

**Summary, Policy Issues, and
Congressional Options**

Contents

	<i>Page</i>
WHAT IS CYSTIC FIBROSIS?	3
WHY IS CYSTIC FIBROSIS CARRIER SCREENING CONTROVERSIAL?	11
WHAT FACTORS WILL AFFECT UTILIZATION?	16
WHAT IS THE ROLE OF CONGRESS?	40
PROSPECTS FOR THE FUTURE	43

Boxes

1-A. Terminology	4
1-B. The Human Genome Project	5
1-C. Cystic Fibrosis Therapies on the Horizon	6
1-D. The Gene Product: The Cystic Fibrosis Transmembrane Conductance Regulator	9
1-E. Cystic Fibrosis Carrier Tests and Detection Sensitivity	13
1-F. Cystic Fibrosis Carrier Screening in the United Kingdom	17
1-G. Federally Funded Cystic Fibrosis Carrier Screening Pilot Projects	18
1-H. Genetic Services: Federal-State Partnership	26
1-I. Bree Walker Lampley and Preventing Versus Allowing Genetic Disability	29

Figures

1-1. Median Survival of U. S. Cystic Fibrosis Patients Over Time	6
1-2. Age Distribution of U.S. Cystic Fibrosis Patients in 1990	7
1-3. The Structure of DNA.	7
1-4. Human Chromosomes	7
1-5. The Cystic Fibrosis Gene	8
1-6. Occurrence of AF508 Mutation in Europe	10
1-7. Techniques for DNA Analysis of Cystic Fibrosis Mutations	12
1-8. Cystic Fibrosis Mutation Test Results at 85 Percent Sensitivity	13
1-9. Cystic Fibrosis Carrier Screening, 1989-92,	20
1-10. Genetic Conditions as Preexisting Conditions: Health Insurers' Attitudes	31
1-11. Carrier Status as a Preexisting Condition: Health Insurers' Attitudes	31
1-12. Genetic Information as Medical Information: Health Insurers' Attitudes	31
1-13. Genetics and the Americans With Disabilities Act of 1990	34

Tables

1-1. Incidence of Cystic Fibrosis Among Live Births in the United States	5
1-2. Test Sensitivity and Risk of Child With Cystic Fibrosis	14
1-3. Privately Funded Cystic Fibrosis Carrier Screening Pilot Projects	19
1-4. Medicaid Reimbursement for Genetic Procedures	28
1-5. Projected Use of Genetic Information by Insurers in 5 and 10 Years	32
1-6. Case Descriptions of Genetic Testing and Health Insurance Problems	34
1-7. Annual Cost of Medical Care for Cystic Fibrosis Patients	38
1-8. Costs for Cystic Fibrosis Carrier Tests at Selected Facilities	39

Summary, Policy Issues, and Congressional Options

Seeking to learn what the future holds is an enduring human quality. What will happen? When will it happen? How will it happen? People have always pondered such questions about their health and that of their families. Folk ways once enjoyed wide favor in medicine, but over the years technology has increasingly eclipsed such methods of divination. Today, medical technology includes genetic tools that can deliver predictive information with ever-increasing accuracy. This report is about one of those tools: a test that can tell people about their potential to pass to their offspring a genetic condition called cystic fibrosis (CF). Some people want and seek this information; others do not.

CF is the most common, life-shortening, recessive disorder affecting Caucasians of European descent. Between 1,700 and 2,000 babies with CF are born annually in the United States. As in many genetic conditions, the diagnosis of an infant with CF often reveals the first clue that the genetic trait exists in the family. In fact, four of five individuals with CF are born to families with no previous history of the illness. In such cases, the parents—as well as their siblings, parents, and other relatives—do not have CF. These individuals, referred to as CF carriers, have no symptoms of CF and might not even have heard of the condition.

In 1989, scientists identified the most common change, or mutation, in the genetic material, deoxyribonucleic acid (DNA), that causes CF. Hard on the heels of this discovery, scientists developed tests to detect mutations in the area of DNA—the CF gene—that is responsible for the disease. This report focuses on using these DNA tests to screen and identify CF carriers before they have a child with CF (box 1-A). Beyond the approximately 30,000 Americans who have CF, as many as 8 million individuals could be CF carriers. The report concentrates on these millions of CF carriers, who are, today, largely unidentified.

Concern about the scientific, legal, economic, ethical, and social implications of the prospect that

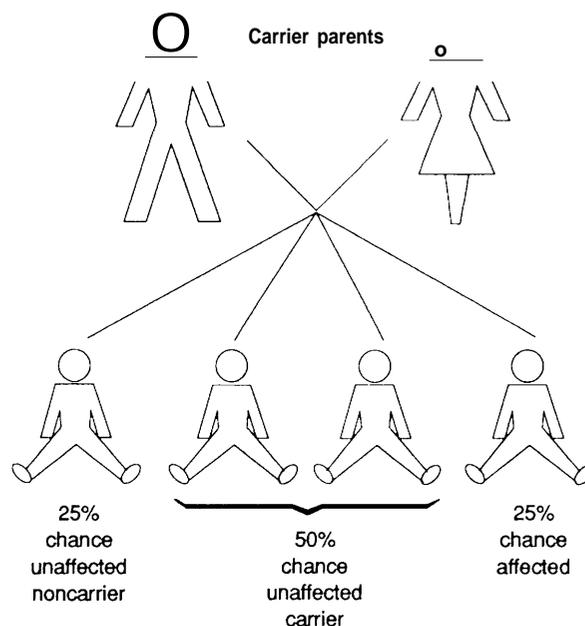


Photo credit: Office of Technology Assessment, 1992

Inheritance of cystic fibrosis.

large numbers of people might be screened for their CF carrier status led the House Committee on Science, Space, and Technology and the House Committee on Energy and Commerce to request, and Representative David R. Obey to endorse, this Office of Technology Assessment (OTA) report.¹ CF carrier screening also commands the attention of Congress because of Congress' interest in the Human Genome Project (box 1-B).

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 sweat glands and the respiratory, gastrointestinal, and reproductive systems. It occurs in all racial and ethnic groups, although more frequently in some than in others (table 1-1). In fiscal year 1991, public and private

¹ Specific analysis of several topics related to CF carrier screening have been assessed in previous OTA reports, including: newborn screening for CF; genetic monitoring and screening in the workplace; the Human Genome Project; the commercial development of tests for human genetic disorders; safety and efficacy of amniocentesis, prenatal care, and pregnancy management; and reproductive technologies and assisted conception.

Box 1-A—Terminology

OTA defines *genetic testing* as the use of specific assays to determine the genetic status of individuals already suspected to be at high risk for a particular inherited condition. While any individual can be considered “at high risk” for a particular unknown trait, and hence be “tested,” “at high risk” in this report denotes the presence of a family history or clinical symptoms. The terms *genetic test*, *genetic assay*, and *genetic analysis* are used interchangeably to mean the actual laboratory examination of samples.

Genetic screening usually uses the same assays employed for genetic testing, but it is distinguished from genetic testing by its target population. OTA uses the term “screening” selectively. In this report, it refers to analyzing samples from individuals without a family history of the disorder, groups of these individuals, or populations. *Carrier screening for CF* (or *CF carrier screening*), then, involves performing tests on persons for whom no family history of the disorder exists to determine whether they have one normal and one aberrant copy of the CF gene, but not the disorder (which results from having two aberrant CF genes).*

Many individuals are CF carriers but do not have a positive family history. In fact, 80 percent of babies born with CF each year are cases where there was no known family history for CF. Thus, a person contemplating procreation could inquire about the availability of an assay to determine the probability that he or she could have a child affected with CF. If there are no relatives with the disorder, the individual could be informed that a test would provide information about his or her genetic status for CF. The person could then elect to be *screened* to determine whether he or she is a carrier for CF. If, however, there is a family history of the disease, a practitioner would ideally inform the individual and his or her partner about CF carrier assays and they might choose to be *tested* to determine if they are both carriers.

Genetic counseling is a clinical service that includes providing an individual (and sometimes his or her family) with information about heritable conditions and their risks. When centered around genetic testing or screening, it involves both education and psychological counseling to convey information about the ramifications of possible test outcomes, prepare the client for possible positive or negative analyses, and discuss the implications of the actual test results. Many types of health professionals perform genetic counseling. OTA reserves the term *genetic counselor specifically* for master’s-level individuals to clarify the legal distinctions in licensing and third-party reimbursement among the different types of practitioners. But, OTA uses the term *genetic counseling* generically to refer to the educational and informational process performed by genetic specialists, including physicians, Ph.D. clinical geneticists, genetic counselors, nurses, and social workers.

OTA avoids using the term “program” in discussing CF carrier screening in the United States. For some, the term connotes a formal public health effort led or sanctioned by Federal, State, or local governments. In analyzing CF carrier screening, OTA’s premise is only that large numbers of Americans could---or will-be screened for their CF carrier status. OTA remains neutral on whether the assays will be a component of a fixed, regulated scheme or another facet of general medical practice.

*In contrast, OTA uses the term *CF screening* (or *screening for CF*), to mean screening individuals to diagnose the presence or absence of the actual disorder, in the absence of medical indications of the disease or a family history of CF. This type of diagnostic screening usually involves newborns, but is rarely done for CF except in Colorado and Wisconsin. CF testing of newborns is common if a family history of the condition exists.

SOURCE: Office of Technology Assessment, 1992.

institutions spent more than \$55 million studying medical and genetic aspects of CF. This section provides a brief overview of what this-and past—research has revealed, providing context for the policy aspects of CF carrier screening that follow.

Pathology, Diagnosis, and Prognosis

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; about 10 percent of cases show symptoms at birth. Other

childhood ailments often share symptoms with CF, which contributes to diagnostic difficulties. In general, most diagnoses occur by age 3.

Physicians diagnose CF using a combination of clinical criteria and diagnostic laboratory testing. Although the sweat test remains the primary diagnostic test for CF, DNA mutation analysis can diagnose over 70 percent of cases, complementing and Confirming sweat test results in some instances.

CF exerts its greatest toll on the respiratory and digestive systems, and the severity of respiratory problems often determines quality of life and length

Box 1-B—The Human Genome Project

As the 21st century approaches, Congress and the executive branch have made a commitment to determine the location on the DNA—as has been done for CF—of all other genes in the human body, i.e., to map the human genome. The Human Genome Project is estimated to be a 15-year, \$3-billion project. It has been undertaken with the expectation that enhanced knowledge about genetic disorders, increased understanding of gene-environment interactions, and improved genetic diagnoses can advance therapies for the 4,000 or so currently recognized human genetic conditions; a premise supported by the fact that even prior to launching the Human Genome Project, advances in medical genetics have directed the development of new treatment strategies and incrementally improved the management of some genetic conditions.

To address gaps in knowledge about the ethical, legal, and social implications, and perhaps forecast such consequences of this undertaking, the National Institutes of Health (NIH) and the Department of Energy (DOE) each fund an Ethical, Legal, and Social Issues (ELSI) program. Funds for each agency's ELSI effort derive from a set aside of 3 to 5 percent of appropriations for the total genome initiative budget. In fiscal year 1991, DOE's ELSI spending was \$1.44 million (3 percent). Fiscal year 1992 spending is targeted at \$1.77 million (3 percent). NIH-ELSI spending for fiscal years 1990 and 1991 has been \$1,558,913 (2.6 percent) and \$4,037,683 (4.9 percent), respectively. For fiscal year 1992, NIH-ELSI aims to spend 5 percent of its human genome appropriation. Several grants supported by NIH/DOE ELSI relate to factors affecting CF carrier screening.

SOURCE: Office of Technology Assessment, 1992.

of survival. Individuals with CF produce thick, sticky mucus. Chronic obstruction and infection of the airways characterize respiratory difficulties and result in lung damage that leads to pulmonary and heart failure. Digestive problems are also common and often predominate over respiratory symptoms early in life. Poor nutrition and impaired growth result because food—particularly fat and protein—is not broken down and absorbed properly.

There is no cure for CF. Treatment focuses on managing the respiratory and digestive symptoms to maintain a stable condition and lengthen lifespan. Again, because of CF's varied progression, the regimen and level of therapy depend 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 (box 1-C).

Table 1-I—Incidence of Cystic Fibrosis Among Live Births in the United States

Population	Incidence (births)
Caucasian.....	1 in 2,500 ^{abc}
Hispanic.....	1 in 9,600 ^d
African American.....	1 in 17,000 ^{a'e} to 1 in 19,000 ^f
Asian American.....	1 in 90,000 ^g

^aT. F. Boat, M. J. Welsh, and A.L. Beaudet, "Cystic Fibrosis," *The Metabolic Basis of Inherited Disease*, C.R. Scriver, A.L. Beaudet, W.S. Sly, et al. (eds.) (New York, NY: McGraw Hill, 1989).

^bK.B. Hammond, S.H. Abman, R.J. Sokol, et al., "Efficacy of Statewide Neonatal Screening for Cystic Fibrosis by Assay of Trypsinogen Concentrations," *New England Journal of Medicine* 325:769-774, 1991.

^cW. K. Lemna, G.L. Feldman, B.-S. Kerem, et al., "Mutation Analysis for Heterozygote Detection and the Prenatal Diagnosis of Cystic Fibrosis," *New England Journal of Medicine* 322:291-296, 1990.

^dS.C. FitzSimmons, remarks at Fifth Annual North American Cystic Fibrosis Conference, Dallas, TX, October 1991.

^eJ. C. Cunningham and L.M. Taussig, *A Guide to Cystic Fibrosis for Parents and Children*, (Bethesda, MD: Cystic Fibrosis Foundation, 1989).

^fJ. MacLusky, F.J. McLaughlin, and H.R. Levinson, "Cystic Fibrosis: part 1," *Current Problems in Pediatrics*, J. D. Lockhart (ed.) (Chicago, IL: Year Book Medical Publishers, 1985).

SOURCE: Office of Technology Assessment, 1992.

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 first two years of life. In 1990, median survival was 28 years (figure 1-1)—i.e., of the individuals born with CF in 1962, half were alive in 1990. According to the Cystic Fibrosis Foundation and others, the life expectancy of an infant born with CF in 1992 cannot be estimated, but a few individuals speculate such survival might be 40 years. On the other hand, data from Canada show the steady increase in lifespan since 1940 has plateaued in the last decade. Currently, the median age of an individual with CF in the United States is 12.6 years (figure 1-2).

Box 1-C-Cystic Fibrosis Therapies on the Horizon

In the last several years, scientists have dramatically increased their comprehension of the intricate cascade of processes that ultimately destroy the airways and lead to death in people with CF. With greater knowledge comes targeted strategies to fight the condition. Established CF pulmonary treatments of the past few decades concentrated on fighting infection and clearing airway mucus. Today, new therapies for CF focus on many facets of ameliorating the disease. Some treatments aim to prevent infection and subsequent inflammation altogether. These therapies attempt to intervene at specific junctures in the disease process by decreasing the viscosity of lung secretions, protecting the airway from destruction and preventing infection, or correcting the ionic imbalance.

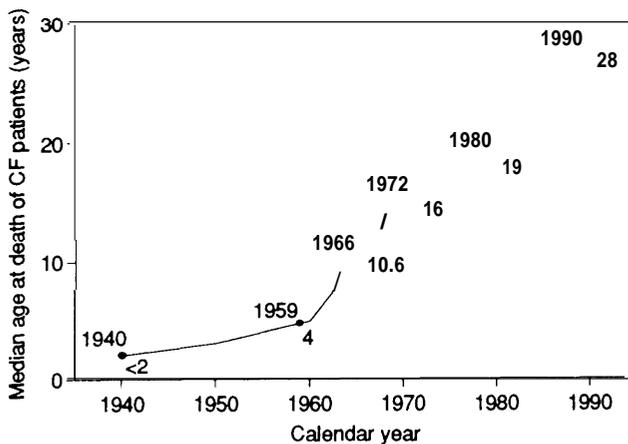
Two substances—DNase and amiloride—thin CF lung secretions, each through a different mechanism. Both are in clinical trials for approval by the U.S. Food and Drug Administration (FDA). Administration of adenosine triphosphate and uridine triphosphate in conjunction with the diuretic amiloride stimulates chloride ion secretion, which is faulty in people with CF; clinical studies also are being carried out for this therapy.

Ironically, the body's natural infection-fighting defense mechanism contributes to the destruction of airways in individuals with CF. Clinical trials are also under way for substances known as antiproteases—including alpha-1-antitrypsin, secretory leukocyte protease inhibitor, and a compound known as ICI 200,880. Antiproteases can protect the airway epitheliums from injury mediated by the body's natural bacteria-fighting substances. Finally, although still in the early research stages, recent *in vitro* evidence demonstrates that cyclic-AMP-stimulating drugs can positively affect chloride balance in some cells from CF patients, suggesting a future avenue for pharmaceutical intervention.

Gene therapy holds the promise of overcoming the condition, perhaps permanently. Unlike treatments that attack symptoms of CF, gene therapy focuses on directly altering DNA to rectify deficits of the disease. In theory, new DNA can be inserted into faulty cells to compensate for the genetic defect. Currently, gene therapy for CF is in the animal experiment stage. Using a crippled virus, the normal human CF gene has been administered directly to the lungs of rats by aerosol spray. Scientists demonstrated this DNA was functional 6 weeks after transfer to the rat lungs—i.e., the genetically engineered DNA was producing normal, human CF gene product. Aerosolized liposomes, fatty capsules that can transport drugs directly into cells, have been used to deliver alpha-1-antitrypsin genes into rabbit lungs, and a similar mechanism might be used to deliver the CF gene to human lungs. Despite significant experimental progress, hurdles remain for gene therapy for CF to be feasible in humans. Long-term safety of the procedure will need to be demonstrated, as will the most appropriate means of transferring the gene and duration of treatment.

SOURCE: Office of Technology Assessment, 1992.

Figure 1-I—Median Survival of U.S. Cystic Fibrosis Patients Over Time “



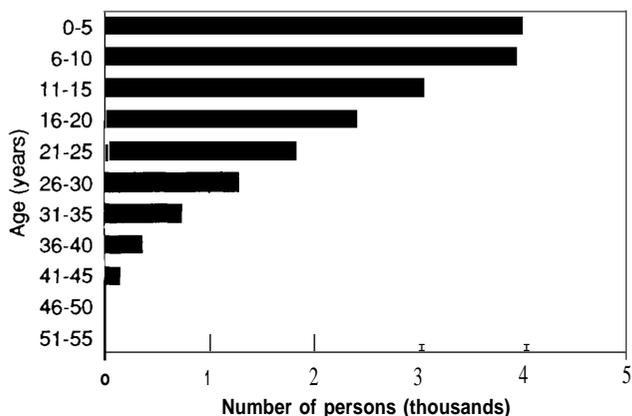
SOURCE: Office of Technology Assessment, 1992, based on S.C. FitzSimmons, "Cystic Fibrosis Patient Registry, 1990: Annual Data Report," Cystic Fibrosis Foundation, Bethesda, MD, January 1992; and S.C. FitzSimmons, Cystic Fibrosis Foundation, Bethesda, MD, personal communication, February 1992.

As with any chronic illness, individuals with CF experience emotional and social strains beyond the physical tolls of the disorder. Children, adolescents, and adults with CF react differently to the condition. For the family of a child with CF, the disease can dominate family activities, particularly if daily therapy is necessary, as is often the case. But while the emotional burden of CF can be difficult, many individuals and their families lead happy, satisfying lives.

The Cystic Fibrosis Gene

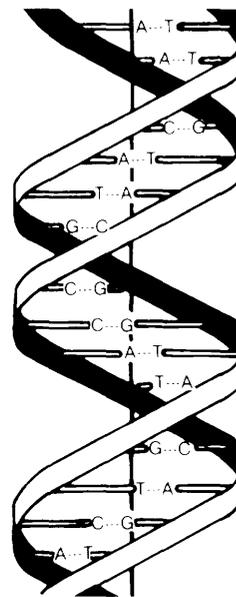
CF is a genetic illness transmitted from parents to their children via genetic instructions stored in DNA (figure 1-3). In humans, DNA stores these directions, including those responsible for CF, in genes arrayed on 46 structures called chromosomes (figure 1-4). The gene responsible for CF lies on chromosome 7.

Figure 1-2—Age Distribution of U.S. Cystic Fibrosis Patients in 1990



SOURCE: Office of Technology Assessment, 1992, based on S.C. FitzSimmons, "Cystic Fibrosis Patient Registry, 1990: Annual Data Report," Cystic Fibrosis Foundation, Bethesda, MD, January 1992.

Figure 1-3—The Structure of DNA



SOURCE: Office of Technology Assessment, 1992.

Figure 1-4—Human Chromosomes



DNA is associated with protein in organized microscopic bundles called chromosomes. Humans have 46 chromosomes: 1 pair of sex chromosomes (two X chromosomes for females; an X and a Y for males) and 22 pairs of autosomes. In 1986, scientists localized the CF gene specifically to chromosome 7.

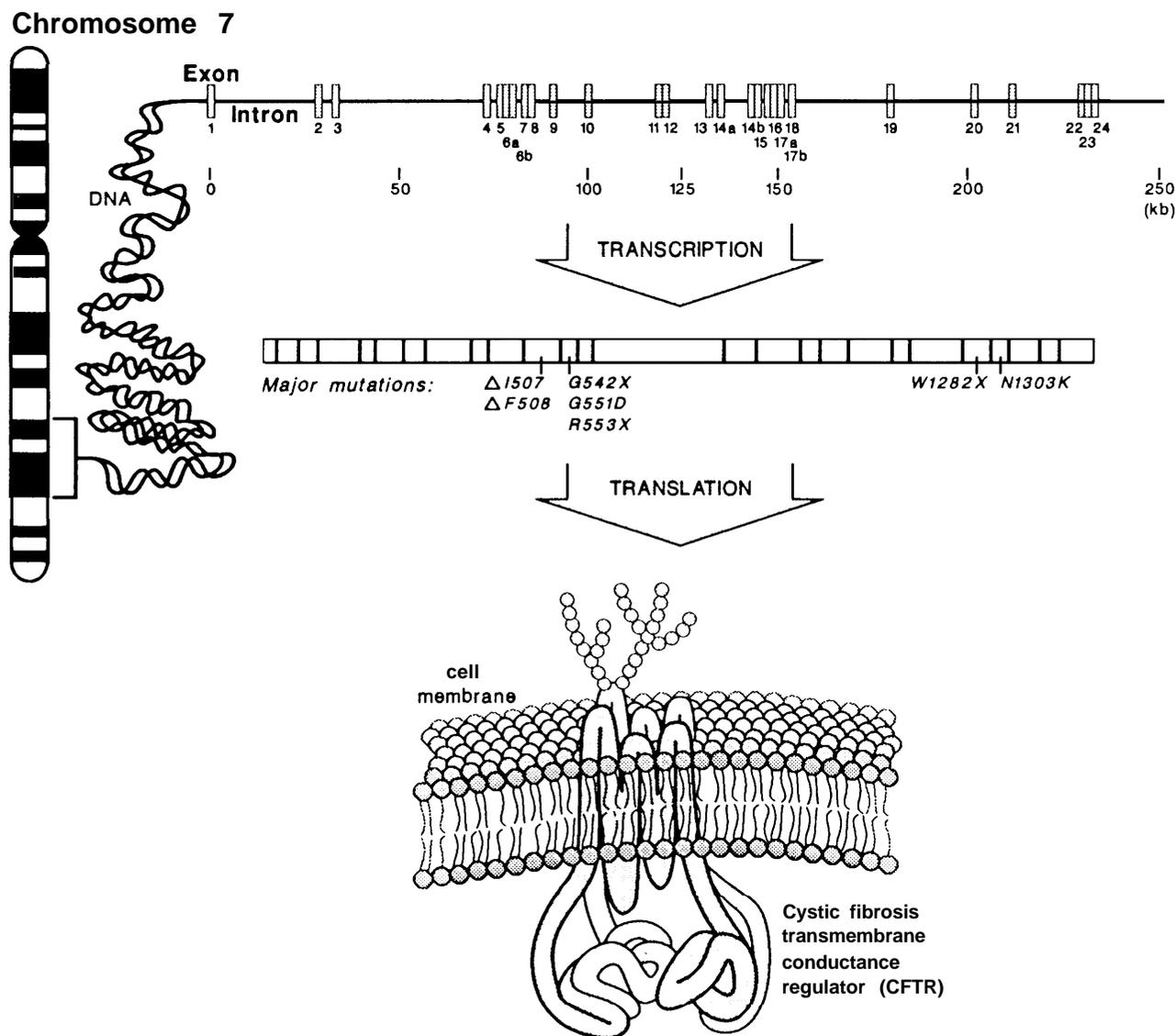
SOURCE: Vivigen, Inc., Santa Fe, NM, 1992.

Since the 1940s, geneticists have known that CF's pattern of inheritance typifies a recessive condition. For recessive disorders like CF, parents display no symptoms of the disorder, but are asymptomatic carriers. All individuals have two chromosome 7s, but for CF, a carrier mother or father has one chromosome 7 with a CF mutation and one without. The single copy of the nonmutant CF gene in carriers

is sufficient to maintain normal physiologic functions. A child is born with CF when he or she inherits the mutant CF gene from each parent---i.e., the child has two chromosome 7s with one CF mutation on each.

The CF gene is distributed over 250,000 contiguous base pairs on chromosome 7 (figure 1-5).

Figure 1-5—The Cystic Fibrosis Gene



The CF gene is located on the long arm of chromosome 7, where it is spread over 250,000 base pairs (250 kb) of DNA. Coding regions of the DNA, or exons, are separated by noncoding regions, or introns. After the DNA is transcribed into messenger RNA (mRNA) comprised of all 27 exons of the gene, the mRNA is exported from the cell nucleus. Finally, instructions in the mRNA are translated, using special structures in the cell to assemble 1,480 amino acids into the final protein product.

SOURCE: Office of Technology Assessment, 1992, based on M.C. Iannuzzi and F.S. Collins, "Reverse Genetics and Cystic Fibrosis," *American Journal of Respiratory Cellular and Molecular Biology* 2:309-316, 1990.

Box I-D—The Gene Product: The Cystic Fibrosis Transmembrane Conductance Regulator

Cells cannot pump water, but must move fluids across their membranes through a process called osmosis. Osmosis depends largely on ion movement through pores in the membrane (channels) or through transport systems designed to convey ions from one side of the membrane to the other. In individuals with CF, regulation of a particular type of ion transport (chloride; Cl⁻) is defective.

The product of the CF gene, a protein called the cystic fibrosis transmembrane conductance regulator (CFTR), mediates Cl⁻ ion flow across membranes. Current evidence suggests that CFTR functions as a channel for Cl⁻ ions. When the gene carries a ΔF508 or other mutation, it produces a defective CFTR, which in turn disrupts ion flow and results in the physiological effects distinctive of CF (e.g., skin with a salty taste and thick mucus). As the workings of CFTR are clarified, new possibilities for treatment arise.

Conceivably, elucidation of the structure and function of CFTR could facilitate assaying CF carrier status without using DNA analysis. Such assays theoretically could offer an immediate advantage over DNA-based tests. Currently, more than 170 different CF mutations exist, and hence more than 170 assays are necessary to detect them. A functional test could measure the presence of normal or altered CFTR to distinguish unaffected, *carrier*, or affected individuals. One test might be able to detect the defective CFTR protein no matter which of the 170+ mutations the individual had.

Despite expectations that a functional CFTR test could obviate the need for DNA-based CF carrier tests (and eliminate uncertainty for individuals whose tests are negative), one does not appear imminent. While research to understand CFTI continues to advance rapidly, some of the results appear to cloud, not clarify, the future of a functional test to identify CF carriers. CFTR activity differs depending on the cell type and methods used to measure its activity. *In vitro* activity also does not correlate with prognosis. Depending on the mutation, a gradient of activity exists; some mutated CFTRs still exhibit activity, while others show none. This variability would make black and white interpretation of a functional assay impossible, and perhaps less informative than DNA analyses.

SOURCE: Office of Technology Assessment, 1992.

Scientists know, however, that not all of these bases get translated into the ultimate CF gene product, called the cystic fibrosis transmembrane conductance regulator (CFTR) (box I-D). What is also known is CF's pathology stems from a faulty CFTR, and that in most people with CF a three-base pair deletion in each of their CF alleles results in the flawed CFTRs. This three-base pair mutation occurs at position number 508 in the CFTR (abbreviated as ΔF508 (DF508)). 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.

About 70 percent of CF carriers have the ΔF508 mutation.² International studies demonstrate ethnic and regional variation in the frequency distribution of this mutation (figure 1-6); 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.

Predicting the precise clinical course of CF—mild versus severe—cannot be done from knowing which mutations are present. Some symptoms (or their lack of severity), however, 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 of CF mutations (figure 1-7). Using today's technologies, CF mutation analysis is usually a one-time

² Quoted mutation frequencies for ΔF508 and other CF mutations always depend on racial and ethnic background. Throughout this report, 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.

Figure 1 -6—Occurrence of DF508 Mutation in Europe



SOURCE: European Working Group on Cystic Fibrosis Genetics, "Gradient of Distribution in Europe of the Major CF Mutation and of Its Associated Haplotype," *Human Genetics* 85:436-445, 1990.

test that can inform an individual whether he or she carries a CF mutation. 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 DF508 mutation (or another CF mutation for which the test is run) is present in the individual's genome, the assay detects 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 DF508, more than 170 mutations in the CF gene also cause CF.

In the United States, about 1 in 25 Caucasians carries one CF mutation. Since tests to detect 170+ mutations are impractical, current assays use DF508

plus 6 to 12 other CF mutations (DF508+6-12) and identify 85 to 90 percent of CF carriers (in Ashkenazic Jews, DF508+6 identifies about 95 percent of carriers).³ Thus, using DF508+6-12 means 10 to 15 percent of actual carriers go undetected. In other words, a negative test result does not guarantee that a person is not a carrier.

As mentioned earlier, a child with CF is born only to couples where each partner is a carrier of one CF mutation—though not necessarily the same one for each partner. Such couples are sometimes referred to as carrier couples, or couples who are positive/positive (+/+). For these couples, the chance of having a child with CF is 1 in 4 for each pregnancy. 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.

³ Again, using DF508 alone identifies about 70 percent of CF carriers among American Caucasians of European descent.

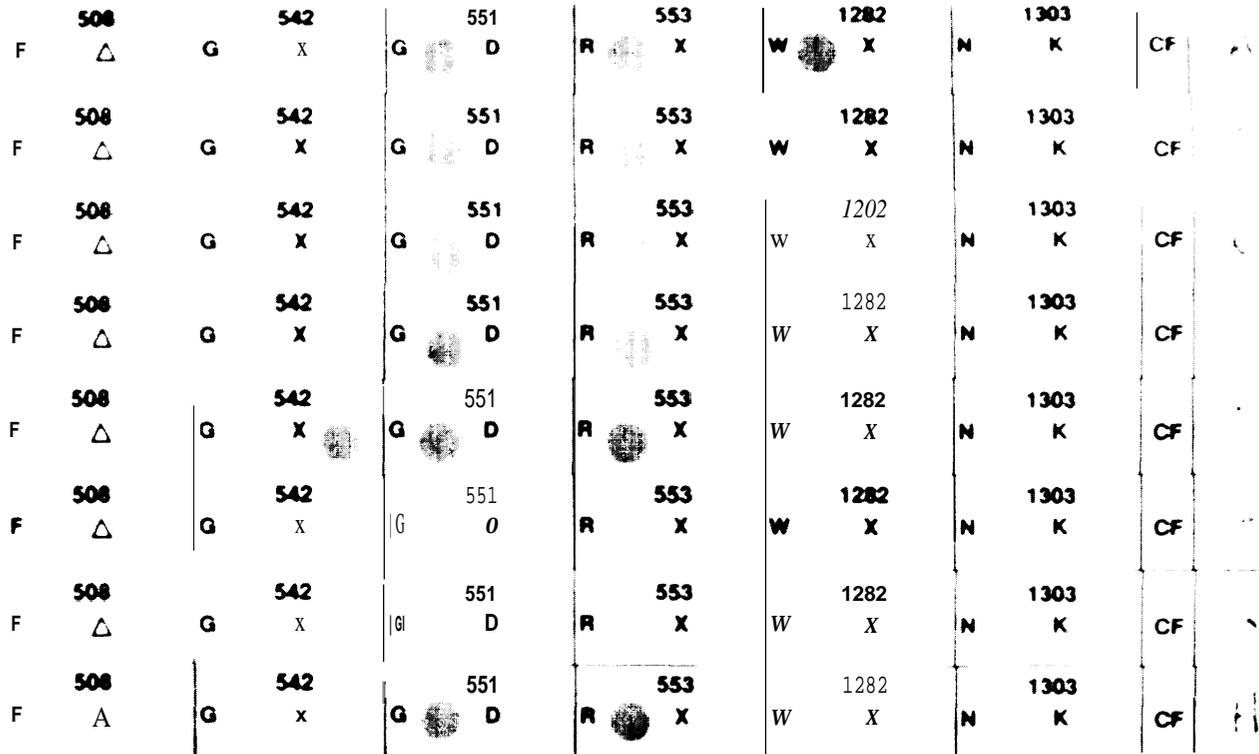


Photo credit: Roche Molecular Systems, Inc.

DNA analysis for six common CF mutations. Unique pieces of DNA, called allele specific oligonucleotide probes, are bound to the test strip to detect six common CF mutations; in this photograph, each individual strip runs horizontally. DNA samples from individuals of unknown CF status are obtained, processed, and applied to separate test strips. Here, test strips for eight different individuals are shown (rows A through H). Following hybridization and calorimetric analysis, the patterns of dots on the strips are revealed—and hence the CF status of the individuals.

For each mutation on the strip (DF508, G542X, G551D, R553X, W1 282X, and N1303K) the left dot, if present, indicates the person has a normal DNA sequence at that part of the CF gene. The right dot, if present, indicates the person has a CF mutation at that site. Individual A, then, has no CF mutations at the six areas of the CF gene analyzed using this test strip, as demonstrated by single dots on the left side for all mutations. In contrast, individuals B,D,F, and H are carriers, as demonstrated by the presence of two dots for one of the CF mutations. Individual C has CF, as demonstrated by a single dot on the right side of the DF508 panel; individual E has CF, as demonstrated by the single dot on the right side of the G542X panel. Individual G also has CF, but this person's CF arises from two different mutations—DF508 and R553X—as indicated by the pairs of dots in each of these panels.

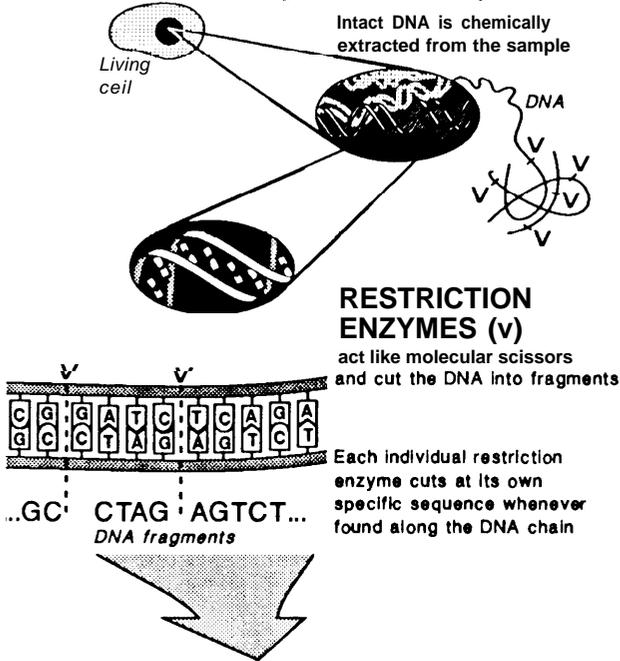
Using DF508+6-12 means that some couples receive test results that indicate one partner is a carrier and one is not, when in fact the negative partner carries one of the rare CF mutations that is not assayed (figure 1-8). Thus, while most couples whose test results are +/- are at zero risk of having 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 and have a false sense of security about having an unaffected child. If, for example, 100,000 couples experienced a first-time pregnancy, 40 fetuses would be expected

to have CF. Prenatal CF mutation analysis with 85 percent sensitivity could detect about 29 fetuses, but 11 would be missed. A few couples who receive a -/- result will also be undetected carrier couples (box 1-E; table 1-2).

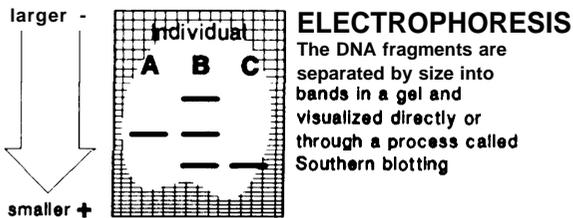
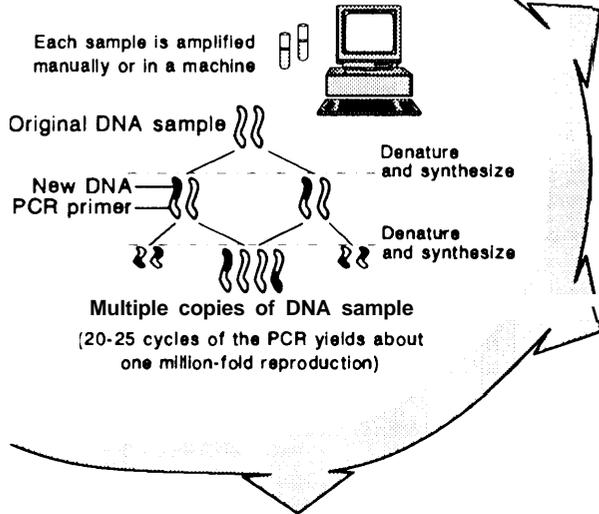
WHY IS CYSTIC FIBROSIS CARRIER SCREENING CONTROVERSIAL?

Prospects of routine CF carrier screening polarize people. Everyone agrees 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

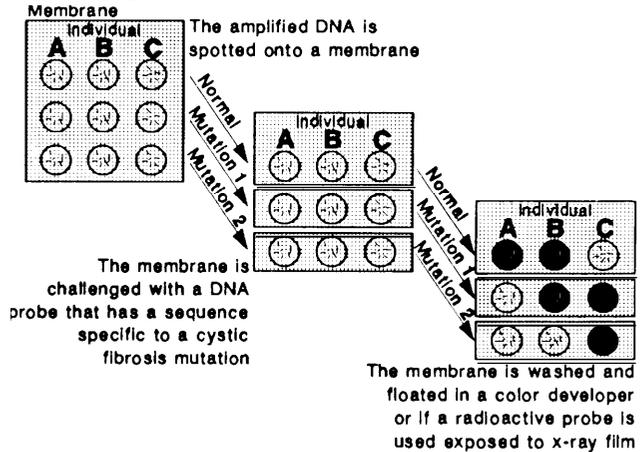
Figure 1-7—Techniques for DNA Analysis of Cystic Fibrosis Mutations



AMPLIFICATION
(Molecular photocopying of DNA)

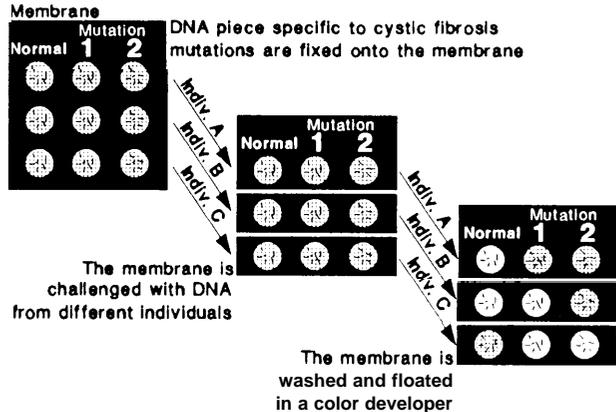


DOT BLOT



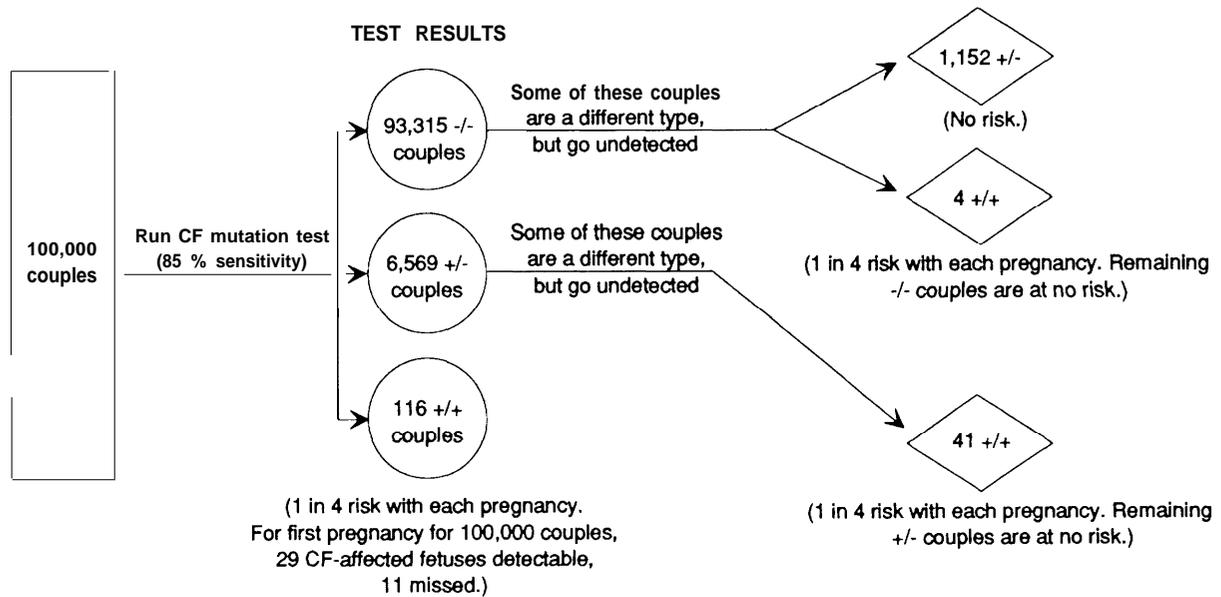
There are over 170 mutations at the cystic fibrosis locus (the most common mutation is $\Delta F508$)

REVERSE DOT BLOT



There are over 170 mutations at the cystic fibrosis locus (the most common mutation is D F508)

Figure 1-8-Cystic Fibrosis Mutation Test Results at 85 Percent Sensitivity



SOURCE: Office of Technology Assessment, 1992.

Box 1-E-Cystic Fibrosis Carrier Tests and Detection Sensitivity

In theory, 4,000 carriers exist among 100,000 random Americans of European descent, because the carrier frequency in this population is about 1 in 25. However, DF508+6-12 assays detect about 85 percent of people with CF mutations, so CF carrier screening of this group would identify 3,400 of the 4,000 probable carriers. If the test were 100 percent specific, all 4,000 carriers would be identified.

Similarly, if 100,000 random couples were screened, 160 couples would be identified as ++ (each partner a carrier) if the test were 100 percent sensitive. One-fourth of first-time pregnancies for the 160 ++ couples would be expected to result in CF-affected fetuses, for a total of 40 expected CF-affected fetuses per 100,000 couples. Instead, at 85 percent sensitivity, about 116 couples will be identified as ++ and with each pregnancy have a 1 in 4 risk of a child with CF. Results for 93,315 will be -/- (neither identified as a carrier), and about 6,569 couples will have +/- test results (one partner a carrier, the other not identified as a carrier). *In fact*, approximately 41 of the 6,569 couples with +/- test results are at 1 in 4 risk of bearing a child with CF in each pregnancy, while the remaining 6,528 have no risk—but these two groups cannot be distinguished with an 85 percent test sensitivity (figure 1-8). About 4 of 93,315 couples with -/- test results are also actually at 1 in 4 risk with each pregnancy of having a child with CF.

Thus, of the theoretical 160 ++ couples, 116 are detectable and 44 are not when the test is 85 percent sensitive. If all 100,000 couples experience a first-time pregnancy, 40 fetuses with CF are expected. With an 85 percent sensitive test, 29 fetuses with CF are detectable via prenatal tests, but 11 will be missed. If the assay elucidates 95 percent of carriers, 144 of 160 couples would be detected. In this case, if all 100,000 couples experience a first-time pregnancy, 36 fetuses with CF could be detected and 4 would be missed.

With a test that detects 85 percent of individuals with CF mutations, a couple whose result is +/- has approximately a 1 in 661 risk of having an affected child with each pregnancy (compared to a general population frequency of about 1 in 2,500). At a detection sensitivity of 95 percent, a couple with a +/- result faces a 1 in 1,964 risk of a newborn with CF with each pregnancy. Detecting a greater proportion of carriers means couples with +/- results can be less anxious about their risk of having a child with CF. Couples who both test negative, while not having zero risk, have a 1 in 109,200 risk of an affected child with each pregnancy at 85 percent test sensitivity.

SOURCE: Office of Technology Assessment, 1992, based on A.L. Beaudet Howard Hughes Medical Institute, Houston TX, personal communications March 1992, April 1992; and W.K. Lemna, G.L. Feldman, B. Kerem et al., "Mutation Analysis for Heterozygote Detection and the Prenatal Diagnosis of Cystic Fibrosis," *New England Journal of Medicine* 322:291-296, 1990.

Table 1-2—Test Sensitivity and Risk of Child With Cystic Fibrosis

Percent mutations detected	Couples at 1 in 4 risk with each pregnancy			Affected fetuses in first pregnancy			
		+/+	+/-	-/-	Actual	Detectable	Missed
	Actual	result	result	result	Actual	Detectable	Missed
85	160	115.6	40.8	3.6	40	28.9	11.1
90	160	129.6	28.8	1.6	40	32.4	7.6
95	160	144.4	15.2	0.4	40	36.1	3.9

*per 100,000 couples.

SOURCE: A.L. Beaudet, Howard Hughes Medical Institute, Houston, TX, personal communication, March 1992.

population. What are the elements of the controversy? Can past experiences with other carrier screening initiatives and current research from CF carrier screening pilots resolve some issues?

Today's Clinical and Social Tensions

For years, experts theorized about confronting the potential consequences of increased knowledge of human genetics. In the early 1990s, the CF mutation test moves the debate from the theoretical to the practical. Today, along with clinical tensions surrounding CF carrier screening, are legal, ethical, economic, and political considerations.

No mandatory genetic screening programs of adult populations exist in the United States; OTA finds it highly unlikely that CF carrier screening will set a precedent in this regard. Nevertheless, people disagree about how CF carrier screening of the general population should be conducted.

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 and become linked to 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. Opponents of widespread CF carrier screening also wonder whether the current number of genetic

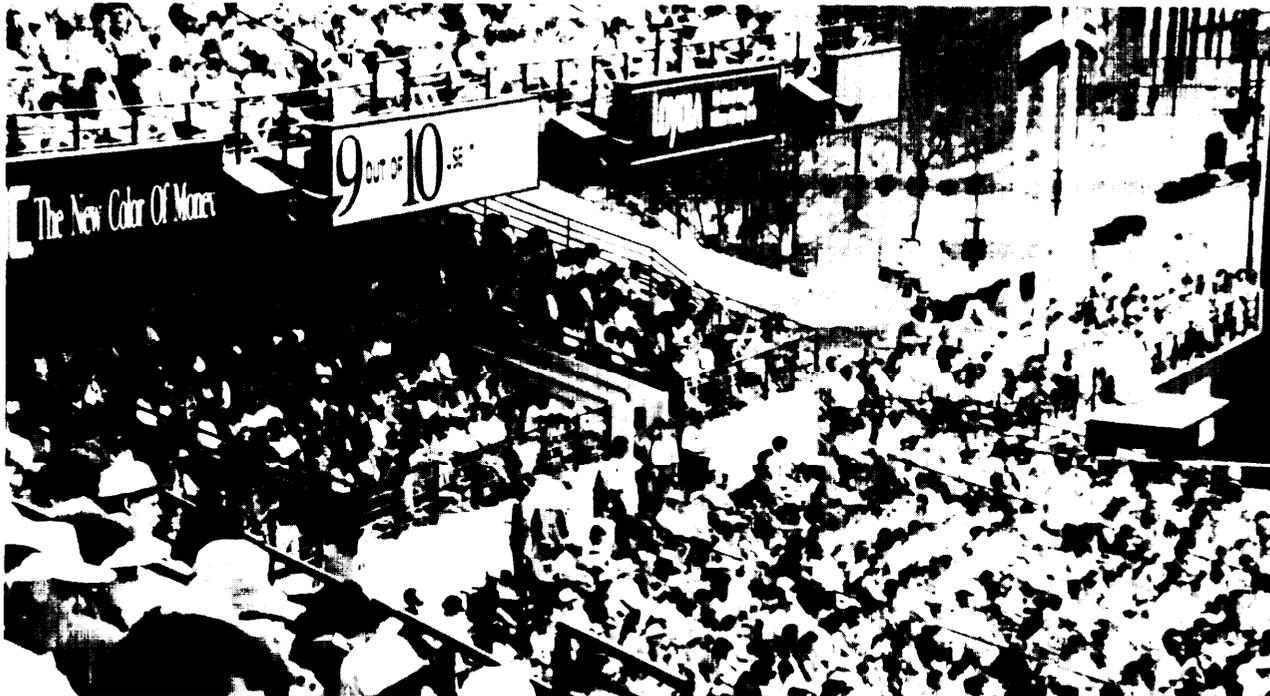


Photo credit: Lauren A. Moore

Approximately 1 in 25 American Caucasians of European descent, 1 in 46 Hispanic Americans, 1 in 60 to 65 African Americans, and 1 in 150 Asian Americans are carriers for CF. About 25 carriers would be expected among this crowd. Current technology would detect 85 to 95 percent of these individuals, depending on their ethnic backgrounds.

specialists can handle a swell of CF carrier screening cases, let alone the 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 no less concerned about the issues just raised. Rather, proponents argue that individuals should be routinely informed about the assays so they can decide for themselves whether to be voluntarily screened. They assert that the tests are sensitive enough for current use and will, like most tests, continually improve. These voices 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.

Lessons From Past Carrier Screening Efforts

Carrier screening is not new to the United States. The 1970s and early 1980s saw a number of genetic screening efforts flourish throughout the country. Federal legislation—chiefly the National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs, and Genetic Diseases Act (Public Law 94-278; hereinafter the National Genetic Diseases Act) and its predecessors—fueled these programs. Today, what might work for CF carrier screening—and what will not work—can be gleaned from carrier screening for other genetic disorders, even though earlier screening occurred through more centralized efforts. In fact, some argue that creating a defined, federally funded program for CF carrier screening could avoid social concerns, although others assert the contrary.

Frequently considered a successful effort, Tay-Sachs carrier screening was initiated in 1971 at the behest of American Jewish communities. Tay-Sachs disease is a lethal, recessive genetic disorder that primarily affects Jews of Eastern and Central European descent and populations descended from French Canadian ancestors. It involves the central nervous system, resulting in mental retardation and death within the first years of life. Fourteen months of technical preparation, education of medical and religious leaders, and organizational planning preceded massive public education campaigns. Since

screening commenced, over one-half million adults have been voluntarily screened; today, it is a part of general medical care.

In contrast, sickle cell programs in the 1970s are generally cited as screening gone wrong. The sickle cell mutation—which like the Tay-Sachs and CF mutations is recessive—affects hemoglobin, the oxygen-carrying molecule in blood. The sickle cell mutation is found predominantly in African Americans and some Mediterranean populations. Most individuals with sickle cell anemia live well into adulthood. Unlike Tay-Sachs screening, much sickle cell screening was mandatory. For the most part, Caucasians designed and implemented programs targeted toward African Americans, leading to proclamations of racist genocide. Even after elimination of most mandatory screening in the late 1970s, actual practice strayed from the stated goals of adequate genetic counseling, public education, and confidentiality of results.

Tay-Sachs carrier screening and sickle cell screening—along with carrier screening for other genetic conditions (e.g., α - and β -thalassemia)---provide perspective for today's discussions about CF carrier screening. Two lessons in particular are clear: Participation should be voluntary and public education is vital. Disagreement exists, however, about the degree to which CF carrier screening can draw on the Tay-Sachs and sickle cell experiences to resolve other considerations (e.g., discrimination). Several factors contribute to questions raised about comparability, including: Today's political climate differs; CF carrier screening has the potential to involve larger numbers of people; and Tay-Sachs and sickle cell screening were implemented, in part, with explicit Government finding in a more programmatic fashion than will be likely for CF carrier screening.

Cystic Fibrosis Carrier Screening Pilot Studies

Opponents of routine CF carrier screening argue that historical perspectives fall short of adequately addressing potential adverse consequences raised by widespread utilization of CF mutation assays, including adequate education and counseling, and prospects for discrimination and stigmatization. They assert that until data are gathered from federally funded pilot projects specific to CF, carrier screening should not be routine. Proponents, on the other hand, argue that sufficient information is

available from privately supported CF carrier screening projects, that much historical experience applies, and that any incremental gain that will be gleaned from federally funded studies is insufficient to a priori prevent routine CF carrier screening from proceeding.

Federally Funded Studies

Despite pleas throughout the genetics community for the Federal Government to fund pilot projects to assess clinical and social considerations raised by the new CF mutation analyses, initial calls for funding of pilots went wanting. In the United Kingdom, the CF Research Trust actively funded and encouraged pilots (box I-F)-unlike the CF Foundation in the United States, which has focused on investigations to find the CF gene and mutation, but divorces itself from CF carrier screening. Concern about abortion apparently played a major role in the latter policy decision.

After some scrambling, the Ethical, Legal, and Social Issues (ELSI) Program of the National Center for Human Genome Research (NCHGR), National Institutes of Health (NIH), stepped forward to coordinate federally financed pilot studies. In October 1991 (fiscal year 1992), three units of NIH-the National Center for Human Genome Research, the National Institute of Child Health and Human Development, and the National Center for Nursing Research-launched a 3-year research initiative to analyze education and counseling methods related to CF mutation analysis.

Seven research teams, conducting eight studies, received support and will coordinate their efforts (box I-G). Two of seven clinical studies focus on relatives of individuals with CF (CF carrier testing); the other five focus on the general population. One study involves theoretical modeling. Where appropriate, some features of the research, such as evaluation measures and tools, cost assessment, laboratory quality control procedures, and human subjects protection will be standardized across sites.

Privately Funded Studies

Prior to the onset of federally sponsored pilot projects, several public and private institutions began to systematically offer CF carrier screening to

subsets of the population; pregnant women and their partners, preconceptional adults, teenagers, and fetuses all have been target populations. Most privately funded efforts have been under way since early 1990, and most have collected, or are collecting, data on the incidence of carrier status and mutation frequencies. Some also follow psychosocial issues such as levels of anxiety and retention of information. Most studies can report results, and the various strategies used and different target populations reflect the lack of consensus on the best approach to CF carrier screening (table 1-3).

WHAT FACTORS WILL AFFECT UTILIZATION?

Initially, routine CF carrier screening will likely occur in the reproductive context; the prenatal population has been the traditional entry point into genetic services for many people. Preconceptional individuals are also a possible population, but for most individuals the first real opportunity for carrier screening takes place post-conception. A focus on pregnant women, however, is not without controversy. Reservations exist about abortion, as do concerns that prenatal testing negatively shapes perceptions of pregnancy, disability, and women. Nevertheless, the primary responsibility for providing CF carrier screening could come to reside with obstetricians, as has occurred with maternal serum alpha-fetoprotein (MSAFP) screening to detect fetuses with neural tube or abdominal wall defects or Down syndrome.

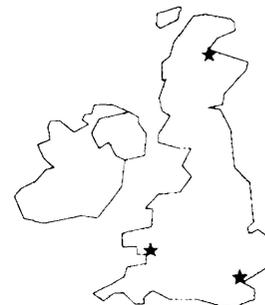
Based on the annual number of births (4.2 million) and spontaneous abortions (an estimated 1.8 million), there are approximately 6 million pregnancies per year for which CF carrier screening might be performed. Twenty-four percent of women giving birth receive no prenatal care until the third trimester, however, so CF carrier screening in the obstetric/prenatal context could initially involve, at most, 10 million⁴ men and women per year, depending on who is screened.

For some, the key question still hovering over carrier screening for CF is if, not when. For others, however, the debate has shifted to when. Several institutions already offer CF mutation analysis to individuals, regardless of family history. OTA pro-

⁴This figure does not account for the estimated 2.4 million infertile couples who are trying to conceive and might be interested in CF carrier screening (would increase overall figure). Nor does it estimate the number of Americans not involved in a pregnancy (would increase), the number of individuals involved in more than one conception per year (would decrease), or those who might have been screened during a previous pregnancy (would decrease).

Box 1-F—Cystic Fibrosis Carrier Screening in the United Kingdom

At least five pilot projects exploring the implications of population screening for CF carriers are under way in the United Kingdom; Italy, Denmark, and Austria also have pilot projects. The U.K. pilot projects, begun in 1990, are the most extensive and advanced studies under way. Although health care delivery in the United Kingdom—and the other countries with pilots—differs significantly from that in the United States, some U.K. strategies and results could bear on how routine CF carrier screening might be approached in the United States. Shared concerns include test protocols and techniques, the appropriate target population, psychological aspects (such as anxiety levels for those contemplating CF carrier screening), and the role of primary care providers.



St. Mary's Hospital Medical School in London is evaluating preconception CF carrier screening through three general practice and three family planning clinics. Individuals are approached while they wait for appointments for other reasons, or contact is made by letter prior to a visit (i.e., opportunistic screening). About 66 percent of people approached through general practitioners request screening, and 87 percent of individuals contacted in the family planning clinic seek the test. Participants have been asked how they thought their future reproductive plans might be affected if both they and their partners were found to be carriers. For those with no experience with CF, 38 percent say they would choose not to have children, 78 percent would request prenatal diagnosis should they conceive, and 16 percent would not consider terminating an affected pregnancy. For those who had a relative or knew someone with CF, 45 percent felt they would not have children, 82 percent would seek prenatal diagnosis should they conceive, and 20 percent would not terminate an affected pregnancy. Through mid-1991, St. Mary's had screened about 1,600 individuals at approximately 50 samples a week.

The pilot at St. Bartholomew's Hospital in London, funded entirely through private sources, only offers "couples screening," which solely aims to identify couples at 1 in 4 risk of an affected pregnancy—i.e., couples in which both partners are CF carriers (+/+ couples). Couples are screened and receive their results as a unit—either high or low risk of bearing a child with CF; individual carrier status is not discussed. Even if the geneticist determines that one partner is a carrier, but the other is not (a +/- couple), that couple is informed the same as a couple who both screen negative (a -/- couple): low risk. Because of ethical concerns about concealing information, couples screening is blind. Samples are gathered from each partner, with one randomly screened. If the test is negative, the couple is informed they are at low risk and the second sample goes unscreened. If the sample is positive, the other sample is tested. If the second sample is negative (a +/- couple), the couple is informed they are at low risk, without either being informed that one of them is, in fact, a carrier. Proponents feel this approach is more economical, and believe it reduces the anxiety associated with knowing one's carrier status, since results are reported as a unit. Most observers agree that such a practice would be considered legally and ethically dangerous in the United States.

Funds for three U.K. pilot projects derive from the Cystic Fibrosis Research Trust (CF Trust). They target different populations and seek, in part, to evaluate different parameters. Screening through the University Hospital of Wales in Cardiff is offered opportunistically to adults between 16 and 45 years; prenatal screening will be part of the pilot in 1993. Investigators in Wales evaluated mouthwash, buccal scrapes, and finger pricks as methods for sample collection and concluded mouthwash is the most desirable overall for patient acceptability, successful DNA extraction, and cost. The pilot at Western General Hospital in Edinburgh, Scotland, focuses on prenatal screening, with a long-term goal of preconception screening. The Edinburgh pilot first screens the woman for three mutations; if she is positive, her partner is tested for 15 mutations. Through 1991, over 2,000 samples had been processed, detecting 74 carriers. Guy's Hospital in London offers carrier screening to individuals 18 to 45 years to assess screening through an urban general practice setting. All projects devote considerable effort to examining acceptability, evaluating maternal and paternal anxiety, assessing self-esteem and perceptions of stigma, and developing effective educational material for patients and professionals.

SOURCE: Office of Technology Assessment, 1992.

Box 1-G-Federally Funded Cystic Fibrosis Carrier Screening Pilot Projects

In October 1991, the National Institutes of Health funded eight clinical assessments of CF carrier testing and screening at seven institutions.

Children's Hospital Oakland Research Institute, Oakland, CA (\$73,196). Adult siblings of CF patients and their spouses will be interviewed to identify factors motivating or interfering with the pursuit of CF carrier testing in siblings and their partners. In addition to examining interest in testing, this study aims to assess understanding of CF, knowledge of medical aspects of CF, and psychological impact following testing.

Johns Hopkins University, Baltimore, MD (\$314,449). The level of general interest in learning about CF of families and individuals receiving care from a health maintenance organization will be examined. In particular, the study will consider: what factors distinguish those interested in participating in a CF education program from those who are not; examining the characteristics that differentiate people who agree to screening from participants who decide against it, and comparing the responses of individuals identified as CF carriers to those identified as noncarriers, with emphasis on the extent to which these responses are influenced by marital or carrier status of the partner.

UCLA School of Medicine, Los Angeles, CA (\$179,067). Women of reproductive age and the partners of those who test positive will be screened, including large numbers of Hispanic and Asian Americans, two groups that have not been studied extensively for either their CF mutation frequencies or their response to screening and counseling. Pre- and post-test questionnaires will be used to determine understanding of CF, predictors of consent to screening, and responses to implications of the test results for the various ethnic and socioeconomic subgroups. Strategies for pre- and post-test counseling will be evaluated for effectiveness.

University of North Carolina, Chapel Hill, NC (\$231,916). Relatives of individuals with CF will receive pretest education, either from a pamphlet in a private physician's office or in a traditional genetic counseling setting. Effectiveness of a precounseling video will be evaluated. Investigators will assess genetic and medical knowledge, psychological status, and selected health behaviors before and after participants receive their test results.

University of Pennsylvania, Philadelphia, PA (\$197,634 and \$180,201). Decision theory and economic techniques will be used to model decisionmaking about CF carrier screening. The study will address: who should be offered screening and the best method; the best course and sequence after results are delivered; rescreening negative individuals as more mutations are identified; and the impact of future treatment on CF carrier screening. Monetary and nonmonetary effects of the alternative strategies raised by these issues will be assessed, as well as the response to screening of groups---i.e., patients, health care providers, and insurers---with varying financial, psychological, and moral perspectives.

A separate clinical study will complement the theoretical work. It will analyze the decisionmaking of couples who are offered CF carrier screening one partner at a time, and whether they choose to have the second partner screened after a negative result for the first. When screening should be offered will be investigated.

University of Rochester, Rochester, NY (\$274,110). CF mutation analysis will be offered to women of reproductive age to determine what proportion desires it, what proportion that elects screening comprehends test results, and what proportion of partners of screened women elects screening. Anxiety, comprehension, requests for prenatal diagnosis despite low risk, and program costs will be assessed.

Vanderbilt University, Nashville, TN (\$206,513). The feasibility of a program that incorporates pre- and post-test education for people with negative results, and provides personal counseling to those who test positive, will be evaluated. **Written** and video materials will be developed. Different settings in which CF carrier screening is offered will be examined, as will factors that affect a couple's decision whether or not to be screened.

SOURCE: Office of Technology Assessment based on National Center for Human Genome Research, National Institutes of Health, October 1991.

jects approximately **63,000** individuals will be screened for their CF carrier status in 1992---about a 7-fold increase over 1991 (figure 1-9). This rapid upward trend is expected, given the nascent stage of the technology's movement into U.S. medical practice.

Without offering judgment on its appropriateness or inappropriateness, OTA finds that the matter of

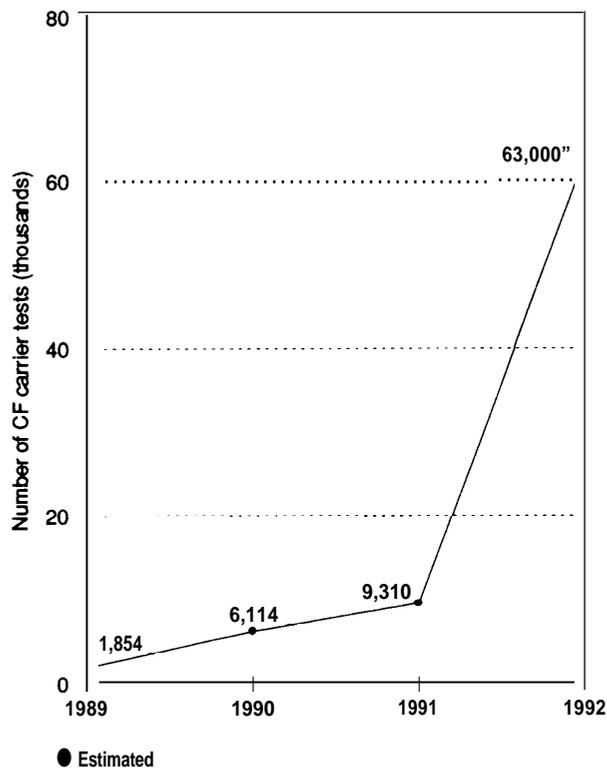
CF carrier screening in the United States is one of when, not if. Regardless of the number of individuals actually screened, it is clear that, increasingly, patients will be informed about the availability of CF carrier assays and a portion will opt to be screened. What is less clear is the timeframe for physicians to begin routinely informing patients about CF carrier tests. It could be within a year or two, but more likely will be a gradual process over several years. What

Table 1-3-Privately Funded Cystic Fibrosis Carrier Screening Pilot Projects

Institution	Target population	Approach	Findings
Baylor College of Medicine (Houston, TX)	Prenatal and preconceptional couples, with and without family history.	Two stages of mutation analysis. Both partners concurrently screened for DF508+5. For +/- couples, the negative partner is analyzed for 12 additional mutations at no extra charge.	<p>From 1990-91, 64 at-risk pregnancies detected, of which 14 affected fetuses were diagnosed. Fifty percent of these were electively terminated. No +/- couples requested prenatal fetal diagnosis, no pregnancies were terminated, and clinical evaluation did not indicate undue anxiety.</p> <p>CF carrier screening has been routinely offered (\$100 per couple) since September 1991 to all couples of reproductive age who have contact for any reason with Baylor's genetic services.</p>
Cornell University Medical College (New York, NY)	Initially, couples with no family history but enrolled in prenatal diagnosis program for other services; currently all couples of reproductive age coming to genetic services, regardless of pregnancy status.	Initially DF508; since July 1991 DF508+W1282X (at least 30 percent of couples are Ashkenazic Jews). Negative partner in +/- couples is screened for an additional four mutations.	<p>As of March 1992, more than 500 couples screened using a mouth rinse specimen at \$100 per couple. About one-third of those offered choose to participate.</p> <p>Followup questionnaires indicate all appear to understand that some at-risk couples will be missed. Virtually all agree screening should be continued, should not be limited to those ethnic groups where detection is highest, nor should be suspended until tests detect more carriers. Primary reason for participation: an interest in learning something relevant to the health of the current pregnancy. Two reasons most often cited by nonparticipants: carrier risk perceived as low or referring physician had not specifically recommended test.</p>
Genetics & IVF Institute (Fairfax, VA)	Women undergoing amniocentesis or chorionic villus sampling (CVS), primarily for advanced maternal age, offered concurrent CF mutation analysis. Some had family history.	Initially DF508; currently with DF508+6.	<p>As of August 1991, 1,327 CVS patients (44 percent) and 370 amniocentesis patients (21 percent) opted for fetal carrier screening. Fifty pregnancies identified as carrier fetuses, 47 to couples with no family history. Twelve couples declined further testing; remaining 38 sought testing for themselves.</p>
McGill University (Montreal, Canada)	High school students.	DF508	<p>Conducted in May 1990, 40 percent of about 600 students chose to participate; two carriers were identified. Interviews of these individuals and their families revealed they were positive toward their new knowledge; other family members requested testing.</p> <p>Followup questionnaires revealed participants who were negative were reasonably well-informed about the clinical phenotype and inheritance of CF. Most understood negative test did not rule out carrier status and were satisfied they had participated.</p>
Permanente Medical Group, Inc. of Northern California-Integrated Genetics (Framingham, MA)-VWigen (Santa Fe, NM)	Pregnant women of European Caucasian descent or Hispanic ethnicity.	Woman is screened first for DF50&5 mutations, with sequential screening for DF508+1 if partner if woman is positive.	<p>As of March 1992, 78 percent of women offered CF mutation analysis have accepted (As enrollees of the Kaiser Permanente health maintenance program, there is no out-of-pocket expense.)</p> <p>Kaiser has developed an informational and educational videotape to test on control and experimental groups, and is using several psychosocial survey instruments to assess individuals' understanding of pathology and genetics of CF, both before and after screening. Once 5,000 individuals have participated, Permanente Medical Group will decide whether, and how, to proceed with CF carrier screening of plan members.</p>
Roche Biomedical Laboratories (Research Triangle Park, NC)	Prenatal couples.	Samples collected simultaneously from both partners. Woman's sample screened first for ΔF508+3; if positive, partner's sample screened for ΔF508+3.	<p>Project is nationwide, since prior to initiation in July 1991, a letter of announcement was sent to 100 obstetricians around the country.</p> <p>CF mutation analyses are performed on buccal cell samples (mouth scrape) collected at home. The brushes are placed in color-coded tubes for each sex, and mailed directly to Roche by the individuals. Originally intended to last 6 months, the timeframe has been extended to 1 year, since subscription rate has been less than expected (50 percent as of September 1991).</p>

SOURCE: Office of Technology Assessment, based on R. Barathur, Specialty Laboratories, Santa Monica, CA, personal communication, September 1991; J.G. Davis, New York Hospital, New York, NY, personal communication, March 1992; S.D. Fernbach, Baylor College of Medicine, Houston, TX, personal communication, January 1992; F. Kaplan, C. Clow, and C.R. Scriver, "Cystic Fibrosis Carrier Screening by DNA Analysis: A Pilot Study of Attitudes Among Participants," *American Journal of Human Genetics* 49:240-243, 1991; J.D. Schulman, Genetics & IVF Institute, Fairfax, VA, personal communication, December 1991; and D.R. Witt, Kaiser Permanente, San Jose, CA, personal communication, March 1992.

Figure 1-9—Cystic Fibrosis Carrier Screening, 1989-92



SOURCE: Office of Technology Assessment, 1992.

factors affect-or will affect-routine carrier screening for CF? Eight aspects predominate:

- genetic services delivery and customs of care,
- public education,
- professional capacity,
- financing,
- stigmatization, classification, and discrimination issues,
- quality assurance of clinical laboratories and DNA test kits,
- automation, and
- costs and cost-effectiveness.

Of these issues, all but cost-effectiveness extend beyond CF to global concerns about future tests to assess other genetic risks. This section describes OTA's findings in each of these areas. Presented later is an analysis of what policy issues emerge from these findings and Congress' role in shaping the debate raised by these issues.

Genetic Services: Standards of Care and Ensuring Quality

One broad question expresses a facet of the current clinical controversy: Who serves as gate-keeper of a new technology? The degree to which large numbers of Americans opt to learn their CF carrier status depends first on their interaction with the genetic services system in the country. Utilization of DNA-based CF mutation analysis will depend on the extent to which physicians, genetic counselors, and other health professionals customarily inform individuals about the test's availability. In turn, moving from innovation to standard practice often depends on professional guidelines or statements. Disagreement exists about the applicability of CF carrier tests to individuals without positive family histories, which has led to tensions, with opposite sides questioning the motives of the other. Additionally, consumer acceptance will depend on perceptions that the professional services they receive with screening are of high quality.

Standards of Care

Should all individuals be informed about tests to identify CF carrier status? Society has no definitive way of determining when physicians should routinely advise people about the availability of tests that could reveal their propensity to have a child with a genetic disorder. Physician practice might be driven by consumer demand, patient autonomy, liability fears, economic self-interest, or a combination of these factors. CF carrier screening presents a classic instance of the perennial problem of appropriately controlling the evolution of practice standards as a new technology becomes available. Thus, deciding the appropriate timing for routinely telling everyone about CF mutation tests is a contentious issue.

Physicians can now offer individuals with no family history of CF a test that can determine, with 85 to 95 percent sensitivity, whether they are CF carriers. With professional opinion in a state of flux-and knowledge of the assay's existence continuing to spread among patients-physicians might wonder whether they are obligated to inform patients of its availability, even before patients ask about it.

Some consumers are interested in genetic tests and CF carrier screening. A 1986 OTA telephone survey of a national probability sample of adult Americans reported that about 9 of 10 approved of

making genetic tests available through doctors. Eighty-three percent said they would take a genetic test before having children, if it would tell them whether their children would probably inherit a fatal genetic disease.⁵ OTA's 1991 survey of genetic counselors and nurse geneticists found that 18.5 percent of respondents said they were "frequently" or "very frequently" asked by clients about DNA-based CF tests; about 71 percent said the number of inquiries increased from 1989 to 1991. On the other hand, some physicians report that actual willingness to undertake CF carrier screening is currently modest. In part, such reticence stems from the cost of CF mutation analysis, which patients must generally self-pay. It might also arise from a barrier common to many types of medical screening: lack of interest and reluctance to uncover what might be perceived as potentially unpleasant news.

Generally, physicians are obligated to inform patients of the risks and benefits of proposed procedures, so that patients themselves may decide whether to proceed. Where a patient specifically asks about a test, physicians would seem obligated to discuss the test, even if they do not recommend that it be taken. Whether physicians are obligated to query patients about their potential interest in a test the provider views as unwarranted by the patient's circumstances depends on the customary practice of similarly skilled and situated physicians.

Customary practice is often determined by the courts, and courts view statements issued by a relevant professional society as evidence of what a reasonably prudent physician might have done. In mid-1992, after extended discussion, the leadership of the American Society of Human Genetics (ASHG) approved a revised statement that CF mutation analysis "is not recommended" for those without a family history of CF. Some argue that the subtle change in language of the new statement retreats from the absoluteness of a 1990 ASHG statement that stated routine CF carrier screening is "NOT **yet** the standard of care." This view holds that the new statement reflects an evolution of debate within the society—that some believe CF carrier screening *may now be offered* to individuals without a family history of CF, although it might not be the "standard of care." Others argue that ASHG's position is unchanged—that the new statement is tantamount to

restating that CF carrier screening *should not be offered* to individuals without a family history of CF. In either case, the statement cannot be interpreted to mean that CF carrier screening *should be offered* to all individuals. The 1990 and 1991 policy statements of professional societies and participants in an NIH workshop stated that CF carrier screening should not be the standard of care.

Today, some physicians take their cues strictly from the early guidelines; the extent to which the 1992 ASHG statement will affect physician practice remains to be seen. Others have concluded that a general population incidence of 1 child with CF per 2,500 births, coupled with the test's imperfect detection sensitivity, makes routinely informing patients about CF mutation analysis unnecessary. Additionally, some physicians might choose not to inform patients of the availability of CF mutation analysis because they judge that the test is too psychologically risky or too expensive to be worth the possible benefits for those without a family history of CF. Still other providers might be unaware of the test or its possible benefits.

Some physicians, however, disagree with existing guidelines and have already chosen to incorporate CF screening into their practices. They believe the assays are sufficiently sensitive for general use, and that even patients with unknown risks of conceiving a child with CF should now have the information to exercise choice in managing their health care. Still other physicians might be offering the assay out of concern that failing to could subject them to charges of medical malpractice if a couple has a child with CF and a court subsequently finds that CF carrier screening had become the standard of care—despite professional statements to the contrary. These practitioners might be concerned by the few cases where courts held that limited adoption of a practice by some professionals is sufficient to call into question the reasonableness of the defendant's Practice—regardless of the extent to which that practice was accepted generally by the profession or suggested by professional societies. In fact, with respect to CF carrier screening, customary physician practice might evolve faster than that recommended by physicians' own professional societies, as has occurred for other practices such as amniocentesis.

⁵Survey respondents were not specifically questioned about CF.

Duties of Care for Genetic Counseling

Once a decision is made to offer information about tests for CF carrier screening—or to provide the assay itself—at least three important issues arise: what constitutes quality genetic counseling, confidentiality of information, and compensation for inadequate counseling or breach of confidentiality.

Components of Genetic Counseling. A genetics professional must understand enough about the patient's health, his or her reproductive plans, and available technologies so that an appropriate family history can be obtained and necessary analyses ordered. Less than this could give patients grounds to complain of a false assurance of safety. More than most aspects of medicine and counseling, genetic counseling involves family issues and family members. For a nonspecialist, it might be enough to recognize the need for a referral.

Having elicited information and obtained test results, the provider must communicate the results in a meaningful way. Translating technically accurate information into understandable information is difficult, but essential. Effective communication also entails recognizing and understanding religious, psychosocial, and ethnocultural issues important to the client and his or her family. People interpret genetic risk information in a highly personal manner and can misperceive, misunderstand, or distort information. For CF carrier screening, an important aspect involves explaining the reproductive risks the client faces and what the condition involves. Perceptions of relative risk significantly affect qualitative decisions. Some consumers could mistake the assay's resolution and perceive that a negative result from use of the latest DNA technology means no risk.

No standard for genetic counseling exists. Some argue in favor of a standard based on what patients would want to know (modeled after informed consent requirements) because there is no freed professional norm as an alternative, and because adequacy of the information conveyed turns more on the values of the patient being counseled than on professional norms. The prevailing approach in genetic counseling, however, appears to be based on a review of what most professionals do, rather than what an individual patient wants.

Confidentiality. Genetics professionals with information on the carrier status of a patient are legally obligated to keep that information confidential



Photo credit: Beth Fine

Genetic counseling can help individuals and families understand the implications of positive and negative test outcomes.

except under a few, specific circumstances. At least 21 States explicitly protect patient information pertaining to medical conditions and treatment; it is also part of the case law in many States without specific statutes. Offending physicians can have their licenses revoked or be subject to other disciplinary action. Patients whose confidential records have been revealed can also bring civil suit against the physician or facility.

Not all genetic information, however, must remain confidential. A provider might wish to reveal genetic information to interested third parties without a patient's permission. Health care professionals are not legally liable or subject to disciplinary action if a valid defense exists for releasing a patient's genetic or other medical information. With CF, the professional might desire to inform a patient's relatives that they also could be at higher than average risk of conceiving a child with CF. If the provider is persuaded that the relatives will not be notified—after a patient has been advised to inform relatives that they too could carry a CF mutation—he or she might believe that breaching confidentiality would be appropriate.

The coming years will see a growing number of situations where health professionals will need to balance confidentiality of patients' genetic information against demands from relatives and other third parties for access to that information. Overall, the

risk to the third party from nondisclosure must be balanced against the benefit of maintaining the expected confidentiality of the provider-patient setting. A provider contemplating disclosure to a patient's spouse must weigh the patient's own confidentiality against a spouse's interest in sharing decisions concerning conception, abortion, or preparation for the birth of a child with extraordinary medical needs.

Compensation for Negligent Genetic Counseling. Inadequate genetic counseling can result in a number of outcomes. Patients might forego conception or terminate a pregnancy when correct information would have reassured them. People might choose to conceive children when they otherwise would have practiced contraception, or they might fail to investigate using donor gametes that are free of the genetic trait they wish to avoid. Finally, they might lose the opportunity to choose to terminate a pregnancy.

The birth of a child with a genetic condition could result in malpractice claims of wrongful birth or wrongful life. For wrongful birth claims, most jurisdictions allow compensation for negligent failure to inform or failure to provide correct information in time for parents to either prevent conception or decide about pregnancy termination. With regard to CF, at least one court has ruled that parents may collect the extra medical costs associated with managing the condition. In this case, the couple maintained they would have avoided conceiving a second child had their physicians accurately diagnosed CF in their first child and thus identified each parent as a CF carrier. In wrongful life claims, the child asserts he or she was harmed by the failure to give the parents an opportunity to avoid conception or birth. Most U.S. courts have been reluctant to allow damages because they have been uncomfortable concluding that a child has been harmed by living with severe disabilities when the only alternative is never to have been born,

Practitioners who provide inadequate genetic counseling, including failing to recommend needed tests, might be subject to sanctions—ranging from a reprimand to license revocation—by a regulatory body or a professional society. M.D.-geneticists, as physicians, are formally licensed by States. Ph. D.-geneticists and master's-level genetic counselors are

not licensed by States, but until 1992 have been certified (along with physicians) by the American Board of Medical Genetics (ABMG). The continued certification of master's-level counselors by ABMG beyond 1992 is uncertain.



CYSTIC FIBROSIS

Could my child have this disease?

A new test can give you the answer.

Should I have this test?

IT'S YOUR CHOICE

*Photo credit: Peter T. Rowley,
University of Rochester School of Medicine*

Educational materials, such as this pamphlet developed at the University of Rochester School of Medicine, Rochester, NY, can be useful for pretest education.

Public Education

Both the way in which a provider communicates information about potential risk to the client (or risk to potential offspring) and the implications of the condition and prognosis influence a client's perception of the information. A person's subjective frame of reference, familiarity with genetics, and ability to understand statistical implications of genetic risks are also important.

Risk perception is always a more important determinant of decisionmaking than actual risk. When confronting the risk of genetic disease in their offspring, and in making reproductive decisions, people tend to place greater weight on their ability to cope with a child with a disability or a fatal disease than on precise numerical risks. One study revealed that regardless of actual risk, parents overwhelmingly see situations as 0 or 100 percent—it will or will not happen—when they believe they cannot cope with the situation.

In addition to subjective factors that influence the interpretation of risk, most individuals have difficulty understanding risk in arithmetic terms, yet comprehending probabilities affects people's understanding of information provided by genetic tests. One study of predominantly Caucasian, middle-class women in Maryland found more than 20 percent thought that "1 out of 1,000" meant 10 percent, and 6 percent of respondents thought it meant greater than 10 percent. A 1991 national survey of public attitudes toward genetic tests reveals that belief in the accuracy of the technology is one of the strongest predictors of favorable attitudes toward genetic tests; that same survey of 1,006 Americans found that less than half were able to answer correctly four of five technical questions regarding genetic tests.

The need for better scientific literacy has been a topic of wide discussion in recent years, and mechanisms to achieve this goal apply equally to genetics education. Increased public education in genetics would benefit individuals' perceptions and understanding about genetic test results—likely reducing time needed for individual counseling,

Public education programs targeted to genetic diseases have been nearly nonexistent since those

established under the National Genetic Diseases Act were phased out in 1981. The National Science Foundation (NSF) has supported teacher training programs in genetics for school teachers in Kansas, for example, but no NSF-funded, national effort exists. Teachers who participated in the Kansas program subsequently increased time devoted to genetics instruction at the high-school level by three-fold. Instruction in elementary schools increased 22-fold. More recently, the U.S. Department of Energy (DOE) began funding a 3-year project to prepare 50 selected science teachers per year to become State resource teachers.

Public education can go a long way toward preparing individuals for the decision of whether and when to be screened. Positive and negative experiences with large-scale Tay-Sachs, sickle cell, and α - and β -thalassemia carrier screening programs—in the United States and abroad—demonstrate the value and importance of pretest community education.

Professional Training and Education

Many types of health professionals perform genetic counseling: physicians, Ph.D. clinical geneticists, genetic counselors/nurses, and social workers. Critics of widespread CF carrier screening question whether the present genetics counseling system in the United States can handle the swell of cases if CF carrier screening becomes routine.

Currently, about 1,000 master's-level genetic counselors practice in the United States. An additional 100 nurse geneticists provide similar services. The ABMG has certified 630 professionals in genetic counseling, including master's-level genetic counselors, nurses, and M.D. and Ph.D. geneticists. If genetic counseling for CF carrier screening were to fall only to board-certified professionals, the available number of professionals might be short of what is needed. OTA's survey of genetic counselors and nurses in genetics also indicates that respondents believe routine CF carrier screening will strain the present genetic services delivery system. Respondents estimated that, on average, 1 hour would be needed to obtain a three-generational family history and to discuss CF carrier screening and genetic risks.

6 & @ OTA uses the term "genetic counselor" to specifically describe master's-level individuals certified by the ABMG (or board-eligible) because legal distinctions in licensing and reimbursement for services exist among the different types of professionals who perform genetic counseling.

Skeptics of a personnel shortage assert that counseling about CF carrier assays is likely to take place in the general obstetric/prenatal context, however, and they believe 1 hour exaggerates the amount of time that suffices for all prenatal tests, let alone only CF carrier screening. Furthermore, counseling related to CF carrier screening is likely to extend beyond board-certified individuals to include other physicians and allied health professionals. For example, an unknown number of social workers, psychologists, and other public health professionals perform genetic counseling, often to minority and underserved populations.

Ultimately, the issue of adequate services and professional capacity could turn on the extent to which patients receive genetic services through specialized clinical settings, as they largely do now, versus access through primary care, community health, and public health settings. Overall, OTA cannot conclude whether increased numbers of genetic specialists are necessary—arguments exist pro and con. One finding is clear: Increased genetics education for all health care professionals is desirable. Routine carrier screening for CF—and tests yet to be developed for other genetic conditions—will require adequate training and education of individuals in the broader health care delivery system.

Increasing professional education in genetics will not be an easy task. The average 4-year medical school curriculum includes 21.6 hours of genetics instruction. Fifteen master's-level programs in genetic counseling exist, producing approximately 75 graduates per year. Of 200 U.S. universities that offer graduate nursing degrees, only 4 offer programs providing a master's-level genetics major. Only 9 of nearly 100 accredited social work graduate programs in the United States offer special courses on genetic topics. Few schools of public health offer genetics as part of their curriculum; none requires it.

Federal support for genetic services, education, and training has changed dramatically since 1981. Prior to 1981, genetics programs applied through their State for Federal funds under the National Genetic Diseases Act (Public Law 94-278). With creation of the Maternal and Child Health (MCH) Block Grant (Public Law 97-35), State genetic services now compete with other maternal and child

health initiatives (box 1-H). Additionally, Federal spending on demonstration projects for service delivery, training, and education has declined after adjustment for inflation. Training support for master's-level genetic counselors is minimal. The U.S. Department of Health and Human Services (DHHS) provides no financial support for training genetic counselors or for improving genetics education in medical schools. Through support to the Council of Regional Networks for Genetic Services (CORN), DHHS provides funds for some continuing professional genetics education programs for physicians, but not for other genetics professionals.

Financing

Health insurance in the United States is not monolithic. U.S. health care financing, which totaled more than \$800 billion in 1991, is a mixture of public and private funds. Federal financing includes Medicare, Medicaid, and the Civilian Health and Medical Program of the Uniformed Services (CHAMPUS). Private funding mechanisms include self-funded plans, commercial health insurance plans, Blue Cross and Blue Shield (BC/BS) plans, health maintenance organizations (HMOs), self-pay, and nonreimbursed institutional funding. State high-risk pools—generally using public and private monies—are also an option in some States for people who cannot obtain private health insurance. Rules and regulations governing each sector vary.⁷ Thus, separating how the current financing paradigm might affect CF carrier screening—and vice versa—is difficult.

For the majority of Americans, access to health care, and the health insurance that makes such access possible, is provided through the private sector. Some acquire health insurance on their own through individual policies; 10 to 15 percent of people with health insurance have this type of coverage. Of group policies, about 15 percent have some medical underwriting—i.e., medical and genetic information are used to determine eligibility and premiums for health insurance. A large majority of insured individuals and their family members—163 million of the 214 million with health care coverage—obtain coverage via employer-offered large group policies with no medical underwriting. The employer, in

⁷Benefit packages offered by the different providers vary, as do laws governing them. Except for self-funded company health insurance plans, State laws govern both group and individual private health insurance. Thus, a patchwork of laws and regulations oversees commercial insurers. Laws and regulations for commercial insurers differ from those for BC/BS plans. HMOs are regulated by States, with some Federal guidance.

Box 1-H-Genetic Services: Federal-State Partnership

Funding for genetic services derives from a medley of Federal and State sources, and varies greatly from State to State. During the 1970s, genetic services enjoyed substantial Federal funding, in part through congressional mandate. The Omnibus Budget Reconciliation Act of 1981 (Public Law 97-35), however, led to the consolidation of genetic services funding—along with seven other programs—into the Maternal and Child Health (MCH) Block Grant. Overall, funding for maternal and child health services was cut, and the responsibility for distributing the monies and for providing services was passed to the States, which also had to begin using \$3 of State funds for every \$4 of Federal money received. Prior to the block grant, no matching funds were required.

Under provisions of the MCH block grant, 85 percent of funds go directly to the States for maternal and child health services. States must decide how to allocate the funds among a number of areas, such as general prenatal care, infant nutritional supplementation, and other maternal and child health needs. MCH funds may be used for health care services, education, and administration. In fiscal year 1990, less than 2 percent of MCH funds were used by States to support genetic services other than newborn screening.

In general, MCH funds account for a small portion of State genetic services. Under terms defined by the block grant, each State decides whether or how much money to designate for genetic services. In 1990, 34 States used MCH funds to support some aspect of general genetic services other than newborn screening, including nonpatient-related activities such as administration and planning. In the majority of States, however, MCH funds accounted for less than 25 percent of fiscal year 1990 funding for genetic services. In fiscal year 1990, MCH funding for genetic services other than newborn screening totalled approximately \$8 million; State funding accounted for approximately \$22 million.

Fifteen percent of the MCH block grant is administered as direct grants for Special Projects of Regional and National Significance (SPRANS). SPRANS monies are grants for specific projects and are not given to each State. SPWS provides seed money for demonstration, or pilot, projects in a number of areas. After the demonstration period ends, usually in 3 years, alternative funding must be found.

In fiscal year 1990, genetic services received about 9 percent of all SPRANS funds. When adjusted for inflation, however, constant dollar funding for genetic services under SPRANS has decreased almost every year since the block grant's inception. Moreover, SPRANS support of genetic services has decreased from about 90 percent of the SPRANS genetic services budget in 1981 to approximately 66 percent in 1991. Initially, most of the SPRANS genetic services budget established statewide genetics programs, with each State receiving seed money for at least 4 years. The last State received funding in 1990. Other areas of genetic services delivery receiving SPRANS support include ethnocultural projects to increase utilization of genetic services by underserved populations; psychosocial studies; and support groups for young adults and families. In fiscal year 1990, 16 States used approximately \$4 million from SPRANS grants to support demonstration projects in clinical genetic services other than newborn screening. In fiscal year 1990, just over one-third of SPRANS' genetic services budget went to the regional networks and the Council of Regional Networks for Genetic Services (CORN). CORN and the regional networks—comprised of genetic service providers, public health personnel, and consumers—serve as resources for communication and coordinate data collection and quality assurance, but do not provide direct services to patients.

In addition to block grant and SPRANS awards, States also fund genetic services from other sources. In fiscal year 1990, at least 26 States derived \$46 million in genetic services funding exclusive of newborn screening from provider in-kind and service charges, third-party reimbursement, grants, contracts, newborn screening fees, health insurance surcharges, and mental health/mental retardation funds. For some States, such funding accounts for most of their genetic services funding. For example, newborn screening fees generated 93 percent of genetic services funding in Colorado and 86 percent in Michigan in fiscal year 1990. Similarly, prenatal screening service fees accounted for more than 83 percent of the genetic services budget in California in fiscal year 1990.

All States, the District of Columbia, and Puerto Rico coordinate genetic services statewide; nearly half experienced a decrease in funding for genetic services from fiscal years 1988 through 1991. Individual State genetic service programs face yearly uncertainty about how much—if any—funding they will receive, which makes planning difficult. As general knowledge and public awareness about genetic diseases continues to emerge out of the Human Genome Project, uncertainty in genetic services funding will be increasingly problematic.

SOURCE: Office of Technology Assessment, 1992 based on E. Duffy, Genetic Services Branch, Maternal and Child Health Bureau U.S. Department of Health and Human Services, Rockville, MD, personal communication February 1992; and F.J. Meaney, "CORN Report on Funding of State Genetic Services Programs in the United States, 1990," contract document prepared for the U.S. Congress, Office of Technology Assessment April 1992.

turn, contracts with a commercial insurer, a BC/BS plan, an HMO, or is self-funded.

Self-funded health insurance plans are group policies that merit specific discussion, since they are creatures of Federal, not State, law. Since enactment of the Employee Retirement Income Security Act of 1974 (ERISA; 29 U.S.C. 1131 et seq.), many companies find self-funding beneficial because their employee benefit plans are not subject to State insurance regulation. With an ERISA plan, the employer directly assumes most or all of the financial liability for the health care expenses of its employees, rather than paying premiums to other third-party payers to assume that risk. Self-funded companies enjoy considerable latitude in designing employee coverage standards. Today, about 53 percent of the employment-based group market is self-funded, and therefore unregulated by the States.

In large measure, the number of people who opt to be screened could hinge on who pays, or will pay, for the cost of CF mutation analyses—the individual or a third-party payor. As mentioned previously, some physicians report that reluctance to undertake CF carrier screening seems to stem from the test's cost. Physicians seeing patients who rely on health insurance to cover part of their expenses usually inform them that their coverage probably precludes reimbursement for CF mutation analysis without a family history of CF,⁸ and so if they opt to be screened, they will likely need to self-pay. For laboratories that perform genetic tests, the issue of reimbursement also might be crucial to the ultimate volume of future business in this area.

Private Sector Reimbursement

Health insurance industry representatives assert that most companies will not pay for tests they consider screening assays. Thus, reimbursement for CF carrier tests in the absence of family history will likely remain on a self-pay basis unless they become

part of routine pregnancy care—again, as happened for MSAFP screening.

OTA's 1991 survey of commercial insurers, BC/BS plans, and HMOs⁹ confirms these policies for individual contracts or medically underwritten groups. OTA found carrier tests for CF, Tay-Sachs, and sickle cell would not be covered by 12 of 29 commercial insurers offering individual coverage for any reason—screening or family history. No company offering individual insurance or medically underwritten policies would cover CF carrier analysis if a patient requested it, but had no family history. If there is a family history, most companies would pay for carrier tests. Similar results were found for BC/BS plans and HMOs, although a few BC/BS plans and a few HMOs reported they would cover carrier tests performed for screening purposes.

As mentioned earlier, initial carrier screening for CF will likely take place in the context of obstetric/prenatal care. For all three respondent populations, prenatal screening tests for CF generally are not covered without a family history, although more would cover prenatal tests solely at patient request (without family history) than cover general carrier screening. Some respondents covered no prenatal tests.

Respondents were asked to indicate whether they agreed or disagreed with the following scenario:

Through prior genetic testing, the husband is known to be a carrier for CF. Before having children, the wife seeks genetic testing for CF. The insurance company declines to pay for the testing, since there is no history of CF in her family.

For commercial insurers who write either individual policies or medically underwrite group policies, or both, 21 medical directors (41 percent) agreed strongly or somewhat with this scenario; 28 respondents (47 percent) disagreed somewhat or disagreed strongly. In part, these results reflect OTA's survey

⁸Under the present health care system and current reimbursement policies by insurers, the reality is that the opportunity to be screened depends on the ability to self-pay (except for Medicaid). Thus, questions of access to CF carrier tests and genetic services arise. However, the issue of access to CF carrier screening is no different—and inextricably linked—to the broad issue of health care access in the United States, a topic beyond the scope of this report.

Some contend that until the issue of access is resolved, widespread carrier screening should not proceed. On the other hand, others argue that inequitable access is true for health care in the United States, generally. Supporters of carrier screening for CF question why access to genetic tests and services should be held to a higher standard. In this report, OTA analyzes the issue in the context of today's health care system, but points out that for some opponents of routine CF carrier screening, nonuniversal access is an a priori reason for why CF carrier screening should not proceed.

⁹OTA's survey of health insurers does not measure actual practice, unless otherwise specifically indicated. The information presented here should not be interpreted to represent numbers or percentages of entities who actually have dealt with these issues. Health insurers who write individual policies or medically underwritten groups were asked to speculate how they would treat certain conditions or scenarios presented (currently or in the future, depending on the question), not whether they, in fact, had made such decisions.

finding that several respondents would not cover any carrier tests, even when medically indicated by a family history. On the other hand, not all respondents who agreed with the scenario represented these companies. These individuals appeared not to understand that the situation was not a case of CF carrier screening, but one of testing to ascertain the couple's risk of conceiving an affected fetus in light of the male's family history.

OTA also found variation in how genetic counseling is covered by commercial insurers, BC/BS plans, and HMOs that offer individual policies or medically underwritten group coverage. OTA's survey of genetic counselors and nurse geneticists confirms these results: Reimbursement for genetic counseling by these professionals is more likely when a family history exists.

Finally, as stated earlier, most people obtain health care coverage through group policies. Determining how these thousands of policies would reimburse for CF carrier screening was not possible for this report. Nevertheless, information gathered informally indicates group policy coverage is unlikely to differ significantly from OTA's survey results—i. e., most policies will not cover CF carrier assays unless there is a family history. The Federal Office of Personnel Management, which oversees Federal employee health benefits, has denied reimbursement for preconception CF carrier screening because it views it as preventive, not therapeutic. On the other hand, one private institute's experience with reimbursement to clients for elective fetal CF carrier screening paints a different picture. In a small survey of clients, 16 of 27 reported they had been reimbursed for their tests. Eleven had been reimbursed fully—by either commercial insurers or BC/BS plans—and five had been partially reimbursed. It is likely that reimbursement occurs more frequently in this population than might be expected from OTA's survey because it occurs in the context of pregnancy management, not preconception.

Public Sector Reimbursement

Although access to CF carrier tests will largely depend on ability to pay because most private insurance does not cover them—at least to the extent that individual policies reflect group policies—some individuals will be Medicaid eligible. Reimbursement for their assays would be partially covered by this State-Federal partnership. In 1991, OTA surveyed directors of State Medicaid programs and

Table 1-4-Medicaid Reimbursement for Genetic Procedures^a

	Covered	Not Covered	Individual consideration	Unknown
Amniocentesis.	45	0	1	0
Chorionic villus sampling.	31	10	4	1
Ultrasound.	44	0	2	0
Maternal serum alpha-fetoprotein test.	44	0	2	0
DNA analysis.	26	6	6	8
Chromosome analysis.	41	1	4	0
Genetic counseling.	11 ^b	19	2	3

^aBased on the responses of 45 states and the District of Columbia to a 1991 OTA survey of Medicaid programs.

^bEleven other States cover genetic counseling only as apart of office visits.

SOURCE: Office of Technology Assessment, 1992.

found State to State variation in both the types of genetics and pregnancy-related services covered (table 1-4) and the amounts reimbursed to providers for those services. Some States do not cover certain services at all. For all States and services, the dollars reimbursed fall short of the procedures' actual charges.

Stigmatization, Classification, and Discrimination

Concern is expressed that CF carrier screening might be sought or offered despite an uncertain potential for discrimination or stigmatization by other individuals or institutions (e.g., employers and insurers). Stigmatization of, or discrimination against, persons with certain diseases is not unique to illnesses with genetic origins. Yet as the number and scope of predictive genetic tests increase, so does concern about how perceptions of and behavior towards carriers (or individuals identified with predispositions) will develop.

Stigmatization and Carrier Status

While a relationship exists between a characteristic's visibility and the amount of stigma it induces, invisible characteristics (e.g., carrier status) are also stigmatized. Stigmatization of CF carriers will probably focus on the notion that it is irresponsible for people who are at genetic risk to knowingly transmit a condition to their children (box I-I). A 1990 national survey of Americans reported 39 percent said "every woman who is pregnant *should* be tested to determine if the baby has any serious genetic defects." Twenty-two percent responded

Box 1-I—Bree Walker Lampley and Preventing Versus Allowing Genetic Disability

In July 1991, Los Angeles radio talk show host Jane Norris launched a firestorm of controversy when she solicited listener comments on Los Angeles television anchorwoman Walker Lampley's pregnancy. Making her disapproval clear, Norris said:

We're going to talk about a woman in the news and I mean that literally. She's a very beautiful, very pregnant news anchor, and Bree Walker also has a very disfiguring disease. It's called syndactyly [sic] and the disease is very possibly going to be passed along to the child that she's about to have. And our discussion this evening will be, is that a fair thing to do? Is it fair to pass along a genetically disfiguring disease to your child?

Bree Walker Lampley has ectrodactyly, a genetic condition manifest as the absence of one or more fingers or toes. It is an autosomal dominant disorder hence her potential offspring have a 50-50 chance of inheriting ectrodactyly. Norris' show highlighted the public tension that exists over attitudes toward preventing genetic disability, illness, and disease.

Some listeners agreed with Norris' opinion against knowingly conceiving a child who would be at 1 in 2 risk of "this deformity—webbed hands. . . ." One caller stated she would "rather not be alive than have a disease like that when it's a 50-50 chance." Other callers compared her comments to racism and eugenic genocide: ". . . this tone of yours that just kind of smacks of eugenics and selective breeding. . . . Are you going to talk in the next hour about whether poor women should have kids?"

The opinions offered illustrate the concern over the potential for discrimination or stigmatization as personal knowledge of one's genetic makeup increases. Shortly after the program aired, one disability rights activist pointed out that the radio show reminded her of her discomfort with the Human Genome Project.

On August 28, 1991, Bree Walker Lampley delivered a healthy baby boy, who has ectrodactyly. In October 1991, arguing that a biased presentation with erroneous information was broadcast, Walker Lampley was joined by her husband, several groups, and other individuals in filing a complaint with the Federal Communications Commission (FCC). Norris and the radio station stand by their right to raise the issue and "have no regrets." The FCC rejected Walker Lampley's complaint in February 1992, and no appeal is planned.

SOURCE: Office of Technology Assessment, 1992, based *unassociated Press*, "FCC Rejects Anchorwoman's Complaint Over Call-In Radio Show," Feb. 14, 1992; J. Mathews, "The Debate Over Her Baby: Bree Walker Lampley Has a Deformity. Some People Think She Shouldn't Have Kids," *Washington Post*, Oct. 20, 1991; and J. Selignann "Whose Baby Is It, Anyway?," *Newsweek*, Oct. 28, 1991.

that regardless of what they would want for themselves, "a woman *should* have an abortion if the baby has a serious genetic defect." Nearly 10 percent believed laws should require a woman to have an abortion rather than have the government help pay for the child's care if the parents are poor.

Few empirical studies have examined stigmatization of CF carriers directly, but relevant research funded through the NIH/DOE ELSI Programs of the Human Genome Project is under way. One study in Montreal, Canada, reports carriers generally expressed positive views about their newly determined carrier status (screening for DF508 only). Most (68 percent) would want their partner tested, and **60** percent said if the partner were a carrier, it would not affect the relationship. Existing research on genetic carriers and stigmatization, generally for Tay-Sachs or sickle cell, have some bearing on carrier screening for CF—chiefly that public education is crucial to overcoming stigmatization.

How CF—as a condition—is viewed by Americans will affect perceptions and potential reproductive stigma of CF carriers. Of prime importance is a commitment to nondirective genetic counseling to reduce perceived biases so individuals can make informed choices about bearing children with CF. Such a professional commitment coupled with increased public awareness and education about CF carrier screening could reduce potential problems of stigmatization of CF carriers, as well as stigmatization for other disorders as genetic screening evolves through the 1990s and beyond.

Health Care Coverage Access

One of the most frequently expressed concerns about CF carrier screening specifically, and genetic tests generally, is the effect they will have on health care access and risk classification in the United States. Consumers fear being excluded from health care coverage due to genetic and other factors. Such



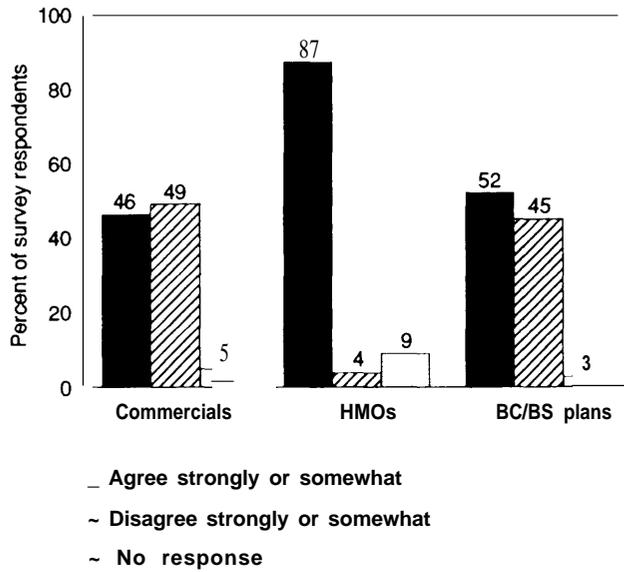
Photo credit: American Philosophical Society

Eugenics Building, Kansas Free Fair, 1929.

fears persist despite the fact that most contracts for individual health insurance coverage preclude blanket nonrenewal. Similarly, an insurer cannot raise rates for an individual who has been continuously covered if the person develops a new condition. Of special import to small group policies is that it is legal for an insurer not to renew a group contract, or to renew with a steep premium increase, based on the results of one individual's genetic, or other medical, test. Group policies are rarely guaranteed renewable, and most people in the United States are covered by group policies. Many group policies have preexisting condition clauses that preclude, for some period of time, reimbursement for expenses related to health conditions present on the policy's effective date.

One nationwide survey revealed 3 in 10 Americans say they or someone in their household have stayed in a job they wanted to leave mainly to preserve health care coverage. A 1989 OTA survey of Fortune 500 companies and a random sample of businesses with at least 1,000 employees found 11 percent of respondents assessed the health insurance risk of job applicants on a routine basis; another 25 percent assessed health risks sometimes. Nine percent of these respondents also took into account dependents' potential expenses when considering an individual's application. Forty-two percent of respondents said the health insurance risk of a job applicant reduced the likelihood of an otherwise healthy, able job applicant being hired.

Figure I-1 O-Genetic Conditions as Preexisting Conditions: Health Insurers' Attitudes^a

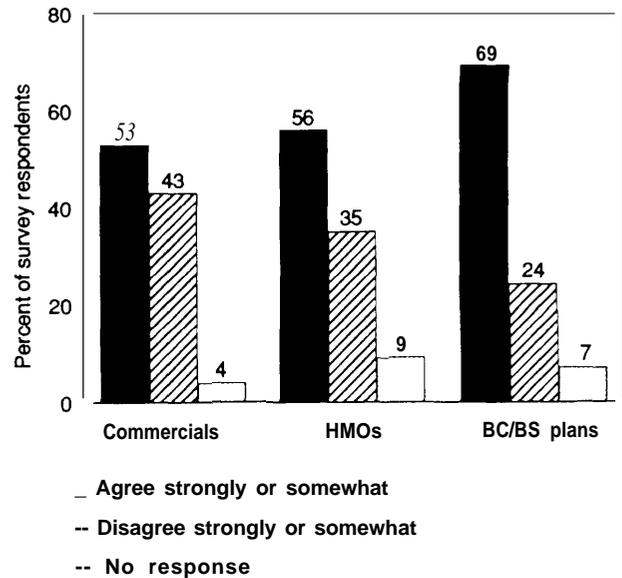


Genetic conditions, such as cystic fibrosis or Huntington disease, are preexisting conditions.

^aBased on responses to a 1991 OTA survey of commercial insurers, health maintenance organizations, and Blue Cross and Blue Shield plans that offer individual policies or medically underwritten group policies.

SOURCE: Office of Technology Assessment, 1992.

Figure 1-1 2-Genetic Information as Medical Information: Health Insurers' Attitudes^a

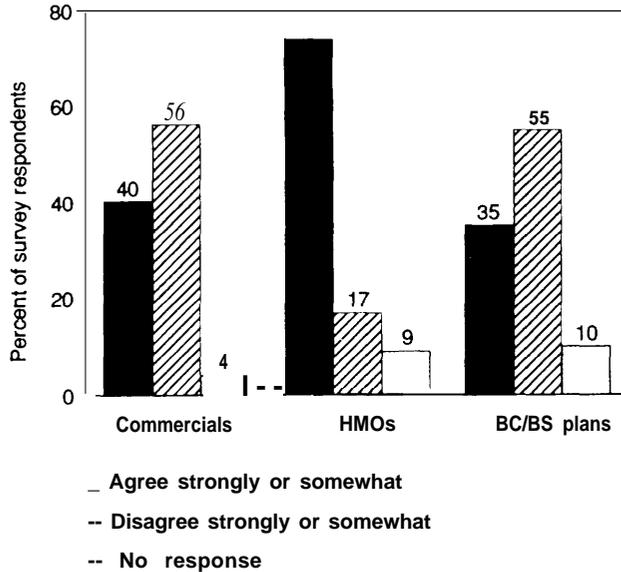


Genetic information is no different than other types of medical information.

^aBased on responses to a 1991 OTA survey of commercial insurers, health maintenance organizations, and Blue Cross and Blue Shield plans that offer individual policies or medically underwritten group policies.

SOURCE: Office of Technology Assessment, 1992.

Figure I-n-Carrier Status as a Preexisting Condition: Health Insurers' Attitudes^a



Carrier status for genetic conditions, such as cystic fibrosis or Tay-Sachs, are preexisting conditions.

^aBased on responses to a 1991 OTA survey of commercial insurers, health maintenance organizations, and Blue Cross and Blue Shield plans that offer individual policies or medically underwritten group policies.

SOURCE: Office of Technology Assessment, 1992.

OTA found the majority of respondents to its health insurers' survey "agree strongly" or "agree somewhat" that illnesses with genetic bases, such as CF or Huntington disease, are preexisting conditions (figure 1-10). Thus, insurers would exclude reimbursement for such conditions for a period of time if the person could obtain individual or medically underwritten insurance at all. More surprising, since carriers have no symptoms of the disorder, is the finding that respondents, collectively, are nearly evenly split on whether carrier status—i.e., for CF or Tay-Sachs—is a preexisting condition (figure 1-11).

OTA's survey also revealed that genetic information is, for the most part, viewed no differently than other types of medical information (figure 1-12). Personal and family medical histories were the most important factors in determining insurability, according to survey respondents. OTA found medical directors and underwriters felt less strongly about "genetic predisposition to significant conditions" as a facet of insurability than they did about medical history. Of significance to CF carrier screening, a minority of all types of insurers found carrier risk "very important" or "important" to insurability.

Twenty-four percent (7 respondents) of medical directors at commercial insurers writing individual policies said "carrier risk for genetic disease" was "very important" or "important" to insurability; 18 percent (2 respondents) of HMOs responded similarly, as did 8 percent (2 respondents) of BC/BS chief underwriters.

Although an insurer might consider carrier status important to evaluating an application, carrier status does not appear to translate into difficulties for applicants in ultimately obtaining health care coverage from OTA's survey respondents. Ninety-three percent of respondents from commercial insurers and all HMOs offering individual coverage would accept the person with standard rates if the applicant was asymptomatic but had a family history of CF. For BC/BS plans, however, 55 percent would accept at standard rates, 21 percent would accept at the standard rate with an exclusion waiver, and 7 percent would decline to cover the CF carrier. For those who responded they would accept with an exclusion waiver or decline to cover, reluctance to offer standard insurance might stem from not wanting to pay for possible children or from a misunderstanding of the meaning of CF carrier status.

Overall, OTA's survey reveals genetic information is not viewed as a special type of information. In making decisions on insurability and rating based on genetics, what seems important is the particular condition (e.g., CF disease, diabetes, sickle cell anemia), not that the condition is genetically based. The increased availability of genetic information, however, adds to the amount of medical information that insurers can use for underwriting. The availability of this additional information leads to concern that risk assessments will become so accurate on an

individual level as to undermine the risk-spreading function of insurance. This, of course, would have profound societal implications.

Perspectives on the Future Use of Genetic Tests by Health Insurers

Commercial insurers, HMOs, and BC/BS plans already use genetic information in making decisions about individual policies or medically underwritten groups. People seeking either of these types of coverage reveal such information as part of the battery of questions to which applicants respond in personal and family history inquiries. OTA is unaware of any insurer who underwrites individual or medically underwritten groups and requires carrier or presymptomatic tests—e.g., for Huntington or adult polycystic kidney diseases. Even a decade from now, OTA's survey data indicate the vast majority of respondents do not expect to require genetic tests of applicants who have a family history of serious genetic conditions, nor do they anticipate requiring carrier assays even if a family history exists (table 1-5).

Health insurers do not need genetic tests to find out genetic information. It is less expensive to ask a question or request medical records. Thus, whether genetic information is available to health insurers hinges on whether individuals who seek personal policies or are part of medically underwritten groups become aware of their genetic status because of general family history, because they have sought a genetic test because of family history, or because they have been screened in some other context.

OTA's survey reveals health insurers are concerned about the potential for negative financial consequences if genetic information is available to

Table 1-5-Projected Use of Genetic Information by Insurers in 5 and 10 Years

Respondent		Very likely	Somewhat likely	Somewhat unlikely	Very unlikely	No response ^a
How likely do you think it is that your company/HMO will in the next 5 years:						
Use information derived from genetic tests for underwriting?	<i>Commercials</i>	7 (14%)	12 (24%)	16 (31%)	16 (31%)	0 (0%)
	<i>HMOs</i>	1 (4%)	5 (22%)	9 (26%)	6 (26%)	2 (9%)
	<i>BC/BS plans</i>	3 (10%)	8 (28%)	10 (34%)	6 (21%)	2 (7%)
In the next 10 years:						
Use information derived from genetic tests for underwriting?	<i>Commercials</i>	12 (24%)	20 (39%)	11 (22%)	7 (14%)	1 (2%)
	<i>HMOs</i>	3 (13%)	6 (26%)	8 (35%)	3 (13%)	3 (13%)
	<i>BC/BS plans</i>	5 (17%)	13 (45%)	3 (10%)	6 (21%)	2 (7%)

^a Percentages may not add to 100 due to rounding.

SOURCE: Office of Technology Assessment, 1992.

the consumer, but not them. Thirty-four medical directors (67 percent) from commercial insurers said they “agree strongly” or “agree somewhat” with the statement that ‘it’s fair for insurers to use genetic tests to identify individuals with increased risk of disease.’ Thirty-eight respondents (74 percent) from commercial insurers agreed strongly or somewhat that an insurer should have the option of determining how to use genetic information in determining risks.’¹⁰

Access to Health Insurance After Genetic Tests

Existing information about how genetic test results currently affect individuals’ health care coverage is largely anecdotal. One case from the Baylor College of Medicine (Houston, TX) illustrates why concern is expressed about health insurance and genetic screening and testing:

A couple in their 30s has a 6-year-old son with CF. Prenatal diagnostic studies of the current pregnancy indicate the fetus is affected. The couple decides to continue the pregnancy. The HMO indicated it should have no financial responsibility for the prenatal testing and that the family could be dropped from coverage if the mother did not terminate the pregnancy. The HMO felt this to be appropriate since the parents had requested and utilized prenatal diagnosis ostensibly to avoid a second affected child. After a social worker for the family spoke with the local director of the HMO, the company rapidly reversed its position.

Consumers and patient advocates maintain such situations represent the tip of an iceberg. They assert individuals who avail themselves of genetic tests subsequently have difficulty obtaining or retaining health insurance. Health insurance industry officials argue to the contrary. If the problem was prevalent, they assert, ample court cases could be cited because patients and their attorneys would not be passive recipients of decisions such as that just described.

To explore this issue, OTA asked third parties—nurses in genetics and genetic counselors—for their experiences. In 1991, at least 50 genetic counselors or nurses in clinical practice (14 percent of survey respondents) reported knowledge of 68 instances of patients who experienced difficulty with health insurance due to genetic tests (table 1-6).¹⁰

It is important to note that most cases described in table 1-6 do not involve recessive disorders and carrier screening for conditions like CF, but involve situations in which genetic test results appear to have been treated the same as adverse test results for nongenetic conditions. Access to health care coverage for CF carriers presumably should not be an issue because CF carriers have no symptoms of the disorder, although OTA’s survey of health insurers indicates otherwise in a small fraction of cases. For genetic testing or screening to detect genetic illness (or the potential for illness), however, the possibilities for problems are already unfolding.

The OTA data permit neither extrapolation about the actual number of cases that have occurred in the United States, nor speculation about trends. An estimated 110,600 individuals were seen in 1990 by the genetic counselors and nurses responding to OTA’s survey, but OTA did not advise respondents to limit descriptions of clients’ insurance difficulties to 1990; it is unlikely that all reported cases occurred in 1990.

The Americans With Disabilities Act of 1990 and Genetics

In 1990, Congress enacted the Americans With Disabilities Act (ADA; Public Law 101-336), a comprehensive civil rights bill to prohibit discrimination against individuals with disabilities. The ADA encompasses private sector employment, public services, public accommodations, and telecommunications. It does not preempt State or local disability statutes.

Under the ADA, a person with a disability includes someone who has a “record” of or is “regarded” as having a disability, even if no actual incapacity currently exists. A “record” of disability means the person has a history of impairment. This provision protects those who have recovered from a disability that previously impaired their life activities (e.g., people recovered from diseases such as cancer who might still face discrimination based on misunderstanding, prejudice, or irrational fear). Additionally, individuals regarded as having disabilities include those who, with or without an impairment, do not have limitations in their major life functions, yet are treated as if they did have such

¹⁰ OTA does not judge the validity—positively or negatively—of the claims. Some cases might have been settled in favor of the individual because the initial judgment was deemed improper or illegal. Others might have been cases where an applicant attempted to select against an insurer by misrepresenting his or her health history, which would have been resolved against the individual.

Table 1-6-Case Descriptions of Genetic Testing and Health Insurance Problems^a

Positive test for adult polycystic kidney disease resulted in canceled policy or increased rate for company of newly diagnosed individual.

Positive test for Huntington disease resulted in canceled policy or being denied coverage through a health maintenance organization.

Positive test for neurofibromatosis resulted in canceled policy.

Positive test for Marfan syndrome resulted in canceled policy.

Positive test for Down syndrome resulted in canceled policy or increased rate.

Positive test for alpha-1 -antitrypsin defined as preexisting condition; therapy related to rendition not covered.

Positive test for Fabry disease resulted in canceled policy.

Woman with balanced translocation excluded from future maternity coverage.

Positive Fragile X carrier status and subsequent job change resulted in no coverage.

After prenatal diagnosis of hemophilia-affected fetus, coverage denied due to preexisting condition clause.

Denied coverage or encountered difficulty retaining coverage after birth of infant with phenylketonuria.

Woman diagnosed with Turner's syndrome denied coverage for cardiac status based on karyotype. Normal electrocardiogram failed to satisfy company.

Family with previous Meckel-Gruber fetus denied coverage in subsequent applications despite using prenatal diagnosis and therapeutic abortion.

Mother tested positive as carrier for severe hemophilia. Prenatal diagnosis revealed affected boy; not covered as preexisting condition when pregnancy carried to term.

After a test revealed that a woman was a balanced translocation carrier, she was initially denied coverage under spouse's insurance because of risk of unbalanced conception. Subsequently overturned.

Woman without prior knowledge that she was an obligate carrier for X-linked adrenoleukodystrophy found out she was a carrier. She had two sons, both of whom were healthy, but each at 50 percent risk. Testing was done so they could be put on an experimental diet to prevent problems that can arise from mid- to late childhood or early adulthood. One boy tested positive. The family's private pay policy (Blue Cross/Blue Shield) is attempting to disqualify the family for failing to report the family history under preexisting conditions.

After birth of child with CF, unable to insure unaffected siblings or themselves.

^a1991 OTA survey of genetic counselors and nurses in genetics. Not all cases, or multiple cases involving same disorder, listed.

SOURCE: Office of Technology Assessment, 1992.

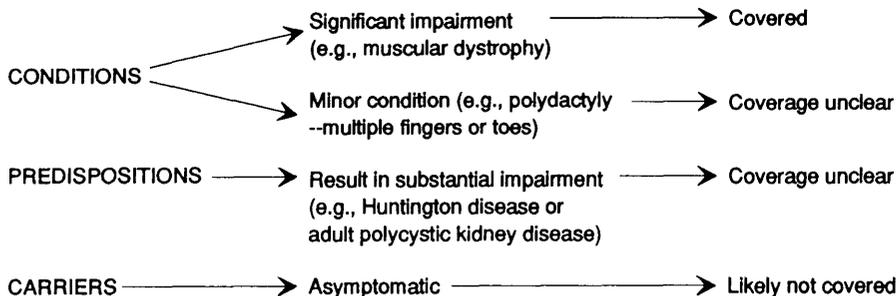
limitations. This provision is particularly important for individuals who are perceived to have stigmatic conditions that are viewed negatively by society.

Examining genetics and the ADA from three broad categories—genetic conditions, genetic predisposition, and carrier status—sheds some light on how the ADA might interface with CF carrier screening and future genetic tests (figure 1-13).

Genetic Conditions. Disability is defined only according to the degree of impairment and how

severely the disability interferes with life activities, with no distinction between those with genetic origins and those without. A genetic condition that does not cause substantial impairment might not constitute a disability, unless others treat the person as disabled. Thus, significant cosmetic disfigurements (e.g., from burns or neurofibromatosis) could be classified as disabilities if public prejudices act to limit the life opportunities of people who have them. Congress and the courts have long recognized disabilities of primary or partial genetic origin,

Figure 1-13—Genetics and the Americans With Disabilities Act of 1990



SOURCE: Office of Technology Assessment, 1992.

including Down syndrome, CF, muscular dystrophy, epilepsy, diabetes, and arthritis.

Genetic Predisposition. ADA judges disability not just by an objective measure of inability to perform tasks, but also subjectively by the degree to which the public makes the condition disabling through misunderstanding or prejudice. This latter definition might apply to individuals who are asymptomatic but predicted to develop disease in the future-if the public perceives them as having a disability because they might or will get ill. Some argue the ADA's legislative history indicates genetic predisposition might be encompassed. One Congressman stated during the 1990 debate over the conference report that persons who are theoretically at risk "may not be discriminated against simply because they may not be qualified for a job sometime in the future." On the other hand, no further discussion on the issue occurred,

Carrier Status. Case law and the ADA's prohibition of discrimination generally hold that employment decisions must be based on reasonable medical judgments that show the disability prevents the individual from meeting legitimate performance criteria. For carriers of recessive conditions such as CF, sickle cell anemia, and Tay-Sachs, there is no disability per se; the ADA appears not to cover carriers. Such individuals are, however, at high risk of having an affected child if their partners also carry the trait and could be misunderstood to be affected by the disease. Discrimination against carriers could arguably constitute discrimination if based on a perception of disability.

The Equal Employment Opportunity Commission (EEOC) Regulations. In 1991, EEOC promulgated regulations for implementing the ADA. The regulations do not specifically prohibit discrimination against carriers or persons who are identified presymptomatically for a late-onset genetic condition (e.g., adult polycystic kidney disease or Huntington disease)---despite the fact that the NIH/DOE ELSI Working Group and the NIH/DOE Joint Subcommittee on the Human Genome urged EEOC to clearly protect these individuals. In its interpretive guidance, EEOC notes "the definition of the term 'impairment' does not include characteristic predisposition to illness or disease." From EEOC's perspective, carriers are not encompassed by the ADA's provisions. With respect to individuals diagnosed presymptomatically, EEOC concluded

that "such individuals are protected, either when they develop a genetic disease that substantially limits one or more of their major life activities, or when an employer regards them as having a genetic disease that substantially limits one or more of their major life activities.

The Americans With Disabilities Act and Health Insurance

The ADA also might prohibit discrimination based on an employer's fear of future disability in an applicant's family that would affect the individual's use of health insurance and time away from the job. Nevertheless, the ADA does not speak to this point directly, and so leaves open for future interpretation whether employers may discriminate against carriers who are perceived as more likely to incur extra costs due to illnesses that might occur in their future children. The ADA specifically does not restrict insurers, health care providers, or other benefit plan administrators from carrying out existing underwriting practices based on risk classification. Nor does the ADA make clear whether employers may question individuals about their marital or reproductive plans prior to offering employment or enrollment in an insurance plan. Furthermore, after a person is hired, ERISA-based, self-funded insurance plans can alter benefits to exclude or limit coverage for specific conditions; the ADA does not preempt ERISA.

Quality Assurance of Clinical Laboratories and DNA Test Kits

Quality assurance for CF carrier screening means ensuring the safety and efficacy of the tests themselves, whether they are performed de novo in clinical diagnostic laboratories or via test kits. The quality of the laboratory's performance affects the quality of the counseling services. Ensuring that consumers receive high-quality technical and professional service is the responsibility of providers, under the shared oversight of the Federal Government, State and local governments, private entities (including professional societies), and the courts.

The Clinical Laboratory Improvement Amendments of 1988

Quality assurance to assess clinical laboratory performance is still in flux, in large measure because 1967 legislation governing regulation of clinical testing facilities was overhauled by Congress in

1988 with enactment of the Clinical Laboratory Improvement Amendments of 1988 (CLIA; Public Law 100-578). CLIA subjects most clinical laboratories to an array of accrediting requirements: qualifications for the laboratory director, standards for the supervision of laboratory testing, qualifications for technical personnel, management requirements, and an acceptable quality control program. CLIA authorizes the Health Care Financing Administration (HCFA) to police an estimated 300,000 to 600,000 physician, hospital, and freestanding laboratories to ensure they adhere to a comprehensive quality assurance program. HCEA may impose sanctions, if necessary.

CLIA clearly encompasses facilities performing DNA-based, clinical diagnostic analyses. But, while it details particular performance standards for several types of clinical diagnostic procedures, CLIA does not specifically address DNA-based tests. This lack of detailed directives for DNA-based diagnostics could be beneficial in the short-term, since the field is rapidly changing.

State Authorities. CLIA does not preclude States from regulating and licensing facilities within certain guidelines. After a pilot study, for example, the California State Department of Health Services intends to seek approval for State-specific licensing laws and regulations for DNA and cytogenetic laboratories. Similarly, New York has regulated clinical laboratories since 1961, and has established a genetics quality assurance program that includes requirements for licensing personnel, licensing facilities, laboratory performance standards, and DNA-based proficiency testing. Nevertheless, the principal State role in quality assurance for clinical facilities is licensure and certification of medical and clinical personnel, which are the sole provinces of States.

The Role of Private Organizations. While CLIA clearly expands the Federal role in clinical laboratory oversight, the law continues to permit, subject to DHHS approval, the involvement of other parties in regulating laboratory practices. Private organizations, including the Joint Commission on Accreditation of Health Care Organizations, may continue to accredit facilities. Private professional societies will likely have the greatest impact in the area of proficiency testing, one component of accreditation. Efforts by CORN and its regional networks, ASHG, and the College of American Pathologists (CAP)

stand at the forefront of developing proficiency tests for DNA-based diagnostics.

In 1989, CAP established a committee to develop appropriate guidelines for all clinical tests involving DNA probes or other molecular biological techniques. The CAP committee has administered two DNA-based proficiency testing pilot programs, although their focus was not genetic disorders. CORN, which receives Federal funding and has been involved in quality assurance of genetics facilities since 1985, sponsored a DNA-based genetic test proficiency pilot of 20 laboratories in 1990. The Southeastern region has a regional proficiency testing program, and will be enlarging its planned second survey into a national test, to be completed in 1992; this effort includes CF mutation analysis. Full proficiency testing for DNA-based genetic diagnostics is planned by 1994. CORN and ASHG have liaisons with the others' efforts, and a joint ASHG/CAP DNA-based proficiency testing pilot for genetic diseases commenced in 1992.

Proficiency testing is widely viewed as a key measure of quality assurance. It can provide a reliable and identifiable benchmark to assess per-



Photo credit: Genetics & IVF/Institute

Facilities that perform DNA-based diagnostic tests (e.g., CF mutation analysis) are subject to the Clinical Laboratory Improvements Amendments of 1988.

formance. In the past, professional societies' involvement in proficiency testing to ensure laboratory quality have predominated, and this situation is likely to continue. Cooperation among each of the groups will be essential, as professional-society-based programs could affect proficiency testing for CF mutations (and other DNA tests) long before HCFA proposes proficiency testing rules under CLIA.

Regulation of DNA Test Kits

Increased use of CF mutation assays for carrier detection will depend, in part, on the development and availability of prepackaged kits. At least two companies—one in the United States and one in the United Kingdom—are testing such kits and anticipate their availability in 1 to 2 years. Before marketing of the kits can occur, however, the U.S. Food and Drug Administration (FDA) must ensure the safety and efficacy of genetic diagnostic test kits, such as those under development for CF mutations. Since genetic diagnostic kits fall within the definition of devices, the extent to which CF mutation kits—or other DNA-based genetic test kits—become available will depend on FDA regulation of devices during development, testing, production, distribution, and use.

FDA's regulatory options range from registering an item's presence in the United States and periodically inspecting facilities to ensure good manufacturing practices, to setting performance and labeling requirements, to premarket review of a device. The agency also may engage in postmarketing surveillance to identify ineffective or dangerous devices. It may ban devices it deems unacceptable. Specific regulation depends on whether FDA classifies the device as Class I, H, or III, with Class III devices receiving the most stringent review.

Since no FDA-approved, DNA-based genetic diagnostic test kit comparable to those being developed for CF carrier analysis exists, it is difficult to predict the ultimate regulatory status of such kits. Preliminary indications are they will be regulated as Class III devices. In response to recent legislation and ongoing congressional concern, FDA appears to be increasing medical device regulation and postmarketing surveillance. If increased FDA scrutiny extends to DNA-based diagnostic test kits, developers can expect more stringent regulation of these products than of previous non-DNA-based genetic test kits. Increased regulation to provide greater

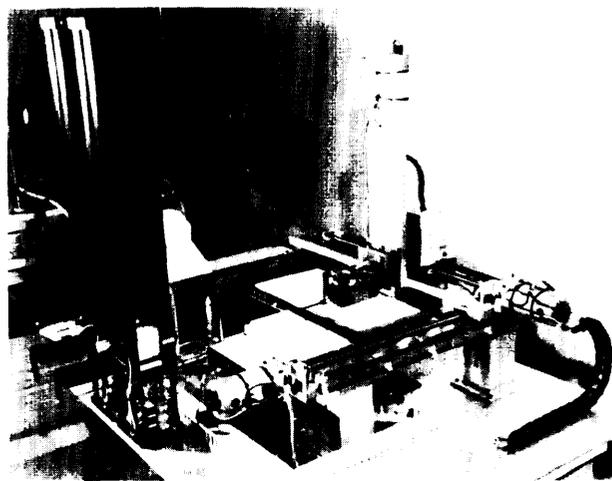


Photo credit: Tony J. Beugelsdijk, Los Alamos National Laboratory

Automated robotic system used in DNA analysis at Los Alamos National Laboratory.

assurance of safety and efficacy might, in turn, slow routine CF carrier screening.

Automation

The extent to which costs for CF carrier tests decline depends, in part, on automation. Instrumentation will be especially crucial to the development of batteries of tests for multiple genetic disorders. Moreover, compared to most routine clinical tests, current DNA-based CF carrier assays are labor intensive.

Over the past few years, private industry and U.S. national laboratories have developed several instruments that increase the speed and volume of routine DNA diagnostic procedures. Goals for improved instrumentation for DNA analyses stem, in part, from the importance of rapid techniques to the Human Genome Project. Spin-off technologies from DNA mapping and sequencing appear amenable to applications for clinical diagnostics.

Currently, all but one step of what generally constitutes DNA diagnosis is automated or involves instrumentation under development. Most components of DNA analysis, however, are automated as individual units; efforts under way seek to coordinate sequential steps. Some machines are not faster than humans, but they can standardize the procedures and decrease human error.

Clearly, the crucial steps in DNA-based CF carrier assays are, or can be, automated. Advances in

instrumentation indicate that automated, rapid carrier screening for CF—or other genetic conditions—is already technologically feasible. OTA finds the field of DNA automation is advancing at a pace that suggests entirely automated DNA diagnosis can be realized in the next few years.

Costs and Cost-Effectiveness

Perhaps the least examined facet of CF carrier screening is cost. Data for parts of OTA's analysis were often lacking and assumptions had to be made. Unlike the seven preceding factors, which in many cases will generically affect utilization of DNA-based tests for disorders other than CF, findings that pertain to cost-effectiveness do not extend beyond CF carrier screening—although the approach used in this report could be applied to screening with other genetic tests.

While economic analyses can inform decisions surrounding resource allocation and access to genetic screening, they have limits. In the context of public policy and genetics, the 1983 President's Commission report on genetic screening articulates solid guidance about the benefits and limits of cost-effectiveness and cost-benefit analyses: These analytical approaches are tools to be used within an overall policy framework, not solely as a method of making or avoiding judgment. There is no intimation in OTA's analysis that something that saves or costs money is more or less desirable from a welfare standpoint.

Cost of Cystic Fibrosis

The cost of any illness is the answer to the hypothetical question: If the disease disappeared and everything else held constant, how many more dollars would be available to the economy? Many elements are needed to answer this question, but broadly speaking they fall into two categories: information about direct medical costs associated with CF and nonmedical direct costs related to the disease (i.e., family caregiving time).

Direct medical expenses for CF include costs of hospitalization, outpatient care, physical therapy, and drugs. These costs are not the same for everyone with the disease (table 1-7). Clinical symptoms of CF vary widely, although broad divisions in its severity can be drawn. Some individuals require only one inpatient visit every 2 years or so; others

Table 1-7—Annual Cost of Medical Care for Cystic Fibrosis Patients

Treatment	Mild ^a	Moderate	Severe
Acute treatment			
Antibiotics.	\$ 2,000 ^b	\$6,000	\$12,000
IV supplies.	300	500	900
Hospitalization.	3,500	14,000	28,000
Miscellaneous.	100	200	400
Total cost acute.	5,900	20,700	41,300
Chronic management			
Visits to CF Center.	600	800	1,200
Medications.	2,000	3,000	4,000
Total cost chronic.	2,600	3,800	5,200
Total cost acute and chronic treatment.	8,500	24,500	46,500

^aThere is another category, "submild," whose illness requires infrequent hospitalization—less than once per year. Based on existing data, about 40 percent of patients are submild and 40 percent are mild (about one hospital episode per year). Approximately 13 percent of all individuals with CF had two or three hospitalizations per year; this group represents the moderate portion. Finally, about 6 percent of all patients had four or more hospitalizations per year and comprise the severe patient group.

No data exist on the average expenses of the submild group, but a reasonable assumption might be their expenses are about twice the average medical care cost of the average American under 65 years of age, or \$2,000. In fact, costs might be slightly higher; actual costs for one submild case (parents providing physical therapy and no hospitalizations in 9 years) were approximately \$4,700 in 1990; the cost of drugs alone was \$1,900. Nevertheless, the OTA analysis errs on the conservative side and uses \$2,000 in determining the average medical care cost of an individual with CF.

^bAll values in 1989 dollars.

SOURCE: Wilkerson Group, Inc., *Annual Cost of Care for Cystic Fibrosis Patients* (New York, NY: Wilkerson Group, Inc., 1991).

have problems so severe as to require four or more hospitalizations per year. Similar variation exists for other medical expenses. Overall, taking these several factors into account, average annual medical expenses for CF patients are estimated at \$10,000. Assuming a median life expectancy in 1990 of 28 years the present value of lifetime medical expenses is approximately \$146,430 (1990 dollars using a 5 percent discount rate).

The main nonmedical direct cost associated with CF is parental time beyond the time required for a child without the illness. CF centers estimate that parents often must spend 2 hours per day on therapy for a child with CF. In addition, parents lose time from work when the person falls ill. Time is also spent on physician and clinic visits. OTA uses an estimate of 938 hours per year of extra caregiving to a person with CF, which is generally provided by family members. Assuming an estimated domestic/nursing wage of \$10 per hour, the present value of CF-related lifetimemedical direct costs is \$139,744 (1990 dollars using a 5 percent discount rate).

Table 1-8-Costs for Cystic Fibrosis Carrier Tests At Selected Facilities

Institution	Price per sample
Baylor College of Medicine.....	\$55 or 200
Boston University.....	170
Collaborative Research, Inc.....	173
Cornell University Medical Center.....	75
GeneScreen.....	165
Genetics & IVF Institute.....	225
Hahnemann University.....	225
Hospital of the University of Pennsylvania.....	150
Integrated Genetics.....	150
Johns Hopkins University Hospital.....	270
Mayo Medical Laboratories.....	200
St. Vincent's Medical Center.....	150
University of Minnesota.....	136
University of North Carolina.....	150
Vivigen, Inc.....	200 to 220

SOURCES: office of Technology Assessment, 1992, and M.V. Pauly, "Cost-Effectiveness of Screening for Cystic Fibrosis," contract document prepared for the U.S. Congress, Office of Technology Assessment, August 1991.

Cost of Cystic Fibrosis Mutation Analysis

Since CF is the most common, life-shortening, recessive disorder among Caucasians in the United States, commercial interest in the test is high. Currently, at least six commercial companies perform DNA-based CF mutation analyses, as do at least 40 university and hospital laboratories. Table 1-8 presents data on test charges for several private and public facilities; the average price per sample is about \$170. With increased volume of tests and automation, however, many predict the cost per CF mutation assay will decrease, OTA uses a cost per test of \$100 because the analysis focuses on the potential future of large-scale CF carrier screening and presumes economies of scale will apply.

Indirectly related to cost-effectiveness, but directly related to how much CF mutation analysis will cost in the future, is the issue of patents, licensing, and royalty fees for genetic diagnostics. A patent is pending for the CF gene, for example. Similarly, royalty licenses must be paid for the process—the polymerase chain reaction, or PCR—by which CF mutation analysis is performed. Thus, royalty licensing fees will be reflected in costs of the tests to consumers. Currently, debate is increasing on the issue of intellectual property protection and the Human Genome Project. A resolution of this controversy, if any, will affect costs of DNA-based diagnostic tests and hence cost-effectiveness of screening for genetic disorders.

Costs and Cost-Effectiveness of Carrier Screening for Cystic Fibrosis

Data about the cost of screening large numbers of individuals for CF carrier status do not exist. In estimating the cost of carrier screening for CF, OTA included costs of the CF mutation analyses, chorionic villus sampling for fetal testing, and costs for pretest education and post-test counseling. Taken together, these costs were analyzed in the context of several scenarios for preconception screening of women (and possibly their partners) and prenatal screening of pregnant women (and if necessary their partners and the fetus).

Regardless of the strategy or scale, CF carrier mutation analysis provides information to an individual about his or her likelihood of having a child with CF should the partner also be a carrier. Hence, at its core, a cost-effectiveness analysis of CF carrier screening involves assumptions about reproductive behavior. A base case was established for the following six variables:

- 80 percent of women elect screening,
- 85 percent sensitivity of the CF mutation assay,
- 8.4 percent of ++ couples are infertile,
- 10 percent of ++ fertile couples choose not to conceive,
- 90 percent of ++ fertile couples conceive, and 100 percent use prenatal testing, and
- 100 percent of CF-affected pregnancies detected are terminated.

As alternatives, other assumptions were made for several additional scenarios by varying the factors in turn (or combination) to yield a series of cost-effectiveness estimates. In evaluating costs and savings, changes in behavior were considered only for ++ couples, and costs and savings were calculated for a hypothetical population of 100,000 eligible women (or couples). The economic costs include costs associated with CF carrier screening. The economic savings include avoiding the direct medical and nonmedical costs associated with having a child with CF. The base case and all scenarios were then compared to costs in the absence of screening.

One scenario, for example, assumed 50 percent of women chose to participate, another assumed all individuals elected screening. Another screened the woman and man simultaneously, rather than screening the man only when the woman was positive.



Photo credit: Robyn Nishimi

Others used 50 percent as the frequency of affected pregnancies terminated. Overall, whether CF carrier screening can be paid for on a population basis through savings accrued by avoiding CF-related medical and caregiving costs depends on the assumptions used—including how many children people will have, average CF medical costs, and average time and cost devoted to caring for a child with CF, as well as variations in reproductive behaviors, costs of CF mutation analyses, and screening participation rates.

Eight of 14 scenarios examined by OTA result in a net cost over no screening. Under six cases, however, CF carrier screening is cost-effective, but most of these scenarios involve 100 percent participation, test sensitivity, or selective termination—all unlikely to be realized in the near term, if ever. Nevertheless, CF carrier screening can save money compared to no screening even under less absolute

circumstances. The balance between net savings versus net cost in nearly all scenarios is fine. How many individuals participate in screening is relatively unimportant to cost-effectiveness, but it is clear the frequency of affected pregnancies terminated and the assay's price will ultimately affect this balance.

WHAT IS THE ROLE OF CONGRESS?

Speculation about the impact of a CF carrier test on individuals and society has existed for years. Today, that speculation is being transformed into reality. In this report, OTA identifies eight factors affecting implementation of CF carrier screening. From the analysis of these factors, OTA concludes that Congress could play a role in six broad policy areas:¹¹

- genetics education and the public,
- personnel,
- genetics and discrimination,
- clinical laboratory and medical device regulation,
- instrumentation, and
- integration of DNA assays into clinical practice.

Genetics Education and the Public

For people to make informed decisions about whether CF mutation assays would be useful to them, they must understand what CF is, know what carrier status means, and have some understanding of the probabilistic nature of genetic tests. Beyond comprehending technical information, the public should also appreciate the positive and negative social implications that could adhere. Better public education would also mean fewer total counseling hours would be needed.

Mechanisms by which Congress can generally improve science and education in the United States were assessed in a separate OTA report,¹² Federal efforts specifically targeted to educating the public about human genetics are diffuse, but do exist. If Congress determines that increased genetics educa-

¹¹ Congress also plays a role in an additional policy issue raised by CF carrier screening and the development of other genetic tests—i.e., health care access. As mentioned, however, access to CF carrier tests, and services related to them, is no different and inextricably linked to the broad issue of health care reform in the United States, a topic beyond the scope of this report.

¹² U.S. Congress, Office of Technology Assessment, *Educating Scientists and Engineers: From Grade School to Grad School*, OTA-SET-377 (Washington DC: U.S. Government Printing Office, June 1988).

tion is a priority, it could urge interagency coordination and/or appropriate increased funds. In particular, Congress could exploit three general avenues to increase public education about genetics: school-based science education, patient education, and widespread public appeal.

Existing agencies and programs have some efforts related to public education in genetics, each serving different purposes. These efforts can serve as the foundation for new initiatives. The National Institutes of Health/U.S. Department of Energy's Ethical, Legal, and Social Issues Programs of the Human Genome Project, for example, have awarded grants that target each of the avenues just described, including curriculum development, science teacher education, evaluation of improved means to deliver genetic information to patients, and a mass media production that will be available through public television. If Congress concludes that ELSI Programs should increase their attention to public education, it could direct them to seek and award a greater number of grants focused on this issue. In doing so, Congress could direct that a greater proportion of such awards be made with existing funds, at the expense of other areas. Or, Congress could direct that more than the expected 5 percent set aside from the fiscal year 1993 Human Genome Project appropriation be devoted to the ELSI Programs—at the expense of the scientific and technical components—and that the increased funds be allocated to public education grants. Finally, Congress could increase the ELSI Programs' funding specifically for public education.

The National Science Foundation serves as the lead Federal agency for science education, particularly teacher education and training. Thus, with respect to specifically enhancing public knowledge through school-based science education, Congress could encourage NSF—directly through appropriations or indirectly through oversight—to increase attention to education in human genetics. Currently, supplemental genetics education for K-12 teachers is piecemeal; NSF has funded a few projects to train high school and grade school teachers about genetics, but no nationwide effort exists.

The DHHS National Center for Education in Maternal and Child Health serves as the Federal repository for a wide range of materials related to human clinical genetics—ranging **from genetics** training manuals for social workers to patient

information pamphlets for a number of genetic diseases; it once served as an active clearinghouse to disseminate information about genetics nationwide. Due to budgetary constraints, the center now functions more as a passive resource to provide information on request, rather than performing aggressive outreach. Through oversight, Congress might judge that the lost function of the center should be reinstated, but it would need to recognize that increased funds would be necessary to achieve this goal.

Personnel

Several types of health care professionals perform genetic counseling—master's level genetic counselors, physicians, Ph.D.-level clinical geneticists, nurses, and social workers. No coordinated Federal training and education framework exists to serve all. The Federal Government provides financial support for education and training of certain health personnel through Title VII and Title VIII of the Public Health Service Act. Title VII provides education support to the fields of medicine, osteopathy, dentistry, veterinary medicine, optometry, podiatry, public health, and graduate programs in health administration. It does so through grants and contracts to institutions, and through loans to individuals. Title VIII focuses primarily on advanced training of nurses. The MCH block grant also supports some genetics-related training and education.

If Congress determines that training of additional genetics personnel—beyond those practicing or in the pipelines essential to maintain quality care, it could enact Legislation that amends Title VII or Title VIII to include master's-level genetic counseling programs. It could also encourage increased genetics education for the other health professions encompassed by these acts. Grantees and contractors that receive Title VII or Title VIII funds, for example, might be required to increase genetics-related curriculum for all health professionals. Congress could also increase appropriations under the MCH block grant, or stipulate that States receiving MCH funds earmark a designated level of State funds to education, training, or both.

Genetics education for those already practicing is as important as genetics training and education for new health professionals. In part, the issue of adequate services and professional capacity depends on whether patients continue to receive genetic

services through specialized clinical settings, as most do now, versus access through primary care, community health, and public health settings. If the nonspecialized clinical route becomes more common, it will require that existing genetic specialists provide adequate genetics education to other practitioners in the U.S. health care system. Congress could focus on two executive branch entities to accelerate this provider-to-provider knowledge transfer. First, it could continue to encourage the NIH/DOE ELSI Programs of the Human Genome Project to fund grants for this purpose. Second, Congress could enhance, through increased appropriations, professional training and continuing education efforts under the MCH block grant.

Genetics and Discrimination

Concern about discrimination arises from new capabilities to assess genetic information. This concern currently focuses on the Americans With Disabilities Act and subsequent rulemaking by the U.S. Equal Employment Opportunity Commission. First, as enacted, the ADA left open the question of whether genetic predisposition to illness or carrier status were covered as protected classes. In its final rule, EEOC rejected the premise that genetic predisposition or carrier status are covered under the ADA for employment purposes. Because some debate exists as to the intent of Congress in this area, Congress could revisit the issue to clarify its intentions with respect to genetic and disability discrimination under ADA. Many opine that litigation will ultimately define the scope of the ADA.

Second, ADA is silent on whether employers may discriminate—for the purposes of hiring—against individuals (e.g., CF carriers) who are perceived as more likely to incur extra costs due to illnesses that could occur in their future children. An OTA survey of Fortune 500 companies and companies with 1,000 or more employees revealed that 9 percent of employers surveyed account for dependents' potential expenses when considering an individual's application. If Congress determines the potential health insurance costs of an applicant's dependent should not be considered in hiring decisions, it could signal its intent through legislation.

Finally, concerns about discrimination in insurance coverage and repercussions on health care access arise in the era of new genetic tests, but insurance regulation in the United States is largely

a matter for the States. Nevertheless, one aspect of health insurance relates to both the ADA and Federal law regarding employee benefits (i.e., the Employee Retirement Income Security Act of 1974). The number of individuals receiving health care coverage via ERISA-based, self-funded plans is increasing. Under ERISA, which preempts State insurance law, any self-funded company can cap, modify, or eliminate employees' health care benefits for a particular condition at any time, as long as the company complies with the notice requirements in the plan agreement. Such conditions are in no way limited to genetic illnesses. Congress could prohibit such actions, if it deems it necessary, by amending ERISA, the ADA, or both.

Clinical Laboratory and Medical Device Regulation

Congress has along legislative history in regulating clinical laboratories and medical devices. In the past 4 years, Congress has moved twice—the Clinical Laboratory Improvement Amendments of 1988 and the Safe Medical Devices Act of 1990 (SMDA)—to address perceived deficiencies in each area. Absent additional action by Congress, the regulatory framework for clinical laboratories and medical devices will evolve from these two statutes. Currently, the regulatory status for both is in flux, as executive branch agencies only now are developing specific rules and regulations.

If Congress believes the new DNA-based genetic diagnostics require clinical laboratory quality assurance considerations beyond the 1988 legislation, it could amend CLIA to specify criteria for DNA assays. On the other hand, the field of clinical DNA diagnostics is changing rapidly. Congress might prefer to maintain the Health Care Financing Administration's flexibility in adapting to these changes. In that case, Congress could monitor HCFA's approach to DNA analyses through its oversight of HCFA's implementation of CLIA, generally.

With respect to medical devices, no FDA-approved DNA test kit for CF mutation analysis exists, although kits are being tested with companies' expectation of their availability in 1 to 2 years. Congress can amend SMDA if it believes DNA test kits constitute so novel a device that SMDA's provisions for premarket evaluation and postmarket surveillance do not suffice. Evaluating FDA's regulation of DNA diagnostics in the absence of a

product could prove difficult, however, and so Congress might prefer to take no action at this time.

Instrumentation

The ability to test quickly and accurately will be crucial to inexpensive CF carrier screening. It will be even more important if panels of genetic assays for an array of disorders are to be developed. Currently, all but one step of techniques used in DNA diagnostic analysis are automated, but there is little integration of the components. If Congress determines that the goal of quick, accurate batteries of DNA tests is important, it could make such integration a Federal research priority under the Human Genome Project by designating that certain levels of appropriations be targeted to tailoring instrumentation and automation to DNA diagnostics. Currently, the Human Genome Project serves as the primary funding locus for developing instrumentation to automate DNA analysis—chiefly through appropriations to U.S. national laboratories.

DNA Assays and Clinical Practice

In today's social, economic, and legal climate, OTA believes that, as a practical matter, a federally funded or controlled program for *population-based* CF carrier screening is not on the horizon. In the 1990s, CF mutation analysis could become routine, but not likely as part of a unified, national program. If Congress determines in the distant future that a programmatic public health model for CF carrier screening or other genetic conditions is necessary, it can look to the National Genetic Diseases Act to craft a population-based program. In 1992, the issue at hand is: How, and to what extent, will CF carrier tests—and other genetic tests in the pipeline—integrate into contemporary medical practice?

Many perspectives on how CF carrier screening should be implemented exist, including a socially regulated program, a free market model, and a focus on patient autonomy and choice. Those who support a regulated framework in the fashion of a public health model (e.g., newborn genetic screening) believe public health's historical use of institutional mechanisms and social approaches is appropriate and necessary for quality assurance and consumer protection. Others take a dim view of a regulated model for CF carrier screening because they believe that consumers are best served by having CF carrier tests available through general medical practice and by providing them the opportunity to choose and

manage their own health care. They argue that formal, government-sponsored structure translates to regulated medicine, which they oppose, because it can interfere with patient care.

No definitive way exists to determine when providers should routinely inform people about the availability of genetic tests, and in some respects, Congress has less a role to play in this policy issue than in the preceding five. Nevertheless, Congress can influence when and how genetic tests are integrated in two specific ways.

First, 2 years lapsed between identification of the CF gene and its mutations and the initiation of federally sponsored pilot studies to assess routine CF carrier screening. Before other DNA-based tests come on-line, Congress could encourage the genetic services delivery and genetic research agencies of the executive branch to coordinate efforts to develop an institutional means to ensure evaluation of genetic tests through federally sponsored consensus conferences, workshops, and pilot projects (if necessary) prior to their being incorporated into routine medical care. In doing so, concerns raised that CF carrier screening is being rushed into practice might be assuaged if future tests receive federally led, timely evaluation. On the other hand, critics of Federal intervention will continue to argue that federally sanctioned efforts will slow access to tests and information that some consumers would find desirable.

Second, once a test becomes fully integrated into clinical practice, Congress can direct the Agency for Health Care Policy and Research to examine whether practice guidelines for CF carrier screening, or other genetic tests, are appropriate. Supporters of practice guidelines believe they offer the potential to decrease malpractice claims, control health care costs, improve quality, and generally influence the use of a technology. Detractors argue such guidelines differ little from professional statements, will increase malpractice claims, and suggest regulated medicine.

PROSPECTS FOR THE FUTURE

Leaving aside the precise timing of routine CF carrier screening, it is clear the number of DNA-based tests for genetic disorders and predispositions will increase rapidly over the next decade, almost certainly by an order of magnitude. OTA considers it likely that the time available, if any, for debate and

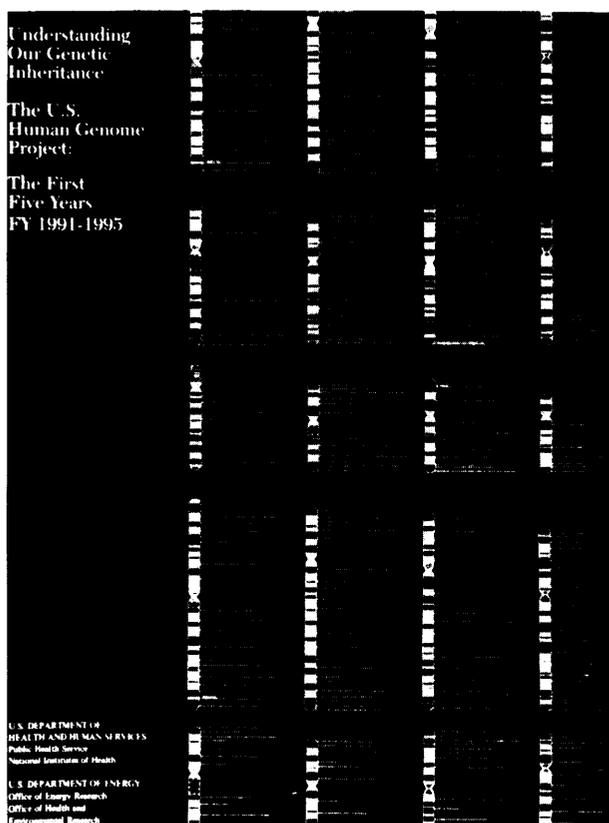


Photo credit: Office of Technology Assessment

The U.S. Human Genome Project, jointly funded by the U.S. Department of Health and Human Services and the U.S. Department of Energy is estimated to be a 15-year, \$3 billion project. As the project continues to unfold, Congress will likely face policy issues stemming from both the discovery of new information and applications of the information.

discussion on dissemination and use of new genetic tests will be compressed as pressure to use them rises. Given this scenario, some of the policy questions raised in this report extend beyond implications for CF carrier screening.

On one hand, CF carrier screening can be used to construct a paradigm that describes a set of policy issues for genetic tests to come. Access to health care merits specific mention because it is repeatedly raised as a concern tied to the increasing availability of genetic information—i. e., will the new knowledge elucidated through the Human Genome Project positively or negatively affect how Americans obtain or retain health care coverage? Certain additional themes will apply: ensuring clinical laboratory competence, quality assurance of the tests, maintaining high-quality service delivery,

promoting public education, supporting provider training, and safeguarding against discrimination and stigmatization. Of course, as American policies and politics change—or remain the same—the approaches to address these issues might differ.

Another generic issue, but one likely to ignite controversy with each new test, is the pace at which the assay should be integrated into general medical practice. Early use of CF mutation analysis is in the obstetric and prenatal context, and this trend will likely continue. As such, it serves as a good model to examine the broader consequences of genetic screening when this context is the chief avenue of a test's introduction. But experience with CF carrier screening is less applicable for tests that detect adult, late-onset genetic disorders (e.g., Huntington disease or familial breast cancer) or tests that predict genetic predisposition to multifactorial conditions (e.g., coronary artery disease, and, again, breast cancer). This issue—how customs of care evolve—could decline as broad categories of predictive genetic tests develop. It might not, however, because every disease and how people perceive each—differs.

One consideration for the future not fully explored in this report is indirectly related to cost-effectiveness, but directly related to how much CF mutation analysis—and other diagnostic genetic tests—will cost in the future. At issue are patents, licensing, and royalty fees for both products (e.g., the CF gene, for which a patent is pending) and processes (e.g., PCR, for which Roche Molecular Systems holds the patent) that are important to DNA-based diagnostics. Although automation appears likely to lower costs of DNA diagnostics, intellectual property protection, the impact of which cannot be fully assessed, to some extent might counter lower prices realized by new instrumentation. Issues surrounding intellectual property, scientific exchange, commercial development, and the Human Genome Project have existed since that project's outset. They continue to loom and might need congressional attention if they become pressing. Witness, for example, the new debate surrounding patenting certain DNA sequences.

Certain factors related to CF carrier screening will be less germane to analyzing the implications of other emerging tests that assess genetic risks. In particular, cost-effectiveness is a case-by-case matter. Likewise, the issue of making automation a

priority through Federal funding for instrumentation research and development presumably will dissipate.

Finally, fundamental to consideration of CF carrier screening is the issue of genetic counseling and abortion. Prenatal screening will probably comprise the largest portion of CF carrier assays, at least initially. Thus, as with prenatal tests generally, the extraordinary friction about abortion in this country is inevitably linked to the implications of CF carrier testing and screening. But as knowledge from the Human Genome Project accumulates, so will the number and definitiveness of genetic tests, and so presumably the social, ethical, and political tension. Some tests will be more likely than others to have prenatal applications, but as long as utilization of the new assays by pregnant women is possible, some will opt for abortion.

While not explicitly overturning *Roe v. Wade*, the 1992 U.S. Supreme Court decision in *Planned Parenthood of Southeastern Pennsylvania v. Casey* means women's access to legal abortions now turns largely on State law. The decision appears to affirm that women may choose to terminate pregnancies prior to fetal viability, but States may make this more difficult than it has been prior to the ruling. The court's ruling in the Pennsylvania case indicates States may enact laws related to information delivery, waiting periods, services provision, and restrictions on public financing or use of public facilities, as long as such laws do not present a substantial obstacle to a woman's choice. If Congress believes States should be preempted from enacting such laws, it could pass Federal legislation prohibiting State restrictions in any of these areas.

As well, the 1991 U.S. Supreme Court decision in *Rust v. Sullivan* upheld Federal regulations stating that patients at clinics receiving certain Federal funds (i.e., from Title X of the Public Health Service Act) may not receive information about the option of terminating a pregnancy at risk for a child with a genetic disorder. In March 1992, an executive order modified the original regulation and stated that such information may be provided by a physician, although the legal standing of that order is in question. The vast majority of practitioners providing services in such clinics—nurses and genetic counselors—still may not inform patients of this option. Congress came close to rescinding the entire restriction when a majority of Members of Congress voted to

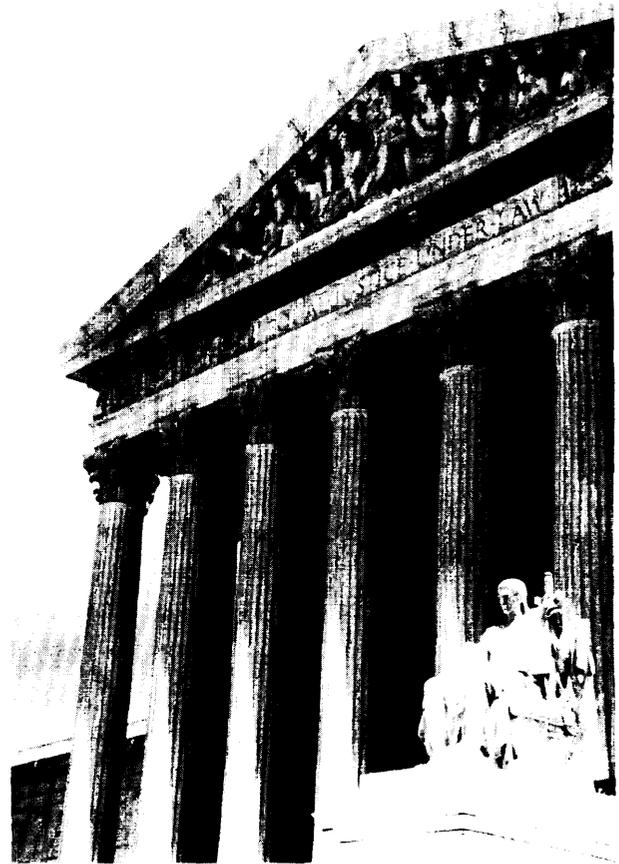


Photo credit: Chip Moore

The U.S. Supreme Court

overturn the regulation in 1991. If Congress believes nonphysician health care professionals should be allowed to counsel patients about abortion following diagnosis of fetal abnormalities, it could reexamine the issue and enact an exception for counseling related to genetic conditions or overturn the regulation entirely.

Nearly 10 years ago, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research concluded the fundamental value of CF carrier screening lies in its potential for providing people with information they consider beneficial for autonomous reproductive decisionmaking. CF carrier screening, however, is not just about a person's future reproductive choices. CF carrier screening represents the first of many DNA-based tests to come and raises many issues. Policy decisions made about it will reverberate far beyond this specific case.