SUMMARY FROM THE PLANNING MEETING
OF THE CYSTIC FIBROSIS STUDIES CONSORTIUM (CFSC)
NOVEMBER 1 AND 2, 1991
NATIONAL INSTITUTES OF HEALTH

The first meeting of the Cystic Fibrosis Studies Consortium (CFSC) sponsored by the National Center for Human Genome Research, the National Center for Nursing Research and the National Institute of Child Health and Human Development was held on the campus of the National Institutes of Health on November 1 and 2, 1991.

After Dr. Juengst welcomed the participants, each Principal Investigator gave an overview of their individual projects. Subsequent to the overview of projects, individual issues common to all of the projects were discussed in detail.

LABORATORY ISSUES

The first issues that were discussed involved laboratory standards and practices. Dr. Haig Kazazian discussed the laboratory methods that he plans to utilize in providing CF testing for Drs. Holtzman and Rowley and possibly others. Initially, he plans to screen for six of the most common CF mutations by using a reverse dot blot method that he is developing in conjunction with the Cetus corporation. He stated that it may be possible to screen for more mutations in the future. The second presenter was Dr. Wayne Grody who plans to utilize PCR analysis to carry out mutation analysis on people having screening through his study. He, too, plans to screen for the six most common mutations. During the discussions it became clear that the technology is moving rapidly. As a result, it will be important to periodically re-evaluate the testing technologies being applied in these projects, to assure that they continue to be at an appropriate level.

The major recommendations that came out of the laboratory issues discussion included:

There should be a meeting of the directors of the laboratories which will be carrying out the tests for these studies.

The directors should explore quality control issues and proficiency testing in order to assure that the results of the tests being carried out are accurate.

PSYCHOLOGICAL TESTING AND EVALUATION

The second topic discussed was psychosocial testing and psychologic evaluation. Dr. Charles Spielberger gave an overview of the Spielberger, State-Trait Anxiety Index (STAI) self-evaluation

questionnaire (Spielberger, 1985) and the Spielberger, State-Trait Personality Index (STPI) self-analysis questionnaire. Dr. Lerman then gave a presentation regarding what she believed should be consistently measured throughout most of the projects. These included knowledge, health beliefs and psychological status. In the knowledge component, there should be attempts to determine the general knowledge about cystic fibrosis and its inheritance. Regarding health beliefs there should be an evaluation of individuals' perceptions about their personal risks about being a carrier, of their spouse being a carrier and of offspring being affected with the disorder. Additionally, there should be assessments about an individual's perceptions about severity of the disorder, efficacy and accuracy of the testing, benefits, risks, barriers and costs associated with screening. Finally, an effort should be made to determine an individual's perceived ability to cope with positive result and their consequences.

Dr. Lerman proposed the following evaluation scheme (including timing):

Proposed Evaluation Scheme

A subset of projects could standardize the evaluation scheme by including some of the timing as described below:

Time	Sample	Measures	Rationale
#1 At time of education	-All eligible subjects	-Demographics -Knowledge about CF/inheritance -Health beliefs	-Identify predictors of acceptance of screening
#2 Post Education Before Screening	Subjects consenting to be screened vs. those not consenting	-Knowledge -Health beliefs -Trait anxiety -Psychological status	-Assess impact of education -Baseline to assess impact of screening
#3 Following receipt of test results*	Subjects tested with both pos/neg results	-Health beliefs -Psychological status	-Assess immediate impact of screening

*Optimal design would assess post-results, but pre-counseling to separate effects of notification from effects of counseling.

#4 About 3 months post-screening	All subjects tested	-Health beliefs -Psychological status	-Assess short-term impact
#5 About 12 months post-screening	All subjects tested	-Health beliefs -Psychological status	-Assess long-term impact

The outcome recommendations from this discussion included:

> A common core set of instruments to be utilized in these studies should be identified. Although it is not necessary for all projects to use all of the same instruments and utilize them at all of the same times, the members expressed interest in hearing the recommendations from the experts in this area.

In regard to assessing psychological status, Dr. Lerman suggested attempting to identify mood disturbances (e.g. STAI, Profile of Mood States.) From the profile of mood states, she stated that one could use the anxiety subscale, the depression subscale and the total mood disturbance score (Mc Nair, 1971). Additionally, there could be an evaluation of functional health status (e.g. Functional Status Questionnaire) which includes physical and social/role functioning (Jette et al, 1986). Finally, she stated that there should be some evaluation of family functioning (Family Relatives Index of the Family Environment Scale (Loveland-Cherry et al, 1989, Dyadic Adjustment Scale)

INFORMED CONSENT AND CONFIDENTIALITY

The third set of issues discussed surrounded confidentiality and informed consent guidelines. Drs. Wright Clayton and Kopelman recommended that the informed consent materials contain up-to-date clinical assessments of cystic fibrosis, indicate that CF does not affect intelligence, and place more emphasis on the experimental nature of such testing and the collateral risks of testing (e.g. misidentified paternity, and the possibility that they might be asked about their status by insurers). Additionally, it was felt that the number of questionnaires that individuals will be asked to complete should be indicated. Finally, there was concern expressed about the focus on women, both preconceptionally and prenatally. Investigators should rethink why they are choosing to test women first, especially in the case of preconception testing.

Dr. Wright Clayton suggested there be a two part consent process.

The first component involves consenting to be educated about cystic fibrosis and CF carrier status. The second component should be a specific consent to carrier testing. In this, there should be a clear statement that the study is evaluating whether screening for CF carrier status is something that should be recommended to the public or not, and that the investigators do not know whether participating in the study will provide a net benefit to the subject. Again there should be a statement about the time commitment they need to make to complete questionnaires, etc.

Other general points discussed included the need for statements regarding the disposition of the blood samples once the test is completed, and the need to point out the limits of testing for six major mutations. Additionally, the point was made that there should be a different consent form for preconception clients vs. prenatal clients since the alternatives, potential benefits and risks may be substantially different.

Following are some suggestions for wording of the consent forms, prepared during the meeting by Ellen Wright Clayton, et. al.:

Pre-education Consent

We want to find out whether it is a good idea to carry out testing to determine if individuals carry a gene that causes CF, and if done, how it would be best done. Would you be interested in learning about CF and the way people get it and consider being enrolled in a research project to attempt to determine if screening for disorders such as CF should be carried out? Learning about genetic diseases may be interesting and useful, but it also may make you worry. In order to study these questions we would like to ask you to fill out the following questionnaire now and again at the end of the education program. Each questionnaire will take you about __ minutes to complete. Sometimes answering questions makes people uncomfortable for a little while but this almost always goes away.

Pre-testing Consent

[There should be a first be a short statement about CF, the disorder itself and a discussion about the fact that at this time, there is no cure for CF. (See Description of Cystic Fibrosis)]

Some people may want to be tested to see if they carry a gene that causes CF while others will not. One possible benefit to testing to see if you carry such a gene is that sometimes, we will be able to tell you if you are likely to have a child with CF and if you are, discuss with you options to lower your risk to have an affected child. In considering those options, there is no right answer about what to do. You may or may not

think that it is worth doing anything to avoid having a child with CF. Even if you would not want to prevent the birth of a child with CF, you might want testing just so you would have a better idea of what your life might hold in the future and can make plans accordingly.

If the present test does not show that you carry a gene that causes CF, you will know that your chances of having a child with CF is much lower than that of people who have not been tested. You would probably be happy to learn this information. However, even if you have no gene for CF identified, we can not be 100% certain that you will not have a child with CF. On the other hand, if a gene that causes CF is present in you (or your partner) we will be certain that you have an increased risk to have children with CF. Knowing this might cause you to be anxious or concerned and as a result, you may be intersted in learning how to reduce you risk to have a child affected with this disorder.

It is possible that finding out you carry a gene that causes CF may also cause other problems. In addition to the risk of becoming anxious, some people have suggested that individuals who carry a gene that causes a disorder such as CF may face discrimination, thus it will be important that the results of your testing be kept confidential and that it is released only to individuals that you choose. We will keep the results of your test confidential, but you must realize that your doctor, your insurance company or even you employer could ask you if you have ever had any genetic testing done. Whether you choose to disclose this information to anyone is totally up to you.

You should also know that if you are identified to carry a gene for CF, other members of you family may also carry the same gene. You will then need to decide if you feel it is important to tell them of their risk. Some individuals may choose to share this information with their relatives, while others will not.

For couples being tested include a statement such as:

You should know that any testing carried out on you and your partner will give only you and the partner who is being tested information about the chance that the two of you will have a child with CF. If you have a child with someone else, the risk may be different.

Additional draft informed consent materials developed by the Vanderbilt team are attached, for your information.

DEVELOPING AND TESTING EDUCATION MATERIALS

The fourth set of issues that were discussed were regarding the development and testing of education materials. Ms. Haddow and Ms. Capra gave an overview of the their concerns about and suggestions for the development and testing of the education materials for these projects. They emphasized that the education materials developed need to be closely linked to the information contained in the informed consent materials, however that they should not be exactly the same set of materials. It was suggested that an attempt be made to identify educational materials about CF that are already available, so that they can be used as guides (or perhaps even in lieu of) developing other brochures about this disorder or the test. The reading level of any materials developed should be evaluated and the importance of field testing was emphasized. Ms. Capra made several specific points in development and testing of educational materials (See enclosed documentation). One other point she raised after the meeting was that she felt that each project needed to define their expectations of participants at each stage of the study. For example, some studies were planning to "see how people felt about receiving information that indicated that no CF mutation was identified." She wondered if it wouldn't be better to have the expectation that such individuals should be reassured by this finding and then identify how to accomplish this goal.

Ms. Capra suggested that before developing educational materials, specific outcome objectives should be developed and then the materials should be aimed at addressing these objectives. The evaluation of these materials should be based on whether these objectives were achieved. No more than three to four key concepts should be included in any educational materials. For example:

> At the end of this educational activity (may be reading a pamphlet, viewing a videotape, or counseling session) the participants will be able to:
>
> 1. Describe cystic fibrosis (in a balanced way).
> 2. Recite their risk to carry a mutation for cystic fibrosis (or have a child affected with cystic fibrosis).
> 3. Identify risks and benefits of testing for cystic fibrosis.
> 4. Decide to be tested for CF mutations or not (without a sense of coercion).

One other important issue that was discussed at the meeting, but should be reemphasized, is that of the reading level of educational materials to be developed. It will be important for each project to identify the average reading level of their targeted population, and adapt their materials accordingly. It has become apparent, by reviewing existing materials, that some members of the genetics

community have developed materials that have a very high reading level, often higher than that present in many intended audiences. Enclosed you will find copies of some of the brochures/pamphlets regarding CF that are available. They may or may not be useful to you in the further development of your projects. There are also a number of computer programs available that attempt to measure textual reading levels that may be useful to the investigators.

ETHNOCULTURAL ISSUES

Dr. Strickland and Ms. Dixson shared their concerns regarding ethnocultural issues that are involved in these projects. It was stressed that investigators should be cognizant of value differences (e.g. perception of healthy vs. non-healthy; value of child-bearing high vs. low; male vs. female attitudes; reproductive decisions-who makes them, women, men or are they joint; value of extended family in decisions; etc.) The issues surrounding stigmatization of carriers should not be minimized. The cause of these altered genes may be viewed as due to "sins of the fathers". Blame may be placed on an individual determined to carry a gene for CF. The issue of consanguinity may be a concern particularly in cultures where consanguineous relationships are acceptable and in some cases promoted. When dealing with immigrants there may be some benefit to determining what generation you are dealing with. (First generation immigrants acculturation may be quite different than second or third generation immigrants.) The regional issues such as rural vs. urban must also not be forgotten.

Ms. Dixson emphasized the importance of recognizing how language-laden the protocols of these project are. Translations into other languages may be difficult or even impossible in some situations. There may be no word in another language that reflects what is meant in English. In making videos, cultural sensitivity is also important. When possible, the models should be from the particular race or ethnic group being targeted. In some cultures the decisions are solely made by the male, thus getting informed consent from a female may be virtually impossible. The importance of having team members who actually speak the language of the group being targeted was emphasized. Finally, the value of face-to-face counseling was discussed.

Since the meeting, concern has been expressed to NCHGR staff that Asian Americans will not be adequately informed of the true value (or non-value) of testing for CF mutations in their population in these projects if the generic risks, benefits and limitations are used. We would like to highlight this concern and urge each project that will be dealing with individuals from the Asian American population to be certain that the limitations of testing in them is emphasized.

COST-EFFECTIVENESS ISSUES

Dr. Asch gave a presentation regarding cost-effectiveness analyses. He discussed the difference between cost-effectiveness and cost-benefit analyses. He presented information about direct costs (costs of reagents, equipment, counseling, travel, etc.) and indirect costs (removal from work force for trip to doctor). Investigators must define effects that will be measured (e.g. years of life lost, number of births avoided, etc.) Finally, he discussed that costs and benefits may vary depending on whose perspective is being considered. Individuals and families may place quite a different value on certain outcomes than insurance companies or society. Enclosed is an article (Eisenberg, 1989) for your reference. This article covers the material that Dr. Asch presented at the meeting.

BALANCED DESCRIPTION OF THE CYSTIC FIBROSIS

One of the generic issues discussed was the importance of presenting the disorder of cystic fibrosis in a balanced way. It was apparent during the discussions that there were varying opinions among participants about the severity and impact of this disorder on individuals and their families. It was agreed that it would be useful to have a guide to describing this disorder so that there would be some consistency among the projects in the descriptions developed in education materials and in informed consent forms. The members of the consortium asked Drs. Wilfond and Wright Clayton to develop and circulate such a description. Following is the description they suggest.

Complete Version

Cystic fibrosis (CF) is an inherited disorder that changes the way the lungs and digestive system work. Children with CF have thick, sticky mucus, making them prone to lung infections. They may also have problems digesting food that may make them grow more slowly. Not all children are affected in the same way. A few will die in infancy, while others may have no symptoms into their teen years. Antibiotics and breathing treatments are used to prevent and treat lung infections. Digestion can be helped with medicines. Daily breathing treatments take time and the medicines are costly. As people with CF get sicker over time, they may need frequent hospitalizations to treat lung infections and other health problems. However, people with CF are as smart as other people, and may go to college, work full time, and get married. New treatments are being discovered each year, and there may even be a cure in the future. As a result, although some children will die at a young age, most children with CF

who are born today will probably live into their 40's or longer.

Abbreviated Version

Cystic fibrosis (CF) is an inherited disorder that changes the way the lungs and digestive system work. While there is no cure for CF, symptoms can be treated with medicines and breathing treatments. Daily care takes time and is costly. People with CF are as smart as other people, and may go to college, work full time, and get married. Not all children are affected in the same way. A few will die in infancy, while others may have no symptoms until they are adults. New treatments are being discovered each year, and there may even be a cure in the future. As a result, although some children will die at a young age, it is likely that most children with CF, who are born today, will probably liver into their 40's or longer.

The previous paragraphs have been evaluated by a MacIntosh computer program for evaluating reading level. they were determined to be at the sixth grade reading level which means that 91% of the U.S. population could read these paragraphs. (That apparently does not necessarily indicate that they also understand the information.) Enclosed is a copy of the computer evaluation that was carried out.

SHOULD SCREENING FOR CYSTIC FIBROSIS BE CARRIED OUT IN THE GENERAL POPULATION?

The goal of the studies involved in this consortium is to identify clinical education, testing and counseling practices that can maximize understanding and minimize the psychosocial risks for individuals and families seeking to learn their CF carrier status. An important policy issue in the background of these studies is the question of whether or not more widespread testing for CF mutations within the general population should be encouraged. This questions was discussed at several points during the meeting, and it was agreed that the answer to this important question is as yet unknown and that the outcome of these studies will make a vital contribution to any sound recommendations in this regard. This position should be kept in mind as technologies advance and professional policies evolve during the course of the these studies.

References:

*Jette, A. M. et al. The Functional Status Questionnaire: Reliability and Validity When Used in Primary Care. Journal of

General Internal Medicine (1986) 1:143-149.

*Loveland-Cherry, C. et al. A Psychometric Analysis of the Family Environment Scale. Nursing Research (1989) 38(5)262-266.

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*Spielberger C.D. Assessment of State and Trait Anxiety: Conceptual and Methodological Issues. The Southern Psychologist (1985) 2:6-16.

*Eisenberg, J.M. Clinical Economics: A Guide to the Economic Analysis of Clinical Practices. JAMA (1989) 262(20) 2879-2886.

*Enclosed

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