“Genetic Screening for Reproductive Planning: Methodology and Conceptual Issues in Policy Analysis”

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David Asch, John Hershey, Mark Pauly, James Patton, Kathryn Jedrzewski and Michael Mennuti
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David A. Asch, M.D., M.B.A.1,2,3,4
John C Hershey, Ph.D.5,6
Mark V. Pauly, Ph.D.3,6
James P. Patton, M.D., M.B.A.2,3
M. Kathryn Jedrzewski, Ph.D.2
Michael T. Mennuti, M.D.7

1 Veterans Affairs Medical Center, Philadelphia, Pennsylvania
2 Division of General Internal Medicine, University of Pennsylvania School of Medicine
3 Leonard Davis Institute of Health Economics, University of Pennsylvania
4 Center for Bioethics, University of Pennsylvania School of Medicine
5 Department of Operations and Information Management, The Wharton School, University of Pennsylvania
6 Department of Health Care Systems, The Wharton School, University of Pennsylvania
7 Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine

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Correspondence and Reprint Requests: David A. Asch, M.D.
Division of General Internal Medicine
317 Ralston-Penn Center
3615 Chestnut Street
Philadelphia, PA 19104-2676
Telephone: (215) 898-0102
Facsimile: (215) 898-0611
E-Mail: asch@wharton.upenn.edu

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Genetic Screening for Reproductive Planning: Methodologic and Conceptual Issues in Policy Analysis
Abstract

Quantitative policy analyses of genetic screening strategies are becoming increasingly important as we expand our knowledge of the genetic basis of many diseases. Even so, the presentation of these analyses often mask an underlying layer of assumptions and methodologic choices. In the case of genetic screening in the reproductive setting, these underlying issues are complex, and at times touch upon deeply felt human values. We discuss several issues we struggled with as we began to model the implications of alternative screening programs to identify cystic fibrosis mutation carriers in the reproductive setting. Each of these issues has required that we make a choice in technique, and most other policy analyses will face similar choices. Often there is no best choice. Space limitations for published papers make it difficult to explain such choices in detail; yet, these decisions determine the way the results should be interpreted. Those who develop these analyses need to make sure that the implications of important assumptions are understood by the clinicians who will use them. At the same time, clinicians need to enhance their understanding of what these models truly mean, and how they address underlying clinical, ethical, and economic issues.
There is an increasing need to perform policy analyses that evaluate alternative ways to use new genetic diagnostic and screening technologies. This need has developed because of our expanding knowledge of the genetic basis of many diseases and conditions, and also because advances in molecular biology have put within reach the ability to detect specific gene mutations for many common conditions. At the same time, the greater availability of these screening technologies may shift the majority of screening from the specialized centers where it now takes place, to the offices of non geneticists, or even to non medical settings, where safeguards for counseling and the appropriate stewardship of these tests may not be well developed.

Decision analyses, cost-effectiveness analyses, and other types of quantitative policy analysis offer the potential to understand the clinical and economic implications of alternative strategies. However these analyses may be particularly challenging in the case of genetic screening for reproductive planning. The difficulties relate to (a) potential changes in individuals’ preferences and goals after screening is initiated; (b) complex ethical dilemmas related to gender, ethnic background, and other characteristics that can differentiate risk; (c) the large number of possible genetic screening strategies available, even for a single disease or condition; (d) the possibilities for blending old and new diagnostic and screening technology; (e) the fact that the value of genetic testing, and perhaps the optimal screening strategy, can vary widely according to target family size and the outcomes of previous births; (f) controversy about the goals of some genetic testing; and (g) problems with economic valuation in the reproductive setting.

In this paper, we illustrate these difficulties using our experience in performing an analysis of alternative genetic screening strategies for the detection of carriers of cystic fibrosis (CF) mutations as part of reproductive planning. None of these difficulties is unique to CF, and none is unique to modeling. In fact, difficulties in modeling a clinical program inevitably reflect parallel difficulties that will be encountered as clinicians try to structure screening strategies to meet patients’ goals.
Prescriptive and Descriptive Concerns

In the abstract, two distinct approaches might be used to build models for policy analysis: a prescriptive and a descriptive approach. A prescriptive policy analysis first lays out a collection of alternative clinical strategies. Given these strategies, one calculates the outcomes that would result if each were followed to completion. Outcomes can include both clinical and economic consequences.

For example, Figure 1 shows two of many clinical strategies for CF screening that might be compared in a prescriptive analysis. In Strategy A, both partners in a couple are screened for a handful of common CF mutations. If both partners screen positive, the couple proceeds to prenatal diagnosis with amniocentesis or chorionic villus sampling. If the fetus has inherited the two CF mutations, the pregnancy is terminated and in all other cases the pregnancy is continued.

Strategy B is the same as Strategy A if both partners screen positive. However, if only one partner is positive, an expanded screening battery—that can detect more CF mutations and so identify more carriers—is used on the other partner. If after the expanded screening both partners are positive, the couple proceeds to prenatal diagnosis. Again, the pregnancy is terminated if the fetus has inherited the two CF mutations.

Why do both of these strategies lead with certainty, for some screening results, to prenatal diagnosis? Doesn't the couple have a choice? And why do both strategies dictate that if the fetus has inherited two mutations the couple will terminate the pregnancy? What if they decide to continue the pregnancy? The apparent inflexibility of the decision options can appear offensive until one recognizes that alternative choices can be reflected in other available strategies in which different decisions are made.

Examples of such strategies are shown in Figure 2. Strategy A' is identical to A, except the couple continues the pregnancy even if the fetus is found to carry two mutations. In Strategy A", the couple does not pursue prenatal diagnosis even if both partners are found to be carriers.
Prescriptive models typically do not include strategies like A' or A". Instead, these models usually follow the maxim that "if you are not going to change your actions with the results of a test, you should not do the test in the first place." The implication of this maxim is that diagnostic information that cannot alter a clinical management plan has no value. Why would a couple engage in Strategy A' or A"? If they are not going to terminate an affected pregnancy, why undergo prenatal diagnosis; and if they are not going to engage in prenatal diagnosis, why undergo carrier screening?

Evidence suggests, however, that many couples pursue genetic screening even though they may decide to continue an affected pregnancy.\textsuperscript{1,2,3} One explanation for this experience is that what seems like a good strategy in the abstract becomes less attractive in reality. Couples might not understand the prescriptive implications of a complex strategy. Or, they might so underestimate the chances of receiving bad news that they do not fully consider what they might do under those circumstances.

Another explanation is that couples may value genetic screening information for another purpose. They value the information screening provides not for the way it helps determine the management of the pregnancy, but for the reassurance. In theory, prescriptive models could incorporate these less tangible benefits of information.\textsuperscript{4,5} In practice, these benefits are hard to value and so are almost never included in prescriptive models. If they are important factors in making good decisions, then these prescriptive models will be incomplete.

The second form of policy analysis is descriptive. In the case of CF carrier screening, one approach to descriptive modeling is to lay out alternative strategies for initial carrier screening, and then make predictions about what clinical results would arise and what actual couples might do with these results. A recent policy analysis of CF carrier screening has used behavioral predictions of this sort.\textsuperscript{6} Whether these predictions are based on intuitions or past experience, the virtue of descriptive models is that they tell you something about the real world. An example of a descriptive model is presented in Figure 3.
The strategies in Figure 3 are similar to the prescriptive strategies in Figure 1, but with the added possibility that couples discontinue screening or testing at various points. Descriptive analyses require knowing not only probabilities of genetic outcomes, but probabilities of behavioral decisions made by couples as well.

Both prescriptive and descriptive approaches have a role. If one wants to predict the actual clinical and economic outcomes across a population given alternative strategies, the descriptive approach—accounting as it does for the way real people make real decisions—is preferred. But the prescriptive approach is preferred if one wants to give advice to a couple about the best way to proceed given their personal goals. The prescriptive approach yields the outcomes one expects of a strategy followed to completion. But even this approach might not meet this goal because individuals sometimes change their mind and sometimes cannot anticipate real clinical decisions. As a result, mixtures of prescriptive and descriptive approaches might at times seem preferable. The reasoning behind these mixed approaches is: “I know that many of you, when initially following one path, eventually switch to another. Therefore, I will tell you the expected outcome of your decision not based on what you say you want, but on my expectation that some of you will not stay your course.”

Differences between prescriptive and descriptive approaches are not unique to the policy analysis of reproductive genetics, but they can highlight special tensions. In particular, the prescriptive approach can seem to challenge the values of those geneticists and genetic counselors who believe strongly in the principle of nondirective counseling. The maxim that a test result that will not change management plans should not be pursued inextricably links the performance of a genetic test with a commitment to a particular course of action. This commitment is seen in strategies A and B in Figure 1 where certain carrier screening results are followed by prenatal diagnosis, and certain prenatal diagnosis results are followed by abortion. The tension arises because genetic counselors provide access to genetic information. To be nondirective, the provision of this information must be independent of what the couple decides. For this reason, some have objected
strongly to the principles of prescriptive decision modeling. Others have questioned whether nondirective counseling is possible, or always desirable.

Strategy Complexity

Whatever approach is used, policy analyses involving reproductive genetics may also be more complex than most other health policy analyses. Most conventional health policy analyses address a single patient and a single condition. For example, a recently published decision analysis has examined strategies for screening for prostate cancer. These analyses are complicated by the need to examine the role of several different diagnostic tests that might be used separately, or in combination—in this case the prostate specific antigen test, digital rectal examination, and transrectal ultrasound. They also must consider the effects of alternative management strategies once prostate cancer is discovered. But even so, they are limited to tests and procedures performed on a single patient.

In contrast, clinical strategies in reproductive genetics typically involve more than one individual. For example, in CF carrier screening one might perform diagnostic tests on both partners in a couple and the fetus. In some cases, one might need to test other members of kindreds as well. The best way to proceed in these complex clinical situations is often unclear.

Formal clinical guidelines for the use of dichotomous tests in combination have been developed to address these issues.

For example, ten unique clinical strategies are created even in the relatively simple case of two available diagnostic tests, or perhaps a single test that could be performed on both partners in a couple. Many options result because the two tests can be performed simultaneously or in sequence, and because when two tests are performed, one must decide whether both tests must be positive or only one or the other positive will suffice.

In the case of population CF carrier screening and prenatal diagnosis, one might use three different kinds of tests: [1] direct mutation analysis employing a battery capable of detecting a handful of
common CF mutations; [2] an expanded direct mutation battery capable of detecting even more CF carriers (although with diminishing marginal returns); and [3] microvillar intestinal enzyme analysis (MIE) of amniotic fluid obtained for prenatal diagnosis.\textsuperscript{14,15,16} Furthermore, because the first two of these tests might be performed on both partners in a couple as well as the fetus there are effectively 7 distinct diagnostic tests that could compose an overall strategy.

There are hundreds of ways 7 diagnostic tests might be arranged into a clinical strategy—particularly since MIE may not provide a unique criterion for positivity. Although many of the possible strategies are not plausible in practice, it is still easy to generate dozens of plausible clinical strategies. Fifteen of these are presented in Table 2, but many more strategies are also plausible.

Models can be complicated further if there are known correlations between phenotype and genotype. Many genetic conditions, and CF is an example, have an extremely variable presentation. Phenotypic variability might be related to the type of mutation in the genome. When this is so, carrier screening would reveal not only who is a carrier, but also something about the specific clinical syndromes progeny would face. Such information is potentially valuable for patients, though complex to present and extremely complex to model. At this time, phenotype-genotype correlations are not well established for CF.

**Blending Old and New Diagnostic Tools**

One reason so many diagnostic tests are available is that new tests, developed from the identification of specific genes, often arise in a setting where less direct tests were used in the past. In the case of CF, haplotyping with closely linked genetic markers\textsuperscript{17} and MIE were used to provide information about a pregnancy to families with a history of CF. To the extent that haplotyping may only represent a proxy for the information available from mutation screening, it may now be obsolete; but the same may not be true for MIE. Often, new technologies only partially replace old ones.\textsuperscript{18}
In the case of CF screening some couples may find themselves in the circumstance where one partner has screened positive for an identifiable CF mutation, but the second partner has screened negative. Depending upon the specific tests used for screening, this couple faces about a 1/650 risk that a pregnancy would result in a child affected with CF. The risk is not zero because not all mutations are detectable and so there is still a chance that the partner who screened negative is in fact a carrier. Couples under this circumstance might decide to undergo amniocentesis for prenatal diagnosis, particularly if they had an independent reason for doing so anyway. If they test the fetus for the known mutation and the fetus tests positive, the chance that the fetus has two mutations is now approximately 1/325. Although this risk is not great, it is higher than the approximately 1/2,500 baseline risk unscreened couples face. More important, the couple can refine this risk further by performing MIE analysis.

In reality, few couples might find the odds favorable enough to pursue such strategies, but they represent legitimate approaches for some. A potential problem with such strategies is that they may lead to the use of less accurate tests in situations where genetic conditions are of low prevalence. Microvillar intestinal enzyme analysis found its best application in the period before direct mutation analysis for those couples known to be at 1/4 risk for delivering a child with CF because of a previously delivered affected child. The relatively high risk of CF these couples face in a subsequent pregnancy somewhat mitigated this test’s incomplete specificity. But the test will perform much more poorly given a prior risk of 1/325. Under these circumstances, most positive results will be false positives.

Nonpaternity, Gender Balance, and Ethnic Balance

The risk of nonpaternity presents special challenges for policy analysis. Simply put, screens of the father are not always informative because of the chance that the individual tested is not the true reproductive partner. At a population level, the solution to this problem is straightforward. The chance that the true father is a carrier is the sum of the chance that the screened individual is a
carrier weighted by the probability of paternity and the chance that an unscreened individual is a carrier, weighted by the probability of nonpaternity. In effect, the risk of nonpaternity dilutes the information available from screening the male partner.

For example, consider a CF screening battery with a sensitivity of 99%, a specificity of 99.9% and a detection rate of 85%—meaning that the battery screens for mutations representing about 85% of CF carriers. Under these circumstances the chance that a woman who screens positive is indeed a CF carrier is 97%. At a background risk of nonpaternity of 5%, the chance that the true father is a carrier given the man in the couple screens positive is 93%. At a background risk of nonpaternity of 10%, the chance is only 88%. These differences may be especially important in aggregate when applied to populations on the whole.

But the special problem of nonpaternity is that although the policy analyst can use a background risk of nonpaternity in assessing clinical strategies, individual women may know for sure whether nonpaternity obtains. From a normative standpoint, women who are aware of nonpaternity ought to make different decisions about carrier screening and prenatal diagnosis.

The risk of nonpaternity also raises issues for clinical strategies that screen partners in series, proceeding to the second partner in a couple only if the first is positive. Because the information provided by screening the male partner is diluted by the risk of nonpaternity, screens of the woman are more informative. As a result, series screening strategies beginning with the woman will be more efficient than those beginning with the man.

Despite the efficiency of these approaches, they do not evenly distribute the benefits and burdens of genetic screening between genders. One of the concerns about genetic screening in general is that the results can lead to stigma and discrimination in social, employment and insurance settings. Strategies that begin by screening the woman may offer the benefit of greater efficiency, but at the same time make it more likely that women will bear the potential stigma and discrimination that may accompany these tests.
These issues parallel the concerns raised when one partner in a couple, because of family history or ethnic background, is either at a higher risk of being a carrier, or is more likely to carry mutations that are detectable by screening batteries. In these circumstances, serial screening strategies that begin with a particular partner will be more efficient. For example, Ashkenazic Jews have a higher incidence of the W1282X CF mutation than other Caucasians and so, on average, Jewish CF carriers are more easily detectable than non-Jewish Caucasians. As a result, in Caucasian couples in which one partner is Jewish and the other is not, the higher detectability of CF carrier status makes a serial screening strategy more efficient if it begins by screening the Jewish partner first.

**Single Pregnancies versus Overall Reproductive Plans**

Most couples who decide to raise a family will have more than one child. For this reason, an important aspect of reproductive genetic screening tests is that the results are reusable. In conventional screening tests, like mammography, the understanding is that after some period the test should be repeated. In CF carrier screening, one test will do for a lifetime—even if partners change.

Almost all costs of population screening are incurred at the initial stage, when individuals are screened for CF mutations. Only a few costs—reflecting the small percentage of couples found to be at risk—will continue in later pregnancies. As a result, a cost of about $400,000 per CF birth avoided determined from a single pregnancy analysis implies a cost of about $200,000 per CF birth avoided for couples who undergo two pregnancies. By the same reasoning, the increased costs of more comprehensive DNA screening may be worth it for couples planning many children, but not worth it for couples planning one child because the increased costs would be distributed over fewer pregnancies. Different reproductive plans may lead to different choices about the best screening strategy to follow.

For these reasons, one cannot evaluate the impact of a screening strategy without understanding how the results will affect, and be affected by, a couple’s overall reproductive plan. In addition,
some couples might screen in the preconception setting with a view toward avoiding reproduction together if both are found to be carriers. Presumably, couples would make this decision if they had high disutilities for both abortion and the birth of an affected child.

Couples willing to consider conception in the face of CF risk, or those who screen during the first pregnancy, might in theory approach family planning in many different ways. They might target a set number of children, as perhaps most do. They might instead target a certain number of pregnancies, particularly if they start later in life. If they are at high risk of CF, they might not target a certain number of total children, but a certain number of unaffected children. Or, the birth of an affected child may greatly alter their future reproductive plans.\textsuperscript{1} Garber and Fenerty have captured some of these elements when they discuss strategies involving “replacement,” or “no replacement”—depending upon whether pregnancies terminated because of a high risk of CF are replaced with new pregnancies. No doubt real strategies represent combinations of all of these elements along with a fair degree of serendipity.

Not all couples truly at risk for a CF birth will be detected by screening, and so even in the face of comprehensive screening programs some couples given reassuring news will nevertheless deliver affected children. For example, given a detection rate of 85\%, even a screening battery with otherwise perfect sensitivity and specificity will miss about a third of couples at risk of a CF birth. About a quarter of these couples will discover they are carriers because their first child will have CF. About a quarter of the remaining couples will make this discovery at a second birth, and so on. The diagnosis of CF in the child in these cases may not be immediate, and may even be delayed because negative carrier screening results of the parents make the diagnosis less likely; nevertheless, information about carrier status is revealed with each birth independent of any deliberate screening process. Nieces, nephews and cousins born with CF would also raise suspicions and provide information. If there were no limit to the number of children individuals have, in time all individuals would learn their carrier status without screening.
In other words, there is a natural screening process that occurs with subsequent births as some children are diagnosed with CF. Whatever explicit screening program is implemented coexists with this natural process. Models to predict the outcomes of screening strategies that move beyond a single pregnancy need to consider that at each additional pregnancy about a quarter of the previously undetected carrier couples will find they are obligate carriers. One or both partners in these couples may have CF mutations that are undetectable. Microvillar intestinal enzyme analysis or explorations for unscreened or previously unknown mutations might be used in these couples or in prenatal diagnosis of subsequent pregnancies, but providing estimates of the overall success of individual strategies under these circumstances is challenging.

Multiple Goals and Atypical Goals

Most systematic approaches to health policy target few and relatively uncontroversial goals. For example policies toward childhood immunization, prostate cancer screening, dietary fat reduction and the like have as explicit goals the reduction of disease and disability, the promotion of health, or related goals easy to share. Most policies also have implicit goals to reduce costs in the process, and these policies become controversial only when these two goals—promoting health and reducing cost—seem in conflict.

Genetic carrier screening for the purposes of reproductive planning leads to outcomes that are more controversial. These strategies often raise issues concerning abortion, eugenics, contraception, and reproductive choice—issues that can incite or challenge strong feelings.

Concerns specific to abortion in its strictest sense can be removed from the consideration of carrier screening policies. Carrier screening could be performed exclusively in the preconception setting and be used to make decisions regarding reproduction. So, for example, couples found to be at risk together might undergo artificial insemination, egg donation, or preimplantation diagnosis. Or, carrier screening could be used to direct the selection of marriage partners as is common in the
Mediterranean to reduce the incidence of thalassemia\textsuperscript{22} or in some orthodox Jewish communities to reduce the incidence of Tay Sachs disease.\textsuperscript{23}

These considerations are essential in policy analyses because the evaluation of clinical strategies requires an understanding of what these strategies are trying to accomplish. Policies to increase childhood immunization have a single clinical goal, which is to improve the health of children. We may measure that goal in a number of ways—including childhood mortality or morbidity, overall life expectancy, school days missed—but the goal remains the same. Any policy involving reproductive planning in the prenatal setting will have an effect on six different clinical outcomes. Our evaluation of these policies will depend on how we feel about each of these outcomes.

Six clinical outcomes result because each pregnancy will end either in delivery, termination, or miscarriage, and the child or fetus either will be or would have been affected with the genetic condition or not. As a result, the six possible outcomes are: [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. Table 2 displays the distribution of a hypothetical cohort of 500,000 pregnancies over these six clinical outcomes for Strategies VIII and IX using plausible assumptions for prevalence, sensitivity, specificity, and detection rates for the involved populations and tests.

These results reveal much about the consequences and tradeoffs of different policies. Fewer children are born with CF with Strategy IX than Strategy VIII, but the price of achieving this goal is that more total abortions are performed, and these tend to be terminations of pregnancies that would have resulted in the delivery of unaffected children had they been continued. The reason for the large number of abortions in Strategy IX is that the identification of each additional affected
pregnancy requires tests of lower and lower specificity used on pregnancies of only intermediate risk. The result is an increasing rate of false positive tests. The rate of miscarriages increases in this strategy as well because more couples undergo prenatal diagnosis, and this procedure induces a slight but tangible risk of miscarriage. Costs, not shown, are also much higher for Strategy IX.

So, even if the goal of CF carrier screening is to reduce the number of children born with this condition, many would want to balance that goal with the outcomes reflected in other cells of the panel. Some would argue that the goal is not the avoidance of CF births, but the identification of pregnancies at risk for CF. Under this notion the information provided through genetic carrier screening is valued independently of the decisions that might be made as a result.

**Problems with Economic Evaluation**

Similar concerns are reflected in the economic evaluation of these clinical strategies. In a cost-benefit analysis, all outcomes are evaluated in monetary terms and compared to a monetary measure of the additional costs incurred. Strategies producing an excess of benefits over costs are classified as desirable. Such an analysis might be used to compare the value of information provided to patients by a screening program with the costs of producing and implementing the information. In a cost-effectiveness analysis, clinical outcomes are measured and related to a measure of costs. Often, the analysis is expressed as a ratio of the cost incurred while achieving these clinical goals—for example, dollars per year of life saved. Even in a cost-effectiveness analysis, however, one must eventually have some sense of how many dollars saving a year of life is worth, or strategies in the end are unevaluable.

Nevertheless, many clinicians are uncomfortable with economic analyses, because the techniques are foreign to them, because they do not believe the measures of value are valid, because they find difficult or offensive the requirement that clinical outcomes be evaluable in monetary terms, or because they think costs ought not to matter. These feelings may be particularly pronounced in the case of reproductive decisions because of the special value placed on reproductive choice.
But even those comfortable with economic analysis in the main may have special problems evaluating outcomes in the case of genetic screening. In a conventional screening strategy for breast cancer, for example, one evaluates strategies that help individuals present at earlier and more easily treated stages. With genetic carrier screening, one evaluates strategies that prevent the births of individuals with the disease, rather than the disease in people already born. From a population perspective, the two approaches can yield identical results, but from an individual perspective conventional screening strategies work by preventing or treating disease, and genetic screening strategies works by preventing the births of persons who might develop the disease.

Such strategies bring the abortion debate to a new level of abstraction. Absent specific therapy, genetic screening in the reproductive setting at best replaces individuals with genetic conditions with those without them. It does nothing positive for the individuals who are affected, or those who would be.

These considerations do not mean that genetic screening programs to limit the number of births of affected individuals are necessarily bad, only that they are difficult to value. How does one evaluate, in dollars or some nonmonetary unit, the value of avoiding a delivery that would have resulted in the birth of a child with CF? Presumably, if the parents attach a positive value to the birth they would not terminate a pregnancy even at high risk and would thus reveal that they value the birth of a CF child as better than abortion. Conversely, a couple that chooses to terminate such a pregnancy reveals a set of values for which the birth of an affected child would be worse than an abortion. Since it is better never to have been pregnant than to have an abortion, such implicit valuations suggest that the birth of a CF child is worse than no pregnancy.

Such a decision would not imply, however, that should a child with CF be born to these parents, having that child survive is worse than having that child die. Most children with CF are deeply loved by their families. More likely the decision to terminate a pregnancy is based on an expectation that the abortion will be followed by a new pregnancy and a second chance at delivering an unaffected child.
In theory, for a specific couple or a specific individual one could engage in an exercise to assess the value, in monetary or non-monetary terms, of each of the six clinical outcomes in the context of an overall reproductive plan spanning several pregnancies. Such an exercise might help individuals understand their values and help them make choices, which is the purpose of policy analysis applied to the individual case. But in this case, great individual variation in values is likely, so it is virtually certain that no general policy could be ideal for everyone. In the case of conventional screening for breast cancer, all are likely to agree that more years of health are better than fewer, though they probably do not agree on how much better they are, and at how much cost in money, pain, or disfigurement. But as hard as it is to set a national policy for breast cancer screening, it is probably impossible and not very useful to set a uniform policy for genetic screening where values are likely to be even more varied.

Conclusions

Genetic screening is rapidly becoming an issue of public health. This is already the case with CF, and may soon be the case for heritable breast cancer. Quantitative policy analysis is increasingly recognized as a valuable tool for evaluating alternative screening programs, and the products of these analyses appear frequently in the medical literature, and frequently form the basis of clinical guidelines and recommendations. Even so, these analyses are difficult to perform because the problems they seek to model are not only complex, but also span clinical, ethical, social, and economic concerns.

In this paper we have discussed several issues we struggled with as we began to model the implications of alternative screening programs to identify CF mutation carriers. Each of these issues has required we make a choice in technique, and most other policy analyses will face similar choices. Often there is no best choice. Space limitations for published papers, and differences in the interests of different readerships, make it difficult to explain such choices in detail; yet, these decisions determine the way the results should be interpreted.
As complicated as these models may be, they are less complex than the actual clinical decisions faced by patients and health care professionals. Difficulties in modeling in the end reflect the complexity of the underlying clinical situation. As the use of genetic screening tests moves beyond the walls of specialized centers accustomed to these issues, policy analyses are likely to become more important as guides for practicing clinicians. Those who develop these analyses need to make sure that the implications of important assumptions are understood by the clinicians who will use them. At the same time, clinicians will need to enhance their understanding of what these models truly mean, and how they address underlying clinical, ethical, and economic issues.
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Table 1. Fifteen Plausible CF Carrier Screening Strategies. Not all possible or all plausible strategies are presented. Note that Strategies II and VI are the same as Strategies A and B shown in Figure 1. Results of Strategies VIII and IX are presented in Table 2.

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<th>Parental Sequence</th>
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<th>Additional Tests if One and Only One Parent Tests Positive</th>
<th>Strategy</th>
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</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. Multiple Clinical Outcomes of CF Carrier Screening Strategies. The two panels reflect Strategies VIII and IX from Table 1. Each strategy is applied to a cohort of 500,000 single pregnancies and reflects the distribution of those pregnancies among the six clinical outcomes described in the text. For a description of the two strategies, see Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Strategy VIII</th>
<th></th>
<th>Strategy IX</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With CF</td>
<td>Without CF</td>
<td>With CF</td>
<td>Without CF</td>
</tr>
<tr>
<td>Delivered</td>
<td>57</td>
<td>487,302</td>
<td>33</td>
<td>487,044</td>
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<tr>
<td>Terminated</td>
<td>142</td>
<td>0</td>
<td>166</td>
<td>170</td>
</tr>
<tr>
<td>Miscarried</td>
<td>1</td>
<td>12,498</td>
<td>1</td>
<td>12,586</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. Prescriptive Strategies for CF Carrier Screening. The tree is read from left to right. The square node indicates a choice to be made among the two strategies labeled A and B. The round nodes indicate outcomes that result from chance. For an explanation of the two strategies, see the text.

Figure 2. Non-Standard Strategies for CF Carrier Screening. The tree is read as in Figure 1. For a description of the two strategies, see the text.

Figure 3. Descriptive Strategies for CF Carrier Screening. The tree is read as in Figure 1, except that as new information is obtained, the couple or individual decides what to do, perhaps ignoring the information from the previous step. These decisions are represented by the square shaded nodes and could be replaced with estimates of the chances of each choice.
Prescriptive Strategy A

Both Partners Screen +

Prenatal Diagnosis

At Least 1 Partner Screens -

Continue Pregnancy

Fetus Inherits 2 Mutations

Terminate Pregnancy

Fetus Inherits <2 Mutations

Continue Pregnancy

Prescriptive Strategy B

One Partner -, One Partner -

Do Expanded Screen of - Partner

Both Partners Screen -

Continue Pregnancy

Continue Pregnancy

Fetus Inherits <2 Mutations

Continue Pregnancy

Both Partners Screen + After Expanded Screen

Prenatal Diagnosis

Fetus Inherits 2 Mutations

Terminate Pregnancy

Additional Prescriptive Strategies...

Figure 1
Figure 2
Figure 3
References


