

Education and Testing Strategy for Large-Scale Cystic Fibrosis Carrier Screening

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Population-based screening for cystic fibrosis carrier mutations presents a number of challenges for genetic counselors, owing primarily to the inability of current DNA testing technology to identify all possible mutations and the difficulty involved in conveying the concept of residual risk to those patients who test negative. To address these issues, we are conducting a pilot study, as part of a consortium established by the National Center for Human Genome Research, to explore the efficacy, acceptance, and psychosocial impact of various approaches to carrier screening in an ethnically diverse Southern California population. This article reports the patient instructional and screening strategies we developed in the initial phase of the project in order to optimize our chances of answering these questions and delivering this service on a large scale.

KEY WORDS: cystic fibrosis; screening; genetic counseling; mutation detection; polymerase chain reaction.

INTRODUCTION

The identification of the gene involved in cystic fibrosis (CF) and the finding that screening for the most common mutations will identify only 80–90% of Caucasian carriers (and less in other ethnic groups) (Kerem *et al.*, 1989; Beaudet, 1990; Davies, 1992) has engendered debate regarding

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the potential efficacy, psychological impact, cost effectiveness, and ethical implications of widespread carrier screening by DNA analysis (Williamson, 1993; Wilfond and Fost, 1993). In response, a consortium was established by the National Center for Human Genome Research to address these issues through pilot CF carrier screening programs. As one of seven groups chosen, we have initiated a program to evaluate the interest, acceptance, and technical feasibility of large-scale CF screening in an ethnically diverse West Coast prenatal population. A major goal of this project is the exploration of efficient and informative methods of patient education and genetic counseling for this yet imperfect screening test administered on a large scale.

Pregnant women with no family history of CF are being recruited from a variety of health care settings including prenatal diagnosis centers, health maintenance organizations (HMO) and private obstetrics/gynecology practices in the Southern California area. This diversity of sites enables us to compare not only the interest and acceptance of CF screening, but the effectiveness of various educational methods, counseling, and health care delivery settings among the different ethnic and socioeconomic groups studied. Our Southern California target population is unique in that it is among the most ethnically diverse in the U.S. and includes such groups as Hispanic Americans and Asian Americans which have not heretofore been studied extensively in this context.

In order to address these questions, a carefully designed protocol was developed in consultation with other members of the NIH CF screening consortium. The counseling aspects of this strategy for assessing population-based CF screening are presented along with its impact on the first 500 subjects. This pre-pilot was conducted to evaluate our research protocol, educational materials, and psychological measurements prior to initiation of the full-scale study.

METHODS

Subject Selection

Pregnant women less than 18 weeks pregnant who had a negative family history for CF were considered eligible for the educational phase of our screening protocol which was adapted to the particular setting of each site. For the pilot phase, subjects were recruited primarily from two sources: an academic prenatal diagnosis center (UCLA) and several prenatal clinics at a large HMO (Kaiser Permanente). All of the patients were approached individually while they were in the waiting room prior to their regular appointment or between procedures.

Protocol

Patients were first asked by one of the genetic counselors or trained research assistants if they were interested in participating in the educational phase of the study where they would learn more about CF and CF screening. In this phase, subjects were given two questionnaires to complete, one before and one after receiving the educational material. In addition, they signed a consent form annotating the slight risk of anxiety engendered by the educational materials.

The measurement framework for the educational phase of the study (Fig. 1) indicates what is contained in each questionnaire. Both the pre- and post-education questionnaires consist of sections on mood assessment (Spielberger State/Trait Anxiety Inventory [Spielberger 1985]), knowledge, and health beliefs thought to be relevant to genetic screening. Some examples of the specific components assessed include social norms, perceived vulnerability, and perceived benefits and barriers to CF testing. The last part of the post-education questionnaire includes a set of open-ended questions where, for example, subjects are asked to elaborate on the reasons why they are choosing to be screened or not.

The educational intervention was either by a brochure or videotape on CF and CF screening, both of which were developed by our project staff of physicians, genetic counselors, and psychologists. These materials cover the clinical features and genetics of CF and the variable sensitivity of the screening test in different ethnic groups. On average, it took the subjects approximately 20 minutes to be educated and complete both questionnaires. After completing this part of the study, they were offered the option to be tested.

For those women who opted for CF testing, a consent form detailing potential psychological risks of testing was reviewed and signed. Specimen collection was by noninvasive cytobrush scraping of the buccal mucosa (Richards *et al.*, 1992). Mutation analysis was performed by polymerase chain reaction (PCR) amplification of subjects' DNA using biotinylated primers, with subsequent hybridization and colorimetric detection on a reverse dot blot (Saiki *et al.*, 1989; Chehab and Wall, 1992) containing oligonucleotide probes for six CF mutations and corresponding normal alleles, kindly supplied by Roche Molecular Systems. The six mutations are $\Delta F508$, G551D, R553X, G542X, N1303K, and W1282X.

Subjects testing negative were sent a result letter within 2 weeks. A short follow-up questionnaire was mailed along with the letter to assess retention of CF knowledge, understanding of the meaning of the negative result, factors motivating subjects to be screened, and feedback from being tested. Patients identified as carriers were notified directly by telephone,

and individual counseling and screening of partners was arranged. Emphasis was placed on maintaining confidentiality of test results at all times.

RESULTS

The overall consent rates to enter the educational phase of the study averaged 64.8%. The most common reasons for declining included patients' perception of lack of time in the busy clinic setting (40%), lack of concern about cystic fibrosis (21%), and too much anxiety about other matters to consider another prenatal test (12%). Sixteen percent of decliners stated they would have participated if they could have taken the laboratory test without having to answer questionnaires. (Percentages do not add up to 100% because these items were not mutually exclusive; subjects could choose more than one response).

As part of our preliminary evaluation of the screening protocol, it was important to ascertain the effectiveness of our educational intervention. Due to some logistical limitations, we were not able to expand utilization of the videotape until recently. Therefore the majority of subjects in the pilot group received education in the form of a brochure. To assess knowledge, subjects were asked to answer 17 True/False statements about CF. The results presented in Figs. 2 and 3 indicate that most subjects came into the study with some prior awareness of the chronic and serious nature of CF, but little knowledge of the genetics of the disorder (Time 1), particularly the implications of autosomal recessive inheritance and the ethnic variability. For instance, only 46.2% knew that CF only occurs when both parents are carriers and only 45.8% knew that Caucasians were more likely to be carriers.

Knowledge in both areas appeared dramatically improved after the educational intervention (Time 2), although there was still significant confusion about the clinical status of carriers and the inability of the DNA test to identify all carriers. While 89.4% indicated they understood that one could carry a CF gene and have no symptoms, only 71.6% recognized that the statement "carriers might develop CF" was false. Also, there was misconception about the test itself, as only 52.4% indicated that they understood that CF testing cannot detect all CF carriers. (All values were statistically significant to a level of $p < 0.05$ or less.) These findings in particular pointed out aspects of the educational intervention that needed to be modified.

Almost all of the subjects (97.2%) desired to undergo DNA testing following the educational intervention (Table I); those declining stated that they felt their risk was too low due to ethnic origin or that they did not feel the information was necessary for this pregnancy. There was high subject satisfaction with the buccal brush collection technique, and the reverse dot blot assay

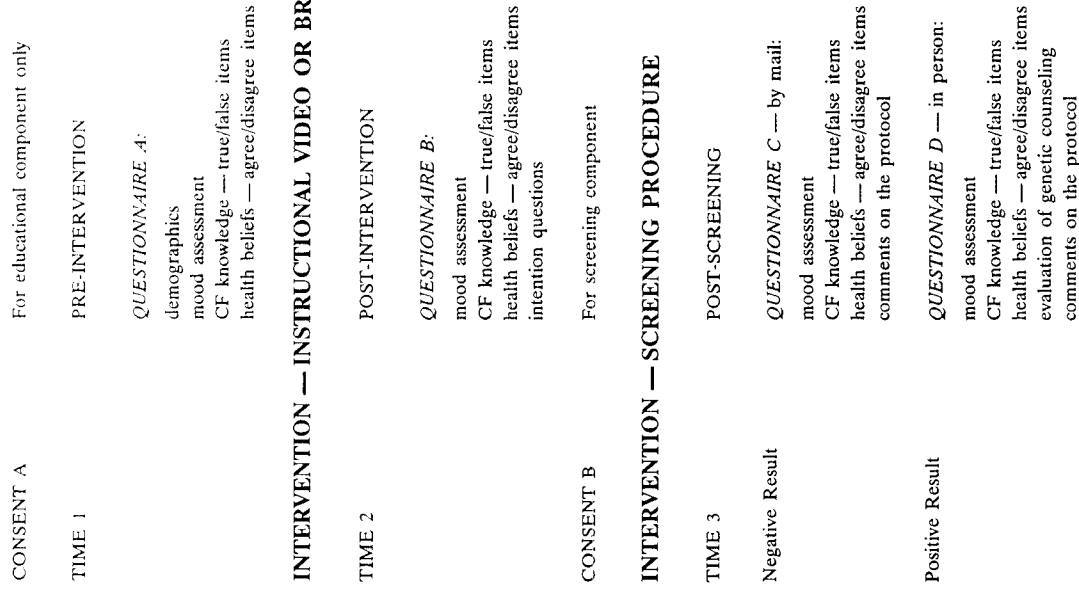


Fig. 1. Sequence of interventions and assessments in cystic fibrosis carrier screening project.

Fig. 2. Subjects' degree of knowledge of the clinical aspects of cystic fibrosis as measured by true/false questionnaires before and after the instructional intervention. All items except the one starred were significant to a level of $p < 0.01$.

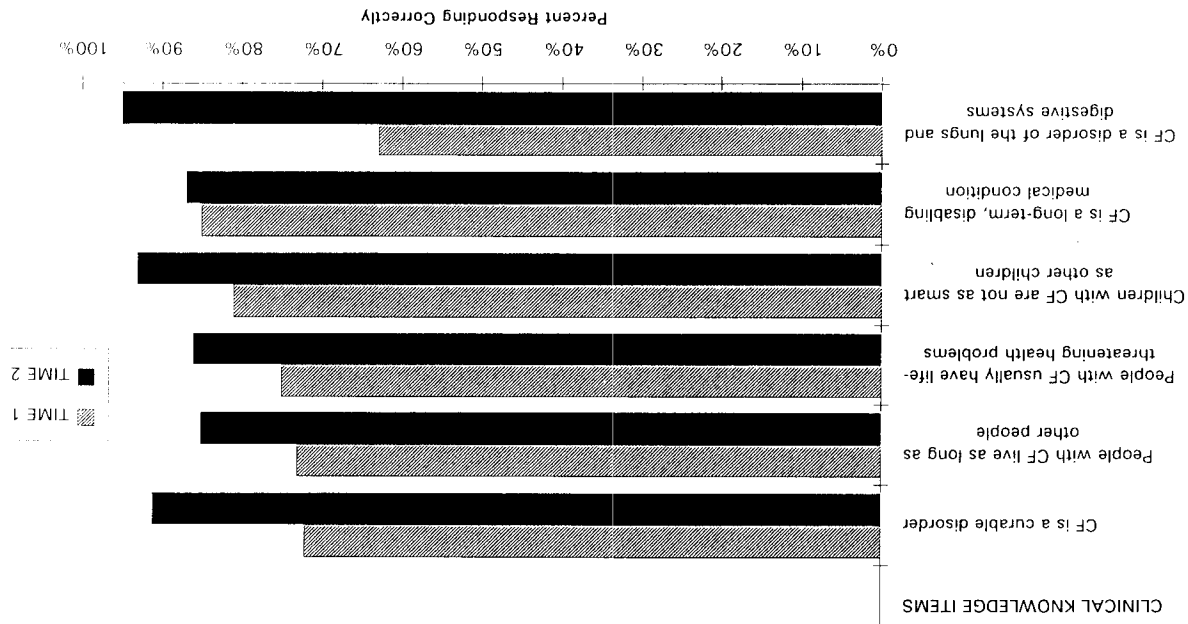


Fig. 3. Subjects' degree of knowledge of the genetic aspects of cystic fibrosis and the DNA test as measured by true/false questionnaires before and after the instructional intervention. All values were significant to a level of $p < 0.01$.

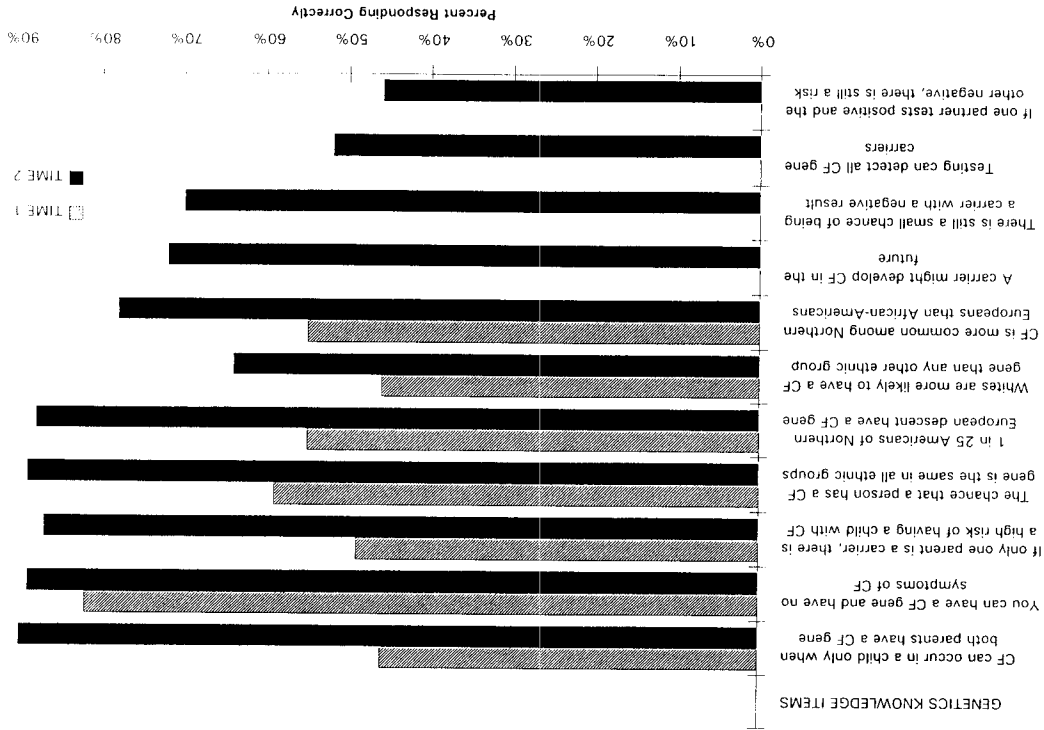


Table I. Triage of 500 Subjects in Screening Pilot

Number of women completing protocol	500
Number of women consenting to CF screening following education	486
Number of carriers identified	10
Numbers of carriers who returned for follow-up counseling	10
Numbers of partners tested	10
Number of at-risk couples identified	0

worked well in our laboratory. Ten mutation carriers were identified in this ethnically diverse cohort (Table II). All returned for counseling and consented to have their partners tested, but no at-risk couples emerged (Table I).

All subjects with a negative test result were sent a follow-up questionnaire. The return response rate was 56.6% ($n = 260/459$). Preliminary analysis revealed only slight anxiety evoked by awaiting the test results, generally good retention of CF knowledge, and substantial feelings of reassurance upon testing negative. Almost all subjects, across all ethnic groups, expressed satisfaction with the screening program and result reporting. Most stated that they would be interested in being screened for other genetic diseases as tests become available, even if the technology were imperfect to the same degree as the CF testing.

One crucial area of concern is the subjects' understanding of their residual risk for being a CF carrier after receiving a negative test result. A small but significant minority (10%) still had the misconception that their risk was now zero. This finding may have important implications for future nationwide screening programs, both for CF and other genetic disorders, particularly in the development of appropriate patient contact and educational materials to target populations.

DISCUSSION

We have completed pilot testing of a CF education and screening protocol and psychological assessment instruments in 500 pregnant women with no family history of CF. Results of this pilot study indicate that the CF knowledge, health belief, and psychological assessment tools we have developed in consultation with other members of the NIH CF screening consortium, as well as the DNA collection and testing methodology utilized in collaboration with Roche Molecular Systems, generally functioned well in evaluating the impact and effectiveness of such a population-based carrier screening program. The findings indicate a rather high baseline interest in being screened following

Table II. Mutations Detected in 500 Subjects Screened

Mutation identified	Number of positives
$\Delta F508$	6
W1282X	2
G542X	2

educational intervention, though admittedly one of our primary recruitment settings, a prenatal diagnosis clinic, served to preselect women who already have an interest in obtaining information about detection of birth defects during pregnancy. While this approach may tend to limit the range of reproductive options that can be offered, our findings concur with earlier screening studies that have shown higher uptake post-conception (Kaback *et al.*, 1993). It is also likely that the free and noninvasive nature of the DNA test offered was partly responsible for the high proportion of consent to screening.

Our knowledge data suggest that subjects came into the study with some prior knowledge or general awareness of the seriousness of the disorder. In comparison, subjects did not have as much baseline knowledge or post-education understanding of the genetics of CF; this will require more intensive instructional intervention as such screening programs are put into practice. The findings also point to the overall effectiveness of a pre-screening instructional intervention (a brochure in our pilot) in conveying information about the CF screening test. However, the residual 10% of subjects misunderstanding the meaning of a negative CF DNA test was disturbing. We realized that such individuals will require further information and/or counseling as a key component in the delivery of this yet suboptimal CF screening technology. Using this important feedback, we have since made modifications to our educational materials and result letters to further stress the point that a negative test result does not eliminate the chance that a person could be a CF carrier.

The vast majority of subjects expressed a high degree of satisfaction with the screening program in their responses to our followup questionnaires. While formal evaluation of the anxiety inventories is pending, we have thus far detected no change in anxiety or depression levels nor evidence of stigmatization or discrimination among those testing positive (though our sample size is still small). There also does not appear to be any change in subjects' anxiety following education about CF and the availability of DNA testing. Specific questionnaire items have been developed to ascertain whether subjects feel uncomfortable about genetic screening. For example, 74.5% of subjects stated that they would not be concerned if others knew they were a CF carrier.

As we have planned, a full-scale project has been initiated. We have expanded to include satellite sites offering routine prenatal care such as the Kaiser facilities of Southern California, the UCLA Obstetrics Clinic, and private obstetricians' offices. These additional sites not only have a more ethnically diverse and varied socioeconomic population, but a significant proportion of monolingual Spanish-speaking patients. Spanish translations of all of our educational materials, questionnaires and consent forms, and bilingual, bicultural research assistants will assist in the recruitment of these patients. These expanded recruiting and counseling procedures should help us to gain a more realistic picture of the acceptance and efficacy of screening for CF mutations in large-scale populations.

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REFERENCES

- Beaudet AL (1990) Carrier screening for cystic fibrosis (Editorial). *Am J Hum Genet* 47:603-605.
- Chehab FF, Wall J (1992) Detection of multiple cystic fibrosis mutations by reverse dot blot hybridization: A technology for carrier screening. *Hum Genet* 89:163-168.
- Davies K (1992) Genetic screening for cystic fibrosis. *Nature* 357:424.
- Kaback M, Lim-Steele J, Dabholkar D, Brown D, Levy N, Zeiger K, International TSD Data Collection Network (1993) Tay-Sachs disease — Carrier screening, prenatal diagnosis, and the molecular era: An international perspective, 1970 to 1993. *JAMA* 270:2307-2315.
- Kerem B-S, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui L-C (1989) Identification of the cystic fibrosis gene: Genetic analysis. *Science* 245:1073-1080.
- Richards B, Skolefsky J, Shuber AP, Balfour R, Stern RC, Dorkin HL, Parad RB, Witt D, Klinger KW (1992) Multiplex PCR amplification from the CFTR gene using DNA prepared from buccal brushes/swabs. *Hum Molec Genet* 2:159-163.
- Saiki RK, Walsh PS, Levenson CH, Erlich HA (1989) Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes. *Proc Natl Acad Sci USA* 86:6230-6234.
- Spielberger CD (1985) Assessment of state and trait anxiety: Conceptual and methodological issues. *South Psychol* 2:6-16.

- Wilfond BS, Fost N (1993) The introduction of cystic fibrosis carrier screening into clinical practice: Policy considerations. *Milbank Quart* 70:629-659.
- Williamson R (1993) Universal community carrier screening for cystic fibrosis? *Nature Genet* 3:195-201.