Office of Technology Assessment
Proposed Project

CYSTIC FIBROSIS: IMPLICATIONS OF POPULATION SCREENING

PROJECT DESCRIPTION: Cystic fibrosis is an inherited disorder often characterized by chronic lung disease. Invariably fatal, it is the most common lethal genetic disease in the United States. The median survival age is 25 years. Approximately 1 in 25 persons of European ancestry is a carrier for cystic fibrosis. Among Caucasians, 1 in 2,000 newborns has the disease; among Blacks, 1 in 20,000 and among Asians, 1 in 100,000.

The cystic fibrosis gene and the most common mutation in the gene leading to the disease have been identified and cloned. Currently, DNA analysis can identify 70 to 75 percent of carriers for cystic fibrosis, and hence about 50 percent of couples at risk. Rare mutations, however, go undetected. Without more definitive tests that would detect 90 to 95 percent of carriers, about 1 in 15 couples tested -- those in which one partner is positive, but one negative with current testing -- would be falsely reassured about having an affected child.

Pressure for widespread carrier screening for cystic fibrosis is already building, despite caution raised by medical experts, including those attending a 1990 workshop sponsored by the National Institutes of Health. Several companies are aggressively marketing the test, and estimates of the potential market for cystic fibrosis screening range from $200 million to more than $1 billion.

This assessment would (1) gather technical information on cystic fibrosis diagnosis and treatment; (2) examine prospects for DNA tests to detect additional cystic fibrosis mutations; (3) analyze legal, ethical, and economic issues of population screening for cystic fibrosis, including issues related to quality assurance, confidentiality, pregnancy termination, disability coverage, health insurance, and reimbursement for screening; (4) survey genetic counselors for their opinions and attitudes toward population screening for cystic fibrosis; and (5) survey commercial health insurers and health maintenance organizations to assess attitudes, policies, and practices -- present and future -- toward cystic fibrosis screening.

CONGRESSIONAL INTEREST: A letter requesting the study has been received from Congressman Robert Roe, Chairman, House Committee on Science, Space, and Technology, and Congressman John Dingell, Chairman, House Committee on Energy and Commerce.

SISTER AGENCY COORDINATION: Neither the Congressional Research Service nor the General Accounting Office have activities addressing cystic fibrosis screening, specifically. CRS is developing an issue brief on genetic screening, generally, including prenatal and carrier screening.

SCHEDULE AND PLAN: The assessment would be carried out over 17 months, beginning in November 1990. Study activities would include: selection and three meetings of an Advisory Panel; identification of issues; development and letting of contracts; analysis of results; drafting and review of Report; delivery to TAB by February 29, 1992; and publication in Summer 1992. Interim products: results from two small OTA surveys of genetic counselors and insurance companies would be published prior to delivery of the final Report.

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BACKGROUND

Cystic fibrosis is the most common lethal inherited disease in the United States. One in every 2,000 live births in this country are cystic fibrosis-affected babies. Median survival for individuals who have cystic fibrosis is approximately 25 years, and about 30,000 Americans have the disorder. Among Americans of European ancestry, 1 in 2,000 is affected; among African-Americans, 1 in 20,000 have the disease, and among Asian Americans, 1 in 100,000.

Cystic fibrosis is a non-sex-linked, recessive genetic disorder, i.e., two defective cystic fibrosis genes, one inherited from each parent, are needed for the disease to be manifest in a child of either gender. Parents of a child with cystic fibrosis do not have the disease1, but are carriers of one defective copy of the gene.

In the United States, approximately 1 in 20 to 1 in 25 persons of European ancestry is a carrier, i.e., has one normal and one abnormal cystic fibrosis gene. Thus, both individuals carry the gene in 1 in 400 to 1 in 625 Caucasian couples. Given the high frequency with which carriers are present in the population, it is not surprising that for most of the 2,000 cystic

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1 Until recently, most patients did not reach reproductive age. Women with cystic fibrosis have a more difficult time conceiving, and 98 percent of men with the disease are sterile. [Orenstein, D.M., Cystic Fibrosis: A Guide for Patient and Family (New York, NY: Raven Press, 1989)].
fibrosis babies born each year, the parents were unaware of their carrier status (i.e., no family history of the disease that would alert an individual to the fact that he or she could be a carrier).

Major symptoms of cystic fibrosis include chronic pulmonary disease, including lung blockage, infection, and damage, and pancreatic blockage that causes poor digestion and absorption of food (leading to poor growth and undernutrition). The sweat glands are also affected, resulting in an increased concentration of salts in secreted sweat. Cystic fibrosis does not affect the brain and nervous system; it does not cause mental retardation.

Manifestation of the severity of symptoms varies widely from child to child. Predicting how long a particular cystic fibrosis patient will live is impossible. One clear fact is that treating cystic fibrosis is expensive. The annual cost of medical care for a cystic fibrosis has been estimated to be at least $7,500. Lifetime medical costs for an individual are at least $200,000. With approximately 30,000 persons affected in the United States, the annual cost to the Nation of cystic fibrosis treatment is a minimum of $225 million.

**What Causes Cystic Fibrosis?**

The cystic fibrosis gene and the most common mutation in the gene that leads to the disease reside on chromosome 7. The defect has been cloned and sequenced. This deletion mutation, commonly referred to delta F508, accounts for 70 to 75 percent of cystic fibrosis defects found in the Caucasian population. The remaining individuals have one of 40+ different, rare mutations in the gene.

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Although the molecular defect causing cystic fibrosis has been identified, precisely how the mutant protein produced by patients results in the clinical symptoms has not been fully elucidated. In August 1990, researchers reported new findings on the mechanism of cystic fibrosis, and many expect definitive results in the near future. Pinpointing the exact nature of the defect is key to better therapies, including the possibility of gene therapy.

**Genetic Screening and Cystic Fibrosis**

Population genetic screening for cystic fibrosis involves screening an asymptomatic individual to determine whether he or she is a carrier of a mutant cystic fibrosis gene. Using today's technology, it is a one-time test that can inform individuals they could pass the mutation to their offspring, who would be affected if it received a second mutant copy from the other parent. Population screening could involve from 100 to 200 million individuals.

In fact, today's technology leaves ambiguity when performed. The delta F508 mutation has been developed into a DNA-based genetic test by several commercial firms and hospitals. But, as mentioned earlier, only 70 to 75 percent of potential carriers can be identified by this test. Thus, reporting a negative test result to a person does not mean the person is not a carrier, since 25 to 30 percent of carriers cannot be detected with the test. One in 99 of individuals who tested negative using the delta F508 test would carry a rare cystic fibrosis mutation.

Only about 50 percent of couples at risk of having a cystic fibrosis-affected baby can be identified using the delta F508 test. Without more definitive tests to detect enough of the rare mutations, about 1 in 15 couples tested -- those in which one partner is positive, but one negative with the delta F508 test -- could not rule out having an affected child. If both partners tested negative, the risk of cystic fibrosis in an offspring would be 1 in 39,200. While this
represents a significant reduction in theoretical risk, 75 to 100 couples who might believe themselves "safe" would still bear a cystic fibrosis-affected baby, since there are about 3 million live births annually.

It should be emphasized that the delta F508 test is not 70 to 75 percent accurate. Evidence indicates that the delta F508 test is considered accurate, sensitive, and specific. For the purpose of this proposal, it can be assumed that if the delta F508 mutation is present in the individual's genome, the test detects it, absent laboratory error. Like all diagnostic tests, a certain number of false positive or false negatives can arise during the course of testing. Laboratory quality control and quality assurance are designed to reduce this number to a small figure.

For couples who test positive for delta F508, prenatal screening can determine whether the fetus will have cystic fibrosis. For nearly all couples with a cystic fibrosis-affected child, prenatal screening can also reveal whether the new child will have cystic fibrosis -- even if the delta F508 mutation is not responsible.

Commercial Interests in Cystic Fibrosis Testing

While genetic screening of any type raises an array of difficult questions for many people (discussed in "Proposed Assessment"), the potential benefits ensure that the technology will be used. For cystic fibrosis, the sheer magnitude of the potential population that could be screened has ensured commercial interest. OTA is aware of at least five companies and 2-3 times as many university affiliated hospitals that offer testing for the delta F508 lesion. The

4 OTA will evaluate data and information on this matter.
cost of testing through commercial ventures is $200 to $250 per sample. With some advocating that the entire U.S. population, or at least those of reproductive age, be screened -- 100 to 200 million people -- the market for this single test is significant.

The majority of companies have adopted the policy that population screening is inappropriate at the present time given the ambiguity of current testing. These companies have various procedures, but essentially will not test individuals unless a family history of cystic fibrosis exists. Yet this situation is not always the case. In one company, a tension between the scientific/medical v. business staff led to a conflict between the director of laboratories (who favors limited testing) and the chairman of the board (who favors general testing). Scientists at the company stopped work over a company plan to carry out any testing; for now testing is performed only on persons with a family history. The company does plan to sign an agreement later this year with a large health maintenance organization (HMO) to provide cystic fibrosis testing for HMO members, which could mean testing tens of thousands of people.5

Additionally, one company recently began offering the test to all patients. At this facility, about 25 percent of those with no family history wanted the test and paid close to $200 for it. One hospital’s policy is that if someone asks for it, the test will be performed.6

CONGRESSIONAL INTEREST

A letter of request has been received from Representative Robert Roe, Chairman of the House Committee on Science, Space, and Technology, and from Representative John Dingell, Chairman, House Committee on Energy and Commerce.

Congress has had an ongoing interest in a range of issues related to human genetics and applications of genetic technologies. Current interest in an assessment of large-scale genetic screening for cystic fibrosis is related to congressional involvement—oversight and funding—of projects to map and sequence the human genome. Because the number of genetic tests will increase as genome projects progress, the request letter specifically cites the need to assess the broad social and policy issues surrounding widespread genetic screening by using cystic fibrosis as a case model now. The letter acknowledges that many feel nationwide cystic fibrosis carrier screening is inappropriate, but seeks OTA's evaluation of the timeframe and technological developments that would be required to overcome perceived and actual barriers.

Finally, congressional interest in genetic screening was signaled by the creation in 1985 (Public Law 99-158) of the congressional Biomedical Ethics Board and its Committee. Presently inactive, the Committee had been specifically asked by the Board to examine the policy issues involved in population genetic screening, but did not address them during its tenure.

**RELATED WORK AT OTA**

This assessment would draw and build on several previous OTA reports, including *Mapping Our Genes -- The Genome Projects: How Big, How Fast?, Medical Testing and Health Insurance,* and *Human Gene Therapy.* The OTA report *Healthy Children: Investing in the Future* analyzed neonatal cystic fibrosis screening, i.e., testing to detect whether newborns have the disease. While newborn screening to identify affected individuals is not the focus of this study, this work will likely address the topic.

One forthcoming OTA report, *Genetic Monitoring and Screening in the Workplace,* addresses policy issues raised by employer genetic screening generically. A few broad areas attendant with any discussion of genetics and public policy overlap between the studies (e.g.,
privacy of medical information, disability rights, and certain counseling aspects), but several issues and the analytical approach are quite different. For example, the magnitude of screening for cystic fibrosis far outstrips genetic screening in the workplace currently performed (and likely to be performed in the foreseeable future). Additionally, the report specifically excludes prenatal genetic screening and, for the most part, insurance considerations.

**RELATED WORK AT OTHER AGENCIES**

None of the other congressional support agencies has activities specifically addressing genetic screening for cystic fibrosis. The Congressional Research Service is preparing an issue brief on genetic screening, generically. The issue brief touches on genetic screening in the workplace, prenatal genetic screening, and carrier genetic screening. While mentioning cystic fibrosis in some examples, the issue brief does not specifically analyze population screening for cystic fibrosis.

Following reports that some parties advocated mass carrier screening for cystic fibrosis, seven institutes, centers, and offices of the National Institutes of Health (NIH) coordinated a workshop on population screening for the cystic fibrosis gene in March 1990. The statement issued from the workshop concluded that large-scale screening would be undesirable at this time, but that pilot programs are urgently needed and that it was critical that Federal funds support such programs.

The NIH National Center for Human Genome Research is sponsoring a small workshop in September 1990 to explore issues surrounding large-scale genetic screening for cystic fibrosis. Individuals familiar with pilot screening projects currently underway in Sweden and the United Kingdom have been invited to participate. Informal proceedings of the workshop may be disseminated.
In 1983, in anticipation of the characterization of the cystic fibrosis defect, the President's Commission for the Study of Ethical Problems in Medicine identified several issues that would be raised by widespread carrier screening for the disease. Although urging policymakers to prospectively address the questions raised by such screening, further discussion or any resolution have not occurred.

Several institutes of the NIH currently fund research and other initiatives related to cystic fibrosis diagnosis and treatment. In addition to funding the efforts that lead to discovery and reporting of the basic cystic fibrosis gene and defect, NIH and the Cystic Fibrosis Foundation recently advertised a joint request for grant proposals to fund additional research related to cystic fibrosis. The Howard Hughes Medical Institute (HHMI), a private, nonprofit medical research organization also provided funds for the research that lead to the isolation of the cystic fibrosis gene and defect. HHMI continues to fund research related to identification of additional lesions.

**PROPOSED ASSESSMENT**

The assessment will be carried out over 17 months beginning in November 1990. It will require 3.5 FTEs and result in three products:

1. a background paper reporting the results of an OTA survey of genetic counselors, to be published in July 1991;
2. a background paper reporting the results of an OTA survey on cystic fibrosis screening and health insurance, to be published in September 1991;
3. a full report, to be delivered to the Technology Assessment Board by February 29, 1992.
The two background papers, both results of OTA surveys, will provide background for the final report. Areas that would be explored in the survey of genetic counselors include: opinion and attitudes about population screening, prenatal screening, patient education efforts, and difficulties encountered in counseling about cystic fibrosis generally, as well as in situations when the delta F508 test has been used.

The health insurance survey will encompass commercial health insurers, Blue Cross/Blue Shield Plans, and HMOs. Its purpose would be to gather data on attitudes, policies, and practices related to cystic fibrosis testing -- carrier screening in cases of family history, prenatal screening, and population screening. Indications are that current third-party payment for testing is diverse\(^7\), and the survey would also attempt to assess this situation. Because insurance underwriting rarely, if ever, requires medical testing of applicants for large group policies, the survey questions would focus on small groups and individuals, and situations where the family history indicates either parent is a carrier or where both parents are clearly carriers because they have at least one affected child.

The principle product of the assessment -- the final report -- will examine the technical, legal, ethical, and economic issues of genetic screening for cystic fibrosis. It will examine the magnitude of the problem, including its prevalence, costs, and impact on patients and families.

The report will evaluate the scientific development of the delta F508 test, which as currently applied is expensive, somewhat tedious and time consuming, and labor intensive. Thus, the report will examine what technological developments would be necessary for delta

\(^7\) Luciano, P., General Manager, Integrated Genetics, Framingham, MA, personal communication, August 1990.
F508 population screening to be cost-effective for companies, as well as the timeframe for improvements to occur. It will also evaluate the prospects of DNA testing for additional cystic fibrosis mutations.

The fact that the current cystic fibrosis test, unlike tests for sickle cell or Tay-Sachs, for example, detects only a fraction of potential carriers, complicates the legal, ethical, and economic analysis. But even if the test or set of tests were 90, 95, or 99 percent inclusive, many questions would remain and would be addressed in the report.

First, who should be screened? At what age? The magnitude of the effort and the costs associated with treating the disease set it aside from analyses of other genetic diseases. From 100 to 200 million Americans could be tested for cystic fibrosis carrier status. In contrast, the Tay-Sachs screening program targeted the 1 to 2 million Ashkenazi Jews of reproductive age.

Second, is the existing structure of quality assurance for clinical laboratories -- the Clinical Laboratory Improvement Amendments of 1988 (Public Law 100-578) -- adequate for DNA-based testing? What are the appropriate roles of Federal Public Health Service agencies? State agencies? Private organizations?

Third, how will professional training and public education about the test be handled? Interpreting and conveying concepts of genetic risk to lay persons is formidable under normal circumstances, and becomes more difficult under the stressful conditions likely to be encountered even in small-scale testing. Data indicate that the country's current capacity to counsel and educate patients could not handle population screening. What Federal resources might be necessary for national screening -- organized or de facto?

Finally, the report will analyze the legal and ethical implications of population screening for cystic fibrosis, including informed consent, confidentiality of screening results, pregnancy termination, disability coverage, and discrimination issues. In evaluating these and other issues,
and in developing congressional options, it will analyze international pilot programs underway in several countries, including the United Kingdom and Denmark, as well as draw on the findings of the two background papers.

**Assessment Plan**

The assessment will involve:

- review of current literature and identification of issues;
- selection of the Advisory Panel;
- collection of information about the demographics of cystic fibrosis and costs associated with treatment;
- analysis of the adequacy of current testing technology, including sensitivity, specificity, and accuracy;
- analysis of Federal and State policies and practices regarding genetic screening;
- collection of information on insurance perspectives;
- evaluation of personnel needs;
- prospectus on future technologies and therapies;
- development of policy options.

**Selection of an Advisory Panel**

An advisory panel of 15 to 17 individuals is planned. The Advisory Panel will meet three times during the course of the study -- twice in fiscal year 1991 and once during fiscal year 1992. Panelists will be selected to include individuals with expertise or experience in the following areas:

- **Pediatrics**: diagnosis and treatment
- **Basic research**: development of tests to detect additional lesions in the cystic fibrosis gene, adaptation of testing technologies to handle large-scale DNA testing, prospects for improved therapies (including gene therapy to correct the primary defect)
- Genetic counseling
- Patient/family/consumer interests
- Law: health, disability rights, regulatory (clinical laboratories, test approval and quality assurance), privacy, civil rights, reproductive issues
- Economics: Federal reimbursement for screening, private health insurance, life insurance, costs of limited and population screening, costs of cystic fibrosis treatment
- Public health: epidemiology, health policy, health planning
- Bioethics
- Clinical genetics reference laboratory operations
- Companies marketing DNA-based cystic fibrosis tests
- Historical perspective of genetic screening
- International programs for cystic fibrosis screening

Schedule

The assessment would begin November 1, 1990 and be carried out over 17 months. Two interim deliverables -- results from small OTA surveys of genetic counselors and health insurance/health maintenance organizations would be published as background papers in fiscal year 1991. Delivery of the final report to TAB is scheduled for February 29, 1992. A detailed schedule is attached.
## Assessment Schedule

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- **Select panel**
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- **Let contracts**
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- **Draft outline**
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- **Publication of genetic counselor survey**
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- **Publication of health insurance/HMO survey**
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- **Panel meetings**
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- **First draft**
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- **Second draft**
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- **Develop policy options**
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- **TAB delivery**
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- **Publication**
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- **Follow-on**
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