, J.R., Collins, F.S., Tsui, L-C., Beaudet, A.L.: Mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis. N. Eng. J. Med. 322:291-296, 1990.

Levenkron, J.C., Loader, S., Rowley, P.T.: Carrier screening for cystic fibrosis: test acceptance and one year follow-up. Am. J. Med. Genet. (In press).

Loader, S., Caldwell, P., Kozyra, A. Levenkron, J.C., Boehm, C.D., Kazazian, H.H., Jr., Rowley, P.T.: Cystic fibrosis carrier population screening in the primary care setting. Am. J. Hum. Genet. 59:234-247, 1996.

Mennuti, M.T., Thomson, E., Press, N.: Screening for cystic fibrosis: Follow-up workshop to the NIH consensus development conference. Obstet Gynecol (in press)

Mercier, B., Raguenes, O., Estivill, X., Morral, N., Kaplan, G.C., McClure, M., Grebe, T.A., et al.: Complete detection of mutations in cystic fibrosis of Native American origin. Hum. Genet. 94:629-632, 1994.

Ramsey, B.W.: Managemetn of pulmonary disease in patients with cystic fibrosis. N. Eng. J. Med. 335:179-188, 1996.

Rosenfeld, M.A., Collins, F.S.: Gene therapy for cystic fibrosis. Chest 109:241-252, 1996.

Rosenstein, B.J., Zeitlin, P.L.: Cystic fibrosis (seminar). The Lancet 351:277-282, 1998.

Rosenstein, BJ and Cutting, GR: The diagnosis of cystic fibrosis: a consensus statement. J Peds132:589-595, 1998.

Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, Braganza J: Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Eng J Med 339:645-652, 1998.

Welsh, M.J., Tsui, L-C., Boat, T.F., Beaudet, A.L.: Cystic fibrosis. In: The metabolic and molecular basis of inherited disease. 7th ed. New York: McGraw-Hill, pp. 3799-3876, 1995.

Wilfond, B.S., Fost, N.: The cystic fibrosis gene: medical and social implications for heterozygote detection. JAMA 263:2777-2783, 1990.

Witt, D.R., Schaefer, C., Hallam, P., Wi, S., Blumberg, B., Fishbach, A., Holtzman, J., Kornfeld, S., Lee, R., Nemzer, L., Palmer, R.: Cystic fibrosis heterozygote screening in 5,161 pregnant women. Am. J. Hum. Genet. 58:823-835, 1996.

Table 1. Incidence and Carrier Risk for Cystic Fibrosis based on Ethnicity

Group	Incidence	Carrier Risk
Caucasians	1/3300	1/29
Hispanics	1/8-9000	1/46
African Americans	1/15,300	1/62
Asian Americans	1/32,100	1/90

Table 2. Risk of CF in Offspring for Couples Tested

Group	Sensitivity	One Parent Positive One Parent Negative	Both Parents Negative
Caucasian European	0.80	1/564	1/79,524
Caucasian Ashkenzi Jewish	0.97	1/3736	1/3,489,424
Hispanics	0.57	1/424	1/44,944
African Americans	0.75	1/980	1/240,000
Asian Americans	0.30	1/512	1/240,100

Table 3. Risk of CF in Offspring when only One Parent Tested

Group	Sensitivity	One Parent Negative	One Parent Positive
Caucasian European	0.80	1/16,356	1/116
Caucasian Ashkenzi Jewish	0.97	1/108,344	1/116
Hispanics	0.57	1/19,504	1/184
African Americans	0.75	1/60,760	1/248
Asian Americans	0.30	1/46,080	1/360

Comments:

1. The Steering Committee concurred that we would try to produce a single document. If so, some sections of the document produced by the Clinical Committee may become redundant and or will have to reference other parts of the document. This will be attended to at a later time.

2. The Steering Committee reached consensus to target Caucasians provided that screening when offered "when in doubt". This has been incorporated.

3. The Steering Committee also reached consensus to indicate the concurrent screening is preferred, and that sequential screening is an option in individual cases or clinical settings. This has been incorporated as well.

4. There was agreement that the Education and Consent Committee would develop materials for the patients (couples), a packet for a woman to take home to her partner, and also a packet for carriers to use to inform their families for purposes of cascade screening.

5. The Laboratory committee will deal with the question of whether an extended panel will be recommended to negative partners of positive/negative couples or for prenatal diagnosis of pregnancies when the mother has a mutation and the father will not be tested. The current draft of the Clinical Committee includes places where an "extended panel" might be referred to if this will be used. Also the algorithms include this.

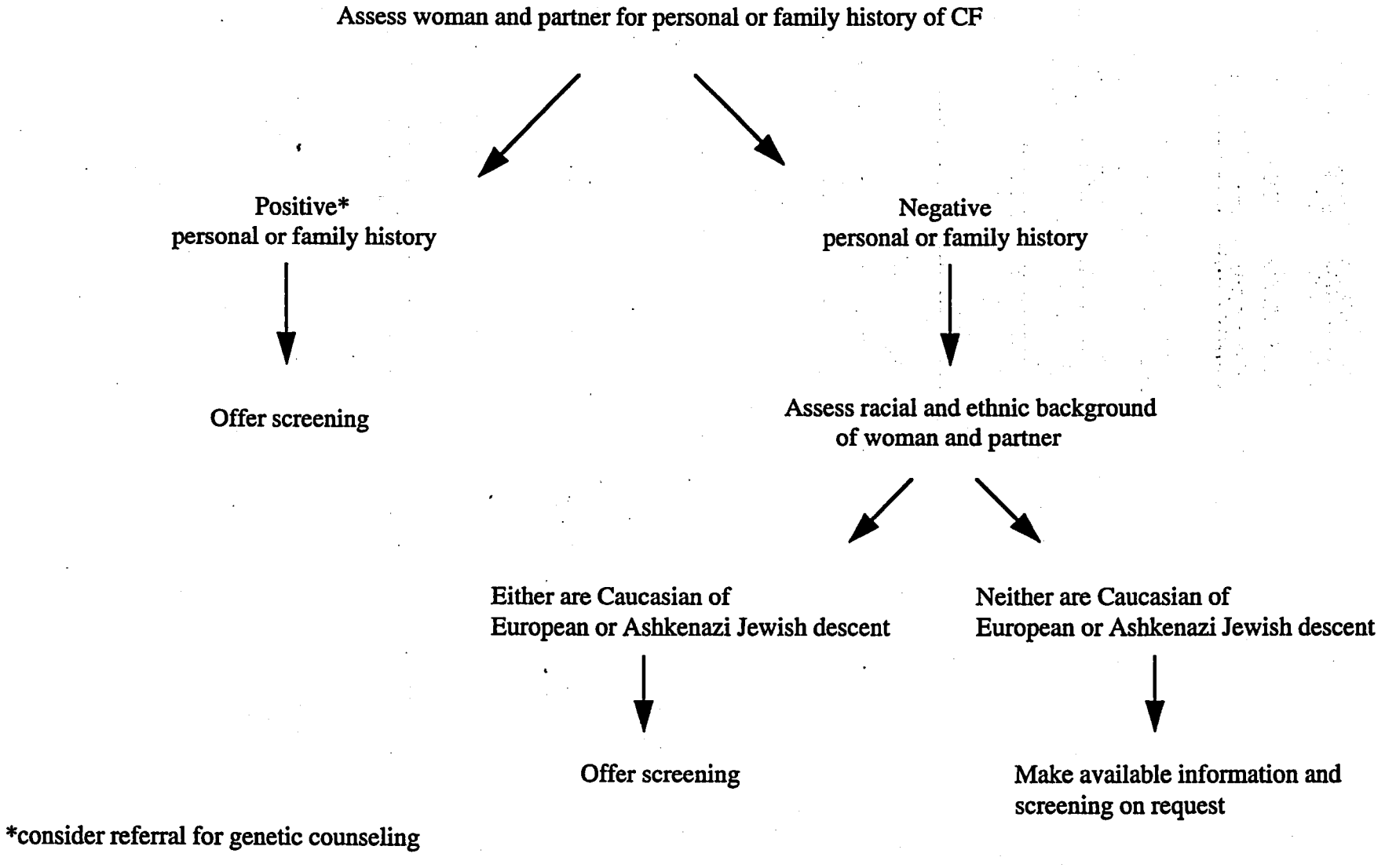
If the laboratory Committee decides on a single panel ---the text should justify the rationale for not testing for a larger number of mutations, and we will delete reference to an exteneded panel in the Clinical Committee document.

6. It was agreed that the Laboratory Committee document would need to contain some discussion of R117 and 5T mutations --- the potential recommendation for family studies to determine phase etc.

7. Some members of the Clinical Committee questioned the necessity for written informed consent since this is not usuaully used for Tay-Sachs, SCD, etc. There was general agreement that there should be written consent. The Education and Consent Committee will consider a consent/decline form that will be a tear-off of the last page of the information brochure.

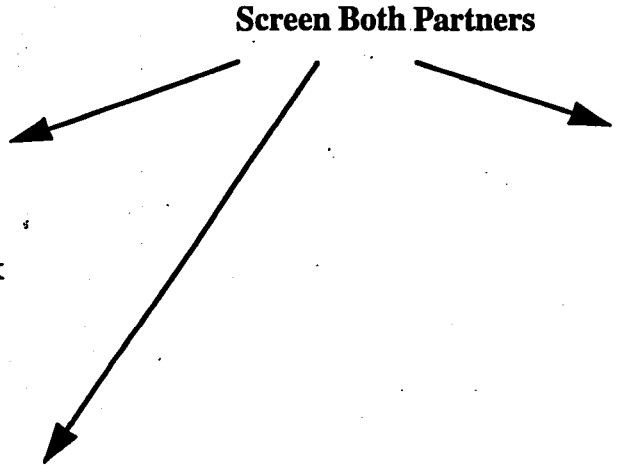
8. The Education and Consent Committee will discuss the issue of individual versus group education for consent -- and possible videos etc.

Implementation of Screening for CF



*consider referral for genetic counseling

Screen Both Partners Simultaneously



Both partners test negative

- Provide results
- Provide estimate of residual risk

One partner tests negative
One partner tests positive*

- Provide results
- Offer screening of negative partner with expanded panel of mutations
- Provide risk estimate for child with CF
- Offer family studies to partner with positive test
- Counsel to inform offspring of carrier risk (1/2 chance) when they reach reproductive age
- Prenatal diagnosis is not recommended

Both partners test positive*

- Provide results
- provide risk estimate for child with CF (1/4)
- Provide counseling regarding CF severity, variability & treatment
- Provide information regarding limitations of prediction of phenotype
- Offer prenatal diagnosis
- Discuss reproductive options for future pregnancies (e.g. donor gamete)
- Offer family studies
- Counsel to inform unaffected offspring of carrier risk (2/3 chance)when they reach reproductive age

* consider referral for genetic counseling

Screen Partners Sequentially

Screen one partner first

First partner tests negative
- Provide results
- Provide estimate of residual risk
- Make screening available to untested partner only on request

First partner tests positive*
- Provide results
- Provide estimate of risk
- Offer screening of untested partner with expanded panel of mutations
- Offer family study
- Counsel to inform unaffected offspring of carrier risk (1/2 chance) when they reach reproductive age

Screen untested partner

Second partner tests negative
- Provide results
- Provide risk estimate for having chld with CF
- Prenatal diagnosis is not recommended

Second partner tests positive*
- Provide results
- Provide risk estimate for child with CF (1/4)
- Provide counseling regarding CF severity, variability & treatment
- Provide information regarding limitations of prediction of phenotype
- Offer prenatal diagnosis
- Discuss future reproductive options (e.g. donor gamete)
- Offer family studies
- Counsel to inform unaffected offspring of carrier risk (2/3 chance)when they reach reproductive age
- Counsel about possibility that couple's children may be undiagnosed and affected

Second partner not tested
- Provide results
- Encourage partner testing
- Provide risk estimate for child with CF (e.g. 1/116 if Caucasian)
- Make prenatal diagnosis with expanded panel available
- Counsel to inform unaffected offspring of carrier risk (1/2 chance) when they reach reproductive age

* consider referral for genetic counseling