Chapter 9

Costs and Cost-Effectiveness

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One of the least examined of the many issues surrounding carrier screening for cystic fibrosis (CF) is that of costs and cost-effectiveness. OTA found no comprehensive studies on the cost-benefit and cost-effectiveness of screening large numbers of people for CF carrier status, although one recent study examined the net economic benefit of prenatal screening for CF (1 1).

How much money might be involved in large-scale CF carrier screening? Under which, if any, conditions would it be cost-effective? What factors are important in optimizing cost-effectiveness? If large numbers of individuals are screened, would one strategy maximize cost-effectiveness and identify the highest number of carriers? This chapter frost discusses costs associated with CF (medical and caregiving) and costs associated with carrier screening. It then analyzes the cost-effectiveness of widespread CF population carrier screening under varying assumptions and approaches. This analysis is necessarily based on *modeling;* experienced-based data are lacking.

A CAUTIONARY NOTE

Exarnining potential costs and savings associated with routine CF carrier screening is fraught with technical and social pitfalls. Some data exist on attitudes of families with CF children or relatives toward CF carrier screening, prenatal diagnosis, and selective abortion (12,31,32). General agreement exists, however, that the perceptions of the general population (i.e., those without a relative or close friend with CF) might well differ from those of people with family histories of CF, but these perceptions are less well documented. Some survey data have been published on what people say they want and, theoretically, would do (6).

Since OTA found a paucity of experienced-based data on the attitudes of the general public toward key factors such as willingness to undergo CF carrier screening and to terminate CF-affected pregnancies, OTA calculated cost-effectiveness for several hypothetical scenarios. As explained later in this chapter, OTA attempted to construct the alternatives based on three sources: population survey data specific to CF carrier screening; survey data on the public's attitudes toward genetic tests, generally; and data from privately funded CF carrier screening pilots.

Aside from uncertainty about reproductive decisionmaking related to CF carrier screening, the costs of CF, itself, are uncertain and variable. As described in chapter 3, CF's clinical course varies widely from person to person; hence, so do medical costs. Even data on 'average' medical costs are less than optimal. The effect of new pharmaceuticals, such as DNase, cannot be measured because data related to their cost or potential to extend median life expectancy do not exist. While new treatments might be expensive, they could be quite successful, with the percentage of women choosing to terminate affected pregnancies shifting dramatically. This chapter examines, to a limited extent, the effect on health care costs if lifespan is extended using current "average' expenses. It does not speculate on how much new pharmaceuticals or gene therapy might cost, nor the effect their availability might have on how individuals make decisions about screening and subsequent reproductive alternatives.

Most importantly, 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 (25). Thus, while economic analyses can help inform resource allocation issues surrounding genetic screening, they have limits. In the context of public policy, the President's Commission articulated solid guidance about the benefits and limits of cost-effectiveness and cost-benefit analyses for genetic screening: These analyses are tools to be used within an overall policy framework, not solely as a method of making or avoiding judgment.

OTA concurs that the value of CF carrier screening is in information gained. No one can place a value on having information. Similarly, valuing births as parents likely value them is speculative, at best. Thus, personal considerations likely outweigh societal considerations of cost-effectiveness. Here an estimate of the impact of CF carrier screening on

systemwide health costs is sought; there is no intimation that something that saves or costs money is more or less desirable from a welfare standpoint.

COSTS OF CYSTIC FIBROSIS

The cost of any illness is the answer to the hypothetical question: If the disease disappeared and everything else stayed the same, how much more output (valued in dollars) would be available to the economy? One part of the calculation to 'answer this question involves the direct medical costs related to CF. Costs used in this chapter represent estimated charges for treating the average person with conventional strategies.

In addition to direct medical costs, disease has other manifestations. If the condition could be eliminated, then CF-specific costs of caring for persons with CF by parents, spouses, or friends could be avoided. Such nonmedical direct costs are included in this analysis.

OTA does not consider other dimensions of benefits and costs that might be included. For example, eliminating or ameliorating disease reduces premature death and permits people to work or carry on normal activities, producing a benefit in terms of future lifetime earnings. OTA does not recognize these benefits in this chapter, but some analysts would include this benefit to the economy in a cost-benefit analysis (the human capital approach) (11,22).

Conversely, anxiety and anguish for parents, fiends, and patients could be counted a cost of illness, although it is almost never included in calculations because of difficulty in assigning a dollar value to such elements. Similarly, a decision to avoid childbearing as a result of CF carrier screening could be included as cost due to lost productivity from any unaffected children who might otherwise have been born (again, a human capital approach)-i.e., when couples choose CF carrier screening to avoid childbearing, society is made worse off by their decision to avoid conception because the output from unaffected children they might have had is lost. Yet, some parents will almost certainly choose to avoid conception, and a societal human capital approach is inappropriate for analyzing costs and savings of avoided births for individual families. It is far from obvious that the value associated with children born with or without CF provides any measure of the value of CF carrier screening to any real person.

Some estimates of the total cost of CF exist, but include indirect costs associated with lost productivity (10, 11,2 1,22). In this chapter, OTA does not account for the present value of earnings that a (potential) child (with or without CF) might contribute to the economy. On a conceptual basis, OTA adopts a conservative approach, valuing only CF-related costs, rather than including future market earnings or non-CF medical costs for either affected or unaffected individuals.

Medical Direct Costs

Estimating savings that might result from CF carrier screening requires an estimate of present value lifetime costs of the disorder. Several groups have compiled figures on the annual costs for medical services obtained by persons with CF (8,33). Hospitalization, CF clinic use, physical therapy, and drugs account for most CF-related medical costs. Calculations indicate annual costs of medical care, projected to 1989 using the Consumer Price Index, range from about $9,000 to nearly $14,000 (table 9-l).

OTA uses estimated "annual costs for CF of $10,000, based on exarnining medical expense data from these other sources (22). Assurning an average life expectancy in 1990 of 28 years, an average expense of $10,000 per year, and using a 5 percent discount rate, the net present value of estimated lifetime medical expenses would be $148,981 (1990 dollars).

Using $10,000 for average annual medical costs might be an underestimate, but it is generally consistent with the estimates reported in table 9-1. For example, data from a 1989 Cystic Fibrosis Foundation (CFF) survey provide measures of hospital and clinic use (8). The average number of outpatient visits to CF centers was 3.9; at an assumed cost of $200 per visit to CF centers, such visits add up to $800 if four visits are made per year (33). Hospital stays for CF-related reasons averaged 8 days; at an average hospital cost of $700 per day, hospital costs for CF are about $5,600 per year. The final major expenses are drugs, including at-home intravenous antibiotics for about 10 percent of patients, and physical therapy. A reasonable estimate of such costs is approximately $5,000 per patient per year (33). Thus, average medical ex-

Table 9-l—Estimated Average Annual Medical Expenses for Cystic Fibrosis Treatment

Average annual expense per patient	Source
$7,500 (1980) 13,870 (1 989)'	M.V. Pauly "The Economics of Cystic Fibrosis," Textbook of *Cystic Fibrosis,* **J.D. Lioyd-Still (cd.) (Boston, MA: PSG, Inc., 1983), using data from Cystic Fibrosis Foundation,** *Cystic Fibrosis Patient Registry, 1980: Annual Data Report.*
8,098 (1985) **9,220 (1 989)'**	**Cystic Fibrosis Foundation, Cystic** *Fibrosis Patient Registry, 1983: Annual Data Report.*
12,300 (1989)	**M.V. Pauly, "Cost-Effectiveness of Screening for Cystic Fibrosis," contract document prepared for the U.S. Congress, Office of Technology Assessment, August 1991, using data from Cystic Fibrosis Foundation,** *Cystic Fibrosis Patient Registry, 1989: Annual Data Report.*
10,885 (1 **989-90)**	**M.V. Pauly, "Cost-Effectiveness of Screening for Cystic Fibrosis," contract document prepared for the U.S. Congress, Office of Technology Assessment, August 1991, using data from Wikerson Group, Inc.,** *Annual Cost of Care for Cystic Fibrosis Patients (New York, NY:* **Wilkerson Group, Inc., 1991).**
11,400 (1989)	**Office of Technology Assessment, 1992, based on M.V. Pauly, "Cost-Effectiveness of Screening for Cystic Fibrosis—Addendum" contract document prepared for the U.S. Congress, Office of Technology Assessment, February 1992.**

[a]Projected to 1989 dollars using the Consumer Price Index.

SOURCE: Office of Technology Assessment, 1992.

penses in 1989 for CF-related care using these assumptions is about $11,400 per person with CF.

Another set of direct medical costs has been calculated based on interviews with CF patients' families and clinicians (33) (table 9-2). This estimate characterizes individuals with CF as ''mild' (one inpatient episode every 2 years), ' 'moderate' (two episodes per year), and ''severe' (four or more episodes per year). Data from the 1989 CFF survey describe the distribution of hospital episodes, which are then used to categorize the number of persons in each of these categories. Similarly, average numbers of outpatient visits, pharmaceutical costs, and other medical expenses are estimated for each patient population. Examining average medical expenses based on data in table 9-2 requires one adjustment, however.

Even if all CF patients were ' 'mild, ' the expected number of persons with no episodes would be no

Table 9-2—Annual Cost of Medical Care for Cystic Fibrosis Patients

Treatment	Mild	Moderate	Severe
Acute treatment			
Antibiotics	**$ 2,000[a]**	**$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**

[a]All values in 1989 dollars.

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

greater than 50 percent; in fact, it was 61 percent. Thus, there is another category, "submild," whose illness requires infrequent hospitalization. If approximately 40 percent of patients were submild and 40 percent were mild, about 60 percent of persons would not be hospitalized and 20 percent would be hospitalized once. About 13 percent of all patients had two or three episodes 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. Medical expenses in table 9-2 need to be adjusted to account for the ''submild' group (22).

No data exist on the average expenses of "submild' persons with CF, 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 (22). 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 (23). Nevertheless, erring on the conservative side ($2,000), the estimated average annual medical costs when the proportion of individuals with submild, mild, moderate, or severe cases of CF is accounted for yields a second estimate of annual medical costs at $10,885.

Nonmedical Direct Costs

The chief nonmedical direct cost of CF is family caregiving time. CF centers estimate parents need to spend about 2 hours per day on therapy for a child with CF (730 hours per year) (22); many families

have therapists provide chest physical therapy (23). In addition, parents, spouses, or other family members lose time from work or housework when an individual with CF misses school or work.

It is difficult to obtain direct estimates of the number of sick days for people with CF—and hence the nonmedical (caregiving) direct costs to family members-because the severity varies considerably across patients and over time. The OTA analysis assumes 20 sick days per CF patient per year, involving 8 hours per day of work or housework missed (160 hours per year). Nonmedical direct costs also must account for time spent taking the person with CF to medical appointments. The average number of hospital days is eight (8,33), and OTA assumes 4 hours of caregiving time are associated with each hospital day (32 hours per year). Time also is spent on physician and clinic visits not associated with an acute episode. The frequency of such visits is assumed to be four per year, at a time cost of 4 hours (16 hours per year). The total number of hours per year for CF-related caregiving is estimated to be 938.

OTA assumes caregiving time costs an estimated domestic/nursing wage of $10 per hour. While no empirical work supports this value, it is taken to be reasonable. Overall, then, the present value of lifetime nonrnedical direct costs associated with CF is estimated at $139,744 (assuming an average life expectancy in 1990 of 28 years and using a 5 percent discount rate), This chapter presents only data using $10 per hour as the cost for time associated with nonmedical direct costs. Using a value that is 30 percent lower changes the relative cost-effectiveness less than changing other parameters, such as reproductive behavior or test sensitivity. It can be an important assumption in scenarios that are borderline net savings, however, since savings decrease.

COSTS OF CARRIER SCREENING FOR CYSTIC FIBROSIS

Since CF is the most common recessive genetic disease among American Caucasians of European descent, there is intense commercial interest in marketing CF mutation assays. At least six commercial companies currently market CF carrier tests and at least 40 university and hospital laboratories conduct CF carrier assays. Table 9-3 lists a sample of prices for commercial facilities and university and hospital laboratories. The number of mutations assayed differs from facility to facility, and test costs reflect this variation. Additionally, some quoted prices include costs of pretest education and post-test counseling, while others do not. Costs of tests reflect differential royalty license fees among the facilities for patents related to the CF tests, as well (box 9-A). Nevertheless, the average charge for CF mutation tests among these facilities is approximately $170.

Table 9-3-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 Cystlc Fibrosis," contract document prepared for the U.S. Congress, Office of Technology Assessment, August 1991.

Photo credit: University of Kansas Medical Center

H.C. Miller Building, University of Kansas Medical Center. University medical centers, as well as commercial companies, perform CF mutation analyses for testing and screening purposes.

Box 9-A—Licensing of Polymerase Chain Reaction

The polymerase chain reaction (PCR) allows minute quantities of an identical sequence of DNA to be replicated millions of times (ch. 4); it is a critical tool for the CF mutation test and virtually all other new DNA-based diagnostic procedures. In 1987, Cetus Corp. received a patent for PCR. Currently, patent rights for PCR diagnostics are held by Hoffmann-La Roche, Inc. Because PCR is used in so many current and potential genetic tests, the terms of PCR licensing agreements are important determinants of future costs of tests to consumers.

Shortly after Hoffrnann-La Roche acquired patent rights for PCR, commercial and hospital laboratories expressed concern that the proposed fee structure would discourage some laboratories from seeking agreements. For example, the terms for commercial facilities would have amounted to roughly 15 percent of the cost of each test that was performed. Any new applications-e. g., for a different diseas---that a laboratory wanted had to be approved by Roche. Such licensing terms might have had a chilling effect on diagnostic companies and hospital laboratories that perform molecular diagnostics. Costs of DNA-based analyses, in general, would likely have risen rather than decreased as many expected they would with greater numbers of tests and increased volume.

Hoffmann-La Roche, Inc. announced in February 1992 that a new company, Roche Molecular Systems, had been formed to handle the development of PCR. The new licensing agreement announced includes permission to use PCR for a broad range of applications. Licenses will be available to all academic and commercial laboratories who request them, and academic and nonprofit licenses will require no down payment or minimum royalty payments and a royalty rate of less than 10 percent.

The saga of PCR licensing illustrates the importance of patents to future costs of DNA-based diagnostic tests, but the intellectual property issue is not solely conffined to the PCR patent. Patents for the CF gene and its mutations, for example are pending. Thus, while automation will likely lower costs of DNA diagnostics, intellectual property protection to some extent might counter lower prices. Royalty licensing fees from patents will be reflected in charges for the tests to consumers. Resolving debates surrounding the Human Genome Project and intellectual property will have important consequences for ultimate cost—and hence, utilization and cost-effectiveness-of DNA-based diagnostics.

SOURCES: Office of Technology Assessment 1992; based on M. Hoffmann, "Roche Eases PCR Restictions," science 225:528, 1992; and D. McQuil.kew Roehe Molecular Systems, Inc., personal communications, January 1992, February 1992.

OTA uses a lower cost per test--$100 per person—in its base case and most other analyses to reflect the expectation that test costs will likely decrease as CF carrier screening becomes routine; many believe economies of scale will be possible with larger volumes of screening assays. This cost includes the test itself and post-test counseling, but not pretest education or marketing. The $100 per individual cost ($200 per couple) also assumes all couples require the same amount of post-test counseling (and therefore incur an equivalent cost). In fact, couples who both screen negative (-/- couples) are likely to require far less post-test counseling than couples where one screens positive and one screens negative (+/- couples) or couples whose results are both positive (+/+ couples), but no assumptions are made about such variation. OTA also presents scenarios with higher and lower costs per test.

Three other components were included in test-related costs of CF carrier screening. First, some expenses will be incurred to inform people about the test's availability and to educate them about CF carrier screening. No estimates exist for costs related to providing such information and services. OTA uses a value of $25 per initial screening contact as the pretest cost of information and education (22).

Some argue $25 far exceeds what should be assigned to this cost—that most individuals will be visiting their physician for other purposes and that promotional pamphlets, videos, or mailings should constitute the sole cost of information services. OTA posits, however, that even if physicians include the cost of informing patients as part of their standard charge for a visit, this does not mean that providing information is costless—it consumes physician time and office space. Attaching a cost of $100 per hour to physician time and office use (equivalent to gross revenues of $200,000 per year), and assuming furnishing information takes 10 minutes, the cost per person informed would be about $17. **To account** for additional expenses related to nonphysician time and promotional materials, OTA uses a total cost of

pretest information and education of $25. No charge is assessed for people who do not elect screening, although such individuals might well receive some pretest information. Similarly, although most scenarios considered here involve screening the woman frost followed by the male only if she is positive, no charge is assessed for informational costs of screening the partner of those 1 in 25 women who test positive (would increase total cost of screening, but not significantly). Thus, others will argue OTA underestimates the total cost of pretest expenses. As results of the analysis show, the total cost associated with performing CF carrier assays is sensitive to assumptions about this charge; further research on actual expenditures related to it is warranted.

Second, because prenatal testing will be part of CF carrier screening when +/+ couples decide on childbearing, the cost of chorionic villus sampling (CVS) is relevant. CVS charges in two northeastern medical centers were investigated (22). As for other procedures, the specitics of what was included at what price varied. CVS sampling and the cost of a CF mutation analysis is priced at $1,200 in this analysis. Third, the cost of an abortion is priced at $900 (22).

KEY VARIABLES AND ASSUMPTIONS

As just described, the cost of CF carrier screening includes providing pretest information and education, the actual test cost, post-test counseling, prenatal testing, and abortion. Beyond direct costs associated with performing CF carrier analyses, however, other key parameters that affect the economic analysis include:

- sensitivity of the CF test;
- percent of individuals who voluntarily elect to determine their CF carrier status;
- family size, percent who alter their reproductive behavior, and how the behavior is altered; and
- screening approach=. g., preconception versus postconception, or women first, followed by men only for positive women, versus couples.

The following sections present the assumptions or values used for each of these factors in OTA's base case. Later sections describe how costs and savings were calculated, and how the assumptions or values for each were varied singly or in combination.

Test Sensitivity

As described in detail in chapter 4, CF mutation analyses using delta F508 and an additional 6 to 12 mutations (DF508+6-12) detect about 85 percent of CF carriers, although depending on ethnic background and the battery of mutations used, test sensitivity can approach 90 percent (3,20). In Ashkenazic Jews, DF508+6 identifies nearly 95 percent of carriers (27). OTA uses 85 percent sensitivity in the base case and in most alternative scenarios, but varies the sensitivity in some scenarios to demonstrate its affect on costs and savings.

Participation

What percent of eligible individuals will elect to be screened for their CF carrier status? Estimates are available for individuals with family histories of CF (12,18,31), as well as for one general population sample from a midwestem urban hospital and suburban health maintenance organization. A survey of this latter population found 84 percent of respondents had a strong interest in CF carrier screening before pregnancy and 69 percent would avail themselves during a pregnancy (6). Other surveys measure the acceptance of the general American populace toward prenatal genetic tests (28,30) and carrier screening (30), although not specific to CF. According to both these surveys, just over 80 percent of Americans say they would avail themselves of such tests.

To what extent, however, do such surveys represent real-life decisions? The key data would come from knowledge about what percent of individuals participate in CF carrier screening, but to date no published data exist. Early results from privately funded pilots, however, offer insights into what participation rates realistically might be expected. Through March 1992, 78 percent of participants (Caucasian Americans of European descent or Hispanic ethnicity) in a California pilot study have elected CF carrier screening (34); these individuals do not pay for their tests. Out-of-pocket costs dramatically affect the percent of people electing CF carrier screening: a Texas study reveals participation dropped from about 80 percent to 20 percent when a pilot ended and charges for screening began (3).

OTA uses 80 percent in the base case. Some might argue such a level is too high, despite experience from pilot projects. On the other hand, while the 80 percent figure will likely exceed participation in CF

carrier screening's early phases of dissemination, it does not seem unreasonable in light of current steady-state data on the percentage of pregnant women who voluntarily elect prenatal testing for maternal serum alpha-fetoprotein or prenatal genetic analysis due to advanced maternal age (34): For both tests, 80 percent accept the procedure(s). OTA also examines , however, a participation rate of 20 percent, in light of OTA survey results that most third-party payers say they are unlikely to currently pay for CF carrier tests without a family history (ch. 7). Nevertheless, should CF carrier screening be incorporated into routine obstetric practice, third-party payment will likely increase, out-of-pocket expenses decrease, and participation increase. OTA also models 50 percent participation.

The population from which the 100,000 women or couples is drawn is assumed to be one for which the overall test sensitivity is at least 85 percent and the carrier frequency is 1 in 25. A more accurate approach might be to adjust the pool for racial and ethnic demographics. Different attitudes toward genetic screening and reproductive behavior prevail and would complicate the calculations. Further, the frequency of newborns with CF within other populations is so low+. g., 1 in 17,000 (4) to 19,000 (16) African American newborns, 1 in 9,600 Hispanic, and 1 in 90,000 Asian American babies (16)---that weighting a random sample would have little net effect.

Finally, the pool is presumed to consist only of individuals who contemplate having children. Some argue CF mutation analysis would be of little interest to those choosing to be childless, although people who do not intend to have children sometimes do. Similarly, arguments can be made that some who do not contemplate children still might seek CF carrier screening solely for informational purposes or because of its impact in informing their relatives.

Reproductive Behavior

Fundamental to the cost-effectiveness analysis of CF carrier screening is reproductive behavior. First, the analysis in this chapter assumes all couples (+/+, +/-, and -/-) seek the current U.S. average of 2.1 children per family (24). Some research indicates that families who have a child with CF alter their reproductive behavior by having fewer children (12,18,32), but these are retrospective analyses. No data exist for the total number of children that couples might ultimately have after identification as +/+ in the absence of a child with CF.

Second, only changes in the reproductive behavior of +/+ couples are modeled, Clearly, +/- couples might choose to avoid conception, seek prenatal testing, or consider pregnancy termination of carrier fetuses because current tests are not 100 percent sensitive, and hence there is some chance a fetus identified as a carrier actually has CF. Results from privately funded pilot studies, however, reveal no such decisions to date (2,26) (ch. 6).

Third, specific assumptions are necessary for precisely how people alter their reproductive behavior once they are identified as +/+ couples. The base case uses an infertility frequency in the general population of 8.4 percent (19,29). Of fertile couples, 10 percent is used as a reasonable estimate of the fraction of +/+ couples who will avoid conception (3). Avoiding conception obviously incurs costs, but fertile couples are also likely to incur contraception costs over their reproductive lives, and so contraception or sterilization costs are not included in this analysis.

Assumptions about the reproductive behavior of +/+ couples are critical to the cost analysis of population carrier screening for CF. The base case assumes all of the remaining 90 percent of+/+ fertile couples become pregnant and seek prenatal testing and that all couples with affected fetuses opt to terminate the pregnancy. Alternative scenarios vary the proportion of +/+ couples seeking or declining prenatal testing and the percentage electing abortion of CF-affected fetuses. Again, limited data exist on reproductive behaviors as they relate to CF carrier screening in the general population. less than 20 CF-affected fetuses have occurred in pilot studies; in one study in Texas, 7 of 14 affected pregnancies were terminated (3). In the attitudinal survey of midwest urban and suburban women, 29 percent said they would terminate a pregnancy if the fetus were found to have CF (6). (As described in chapter 5, data from families of children or relatives with CF have been reported (18,3 1,32), but those data are not thought to be wholly representative of the general population.)

Screening Strategies

Should both a man and woman be screened as a couple, or should the man be screened only if the woman's results are positive? Should the negative

partner in a +/- couple be screened for additional mutations to detect a higher proportion of carriers? Is there an effect on cost whether screening is preconception or postconception? The strategy employed in a CF carrier screening protocol affects costs and savings.

If the CF mutation assay detected 100 percent of mutations, it only would be necessary to screen one partner-usually the woman-because paternity is never assured. Placing primary focus on women is objectionable to some, however (14,15). Additionally, men and women are not always linked as a unit through their reproductive lives. Finally, limiting carrier screening to only men who are partners of positive women loses the opportunity to identify male carriers for whom CF carrier status might be of personal interest or future importance-to them and their relatives. On the other hand, from a cost perspective, it is clear the total number of individuals who will be screened in a "woman, then man" strategy will be less thanina''couple' strategy, and hence CF-related screening costs will be less—but to what extent?

Strategies for CF carrier screening can be preconception or postconception. The analysis in this chapter examines preconception screening. Modeling a postconception strategy is difficult because, although much CF carrier screening is of pregnant women and their fetuses, such screening is offered because the patients are being seen for other prenatal or genetic services+. g., advanced maternal age or a family history of another disorder. Modeling reproductive behavior would be more complex because it becomes confounded by results for these other tests. Nonpaternity might be expected to be a greater factor in postconception CF carrier screening. Some fraction of postconception individuals will receive test results of an affected fetus in the late stages of pregnancy, where termination might not be feasible, which could then affect subsequent decisions about total family size.

Cost estimates for preconception strategies that screen only women frost, as well as the strategy of screening couples, are presented. (The base case involves the former.) The analysis also examines the effect on costs and savings of screening the negative partner of +/- couples for additional mutations to detect a higher proportion of carriers. OTA assigns no additional cost for the followup analysis because at least three institutions follow such a protocol and do not charge extra for the additional mutations tested (3,9,34).

COSTS AND SAVINGS

The analysis models a steady-state equilibrium, in which CF mutation analysis is available to all prospective parents at the outset of their reproductive planning-i. e., before the birth of any children. This assumption incorporates the fact that identification of CF carrier status affects all subsequent pregnancies.

Costs With No Carrier Screening

At a carrier frequency of 1 in 25, 160 of 100,000 couples would be +/+, and be at 1 in 4 risk of having a child with CF in each pregnancy. Of these couples, 13.4 would be infertile (0.084x 160). The remaining 146.6 couples each would have, on average, 2.1 children, of which 0.53 would theoretically have CF. Overall, the total lifetime CF-related medical costs without CF carrier screening are $11,575,536 (0.53 children/couple x$148,98 1 lifetime medical spending child x 146.6 couples). Total nonmedical direct costs are $10,857,782 (0.53 children/couple x $139,744 lifetime CF-related caregiving costs x 146.6 couples). Total direct costs systemwide in the absence of screening are $22,433,318.

In fact, 36.7 couples of the 146.6 preconception couples will have a child with CF for their first pregnancy. As a result, some of these couples will alter their reproductive behavior (12,18,31,32) and avoid further conception (thereby saving potential costs associated with having an affected pregnancy in the future-i. e., cost offsets). Others will seek prenatal tests and consider abortion in subsequent pregnancies (thereby adding costs, but if abortion is chosen, contributing cost offsets). overall, however, the net effect on total direct costs of altered reproductive behaviors for the 36.7 couples in the absence of DNA-based CF mutation analysis is negligible.

Calculating Costs

The ways in which costs were calculated for the base case are presented in this section for illustrative purposes (table 9-4). Calculations for the alternative scenarios are not presented, but were performed in the same manner. Again, the base case involves the following:

Table 9-4-Costs, Cost Offsets, and Net Savings for Base Case[a]

Description	Number	costs: cost of CF carrier screening per couple	costs: Total CF carrier screening costs	Cost offsets (savings): Total medical savings	Cost offsets (savings): Total caregiving savings	Cost offsets (savings): Medical plus caregiving savings
Woman tests negative, ., .	77,280	$125	$9,727,500	0	0	0
Woman tests positive, man tests negative	2,627.5	225	591,188	0	0	0
Woman tests positive, man tests positive	92.5	—	—	—	—	—
Infertile	7.8	225	1,755	—	—	—
Fertile, voluntary childless	8.5	225	1,913	$670,415	$628,848	$1,299,263
Fertile, prenatal testing, and abortion	76.2	4,215	321,183	6,018,832	5,645,658	11,664,490
Total cost of CF carrier screening	—	—	10,643,539	—	—	—
Total caregiving and medical offsets	—	—	—			12,963,753
Net savings per 100,000 couples						
Net *savings per 100,000 couples*	—		—			2,320,214

[a]Eighty percent elect to participate in screening; cost per test is $100; test sensitivity is 85 percent; all +/+ couples seek prenatal testing and terminate affected pregnancies.

SOURCE: Office of Technology Assessment, 1992.

- lifetime direct CF medical costs of $148,981 and lifetime CF-related caregiving costs of $139,744 per child with CF;
- carrier frequency of 1 in 25;
- 100,000 preconception women are screened, followed by screening the partner if the woman is positive;
- $25 cost per initial screening contact; test cost of $100 per test performed; and test sensitivity of 85 percent;
- 2.1 children per couple regardless of test results;
- 8.4 percent infertility and 10 percent of fertile +/+ couples choose to avoid conception; and
- 80 percent who are offered CF mutation analy - sis participate, all +/+ fertile couples seek prenatal testing (CVS at a cost of $1,200 per pregnancy) (22) and terminate all affected fetuses ($900 per pregnancy) (22).

Of 100,000 women offered screening, 80,000 elect to participate. Of these 80,000 women, 2,720 carriers are identified and so 2,720 men are tested. Of these, 92.5 males will be identified as carriers, and hence 92.5 +/+ couples are identified and 2,627.5 receive results indicating they are +/-. In fact, among these +/- couples are 16.3 +/+ couples who are missed, of whom 14.9 are fertile. Of the 92.5 +/+ couples who are identified, 7.8 are infertile (0.084 x 92.5) and 8.5 are voluntarily childless (0.10 x [92.5-7.8]). Thus, 76.2 fertile couples seek prenatal testing. Finally, 51.2 +/+ couples are missed (46.9 me fertile), among the 20,000 women who elected not to participate or who were undetected because the test is 85 percent sensitive, not 100 percent.

The cost per woman screened is $125 ($25 pretest for information and education + $100 for CF mutation analysis and post-test counseling). Women with negative results do not incur additional costs for screening. For identified carriers, there is an additional cost of $100 for CF mutation analysis and post-test counseling for the man, for a total of $225 per couple. This cost applies to couples who are identified as +/-, couples who are +/+, but infertile, and +/+ couples who decide not to have children. For +/+ couples who chose to conceive, costs are $225 plus the additional cost of prenatal screening and abortion. Since these couples seek a final family size of 2.1 children, a theoretical 2.8 pregnancies must be undertaken and 0.7 abortions per couple performed. Therefore prenatal screening and abortion costs add $3,990 per couple ($1,200 x 2.8 + $900 x 0.7). Screening related costs per +/+ couple, then, are $4,215 ($25 + $100+ $100+ $3,990).

The total cost related to performing CF carrier screening for this base case is $10,643,539.

Calculating Cost Offsets

Two types of systemwide cost offsets (i.e., savings) flow from CF carrier screening: avoiding direct medical costs and avoiding nonmedical direct costs associated with time for caregiving. The benefit calculations that follow are a means to examine systemwide economic effects from CF carrier screening, not to positively or negatively reflect the intrinsic or extrinsic value to any individual or couple.

Neither medical nor caregiving cost offsets flow from infertile couples. The voluntarily childless couples, however, avoid medical and caregiving costs. Of 2.1 total expected children, 0.53 with CF would be expected per couple; overall, 4.5 CF-affected births would be avoided for this population (8.5 couples x 0.53 affected births/couple). Total medical cost offsets from those choosing to be childless are $670,415 ($148,981 per birth x 4.5 births). Savings from caregiving cost offsets for this group are $628,848 ($139,744 x 4.5).

Similarly, cost offsets arise from +/+ couples who use prenatal testing and, in the base case, terminate all fetuses diagnosed with CF. Some 40.4 affected births are avoided (76.2 couples x 0.53 affected births per couple). Total medical cost offsets for this group are $6,018,832 ($148,981 per birth x 40.4 births); total caregiving offsets are $5,645,658, Total medical and caregiving savings---costs avoided—are $12,963,753.

Because the test is less than 100 percent sensitive and because 20,000 women elect no screening, some +/+ couples are missed and some children with CF are born. Thus, the costs avoided fall short of the $22,433,318 spent in the absence of CF carrier screening. Overall, 77.7 babies with CF would be expected in the base case from the pool of 100,000 couples (146.6 fertile +/+ couples x 0.53 children with CF/couple), but 49.9 affected births are avoided (4.5 + 40.4). Systemwide, $12,963,753 are saved, but $10,643,539 are spent on screening, for a net savings over no screening of $2,320,214. That is, in the base case, sufficient savings accrue from avoided medical and caregiving costs to pay for costs associated with screening.

Alternative Scenarios

Costs and savings for several alternative scenarios were developed. Table 9-5 presents the base case and 14 representative scenarios that demonstrate the effects of varying price, participation, test sensitivity, reproductive behavior, and screening strategy (a strategy that screens partners of positive women with a more sensitive test (90 percent) and a couples strategy).

Six alternative cases actually yield sufficient savings from avoided medical and caregiving costs to pay for all costs associated with screening—scenarios A, B, E, F, G, and J. All but scenario J, however, include the unlikely assumption of 100 percent termination of affected pregnancies. These scenarios are presented for illustrative purposes only or to examine the effect of other variables on cost-effectiveness, not as representations of likely occurrences or a goal to be achieved.

Scenario J also yields net economic savings over no screening from a systemwide perspective. It assumes 80 percent participation, a goal that might be achieved if CF carrier becomes as accepted as other prenatal tests (34) or as in the pilot studies in California and Texas described earlier (2,34). However, unlike in these pilots, a cost per test of $75 is assumed; participants in the pilots are/were not charged, and it is known that participation declines when out-of-pocket costs rise (2). Finally, scenario J assumes 64 percent[1] of affected fetuses detected are terminated, which could well be more frequent than will actually occur.

The remaining eight scenarios (C, D, H, I, K, L, M, N) do not yield net savings on a systemwide basis—i.e., they cost more than if no screening exists. As discussed below, several factors account for why population CF carrier screening is not cost-effective under assumptions used in these scenarios.

[1] Eighty percent of +/+ couples undergo prenatal diagnosis, and the remaining 20 percent choose no prenatal diagnosis because they would not consider terminating an affected pregnancy, regardless of outcome. The parents of 80 percent of affected fetuses diagnosed through the prenatal test elect to terminate, but 20 percent do not. This latter group might have sought prenatal testing with the thought of terminating, but then chose not to. Or they might have chosen prenatal testing knowing they would not terminate, but wanted information to prepare for the birth of a child with CF. The net frequency of abortion is 64 percent after combining the split decision process-i. e., that some will not seek any prenatal testing, but others might (which costs the system), but then opt not to terminate an affected pregnancy (also adds costs).

Table 9-5—Effect of Assumptions on Net Savings Over No Screening

	Test sensitivity (Ol.)	Cost per test	Participation	Percent +/+ who seek prenatal testing	Percent +/+ who abort affected pregnancies	Net systemwide savings compared to no screening
Base case.	85	$100	800/0 of 100,000 women; man only if woman positive	100	100	$2,320,214
A.	100	100	100% of 100,000 women; man only if woman positive	100	100	9,007,651
B.	85	100	100% of 100,000 women; man only if woman positive	100	100	2,977,225
c.	85	100	80% of 100,000 women; man only if woman positive	100	50	(3,456,025)[b]
D.	85	100	80% of 100,000 women; man only if woman positive	80	64[c]	(1 ,786,030)
E.	85	100	20% of 100,000 women; man only if woman positive	100	100	589,498
F.	85	100	500/0 of 100,000 women; man only if woman positive	100	100	1,474,375
G.	100	100	800/0 of 100,000 women; man only if woman positive	100	100	7,188,877
1-f.	85	100	20% of 100,000 women; man only if woman positive	100	50	(840,078)
I.	85	100	20%0 of 100,000 women; man only if woman positive	80	64[c]	(430,182)
J.	85	75	800/0 of 100,000 women; man only if woman positive	80	64'	338,729
K.	85	100	50% of 100,000 women; man only if woman positive	80	64[c]	(1 ,075,074)
L.	85190	100	50% of 100,000 women; if the woman is positive, the man is tested with additional mutations at 900/0 sensitivity	80	64[c]	(765,919)
M.	85	100	1OO% of couples participate	100	100	(6,682,775)
N.	85	50	1 00°/0 of couples participate	100	50	(4,077,693)

[a]Per 100,000 eligibles.
[b]( ) denotes a negative value.
[c]Eighty percent choose prenatal diagnosis. Of these, 80 percent terminate affected pregnancies and 20 percent do not, either because when faced with the choice they decide against it or because they did not plan to, but sought prenatal diagnoses to prepare for the birth of a child with CF. Twenty percent do not undergo prenatal diagnosis because they will not terminate regardless of the outcome.

SOURCE: Office of Technology Assessment, 1992.

Effect of Varying Rates of Selective Termination

Varying the ratio of those who elect to continue pregnancies diagnosed with CF to those who elect termination exerts a significant effect on net savings over no screening. The base case and scenarios D have similar assumptions except the fraction of affected pregnancies terminated varied—100 percent and 50 percent, respectively. Net savings per 100,000 women screened compared to no screening declines from $2,320,214 to -$1,786,030. Scenarios E and H are likewise identical except for the fraction

of affected pregnancies terminated, and cost savings are eliminated when the frequency is halved.

Effect of Test Cost

Reduced test costs appear as important as reproductive behavior, especially when participation is high. Not surprisingly, decreasing the cost of CF mutation analysis results in increased net savings (compare scenarios D and J)---to a point where cost-effectiveness can be achieved when the price per test is dropped 25 percent under the assumptions used. Net savings of -$1,786,030 in scenario D rise to $338,729 in scenario J when the cost per test drops from $100 to $75 per individual.

Effects of Test Sensitivity or Screening Strategy

Increasing test sensitivity results in net system savings, if reproductive behavior and other variables are constant (scenarios A versus the base case, and scenarios L versus K). And as expected, the strategy of screening both individuals (scenario M), rather than only the male when the woman is positive (scenario B), decreases savings from $2,977,225 per 103,400 total individuals screened for the woman first strategy ($28.79 saved per person screened) to -$6,682,775 per 200,000 individuals screened in the couples strategy (cost of $33.41 per person). Decreasing the cost of screening by 50 percent in the couples strategy (scenario M versus N) is still not cost-effective under the assumptions used. But again, since the primary value of CF carrier screening is information, for which no cost can be assigned, the informational value to +/- couples where the male is positive and the female is negative would be entirely missed in the woman-first strategy.

Effect of Participation

The percent of individuals electing CF carrier mutation analysis has an effect on system savings, all other factors being equal. Participation rate is less important, however, than test cost or reproductive behavior. In fact, lower participation is more cost-effective, depending on test cost or selective termination, because costs associated with screening are not incurred, although high participation and a high frequency of termination or low test cost is most cost-effective. Scenarios D, I, K, and J best illustrate this point for test cost. The first three scenarios assume a test cost of $100, 85 percent sensitivity, and the bifurcated reproductive decision option that results in a net terrnination of 64 percent of affected pregnancies; scenario J assumes the same at a test cost of $75. What differs among the first three is agreement to be screened—80 percent, 20 percent, and 50 percent, respectively; scenario J assumes 80 percent participation to compare it to scenario D. At 80 percent acceptance and $100 test cost per 100,000 eligibles, CF carrier screening is not cost-effective (net cost of $1,786,030), but when test cost is reduced to $75, CF carrier screening is cost effective (net savings of $338,729). In contrast, when participation falls to 50 percent and test cost is $100, net cost drops to $1,075,074; when acceptance is only 20 percent the net cost is $430,182. Scenarios C, E, and H demonstrate the effect of participation versus selective termination).

QUALIFICATIONS ON THE ANALYSIS

Results of this analysis are highly dependent on the assumptions made. Some of the more critical or controversial assumptions are highlighted, including:

- Agreement to be screened. The results are sensitive to the proportion of the eligible population who consent to initial screening, but less so than reproductive behavior or test sensitivity. Even with 20 percent participation, screening can be cost-effective, depending on the other variables.
- Reproductive behavior. Assumptions about reproductive behavior are the most important factor in the analysis, but experience-based data are sparse. How completed fertility is affected by the occurrence of CF (in the absence of screening), how the availability of CF carrier screening affects potential parents' choices between remaining childless versus prenatal screening with selective termination, and how both CF carrier screening and prenatal testing availability affect final average family size are critical.
- Pretest costs. A cost for marketing CF carrier screening and for pretest education is assessed as a screening expense. Although this cost is small per eligible individual, it is an important part of the total cost because it is incurred for all first contacts who elect screening. No data empirical data exist to support the $25 used. OTA estimated the value by analogy. While it might be such costs are higher for those who

elect screening, balanced against higher pretest costs for these individuals is the likelihood of lower or no costs for those who do not participate.

. Cost of the CF carrier assay. A cost of $100 per test is assumed in most scenarios, which is lower than current charges, Using costs of $75 and $50 per test increases net savings. Ultimately, the assay's cost might be less important overall to net savings than it is to its impact on the willingness of individuals to elect screening if they must pay the cost themselves. Nevertheless, should the cost reach $50 to $75 per individual, savings are achieved, depending on the frequency of pregnancy termination.

. Median life expectancy. A median life expectancy of 28 years in 1990 is used. Using a longer life expectancy increases net savings if CF-affected births are avoided, but also increases costs of the disease when +/+ couples are missed because of test sensitivity, when people elect no screening, and when reproductive behavior is not altered. Overall, the effect of median life expectancy on costs and savings, however, is negligible if the other variables in the analysis are held constant. More importantly, as median life expectancy increases, individuals might be less likely to alter their reproductive behavior, which will likely result in fewer CF-affected births avoided and lower net savings.

| Present value of avoided CF-related costs. An estimate of $10,000 as the annual medical cost per person with CF is used, which is at the low end of annual cost estimates compiled by several sources. Higher estimates, however, are based on calculations that appear to conflict with actual data on use of care by CF patients (21,22). Another potentially important adjustment to this estimate is the assumption that the $10,000 occurs uniformly every year over the person's lifetime. As CF patients live longer and are treated more effectively, the period of high medical costs likely will be pushed further into the future. Even if those costs eventually are substantial, however, they are discounted back to the present, which means they add little to the present value of CF-related medical costs. Conversely, some new treatments and technologies likely will be expensive. Greater use of heart-lung transplants or even gene therapy, for example, will increase CF-related medical costs—significantly if the therapies become a common option. The choice of discount rate is also important.

- Paternity. The analysis assumes the prospective father can be identified and screened and that each woman has the same partner for all births, so that CF carrier screening need be done only once per couple. Uncertainty of paternity already confounds real-world use of genetic tests, with frequencies of nonpaternity reported or estimated from 2 to 15 percent (1,17). People also may have multiple partners over their reproductive years. Both behaviors reduce net savings.
- Test precision. Any costs (e.g., anxiety) that theoretically might be imposed by a less that 100 percent sensitive test were unaccounted for, although post-test costs related to counseling were included. Similarly, psychological costs associated with false positive findings—most likely from laboratory handling error—were also unaccounted for, since evidence indicates DNA tests per se yield accuracy greater than 99 percent (5,13). False positive findings would not result in a CF-affected pregnancy, but could result in the cost of a prenatal test for a fetus not actually at risk.
- Preferential screening of relatives of carriers. Although no specific scenario is examined, close relatives of carriers might seek and use CF mutation analysis at a greater frequency, at least initially. The effect of preferential screening of relatives would be to enhance the efficiency of CF carrier identification. For example, in a population of 100,000 individuals with 50 percent participation, 75.2 percent of +/+ couples would be identified. If the population were relatives of previously identified CF carriers, 50 percent participation identifies 88.3 percent of +/+ couples (7). If the reproductive behavior were similar, then preferential screening would increase net savings. On the other hand, if acceptance of CF carrier screening approaches the 80 percent level that exists for similar tests, preferential screening of relatives will have little net economic effect.
- Subsequent generations. Future offspring of +/- couples might preferentially seek CF mutation analysis because their carrier risk will be 1 in 2. In contrast, offspring of -/-couples will have a very low risk of being carriers and might be less likely to utilize CF tests. Such a scenario

would decrease costs of screening and increase net savings.

SUMMARY AND CONCLUSIONS

One of the least examined of the many issues surrounding CF carrier screening is the potential systemwide savings or costs if large numbers of individuals are screened. Examining cost-effectiveness for CF carrier screening, however, is fraught with technical and social pitfalls. In 1983, 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 rests in its potential for providing people with information they consider beneficial for autonomous reproductive decision-making. In short, personal considerations of having information-as well as societal considerations of avoiding eugenics, stigmatization, and discrimination—outweigh considerations of cost-effectiveness. There is no intimation in OTA's analysis that something that saves or costs money is more or less desirable from a welfare standpoint. Nevertheless, while a cost-effectiveness analysis of CF carrier screening is useful to examine issues of resource allocation, some will find it offensive that such calculations are even performed in the context of genetic screening, since at its core it involves the potential to terminate affected pregnancies.

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 result in a net negative output to the economy over no screening. In the remaining scenarios, 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 costs in nearly all scenarios is free. 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.

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