

Statement of The American Society of Human Genetics on Cystic Fibrosis Carrier Screening

The identification in 1989 of the cystic fibrosis (CF) gene and its most common mutation immediately raised the possibility of CF carrier detection by DNA analysis. The American Society of Human Genetics (ASHG) issued a statement recommending that CF carrier testing should be made available to individuals with a family history of CF (American Society of Human Genetics Board of Directors 1990). It was also stated that screening of individuals or couples in the general population should not be offered until the rate of CF carrier detection improves. An additional prerequisite emphasized the need for the establishment of effective educational and counseling programs consistent with previous widely accepted principles. An NIH workshop, convened in February 1990, reached similar conclusions (NIH Workshop on Population Screening for the Cystic Fibrosis Gene 1990). The statement of the workshop was endorsed by ASHG.

Since then, substantial progress has been made in defining the mutational basis of the disease and the basic biochemical defect. As recommended by the NIH workshop, pilot projects to study the complex issues involved in offering CF carrier detection to the general population of the United States have been initiated, but substantive results are not anticipated for at least 2 years. Other pilot projects are underway in Canada and Europe. Interest in CF carrier screening has expanded in the medical community, the biotechnology industry, and the public. Accordingly, the ASHG Ad Hoc Committee on Cystic Fibrosis Carrier Screening reassessed the issues surrounding CF carrier detection.

CF is an autosomal recessive genetic disorder characterized by chronic lung disease and pancreatic insufficiency. There is a broad range of clinical severity. Recent advances in clinical care, including postural drainage, pancreatic enzyme replacement, and improved antibiotics, have increased survival, although

a small fraction of patients still die in the first decade. Even without anticipated improvements in therapy, most individuals born today with CF are expected to survive into their 30s or 40s. CF occurs in about 1 in 2,500 newborns of European ancestry. It is less frequent among other ethnic and racial groups. About 1 in 25 persons of European ancestry is a carrier, having one normal and one abnormal CF gene.

A single mutation, denoted $\Delta F508$, is found in approximately 70% of carriers of European ancestry. Currently, over 160 other mutations have been identified. Many of these are extremely rare, but a few reach frequencies of 1%–3% of CF carriers. Current surveys indicate that 85%–90% of CF carriers in the North American white population can be detected by testing for 6–12 mutations. The detection rate is even higher in some populations (e.g., Ashkenazi Jews) but is substantially lower in blacks, Hispanics, and Asians. In view of this mutational heterogeneity, it is unlikely that DNA-based CF carrier detection rates will exceed 95% in the foreseeable future.

The severity of disease in a given patient is to some extent correlated with the particular mutations present. However, it is difficult, on the basis of DNA testing, to make meaningful predictions about the clinical course of the disease, because the spectrum of disease for a given genotype is quite broad. Furthermore, for all but the most common genotypes there are insufficient numbers of affected individuals to define adequately the clinical spectrum. A few mutations are associated with phenotypes that are much milder than classical CF.

Analyses of the CF gene and its protein product indicate that the gene encodes a membrane protein that has properties of a chloride channel. Recent data indicating that the $\Delta F508$ mutant protein may have residual activity increase the possibilities of specific drug therapy. Intense efforts also are underway to develop gene therapy strategies to deliver the normal CF gene to the respiratory tract. The success of these approaches to the amelioration or cure of CF is uncertain. The perceived rate of progress of these and other developments will undoubtedly affect the level of public interest in CF carrier screening.

These scientific developments do not in themselves

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0002-9297/92/5106-0027\$02.00

resolve the question of whether CF carrier screening programs should be implemented at present. Population-based screening implies offering a program of carrier testing with appropriate informed consent and genetic counseling to potentially millions of healthy people. The primary purpose of such screening would be to allow people to make more informed reproductive decisions.

There is widespread agreement that carrier testing should be offered to individuals with a family history of CF or with a blood relative identified as a CF carrier. Carrier identification in such individuals is essentially 100% accurate, because both mutation analysis and linkage studies can be used, if necessary, to make this determination. Also, such persons usually will have had direct experience with CF in a family member, thereby making their decisions regarding carrier testing more informed and less of an abstraction. Consistent with this recommendation, it is important for all health-care professionals to obtain accurate family histories, especially for patients of reproductive age.

It is acknowledged that testing of highly motivated individuals in the general population may occur. As previously stated, testing should only be provided by knowledgeable health-care professionals after appropriate education and counseling.

Although the carrier detection rate is approaching 90%, other important prerequisites must be further addressed before carrier detection is offered to individuals or couples in the general population. These include the effectiveness of educational materials, aspects of screening laboratory practices (e.g., quality assurance and proficiency testing), counseling issues, and the beneficial and deleterious effects of screening. Pilot projects currently underway may help to address these issues. Of particular importance are the consequences of screening couples in which one partner has an identified CF mutation and the other partner tests negative but cannot be excluded as a carrier of a rare CF mutation. Approximately 1 of 15 white couples tested will fall into this category and will be left at a modestly increased risk of having a child with CF (approximately 1 in 1,000, if we assume a 90% carrier detection rate). Finally, CF screening must be viewed within the perspective of available resources and other health-care priorities.

Recommendations

- Although the sensitivity of carrier testing for CF has improved and pilot studies are under way, CF testing is not recommended, at this time, for individuals or couples who do not have a family history of CF.

- Individuals with a positive family history of CF or who have a blood relative identified as a CF carrier should be offered CF testing with appropriate education and counseling. Optimally, carrier testing should be offered prior to conception, to provide a couple the broadest range of reproductive options.
- When indicated, CF counseling and testing should adhere to the following guidelines:
 - a. Screening should be voluntary, and confidentiality must be ensured.
 - b. Screening requires informed consent. Pretest education should explain the benefits and hazards (e.g., stigmatization and possible loss of insurability).
 - c. Providers of screening services have the obligation to ensure that adequate posttest counseling is provided.
 - d. Quality control of all aspects of laboratory testing, including systematic proficiency testing, is required.
 - e. As with all indicated health-care services, there should be equal access to testing.
- Efforts should be expanded to educate health-care providers and the public, regarding the complexities of CF screening in particular and issues involved in genetic health-care services in general.

Acknowledgment

This document was drafted by the ASHG Ad Hoc Committee on Cystic Fibrosis Carrier Screening. The ad hoc committee included Sherman Elias, M.D., and Michael M. Kaback, M.D., co-chairpersons; Arthur L. Beaudet, M.D.; James E. Bowman, M.D.; C. Thomas Caskey, M.D.; Francis S. Collins, Ph.D., M.D.; Jessica G. Davis, M.D.; Norman Fost, M.D., M.P.H.; Philip R. Reilly, M.D., J.D.; Peter T. Rowley, M.D.; Charles R. Scriver, M.D.; Elizabeth M. Short, M.D.; Ann C. M. Smith, M.A.; James Sorensen, Ph.D.; Lap-Chee Tsui, Ph.D.; and Nancy Wexler, Ph.D. The document was amended and approved by the ASHG Board of Directors on May 17, 1992. The views expressed are those of the board and do not necessarily represent the views or judgment of any individual member.

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