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# Prenatal Screening for Cystic Fibrosis Carriers: An Economic Evaluation

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## Summary

**The cloning of the CFTR gene has made it technically possible to avert the unwanted birth of a child with cystic fibrosis (CF). Several large trials offering prenatal CF carrier screening suggest that such screening is practical and that identified carriers generally use the information obtained. Therefore, a critical question is whether the cost of such screening is justified. Decision analysis was performed that used information about choices that pregnant women were observed to make at each stage in the Rochester prenatal carrier-screening trial. The cost of screening per CF birth voluntarily averted was estimated to be $1,320,000–$1,400,000. However, the lifetime medical cost of the care of a CF child in today's dollars was estimated to be slightly >$1,000,000. Therefore, despite both the high cost of carrier testing and the relative infrequency of CF conceptions in the general population, the averted medical-care cost resulting from choices freely made are estimated to offset ~74%–78% of the costs of a screening program. At present, if it is assumed that a pregnancy terminated because of CF is replaced, the marginal cost for prenatal CF carrier screening is estimated to be $8,290 per quality-adjusted life-year. This value compares favorably with that of many accepted medical services. The cost of prenatal CF carrier screening could fall to equal the averted costs of CF patient care if the cost of carrier testing were to fall to $100.**

## Introduction

Cystic fibrosis (CF) (MIM 219700) is the most common serious genetic disease in Caucasians (Welsh et al. 1995). Treatment, although improving, remains burdensome and expensive. Until markedly improved treatment is available, prevention deserves consideration. Prevention involves offering population carrier screening before or early in pregnancy, prenatal diagnosis of carrier couples, and selective pregnancy termination. The cloning of the CFTR gene (Riordan et al. 1989; Rommens et al. 1989) has made population carrier screening possible. Several features of CF screening have raised serious concerns, including the very large number of potential testees, the imperfect sensitivity of the test, and the significant cost of the test.

Since genetic screening is expensive, there is increasing pressure to weigh the benefits of screening programs against their costs. Economic evaluations have been performed for a number of types of genetic screening—for example, carrier screening for Tay-Sachs (Nelson et al. 1978) and for beta-thalassemia (Attanasio et al. 1980; Ostrowsky et al. 1985; Old et al. 1986; Modell and Kuliev 1991), prenatal screening for Down syndrome (Hagard and Carter 1976; Sadovnick and Baird 1981; Gill et al. 1986) and for neural tube defects (Chamberlain 1978; Henderson 1982; Modell and Kuliev 1993), and newborn screening for phenylketonuria (Barden et al. 1984).

When the U. S. Congress Office of Technology Assessment (1992) analyzed CF carrier screening, it found a paucity of experience-based data on the general public's attitudes toward key factors such as willingness to undergo CF carrier screening and to terminate CF affected pregnancies. We recently have reviewed published trials of prenatal CF carrier screening (Rowley et al. 1997). A trial that we have conducted in Rochester, NY (Loader et al. 1996), assessed what proportion of pregnant women are likely to be offered screening and what proportion are likely to accept the test if it is offered free by their own physician. Women found to be carriers generally followed through with partner testing and, if they were found to be at risk, with prenatal diagnosis. Women who would not consider pregnancy termination for CF generally declined screening.

In this article, we use data from the Rochester trial for an economic evaluation of population carrier screening. We present data intended to answer the following questions: (1) what is the cost per CF birth voluntarily averted? (cost-effective analysis), (2) to what extent is

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this cost balanced by costs of medical care averted? (cost-benefit analysis), (3) how is the evaluation altered by consideration of the effect that CF has on the quality of life of the child and parent? (cost-utility analysis), and finally, how are future technological changes apt to affect CF carrier screening cost-effectiveness?

This analysis does not argue for or against population carrier screening for CF. In particular, it is not intended to imply that such screening should be adopted only if it saves money; rather, the purpose of our analysis is to inform the policy-making process, a process that must take into account a variety of medical, social, and ethical perspectives.

## Methods

### *Design of Trial*

Elsewhere we have described the design and preliminary results of this study, with regard to participation by both providers (Rowley et al. 1993) and patients (Loader et al. 1996; Levenkron et al. 1997). In brief, we enlisted providers by presenting a description of the trial to the obstetrical staffs of the five hospitals in Monroe County that have delivery services. We offered both free testing to all their female patients who were of reproductive age, $\geqslant$18 years old, and free counseling of all carriers, with the understanding that providers would offer screening to all such patients, pregnant or not. Subsequently, our genetic counselor made a personal visit to each practice expressing an interest in participating, to explain the project to the office staff and to leave brochures (reproduced in Loader et al. 1996), as well as consent/decline forms, to assist the practice in the pretest education of patients.

If a patient was found to be a carrier, she was notified by telephone and was invited to receive an explanation by the project's genetic counselor. On arrival for counseling, the carrier was invited to participate in an evaluation of CF carrier screening involving both the completion of several questionnaires and follow-up. At the time of counseling, the manifestations, inheritance, and treatment of CF, as well as the patient's options, were presented; the patient's questions were answered; and the patient was offered carrier testing of the fetus's father (hereafter called "partner").

If the partner was tested and found to be negative, the patient was informed that the residual probability of having a child with CF in any given pregnancy was ~1/666. If the partner tested positive, the couple was invited for a more detailed description of the clinical manifestations and management of CF and was offered prenatal diagnosis. Of the 4,879 women tested, 124 were found to be CF carriers. Of these 124, 106 partners (85%) were tested. In 5 of these 106 couples, the partner also was shown to be a carrier, and prenatal diagnosis was chosen by 4 of these 5 couples. At least three of the four couples having prenatal diagnosis said that they would terminate if the fetus were affected (the fourth couple was not resolute), although none of the fetuses proved to be affected. Ninety percent of the 4,879 women tested were pregnant; providers did not find the offering of testing to nonpregnant women to be an urgent matter. Among pregnant women, the acceptance rate was 57%.

### *Methods of Economic Analysis*

For this analysis, we adopted the perspective of society; that is, we attempted to include all significant costs, regardless of the identity of the payer. The family was chosen as the unit of analysis, in order to consider the impact on the quality of life and earnings of parents having a CF child and the effect that the risk had on their reproductive plans. For each couple, the calculations consider only a single pregnancy, unless the couple terminates a pregnancy because of CF; in such a case, a replacement pregnancy also is considered.

The economic appraisal was included prospectively as part of a clinical trial, as suggested by Drummond and Davies (1991). Our CF carrier screening trial differed from many others in one regard that significantly affects costs. Many trials have been conducted, predominantly in teaching hospitals, and, in some cases, the offer of screening has been made by research staff. To identify outcomes likely to occur should CF carrier screening become widespread, our trial was region wide, utilized all providers willing to participate, and involved the offer of screening by patients' own physicians or the physicians' staffs. The economic result is a saving of the cost of pretest education by a genetic professional, although, as has been noted elsewhere (Loader et al. 1996), a cost was incurred in terms of imperfect understanding of the fact that a negative test result does not guarantee that one cannot have a child with CF.

Most of the probabilities used in this analysis reflect the data collected in our trial. Two exceptions should be noted here. First, although five pregnancies underwent prenatal diagnosis, one pregnancy was lost shortly thereafter, presumably as a result of the procedure. This 20% loss rate from amniocentesis is not used in the calculation, because the loss rate in large series is only ~0.3% (National Institute of Coronary Heart Disease National Registry for Amniocentesis Study Group 1976) and, therefore, has not been included in our calculations. Second, none of the six pregnancies at risk involved a homozygously affected offspring. Yet, one can be confident that, in a large series, close to 25% of the fetuses will have CF; and therefore a value of 25% is used in the analysis.

In contrast to the probabilities, the cost estimates, in many cases, are derived from national samples. We did not use our actual cost of laboratory testing, because the latter was performed under contract, at less than the current commercial price. We also did not use Rochester figures for the cost of care of a CF child, because Rochester traditionally has had health-care costs below the national average. The software package used was SMLTREE (Hollenberg 1988).

### *Assumptions*

It is generally agreed that individuals who are close adult relatives of either persons with CF or known CF carriers and who are planning to have children should be offered carrier testing ("Genetic Testing for Cystic Fibrosis" statement of the National Institutes of Health [1997]). Of the 4,879 women screened in our study, only 7 indicated that they or their partner had such a family history. Therefore this analysis assumes that no one offered testing had such a family history.

We have assumed that women are tested only when pregnant. In the trial that we conducted, even though we urged obstetrician-gynecologists to offer screening to all their patients, pregnant or not, and although testing and carrier counseling were offered free, 90% of the women who actually were offered screening were pregnant. Therefore, on these grounds and others, we are confident that, in a nonresearch setting, those who are offered screening will be predominantly pregnant women.

We also have assumed that screening will be offered in time for the consideration of prenatal diagnosis, should the couple be found to be at risk. If the sample tested is blood, as was the case for most of our patients, the sample is conveniently collected when blood is drawn for other purposes, during the first prenatal visit. In our study, only 1 of the 109 pregnant women who were identified as being carriers was too late in gestation for consideration of prenatal diagnosis. In a population in which the first prenatal visit often is late in gestation, this constraint would have to be considered. We further assumed that, if screening was declined or if the result was negative, the pregnancy was carried to term. Even though some pregnancies are lost after prenatal care is initiated, a maternal-carrier diagnosis made in that pregnancy will inform a subsequent pregnancy.

We have not taken into account the small risk of a false-positive result in carrier testing. The false-negative rate is considered under the heading of test sensitivity. We assumed that fetal diagnosis was 100% accurate, since it was offered only if both parents had a detectable mutation. We have not considered misidentification or unavailability of the fathers of the fetuses. In each pregnancy of carrier women in our study, the father allegedly was identifiable and locatable, although this may not be the case in other locales.

We have assumed that women found to be carriers are offered fetal testing only if the father of the fetus also is found to be a carrier. In our study, 0 of the 101 couples in which the woman was a carrier but in which the partner was negative requested fetal testing; all seemed reassured that their risk of having a CF child (~1/666) was acceptably low.

To estimate treatment benefits, we used a methodology known as "quality-adjusted life-expectancy analysis." In this method, published life expectancy is adjusted by health-related quality of life. For example, in traditional life-expectancy analysis, an individual is scored 1.0 for each remaining year of life and is scored 0.0 if dead. In quality-adjusted life-expectancy analysis, wellness scores of 0.0–1.0 are assigned on the basis of health-related quality of life.

To estimate the level of wellness on the 0.0–1.0 continuum, we used the time–trade-off method. In this method, the subject is offered a choice of living either for a defined period of time in perfect health or for a variable amount of time in an alternative state that is less desirable. Presumably, all subjects would choose a year of wellness versus a year with some health problem. However, by reducing the time of wellness and leaving the time in the suboptimal health state fixed (such as 1 year), an indifference point can be determined. For example, a subject may rate being in a wheelchair for 1 year as equivalent to perfect wellness for $\frac{1}{2}$ year. The time–trade-off method is appealing theoretically because it generates results conceptually equivalent to a quality-adjusted life year (QALY). The health-related quality of life was assessed, for teenage children, by asking them the question; in the case of younger children, their parents were asked the question and to adopt the child's point of view. In addition, all parents were asked not about their own health but about the effect of having a child with CF on their own quality of life. All families with CF children cared for in the Cystic Fibrosis Clinic of the University of Rochester Medical Center were invited to participate. Those participating represented the full range of severity of the disease.

These analyses assumed that the parents were each 25 years of age when the pregnancy occurred. Expected age at death was assumed to be 78.8 years for mothers, 71.9 years for fathers, 73 years for unaffected children, and 30 years for affected children (Cystic Fibrosis Foundation, personal communication). Costs were estimated in terms of 1996 dollars.

## Results

For our analysis we created a base model using the most probable assumption and conducted sensitivity analyses using a range of values for most variables.

*Estimate of Costs*

Cost estimates for the base case and sensitivity analyses are presented in table 1. Noteworthy is the recent rapid increase in annual direct medical cost of care for CF—from ~$10,000 in 1990 (U.S. Congress Office of Technology Assessment 1992) to >$43,000 today (Cystic Fibrosis Foundation, personal communication)—as a result of therapeutic advances such as lung transplantation and mucolytic therapy. CF is distinguished also by a large investment in caregiver time, estimated to average 938 h/year (U.S. Congress Office of Technology Assessment 1992). At $10/h, this amounts to $9,380. The base cost of the carrier test is assumed to be $150 (Genzyme, personal communication). In the calculation of the cost of screening, research-related activities that would not be required in a service setting were not included.

*Probabilities*

The probabilities used are summarized in table 2. We found that among pregnant women the acceptance rate for screening was 57%. Others have observed higher rates, and a rate as high as 100% is considered in the sensitivity analysis. The test sensitivity assumed for the base case analysis was 85%, for our largely Caucasian acceptor group, although Genzyme claims 90% sensitivity for persons of northern European descent for its current 70-mutation test (Klinger 1997).

Most of the women whom we identified as being carriers either had the father of the fetus tested or had a specific reason for not doing so (Loader et al. 1996). The 85% rate of partner testing is derived from our study (for 124 carriers identified, 106 partners were tested).

Since prenatal diagnosis was offered only to trait-by-trait couples, and since we identified only five of these, the acceptance rate that we observed for prenatal diagnosis—four of five, or 80%—is not considered reliable. An important determinant is whether pretest education permitted women who would not terminate an affected pregnancy to choose not to be screened. Such was generally the case in our study, as assessed by detailed questioning of acceptors and decliners of screening (even though pretest education was suboptimal in some respects, as mentioned above). Since we identified no affected fetuses, we based our rate for termination of affected fetuses (75%) on questioning at-risk couples, prior to prenatal diagnosis, about what they would do if their fetus were found to be affected. In a study of 25,000 women in Scotland, all at-risk couples found to have an affected fetus terminated the pregnancy (Brock 1996). Thus the low termination rates in couples who already have an affected child (Wertz et al. 1992) do not apply to couples whose risk is identified by carrier screening.

There is limited information on decisions made by couples whose at-risk status is identified on the basis of carrier screening—as opposed to couples whose at-risk status is identified on the basis of having an affected child—in serial pregnancies. In a small series of couples whose at-risk status was identified on the basis of having a CF child, couples who had used prenatal diagnosis in one pregnancy used it also in subsequent pregnancies (Evers-Kiebooms et al. 1990). The probabilities used are shown on a decision tree in figure 1.

*Do Costs Exceed Benefits?*

A cost-benefit analysis based on the assumptions and probabilities shown in tables 1 and 2 is shown in table 3. To calculate unit costs, it is conventional to consider the screening of a population sufficiently large to allow identification of multiple instances of the disease in ques-

**Table 1**

**Cost Values Used for Base Case and Sensitivity Analysis**

| Variable | Base Value | Sensitivity Range | Source(s) |
|---|---|---|---|
| Direct-care costs per CF child per year | $43,083 | $10,000–$60,000 | Cystic Fibrosis Foundation |
| Amount of time spent on indirect care per year | 938 h | 700–1,000 h | U.S. Congress Office of Technology Assessment (1992) |
| Indirect-care cost per hour | $10 | (Not varied) | U.S. Congress Office of Technology Assessment (1992) |
| Cost of offering screening[a] | $20 | $20–$100 | U.S. Congress Office of Technology Assessment (1992), present study |
| Cost of laboratory test | $150 | $20–$200 | Genzyme |
| Cost of counseling carriers | $150 | $100–$200 | Market survey |
| Cost of couple counseling | $60 | (Not varied) | Present study |
| Cost of prenatal diagnosis | $900[b] | (Not varied) | Present study |
| Cost of termination | $900 | $400–$1,200 | U.S. Congress Office of Technology Assessment (1992) |
| Cost of normal delivery | $3,700 | $1,800–$5,000 | Present study |
| Discount rate | 3% | 0%–7% | |

[a] Includes professional time, clerical time, cost of brochure, and cost of consent form.
[b] Includes cost of amniocentesis ($315) and cost of DNA analysis ($585).

**Table 2**

**Probability Estimates Used in Base Case and Sensitivity Analysis**

| Variable | Base Value | Sensitivity Range | Source |
|---|---|---|---|
| Woman chooses to be screened | .57 | .20–1.0 | Loader (1996), present study |
| Woman or partner is a carrier | .04 | (Not varied) | U.S. Congress Office of Technology Assessment (1992) |
| Sensitivity of screening test | .85 | .75–.90 | Cutting (1997), Klinger (1997) |
| Partner tested if woman is a carrier | .85 | .5–1.0 | Present study |
| Prenatal diagnosis if couple is at risk | .80 | .5–1.0 | Present study |
| Prenatal diagnosis reveals affected fetus | .25 | (Not varied) | |
| Abortion of first affected fetus | .75 | .5–1.0 | Present study |
| Replacement of affected fetus | 1.0 | 0–1.0 | Garber and Fenerty (1991) |
| Probability of repeat prenatal diagnosis | .80 | .5–1.0 | |
| Probability of abortion of second affected fetus[a] | 1.0 | .5–1.0 | |

[a] After abortion of a previous affected fetus.

tion. Here we postulate that screening is offered to 100,000 pregnant women. In table 3, screening costs are shown in section A, medical-care costs avoided are shown in section B, and net screening costs are shown in section C. In each of the three sections, two cases are considered: one of them assumes that a couple whose pregnancy is terminated because of CF does not replace it by another; the other assumes that a couple whose pregnancy is terminated because of CF conceives again, with the same probabilities of having a normal child or a CF child.

Section A of table 3 shows that the estimated cost of screening per CF birth voluntarily averted is $1,322,376, the assumption being that a pregnancy terminated because of CF is not replaced. If a terminated pregnancy is replaced, the cost per unwanted CF birth averted is slightly higher, $1,396,038. The reason for the higher cost is that the replacement pregnancy entails both increased costs (for additional deliveries, prenatal diagnoses, and terminations) and the additional possibility of a CF birth (because we conservatively assumed that only 80% of such couples would have prenatal diagnosis for the replacement pregnancy).

To continue the cost-benefit analysis for the population of 100,000 women offered screening described in table 3, we must calculate the cost of medical care for one individual with CF. This calculation is shown in table 4. "Direct" cost of care refers to expenses paid by either the family or its insurer. At $43,083/year for 30 years, this amounts to $1,292,490/patient. "Indirect" cost of care refers to the estimated cost of care given by parents. At an average hourly wage of $10, this amounts to $9,380/year; for the current average CF life span of 30 years, the total is $281,400. The lifetime costs for direct and indirect care thus total $1,573,890 and equal the amount saved per case averted. Since the costs of care are future costs, they must be discounted to allow for the fact that to have a given amount available at a future time requires less than that amount today, because of expected accrual. If a discount rate of 3%/year is applied, these savings are reduced to $1,028,298/CF case averted, in today's dollars.

Table 4 then calculates the cost-effectiveness of CF carrier screening, by subtracting the discounted medical-care costs avoided, $1,028,298, from the cost of averting the birth of a single unwanted CF child, as shown in section A of table 3 ($1,322,376). The net cost of screening per CF birth averted when there is no replacement is thus $294,078. The higher cost of replacement, $1,396,038, yields a higher net cost, $367,740. To express it in relative terms, the savings in medical-care costs is estimated to cover 78% of the cost of screening when there is no replacement and 74% of the cost of screening when there is replacement.

To return to the calculation at the population level, section B of table 3 calculates medical-care costs by multiplying the cost per birth averted (from table 4) by the number of such terminations (from section A of table 3). Without replacement, the 8.4 CF births averted generate a total savings of $13,220,676, which is discounted to $8,637,703; on the assumption of replacement, the 7.98 births averted generate a total savings of $12,559,642, which is discounted to $8,205,818. As shown in section C of table 3, the net cost to offer screening to 100,000 pregnant women is either $2,470,252, without replacement, or $2,934,561, with replacement; this represents a net cost of $24.70 or $29.35, respectively, per woman offered screening. From this point on in the analysis, replacement is assumed (for justification, see the Discussion section).

### *Does Consideration of the Quality of Life of Child and Parent Affect the Analysis?*

The average utilities by the time–trade-off methodology were as follows: 0.70 for affected individuals, 0.90 for their mothers, and 0.95 for their fathers. The value of .70 for affected individuals means that they reported, in effect, that they would trade 1.0 year of life with CF for 0.7 years of life without CF. Mothers reported, in effect, that they would trade l.0 year of life having a

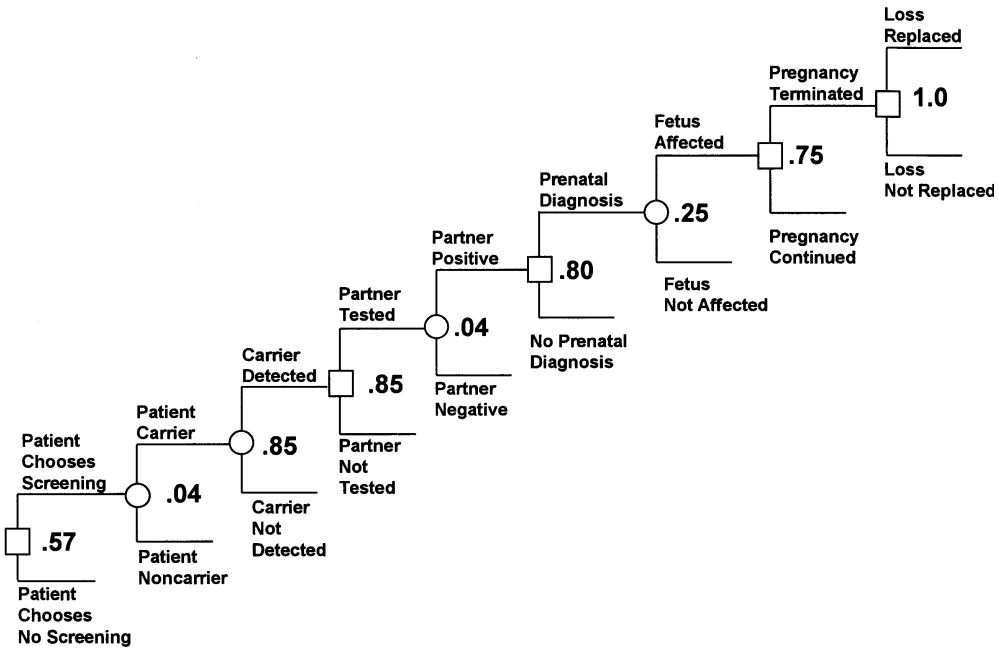


**Figure 1** Decision tree for analysis of prenatal CF carrier screening. Probabilities shown are derived from the Rochester trial (Loader et al. 1996).

child with CF for 0.9 year of life having a child without CF; fathers reported that they would trade 1.0 year of life having a child with CF for 0.95 year of life having a child without CF

A cost-utility analysis is presented in table 5. The average number of years accrued is simply the sum of the life expectancies of father, mother, and child, at the time of the CF child's birth. For the family destined to conceive a CF child, this is a large adjustment, because the CF child contributes only 30 years, whereas a healthy child resulting from the replacement strategy contributes 73 years. In terms of QALYs, the difference is larger for the affected family; for example, the 30 years expected for the CF child become only 21 QALYs (30 years × 0.7, for quality adjustment). For the whole population, this difference represents 354 years, as shown in section B of table 5. The marginal cost utility is the change in cost per QALY, as a result of the offering of testing. This value is $8,290, obtained by dividing the medical-costs difference of the two strategies ($2,934,560) by the difference in the average number of QALYs, 354, accrued by families.

### *Under What Circumstances Would the Cost of Screening Be Balanced by Averted Medical-Care Costs?*

A sensitivity analysis is presented in tables 6 and 7. In sensitivity analysis, the most uncertain features and assumptions are varied, one at a time, over a wide range of possible values. If the basic conclusions do not change when a particular feature or assumption is varied, confidence in the conclusion is increased (Weinstein and Stason 1977).

Our sensitivity analysis considered marginal cost-effectiveness—that is, the cost difference, per QALY, between the offering of screening and no offering of screening. For each variable considered, we chose a range of values intended to reflect conceivable differences among different types of populations, programs, or technologies. Variables can be classified as to whether, over the arbitrarily chosen range of variation, they had a minor, major, or dominating effect.

As shown in table 6, variables having a *minor* effect included the indirect cost of care; the costs of carrier counseling, of abortion, and of normal delivery; the probability of either prenatal diagnosis or of abortion of an affected fetus for a couple having previously aborted an affected fetus; and the quality-of-life adjustments. Variables having a *major* effect included the direct cost of care; the cost of offering screening; the sensitivity of the test; and the probabilities of choosing screening, of a carrier having her partner tested, of a carrier-carrier couple having prenatal diagnosis, and of the couple terminating the pregnancy if the fetus has CF. Finally, certain variables *dominated;* that is, in the range considered, for certain values of the variables there was no marginal cost per QALY, because the decision to test not only generates QALYs but also saves money rather than costs money. As shown in table 7, offering testing saves money if the cost of the laboratory test falls from $150 to $\leqslant$$100, if the life expectancy of a CF child increases from 30 years to $\geqslant$54 years, or if the discount

## Table 3

**Cost-Benefit Analysis: Base Case for 100,000 Screening Offers**

| A. Cost of Screening Program | | |
|---|---|---|
| No. of Individuals/Couples/Fetuses or Type of Cost | Unit Cost or Rate/Probability | Total |
| Without replacement: | | |
| Women offered screening = 100,000 | × Cost of offering test = $20 | = $2,000,000 |
| Women accepting = 100,000 | × 57% Acceptance rate | = 57,000 Women |
| Women tested = 57,000 | × Cost of testing = $150 | = $8,550,000 |
| Women tested = 57,000 | × Carrier rate = .04 × test sensitivity = .85 | = 1,938 Carriers identified |
| Carriers counseled = 1,938 | × Cost of counseling = $150 | = $290,700 |
| Carriers counseled = 1,938 | × 85% of partners tested | = 1647.3 Partners tested |
| Partners tested = 1647.3 | × Cost of testing = $150 | = $247,095 |
| Partners tested = 1647.3 | × Carrier rate = .04 × test sensitivity = .85 | = 56 Couples at risk |
| Couples at risk = 56 | × Cost of repeat counseling = $60 | = $3,360 |
| Couples at risk = 56 | × Probability of accepting PD = .80 | = 44.8 Couples having PD |
| Couples having PD = 44.8 | × Cost of PD = $900 | = $40,320 |
| Couples having PD = 44.8 | × Probability of affected fetus = .25 | = 11.2 Affected fetuses |
| Affected fetuses = 11.2 | × Probability of termination = .75 | = 8.4 Terminations |
| Terminated pregnancies = 8.4 | × (Cost of termination − averted cost of delivery) = (−$2,800) | = −$23,520 |
| Total cost/100,000 women offered screening | | = $11,107,955 |
| Cost of screening per CF birth voluntarily averted | (Total cost of screening = $11,107,955) ÷ (no. of terminations = 8.4) | = $1,322,376 |
| With replacement: | | |
| Terminations = 8.4 | × Probability of replacement of aborted fetus = 1 | = 8.4 Pregnancies |
| Pregnancies = 8.4 | × Probability of having PD = .80 | = 6.72 Couples having PD |
| Couples having PD = 6.72 | × Cost of PD = $900 | = $6,048 |
| Couples having PD = 6.72 | × Probability of affected fetus = .25 | = 1.68 Affected fetuses |
| Affected fetuses = 1.68 | × Probability of termination = 1 | = 1.68 Terminations |
| Terminations = 1.68 | × Cost of termination = $900 | = $1,512 |
| Replacement fetuses carried to term = 6.72 | × Cost of delivery = $3,700 | = $24,864 |
| Extra cost of replacement | | = $32,424 |
| Total cost/100,000 women offered testing | $11,107,955 + $32,424 | = $11,140,379 |
| Replacement fetuses = 8.4 | × (1 − Probability of having PD) = .2 | = 1.68 Couples not having PD |
| Couples not having PD = 1.68 | × Probability of affected fetus = .25 | = .42 CF births |
| CF births averted from first pregnancy = 8.4 | − No. of CF births from second pregnancy = .42 | = 7.98 CF births averted |
| Cost of screening per CF birth voluntarily averted | (Total cost of screening = $11,140,379) ÷ (no. of CF births averted = 7.98) | = $1,396,038 |

| B. Medical-Care Costs Avoided | |
|---|---|
| Type of Cost | Total |
| Without replacement: | |
| Total cost (direct + indirect) = $1,573,890[a] × 8.4 CF births averted | = $13,220,676 |
| Total cost discounted at 3% | $8,637,703 |
| With replacement: | |
| Total cost (direct + indirect) = $1,573,890[a] × 7.98 CF births averted | = $12,559,642 |
| Total cost discounted at 3% | $8,205,818 |

| C. Screening Costs | | |
|---|---|---|
| | Without Replacement | With Replacement |
| Total screening costs | $11,107,955 | $11,140,379 |
| Care costs avoided | $8,637,703 | $8,205,818 |
| Net screening costs | $2,470,252 | $2,934,561 |

NOTE.—PD = prenatal diagnosis.

[a] From table 4.

**Table 4**

**Summary of Analysis of Cost per CF Birth Averted**

| A. Medical-Care Costs Avoided per CF Birth Averted | |
|---|---|
| Type of Cost | Total |
| Direct: \$43,083/year × 30 years | = \$1,292,490 |
| Indirect: \$10/h × 938 h/year × 30 years | = \$281,400 |
| Total | \$1,573,890 |
| Total discounted at 3% | \$1,028,298 |

| B. Screening Costs per CF Birth Averted | | |
|---|---|---|
| | Without Replacement | With Replacement |
| Total screening costs | \$1,322,376 | \$1,396,038 |
| Care costs avoided discounted at 3% | −\$1,028,298 | −\$1,028,298 |
| Net screening costs | \$294,078 | \$367,740 |

rate falls from 3% to $\leqslant$0.9%; in contrast, offering testing both costs money and decreases QALYs if the probability that a pregnancy follows abortion of an affected fetus falls to <.25.

### *How Much Is CF Screening Worth to Patients?*

Although our study offered free screening, we asked, when women accepted, how much they would be willing to pay for it had there been a charge. The results are shown in table 8. The answer chosen by the vast majority was the cheapest of the alternative answers provided, \$0–25, a price far below the current commercial charge.

## Discussion

The adoption of new health-care services is constrained by limited health-care resources. As a result, economic analysis is appropriate before new services are adopted. An economic analysis attempts to identify and quantitate all relevant variables. These include all health benefits and burdens and all current and future costs and savings. This study considered the value of prenatal CF carrier screening by using three different analytic approaches. One approach evaluated the net cost of screening, or cost-benefit; a second approach analyzed cost-utility, which takes into account quality of life; a third approach examined patient willingness to pay for the service.

### *The Cost-Benefit Approach*

The results of our analysis show that, given our baseline assumptions, the costs of screening are not offset by the expense avoided. Even though the costs of caring for an affected child are substantial, identification of an affected fetus is a relatively rare event. In Rochester, 4,879 tests resulted in identification of only five at-risk couples.

Nevertheless, the costs of screening would be balanced by the medical-care costs averted if there should be a change, in a favorable direction, in any one of several variables (table 7). Some of the changes listed are unlikely to occur. For example, it is unlikely that a discount rate of <0.9% would ever be justified. A mean life expectancy of $\geqslant$54 years for an individual with CF would require unanticipated improvements in management. However, a decrease in test cost to <\$100 is a distinct possibility. The recent National Institutes of Health recommendation for routine prenatal CF carrier screening ("Genetic Testing for Cystic Fibrosis" statement of the National Institutes of Health 1997) may increase the utilization of carrier screening and ultimately increase competition among laboratories, reducing the cost of testing. Furthermore, hybridization to high-density oligonucleotide arrays can provide efficient screening for large numbers of mutations (Chee et al. 1996) and ultimately may reduce costs.

Our economic analysis did not take into consideration the anxiety associated with testing, except as it was reflected in choices that individuals made. We have since conducted a 1-year follow-up of women identified as being carriers and have found that most women identified as being carriers were, in retrospect, content with the screening decision that they had made (Levenkron et al. 1997). On the benefit side, we did not consider that the individual identified as a carrier (*a*) is informed for any subsequent pregnancy and (*b*) may alert relatives to their increased risk. Thus there are potential benefits beyond the pregnancy in which testing occurs.

### *The Cost-Utility Approach*

The second model used cost-utility analysis. Cost-utility analysis may be preferable to cost-effectiveness analysis in cases in which the quality of life is the most important outcome characteristic (Drummond and Davies 1991). In contrast to the cost-benefit model, which creates a ratio of treatment costs to costs averted, the cost-utility model considers the cost necessary to achieve

**Table 5**

**Cost-Utility Analysis for Screening Assuming Replacement**

A. Base Case for Screening Offered to 100,000 Women

| Category | Total |
|---|---|
| I. Test not offered: | |
| 100,000 Pregnant women × carrier rate = .04 | = 4,000 Carriers |
| 4,000 Carriers × carrier rate for spouse = .04 | = 160 Couples at risk |
| 160 Couples at risk × probability of affected fetus = .25 | = 40 CF children |
| Medical cost: | |
| Per CF child, discounted at 3% (from table 4) | $1,028,298 |
| For 40 CF children = 40 × $1,028,298 | = $41,131,920 |
| Life years expected: | |
| CF present: | |
| Individual with CF: 30 years × .7 quality adjustment | = 21.0 years |
| Mother: 78.8 − 25 (current age) = 53.8 years × .9 quality-of-life adjustment | = 48.4 years |
| Father: 71.9 − 25 (current age) = 46.9 years × .95 quality adjustment | = 44.6 years |
| Total | = 114.0 years |
| CF absent: | |
| Individual without CF | = 73.0 years |
| Mother | = 53.8 years |
| Father | = 46.9 years |
| Total | 173.7 years |
| Per 100,000 families with pregnancies: | |
| 40 CF families × 114 years | = 4,560 years |
| 99,960 Non-CF families × 173.7 years | = 17,363,052 years |
| Total | = 17,367,612 years |
| II. Test offered: | |
| No. of CF children: 40 − 7.98 CF births averted (from table 3) | = 32.02 |
| Medical-care costs (discounted at 3%) for 32.02 CF children × $1,028,298 | = $32,926,101 |
| Life years expected, for families with: | |
| CF child: 32.02 × 114 years/family | = 3,650.3 years |
| No child: 1.68 × (53.8 + 46.9) years/family | = 169.2 years |
| Normal child: 99,966.3 × 173.7 years/family | = 17,364,146.3 years |
| Total | = 17,367,965.8 years |
| Cost of offering screening (from table 3) | $11,140,379 |
| Total costs of screening (discounted medical costs + screening costs) | $44,066,480 |

B. Marginal Cost-Utility

| | Without Screening | With Screening | Difference |
|---|---|---|---|
| Medical-care costs | $41,131,920 (care of 40 CF children) | $32,926,101 (care of 32.02 children) | |
| Screening costs | 0 | $11,140,379 | |
| Total costs | $41,131,920 | $44,066,480 | $2,934,560 |
| QALYs | 17,367,612 | 17,367,966 | 354 |
| Marginal cost per QALY | | | $290 |

the equivalent of 1 year of healthy life. The method uses a metric, QALY, that adjusts life expectancy for quality of life. In traditional life-expectancy analysis, each individual in a birth cohort is coded as 1.0 for each remaining year of life and is coded as 0 if dead. Quality-adjusted life-expectancy analysis assigns wellness scores of 0.0–1.0 on the basis of health-related quality of life.

The estimates of the cost necessary to produce a QALY depend on assumptions about replacement pregnancy. If we assume that a family loses life years by terminating a pregnancy, then the program causes a loss of life years and would not be beneficial in cost-utility terms, because it would result in a net loss of family QALYs. However, if the pregnancy is replaced, then the program would produce ~354 QALYs from 100,000 screening offers. The cost to produce each additional QALY thus is estimated to be $8,290. Table 9 shows the marginal cost per QALY of the CF screening program, compared with those of many other widely advocated interventions. As the table shows, the cost-utility ratio for prenatal CF carrier screening is comparable to that for newborn screening for phenylketonuria and is more advantageous than the ratios for many widely advocated preventive interventions. Whether a preventive measure involving prenatal diagnosis and selective termination can be fairly compared with prevention measures that do not involve these choices is discussed further in the Pregnancy-Related Issues subsection (below).

In the present study, utilities were assessed by means of a time–trade-off method with individuals with CF and

**Table 6**

**Marginal Cost-Utility for Screening Assuming Replacement: Sensitivity Analysis**

| Variable (Range) | Cost per QALY for ($) | |
|---|---|---|
| | Minimum Value of Variable | Maximum Value of Variable |
| Direct-care costs per CF child per year ($10,000–$60,000) | $22,823 | $729 |
| Indirect-care costs per CF child per year (700–1,000 h) | $9,256 | $7,930 |
| Cost of offering screening ($20–$100) | $8,290 | $30,742 |
| Cost of laboratory test ($20–$200) | (Dominated [offering of test is preferred option]) | $16,466 |
| Cost of carrier counseling ($100–$200) | $7,931 | $8,477 |
| Cost of termination of pregnancy ($400–$1,200) | $8,190 | $8,213 |
| Cost of normal delivery ($1,800–$5,000) | $8,213 | $8,198 |
| Sensitivity of test (.75–.90) | $16,861 | $4,909 |
| Probability that screening is chosen (.2–1) | $18,628 | $5,782 |
| Probability that partner is tested if woman is a carrier (.5–1) | $29,721 | $3,693 |
| Probability of prenatal diagnosis if both partners are carriers (.5–1) | $26,953 | $1,955 |
| Probability of abortion of affected fetus (.5–1) | $23,855 | $364 |
| Probability of pregnancy after abortion of an affected fetus (0–1) | (Dominated [no offering of test is preferred option]) | $8,290 |
| Probability of prenatal diagnosis after abortion of an affected fetus (.5–1) | $9,801 | $7,097 |
| Probability of abortion of an affected fetus after abortion of a previous affected fetus (.5–1) | $10,326 | $8,290 |
| Quality-of-life adjustment for mother of CF child (.2–.95) | $4,437 | $8,734 |
| Quality-of-life adjustment for CF child (.1–1.0) | $5,836 | $10,293 |
| Life expectancy of CF child (30–73 years) | $8,290 | (Dominated [offering of test is preferred option]) |
| Discount rate (0%–7%) | (Dominated [offering of test is preferred option]) | $16,710 |

their parents. It is acknowledged that the time–trade-off method asks subjects to make judgments in hypothetical situations that many patients find difficult to make. A possible bias is for such individuals to minimize the toll that CF exacts. However, if the burden thus estimated has been underestimated, the benefit of screening also has been underestimated. A few might even argue that having a child with CF improves rather than impairs health-related quality of life. Some parents report a higher degree of satisfaction and bonding with children who confront serious health problems (Botkin 1990; Hilgers and Horan 1972). Another concern with quality-of-life adjustment is that we used a constant value for the adjustment over the whole course of the disease, rather than illness-stage–specific values. Thus the adjustment must be considered to be very crude.

### *The Willingness-to-Pay Approach*

For most consumer services and products, market forces influence price. Health-care services are different. Medical care is unusual because there is often no clear connection between price and consumer willingness to pay.

The willingness-to-pay approach to valuation of health services is considered to have the advantage of enabling the respondent to express the benefits of health care in terms of their effect on quality of life, as well as on quantity of life. This approach was used by Miedzybrodzka et al. (1995) and Donaldson et al. (1997) in comparisons of stepwise versus couple-carrier screening for CF.

In the present study, women were asked what they would be willing to pay for the genetic-screening test if it were not covered by insurance. The modal response (77%) was $\leqslant$\$25. Nearly 94% of the respondents would pay $\leqslant$\$50 for the test. It was similar for the 427 women who declined screening. On the one hand, these findings may suggest that women may not be unusually concerned about obtaining screening. On the other hand, in asking subjects how much they would be willing to pay for CF screening, we found that people had great difficulty in providing an estimate. One reason is that many people do not receive bills for laboratory tests and therefore have no frame of reference for answering such a question.

### *Economic Feasibility of Widespread CF Carrier Screening*

At the time of the writing of this article, it was unclear how widely the National Institutes of Health recom-

**Table 7**

**Threshold Values for Cost-Utility for Screening Assuming Replacement**

| Variable | Base-Case Value | Option That Becomes Dominant | When Variable Is Changed To |
|---|---|---|---|
| Cost of laboratory test | $150 | Offer screening | <$100.35 |
| Life expectancy of CF child | 30 years | Offer screening | >53.8 years |
| Discount rate | 3% | Offer screening | <.9% |
| Probability of replacement of aborted fetus | 1.0 | Do not offer screening | <.24 |

mendation to routinely offer prenatal CF carrier screening will be adopted. If it is widely adopted, there will be pressure on third parties to pay for it even though the costs are immediate whereas the economic benefits are delayed. However, if such screening does not become routine, our studies suggest that it is unlikely that many providers will offer it or that many patients without a family history of CF will request it. Patients are unlikely to pay for screening themselves because of a generally modest interest in being tested, the test's current significant cost, and their being unaccustomed to paying out-of-pocket for prenatal care.

### *Methodological Issues*

*1. Quantifiability.*—Botkin (1990) lists some intangible benefits and harms that may be associated with prenatal screening—for example, anxiety generated by the testing procedure and by waiting for the result, reassurance associated with receiving a normal result, and anguish associated with the abortion of an abnormal fetus. He concludes that cost-benefit approaches are too crude for dealing with the value-laden issues associated with prenatal screening and that utilitarian considerations will not produce a clear and morally acceptable standard by which resources can be distributed, without our placing explicit values on complex intangibles, including the social worth of a disabled child. The quality-of-life adjustment may be too crude to identify those subtle variations in psychological state.

*2. Pregnancy-related issues.*—Morris (1994) has criticized analyses of prenatal screening programs by cost-benefit methods on the grounds that they fail to quantify psychological effects, in three regards. First, in such programs, prevention necessarily involves pregnancy termination, and abortion is not an option for many women. Second, he states that those who do countenance abortion do not agree on what fetal conditions justify it and that abortion for a given condition may stigmatize persons with that condition. Third, he fears that a prevention-oriented screening program may replace the individual's appreciation for the value inherent in raising a disabled child.

**Table 8**

**Amount That Women Would Be Willing to Pay for Screening**

| Cost Range ($) | No. of Women | Percentage |
|---|---|---|
| 0–25 | 1,678 | 77.2 |
| 26–50 | 371 | 17.1 |
| 51–75 | 68 | 3.1 |
| 76–100 | 30 | 1.4 |
| 101–125 | 8 | .4 |
| 126–175 | 1 | .0 |
| 176–250 | 4 | .2 |
| >250 | 14 | .6 |

We acknowledge that pregnancy termination is not regarded as an option by all patients, even when the fetus is shown to have the genotype for a serious genetic disease—and that this is particularly so for a disease that confers neither mental retardation nor malformations. In such a context, it is especially important that a projection of outcomes utilizes data on choices that couples are observed to make in this situation, as we have tried to do.

The results of our analysis are very sensitive to assumptions about replacement. First of all, we acknowledge that our analysis, insofar as we have assumed replacement, is making an analogy between a replacement pregnancy and effective treatment of the affected fetus, an analogy that many would not accept.

Typically, cost-utility analysis begins at birth. Thus, therapeutic abortion is not associated with either gains or losses of life years. Once a child is born, years of life accrue. A child with CF would have fewer QALYs than would a well child. Thus, in the analyses shown in tables 5–9, we have assume that an aborted pregnancy will be replaced by another pregnancy. Since there are few published data on serial pregnancies in couples whose risk of having a CF child is discovered by carrier screening, we have adopted the assumption made by Garber and Fenerty (1991)—that, since the desire to give birth to an unaffected child is the primary reason for testing, individuals who choose testing and who terminate a pregnancy for CF would be expected to pursue a replacement strategy.

An alternative scheme begins cost-utility analysis at conception or at the time when a fetus becomes physiologically viable. Thus, an aborted fetus could accrue the number of QALYs equal to the total life expectancy (Ganiats 1996). Similarly, the estimate of the family life-

**Table 9**

**Marginal Cost per QALY for Selected Preventive Measures**

| Intervention | Marginal Cost per QALY[a] ($) | Reference |
|---|---|---|
| Pneumococcal vaccine for elderly | 1,765 | U.S. Congress Office of Technology Assessment (1979) |
| Postpartum anti–rhesus D injection | 2,109 | Torrance and Zipursky (1984) |
| Smoking-cessation counseling | 6,463 | Schulman and Linas (1997) |
| $T_4$ thyroid screening | 7,595 | Epstein et al. (1981) |
| Prenatal CF carrier screening[b] | 8,290 | Present study |
| Newborn phenylketonuria screening | 8,498 | Bush et al. (1973) |
| Postmenopausal estrogen therapy | 32,057 | Weinstein (1980) |
| School tuberculin-testing program | 43,250 | Bush et al. (1972) |
| Screening mammography | 167,850 | Eddy (1989) |

[a] Costs are adjusted to current dollar values.
[b] This preventive measure, unlike the others, involves prenatal diagnosis and selective pregnancy termination.

years would be those of the parents, less those that would have accrued to the aborted fetus. We believe that such an accounting system would be unusual and not clearly justified. However, we have included this case in the analysis, within the category termed "without replacement." In view of the small number of terminated pregnancies, the replacement variable had only a small effect on average life-years per family, but it did swing the conclusion either away from screening, if there were no replacement, or toward screening, if replacement were assumed.

With regard to the accounting for the costs of a terminated pregnancy, there is some inconsistency in the literature . Ganiats (1996) reviewed the 41 English-language papers published during 1993–96, using "amniocentesis," "cost," and "quality of life" as the search terms. The dominant methodology was to value impact on patients, without attempting to consider life lost by the aborted fetus. The difficulty is that the analyses often account for medical savings that are prevented through pregnancy termination, without considering any potential benefits that would accrue if the pregnancy were completed.

*3. Unaffected children.*—Another important assumption was the exclusion of medical-care costs incurred for unaffected children. Many analysts believe that these costs should be included. Children accrue medical-care costs, whether or not they are affected by CF. The issue is the differential health-care cost; in other words, what are the incremental expenditures required for a child with an illness such as CF? Although this is an interesting philosophical issue, using incremental costs in this analysis would not have altered the conclusions.

*Discounting.*—Although there is no question that future costs must be discounted, there is currently a difference of opinion about which discount rate is most appropriate. Although a 5% rate traditionally has been used, a rate of 3% recently has been recommended (Weinstein et al. 1996). A broad range of discount rates (0%–7%) is included in the sensitivity analysis.

Some also would discount expected years of life, on the grounds that persons may value future benefits less they value than current benefits. However, we have not chosen to do this, since such discounting is based not on any economic reality (Ganiats 1996) but, rather, perhaps, on a psychological bias that may not merit being promoted.

### *Limitations*

*1. Comprehensiveness.*—In our model system, even with economic barriers removed, screening proved to be very incomplete. The probability that a fetus with a CF genotype who was carried by a woman in our region during the period of study would have been identified in our trial can be calculated as follows: (proportion of providers offering screening = 30%) × (proportion of pregnant women accepting screening = 57%) × (proportion of carriers identified = 85%) × (proportion of carrier women having their partners tested = 85%) × (proportion of at-risk couples who accept prenatal diagnosis = 80%) = 9.9%. In other words, despite the offer of free testing and counseling, which was made known to all prenatal-care providers, the chance that an affected fetus in this region during this time period would have been identified was <1/10. The greatest barrier to universal screening was that fewer than one-third of the providers offered screening. The second greatest barrier was patient reluctance to accept screening. However, insofar as our 57% patient-acceptance rate was based on an understanding of the significance of what was being offered, one cannot wish that it had been higher; the foremost purpose of prenatal screening is not to reduce the incidence of genetic disease but to fulfill a couple's reproductive goals.

*2. Unidentified burdens.*—We are aware that burdens

to be encountered elsewhere may have gone undetected in Rochester. Rochester is a community with low unemployment and an extensive health-care system.

Although we offered participation to all prenatal-care providers in the county, only a minority submitted samples, and this minority may have accorded a higher priority to such screening and therefore may have devoted more effort to it than would providers who offer screening only because of external pressures. Providers who feel coerced may spend even less time educating patients, with consequently less favorable outcomes.

### *Comparison with Other Analyses of Cost-Effectiveness of CF Carrier Screening*

Economic analyses of population carrier screening for CF also have been reported by others. Garber and Fenerty (1991) found a small surplus of economic benefits over costs if any fetus lost because of a prenatal diagnosis of CF was followed by the birth of a healthy child, but not otherwise. Mennie et al. (1992) predicted an excess of economic benefits over costs but assumed a very low test cost and, apparently, that 100% of partners of carriers would be tested. Wilfond and Fost (1992) estimated a cost of $2,400,000/CF child averted; however, they assumed that everyone screened would receive professional genetic counseling, whether identified as being a carrier or not, and that only a small proportion of trait-by-trait couples would be willing to undergo prenatal diagnosis. However, professional genetic counseling for those testing negative is unlikely to be prescribed, and our study found that, even in a primary-care setting, women who were not interested in prenatal diagnosis generally declined the offer of screening.

The detailed study by the U.S. Congress Office of Technology Assessment (1992) concluded that an excess of costs over benefits was likely unless either the test cost <$100 or all at-risk couples had prenatal diagnosis and terminated the pregnancy if the fetus were identified as being affected. Their analysis assumed that screening would be preconceptional; this type of screening is less efficient, because some of the identified carriers never become pregnant. In fact, our study found that obstetrician-gynecologists generally did not offer screening to nonpregnant women, because it was less convenient or appeared to be less urgent.

Asch et al. (1993) estimated the cost per CF birth averted as being $449,823 for two-step screening but $821,692 for couple screening. "Couple screening" is the screening of both members of a couple at the same time and informing them about carrier status only if both of them are carriers. Brock (1996) prefers couple screening over the two-step method employed here, because it avoids the anxious period, in two-step screening, between informing a woman that she is a carrier and receiving a negative result for her partner. However, the couple method is even more expensive per CF birth averted, because it requires the testing of every partner, not just partners of carriers. More recently, Asch et al. (1996) have compared 15 strategies for prenatal CF carrier screening and have discussed thoughtfully the special issues that complicate the economic analysis of genetic screening for reproductive purposes.

Lieu et al. (1994) reported a cost of $1,411,000/unwanted CF birth averted and that the principal determinants were test cost, test sensitivity, and the proportion of at-risk couples choosing prenatal diagnosis. Analyses also have been conducted in the United Kingdom (Watson et al. 1991; Cuckle et al. 1995), Denmark (Schwartz et al. 1993), and Israel (Ginsberg et al. 1994).

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## Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for CF [MIM 219700])

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