Chapter 1
Introduction and Background

Cystic fibrosis (CF) is the most common, life-shortening, recessive genetic disorder affecting Caucasians of European descent. From 1,700 to 2,000 babies with CF are born annually in the United States. The diagnosis of an infant with CF often reveals the first and only clue that the genetic trait exists in the family.

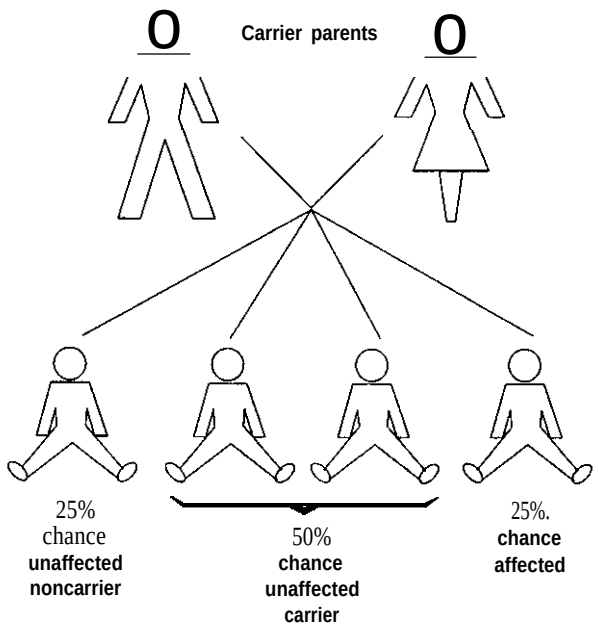
Parents of a child with CF are, by definition, obligate CF carriers. They have no symptoms of CF, but with each pregnancy are at 1 in 4 risk of having a child with CF and 1 in 2 risk of having a child who is a carrier (figure l-l). Such couples are sometimes referred to as carrier couples, or couples who are positive/positive (+/+). If a couple is positive/negative (+/-)—the father is a carrier, but the mother is not, or vice versa—their offspring can be CF carriers, but cannot have CF. Couples are not at risk of having a child with CF if only one or neither partner is a carrier.

Four of five individuals with CF are born to families with no previous history of the illness. Beyond the approximately 30,000 Americans who have CF, as many as **8** million individuals could be CF carriers. With no knowledge of a family history of CF, American Caucasians have about a 1 in 25 risk of being a CF carrier. The risk of carrier status increases when an individual in a family is diagnosed with CF, with risks calculated by relationship to the affected individual (table l-l).

Prior to 1989, the absence or presence of CF in one's family, as well as ethnic and racial background, were the only indicators available to determine risk of carrier status. In 1989, however, scientists identified the most common change, or mutation, in the genetic material-deoxyribonucleic acid (DNA)-that causes CF. Following this discovery came tests to detect mutations in the specific area of DNA—the CF gene-that is responsible for the disease.

The Office of Technology Assessment (OTA) report *Cystic Fibrosis and DNA Tests: Implications of Carrier Screening* (1) focuses on using these DNA tests to screen and identify CF carriers among the general population before they have a child with CF. This background paper, conducted in support of the OTA assessment, reports the results of an OTA survey of 431 members of either the National Society of Genetic Counselors (NSGC) or the International Society of Nurses in Genetics (ISONG). Conducted in summer 1991, the survey was designed to evaluate genetic counseling attitudes and practices regarding widespread CF carrier screening, a prospect that has been viewed with mixed feelings.

Figure I-l—Inheritance of Cystic Fibrosis



SOURCE: Office of Technology Assessment, 1992.

Table I-l—A Priori Carrier Risks for Cystic Fibrosis

Negative family history	
Caucasian	1 in 25 (4%)
African American	1 in 60 to 65 (1.5 to 1.7%)
Asian American	1 in 150 (0.79'.)
Hispanic American	1 in 40 to 50 (2 to 2.5%)
Positive family history	
Parent of child with CF	1 in 1 (1OO%)
Sibling with CF	2 in 3 (67%)
Aunt or uncle with CF[a]	1 in 3 (33%)
First cousin with CF	1 in 4 (25%)
Niece/nephew with CF[a]	1 in 2 (50%)

[a] Consanguineous.

SOURCE: Office of Technology Assessment, 1992.

Consensus exists that individuals who have relatives with CF should be told about the availability of CF carrier tests; the disagreement is whether *everyone* should be informed about the assays, since 80 percent of babies with CF are born to couples with no previous family history of the condition. Concern about the scientific, legal, economic, ethical, and social implications of the prospect that large numbers of people might be screened for their CF carrier status led the House Committee on Science, Space, and Technology, the House Committee on Energy and Commerce, and Representative David R. Obey to request the OTA assessment.

WHAT IS CYSTIC FIBROSIS?

CF is not a new disease. First described in 17th century folklore, medical literature has long documented that CF compromises many functions throughout the body--chiefly the respiratory, gastrointestinal, and reproductive systems and the sweat glands.

Many affected babies are not immediately diagnosed as having CF Although the disease is always present at birth in affected individuals, the onset of recognizable clinical symptoms varies widely. Physicians diagnose CF using a combination of clinical criteria and diagnostic laboratory tests. Although an assay called the sweat test remains the primary diagnostic test for CF DNA mutation analysis can diagnose more than 70 percent of cases.

CF exerts its greatest toll on the respiratory and digestive systems, and the severity of respiratory problems often determines the quality of life and survival. There is no cure for CF Treatment focuses on managing the respiratory and digestive symptoms to maintain a stable condition and lengthen lifespan. Because of CF's varied progression, the regimen and level of therapy depends on the individual. Most therapy involves home treatment (e.g., chest physical therapy to clear mucus from the lungs), outpatient care at one of more than 110 clinics devoted specifically to CF health care, and occasional hospital stays. Today, physicians can look to an ever-expanding array of new pharmaceutical options to manage the care of CF patients; on the horizon are hopes for gene therapy.

Over the last half-century, treatment of CF has evolved so that an illness nearly always fatal in early childhood is now one where life expectancy into adulthood is common. Fifty years ago, most infants born with CF died in the frost 2 years of life. In 1990, median survival was 28 years--i.e., of the individuals born with CF in 1962, half were alive in 1990.

THE CYSTIC FIBROSIS GENE

CF is a genetic illness transmitted from parents to their children via genetic directions stored in DNA. In humans, these directions, including those responsible for CF are stored among genes arrayed on 46 structures called chromosomes. The gene responsible for CF lies on chromosome 7 and results in a product called the cystic fibrosis transmembrane conductance regulator (CFTR). In most people with CF a three-base pair deletion in both of their CF alleles results in a faulty CFTR, which leads to CF pathology. This three-base pair mutation occurs at position number 508 in the CFTR and is abbreviated as delta F508 (AF508). More than 170 additional mutations in the CF gene also lead to faulty CFTRs. Individuals with CF have two of the same, or two different, mutations. CF carriers have only one mutation; their second CF allele produces normal CFTR.

About 70 percent of CF carriers have the AF508 mutation.[1] International studies demonstrate ethnic and regional variation in the frequency distribution of this mutation; as expected, the multicultural nature of the United States reflects this variation. Most of the other 170+ mutations appear in a small fraction of individuals or families, although a few occur at a frequency as great as 1 to 3 percent. Some symptoms (or their lack of severity) correlate with particular mutations. Digestive difficulties from pancreatic insufficiency, for example, generally associate with ΔF508.

CYSTIC FIBROSIS MUTATION ANALYSIS

With localization of the CF gene, ΔF508, and other CF mutations, it is now possible to directly analyze DNA from any individual for the presence

[1] Quoted mutation frequencies for ΔF508 and other CF mutations always depend on racial and ethnic background. Throughout this background paper, OTA presents current expert estimates of appropriate ranges of detection frequencies or sometimes uses a specific figure with qualification (e.g., about 90 percent; approximately 95 percent). OTA adopts such language to avoid restating each time that a frequency depends on racial and ethnic background, not to underemphasize the importance in the distribution variation of CF mutations. In some cases-made clear within the text-a specific frequency is chosen for illustrative or hypothetical purposes.

of CF mutations. Using today's technologies, CF mutation analysis is usually a one-time test that can inform an individual whether he or she carries any of the CF mutations for which tests are conducted. Carrier *screening* for CF (or CF carrier screening) refers to performing CF mutation analysis on DNA from an individual who has no family history of CF

Current technology, however, can leave ambiguity, but not because the tests per se are imprecise. Properly performed, DNA-based tests for CF mutations are accurate and specific-meaning if the ΔF508 mutation (or another CF mutation) is present in the individual's genome and an assay is performed to search for that mutation, the test will detect it more than 99 percent of the time, absent laboratory error. Instead, ambiguity stems from the intrinsic nature of the cause of the disease: Besides ΔF508, more than 170 mutations in the CF gene also cause CF

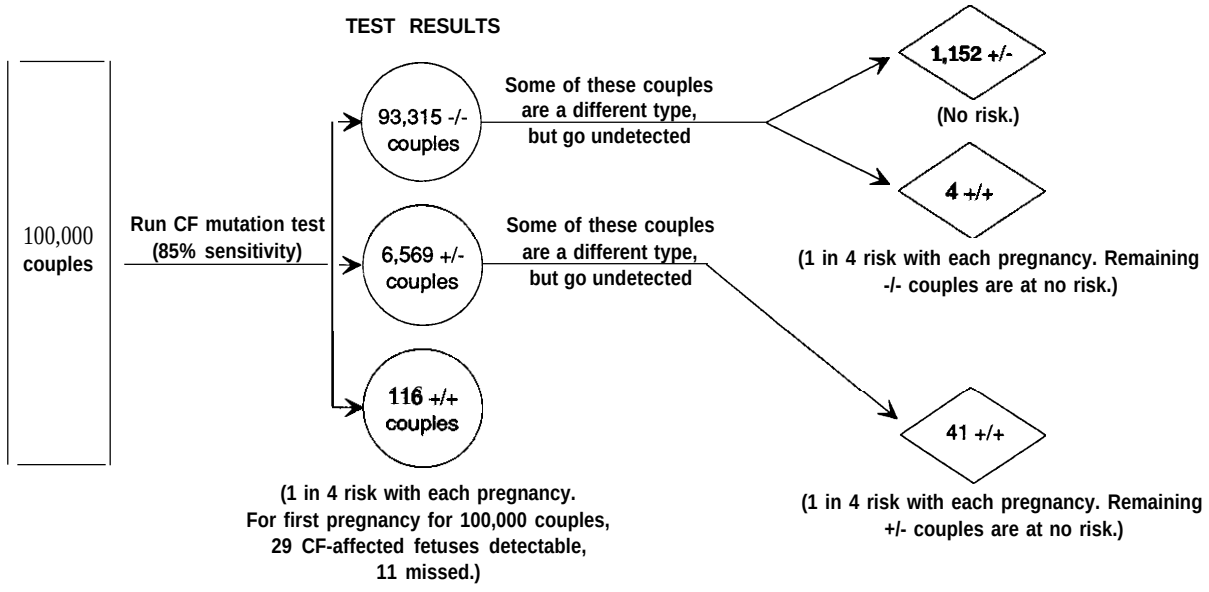
In the United States, about 1 in 25 Caucasians carries one CF mutation. Current assays use ΔF508 plus 6 to 12 other CF mutations (ΔF508+6-12) and identify about 85 percent of CF carriers (in Ashkenazic Jews, ΔF508+6 identifies about 95 percent of carriers). Thus, using ΔF508+6-12 means 10 to 15 percent of actual carriers go undetected. In other words, since tests to detect 170+ mutations are impractical, a negative test result does not guarantee that a person is not a carrier.

Using DF508+6-12 means that some couples receive test results that indicate one partner is a carrier and one is not, when in fact the negative partner carries one of the rare CF mutations that is not assayed. Thus, while most couples whose test results are +/- are at zero risk of having a child with CF some couples with a +/- test result actually are couples whose genetic status is +/+ (but goes undetected) and who are at 1 in 4 risk of a child with CF for each pregnancy. Couples with a +/- test result, then, might misunderstand that their reduced risk of bearing a child with CF is not zero risk (figure 1-2).

CONTROVERSY ABOUT CYSTIC FIBROSIS CARRIER SCREENING

Prospects of routine CF carrier screening polarize people. No mandatory genetic screening programs of adult populations exist in the United States. OTA has found it highly unlikely that CF carrier screening will set a precedent in this regard (l). People agree that persons with a family history of CF should have the opportunity to avail themselves of CF mutation analysis, yet controversy swirls around using the same tests in the general population.

Figure 1-2—Cystic Fibrosis Mutation Test Results at 85 Percent Sensitivity



SOURCE: Office of Technology Assessment, 1992.

Proponents of a measured approach to CF carrier screening express concern about several issues that might be raised if use of CF carrier tests becomes routine. Invariably, discussions about CF carrier screening raise concerns about the use of genetic information by insurance companies (2) and become linked broader social concerns about health care reform in the United States. Related to this are concerns about commercialization of genetic research, i.e., that market pressures will drive widespread use of tests before the potential for discrimination or stigmatization by other individuals or institutions (e.g., employers and insurers) is assessed. Also expressed are questions about the adequacy of quality assurance for DNA diagnostic facilities, personnel, and the tests themselves. Others also wonder whether the current number of genetic specialists can handle a swell of CF carrier screening cases, let alone cases from tests for other genetic conditions expected to arise from the Human Genome Project. Finally, the extraordinary tensions in the United States about abortion affect discussions about CF carrier testing and screening.

Those who advocate CF carrier tests for use beyond affected families are equally concerned about these issues. They assert, however, that individuals should be routinely informed about the assays so they can decide for themselves whether to be voluntarily screened. Proponents of providing such information believe that failing to inform patients now about the availability of CF carrier assays denies people the opportunity to make personal choices about their reproductive futures, either prospectively-e. g., by avoiding conception, choosing to adopt, or using artificial insemination by donor-or by using prenatal testing to determine whether a fetus is affected.

SCOPE AND ORGANIZATION OF THIS BACKGROUND PAPER

One of the tasks of genetic specialists is to provide the educational and counseling services necessary to successful implementation of new technologies. Increasingly, genetic counselors and nurses working in genetics will be at the front line on the issues raised by DNA technologies' assimilation into practice.

The OTA survey was conducted to better understand the environment in which the average genetic counselor or nurse in genetics works, to describe the infrastructure and tools available to these professionals, to assess the state of practice in the provision of CF carrier screening, and to evaluate their attitudes regarding CF carrier screening. The results of the survey are reported in chapters 2 and 3. A summary appears in chapter 4. A description of the survey methodology is in appendix A, and the survey instrument is reproduced in appendix B.

CHAPTER 1 REFERENCES

1. U.S. Congress, 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).
2. U.S. Congress, Office of Technology Assessment, ***Genetic Tests and Health Insurance+Results of a Survey, OTA-BP-BA-98*** (Washington, DC: U.S. Government Printing Office, October 1992).