"Carrier Screening for Cystic Fibrosis: Costs and Clinical Outcomes"

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Carrier Screening for Cystic Fibrosis: Costs and Clinical Outcomes

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Abstract

Background. Approximately one in 25 Caucasians in the US carries the gene for cystic fibrosis (CF), and approximately one in 2,500 babies born is affected. The discovery of the CF gene offers the possibility of population-based carrier screening that might reduce the number of affected children born. Many alternative carrier screening strategies are possible, with different clinical, economic, and ethical outcomes.

Methods. We used decision analysis to compare the outcomes of 12 alternative carrier screening strategies and a no screening alternative.

Results. A sequential screening strategy has the lowest cost per CF birth avoided. In this strategy, the first partner is screened with a standard test. The second partner is screened with an expanded test if the first partner’s screen is positive. This strategy prevents 75% of anticipated CF births at a cost of $367,000 each. The cost per CF birth avoided is approximately half this figure when couples plan two children. Even so, this figure assumes that couples who identify a pregnancy at risk will choose to terminate it.

Conclusions. The cost-effectiveness of CF carrier screening depends greatly on couples’ reproductive plans. Carrier screening is expensive but the cost per CF birth avoided can be less than the cost of managing CF when couples plan more than one child and will terminate affected pregnancies. These conclusions are important for the case of CF, and possibly for other genetic screening programs in the reproductive setting.

MeSH Terms: Cost-Effectiveness, Cystic Fibrosis, Decision Making, Economics, Ethics, Genetics, Health Policy, Health Screening, Methodology, Modeling
Approximately one in 25 Caucasians in the US carries the gene for cystic fibrosis (CF), and approximately one in 2,500 babies born is affected. Most of these children are born to couples without a family history of CF who learn they are carriers only through the birth of an affected child. The recent discovery of the CF gene has offered the possibility of population-based CF carrier screening that might identify these carriers in advance. However, the identification of hundreds of distinct mutations makes it impractical to screen for all of them. For this reason, most DNA-based screening tests for only five or six of the most common mutations representing in aggregate about 85% of carriers.

Population-based CF carrier screening is controversial, in part because genetic screening in the setting of reproductive planning raises important social and ethical issues, and also because even very good tests perform poorly when applied to low prevalence conditions. Furthermore, the application of CF carrier screening is not limited to a single clinical strategy. Many plausible strategies may be constructed using different decision rules for proceeding to further testing or deciding whether to continue a pregnancy.\textsuperscript{1} In turn, each strategy yields different clinical and economic outcomes. Thus, the clinical question is not only whether widespread CF carrier screening should be done but how it should be done.

We used a decision analytic model to define the clinical and economic outcomes expected from several plausible population CF carrier screening strategies.

Methods

Decision analysis is a quantitative method of evaluating the consequences of alternative programs. The model has three main components: A basic tree structure that reflects the alternative clinical strategies; the probabilities associated with chance events given each strategy; and the clinical and economic consequences of those chance events. The decision model was constructed using Microsoft Excel 4.0 for the Macintosh computer.
Subjects

The model considers only single gestations carried by women with no independent reason for undergoing amniocentesis other than the possible results of CF carrier screening. The model also considers only women with identifiable reproductive partners who also can be screened if necessary. However, the risk of nonpaternity is incorporated into the sensitivity analysis.

Clinical Strategies

Each clinical strategy evaluated was composed of a plausible arrangement of the following component tests.

*Standard Mutation Analysis.* Most centers that screen for CF mutations employ a battery of tests targeted at about five to ten common mutations that in aggregate represent approximately 85% of CF alleles (for example, ΔF508, G542X, G551D, R553X, N1303K, W1282X, ΔI507). Members of a couple are screened in parallel or in series. For example, in one parallel strategy both partners undergo standard screening and the couple proceeds to prenatal diagnosis with amniocentesis if both partners are found to screen positive. In one sequential strategy, one partner is screened first; the second partner is screened only if the first screens positive; and the couple proceeds to prenatal diagnosis only if both are positive.

*Expanded Mutation Analysis.* Although standard mutation batteries will identify most carriers who can be identified, one might screen for another 20 to 30 mutations beyond the standard panel. We investigated strategies that use this expanded analysis at the time of the initial screen. In addition, we considered “mixed” strategies that use the expanded analysis only after one parent screens positive on the standard battery—for example, when one and only one partner in a couple screens negative in parallel testing, or when the first partner screens positive in sequential testing.
**Microvillar Intestinal Enzyme Analysis (MIE).** Amniotic fluid activity of microvillar intestinal enzymes is lower in fetuses with CF. Measurement of these enzymes has been used for prenatal diagnosis, but it has been largely supplanted by mutation analysis. However, MIE might still be useful as an adjunct for situations in which only one partner is found to carry a detectable mutation and that mutation has been inherited by a fetus.

**Prenatal Diagnosis with Amniocentesis.** We assumed that all women who proceed to prenatal diagnosis would undergo amniocentesis for the purposes of direct mutation tests of the fetus.

In summary, several different test elements can be combined to produce an overall screening strategy. Although not every combination of these tests in every order is plausible, many are. In addition to the no screening alternative, we investigated 12 unique ways of performing population CF carrier screening. These strategies are listed in Table 1.

**Decision Tree Structure**

**Prescriptive Modeling.** We followed the conventional practice of making the model prescriptive, meaning that we evaluated strategies according to the outcomes that would result if couples followed the strategy to completion. We observed the maxim that “if you are not going to do something different with the results of a test, you should not do the test in the first place.” As a result, all strategies have the potential to lead to the termination of a pregnancy, although the strategies differ in the likelihood of this decision. For example, we assume that all couples who identify a fetus inheriting two CF mutations will terminate the pregnancy. These considerations raise important social and methodologic issues that we have discussed elsewhere. 

In some cases, couples might find themselves deciding whether to terminate a pregnancy at a relatively low risk that the fetus has inherited two mutations. We expect that few couples would elect to terminate a pregnancy under such circumstances, and so we eliminated these
strategies as described below. For strategies that remain, there may still be a difference between the resulting clinical and economic outcomes as reported by the model, and what might happen in actual practice—largely because many couples who embark on these strategies may later decide not to terminate pregnancies even at very high risk. These possibilities are reflected in the sensitivity analyses.

**Sample Tree Branches.** The many strategies evaluated makes it difficult to present the entire decision tree except as in Table 1. However, several representative tree branches are shown in Figure 1. All branches end in one of six clinical outcomes that reflect the alternatives of delivery, miscarriage, or abortion and whether the fetus or child is or is not affected with CF.

**Data, Assumptions, and Perspective**

**Probability Estimates.** Probability estimates used in the model are listed in Table 2 along with a range of plausible values to reflect uncertainty. Estimates were obtained by surveying the literature and consulting experts in obstetrics, genetics, and prenatal diagnosis. We used a plausible value for the specificity of a single-mutation screen (0.999) and adjusted this value downward to reflect changes in specificity expected when multiple screens are performed simultaneously. In the base-case analysis, the resulting specificities for the standard and expanded screening batteries were 0.995 and 0.990. Because prenatal diagnosis typically involves searches for known mutations, specificity in this case was assumed to equal 0.999.

**Costs and Resource Use.** The base-case analysis is based on costs rather than charges. Cost estimates used in the model were collected from a variety of sources as shown in Table 3 and inflated to 1995 dollars by 4% per year as necessary. Cost estimates for the 6-mutation DNA test were constructed by calculating the cost for technical and professional
personnel, reagents, equipment, royalties, and 100 square feet of laboratory space with utilities, distributed over an annual capacity of 5,625 tests.

Estimates for the cost of midtrimester pregnancy termination, miscarriage, and delivery were calculated as 80% of charges using estimates from the Hospital of the University of Pennsylvania and surrounding centers. We assumed that 85% of deliveries would be vaginal and the remainder performed by cesarean section.

Estimates for the cost of patients’ time were collected from the census, and genetic counseling time (including benefits) were collected from published reports and the Bureau of Labor Statistics. We estimated that couples would receive 30–45 minutes of genetic counseling before screening and about the same amount again if the screening test were positive. These sessions would require 80 square feet of office space with utilities. We assumed that negative results would be communicated by telephone at approximately no cost.

Estimates for the cost of prenatal diagnosis with amniocentesis (excluding karyotyping) were constructed by calculating the costs for technical and professional personnel (one obstetrician, one ultrasonographer, one nurse, one secretary, and one billing clerk), ultrasonography equipment, supplies, and 300 square feet of office space with utilities distributed over an annual capacity of 2,700 amniocenteses.

Estimates of the lifetime direct medical and nonmedical costs of CF, provided for comparison, were obtained from a recent Office of Technology Assessment report, and inflated to 1995 dollars.

Perspective. We used three different perspectives for the model: patient, payer, and society. For patient and payer perspectives, we used estimates of charges and assumed that patients would bear 20% of medical charges as a personal cost, and 100% of non medical costs such as transportation and time lost from work. Payer costs were assumed to be 80%
of charges. Societal costs, as discussed above, were assumed to be net costs independent
of charges.

Clinical Outcomes

Each strategy was evaluated according to its overall cost and the distribution of a
hypothetical cohort of 500,000 pregnancies among six clinical outcomes. The six clinical
outcomes were: [1] the delivery of a child without CF; [2] the delivery of a child with CF;
[3] the termination of a pregnancy that, if delivered, would have resulted in the birth of a
child without CF; [4] the termination of a pregnancy that, if delivered, would have resulted
in the birth of a child with CF; [5] the spontaneous miscarriage of a pregnancy that, if
delivered, would have resulted in the birth of a child without CF; [6] the miscarriage of a
pregnancy that, if delivered, would have resulted in the birth of a child with CF. We
considered only those terminations of pregnancy attributable to CF carrier screening.
Although couples may decide to terminate a pregnancy for other reasons, the cohort we
examined excludes those pregnancies. Amniocentesis carries a small risk of procedure-
related miscarriage. We considered baseline miscarriages occurring after the first trimester
as well as miscarriages attributable to amniocentesis.

Analyses

We first performed a base-case analysis for each of the 13 strategies, assuming one
pregnancy per couple. We examined each strategy according to its overall cost from a
societal perspective and its distribution of pregnancies among the six clinical outcomes.
We assumed that couples would follow the strategy’s decision rules exactly, and then
eliminated strategies that might suggest pregnancy terminations at very low risks of CF.
Finally, we performed sensitivity analyses on the remaining strategies, and extended the
model to reflect more than one pregnancy per couple.

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Results

Base-Case Analysis

Table 4 reports the base case analysis for all 13 screening strategies applied to a cohort of 500,000 single gestation pregnancies. The table shows the number of pregnancies falling into each of the six clinical outcomes, the total cost from a societal perspective, and a summary cost-effectiveness measure presented as the cost per CF birth avoided relative to the no screening alternative (strategy A). Figure 3 presents this cost-effectiveness ratio for each of the 13 strategies. Strategies A, L, I, M, C, G, and E present an efficient frontier: screening programs to the upper left of the frontier are inefficient either because they cost more or because they are less effective at reducing CF births compared to strategies on the frontier.

Compared to no screening, strategy L has the lowest cost per CF birth avoided. In this sequential strategy, the first partner is tested with the standard battery. The second partner is tested with the expanded battery if and only if the first partner’s screen is positive. If the second partner is also positive, prenatal diagnosis is performed.

Strategies involving MIE are more successful than other strategies at identifying affected fetuses and reducing the number of children born with CF. However, these strategies increase total costs and the cost per CF birth avoided. In addition, for many of these strategies the incremental cost per CF birth avoided exceeds $1 million. For example, although strategy C identifies 41 more CF births out of a possible 200 than strategy L, these additional CF births are prevented at a cost of about $1.4 million each.

Strategies that involve MIE are associated with relatively high frequencies of elective abortions and many of these are terminations of unaffected pregnancies. In addition, the greater use of prenatal diagnosis in these strategies conveys a higher risk of spontaneous abortion attributable to amniocentesis. These figures would be even higher if we
substituted chorionic villus sampling in the model for amniocentesis. Because we expect few couples would select such strategies, we did not analyze them further.

The six strategies involving only direct mutation tests (B, D, F, H, J, L) and the no screening alternative (A) were analyzed further. As would be expected, parallel screening strategies are relatively disfavored because both partners are tested and the test of the second partner often cannot provide information clinically useful for the couple. Figure 3 shows that D and F offer no additional effectiveness compared with strategy J for great additional cost. Strategy B is dominated by all three sequential strategies (H, J, and L) because the former is both more costly and no more effective at preventing CF births.

The three sequential strategies also differ in other dimensions that might be important. For example, each strategy carries the risk that unaffected pregnancies will either be terminated because of false positive results, or will miscarry because of complications related to amniocentesis for prenatal diagnosis. Although these strategies might be compared along this dimension, the risk of these events is small and similar across programs. For each of these strategies, only 3 or 4 additional unaffected pregnancies would be lost in a cohort of 500,000.

The best choice among strategies H, J, and L depends on how one values the tradeoff between cost and preventing affected births. Of these three strategies, H is the least costly and also the least effective. Compared with strategy H, L prevents 8 more affected births, and these are detected at an incremental cost of $129,000 each. If strategy H is considered cost-effective compared to the no screening strategy at a cost of $381,000 per CF birth avoided, then strategy L will almost certainly be preferred because the additional 8 affected births are prevented at an even lower cost. This is the principle of extended dominance, and it might be used to eliminate strategy H from further consideration.9
Compared with strategy L, strategy J prevents 9 more affected births, but these additional births are detected at an incremental cost of almost $26 million or approximately $2.9 million each. Seen from this perspective, strategy J is very expensive.

These results suggest that the lowest cost per CF birth avoided is achieved with screening strategy L. In this strategy, partners are screened in sequence and, if the first partner is positive with a standard battery, the second partner is screened with an expanded test designed to detect more mutations.

Sensitivity Analyses

Although the overall cost-effectiveness ratios for the screening strategies are sensitive to many of the assumptions in the model, the relative rankings of the strategies are generally stable.

Cost and Detection Rate of Expanded Battery. Strategies using expanded testing batteries that screen for many mutations are progressively favored as those batteries can be designed to detect more mutations at a lower additional cost compared to standard screening. Our base-case analysis assumed that the standard battery could detect 85% of carriers at a cost of $50 and the expanded battery could detect 90% of carriers at a cost of $100. Figure 4 shows a two-way sensitivity analysis in which the assumed cost and detection rate of the expanded battery are varied simultaneously. A limited battery alone (strategy H) has the lowest cost per CF birth avoided when the cost of an expanded battery is high and the expanded battery does not provide much more detection. Screening from the start with an expanded battery (strategy J) has the lowest cost per CF birth avoided only when the detection rate of the expanded test is high and the cost of the test is low compared with the standard battery.

Costs of Standard and Expanded Test Batteries. The cost per CF birth avoided decreases somewhat with the cost of the mutation screen. If the cost of the standard and expanded
batteries were reduced to $10 and $20, the cost-effectiveness of strategies H, L, and J would be about $230,000, $219,000, and $242,000 per CF birth avoided, respectively. The effects are modest because the direct medical costs of the screening test itself are only a portion of the total societal cost of screening. Counseling, time lost from work, and other related items represent societal costs incurred as individuals engage in screening. On the other hand, if the cost of the standard and expanded batteries were increased to $100 and $200, the cost-effectiveness of strategies H, L, and J would be about $569,000, $551,000, and $850,000 per CF birth avoided, respectively.

*Cost Perspective.* The relative rankings of the several strategies are not sensitive to the cost perspective assumed. Strategy L maintains the lowest cost per CF birth avoided when costs are seen by society, the patient, or the payer. However, the cost per CF birth avoided is highest in the societal perspective. This is so because neither patient nor payer individually bears the full cost of screening. One would expect, under these circumstances, that patient demand for CF screening might exceed its social value. This is a manifestation of the economic principle of moral hazard, in which insured individuals will consume more health care resources than uninsured individuals. Of note, the costs seen from the patient and payer perspectives combined exceed the societal costs. This difference reflects the profits realized by the medical industry in the process of CF carrier screening. These profits are not societal costs, but rather transfers from patients and payers to health care professionals and institutions.

*Specificity.* The results presented in the base case-analysis were relatively unaltered when the specificity of the DNA test was varied from 0.99 to 0.9999. However, at the lower range of specificity, 11 to 19 more unaffected pregnancies will be lost in strategies H, L, and J because of terminations of pregnancies falsely presumed to be affected. In addition, 12 to 33 more unaffected pregnancies will be lost as the result of miscarriages induced by the increased use of amniocentesis.
Chance of Nonpaternity. In any screening program involving reproduction, screens of the male partner are not always informative because of the chance that the individual tested is not the biological father. In our model, the chance of nonpaternity affects overall screening performance, although it does not change the relative preference for alternative strategies. The chance of nonpaternity is generally unknown, and is likely to vary across subpopulations. The base case analysis assumes no chance of nonpaternity. If the chance of nonpaternity is 0.1 to 0.5, the cost per CF birth avoided for strategy L increases to between $406,000 and $702,000 per CF birth avoided. These results reflect the inefficiency of carrier screening when paternity is uncertain.

Proportion of Couples Choosing to Terminate Affected Pregnancies. The cost per CF birth avoided, but not the relative rankings of the alternative strategies, is extremely sensitive to the proportion of couples who decide to terminate an affected pregnancy. For the single pregnancy case, the most efficient CF screening strategy is able to prevent CF births at a cost of $367,000 per CF birth avoided. However, this figure assumes that all couples who identify a fetus as high risk choose to terminate the pregnancy. If only half of couples will proceed to abortion under these circumstances, the cost per CF birth avoided would increase to $734,000 per CF birth avoided. One might ask why couples who would not terminate an affected pregnancy would engage in carrier screening. However, some couples may change their mind in the course of a pregnancy, particularly during the period between carrier screening and learning the results of prenatal diagnosis. Others may engage in carrier screening to obtain the reassurance that they are not carriers without fully considering what they will do should they learn otherwise.

Number of Pregnancies. Similarly, the cost per CF birth avoided is sensitive to the number of pregnancies a couple plans. The information obtained from CF carrier screening performed early in a couple’s family planning can be used for more than just a single pregnancy. The relative performance of each of the screening programs does not change
births at a cost of $367,000 each when screening is used in only a single pregnancy. Even so, this figure assumes that all couples who identify a pregnancy at risk will choose to terminate it. One might ask why couples who would not terminate an affected pregnancy would engage in carrier screening, but perhaps only 20-50% will terminate a pregnancy under these conditions.\textsuperscript{14,15,16} If about a third of couples terminate under these conditions, the cost per CF birth avoided will be approximately $1.1 million.

On the other hand, most couples who plan to have children will have more than one. CF carrier screening information is reusable, and only a few costs—reflecting the small percentage of couples found to be at risk—will continue in later pregnancies. The overall cost-effectiveness of carrier screening improves as the costs are distributed over more pregnancies per couple. If CF carrier screening were performed only for individuals who are sure to terminate a pregnancy found to be at risk, and if these couples planned two children, then a mixed strategy could prevent CF births at a cost of approximately $183,000 each. This figure compares favorably with the likely direct medical costs of caring for an individual with CF.

Finally, the relative preference for alternative screening strategies does not depend on the perspective used in the analysis. However, costs seen from either the patient or the payer perspective understate total societal costs of carrier screening. Moreover, costs from the payer’s perspective, when averaged over a population of insured individuals, will depend greatly on the proportion of individuals who choose to engage in screening. Although some reports from Britain have suggested very high uptake of CF carrier screening,\textsuperscript{17} demand has been much lower in the US.

This analysis is subject to several limitations. First, as with any model, the conclusions depend on critical assumptions regarding costs and probabilities. Nevertheless, our findings are generally stable over wide ranges of plausible assumptions. The overall cost-effectiveness of clinical strategies is most sensitive to assumptions about the proportion of
couples who will terminate pregnancies found to be affected, and about the number of pregnancies couples have. These decisions are personal and can be made by couples before they decide to engage in carrier screening. The choices they make in advance can help select the best option.

Second, we did not evaluate many of the intangible effects that accompany CF carrier screening. Couples who receive negative results through screening get reassurance that has value for them. In fact, for many couples the motivation for screening may be to seek this reassurance. On the other hand, couples who find themselves at risk may suffer anxiety and concern that would not occur without screening. These effects may be emotionally costly, and yet they are hard to value. Because we did not measure the value of screening information independent of the decision to continue a pregnancy, we cannot answer whether this information is worth the cost.

Third, we also did not measure the costs of caring for individuals with CF. Although we report some previously published estimates to use as a rough guide, the relevant costs are difficult to estimate, particularly since the future management of patients with CF is likely to change.

In fact, the clinical management of patients with CF has been improving steadily and so the life-expectancy of children born with the disease today is much better than in the past. The prospect of revolutionary treatment, with gene therapy for example, also looms on the horizon. If CF becomes more easily treated, then identifying carriers in order to avoid affected births may become a less attractive strategy. In this regard, it is interesting to note that in a recent survey only 2-3% of individuals undergoing CF carrier screening thought they would decline screening if the quality or the life expectancy of individuals with CF roughly doubled, and only 13% thought they would decline screening if the life expectancy became normal.18
A central conclusion of this analysis is that the cost-effectiveness of CF carrier screening depends greatly on the goals and plans of the individuals who seek screening. When measured against a goal of reducing the number of children born with CF, carrier screening is expensive unless couples enter a screening program with the intention of terminating affected pregnancies. Carrier screening can be cost-effective when couples follow this path, particularly when couples are screened prior to reproduction and anticipate two or more pregnancies.

This result is important for the special case of CF, but it is also relevant to screening for other genetic conditions in the reproductive setting. Most geneticists and genetic counselors believe their interactions with patients should be as neutral and nondirective as possible. Such a stance is meant to foster patient autonomy in a setting that is deeply personal. Moreover, alternative stances that might encourage individuals and couples to make certain decisions in this setting raise troubling concerns of eugenics. Nevertheless, the results reported here suggest that carrier screening will be cost-effective only if those who engage in screening use the information in a particular way. Much of the nondirective nature of traditional genetic counseling would be lost if health care professionals were to recommend screening or no screening on the basis of couples’ willingness to terminate affected pregnancies. Yet, these are the conditions required for screening to be cost-effective.

Others might not view such a change in stance as a problem. As genetic screening technologies become more widely available, the majority of screening may shift from the specialized centers where it now takes place to the offices of non geneticists. These health professionals, and their patients, may be comfortable with a more directive approach. Even so, CF is the most common serious genetic disease in the Caucasian population. If the appeal of CF carrier screening is limited unless couples are willing to use the results in the
prescribed manner, then screening for less common conditions of similar clinical impact is likely to be even less appealing.
<table>
<thead>
<tr>
<th>Parental Sequence</th>
<th>DNA Test Battery</th>
<th>Additional Tests if One and Only One Parent Tests Positive</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Screening</td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Parallel</td>
<td>Standard</td>
<td>None</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MIE</td>
<td>C</td>
</tr>
<tr>
<td>Expanded</td>
<td>None</td>
<td></td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>MIE</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>Mixed(^a)</td>
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<td></td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>MIE</td>
<td></td>
<td>G</td>
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<tr>
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<td>None</td>
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</tr>
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<td></td>
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<td>MIE</td>
<td>I</td>
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<tr>
<td>Expanded</td>
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<tr>
<td></td>
<td>MIE</td>
<td></td>
<td>K</td>
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<tr>
<td>Mixed(^b)</td>
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<td></td>
<td>L</td>
</tr>
<tr>
<td></td>
<td>MIE</td>
<td></td>
<td>M</td>
</tr>
</tbody>
</table>

MIE = microvillar intestinal enzyme analysis.

a. If one and only one partner is negative with the standard battery, rescreen that partner with the expanded battery.

b. If the first partner is positive, screen the second partner with the expanded battery.
Table 2. Probabilities Used for the Analysis of Carrier Screening for Cystic Fibrosis

<table>
<thead>
<tr>
<th>Model Input</th>
<th>Baseline Estimate</th>
<th>Range</th>
<th>Source</th>
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<tr>
<td>CF mutation carrier frequency</td>
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<td>Wilfond &amp; Fost(^1^9)</td>
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<td>Detection rate for an &quot;expanded&quot; mutation screen</td>
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<td>0.86–1.00</td>
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<tr>
<td>Sensitivity of the DNA direct mutation screen</td>
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<td></td>
<td>EP</td>
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<td>Specificity of the DNA direct mutation screen</td>
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<td>EP</td>
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<td>Sensitivity of MIE</td>
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<td></td>
<td>Brock, et al.(^4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mulivor, et al.(^20)</td>
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<td></td>
<td>Mulivor, et al.(^21)</td>
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<td></td>
<td>Wilson, et al.(^21)</td>
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<td></td>
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<td>Mackenzie, et al.(^22)</td>
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<td>Simpson, et al.(^23)</td>
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<td>Chance of spontaneous abortion attributable to amniocentesis</td>
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<td>Globus, et al.(^27)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Crandall, et al.(^28)</td>
</tr>
<tr>
<td>Chance of nonpaternity</td>
<td>0.0</td>
<td>0.0–0.5</td>
<td></td>
</tr>
</tbody>
</table>

\(^{CF}\) = cystic fibrosis; \(^{MIE}\) = microvillar intestinal enzyme analysis; \(^{EP}\) = expert panel.
### Table 3. Cost Estimates Used for the Analysis of Carrier Screening for Cystic Fibrosis

<table>
<thead>
<tr>
<th>Event or Procedure</th>
<th>Baseline Societal Cost Estimate</th>
<th>Patient Perspective Cost</th>
<th>Payer Perspective Cost</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA screen (6 mutation)</td>
<td>$50</td>
<td>$20</td>
<td>$80</td>
<td>HUP, see text</td>
</tr>
<tr>
<td>DNA screen (&quot;expanded&quot;)</td>
<td>$100</td>
<td>$40</td>
<td>$160</td>
<td>HUP, see text</td>
</tr>
<tr>
<td>Genetic counselor's time per hour with benefits</td>
<td>$26</td>
<td>$0</td>
<td>$0</td>
<td>Uhlmann&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patient time per hour with benefits</td>
<td>$15</td>
<td>$15</td>
<td>$0</td>
<td>Census&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amniocentesis (excludes karyotyping)</td>
<td>$200</td>
<td>$160</td>
<td>$640</td>
<td>see text</td>
</tr>
<tr>
<td>MIE</td>
<td>$100</td>
<td>$40</td>
<td>$160</td>
<td>HUP</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>$260</td>
<td>$65</td>
<td>$260</td>
<td>HUP</td>
</tr>
<tr>
<td>Midtrimester abortion</td>
<td>$2,800</td>
<td>$700</td>
<td>$2,800</td>
<td>HUP</td>
</tr>
<tr>
<td>Delivery</td>
<td>$3,120</td>
<td>$780</td>
<td>$3,120</td>
<td>HUP</td>
</tr>
<tr>
<td>Travel (per office visit)</td>
<td>$5</td>
<td>$5</td>
<td>$0</td>
<td></td>
</tr>
<tr>
<td>Lifetime medical and nonmedical direct costs of CF</td>
<td>$351,278</td>
<td></td>
<td></td>
<td>OTA&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

HUP = based on charges at the Hospital of the University of Pennsylvania and surrounding centers.


<table>
<thead>
<tr>
<th>Strategy</th>
<th>CF Births</th>
<th>Abortions</th>
<th>Miscarriages</th>
<th>Non CF Births</th>
<th>Abortions</th>
<th>Miscarriages</th>
<th>CF Births Avoided (rel. to A)</th>
<th>Total Cost</th>
<th>Cost Per CF Birth Avoided (rel. to A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>195</td>
<td>0</td>
<td>5</td>
<td>487.305</td>
<td>0</td>
<td>12.495</td>
<td>0</td>
<td>$1,530,313,000</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>57</td>
<td>142</td>
<td>1</td>
<td>487.302</td>
<td>0</td>
<td>12.498</td>
<td>138</td>
<td>$1,623,710,000</td>
<td>$676,000</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
<td>191</td>
<td>0</td>
<td>486.787</td>
<td>340</td>
<td>12.673</td>
<td>187</td>
<td>$1,641,185,000</td>
<td>$594,000</td>
</tr>
<tr>
<td>D</td>
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<td>159</td>
<td>1</td>
<td>487.300</td>
<td>0</td>
<td>12.499</td>
<td>155</td>
<td>$1,674,352,000</td>
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<tr>
<td>E</td>
<td>6</td>
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<td>358</td>
<td>12.705</td>
<td>189</td>
<td>$1,694,522,000</td>
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<tr>
<td>F</td>
<td>39</td>
<td>160</td>
<td>1</td>
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<td>0</td>
<td>12.499</td>
<td>156</td>
<td>$1,627,544,000</td>
<td>$625,000</td>
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<tr>
<td>G</td>
<td>8</td>
<td>192</td>
<td>0</td>
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<td>338</td>
<td>12.673</td>
<td>187</td>
<td>$1,647,277,000</td>
<td>$626,000</td>
</tr>
<tr>
<td>H</td>
<td>57</td>
<td>142</td>
<td>1</td>
<td>487.302</td>
<td>0</td>
<td>12.498</td>
<td>138</td>
<td>$1,582,937,000</td>
<td>$381,000</td>
</tr>
<tr>
<td>I</td>
<td>33</td>
<td>166</td>
<td>1</td>
<td>487.044</td>
<td>170</td>
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<td>162</td>
<td>$1,593,161,000</td>
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<tr>
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<td>40</td>
<td>159</td>
<td>1</td>
<td>487.300</td>
<td>0</td>
<td>12.499</td>
<td>153</td>
<td>$1,609,657,000</td>
<td>$512,000</td>
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<tr>
<td>K</td>
<td>23</td>
<td>177</td>
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<td>487.019</td>
<td>179</td>
<td>12.602</td>
<td>172</td>
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<td>$530,000</td>
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<tr>
<td>L</td>
<td>49</td>
<td>150</td>
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<td>487.301</td>
<td>0</td>
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<td>146</td>
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<td>$367,000</td>
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<tr>
<td>M</td>
<td>32</td>
<td>157</td>
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<td>487.045</td>
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<td>12.586</td>
<td>163</td>
<td>$1,593,807,000</td>
<td>$391,000</td>
</tr>
</tbody>
</table>

The figures represent the results of a strategy applied to a cohort of 500,000 pregnancies. Strategies are defined in Table 1.
Figure Legends

Figure 1. Three sample clinical strategies (B, C, and L from Table 1) expressed as a decision tree. The tree is read from left to right. The square node indicates a choice to be made among the strategies labeled B, C and L. The round nodes indicate outcomes that result from chance. Each branch ends on a letter indicating a subtree, shown in Figure 2. MIE = Microvillar intestinal enzyme analysis. For an explanation of the three strategies, see Table 1.

Figure 2. Two subtrees for Figure 1. Each pregnancy can either be terminated (subtree A) or continued (subtree B). If it is terminated, it might have led to the birth of a child with CF or without CF. If it is continued, it might lead to a miscarriage or to delivery, and in either case might be affected with CF or not.

Figure 3. Societal cost effectiveness of 13 alternative screening strategies. Each strategy is represented by a point reflecting the number of CF births avoided compared to a no screening alternative and the additional societal cost for that strategy also compared to a no screening alternative. The thin line connects strategies representing an efficient frontier: No other strategies can achieve a greater reduction in CF births at a comparable or lower cost than strategies on this frontier. Strategies to the upper left of the frontier are less efficient at preventing CF births than strategies on the frontier. However, many of the efficient strategies also result in a large number of unaffected pregnancies being lost to spontaneous or therapeutic abortion. The bold line creates a new frontier that excludes strategies that result in significant loss of unaffected pregnancies.

Figure 4. Two-way sensitivity analysis for the societal cost and detection rate of expanded carrier screening. The three areas represent combinations of cost and detection rate for which the indicated strategies have the lowest cost per CF birth avoided (relative to other
strategies with few non CF fetal losses). In the base case, for example, strategy L has the lowest cost per CF birth avoided.

Figure 5. The effectiveness of three sequential testing strategies and the no screening strategy over subsequent pregnancies. Each point reflects a cohort of 500,000 pregnancies. Results for the first pregnancy are as reported in Table 4 and Figure 3. Results for subsequent pregnancies reflect only the number of CF births avoided in that pregnancy. In each pregnancy, approximately 25% of undetected CF carrier couples are discovered though the birth of an affected child. These couples are assumed to undergo comprehensive direct mutation testing at the time of their next pregnancy. The outcome of the no screening strategy converges with those of the other strategies because an increasing proportion of obligate carriers are identified with each pregnancy through of the birth of an affected child.
References


