CLINICAL UTILITY

Question 26: What is the natural history of the disorder?
Question 27: What is the impact of a positive (or negative) test on patient care?
Question 28: If applicable, are diagnostic tests available?
Question 29: Is there an effective remedy or acceptable action, or other measurable benefit?
Question 30: Is there general access to that remedy or action?
Question 31: Is the test being offered to a socially vulnerable population?
Question 32: What quality assurance measures are in place?
Question 33: What are the results of pilot trials?
Question 34: What health risks can be identified for follow-up testing and/or intervention.
Question 35: What are the financial costs associated with testing?
Question 36: What are the economic benefits associated with actions resulting from testing?
Question 37: What facilities/personnel are available or easily put in place?
Question 38: What educational materials have been developed and validated, and which of these are available?
Question 39: Are there informed consent requirements?
Question 40:What methods exist for long term monitoring?
Question 41: What guidelines have been developed for evaluating program performance?

CLINICAL UTILITY

Question 26: What is the natural history of the disorder?

Summary

- In the year 2000, the median age at death for individuals with cystic fibrosis is 24 years
- The projected median age for survival in the year 2000 is 32.2 years
- Respiratory morbidity is the most frequent cause of death, and liver disease is the second most frequent cause
- Improved survival time in recent years can be largely attributed to more effective management, delivered by specialized centers
- Examples of newer treatments include enzymes to digest mucus and lung transplantation
- Research is ongoing to develop strategies for gene therapy

Respiratory morbidity is the most frequent cause of death among individuals with cystic fibrosis. The highly viscous mucus secretions in the respiratory tract cannot be adequately cleared. This provides an ideal habitat for bacterial colonization and subsequent lung infection. This, in turn, results in chronic bronchial and lung inflammation. Bacterial infections associated with a marked inflammatory response occur frequently in untreated infants under three months of age (Armstrong *et al.*, 1995; Khan *et al.*, 1995). Some primary lung changes may precede postnatal lung infection (Ornoy *et al.*, 1987). Occasionally, inflammatory responses have been seen even in the absence of positive bacterial cultures, suggesting that some intrinsic factor, such as the biochemical defect itself, may act as a trigger (Khan *et al.*, 1995). The severe inflammatory response is responsible for progressive tissue damage which eventually results in destruction of the bronchial passages and, together with plugging of the airways, leads to respiratory failure. Airway obstruction, caused by abnormal secretion, inflammatory exudate and epithelial debris, results in further hyperinflation or collapse. Chronic hypoxia is a major factor causing pulmonary hypertension and cor pulmonale. Pneumothorax and hemoptysis are common complications in those with advanced disease.

Cystic fibrosis related liver disease is the second most common cause of mortality after lung disease. The incidence increases with age from about 0.3 percent before the age of 5 years to a peak of 8.7 percent in those aged 16-20 years (Scott-Jupp *et al.*, 1991). The exact pathogenesis of the disease is unknown; however, recent evidence suggests that defective CFTR chloride channel function may cause abnormal biliary secretions resulting in mucus plugging of intrahepatic bile ducts (Grubman *et al.*, 1995). This, in combination with other factors such as increased levels of toxic bile acids and inflammatory cytokines, has been implicated in the development of portal hypertension and associated cirrhosis (Maurage *et al.*, 1989; Tanner, 1992).

Severe gastrointestinal disease in the form of intestinal obstruction caused by meconium ileus is the first clinical manifestation in 10-18 percent of newborns with cystic fibrosis (Rescorla *et al.*, 1989; Littlewood 1992). Meconium ileus is frequently associated with peritonitis, volvulus and atresia. Because of the severity of these complications, mortality in the first month of life is higher when meconium ileus is present. Thereafter, the clinical course is similar whether or not meconium ileus was present (Coutts *et al.*, 1997), although those with meconium ileus may have a higher risk of developing liver complications (Padoan *et al.*, 1997).

Many of the subsequent clinical manifestations related to the gastrointestinal tract are due to malabsorption, the main cause of which is insufficient pancreatic enzyme and bicarbonate activity. In the absence of pancreatic enzyme secretion, protein and fat malabsorption occurs, leading to bulky, frequent malodorous stools with an abnormally high fat (steatorrhea) and nutrient content (Murphy *et al.*, 1991). Approximately 60 percent of neonates diagnosed with cystic fibrosis through neonatal screening already suffer from pancreatic insufficiency and require dietary pancreatic enzyme supplements (Waters *et al.*, 1990). By 12 months, the frequency of pancreatic insufficiency has risen to 92 percent (Bronstein *et al.*, 1992). Most of those who develop pancreatic insufficiency will do so before the age of 10 years (Cooper *et al.*, 1992). The prevalence of pancreatic insufficiency in adults with cystic fibrosis exceeds 85 percent (Gaskin *et al.*, 1982) and is probably closer to 95 percent. Further complications of pancreatic dysfunction include impaired glucose tolerance, leading to diabetes mellitus. As adults, cystic fibrosis patients are approximately six times more likely than unaffected individuals to develop digestive tract cancers (Neglia *et al.*, 1995; Schöni *et al.*, 1996). As with digestive tract cancer, the prevalence of diabetes is increasing in cystic fibrosis patients because of improved survival. In a recent study performed over a 5-year period, the average annual incidence was 3.8 percent, and prevalence increased from 11 percent to 24 percent, overall. In those aged over 20 years, the annual incidence was 9.3 percent, and the prevalence rose from 25 percent to 53 percent (Lanng *et al.*, 1994). Reports of microvascular complications such as retinopathy, nephropathy and neuropathy among cystic fibrosis patients with diabetes are also increasing.

Esophageal problems include frequent gastroesophageal reflux, peptic esophagitis or esophageal varices. Approximately 25 percent of cystic fibrosis patients aged 5 years or more have gastroesophageal reflux (Malfoot *et al.*, 1991). In the small intestine, viscous mucin leads to obstruction of the goblet cells, Brunner cells and even the lumen. Clinical problems include rectal prolapse, distal intestinal obstruction syndrome, intussusception and volvulus. More recently, fibrosing colonopathy leading to colonic strictures has been observed as a rare complication of high lipase pancreatic enzyme treatment.

Lung transplantation was introduced as a therapeutic modality for cystic fibrosis in 1988; three of those procedures were performed for that reason in 1988, and the number rose steadily on an annual basis until 1995, when 136 transplantations were carried out. The number leveled off, thereafter (Cystic Fibrosis Foundation, 2000). In the year 2000, 161 lung transplants of various types were carried out (bilateral 134, heart-lung 1, lobar-cadaveric 10, lobar-living related donor 11, lobar-unrelated donor 5). In addition, 18 liver transplants and 6 "other" transplants were performed. Patients with cystic fibrosis now account for an important portion of lung transplants done annually in the United States. Kurland and Orenstein [2001] wrote a commentary explaining the difficulties encountered by families in this situation. This article highlighted the psychological, social, medical and financial costs faced by patients, families, and caregivers, over and above the traditional stresses associated with managing this chronic, progressive disorder. Even in the absence of transplantation, patients with cystic fibrosis often face increasing psychosocial, as well as medical, difficulties as they reach adulthood. One young woman with cystic fibrosis recently described her day-to-day struggles (Hillyard, 2001). One important hope for the future is gene therapy, and research currently focuses on how this treatment might be effectively delivered to the lungs of affected individuals (McCray, 2001). Although promising, this treatment modality has not yet proven successful.

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Question 27: What is the impact of a positive (or negative) test on patient care?

Summary

When both partners have an identifiable mutation, genetic counseling is provided to advise the couple of the risk that the fetus is affected (1 in 4) and possible options

When one partner has an identifiable mutation but the other does not there are two possibilities depending on the screening model employed

- With the two-step (sequential) and expanded one-step (concurrent) models, the couple is notified and counseled that there is an increased risk over background, but no further testing is recommended
- With the one-step (couple) model, the couple will be classified as having a negative test result and not counseled.

When the first, or both, partners have a negative test, the couple receives a negative test result and no further testing is recommended.

Screening models

The initial impact of prenatal screening for cystic fibrosis on patient care depends upon which of three published models is being used.

The two-step (sequential) model, the pregnant woman's sample is collected and analyzed. If a mutation is identified, the woman is made aware of this finding, counseled, and her cooperation sought in obtaining a sample from her partner for DNA analysis. Approximately 1 in 30 screened non-Hispanic Caucasian women will require counseling in this model. When the partner is also identified as having a mutation, the couple will then be provided with more intensive counseling, given the 1 in 4 risk that the fetus will be affected by cystic fibrosis. Approximately 1 in 900 screened pregnancies will fall into this category. The uptake of diagnostic testing and decision-making about termination of affected fetuses found in pilot trials is summarized in Question 33, Table 4-3.

The one-step model, samples are collected from both the pregnant woman and her partner at the outset. DNA analysis is then performed on the woman's sample, but the partner's sample is tested only if a mutation is identified in the woman. Notification of a positive screening result is made only when both partners are found to carry a mutation (unless the woman specifically requests a report of her carrier status). In this model, more effort is required initially to obtain samples from both partners, but the need for counseling is reduced; being restricted to the 1 in 900 couples who will need to make decisions about diagnostic testing.

The modified one-step model, has been recommended by the American College of Medical Genetics (Grody *et al.,* 2001). It calls for samples to be collected at the outset from both partners (as in the one-step model, above). DNA testing is then performed on all of the samples from both partners. Notification is made when a mutation is found in either partner, and counseling is provided.

If all couples with positive screening results for cystic fibrosis were to choose diagnostic testing, this would lead to one additional amniocentesis (or CVS) for every 900 couples screened. The impact on prenatal diagnostic testing services is relatively small, in comparison to demands incurred by other prenatal screening tests. For example, if a woman's age of 35 is used as a screening test for Down syndrome, 100 amniocenteses would be performed for every 1,000 women screened. Even with more

efficient serum screening tests for Down syndrome, between 30 and 50 amniocenteses would be indicated for every 1,000 screened women.

Other data indicate that during the two-step process, the women identified as being carriers of a CF mutation usually experience some anxiety while awaiting the partner's results. However, this worry usually resolves when the partner is found not to carry and identifiable mutation (Miedzybrodzka *et al.*, 1995; Mennie *et al.*, 1992; Grody *et al.*, 1997). In both the two-step and modified one-step process, couples will be identified where one partner is a carrier and the other is not. These couples are at a higher risk than background (Question 23), but no definitive testing is available to provide diagnostic testing for their fetus.

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CLINICAL UTILITY

Question 28: If applicable, are diagnostic tests available?

The purpose of prenatal screening for cystic fibrosis is to determine whether or not that disorder is present in the fetus. The diagnostic test is DNA testing for cystic fibrosis mutations in fetally derived cells obtained via amniocentesis, or chorion villus sampling (CVS). If two disease-causing mutations are identified, the couple is counseled that the fetus will have the disorder.

Question 29: Is there an effective remedy, acceptable action, or other measurable benefit?

There is no effective treatment *in utero* for cystic fibrosis identified in the fetus. However, the pregnant woman and her partner can choose to terminate the pregnancy and thus avoid the birth of an affected child. For couples who choose to terminate an affected pregnancy, there is an assumption of benefit, although little research exists on the psychological sequelae of this decision. The couple might also choose to continue the pregnancy and plan for initiating treatment immediately after birth. There is little information about the psychological sequelae of this decision, either. The couple might want to consider alternatives for future reproductive planning, including adoption and preimplantation genetic testing. Some couples identified as carriers might be unwilling to undergo further testing in their current pregnancy but might, nevertheless, alter their reproductive behavior in future pregnancies. There are some studies that suggest that carriers misunderstand the implications of carrier status for their own health and for the health of their children.

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CLINICAL UTILITY

Question 30: Is there general access to that remedy or action?

Pregnancy termination before the third trimester is legal through federal statute, but access is limited by two factors. First, there are areas of the country where health care practitioners providing this service are scarce. Secondly, there are many states in which pregnancy termination is not a reimbursable service; this affects access by women with limited economic resources. For couples choosing to continue the pregnancy, resources for treating the infant and child exist throughout the United States.

CLINICAL UTILITY

Question 31: Is the test being offered to a socially vulnerable population?

Pregnant women are considered a medically vulnerable population, and a case can be made for their being psychosocially vulnerable, as well. There is often a time-related urgency involved in medical decisions during pregnancy, which can foreshorten time to carefully consider options. In addition, data have shown that women's motivation to do whatever they can to protect the health of their fetus can lead to overestimates or misunderstandings of the benefits of prenatal testing. Offering screening for cystic fibrosis early in pregnancy (at the first prenatal visit between 8 and 12 weeks' gestation) allows for more time to consider further testing if both members of the couple are found to be carriers. Carefully constructed and validated patient informational materials will also be important (Question 38). It may be helpful to develop strategies for educating the public about this testing to alleviate the burden of 'learning' at the time of pregnancy.

CLINICAL UTILITY

Question 32: What quality assurance measures are in place?

Summary

A quality assurance plan assists laboratories in ensuring reproducible, high quality results in a timely manner that are clinical useful to patients and providers.

The components of a generic molecular quality assurance program are well described and are available from national and state regulatory agencies and professional organizations.

Specific professional guidelines for prenatal cystic fibrosis quality assurance do not yet exist, but ACMG is in the process of producing such a guideline.

Quality assurance oversight is provided by the laboratory certification process administered by Federal or State agencies (CLIA and New York State) or by professional organizations (College of American Pathologists).

Definition Quality assurance is the program that laboratories develop to ensure reproducible, high quality results in a timely fashion, which are clinically useful to patients and providers. A major goal is to minimize the human error that accounts for the majority of laboratory errors.

Standards and guidelines and checklists

Clinical molecular genetic testing laboratories must follow good laboratory practice guidelines and subscribe to external quality assessment programs. Guidelines, recommendations, and checklists are available from national and state regulatory agencies and professional organizations regarding quality control/quality assurance, inter-laboratory comparison/proficiency testing, and laboratory personnel requirements (Table 4-1). While multiple standards and guidelines exist, only three are enforceable and require laboratory inspection for certification. These include: Clinical Laboratory Improvement Amendments (CLIA), College of American Pathologists (CAP), and New York State. All other guidelines are efforts of genetics and other professional organizations to regulate the genetic testing industry, but are without enforcement.

Table 4-1. Guidelines, Recommendations, and Checklists that Address Quality Assurance

Guidelines, Recommendations and Checklists	Source / Reference
Clinical Laboratory Improvement Amendments of 1988	Federal Register 1992;57:7002-3
Genetic Testing Under the Clinical Laboratory Improvement Amendments	Federal Register 2000;65: 25928-24934
New York State Department of Health Laboratory Standards (9/00)	www.wadsworth.org/labcert/download.htm
Molecular Diagnostic Methods for Genetic Diseases: Approved Guidelines	National Committee for Clinical Laboratory Standards MM1-A Vol 20 #7
CAP Checklist	College of American Pathologists Www.cap.org
Standards and Guidelines for Clinical Genetics Testing	American College of Medical Genetics Www.faseb.org/genetics/acmg/stds
European Concerted Action on Cystic Fibrosis	(BMH-4-CT96-0462)

To address concerns raised through the ACMG/CAP proficiency testing program for cystic fibrosis (i.e. variability of from one to 70 mutations in the cystic fibrosis test panel), laboratory standards and guidelines for cystic fibrosis carrier testing have now been developed (Grody *et al*, 2001). Cystic fibrosis mutation analysis is a complex laboratory procedure which benefits from a uniform testing policy and test interpretation. Because of this, testing should to be restricted to laboratories with the necessary expertise, experience, and resources. Most components of generic quality assurance are well-established and consistent among the published guidelines. However, some are controversial. For example, the qualifications for clinical laboratory directors have not been universally agreed upon by professional and licensing organizations. Overall, the components of quality assurance can be sub-divided into three stages: pre-analytical, analytical, and post-analytical.

Pre-analytic

The pre-analytic components of a quality assurance program include those activities that occur prior to the sample being tested. A general overview of these components is provided below.

- Informed consent: This is one of the most controversial areas of genetic testing. Issues surrounding informed consent vary depending upon the guideline and when it was written, and. The NCCLS describes informed consent as a voluntary process that is non-coercive and easily understood. The information should include risks and benefits of testing and specific information about test performance. Consent requirements are based on applicable state and federal laws. New York requires that informed consent state the purpose of testing, include genetic counseling, the meaning of a positive test result in the context of disease, the positive predictive value of the test, the test disclosure process, and the stipulation that no additional testing be allowed on the specimen without consent. Neither CAP nor ACMG specifically addresses the informed consent requirement in either the checklist or technical standards and guidelines. More recently, the ACMG Laboratory Standards and Guidelines for Cystic Fibrosis Carrier Screening (Grody *et al,* 2001) included a recommendation that informed consent be obtained. The Task Force on Genetic Testing requires written informed consent, and CLIAC states that an authorized person obtain the informed consent. While there is now general agreement that informed consent should be obtained, the controversial issue has been over who is responsible. According to the Genetic Testing Workgroup of CLIAC, informed consent is now required for all genetic tests. It is the responsibility of the person ordering the test to obtain informed consent from the patient. The level of informed consent depends on whether the test is used for predictive or diagnostic purposes. The laboratory should be available to assist in determining the appropriate level of consent. The requisition must include a space for the person ordering the test to signify that the appropriate level of consent was obtained. The inclusion of a re-use acceptance (opt-out) check-off box should also be on the consent form.
- Confidentiality: All genetic testing is confidential. HIPAA Final Regulation, published December 28, 2000, addresses confidentiality of personal health information (Question 44).
- Specimen types: Specimen types include blood or buccal swabs for carrier testing; direct or cultured amniocytes or chorionic villi samples for prenatal diagnosis. Each laboratory determines the exact sample type and amount required for its testing method, and furnishes that information to referring centers. Prenatal samples are usually tested during the first trimester. For fetal testing, maternal cell contamination studies must be performed on fetal and maternal specimens using highly polymorphic STR markers to detect the presence of contamination.
- Standard information for the requisition slip: This include patient-specific information such as name, date of birth, sex, ethnicity and week of gestation, and sample information such as sample type, date

of collection, and indication for testing. Also included is reporting and billing information, such as referring physician/health professional and source of payment.

- Criteria for sample rejection: Each laboratory develops its own written criteria for sample rejection.
- Accessioning. Each specimen is assigned a unique identifier. Specimens from the same patient will have individual identifiers.
- Specimen transport and storage: Each laboratory determines its own criteria based upon experience and furnishes that information to clients.

Analytic

- Test validation and characterization: All guidelines agree that the laboratory is responsible for documenting the validity of its tests. However, the components of test validation have only been addressed by the New York State guidelines and guidelines proposed by the US Food and Drug Administration. Literature review and analytical/clinical studies provide necessary information, including description of the mutations tested, the performance properties of the test, the clinical utility, and limitations. One controversial area in test validation surrounds the number of probands (positive controls) that must be tested in order to validate a test. The Genetic Testing Workgroup for CLIAC recommended that the appropriate number of positive probands required for test validation should be subject to professional guidelines rather than regulations and be disease-specific. These recommendations have been endorsed by ACMG.

  New York State requirements for test validation The following information is required by New York State for each new test:

  - A description of the disease, the gene, the test, the principle of the test, and indications for testing.
  - Assay description, including: all information relevant to the test, DNA extraction protocol, dilution, quantitation; reagent recipes; vendor/catalog information; reagent quality control (in/out dates, storage requirements); required equipment/vendors; step-by-step protocol; primer list with sequences, source of primers; description of positive controls, source, how verified; description of negative controls; technical limitations and troubleshooting guide; equipment, and procedures for quality control.
  - Description of expected results from controls and what an indeterminate result looks like.
  - Sample requisition form, including physician name, address, phone number, fax, date specimen collected, patient name, and accession number.
  - Sample reports for negative, positive, indeterminate or rejected results, including interpretive statement explaining test results for each example, test limitations and relevant disclaimers, specimen information, and signature of laboratory director.
  - Consent form.
  - Explanation of how validation studies were performed, results, and interpretation. High quality original results showing homozygous normal, carrier, homozygous mutant.
  - Reproducibility, sensitivity, specificity, positive predictive value.

  Proposed FDA requirements for test validation The following information has been proposed as the components of a validation study by the FDA that would be completed prior to offering testing. Laboratories would submit an application for each new test based on FDA guidelines.

  - Intended use of test
  - Indications of test

- Method category
- Methodology, specific
- Examples of test results
- Analytical validity (control specimens, number tested, types of specimens, results, sensitivity, specificity, accuracy, reproducibility, confirmation, proficiency testing, statistical analysis)
- Quality control procedures (external controls, checks of results, repeat specimens, frequency of QC assessments)
- Clinical validity (literature citations or study results and summary)
- Clinical interpretation (report templates, information for risk analysis)
- Limitations (technical, biological)
- Clinical utility (interventions available for positive test result; level of efficacy)

- External proficiency testing: The goal of proficiency testing, which is currently the main indicator of quality assurance, is to allow laboratories to identify individual areas of weakness and take steps to improve. The College of American Pathologists requires participation in proficiency testing as part of the laboratory accreditation process. The ACMG/CAP proficiency testing program has provided participating laboratories in the MGL (molecular genetic laboratory) survey with two or three cystic fibrosis challenges once or twice yearly since 1995. Interpretive questions are also included in this survey. CAP estimates that approximately 85 percent of molecular genetic testing laboratories participate in this program. Proficiency test performance is anonymously reviewed and analyzed. The ACMG/CAP Committee develops a report for each participating laboratory. The performance of clinical molecular laboratories on these proficiency tests will be graded beginning in 2002, and consumer groups will have access to aggregate information. The proficiency testing program will also provide more challenges for laboratories. Laboratories that test patients from New York State must obtain a license from the New York State Department of Health. While the New York State program does not provide proficiency testing for clinical molecular genetic laboratories, it does require these laboratories to participate in an established proficiency testing program, internal or external, at least twice each year. New York State certified laboratories must undergo on-site inspections every other year and submit validation materials for each assay performed.

  External proficiency testing programs outside the United States
  The European Concerted Action on Cystic Fibrosis has surveyed over 150 clinical molecular genetic laboratories in Europe for cystic fibrosis test performance and has made the following recommendations for quality improvement:
  - Develop quality systems leading to their accreditation by national or European agencies
  - Participate regularly in external quality assessment schemes
  - Test for at least 80 percent of the mutations found in the laboratory's region
  - Use validated testing methods appropriate to detect at least 80 percent of the mutations based on technical and economic considerations
  - Monitor the indications for cystic fibrosis testing
  - Provide relevant information to the clinical staff for risk calculation and counseling
  - Network with other laboratories in their region, country or at the European level

  The European Molecular Genetics Quality Network (EMQN) is focused on improving the standards of European clinical molecular genetics laboratories by providing external quality assessment programs and best practice guidelines. A basic difference between the ACMG/CAP proficiency

testing program and that of EMQN is survey administration. The ACMG/CAP program coordinates all disease-specific challenges from a single source, while EMQN identifies a management group to develop disorder-specific proficiency testing and a national partner to disseminate the results to participating laboratories. This program has not yet begun the cystic fibrosis module, which is intended to allow continuation of the trial developed by the European Union funded Concerted Action on Cystic Fibrosis (ECACF).

- Control of PCR contamination: A major concern for any clinical molecular laboratory is false-positive results due to contamination by PCR products. This concern can be addressed by following the recommended guidelines for laboratory design, laboratory practice, selection and preparation of controls. This quality assurance standard is generic but applies to cystic fibrosis testing.
    - Laboratory design: physically separated into three areas: reagent preparation, specimen preparation, and PCR and product detection
    - Laboratory practice: the use of positive displacement pipettors, cotton plug tips, gloves, lab coats, and careful preparation of reagents
    - Selection and preparation of controls: Include positive controls for each allele targeted in the test (e.g., a 25 mutation panel should have 25 positive controls). Positive controls should amplify weakly to minimize large quantities of PCR product. No-DNA controls should be included in every run. Assays based on the presence or absence of PCR product must include a known positive control as an amplification control. Include a sizing ladder if the assay is based on fragment size. Include appropriate controls in mobility shift assays. Confirm unexpected results.

Post-analytic

Some issues of post-analytical testing, such as reporting, mutation nomenclature, and retention of records, are held in general agreement by various professional societies and regulatory groups.

- Laboratory reports: Laboratory reports are to the physician or healthcare professional, not the patient. The report should echo any information collected on the requisition slip that is used for identification or as part of the interpretation. In addition, test-specific information should be included such as laboratory identifiers, testing method, test result, interpretation, recommendations (e.g., genetic counseling) and the signature of the laboratory director. The ACMG recommendations for cystic fibrosis testing (Grody *et al.*, 2001) have included model reports for negative results, including residual risk based on ethnicity, positive report templates, and complex interpretations.
- Nomenclature for mutations: The nomenclature developed by the Ad Hoc Committee on Mutation Nomenclature and Antonarakis *et al*. is recommended. The nomenclature established for cystic fibrosis mutations follows these guidelines and is found in the cystic fibrosis mutation database at http://www.genet.sickkids.on.ca/cfr.
- Retention of records and specimens: The CLIAC Workgroup recommended that a minimum of 10 years was appropriate for records retention of both positive and negative results. However, guidelines for specimen retention time have not been agreed to. There is some controversy over specimen retention, particularly surrounding the opt-out requirement.
- Genetic counseling: All current standards and guidelines address the responsibility of the laboratory to recommend genetic counseling, when appropriate. However, none require the laboratory to actually provide genetic counseling to patients. The laboratory can help guide healthcare professionals to genetic counseling resources.

Is there ongoing review of quality assurance?
The CAP ACMG Molecular Genetics Resource Committee has the main responsibility for the review of the external proficiency testing results. In addition, the ACMG Quality Assurance Subcommittee of the Laboratory Practice Committee reviews these same proficiency testing results at semi-annual meetings. This Committee is composed of clinical laboratory directors (including molecular, biochemical, and cytogenetic laboratories) and representatives from the ACMG/CAP proficiency testing program. Threshold indicators are set for addressing laboratory problems related to specific disease testing, including cystic fibrosis. An additional charge for this committee is to develop of disease-specific technical standards and guidelines. A workgroup composed of laboratory directors with extensive experience in cystic fibrosis testing is in the process of developing these guidelines, anticipated to be released in 2002. Additional goals of the Committee include the development of technology-specific guidelines targeting the methodology used most commonly in laboratories performing cystic fibrosis testing.

Concerns about the quality of genetic testing: The McGovern Report
Although all laboratories performing genetic testing must comply with general regulations under the Clinical Laboratory Improvement Amendments (CLIA), the Task Force on Genetic Testing concluded that the current CLIA requirements are insufficient to ensure quality of molecular genetic testing. The McGovern Report (McGovern *et al.*, 1999) concluded that a number of laboratories had suboptimal quality assurance practices. This survey included 245 molecular diagnostic laboratories across all settings performing testing for over 90 genetic diseases. The main outcome measure was a QA score based upon ACMG Laboratory Practice standards. The report concluded that many molecular genetic laboratories are not performing well. Unfortunately, the study did not focus on clinical laboratories that special in testing for genetic disease. Nevertheless, the report did provide some useful information. It found that 33 percent of the lower scoring laboratories were headed by non-board-certified directors and that 45 percent of lower-scoring laboratories were in a research setting. Indicators of good performance included a larger menu of tests, a larger number of tests performed annually, and a clinical laboratory certified by CLIA '88. While concerns have been raised about the quality of molecular genetic testing, few data exist to substantiate these fears. In a recent report (Hofgartner *et al.*, 1999) which surveyed 42 genetic testing laboratories, significant problems during genetic testing were found to occur infrequently (<0.5 percent in most laboratories), and problems resulting in patient harm were found to be rare (0.0008 percent).

CDC recommendations for quality assurance programs
The following are genetic testing quality assurance recommendations developed for the Centers for Disease Control and Prevention. They include:

- conduct pilot research to develop positive controls and test samples for pilot performance evaluation programs
- develop pilot evaluation programs to supplement what already exists, particularly for diseases and/or methodologies not covered by existing programs
- establish laboratory-oriented, disease-specific consortia to provide quality assurance support as a forum for information networking, and providing methods validation through results comparison;
- To establish and link laboratory oriented and disease-specific databases with other appropriate internet resources
- To improve training and continuing education for clinicians, laboratory scientists, and technicians

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CLINICAL UTILITY

Question 33: What are the results of pilot trials?

Summary
At least thirteen pilot trials of prenatal screening for cystic fibrosis have been published.

- They use all three screening models successfully (two-step, one-step, and expanded one-step)
- Both blood and buccal samples have been used
- Relatively few mutations were included in the panels; usually about 6 and none more than 16.
- Populations were usually non-Hispanic Caucasian and/or Ashkenazi Jewish
- Where screening uptake could be measured, it ranged between 57 and 99 percent (median 78 percent)
- Of 54 screen positive couples, 49 (91 percent) chose to have prenatal diagnosis.
- Of 18 couples with an affected fetus, 15 (83 percent) chose to terminate the pregnancy.

Pilot trials are an important step in translating research knowledge into practice. Types of data collected in pilot trials that cannot be obtained in other ways include:

- the rates at which health practices offer testing,
- the acceptance rates by the target population,
- the acceptance rates for diagnostic testing,
- the decision-making process when an affected pregnancy is identified,
- the overall satisfaction with the screening process,
- the analytic performance in a routine testing environment,
- the verification of prevalence estimates in the 'real world',
- the costs and benefits of screening.

The last three listed topics are addressed further in other sections. Pilot trials should be run in an environment where the data can be collected, analyzed and reported promptly. Often, pilot trials are short-lived and test relatively few subjects; these constraints place limitations on reliable estimates. This disadvantage can sometimes be overcome by combining information from multiple trials. In addition, some trials are translated into routine practice upon completion. In such instances, it might be possible to obtain supplementary information that accumulates after the trial itself has been analyzed and published.

Prenatal screening for cystic fibrosis is usually offered using either a two-step or one-step model. In the two-step (or sequential) model, the woman's sample is collected and tested. Carrier status is routinely reported. Only when a mutation is detected in the woman (about 1 in 30 women) is the partner asked to provide a sample. If a mutation is also detected in the partner (about 1 in 900 couples), the fetus is at a 1 in 4 risk of having cystic fibrosis, and prenatal diagnostic testing can be offered. In the one-step (or couple) testing, both partners provide samples prior to testing. The couple is considered positive only when an identifiable mutation is found in both (about 1 in 900). Carrier status is not routinely reported, unless a mutation is found in both the woman and the partner. In some studies, the one-step protocol is expanded to test samples from both partners, with all carriers notified. This will be called expanded one-step screening. The following three tables summarize published (and some unpublished) data from the population-based pilot trials of prenatal cystic fibrosis screening. The first pertains to descriptive and

methodologic characteristics of the studies, the second describes the setting and population, along with screening and partner uptake rates, and the third presents the decision-making of screen positive couples.

Table 4-2 shows the location of each study, along with the date of its earliest published report. The number assigned to each pilot trial in Table 4-1 will be used in Tables 4-2 and 4-3 to identify it in relation to its specific results. The number screened is the actual number of women/couples who accepted testing. Data relating to women/couples with a family history of cystic fibrosis have been removed, so, in a few instances, this number is slightly smaller than that reported by the authors. Table 4-1 lists the time period for each of the studies and the methodology used in screening.

Table 4-2. Descriptive and Methodologic Characteristics of Prenatal Cystic Fibrosis Pilot Trials

Location (first published)	Study Number	Time Period	Model Type*	Sample Type**	Number of Mutations Tested	Women (Couples) Screened
Edinburgh, Scotland (1992)	1	1990-5	2 then 1	Bl or M	6	17,544
Copenhagen, Denmark (1993)	2	1990-2	2	Bl	1 then 6	6,599
Manchester, England (1993)	3	1991-4	1 (E)*** or 2	M	4	529
Oxford, England (1993)	4	1990-2	1	Bu	3 then 6	543
East Berlin, Germany (1994)	5	1990-3	2	Bl	1 or 3	637
Maine, USA (1994)	6	1994-2000	1	Bu	7 then 11	5,747
Aberdeen, Scotland (1995)	7	Not reported	1 or 2	M	4	1,815
Rochester, NY USA (1996)	8	1993-4	2	Bl or Bu	6 then 16	4,879
N California, USA (1996)	9	1991-2	2	Bl	6 or 12	5,161
Leeds, England (1996)	10	1993-4	2	Bl or Bu	1	3,773
Milan, Italy (1996)	11	1992-4	1 (E)	Bl	7	1,114
Los Angeles, USA (1997)	12	1993-5?	2	Bu	6	3,192
New York City, USA (1997)	13	Not reported	1 (E)	Bl	5	3,792

* 1 = one-step (or couple) model, 2 = two-step (or sequential) model, 1 (E) = expanded one-step model in which both partners are tested and both results are reported

** Bl= blood, Bu = buccal scrapings, M = mouthwash

*** (E) = indicates an expanded one-step protocol, in which samples are tested from all women and all partners, with all carriers notified.

Table 4-3 provides more specific information about the screening process for each of the pilot trials. The trials are coded according to the study numbers assigned in Table 4-2. In some cases, a single report includes data from both one-step and two-step components of a given trial. Screening uptake rate is defined as the number of women/couples accepting testing, divided by the number offered testing. Partner uptake is defined differently for one-, or two-step trials. In two-step trials, it is the number of partners of screen positive women who opt for testing, divided by the number of screen positive women. In one-step trials, it is the number of couples who both provide samples, divided by the total number of

couples who provide at least one sample. For trials employing both models, both rates are provided. Uptake rates are all higher than 50 percent, with most above 70 percent. Partner uptake rates are all high, but nearly all studies report less than 100 percent partner compliance. Most screening programs chose to focus in the first trimester of pregnancy.

Table 4-3. Prenatal Cystic Fibrosis Pilot Trials: Population Description and Screening Uptake Rates

Study Number	Study Setting	Payment Source	Gestational Age (wks)	Race/ Ethnicity	Screening Uptake (%)	Partner Uptake (%)	
						One-step	Two-step
1	Hospital Clinic	Routine	12	Scottish	78	ND	99
2	Hospital Clinic	Funded Study	12	Danish	89	-	94
3	Primary Care	Funded Study	7	English	85	92	100
4	Hospital Clinic	No Charge	< 19	English	67	ND	-
5	Prenatal Clinic	No Charge	< 16	German	99	-	100
6	Primary Care	Insurance	12	NEC	NA	98	-
7	Hospital Clinic	Funded Study	~11	Scottish	90	94	98
8	Primary Care	Funded Study	NA	Mixed	~57	-	85
9	HMO	Funded Study	≤ 16	Mixed	78	-	86[1]
10	Hospital Clinic	Funded Study	~13	English	62	-	98
11	Private Clinic	Self-Pay	~11	Italian	98	ND	-
12	HMO/Hospital	Funded Study	< 18	Mixed	75	-	85
13	Referral Center	Funded Study	~12	Jewish	NA	NA	-

NA = not available, ND = not done, NEC = northern European Caucasian

[1] Excludes 7 spontaneous losses that occurred prior to the partner's sampling. Were these included, the rate would be 82 percent.

Table 4-4 shows the number of couples with positive screening results and their subsequent decision-making. Of the 54 screen positive couples, 49 (91 percent) chose to have prenatal diagnosis. In those, diagnosis was successfully completed in 46 (94 percent). Of the 18 couples with affected fetuses, 15 (83 percent) chose to terminate the pregnancy.

Table 4-4. Prenatal Cystic Fibrosis Pilot Trials: Results of Testing

Study Number	Number of Screen Positive Couples (%)	Number of Couples Choosing Prenatal Diagnosis		Number of Affected Fetuses	Number of Couples Choosing Termination of Pregnancy
		Chosen	Completed		
1	**16**[1]	**14**	**14**	**7**	**7**
2	3	3	3	1	1
3	1	1	1	0	-
4	0	-	-	-	-
5	1	1	1	1	1
6	7	6	6	3	1
7	2	2	2	0	-
8	5	4	4	0	-
9	7	7	5[2]	1[3]	0
10	3	2	1	0	-
11	2	2	2	1	1
12	1	1	1	1	1
13	6	6	6	3	3
Totals	54	49	46	18	15

[1] Subsequent pregnancies in carrier couples have been removed.
[2] Three pregnancies miscarried prior to prenatal diagnosis; cystic fibrosis was identified in one of these, using abortus material.
[3] delF508 homozygous twins were identified

The following is a brief summary for each of the 13 prenatal cystic fibrosis screening pilot trials contained in the previous three tables. The number preceding the location is the study number referred to in the tables.

1. Edinburgh, Scotland – Prenatal screening for cystic fibrosis using the two-step model was offered at a hospital maternity clinic between 1990 and 1992 (Mennie *et al.*, 1992). Overall, 4,978 women provided blood samples that were tested for six mutations (delF508, G551D, G542X, R553X, delI507, 621+1G-T). The ARMS™ methodology (both in-house and from Cellmark) was used. Mouthwash samples were collected from the partners when the woman tested positive. The trial was considered by the authors to be successful, but one drawback was noted - the need for a nurse to counsel the one in 26 women with positive results. In response to this, the group then employed the one-step model between 1992 and 1994 (Livingstone *et al.*, 1994). During that portion of the study, 5,922 women were screened at two hospital maternity clinics using only mouthwash samples and the same 6 cystic fibrosis mutations. The one-step model was also considered by the authors to be satisfactory, and they reported it to be associated with less anxiety than the two-step model. In 1994, prenatal screening for cystic fibrosis using the one-step model was integrated into routine service (Brock, 1996). Between 1994 and 1995, an additional 6,664 women opted for screening. Overall, 17,544 women were screened, 22 at-risk couples were identified, and eight affected fetuses were diagnosed. All eight couples opted for termination. Several screen

positive couples had subsequent pregnancies, including at least one affected pregnancy. These have been removed from the summaries.

2. Copenhagen, Denmark – Over two years, prenatal screening for cystic fibrosis using the two-step approach was offered to two groups of women; those attending clinic for a CVS and those attending clinic for routine prenatal care (Schwartz *et al.*, 1993). A sample of whole blood from the woman was tested for the delF508 mutation. Partners of screen positive women were tested for 6 mutations (delF508, G551D, G542X, R553X, delI507, 621+1G-T). The Cellmark ARMS™ technology or an in-house assay were used. The authors considered the pilot trial to be successful in both settings. There is no indication that screening continued in Copenhagen after the study concluded.

3. Manchester, England – Over three years in six general practices, prenatal screening for cystic fibrosis was offered and accepted by 529 couples at the first prenatal booking; 267 allocated to the two-step model and 262 allocated to a modified one-step model (both samples were tested simultaneously and individual results were reported). Screening uptake rates were similar in the two arms. Mouthwash samples were collected and tested for the four most common mutations (delF508, G551D, G542X, 621+1G-T). The Cellmark ARMS™ kit was used. If the couple were of Jewish heritage, W1282X was also tested. The authors concluded that screening was efficient, uptake was high, but the process was associated with some anxiety (Harris *et al.*, 1992; Harris *et al.*, 1993; Hartley *et al.*, 1997).

4. Oxford, England – Over one year, 543 couples attending the antenatal clinic prior to 19 weeks' gestation accepted screening using the one-step model (Wald *et al.*, 1993). Buccal samples were collected and tested for delF508, G551D and R553X during the first four months and for an additional four mutations (G542X, 621+1G-T, W1282X/R1283M). The Cellmark ARMS™ technology was used after the first four months. The authors reported that screening was acceptable to both staff and patients and could be readily incorporated into antenatal care, but felt that the process would be better if done earlier in pregnancy. Screening was not offered after the conclusion of this study.

5. East Berlin, Germany – Over approximately two and one-half years, two-step screening was offered in two prenatal clinics with 638 women being tested prior to 16 weeks' gestation (Jung *et al.*, 1994). Initially, whole blood was collected, but, later, dried blood spots were collected and tested for delF508. An in-house assay protocol was used. Partners of screen positive women were tested for two additional mutations (R553X and G551D). Uptake was very high, with only one woman declining to be screened. The authors concluded that screening is generally acceptable in Germany.

6. Maine, USA – Over a five year time period, one-step screening was accepted by 4,102 couples throughout the state, when offered by primary care providers (Doherty *et al.*, 1994; Doherty *et al.*, 1996; Bradley *et al.*, 1998; Bradley, personal communication, 2001). Buccal scrapings were collected. During the pilot phase, seven mutations were tested, using the Cellmark ARMS™ technology (delF508, G551D, R553X, G542X, 621+1G-T, and W1282X/R1283M). Later, 5 mutations were added to the panel (N1303K, 1717-1G-T, 3849+10kbC-T, R1162X, and R334W). Couples of French Canadian heritage were tested for an additional three mutations (A455E, 711+1G-T and I148T). The authors concluded that it was feasible to incorporate one-step prenatal screening into the routine of primary care practices. Since the conclusion of the pilot trial, prenatal screening has been offered in Maine with reimbursement by nearly all third party payors. For this reason, the table includes some unpublished data.

7. Aberdeen, Scotland – Over an unstated time period women/couples were randomly allocated to one of two arms of the pilot study; 1487 women accepted two-step screening and 321 accepted one-step screening (Miedzybrodzka *et al.*, 1995). Screening uptake rates were similar for the two groups. Mouthwash samples were collected in the second trimester or earlier and tested for four mutations (delF508, G551D, G542X and 621+1G-T). The authors reported that both methods of screening worked well in practice, with more laboratory time necessary to match samples in one-step screening, but more counseling time necessary for two-step screening.

8. Rochester, New York – Over an unstated time period, 4,879 women were screened using a two-step protocol (Loader *et al.*, 1996). A relatively small number of these women were not pregnant and the published results did not distinguish between pregnancy and non-pregnancy. However, the overall reported rates were similar to those for pregnant women only (Rowley, personal communication, 1999). About 5 percent of the population was non-Caucasian (2.1 percent African, 1.6 percent Hispanic, 1.1 percent Asian, and 0.4 percent Native American). Blood samples were collected and tested for six mutations (delF508, G542X, G551D, R553X, W1282X and N1303K). A reverse dot blot technology from Roche Molecular Systems was used. Later in the study, 10 mutations were added (R117H, R334W, R347P, A455E, delI507, 1717-1G-A, S549N, R560T, 621+1G-T, 3849+10kbC-T). The authors reported that prenatal screening can be offered by prenatal care providers without incurring adverse outcomes associated with the process.

9. Northern California, USA – Over a 10 month time period, this large HMO offered two-step screening to its members; 5,161 women consented (Witt *et al.*, 1996). Blood samples were collected at 16 weeks' gestation or earlier and sent to one of two laboratories. The first measured six mutations (delF508, G542X, G551D, R553X, W1282X and N1303K) the second measured six additional mutations (R117H, 621+1G-T, delI507, 1717G-A, R560T, and S549N). After six months, all specimens were tested for 12 mutations by the second laboratory. Males were always tested using the larger panel. Overall, 73 percent of the participants were Caucasian, 20 percent Hispanic, and 7.1 percent other racial/ethnic groups. The authors reported that large-scale prenatal population screening was acceptable. No significant deterrents to population screening were identified. In 2000, this program began offering screening for cystic fibrosis to its members as part of routine prenatal care.

10. Leeds, England – Over a 21 month period two-step screening was offered at two hospital obstetric units and eight general practices in greater Leeds; one-step screening was available upon request (Cuckle *et al.*, 1996). A total of 3,773 women accepted testing for one mutation (delF508). An in-house assay was used. Additional, unspecified mutations were added, if the participants were of Jewish heritage. At one hospital, blood was initially collected, but eventually all sampling was by mouthwash. The authors reported that screening could be readily integrated into existing obstetric care, in both hospital and general practice settings.

11. Milan, Italy – Over a three year time period, women referred to a private, high risk obstetric clinic were offered two options: be tested using the expanded one-step model, or have the fetus tested (after a diagnostic procedure for other reasons) without knowledge of parents' carrier status (Brambati *et al.*, 1996). A total of 1,114 couples provided blood samples in the first trimester. Initially, the samples were tested for a single mutation (delF508). An in-house ARMS™ assay was used. Later, a modified commercial kit (Innogenetics, Belgium) was used to identify an additional 7 mutations (N1303K, G542X, 1717-1G-A, W1282X, R553X, G551D and delI507). The results for couples choosing fetal

testing were not always clearly distinguishable from the couples opting to be tested themselves. The authors concluded that offering testing to couples undergoing first trimester diagnostic testing is not a model for mass screening, although it may provide a useful service.

12. Los Angeles, California – Over an unstated time period, two-step screening was offered to couples attending prenatal clinics at an academic medical center and a large health maintenance organization (Grody *et al.*, 1997). The population of 3,192 couples accepting testing was racially and ethnically diverse (50 percent non-Hispanic Caucasian, 28 percent Hispanic, 11 percent Asian, 7 percent African American, and 1 percent Native American). Buccal scrapings were collected and tested for six mutations (delF508, G542X, G551D, R553X, W1282X and N1303K). A commercial reverse dot blot system (Roche Molecular Systems) was used. The authors reported that their approach resulted in relatively high uptake in an ethnically diverse population, with satisfactory understanding of the subtleties of the genetics and test results and with no adverse psychosocial consequences detected.

13. New York City, USA – Over an unstated time period, couples of Jewish heritage were offered prenatal screening for Tay-Sachs disease, cystic fibrosis and Gaucher disease using the extended one-step model (Eng *et al.*, 1997). A total of 3,792 individuals (1,896 couples) accepted testing for cystic fibrosis. Blood samples from both partners were tested for five mutations (delF508, W1282X, G542X, N1303K and 3849+10kbC-T) using an in-house assay. The authors reported that, for this population, combining DNA testing for several disorders at one time was feasible and that with proper education, informed choices could be made.

Pilot trials of cystic fibrosis screening in other settings have also been reported. Some trials have focused on identifying carrier couples prior to pregnancy, or identifying carrier status among the general populations. These studies are often called 'population screening' trials and have been summarized elsewhere (Murray *et al.*, 1999; Rowley *et al.*, 1999). Screening for affected individuals could also occur soon after birth as part of newborn screening. This setting will be reviewed separately. Lastly, a program could target testing the relatives of recently diagnosed index cases. This 'cascade' testing has been proposed as a method of population screening (Super *et al.*, 1994), but its usefulness has been questioned (Holloway and Brock, 1994).

Additional information derived from the 13 prenatal cystic fibrosis pilot trials can be found in the following sections: estimated prevalence (Question 24), financial costs (Question 37), educational materials (Questions 39 and 40), and ELSI issues (Questions 43 through 46).

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CLINICAL UTILITY

Question 34: What health risks can be identified for follow-up testing and/or intervention?

Summary

Approximately 1 in 900 non-Hispanic Caucasian couples screened for cystic fibrosis will need to consider amniocentesis or chorion villus sampling

The risk for the pregnancy to be affected will be 1 in 4

The procedure-related fetal loss rate is about 9 per 1000 procedures for amniocentesis and somewhat higher for chorion villus sampling

The ratio of cystic fibrosis cases identified to fetal losses is about 25 to 1.

Non-fatal procedure-related risks to the fetus are minimal, if the procedures are done at the proper gestational age by experienced operators

Follow-up diagnostic testing is recommended relatively uncommonly for couples who have chosen prenatal screening for cystic fibrosis. This situation arises only when both partners are identified as carriers of mutations in the screening panel. Approximately 1 in 900 non-Hispanic Caucasian couples will fall into this category and will need to consider diagnostic testing of the fetus. This low rate of need for an invasive procedure means that procedure-related complications are very low in the population of screened couples as a whole, even though their frequency of occurrence is unchanged for those who actually undergo the procedure. The risk for the fetus to have inherited both mutations from the two carrier parents is 1 in 4 (odds of 1:3). This high likelihood of detecting a medical disorder is another factor to be considered, when attempting to place procedure-related risks in context.

Either amniocentesis or chorion villus sampling (CVS) can be used for obtaining fetal cells for DNA analysis. Both of these procedures are considered invasive, and both carry a small, but important, risk for procedure-related fetal loss. CVS is offered primarily in the first trimester (between 10 and 13 weeks' gestation), and amniocentesis is offered in the second trimester (beginning at 14 weeks' gestation). Information about procedure-related risks can be obtained most confidently from randomized trials. The opportunity for bias in non-randomized trials involving either amniocentesis or CVS is so great that interpretation of the data can be difficult, if not impossible. Analysis of even a randomized trial needs to be carefully thought out, because so many variables come into play. For example, when assessing the safety of amniocentesis, it is necessary to determine the rate of miscarriage attributable to the procedure itself, excluding the background rate of spontaneous miscarriage, (which is about 1 percent during the second trimester). A randomized trial is the most reliable study design for determining the fetal loss rate attributable to the amniocentesis procedure, because it allows the background rate of spontaneous miscarriage to be observed in the same study population.

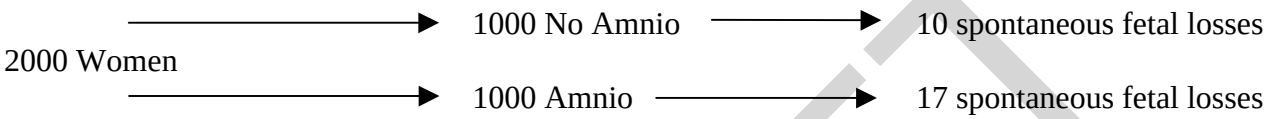
Analytic approaches to analyzing procedure-related fetal losses in a hypothetical randomized trial of amniocentesis

Figure 4-1A displays a hypothetical trial where 1,000 women are allocated to the procedure, 1,000 are not, and spontaneous fetal loss rates are recorded for both groups. Initially, it might be thought that the observed difference in losses between the two groups (17-10) represents the fetal losses attributable to the procedure. However, this calculation does not take into account the fact that some affected fetuses in the intervention arm would miscarry spontaneously in the absence of diagnosis and termination. Among

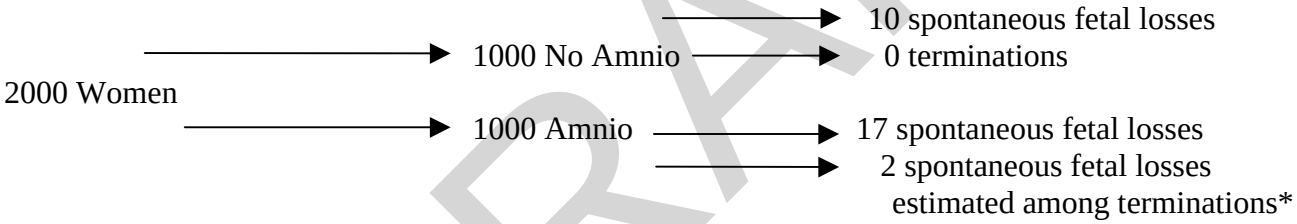
pregnancies affected with Down's syndrome, 23 percent will miscarry between 16 weeks of pregnancy and term. In the hypothetical trial, 8 cases of Down's syndrome are diagnosed and terminated. Two of those cases would spontaneously miscarry, even if amniocentesis were not done. Figure 4-1B takes this into account, and these two estimated losses are then added to the 17 observed losses. This, in turn, indicates that the fetal losses attributable to amniocentesis (19-10) are, in fact, more numerous than estimated in Figure 4-1A.

Figure 4-1. Approaches to Calculating Procedure-related Risk of Fetal Loss in a Randomized Trial for Identifying Down's Syndrome in Which 1000 Women are Assigned to Undergo Amniocentesis, and 1000 Women are Controls

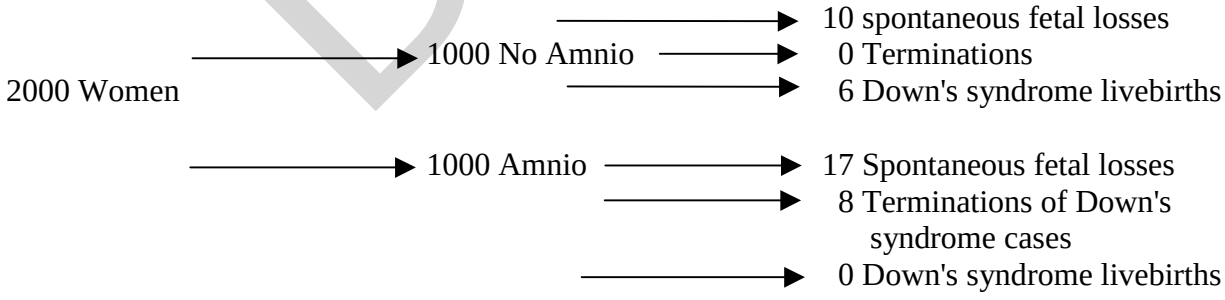
A) Assessment based only on observed losses



B) Assessment based on observed losses plus losses which might have occurred spontaneously in the absence of termination



C) Assessment based on observed losses plus cases of Down's syndrome identified among pregnancies terminated and among livebirths



*the remaining 6 terminations estimated to not be associated with spontaneous fetal loss

Table 4-5. Two Approaches to Expressing Risk of Spontaneous Fetal Loss That Is Attributable to Amniocentesis

	Relative Risk	Excess Risk
Data derived from Figure 4-1B	19/10, or 1.9	19-10, or 9 per 1,000 (0.9%)
Data derived from Figure 4-1C	25/16, or 1.6	25-16, or 9 per 1,000 (0.9%)

Another strategy to take the estimated miscarriage rate in the intervention group into account would be to tally the number of terminations of pregnancies with diagnosed abnormalities and also the number of liveborn babies with the same abnormalities (in this case, Down's syndrome) as those fetuses where termination was performed. Figure 4-1C shows that no babies with Down's syndrome are born among the procedure group, but six affected babies are born in the group not undergoing amniocentesis. The difference between the number of cases identified prenatally and the number identified among liveborns is another way to estimate the spontaneous fetal loss rate. The cases of Down's syndrome found in each arm of the study can be added to the respective observed spontaneous fetal losses, and the difference between those totals (25-16) represents the attributable losses.

Table 4-5 shows two ways in which attributable risk is commonly expressed, using data from Figures 4-1B and 4-1C. Attributable risk is expressed here both in terms of relative risk and excess risk. The table shows that excess risk is a more stable estimate, because it is not susceptible to changes in the numerator or denominator. It is also more readily understood by health providers and by women being offered the procedure.

Analyzing procedure-related loss in an actual randomized trial of second trimester amniocentesis
Only one randomized trial of amniocentesis has been carried out, and it is unlikely that another study of this type will be carried out, in the future (Tabor *et al*., 1986). That trial was carried out in a population of women aged 25-34 years with low risk pregnancies in the early 1980's. At that time, real-time ultrasound was available for guiding needle insertion, and considerable experience had been gained by those performing the procedure. This study therefore represents the most reliable guide for estimating risk of fetal loss in women undergoing second trimester amniocentesis.

The original analysis concluded that the excess risk of fetal loss from the procedure was 10 per 1000. This analysis counted spontaneous losses from the 16th week of gestation in cases and controls. It did not count spontaneous losses between randomization and the 16th week, stillbirths, or estimated spontaneous losses that might have occurred in the absence of terminations in the amniocentesis group.

A revised analysis concluded that the excess risk of fetal loss from the procedure was 9 per 1000 (95% CI = 1 to 16 per 1000). This analysis counted all spontaneous losses from randomization, including stillbirths (Wald, 1995). It also estimated spontaneous losses that might have occurred in the absence of terminations of chromosomally abnormal fetuses (as in Figure 4-1B).

A second revised analysis concluded that the excess risk of fetal loss from the procedure was 9 per 1000 (95% CI = 0 to 19 per 1000). This analysis was similar to the first revised analysis, except that it did not estimate the spontaneous fetal losses (Gosden *et al.,* 2000). Instead, all terminations in cases and controls, as well as all livebirths of infants with anomalies being tested for (as in Figure 4-1C).

Analyzing procedure-related loss in randomized trials of chorion villus sampling

Two CVS approaches are used for obtaining tissue for analysis: transcervical and transabdominal. Randomized trials have been carried out in which these two approaches are compared with each other, or with amniocentesis. None of the randomized trails include women assigned to have no invasive diagnostic procedure. Gosden and her associates (2000) recently summarized these trials, including re-analyses of the type shown in Figure 4-1C. Table 4-6 lists the two studies in which transcervical CVS was compared with amniocentesis (Lippman *et al.,* 1992; Smidt-Jensen *et al.,* 1992). While both show an increased risk of CVS over amniocentesis, only one is associated with confidence intervals that exclude a zero effect. Table 4-7 shows the one study (Smidt-Jensen *et al.,* 1992) which compared transabdominal CVS with amniocentesis. Total fetal losses are virtually identical for the two groups. In this trial, about 70 percent of the CVS procedures were performed by a single, highly experienced operator, meaning that this may not be representative of procedure-related risks in general practice (Ward *et al.,* 1993). One other randomized trial (not shown) compared a mix of transcervical and transabdominal CVS with amniocentesis (MRC Working Party on the Evaluation of CVS, 1991). That study reported a 4.3 percent excess fetal loss rate with CVS (95 percent C.I. 2.2 to 6.5%). Table 4-4 shows the findings from four studies which compared transcervical and transabdominal CVS (Bovicelli *et al.,* 1986; Brambati *et al.,* 1991; Grant, 1992; Smidt-Jensen *et al.,* 1992). Three of the four studies find no difference in risk between the two procedures, while the fourth reports a considerably higher risk with the transcervical approach. There is no obvious explanation for the discrepancy in these findings, although operator experience may be a factor (Ward and Rodeck, 1993). Some limitations exist for the re-analysis of studies in Table 4-8, due to unavailability of selected raw data (Gosden *et al.,* 2000).

Table 4-6. 'Total' Fetal Loss in Randomized Trials Comparing Transcervical CVS and Second Trimester Amniocentesis, as Re-analyzed by Gosden *et al.* (2000)

Location Of Trial	Number of Pregnancies	Total Fetal Losses		Difference in % (95% CI)
		Number	(%)	
Canada				
CVS	1,363	230	16.9	1.6 (-1.2 to 4.4)
Amniocentesis	1,361	208	15.3	
Canada (subset)*				
CVS	1,164	89	7.6	0.5 (-1.6 to 2.7)
Amniocentesis	1,149	83	7.1	
Denmark**				
CVS	1,010	110	10.9	4.5 (2.0 to 6.9)
Amniocentesis	1,042	67	6.5	

* The first summary from Canada includes all randomized pregnancies. The second is limited to the subset remaining eligible at first ultrasound.

** Excludes those refusing to participate or judged ineligible and those with translocation or later termination or a fetal risk of metabolic disease. Neonatal deaths included in tally of 'total' fetal losses.

Table 4-7. Total Fetal Loss in A Randomized Trial Comparing Transabdominal CVS and Second Trimester Amniocentesis, as Re-analyzed by Gosden *et al.* (2000)

Location Of Trial	Number of Pregnancies	Total Fetal Losses		Difference in % (95% CI)
		Number	(%)	
Denmark				
CVS	1,027	65	6.3	-0.1 (-2.2 to 2.0)
Amniocentesis	1,042	67	6.4	

Table 4-8. 'Total Fetal Loss in Randomized Trials Comparing Transcervical and Transabdominal CVS as Re-analyzed by Gosden *et al*. (2000)

Location Of Trial	Number of Pregnancies	Total Fetal Losses		Difference in % (95% CI)
		Number	(%)	
Bologna, Italy				
TC CVS	60	5	8.3	0.0 (-9.9 to 9.9)
TA CVS	60	5	8.3	
Milan, Italy				
TC CVS	592	91	15.4	-0.5 (-4.7 to 3.6)
TA CVS	591	94	15.9	
United States				
TC CVS	2,001	157	7.8	-0.3 (-1.9 to 1.4)
TA CVS	1,978	160	8.1	
Denmark				
TC CVS	1,010	110	10.9	4.6 (2.1 to 7.0)
TA CVS	1,027	65	6.3	

Non-fatal Risks to the fetus from amniocentesis and CVS

Reports from individual trials of amniocentesis (both randomized and non-randomized) have on occasion listed fetal complications, such as congenital dislocation of the hip and talipes equinovarus or respiratory distress syndrome of the newborn. Following a comprehensive review of all of these studies, Gosden and her associates (2000) concluded that: "second trimester amniocentesis has no proven ill effects on offspring who survive until late pregnancy, although there is some evidence that it increases the risk of respiratory problems".

An association between early CVS and severe limb deficiencies (often in combination with oromandibular abnormalities) was first reported in 1991 (Firth *et al.*, 1991). Data have now accumulated which document both the higher risk and the severity in relation to gestational age. The further along in

gestation that the procedure is performed, the more distal is the limb reduction defect. By the 11th week of gestation, no excess risk over background can be detected for this type of fetal damage. Prior to 10 weeks', CVS the estimated extra risk of limb reduction defect ranges between 20 and 70 per 10,000 procedures (Gosden *et al.*, 2000).

Reliability of diagnostic process and laboratory studies

For prenatal cystic fibrosis screening to be useful, there needs to be a reliable diagnostic process available to high risk couples. That process begins with an invasive procedure to obtain fetal cells, so that DNA analysis can be performed. An immediate source of failure in diagnostic testing occurs when a sample cannot be obtained. This occurs about twice per 1000 procedures for amniocentesis and 18 per 1000 procedures for chorion villus sampling (Gosden *et al.*, 2000). For chorion villus sampling, failure to obtain a sample occurs about twice as often when the transcervical route (as opposed to the transabdominal route) is used. Once a sample is available, it may occasionally not be possible to obtain a useable result. When fetal chromosomes are being measured, laboratories are unable to provide a definitive answer about 4 times per 1000 procedures for amniocentesis and about 8 times per 1000 procedures for chorion villus sampling. Insufficient data exist at present to estimate how often diagnostic samples fail to yield a useable DNA result for cystic fibrosis mutations. This failure rate may, however, be lower than when fetal cells are being subjected to chromosome analysis.

A third potential source of failure arises from the sample's being contaminated with maternal cells. In this situation, a useable result can be obtained, but the result is wrong. For chorion villus samples, maternal tissue needs to be dissected away manually as part of routine preparation, and it is difficult to remove all of the contaminating cells. When DNA analysis is performed on samples prior to culture, interpretation is further complicated by signals arising from cytotrophoblastic cells. These may at times not be representative of the fetus. Cells from chorion villi that grow in culture are from the embryonic epiblast. This source provides a more reliable representation of fetal karyotype and DNA, but contaminating cells from the mother may occasionally predominate. This occurs when maternal cells divide more rapidly in culture than fetal cells. Confined placental mosaicism also can be represented in the preparation, from time to time.

When analyses are being carried out on cells obtained by amniocentesis, maternal cell contamination is also an occasional problem. Again, most information is available from cytogenetic analysis, but this can provide some guidance for DNA analysis, as well. Table 4-9 gives ranges of maternal cell contamination for amniocentesis and chorion villus sampling.

Table 4-9. Frequency of Diagnostic Sample Contamination with Maternal Cells During Karyotype Analysis

Procedure	% of Samples Contaminated (Range)
Amniocentesis (Culture)	0.6 – 1.0
Chorion Villus Sampling (Direct Preparation)	0.1 – 0.9
Chorion Villus Sampling (Long Term Culture)	1.8 – 12.6*

*But long term culture is more accurate for fetal karyotype in non-contaminated samples.

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CLINICAL UTILITY

Question 35: What are the financial costs associated with testing?

Summary

From the literature, eight cost components have been identified and assigned a reasonable unit cost estimate

- Providing education/information to the entire population — $1 to $3
- Obtaining informed consent — $5 to $10
- Collecting and transporting the sample — $10 (blood) $4 (buccal)
- Performing the DNA test — $80 to $100
- Reporting negative results — $2 (by mail/fax/electronic)
- Reporting positive results — $20 (individual) $50 (couple)
- Performing diagnostic testing — $400 to $600 (w/o karyotype)
- Accounting for procedure-related fetal losses — $400

The costs per case of cystic fibrosis prenatally diagnosed are then computed using the above cost estimates, uptake rates, prevalences and proportions of mutations identified for each of five racial/ethnic groups. The costs per case detected using either the two-step (sequential) or the one-step (couple) model are

- $ 500,000 for non-Hispanic Caucasians (the largest target population)
- $ 400,000 for Ashkenazi Jewish
- $ 4,000,000 for Hispanic Caucasians
- $ 7,000,000 for African Americans
- $19,000,000 for Asian Americans

Using the expanded one-step (concurrent) model increases cost by about two-thirds.

The costs per couple tested are essentially the same for various racial/ethnic groups, but are not the same for the various screening models

- $120 to $140 using the two-step (sequential) or one-step (couple) model
- $220 to $240 using the expanded one-step (concurrent) model

Introduction

Economic costs and benefits can be categorized in multiple ways, varying with the purpose and perspective of the analysis. The simplest approach, used in most published evaluations of prenatal cystic fibrosis screening, is to analyze financial costs accruing to the health care system. The present analysis follows the health care system perspective. Only a few of the studies include more general societal costs (e.g., individual time and travel costs). A presupposition of the societal perspective is that the outcome of the intervention is socially valued as a good (e.g., prevention of early death). Since prenatal cystic fibrosis screening may lead to pregnancy termination, for which a social consensus is lacking, the societal perspective is not an appropriate choice. Analytic perspective also determines whether resource costs or charges should be assessed. The health care system perspective estimates the expenditure of real resources, adjusting for cost-shifting, economic rents, and transfer payments. Methods for estimating resource costs include use of internal accounting data, cost-to-charge ratios, or payments made by payers with strong market power. Each of these approaches may lead to an understatement of costs, either as a

result of exclusion or undervaluation of costs or as a result of cost-shifting to other services. The alternative is to use stated charges or fees, which is appropriate if the analysis is being done from the perspective of a third-party payer with little market power. This review is restricted to direct financial costs and benefits to the medical care system and is divided into three parts.

Financial costs to the health care system include eight components:

1. Providing education/information to the entire population prior to offering the test
2. Obtaining informed consent from those choosing to be tested
3. Collecting and transporting the specimen (i.e., blood or buccal)
4. Performing the DNA test for *CFTR* mutations
5. Reporting negative results to the provider
6. Reporting positive results to the provider and patient with appropriate counseling
7. Performing diagnostic testing of the fetus (including counseling)
8. Accounting for fetal losses attributable to diagnostic testing

This section first presents published estimates of unit costs (or charges) for each of these eight components, followed by a brief discussion of each estimate and a summary conclusion. Once reasonable costs (and ranges) for each of seven components have been determined, a summary of the published assumptions relating to behavioral and epidemiologic parameters will be compared to results from actual pilot trials of prenatal cystic fibrosis screening. A final summary of the total cost of the screening process will then be provided. No two economic evaluations of prenatal cystic fibrosis screening evaluate the same protocol or protocols. Many compare one protocol with no screening for the purpose of evaluating whether screening makes economic sense. A few compare multiple protocols. Because even broadly similar protocols can be implemented in varying ways, it is difficult to develop generalizable cost estimates. All of the economic studies agree that the largest component of total cost is performing the DNA test (Component 4). The rapid evolution of molecular testing has continually altered both costs and the number of mutations that can be tested.

The published studies provide cost estimates in various currencies for currency years from 1993 to 1997. All estimates from other currencies are converted to US dollars at prevailing exchange rates. To standardize the estimates, costs are adjusted to 1996 dollars, using a relevant inflation index. For labor costs, this is the employment cost index and for other costs it is the GDP deflator for medical care. The laboratory cost of DNA testing is not adjusted for currency year, because laboratory costs likely reflect the rate of technological progress rather than general inflation. To adjust for inflation since 1996, it would be possible to inflate the cost estimates below by 10 to 14 percent to reflect 2000 year equivalents.

It is important that focus be kept on the overall costs of screening and not on single components. For example, it would be a mistake for third party payers to assume that an estimate of laboratory costs to perform the DNA test reported here should be equivalent to any given laboratory's overall charge. The laboratory charge would also include the provision of educational materials, sample collection and/or shipment and, possibly, follow-up counseling. In addition, the laboratory needs to include an additional component to allow for ongoing development. Lastly, a laboratory's advertised 'list price' is not representative of the actual price charged to clients. Discounted charges are widely available, usually based on volume.

Components 1 and 2: Providing education/information and obtaining informed consent

Component 1: A reasonable cost of providing education/information to pregnant women/couples is about $3.00 (1996 dollars). According to published studies, the median cost of providing such education/information is $2.48 (range $0.80 to $3.33). The costs do not appear to differ significantly based on the screening model chosen. Only one estimate is from the US and it is relatively high ($3.28). Several studies do not include overhead costs.

Component 2: A reasonable cost of obtaining informed consent is about $10.00 (1996 dollars). Three reports (all from the US) assume the need for specialized genetic counselors or physicians to provide education/information and to collect informed consent and estimate higher costs. The ACOG/ACMG Guidelines recommend that prenatal cystic fibrosis screening be integrated into routine prenatal care. This means that office staff rather than highly trained counselors will be utilized. Thus, the remaining lower estimates are more likely to be appropriate. Three studies provide a cost for the more explicit dialogue necessary for informed consent. The median value is $4.23 (range $3.79 to $8.60). None of these estimates is from the US, and several do not include overhead costs.

When offering prenatal cystic fibrosis screening to pregnant women or couples, it is essential to offer information about the potential benefits and risks. In pilot trials, this has been accomplished through a combination of pamphlets, videos, and face-to-face communication (Question 38). Several of the economic studies have bundled the provision of education/information with the process of obtaining informed consent. For accurate modeling of costs, it is necessary to separate these two components, since the first is provided to the target population as a whole, while the second is provided only to those who accept screening. The unit cost of providing education/information is multiplied by the number offered testing, independent of how many choose to accept screening. In contrast, the cost of obtaining informed consent is a function of the number who agree to participate.

Most studies assume that information is provided as part of a routine prenatal care visit. This approach has been endorsed by the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) (Grody *et al*., 2001). A few studies assume that information is provided by specialized counselors, which raises costs considerably (Asch *et al*., 1998; Rowley *et al*., 1998). Two studies assume the existence of a mass media campaign to publicize and promote prenatal cystic fibrosis screening to the entire population (Ginsberg *et al*., 1994; Wildhagen *et al*., 1998), a process which may lower education costs. The remaining studies assume that screening will be offered through practitioners or clinics.

Eight studies have published cost estimates of providing education/information in a prenatal cystic fibrosis screening setting (Table 4-10). Five have bundled together information and informed consent in a single cost. One does not provide a cost for obtaining informed consent. Only one study separately reports the cost of providing information and the cost of obtaining informed consent. The majority of the costs are derived by taking an estimate of staff time and multiplying it by a cost per staff hour. Such estimates may substantially understate costs by failing to include indirect and overhead costs. Pre-screening information provision may differ for couple (or concurrent) screening and sequential screening. For sequential screening, pre-screening information need only be provided to the pregnant woman. For

couple (or concurrent) screening, both partners must be informed. Finally, some of the estimates are apparently based on charge rather than actual costs.

Table 4-10. Published Costs of Providing Education/Information and/or Collecting Informed Consent in a Prenatal Cystic Fibrosis Screening Program

Author	Country	Model	Cost	Comment
Combined Education and Consent				
Asch	US	Couple	$16.70	Assumes use of genetic counselors
Rowley	US	Sequential	$20.00	Assumes use of specialized counselors
OTA	US	Sequential	$32.23	Assumes use of physician
Providing Education Only				
Cuckle	UK	Seq or Couple	Low	
Morris	UK	Seq or Couple	$ 0.86	
Ginsberg	Israel	Sequential	$ 1.24	Assumes mass media campaign
Beech	UK	Sequential	$ 1.51	
Wildhagen	Neth.	Couple	$ 2.48	Assumes mass media campaign
Beech	UK	Couple	$ 2.65	
Lieu	US	Sequential	$ 3.28	
Obtaining Consent Only				
Cuckle	UK	Seq or Couple	$ 3.33	
Wildhagen	Neth	Couple	$ 3.79	
Ginsberg	Israel	Sequential	$ 4.23	
Morris	UK	Seq or Couple	$ 8.60	

- Rowley and colleagues (1998) state that the unit cost of offering screening is $20 (1996 dollars). This estimate includes professional time (specialized counselors), clerical time, the cost of the informational brochure, and the cost of the consent form. Estimates are derived from a pilot screening program in Rochester, New York. No disaggregated estimates of cost or time are provided.
- Asch and colleagues (1998) assume that the initial offering of screening to a couple will require 37.5 minutes by a genetic counselor. At $26 per hour, this amounts to $16.25 (1995 dollars). This amount does not appear to include the full cost of the genetic counselor's time, including fringe benefits, nor does it include overhead costs, or materials.
- The Office of Technology Assessment (1992) calculates the cost of offering screening to women to be $17 of physician's time and $8 of office staff's time (1991 dollars) and promotional materials. The physician cost is calculated as 10 minutes of time, valued at $100 per hour.
- Ginsberg and colleagues (1994) divide pre-screening information into two components. Publicity for the program is assumed to be a fixed cost of $21,000 per year (1993 dollars). Given 18,522 pregnancies screened and adjusting to 1996 dollars, the cost per pregnancy is $1.24. According to

that report, 10 minutes of counseling will be provided before screening is offered. At a labor cost of $10 per hour, this works out to $1.67 in 1993 dollars. No overhead costs are included. No explicit mention is made of obtaining informed consent, but since counseling is provided at a genetics clinic, it is presumably included. Thus, the unit cost of providing counseling prior to testing is $3.87 per couple ($4.23 in 1996 dollars).

- Lieu and colleagues (1994) include a $3 cost (1993 dollars), for pre-test education. This cost is derived from an unspecified project that provided information prior to prenatal screening for Down syndrome or HIV infection. No mention is made of obtaining informed consent from those who choose screening.
- Wildhagen and colleagues (1998) report separate costs for a mass media promotion and individual education of couples choosing screening. The mass media campaign is assumed to cost 136,957 pounds, based on 60 percent of the cost of a media campaign for breast cancer screening. Given 88,241 pregnant couples included, the cost is $2.48 per couple. A second component consists of individual education and is assumed to be twice the observed cost of providing education for breast cancer screening (2.37 pounds, or $3.79 in 1996 dollars). Although not directly mentioned, it is assumed that informed consent was the aim of this second component.
- Beech and Bekker (1995) distinguish the cost of publicizing screening from the cost of encouraging screening. For sequential screening, publicity is accomplished through the distribution of leaflets in prenatal care practices. The cost per pregnancy is estimated to be 0.85 pounds ($1.38 in 1996 dollars). The analysis implicitly assumes a perfect one-to-one distribution of materials to each pregnant woman, with no one missed, no duplicates, and no wastage. For the couple strategy, the cost of publicity rises to 1.49 pounds ($2.41 in 1996 dollars), which covers the cost of postage and mailing of sample collection tubes. The authors assume that with the distribution of educational materials, there is no need to obtain informed consent.
- Cuckle and colleagues (1995) assume that pre-screening education consists of a printed leaflet backed up by an interview with a midwife (Mennie *et al.*, 1992). The cost of creating, printing, and distributing the leaflet was "negligible." The average time per interview is 10 minutes. It is assumed that a half-time midwife dedicated to this purpose could see 5,000 patients annually, at a cost of 2 pounds per person ($3.33 in 1996 dollars). The study reported that no additional information cost is required for couple screening. Although no mention is made of obtaining informed consent, it is likely that this is the aim of the midwife's interview.
- Morris and Oppenheimer (1995) report separate costs for an informational brochure, at 0.50 pounds ($0.86 in 1996 dollars), and for a 5-10 minute session to obtain informed consent, at 5.00 pounds ($8.60 in 1996 dollars). The study assumes the same costs apply regardless of whether information is being provided to an individual woman or to a couple.

Gaps in knowledge: There are unresolved issues about the cost of pre-screening education and information. The minimum time required to provide detailed information and obtain informed consent is generally regarded to be 10 minutes (Wilfond and Fost, 1992). Key questions include:

a. Is it reasonable to conclude that face-to-face information should only be provided to those who express interest after reading printed materials?
b. Does screening uptake vary with the level of information provided?

Component 3: Obtaining a sample

A reasonable cost for obtaining and shipping a single blood sample is about $10.00. A reasonable cost for obtaining and shipping a single buccal sample is about $4.00. Costs for obtaining buccal samples are lower for two reasons: sampling can be done by the individual, and shipping can be by regular mail. Obtaining a blood sample requires a phlebotomist, and sample shipment is usually by a courier service or express mail.

The cost of collecting blood or buccal samples and transporting them to the laboratory is sometimes not included in analyses of prenatal screening for CF. One study did not include this because almost all blood samples were collected during routine prenatal care for other purposes (Rowley *et al.*, 1998). Some other studies appear to assume that collection cost is included in the laboratory cost of DNA analysis or, it is not considered in the analysis at all. One study includes ten pence as just the cost of providing a tube for the buccal sample (Morris and Oppenheimer, 1995). Another study combines administrative costs with sample acquisition costs (Wildhagen *et al.*, 1998). Table 4-11 shows the four studies that provide a separate cost estimate for sample collection.

Table 4-11. Published Costs of Collecting and Transporting a Sample Specimen as Part of a Prenatal Cystic Fibrosis Screening Program

Author	Country	Sample	Cost	Comment
Asch	US	Blood	$20.00	Charge rather than cost?
Wildhagen	Neth	Buccal	$14.45	Includes other costs as well
Beech	UK	Blood	$ 0.62	No shipping costs
Morris	UK	Buccal	$ 5.37	No shipping costs
		Buccal	$ 0.44	Includes postage

- Asch and colleagues (1998) state that the cost of collecting a single blood sample for DNA analysis is $20, in 1995 dollars. Their analysis includes this as an extra cost in couple-screening strategies but does not apparently include this in their analysis of sequential screening strategies. It is not clear whether this is a cost or charge.
- Wildhagen and colleagues (1998) assume that the costs of collecting and shipping two buccal samples from a couple and administering the screening process amounts to 9.04 pounds per couple, or $14.46 (1996 dollars). No breakdown is provided between collection and administration.
- Beech and Bekker (1996) assume that a nurse working 4 hours per week can collect blood samples from 8,000 patients per year. At an annual labor cost of 19,550 pounds, it costs an average of 0.30 pounds per sample (at a rate of 38 blood samples collected per hour). In addition, they assume a cost of 7 pence for the collection tube. The total cost is $0.62 in 1996 dollars. They do not include shipping costs.
- Morris and Oppenheimer (1995) report that buccal samples can be collected either by post, at a unit cost of 0.30 pounds, or by a cheek swab during a clinical visit, at a unit cost of 5 pound. It is assumed that almost all pregnant women will agree to submit samples by post, for an average cost of 0.31 pounds. The cost of a sample collection tube is put at 0.10 pounds, for a total of 0.41 pounds, or $0.44 (1996 dollars).

Component 4: Performing the DNA test

A reasonable cost for performing the DNA test for about 25 to 30 *CFTR* mutations in a single blood or buccal sample is $80 to $100. This estimate includes the costs of reagents, supplies, licenses, royalties, technician time, administrative time and overhead. In the future, it is likely that automation and competition will reduce these costs. Although less likely, it is possible that the costs will remain at this level (or decrease less), as technical advances might be used to test for more mutations.

Given the decrease in the costs of DNA analysis resulting from technological progress, adjustments for inflation will not be made for this component. One of the key influences on this cost is the number of mutations included in the panel. According to the ACMG/ACOG guidelines, the panel should include a minimum of 25 mutations. Another key factor is whether estimates are based on actual laboratory costs or the charges from commercial laboratories. Listed charges are considerably higher and include more than the laboratory component. Non-US studies report lower estimates of the cost of DNA testing. The US studies, with one exception, cite commercial charges, rather than actual costs. Most of these studies assume that the costs will be reduced with the introduction of routine screening because of competition, automation and economies of scale. Table 4-12 shows information about DNA testing costs in various publications.

Table 4-12. Published Costs of Performing DNA Analysis as Part of a Prenatal Cystic Fibrosis Screening Program

Author	Country	Mutations	Cost	Comment
Murray	UK		$ 29	
Haddow	US	8-11	$ 45	
Asch	US	6	$ 50	Based on laboratory costs
Beech	UK	6 or 11	$ 52	
Cuckle	UK	6	$ 53	Reagents only
Morris	UK	6	$ 62	
Ginsberg	Israel	5	$ 72	Jewish mutations only
Asch	US	25-35	$100	Projection
Lieu	US	Not stated	$100	Projected cost by experts
OTA	US		$100	Average charge
Rowley	US	70	$150	Commercial laboratory charge
Vintzileos	US		$150	Unknown source

- Rowley and colleagues (1998) cite a current charge of $150 for DNA analysis from a single commercial laboratory (Genzyme) testing 70 mutations. They acknowledge that their own laboratory costs are lower.
- Vintzileos and colleagues (1998) assume a DNA analysis cost of $150 for their cost-effectiveness analysis, but no documentation is provided.
- Asch and colleagues (1998) distinguish two testing approaches. A standard analysis includes 5 to 10 common. An expanded analysis includes an additional 20 to 30 mutations. The cost for a six-mutation analysis is reported to be $50 and is based on the costs for technical and professional

personnel, reagents, equipment, royalties, laboratory space, and utilities. The expanded battery is assumed to cost $100, but no explanation is provided for this estimate.

- Lieu and colleagues (1994) assume a cost of $100, based on a 1992 survey of experts at four diagnostic laboratories, who projected future charges assuming much higher utilization. The number of mutations tested is not stated.
- The Office of Technology Assessment (1992) conducted a survey in 1991 of laboratories conducting DNA analyses and found an average charge of $170. They use an estimate of $100, including post-test counseling, based on an assumption of economies of scale.
- Haddow and colleagues (1999) cite an unpublished presentation reporting that the cost of DNA laboratory analysis is approximately $45. This estimate does not include laboratory administration.
- Wildhagen and colleagues (1998) use Cuckle's cost estimate of 33 pounds ($53) for multiple mutation analysis. For single mutation analysis of the delF508 mutation, they arbitrarily assume that the cost is one fourth as great, 8.25 pounds, or $13. This is not included in the table because it is derivative.
- Beech and Bekker (1995) report that the cost of a Cellmark Kit used for DNA analysis of *CFTR* mutations is 30 pounds per person tested. Laboratory staff time to perform each analysis is 2.40 pounds, and laboratory capital cost is 0.11 pounds per person tested, for a total of 32.51 pounds, or $52.02.
- Cuckle and colleagues (1995) report that the cost of the only commercially available reagent kit for testing multiple CFTR mutations is 33.21 pounds. For delF508, an in-house assay in Yorkshire costs 16.10 pounds per specimen, including 6.70 pounds for consumables, 6.20 pounds for staff, and 3.20 pounds for overhead. They use an estimate of 16 pounds for single mutation analyses ($26) and 33 pounds for multiple mutation analyses ($53). The latter estimate does not include any allowance for laboratory staff or overhead. Also, the number of mutations tested is not stated.
- Morris and Oppenheimer (1995) report that the cost of the reagents needed to analyze one sample is 25 pounds. The laboratory and clerical costs add 14 pounds per sample, for a total of 39 pounds, or $62.40. The number of mutations tested is not stated.
- Murray and colleagues (1999) state that a UK commercial supplier of mutation test kits, Zeneca Diagnostics, would provide kits at 12 pounds per test, if purchased in volumes of at least 5,000. Reagents, labor costs, and administrative overhead would raise this to 18 pounds per test, or $28.80 in US dollars.
- Ginsberg and colleagues (1994) report a screening cost of $72.32, based on cost estimates from a single testing laboratory in Israel which includes the costs of labor, raw materials, depreciation and a 16.1 percent overhead.

Component 5: Reporting negative results

A reasonable cost for providing a written report of a negative test result is $2. This covers the cost of clerical time and postage.

Only two studies calculate a cost of reporting test results to everyone screened (Ginsberg *et al.*, 1994; Morris and Oppenheimer, 1995). Other studies implicitly assume that the cost of communicating negative test results is trivial.

- Morris and Oppenheimer (1995) report a cost of reporting test results of 1 pound, equally divided between administrative costs and the cost of writing and posting a letter. This cost amounts to $1.73 (1996 dollars).
- Ginsberg and colleagues (1994) report communication of negative test results to an individual woman costs $0.97 in 1993 dollars ($1.06 in 1996 dollars). In addition, 10 percent of those testing negative still request counseling and receive it, at 40 minutes per woman. The cost of staff time is $10 per hour (1993 dollars). The cost per negative test result is therefore $1.64 in 1993 dollars ($1.80 in 1996 dollars).

Component 6: Reporting positive results

A reasonable cost for reporting and counseling carrier individuals is $20. It is assumed that a telephone call that costs about $15 will be sufficient for most individuals. In some instances, however, a full counseling session may be necessary. For this reason, the cost has been increased to $20, consistent with all but one of the reported costs in Table 4-4. That study assumed that all individual carriers would need a full genetic counseling session. Unpublished evidence from a large HMO in California has recently demonstrated that such counseling is not necessary (Witt, 2001).

A reasonable cost estimate for reporting and counseling a carrier couple is $50. This cost is consistent with all but one study in Table 4-14. That study reported the charge for a genetic counseling session rather than a cost.

Only two studies have modeled the cost of reporting test results to everyone screened (Ginsberg *et al.*, 1994; Morris and Oppenheimer, 1995). Others implicitly assume that the cost of reporting negative test results is negligible. Most studies focus on communicating positive test results and their genetic implications. This is an important cost component. For sequential screening strategies that disclose carrier status, this can be separated into two stages: 1) notifying and counseling individuals with positive test results (i.e., carriers), and 2) notifying and counseling couples where both partners are found to be carriers. For couple screening (where only carrier couples are notified as being positive), only the second stage described above is relevant. For concurrent screening (couple screening where carrier status on both partners is always disclosed) both stages are again relevant.

Notifying and counseling of individual carriers

The following results (Table 4-13) exclude one study in which no separate costs for reporting test results are listed (Office of Technology Assessment, 1992). They also exclude two studies in which only couple screening strategies were modeled, since no results were reported for individual carriers (Cuckle *et al.*, 1994; Beech and Bekker 1996).

Table 4-13. Published Costs of Reporting and Counseling a Carrier Individual as Part of a Prenatal Cystic Fibrosis Screening Program

Author	Country	Cost	Comment
Ginsberg	Israel	$ 8.46	Provides a counseling session
Lieu	US	$ 16.41	Assume a telephone call is sufficient
Asch	US	$ 16.70	Assume a genetic counseling session is needed
Wildhagen	Neth	$ 18.59	Assume a genetic counseling session is needed
Morris	UK	$ 19.03	Provides a genetic counseling session
Rowley	US	$150.00	Provides a genetic counseling session

- Rowley and colleagues (1998) report that each woman found to be a carrier was provided genetic counseling at a unit cost $150. This estimate is based on a "market survey," not data from their own study.

- Asch and colleagues (1998) report that positive results are communicated in a counseling session lasting 30 to 45 minutes. The cost of a genetic counselor's time is given as $26 per hour. This works out to an average of $16.25, or $16.70 (1996 dollars).
- Lieu and colleagues (1994) assume that if only one parent is a carrier, it is sufficient to convey the test results in a telephone call with no need for a personal counseling appointment. The unit cost for the telephone call is given as $15 in 1993 dollars, or $16.41 (1996 dollars). The source of the estimate is the charge by the University of California at San Francisco Medical Center for this service.
- Wildhagen and colleagues (1998) assume that counseling couples where one partner tests negative and the other tests positive will take 30 minutes. The cost of the time of a qualified nurse in a genetics clinic is given as 16.60 pounds per hour, plus 40 percent overhead, or 11.62 pounds for a 30-minute session ($18.59 in 1996 dollars).
- Morris and Oppenheimer (1995) report that the cost of reporting test results is 1 pound, equally divided between administrative costs and the cost of writing and posting a letter. This cost amounts to $1.73 (1996 dollars). In addition, the cost of counseling individual carriers with a positive test result is 10 pounds, or $17.30 (1996 dollars). Ignoring the cost of reports for negative test results, the cost per positive test result is $19.03.
- Ginsberg and colleagues (1994) report that communication of negative test results to an individual woman costs $0.97 in 1993 dollars ($1.06 in 1996 dollars). In the case of a positive test result, no cost for notification is provided. Instead, it is assumed that women who test positive receive counseling that lasts 30 minutes. In addition, 10 percent of those testing negative still request counseling and receive it, at 40 minutes per woman. The cost of staff time is figured as $10 per hour (1993 dollars). The cost for each carrier is $7.47 in 1993 dollars ($8.46 in 1996 dollars).

Notifying and counseling of carrier couples

Most studies assume that counseling carrier couple is relatively time consuming and expensive. Two studies, however, assume that this cost is the same as the cost of counseling an individual carrier (OTA, 1992; Asch *et al.*, 1998). Another study assumes a lower cost for counseling couples (Rowley *et al.*, 1998). Table 4-14 lists studies that report costs for counseling carrier couples.

Table 4-14. Published Costs of Reporting and Counseling a Carrier Couple as Part of a Prenatal Cystic Fibrosis Screening Program

Author	Country	Cost	Comment
Asch	US	$ 17	Assume a genetic counseling session is needed
Ginsberg	Israel	$ 21	Counseling session (90 min)
Wildhagen	Neth	$ 37	Counseling session (60 min) by qualified nurse
Cuckle	UK	$ 41	Counseling session (60 min) by trained nurse
Morris	UK	$ 51	Counseling session (30 min)
Beech	UK	$ 54	Counseling session (60 min) by geneticist or OB
Rowley	US	$ 60	Cost of a genetic counseling session
Lieu	US	$186	Charge for a genetic counseling session

- Rowley and colleagues (1998) state that the unit cost of counseling couples in their study is $60. No further explanation is provided.

- Lieu and colleagues (1994) state the cost of providing genetic counseling to a carrier couple is $170, in 1993 dollars, or $186 in 1996 dollars. The source of the estimate is the charge by the University of California at San Francisco Medical Center for this service. This estimate is substantially higher than the other estimates, all of which are based on actual costs, not charges.
- Wildhagen and colleagues (1998) assume that counseling carrier couples will take 60 minutes. The cost of the time of a qualified nurse in a genetics clinic is given as 16.60 pounds per hour, plus 40 percent overhead, or 23.24 pounds for an hour-long session ($37.18 in 1996 dollars).
- Beech and Bekker (1995) assume that genetic counseling for a carrier couple will require 60 minutes and that it will be provided by a geneticist or obstetrician, at a cost of 31 pounds per hour ($54.26 in 1996 dollars).
- Cuckle and colleagues (1995) assume that a 60 minute genetic counseling session is necessary and that it is provided by a nurse, at a cost of 25 pounds ($41.11 in 1996 dollars).
- Morris and Oppenheimer (1995) report that the cost of counseling carrier couples is 30 pounds, or $50.75 in 1996 dollars
- Ginsberg and colleagues (1994) report 90 minutes of counseling for couples after the second stage test, regardless of whether the second partner is found to be a carrier or not. The cost of staff time is figured as $10 per hour, in 1993 dollars. The cost for each carrier is $19.35 in 1993 dollars ($21.17 in 1996 dollars).

Component 7: Performing diagnostic testing

A reasonable cost for prenatal diagnosis is about $400 to $600, depending on whether karyotyping is performed. These estimates are consistent with the reported costs, after taking into account that several of the reported figures are actually charges. These costs include performing the amniocentesis, DNA analysis and follow-up genetic counseling. Since the indication for diagnostic testing is to rule out cystic fibrosis, the likelihood of identifying a chromosome abnormality is small. However, many programs may feel that the additional cost of karyotyping is warranted.

Most cost analyses of prenatal cystic fibrosis screening include the cost of prenatal diagnosis for carrier couples (Table 4-15). Although relatively infrequent, the cost of this component is high and is necessary in order to calculate the cost per affected fetus detected. Two studies stop short of this step (Beech and Bekker, 1995; Morris and Oppenheimer, 1995). The studies that include a cost for fetal diagnosis do not include a separate cost item for counseling following fetal testing, with the exception of Ginsberg *et al.* (1994). For three of the remaining studies, we have assumed that the cost of providing counseling was included in the reported diagnostic charges (Lieu *et al.*, 1994; Vintzileos *et al.*, 1998; Wildhagen *et al.*, 1998). Three other studies do break down the costs of fetal diagnostic testing (Cuckle *et al.*, 1995; Rowley *et al.*, 1998; Asch *et al.*, 1998).

Table 4-15. Published Costs of Diagnostic Testing for Carrier Couples as Part of a Prenatal Cystic Fibrosis Screening Program

Author	Country	Cost	Comment
Asch	US	$ 310	Cost does not include karyotype
Ginsberg	Israel	$ 356	Cost does not include karyoty
Cuckle	UK	$ 383	Cost does not include karyotype
Rowley	US	$ 900	Cost
OTA	US	$1200	Charge
Vintzileos	US	$1264	Charge
Lieu	US	$1345	Charge
Wildhagen	Neth	$1770	Charge

- Rowley and colleagues (1998) state that the cost of fetal testing is $900, with the estimate of cost derived from their own study. The total includes $315 for amniocentesis and $585 for DNA analysis of the fetal sample. Presumably, karyotyping for chromosomal abnormalities is not included in this cost estimate, but this is not made explicit in the discussion.
- Vintzileos and colleagues (1998) assume that the cost of prenatal diagnosis is $1300 in 1997 dollars, including $595 for karyotype determination. The total is equivalent to $1264.54 in 1996 dollars.
- Asch and colleagues (1998) report a much lower total fetal testing cost of $300, which they break down into $200 for amniocentesis without karyotyping and $100 for DNA analysis. They assume that the fetal DNA analysis costs the same as the screening test. The amniocentesis cost analysis is based on the costs of personnel, equipment, supplies, and office space, assuming 2,700 amniocenteses performed per year. In 1996 dollars, the total cost is $310. They also report that the total cost from

the payer perspective, based on 80 percent of standard hospital charges, is $800, including $640 for the amniocentesis and $160 for the DNA analysis.

- Lieu and colleagues (1994) report that the charge by the University of California at San Francisco Medical Center for amniocentesis is $1200 and for chorionic villus sampling (CVS) is $1175. The analysis assumes that the cost of mutation testing is included.
- The Office of Technology Assessment (1992) assumed a cost of $1,200 using CVS as the diagnostic procedure.
- Wildhagen and colleagues (1998) use the Dutch reimbursement rate for prenatal diagnosis of 1106.72 pounds ($1770 in 1996 dollars).
- Cuckle and colleagues (1995) assume a cost of 200 pounds for amniocentesis without karyotyping and 33 pounds for DNA analysis, the same as for carrier testing. Translated into 1996 dollars, the total of 233 pounds equals $383.
- Ginsberg and colleagues (1994) report a direct cost of tissue sampling of $293 in 1993 dollars, or $332 in 1996 dollars. Genetic counseling requires 90 minutes for couples whose fetus tests negative and 120 minutes for couples whose fetus tests positive. In Israel in 1993 dollars, costs were $19.35 and $25.16, respectively. The weighted average (with one quarter of fetuses testing positive) is $20.80, or $22.75 in 1996 dollars. When added to the other costs, the total amounts to $356 (1996 dollars).

Component 8: Procedure-related fetal loss

Component 8. A reasonable cost for procedure-related fetal loss is $400. This estimate is based on the two studies reporting costs rather than charges

A risk of amniocentesis or chorion villus sampling is the possibility of a procedure-related loss, which can also be expected to lead to additional incurrence of health care costs. The contribution of this component to overall costs is small, considering the limited number of diagnostic procedures performed (about 1 in 900 couples screened). Table 4-16 shows the four studies have estimate costs for procedure related fetal loss.

Table 4-16. Published Costs Associated with Procedure-Related Fetal Losses Occurring as Part of a Prenatal Cystic Fibrosis Screening Program

Author	Country	Cost	Comment
Asch	US	$ 269	Cost
Ginsberg	Israel	$ 396	Cost
Wildhagen	Neth	$ 619	Reimbursement
Lieu	US	$1133	Charge

- Asch and colleagues (1998) report the health cares costs associated with a spontaneous abortion to be $260, based on data from the Hospital of the University of Pennsylvania.
- Ginsberg and colleagues (1994) report the medical cost of miscarriage to be $350 in 1993 dollars ($396.57 in 1996 dollars).
- Lieu and colleagues (1994) report that the charge by the University of California at San Francisco Medical Center for medical care following a spontaneous abortion is $1000 in 1993 dollars ($1133 in 1996 dollars).
- Wildhagen and colleagues (1998) report the Dutch reimbursement rate for late spontaneous abortion is 387.06 pounds ($619.30 in 1996 dollars).

Cost per case of cystic fibrosis detected prenatally

In order to determine prenatal cystic fibrosis screening total costs, it is necessary to include several additional factors beyond the seven component costs already described. These factors include: screening uptake rates, partner uptake rates, proportion of carrier couples choosing diagnostic testing, the carrier rate (or prevalence) of cystic fibrosis in the population being tested, the proportion of mutations detected by the DNA analysis, and the procedure-related fetal loss rate. Table 4-17 shows a summary of the factors selected by the published economic analyses. The last line contains estimates based on a summary of actual cystic fibrosis prenatal screening pilot trials (Question 33). Many studies assume uptake rates of 100 percent, since actual rates were not available. Nearly all of the published economic analyses (as well as the pilot trials) study mainly European (or non-Hispanic) Caucasians. Variations by race/ethnicity will be considered later in this section. For the purposes of analysis, we assume that the recommended panel of 25 mutations will identify about 88 percent of the mutations present in a non-Hispanic Caucasian population (Question 18).

Table 4-17. Published Uptake Rates, Prevalence, Proportion of Mutations Detected and Procedure-Related Fetal Loss Rate Used to Model Prenatal Cystic Fibrosis Screening Program Costs

Author	Country	Uptake Rates (%)			Carrier Rate (1 in n)	Proportion Mutations Identified	Fetal Loss
		Screening	Partner	Dx Test			
Rowley	US	57	85	80	25	85%	NR
Vintzileos	US	78	100	100	28	90%	NR
Asch	US	100	100	100	25	90%	1 in 200
Lieu	US	72	85	80	25	85%	1 in 160
Wildhagen	Netherlands	90	100	85	33	86%	1 in 133
Beech	UK	76	100	100	25	85%	NR
Cuckle	UK	75	100	100	25	Variable	NR
Morris	UK	87	100	100	25	85	NR
Ginsberg	Israel	50	100	97	29	97%	1 in 83
Pilot Studies		75	95	85	25	90%	NR

NR = not reported

Reported cost per case of cystic fibrosis detected prenatally

Table 4-18 summarizes an analysis performed by us using each of the authors' own assumptions and costs. The analysis is based on offering testing to 100,000 pregnant women/couples and no couple is included twice. The analyses and associated comments concerning strengths and weaknesses can be found in Appendix 1 at the end of this section. All costs are reported in 1996 dollars. The estimates range from a low of $189,000 to a high of $993,000 dollars. Much of the variability in these estimates can be attributed to differences in unit costs explored earlier, differences shown in the estimates shown in Table 4-17, or differences in the cost components included in their analysis. The next section provides a unifying analysis of cost per case detected.

Table 4-18. Costs per Case of Cystic Fibrosis Identified Prenatally According to Published Analyses

Authors	Country	Cost per Women/Couple Screened (1996 $)	Cost per Case of Cystic Fibrosis Identified (1996 $)
Beech	UK	54	189,000
Cuckle	UK	60	207,000
Ginsberg	Israel	84	242,000
Morris	UK	77	266,000
Asch	US	144	342,000
Wildhagen	Netherlands	76	418,000
Lieu	US	116	501,000
Vintzileos	US	156	647,000
Rowley	US	195	993,000

A unifying analysis of cost per case of cystic fibrosis detected prenatally

The following analysis is aimed at arriving at a consensus cost per case detected. Previously reported low estimates could be caused by ignoring some cost components while high estimates could be caused by using charges rather than costs. This analysis relies on consensus component costs described earlier in this section and actual screening factors (last row of Table 4-17) to arrive at costs that are more reliable than any single analysis. This example consider offering prenatal cystic fibrosis screening to 1,000,000 non-Hispanic Caucasian couples, using the sequential screening model (Table 4-19). The prevalence of the disorder is 1:2500, and the 25 mutation panel can identify 88 percent of mutations. One additional assumption is made with regards to uptake rates. A rate of 75 percent is used for sequential screening, but a lower value of 70 percent is used for couple and concurrent screening. It is also assumed, that analytic performance is 100 percent.

Table 4-19. Derivation of Cost per Case of Cystic Fibrosis Detected Prenatally, in a Hypothetical Cohort of 1,000,000 non-Hispanic Caucasian Couples

Activity	Number	Unit Cost (in $)	Total Cost (in $1,000,000)
Provide educational materials	1,000,000	3	3.00
Obtain informed consent	750,000	10	7.50
Collect and send blood sample	750,000	10	7.50
Perform DNA test	750,000	100	75.00
Detect and inform carrier women	26,400	20	0.53
Inform women with negative results	723,600	3	2.17
Collected and send Partner blood sample	25,080	10	0.25
Perform DNA testing	25,080	100	2.51
Detect and inform carrier couples	883	50	0.04
Perform prenatal diagnostic testing	751	600	0.45
Unaffected fetuses lost	8	400	<0.01
Total costs			$98.96

In this population, 188 cases of cystic fibrosis will be identified prenatally. Thus, the cost per case detected is $526,000. DNA testing accounts for nearly 80 percent of the total costs. Taken together, the three most expensive components (obtaining consent, collecting the sample, and DNA testing) account for 96 percent of all costs. Costs per case detected for various combinations of sample collection strategies and screening model are shown in Table 4-20. In general, the cost per case detected remains constant at about $500,000 for the sequential and couple model. The concurrent model is associated with about double the cost per case detected, mainly because nearly twice as many samples are subjected to DNA testing. In all three scenarios, approximately the same number of prenatal cases of cystic fibrosis are identified. The cost per couple screened is relatively constant for sequential and couple screening at about $120 to $140. The cost per couple screened using the concurrent model is higher at about $220 to $240.

Table 4-20. Costs per Case of Cystic Fibrosis Detected Prenatally For Various Combinations of Screening Models and Sample Collection Strategies

Screening Components Varied	Total Cost (in $1,000,000)	CF Cases Detected	Cost per Case (in $1,000)
Sequential model, blood sample	98.96	188	526
Couple model, blood sample	98.98	184	538
Concurrent model, blood sample	167.41	184	909
Sequential model, buccal sample	93.53	188	497
Couple model, buccal sample	89.18	184	485
Concurrent model, buccal sample	157.61	184	857

Cost per case of cystic fibrosis detected prenatally in various racial/ethnic groups

Costs per case detected are considerably higher when the prevalence of cystic fibrosis is relatively low in the population being screened, or when the test panel can only identify a relatively small proportion of mutations. This is due to fewer cases being present, and/or fewer of those cases being detectable. Table 4-21 shows the cost per case detected for populations other than non-Hispanic Caucasians. For comparison, the first row presents the summary data for non-Hispanic Caucasians derived in Table 4-20. The total cost of screening is nearly constant across the groups yielding a relatively consistent cost per couple tested. The major difference is the number of cases of cystic fibrosis detected and, consequently, the cost per case detected.

Table 4-21. Costs per Case of Cystic Fibrosis Detected Prenatally For Various Combinations of Prevalences and Proportions of Detectable Mutations Among 1,000,000 Couples Receiving Sequential Screening via Blood Sampling

Racial/Ethnic Group	Prevalence of CF (1:n)	Prop. of Mutations Detectable	Total Cost (millions)	CF Cases Detected	Cost per Case (in $1000)
Non-Hispanic Caucasian	2500	88	98	188	526
Ashkenazi Jewish	2270	94	99	236	421
Hispanic Caucasian	13,530	72	96	23	4,193
African American	15,100	65	96	17	6,662
Asian American	31,000	49	96	5	19,154

Appendix A

This appendix contains a reanalysis performed by us of each published economic analysis of prenatal cystic fibrosis screening. The studies have been standardized to a testing population of 100,000 couples. No other changes in the reported numbers for these studies have been made. Each of the tables summarizing the individual studies have been made with the same entries in order to aid the reader in identifying those areas in which the study did not report a cost estimate. Finally, the cost per couple offered screening and cost per couple screened (after uptake rates are taken into account) are also provided for each study.

Rowley *et al.*, 1998

The analysis is unique in that key model parameters, including costs, were derived from a pilot study of prenatal cystic fibrosis screening, in Rochester, NY. The authors concluded that the cost of offering screening to 100,000 pregnant women would total $11,107,955. Of this, $2,000,000 would consist of pre-screening education (including obtaining informed consent), $8,797,095 for DNA analysis (including partner testing), and $294,060 for genetic counseling. No allowance was made for specimen collection and processing, genetic counseling, or fetal loss following fetal testing.

	Number	**Unit Cost**	**Total cost**
Pre-screening education	100,000	$ 20	$ 2,000,000
Obtaining informed consent			
Specimen collection			
DNA mutation test	57,000	$150	$ 8,550,000
Result notification & counseling	1,938	$150	$ 290,700
Partner testing	1,647	$150	$ 247,095
Couple counseling	56	$ 60	$ 3,360
Fetal testing	44.8	$900	$ 40,320
Fetal losses			
Total costs			**$11,107,955**
Cost per woman offered screening		**$111**	
Cost per woman screened		**$195**	

Lieu *et al.*, 1994

Probability and cost data for screening being offered to 1,000,000 pregnant women was presented in Tables 3 and 4 of that report. The current analysis divides those numbers by 10 and combines them with unit costs reported. Some categories had to be changed to fit our format, including separating DNA tests between women and partners. Of 100,000 women offered screening, it is assumed that 7,000 women will be too late in pregnancy to receive screening, and that 78 percent of the remainder accept screening. With 72,300 women tested, a prevalence rate of 4 percent, and sensitivity of 85 percent, 2,458 positive results would be expected. Only 85 percent of these women, or 2,090, would have partners available for testing. Of those with partners, only those without a positive partner, or 2,019, receive telephone notification in this model. The model should have included notification cost for all positive results, since there is no way to determine partner status without result notification occurring first. According to the text, genetic counseling is provided to couples where both partners test positive, although fetal testing is also offered to women who test positive where the partner cannot be tested. Only 71 carrier couples

would be detected out of 100,000 women offered screening. At a unit cost of $170, total cost of $75,000 implies 441 women or couples provided counseling. That implies 370 women where the partner was not available undergoing fetal testing. No other analysis has assumed fetal testing for women with positive test results where no positive test result for a male partner was available.

The following table also shows several gaps. First, no allowance was made for obtaining informed consent or for collecting and transporting specimens. Second, no allowance was made for reporting test results to women who tested negative or even for some of those who test positive. All women who test positive would presumably have to be notified, but it was assumed that no notification was needed for women who tested positive whose partners subsequently tested positive. Finally, it was assumed that no genetic counseling is needed following fetal testing.

	Number	**Unit Cost**	**Total cost**
Pre-screening education	100,000	$ 3.28	$ 328,000
Obtaining informed consent			
Specimen collection			
DNA mutation test	72,300	$100	$ 7,230,000
Result notification & counseling	2,024	$ 16.41	$ 33,214
Partner testing	2,095	$100	$ 209,500
Couple counseling	441	$186	$ 82,026
Fetal testing	353	$1346	$ 474,966
Fetal losses	2.2	$1133	$ 2,496
Total costs			**$ 8,360,801**
Cost per woman offered screening		**$ 84**	
Cost per woman screened		**$116**	

Asch *et al.*, 1998

This cost analysis, unlike the preceding studies, is a clinical decision analysis of optimal screening strategies, not a study of population-based screening. Their analysis assumes a highly motivated group interested in undergoing screening. For that reason, uptake rates are all set to 100 percent. The article does not present disaggregated tabulations of costs for the screening process. Below, we calculate costs for one of the 15 strategies modeled, involving sequential screening using an expanded DNA mutation panel. This study, unlike most, included the full cost of sample acquisition and processing. For partner testing, this figure, $20 in 1995 dollars or $20.70 in 1996 dollars, is added to the cost of the DNA analysis, which is $100.

(Strategy K)	Number	Unit Cost	Total cost
Pre-screening education	100,000	$ 16.70	$ 1,670,000
Obtaining informed consent			
Specimen collection	100,000	$ 20.70	$ 2,070,000
DNA mutation test	100,000	$100	$10,000,000
Result notification & counseling	4,192	$ 16.70	$ 70,006
Partner testing	4,192	$120.70	$ 505,947
Couple counseling	168	$ 16.70	$ 2,806
Fetal testing	168	$310.48	$ 52,161
Fetal losses	0.8	$269.80	$ 215
Total costs			**$14,371,162**
Cost per woman offered screening		**$144**	
Cost per woman screened		**$144**	

Ventzileos *et al.*, 1998

This cost analysis refers to population-based screening, but excludes almost all of the true costs of the screening process. This is compensated for by a high estimate of the cost of DNA analysis. The model is presented separately for four racial groups; this is a summary of the model for Caucasians only. The model assumes that 2,880,000 white women are offered screening and that 78 percent accept. The numbers have been modified to the standard population of 100,000 for purposes of comparison.

(Caucasians)	Number	Unit Cost	Total cost
Pre-screening education	100,000		
Obtaining informed consent			
Specimen collection			
DNA mutation test	78,000	$150	$11,700,000
Result notification & counseling			
Partner testing	2,421	$150	$ 363,104
Couple counseling			
Fetal testing	75	$1264.54	$ 94,999
Fetal losses			
Total costs			**$12,158,103**
Cost per woman offered screening		**$122**	
Cost per woman screened		**$156**	

Wildhagen *et al.*, 1998

This article compares hypothetical costs of four broad strategies of population-based screening for cystic fibrosis: prenatal, preconceptional, neonatal, and school-based, based on estimates for the Netherlands where available, or from the United Kingdom. The costs are expressed in British pounds. For prenatal screening, costs are presented for a cohort of 88,241 pregnant couples, the annual estimate for the country as a whole. Two prenatal screening strategies are modeled, in both of which couples are educated together and blood samples are drawn from both partners at the same time. In single entry couple screening, only one sample is analyzed from each couple; only if that sample tests positive is the other sample analyzed. In double entry screening, both samples are analyzed, with laboratory costs of almost twice as much as in the first approach. Below, we calculate costs just for the first strategy.

(Single entry couple screening)	Number	Unit Cost	Total cost
Pre-screening education	100,000	$ 1.55	$ 155,000
Obtaining informed consent	90,000	$ 3.84	$ 345,600
Specimen collection	180,000	$ 7.23	$ 1,301,400
DNA mutation test	90,000	$ 53	$ 4,770,000
Result notification & counseling	2,565	$ 18.59	$ 47,683
Partner testing	2,565	$ 53	$ 135,945
Couple counseling	65.8	$ 37.18	$ 2,446
Fetal testing	65.8	$1770.75	$ 116,515
Fetal losses	0.5	$ 619.30	$ 310
Total costs			**$ 6,874,900**
Cost per woman offered screening		**$ 69**	
Cost per woman screened		**$ 76**	

Ginsberg *et al.*, 1994

The article presents estimates of setting up a national cystic fibrosis prenatal screening program for Israel and offering it to Ashkenazi Jews who are not part of the Haredi Orthodox community. Costs are presented in the original article for a cohort of 18,452 pregnant couples, half of whom would be assumed to be screened.

	Number	Unit Cost	Total cost
Pre-screening education	100,000	$ 1.13	$ 113,000
Obtaining informed consent	50,000	$ 4.23	$ 211,500
Specimen collection			
DNA mutation test	50,000	$ 72.32	$ 3,616,000
Result notification (negatives)	48,328	$ 1.06	$ 51,227
Result counseling (positives)	1,672	$ 8.46	$ 14,149
Partner testing	1,672	$ 72.32	$ 120,919
Result notification	1,672	$ 21.17	$ 35,396
Couple counseling	71.4	$ 21.17	$ 1,511
Fetal testing	69.2	$ 355.75	$ 24,623
Fetal losses	0.8	$ 396.57	$ 317
Total costs			**$ 4,188,642**
Cost per woman offered screening		**$ 42**	
Cost per woman screened		**$ 84**	

Morris and Oppenheimer, 1995

This article discusses nine CF carrier screening strategies, including one sequential prenatal screening option, summarized below. Like the analysis by Ginsberg *et al.* (1994), this analysis is relatively thorough in including cost components for information and reporting results. Unlike Ginsberg, *et al.* (1995) this analysis did not consider the cost of fetal testing.

	Number	Unit Cost	Total cost
Pre-screening education	100,000	$ 0.86	$ 86,000
Obtaining informed consent	87,000	$ 8.60	$ 748,200
Specimen collection	87,000	$ 0.44	$ 38,280
DNA mutation test	87,000	$ 62.40	$ 5,428,800
Result notification (negatives)	84,402	$ 1.73	$ 145,393
Result counseling (positives)	2,958	$ 17.30	$ 51,173
Partner testing	2,958	$ 62.84	$ 120,919
Result notification			
Couple counseling	101	$ 50.75	$ 5,104
Fetal testing			
Fetal losses			
Total costs			**$ 6,688,831**
Cost per woman offered screening		$ 67	
Cost per woman screened		**$ 77**	

Beech and Bekker, 1996

This study analyze three screening protocols: carrier testing in primary practice and two prenatal screening strategies, sequential and couple. We consider only the sequential prenatal screening strategy. This analysis is relatively sparse in terms of costs included.

	Number	Unit Cost	Total cost
Pre-screening education	100,000		
Obtaining informed consent			
Specimen collection	76,400	$ 0.62	$ 47,368
DNA mutation test	76,400	$ 52	$ 3,972,800
Result notification (negatives)			
Result counseling (positives)			
Partner testing	2,598	$ 52.62	$ 136,686
Couple counseling	88	$ 54.26	$ 4,792
Fetal testing			
Fetal losses			
Total costs			**$ 4,161,646**
Cost per woman offered screening		**$ 42**	
Cost per woman screened		**$ 54**	

Cuckle *et al.*, 1994

This analysis considered sequential prenatal screening offered to a cohort of 1,000,000 pregnant women. It is similar to that of Beech and Bekker (1996), except that both pre-screening education and the cost of fetal testing is included.

	Number	Unit Cost	Total cost
Pre-screening education	100,000	$ 3.33	$ 333,000
Obtaining informed consent			
Specimen collection			
DNA mutation test	75,000	$ 53	$ 3,975,000
Result notification (negatives)			
Result counseling (positives)			
Partner testing	2,550	$ 53	$ 135,150
Couple counseling	87	$ 41.11	$ 3,564
Fetal testing	87	$383.13	$ 33,217
Fetal losses			
Total costs			**$ 4,479,932**
Cost per woman offered screening		**$ 45**	
Cost per woman screened		**$ 60**	

Summary of screening costs

The following table summarizes the information from the preceding tables on cost per woman screened. In addition, this table presents the average cost per case of CF identified from one year of screening. The number of cases detected is calculated as one fourth the number of fetal tests performed, except for Lieu *et al.* (1994), where the number is taken from the article. It should be noted that the cost per case identified is lower for studies which assume 100 percent uptake for partner testing and fetal testing compared to studies which allowed for less than complete uptake.

Authors	**Country**	**Cost per woman screened**	**Cost per CF case identified**
Rowley *et al.*	US	$195	$991,782
Vintzileos *et al.*	US	$156	$647,352
Asch *et al.*	US	$144	$342,171
Lieu *et al.*	US	$116	$500,647
Wildhagen *et al.*	Netherlands	$ 76	$417,927
Beech *et al.*	UK	$ 54	$189,166
Cuckle *et al.*	UK	$ 60	$206,687
Morris *et al.*	UK	$ 77	$266,031
Ginsberg *et al.*	Israel	$ 84	$242,066

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CLINICAL UTILITY

Question 36: What are the economic benefits associated with actions resulting from testing?

Summary

According to the majority of studies done in the early 1990's , the annual direct medical care costs for an average individual with cystic fibrosis are $15,000 to $20,000 (1996 dollars).

Based on realistic annual direct medical care costs, expected lifetimes and recommended discount rates, the discounted lifetime medical care costs for an average individual with cystic fibrosis are between $300,000 and $500,000.

The outcome of a cost effectiveness analysis can help guide program decision-making but should not be used as a single deciding factor in offering screening.

In the non-Hispanic Caucasian and Ashkenazi Jewish populations, about half of the screening costs can be accounted for by averted direct medical care costs

In other populations, less than 10 percent of screening costs can be accounted for by averted direct medical care costs.

The actual cost-effectiveness is likely to be better than presented here since many subsequent pregnancies would not need testing. This reduction would only be possible with reliable record-keeping.

Introduction

Published estimates of direct medical costs of care for people with cystic fibrosis may be reported in terms of annual costs of care, and/or discounted lifetime total costs. To convert annual cost of care to lifetime cost (or vice versa), it is necessary to multiply the annual costs times the expected lifetime, while applying a discount rate. The discount rate is the return on investments possible above inflation over that lifetime. For example, assume that an annual bill of $100 must be paid each year for 10 years and the inflation rate is zero. It is not necessary to have all $1000 at the beginning of the time period, if the remaining money is invested and earns interest. This smaller 'discounted' amount is all that is necessary. If, for example, the discount rate were 3percent, only $879 would be needed. If the discount rate were 5 percent, only $811 would be needed. Two studies with the same annual direct costs of care can have different lifetime discounted costs because of differences in life expectancies and/or discount rates. For example, assume that the annual direct care costs of an individual are $20,000. If one study assumed a life expectancy of 35 years with a 3 percent discount rate, the total lifetime costs would be $442,000. Another study assuming an average life expectancy of 25 years with a 5 percent discount rate would report total lifetime costs of $296,000.

To the extent possible, the following annual cost estimates only include direct costs of care excluding, for example, costs of the family's time for treatment and travel. Studies differ in what is included as costs of care. One area of difference is paid home health care. According to one estimate, 20 percent of all direct care costs are home care (Wildhagen *et al.*, 1996a). Using a broader definition of costs of care that includes indirect costs, the same investigators report that 50 percent of the total cost of care for cystic fibrosis is incurred outside the formal medical system (Wildhagen *et al.*, 1996b).

Annual cost of care

Table 4-22 contains a summary of published annual direct costs of care. All costs are adjusted 1996 dollars using the medical care component of the Consumer Price Index. Each study is then summarized after the table.

Table 4-22. Reported Annual Direct Medical Care Costs for an Individual with Cystic Fibrosis

Author	Year Pub	Year Collected	Site	Annual Costs	Comments
Lieu	1999	1996	N CA	$13,650	No home health costs included
Rowley	1998	1989	US	$43,083	Charge? Biased toward severe disease
Wildhagen	1996	1991	Netherlands	$18,226	Excludes $4,556 in home health costs
Lieu	1994	Pre-1994	US	$18,233	From the OTA (1992)
OTA	1992	Pre-1989	US	$16,637	Direct medical costs only

- Lieu and colleagues (1999) estimate the average annual direct medical cost of care based on 1996 health service utilization data from Northern California Kaiser Permanente for 136 patients who were continuously enrolled in the health plan for the whole year. Patients ranged in age from 9 months to 56 years. They were classified as mild (41 percent), moderate (31 percent) and severe (15 percent). This estimate includes hospital, laboratory, radiology, outpatient, and pharmaceutical services. It does not include any home health care services. The estimated annual cost of care is $13,650. Cost of care averaged $6,300 for mild, $11,400 for moderate, and $43,300 for severe cases of CF. For the US population, 56 percent have mild, 28 percent have moderate, and 16 percent have severe disease.
- Rowley and colleagues (1998) cite unpublished data from the Cystic Fibrosis Foundation that the direct cost of medical care amounted to $43,083 per year, in 1996 dollars. They do not provide information on how the CF Foundation came up with this estimate. Lieu *et al.* (1999) state that it was based on an inflation-adjusted 1991 estimate derived from 1989 data on hospital charges for a group of cystic fibrosis patients that may not have been representative of all patients. According to Lieu *et al.* (1999), the lower magnitude of their estimate results in part from changes over time in patterns of care, changes in costs, use of costs rather than charges, and a representative inclusion of mild and moderate cases. They do not mention the possibility that other direct costs such as home care may have been included in the CF Foundation estimate but excluded from their own analysis.
- Wildhagen and colleagues (1996) collected data on the direct costs of hospital care, hospital and non-hospital medication, and home care from a survey of medical records and a patient questionnaire. On average the annual cost of a patient with cystic fibrosis in 1991 was 10,908 pounds (hospital care 42 percent, medication 37 percent, home care 20 percent). Converted to 1996 US dollars using the medical care CPI, this is $22,782. This estimate differs from the Lieu *et al.* (1999) estimate by including the cost of home care. If home care were excluded, the Dutch estimate would be $18,226.
- Lieu and colleagues (1994) state that they took a published estimate from a study by the U.S. Congress's Office of Technology Assessment (1992), although the original figure is not mentioned. Adjusted for inflation, this is stated to be $16,092 in 1993 dollars. In 1996 dollars, this is equivalent to $18,233.
- The OTA (1992) report reveals a set of estimates, based on a contract document prepared by M.V. Pauly. First, data were collected by the Wilkerson Group from interviews with cystic fibrosis patients, their families, and clinicians. Three groups of patients were defined, with average annual cost of medical care of $8,500 for 'mild', $24,500 for 'moderate', and $46,500 for 'severe' cases. Only patients with hospitalizations were included in the survey. The OTA analysis adjusted these estimates to take into account 'submild' cases with no hospitalizations in a given year and came up with a weighted average of $10,885 in annual medical expenses. This was based on an arbitrary assumption that medical care costs were $2,000 for 'submild' cases. These estimates are given in

1989 dollars. Adjusted for inflation on the basis of the medical care component of the CPI, the estimate is $16,637 in 1996 dollars.

Discounted lifetime cost of care

A number of estimates of discounted lifetime costs of care for cystic fibrosis patients have also been published. One of these (Ginsberg *et al.,* 1994), contains no estimate of annual cost of care. The other studies all calculate lifetime estimates based on annual costs of care included either in the same publication or an earlier publication that is cited (Table 4-23). To the extent possible, the following estimates relate specifically to the direct cost of care. Some estimates include both medical and non-medical costs, others relate only to medical costs. The definition of medical costs varies across studies, notably in whether home health care costs are included. Published estimates have been converted to 1996 dollars, as needed. The U.S. Public Health Service Panel on Cost-Effectiveness in Health and Medicine recommends that studies conducted from the societal perspective publish estimates using both 3 percent and 5 percent discount rates. None of the prenatal cystic fibrosis screening evaluations has followed that practice. The choice of a 3 percent discount rate is appropriate from the societal perspective. From the health system perspective, a higher discount rate may be more appropriate. Most studies have used current estimates of historical survivorship, reflected in median age at death of affected patients (typically, 30 years). The cost estimates from the Netherlands assume a life expectancy of 35 years, which raises their cost estimates relative to the others. The Israel study assumed a life expectancy of 45 years.

In principle, cost of illness studies subtract the cost of care for unaffected individuals from that of affected persons in order to calculate the incremental cost of care. Only one of the studies in this table (Ginsberg *et al.,* 1994) has explicitly done so. The remaining estimates likely include some degree of overestimation of the cost of cystic fibrosis by failing to present net costs of care.

Table 4-23. Reported Lifetime Direct Medical Costs for an Individual with Cystic Fibrosis

Author	Year Pub	Site	Discount Rate (%)	Life Expectancy	Lifetime Costs ($1,000)
Lieu	1999	US	5	30	220
Lieu	1994	US	5	30	276
Lieu	1999	US	3	30	276
Van der Riet	1997	N'lands	5	30	324
Ginsberg	1994	Israel	5	45	329
Asch	1998	US	5	30	364
Wildhagen	1996	N'lands	5	35	388
Vintzileos	1998	US	3	30	778
Rowley	1998	US	3	30	844

- Rowley *et al.* (1998) report that the annual direct cost of care, in 1996 dollars, is $43,083 per year and the "indirect" (parental) care is $9,380 per year, based on parental time of 938 hours per year valued at $10 per hour. Assuming that costs are invariant with age, they sum up the total cost, direct plus indirect, over a life expectancy of 30 years. The undiscounted total is $1,573,890. Discounted at 3 percent, the total is $1,028,298. Although the authors do not report the discounted total medical cost

of care, it is possible to calculate this by multiplying $1,028,298 by the ratio of $43,083 to $52,463. The resulting total for discounted total medical costs is $844,446.

- Vintzileos *et al.* (1998) cite the 1997 NIH Consensus Development Conference Statement (1999) as stating that the lifetime cost of care is $800,000, which supposedly includes both direct medical and indirect costs. The NIH appears to have relied, without attribution, on the same CF Foundation estimates (over $40,000 per year in direct costs and over $9,000 per year in indirect costs) as did Rowley *et al.* (1998). The NIH statement that the discounted total for direct and indirect costs is approximately $800,000 was in error. Based on an annual cost of $49,000 per year for 30 years and a 3 percent discount rate, the discounted total is close to $1 million; the discounted total for direct costs alone was approximately $800,000. In any case, the $800,000 figure in 1997 dollars is adjusted for inflation to $778,166 in 1996 dollars.
- Wildhagen *et al.* (1998) report that the lifetime cost of care for a CF patient in the Netherlands is 238,634 pounds sterling, calculated using a 5 percent discount rate and assuming a life expectancy of 35 years. This estimate is equivalent to $387,586 in 1996 dollars. This estimate is based on an examination of medical records for 81 CF patients complemented by additional information on use of health services obtained through a questionnaire filled out by 73 CF patients. Further details of the methods are provided in two other publications (Wildhagen *et al.*, 1996a; 1996b). The original estimate, in 1991 currency, was a discounted total of 164,365 pounds, which implies a 45 percent adjustment for inflation between 1991 and 1996. This ratio is high, compared to a 29 percent increase in the medical care CPI in the United States during the same period.
- Van der Riet *et al.* (1997) rely on an unpublished version of the Wildhagen *et al.* (1996a) estimate of cost of care. They express this as 545,968 Dfl, in 1994 currency, and provide an exchange rate of 1.82 Dfl to 1 US$. This converts to $299,982 in 1994 dollars, or $324,436 in 1996 dollars.
- Asch *et al.* (1998) report lifetime medical and nonmedical direct cost of care for CF of $351,278 in 1995 dollars. This is taken from the OTA study, adjusted for inflation at an arbitrary rate of 4 percent per year. They also report that the OTA estimate has two components, $181,258 in direct medical costs and $170,020 in direct nonmedical costs. In 1996 dollars, the total estimate is $363,545.
- Lieu *et al.* (1994) also derived their lifetime cost of care from the OTA report, but only for the medical cost of care component. This estimate is $243,650 in 1993 dollars, or $276,072, in 1996 dollars.
- Ginsberg *et al.* (1994) report a lifetime CF cost estimate of $328,431 in 1993 dollars, discounted to present value with a 5 percent discount rate. This total consists of $290,528 in medical costs, $6,938 in extra food, $18,845 in earnings losses, $1,806 in transport costs, and $10,316 in mortality cost. For physiotherapy, only the one sixth of sessions that are delivered by paid professionals are included in the medical care component; home care provided by family members is excluded. The medical care cost estimate when adjusted for inflation is equivalent to $329,188 in 1996 dollars. The medical cost estimates in this are based on a projection of future care standards, not current care. It was assumed that all patients would receive heart-lung transplants and that this would prolong survival by an average of 15 years. Offsetting these assumptions, which inflate costs quite substantially compared to other studies, is the lower cost of health care in Israel because of lower wage levels. The authors acknowledge that assuming a life expectancy of 45 years raises their cost estimates. They also report a cost estimate to age 25 of $192,000, which they note is more comparable to other estimates.

A unifying analysis of the lifetime direct medical costs of cystic fibrosis

The three components of the lifetime direct medical costs of cystic fibrosis are the annual costs of direct medical care, the expected lifetime, and the discount rate. From the literature, the annual costs of direct medical care in the early to mid 1990's are between $15,000 and $20,000 per year for the average patient. Given the increasing use of lung transplants and drugs, the costs in the near future are likely to be even higher. Thus, a third annual cost of $25,000 will also be included. Guidelines for economic analyses like these suggest using discount rates of both 3 and 5 percent. Both will be utilized. The average lifetime of an individual with cystic fibrosis had not increased significantly in the last decade and, therefore, the current lifetime of 30 years is a reasonable estimate. For purposes of sensitivity analysis, an additional lifetime of 35 years will also be included. Figure 4-2 shows the total costs for annual costs varying from $15,000 to $25,000, discount rates of 3 percent and 5 percent, and lifetime of 30 and 35 years. Overall, nearly all lifetime direct medical costs are between $250,000 and $500,000.

Figure 4-2. Total Lifetime Direct Medical Costs for an Individual with Cystic Fibrosis. This cost analysis considers annual direct medical expenses from between $15,000 and $25,000 dollars (x-axis) and total lifetime direct medical costs (y-axis). The analysis is performed at two life expectancies (labeled 30 and 35 years) and at two discount rates (solid lines 3 percent and dashed lines 5 percent).

Balance of costs and benefits of prenatal cystic fibrosis screening

Definitions: A cost-effectiveness analysis estimates the net cost of an intervention (defined as the cost of delivering the intervention minus averted costs), divided by the number of desired outcomes achieved. Although not addressed in this report, a cost-benefit analysis places a monetary value on the desired outcome (the denominator in a cost-effectiveness analysis), which is then subtracted from the other costs to derive the net cost or benefit of the intervention.

Cost effectiveness evaluations of prenatal screening for cystic fibrosis

Two different outcomes can be evaluated. The first is the number of affected fetuses detected and the second is the number of births of affected children averted. For the first outcome, the cost-effectiveness ratio is the screening cost per case identified. This type of cost-effectiveness analysis is non-directive in terms of what is done with the information, which is assumed to be of some value to the couples involved. Question 35 concludes that the cost per case detected is $500,000 in non-Hispanic Caucasians. For the second outcome the cost-effectiveness ratio is the cost per case averted. Analyses of this type find that the higher the rate of pregnancy termination, the more cost-effective screening appears. For either of these outcomes, two questions can be asked: 1) Is prenatal screening a cost-effective option to offer? and 2) Which prenatal screening protocol is the most cost-effective? Studies focusing on the first question typically analyze a single prenatal screening strategy and overall cost-effectiveness is closely tied to magnitude of averted cost of care from terminated pregnancies. The cost comparison of screening strategies does not depend on this, since the relevant outcome is minimizing the cost per case detected.

Studies of the value of information – willingness to pay

Estimates of the average cost of prenatal screening for cystic fibrosis have been calculated in terms of both cost per couple screened and cost per affected fetus detected (Question 35). The average cost is at least $120 per couple screened and $500,000 to $800,000 per case detected. The cost of obtaining this information (which fetus would develop cystic fibrosis) can be directly compared to the perceived value of the information. A few of these willingness to pay (WTP) analyses have been conducted.

The only willingness to pay analysis conducted in the United States (summarized by Rowley *et al.*, 1998) was based on responses to a single question that elicited from respondents how much they would have been willing to pay for screening that was provided free of charge in the context of a research protocol. Most (77 percent) of the respondents were willing to pay less than $25. Only 6 percent of the respondents were willing to pay more than $50 for the test. The average cost of screening in this study was calculated to be almost $200. The perceived value of information from cystic fibrosis screening did not come close to justifying the cost of the screening, as carried out in Rochester, New York in the mid-1990s.

A more sophisticated willingness to pay study was conducted earlier in Great Britain (Donaldson *et al.*, 1995). In Aberdeen, a group of pregnant women who had undergone cystic fibrosis screening in a randomized trial were surveyed regarding their willingness to pay. Overall, 51 percent responded. The median response was 20.5 pounds ($34), higher than was the case for the respondents in the Rochester survey. One difference was where the information was obtained. Median response in the Aberdeen survey was 24 pounds for those who filled out the survey at home, compared to 14 pounds for those who answered the questions at the clinic. Further, respondents who were given prompts had a mean response of 22 pounds, compared to 11 pounds for those who were asked an open-ended question. The main

predictors of willingness to pay were found to be the willingness to terminate an affected pregnancy, higher social class, and greater knowledge about cystic fibrosis.

The open-ended version of the Aberdeen survey was repeated in a group of women attending prenatal care who indicated that they would accept cystic fibrosis screening if it were offered (Donaldson *et al.*, 1997). The median estimate from this survey was 19 pounds (or $32). Like the other surveys cited, the WTP estimates exclude women who do not consider screening to be of value and are unwilling to be tested. It is possible than many of the non-respondents did not place a high value on the information. One limitation of the WTP estimates from Aberdeen is that many of the respondents appear to have based their estimates on their perceptions of the cost of screening, not their actual willingness to pay. That is, when asked how much people are willing to pay for a service, many people may give a response based on their idea of what a reasonable price is for the service.

Cost effectiveness analyses that include averted costs

Differences between cost-effectiveness analyses hinge on the proportion of affected fetuses that are selectively terminated. The following sections summarize and critically evaluate the four cost-effectiveness and cost-benefit studies published since 1994.

- Lieu and colleagues (1994) concluded that providing screening to one million white women in the United States would cost $83 million. The base line assumptions of the model are that 72.3 percent would accept screening, 80 percent of those who accept screening would accept prenatal diagnosis, and 30 percent of those whose fetuses test positive would be selectively terminated. Under these assumptions, screening would save $12 million in averted lifetime direct medical costs from 50 selective terminations, resulting in a net cost of $71 million (83-12). The net cost per affected birth averted is $1,420,000 ($71 million/50). This study has been criticized for assuming that only 30 percent of affected fetus would be selectively terminated (Petrou *et al.*, 2000). Pilot trials (Question 33) have shown that at least 80 percent of couples who pursue fetal testing and are found to have an affected fetus will make that choice. If this higher number were used, 133 termination (compared to 50) would occur and reduce the net cost per affected birth averted to $383,000 (compared to $1,420,000).
- Rowley and colleagues (1998) report that the screening cost per cystic fibrosis birth averted is $1,322,376, assuming no replacement pregnancy. They report that the discounted lifetime cost of care is $1,028,298, and that averted costs of care amount to 78 percent of the cost of providing screening. This is a mixed-perspective analysis. The authors used the health care system perspective for calculating costs of screening and the societal perspective for calculating cost of care. The same perspective should have been used throughout the analysis. If only medical costs of care were included ($844,446), the cost offset ratio would fall from 78 percent to 64 percent. Even this cost of care estimate is based on unpublished data that refer to costs for relatively severe cases. Population-based data yield lower estimates of cost of care. If the estimate from Lieu *et al.* (1999) using a 3 percent discount rate ($275,572) is substituted, the cost-offset ratio declines to 21 percent. Some of the cost parameters in Rowley *et al.* (1998) appear surprisingly high. In particular, the pre-screening education cost of $20 likely reflects a research protocol rather than a routine screening protocol. The cost of DNA analysis is also high, at $150, and the cost of genetic counseling for carriers, at $150, is much higher than in other studies. With alternative estimates of $10 for pre-screening education, $100 for DNA analysis, and $30 for carrier counseling, the screening cost per case averted would fall

to $826,556. On the other hand, it should be noted that the analysis excluded the cost of specimen collection and processing.

- Vintzileos and colleagues (1998) have published the least complete analysis of screening, but their report is the only U.S. study that concludes that screening for cystic fibrosis in pregnancy is likely to be cost saving. In particular, the study concluded that under most assumptions considered, screening is cost saving for Caucasians, although not for African Americans, Asians, or Hispanics. The authors maintain that, "Because the overwhelming majority of pregnant women are white, the savings from this group is more than enough to compensate for the small losses observed among the three other racial or ethnic minorities." This analysis includes only two costs of screening: DNA analysis and prenatal diagnosis. No costs are allowed for pre-screening education, sample acquisition, result notification, genetic counseling, fetal loss, or induced abortion. The model includes implausible assumptions about program uptake, including 100 percent partner testing and 100 percent use of prenatal diagnosis. Further, the authors arbitrarily reduced all screening costs by half, under the assumption that each affected pregnancy identified today would, without additional cost, avert an additional cystic fibrosis pregnancy in the future. Finally, this study used a relatively high estimate of cost of direct medical care care.
- Asch and colleagues (1998) report a relatively rigorous decision analysis of prenatal screening. The authors modeled three approaches: expanded one-step (couple screening with both partners tested termed "parallel parental sequence" in the report), one-step (couple screening with sequential testing termed "sequential parental sequence" in the report) and two-step (sequential screening with only female sample collected initially termed "sequential parental sequence" in the report). For each model, three types of DNA testing were modeled: a "standard" molecular test for 6 mutations, an "expanded" molecular test for 20-30 mutations, and "mixed" testing, with the standard test for the first partner and the expanded test used only if the first partner tests positive. The analysis was conducted from three perspectives: societal, patient, and payer. Societal perspective was based on resource costs, the individual perspective on out-of-pocket and opportunity costs, and the payer perspective on an assumption that payers would pay 80 percent of stated charges. The base-case analysis was conducted from the societal perspective. The average cost per cystic fibrosis birth avoided is calculated for three sequential screening strategies. According to the authors, it was $381,000 for standard (6-mutation) screening, $512,000 for expanded (20-30 mutation) screening, and $367,000 for mixed screening. The difference in results between the standard and expanded screening strategies reflects the difference in cost of $100 for the expanded mutation test and $50 for the 6-mutation test. The authors note that these estimates all assume 100 percent uptake of abortion in cases of affected fetuses. Unlike most other analyses, these authors did not subtract averted costs of care from screening costs to calculate net costs. Consequently, their results cannot be directly compared with the other estimates in this section.

A unifying analysis of cost effectiveness with averted costs

Screening costs are just over $500,000 per prenatal case of cystic fibrosis detected in a population of non-Hispanic Caucasians (Question 35, Table 4-21). Analysis of pilot trials (Question 34) show that about 80 percent of affected fetuses identified as part of screening programs are terminated. Lifetime direct medical care costs for the average individual with cystic fibrosis is between $250,000 and $500,000. Table 4-24 shows the cost effectiveness of prenatal cystic fibrosis screening for various racial/ethnic groups when averted costs are included. The analysis assumes one-million couples approached for screening (for a more complete discussion of the assumptions for this analysis, see Table 4-17, Question 35). In the non-Hispanic Caucasian and Ashkenazi Jewish population, about half, or more of the screening costs are covered by averted direct medical care costs. For the remaining racial/ethnic groups, less than 10 percent of screening costs are accounted for by averted direct medical care costs.

Table 4-24. Cost Effectiveness of Prenatal Screening for Cystic Fibrosis when Averted Costs are Taken into Account

Racial/Ethnic Group	Total Costs Of Screening (millions of $)	Cases Detected	Cases Averted	Direct Medical Costs Averted		Offset Ratio Range (%)
				$250k	$500k	
Non Hispanic Caucasians	98	188	150	37	75	36 to 75
Ashkenazi Jewish	99	236	189	47	95	47 to 95
Hispanic Caucasians	96	23	18	5	9	5 to 9
African Americans	96	17	14	3	7	3 to 7
Asian Americans	96	5	4	1	2	1 to 2

Implications of 'Steady State' Screening

In all of the discussions to this point, one underlying assumption has been implicitly made. That is, all pregnancies are tested for all couples regardless of test results from a previous pregnancy. Several studies have pointed out that the 'steady state' of screening would actually result in reduced costs as most subsequent pregnancies would not need to be tested again. A couple would need to be tested in a subsequent pregnancy if 1) the partner has changed or 2) the test will detect a higher proportion of mutations. No formal estimate of the effect of 'steady state' screening will be made, but it can be easily seen that a large proportion of the population would not need to be tested in a subsequent pregnancy, if reliable records of testing could be maintained.

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CLINICAL UTILITY

Question 37: What facilities are necessary for prenatal screening for cystic fibrosis?

Summary
Facilities are necessary for three phases of screening activities and need to be centrally administered as a comprehensive program. The three phases include

- Pre-analytic activities occur at the primary care sites and include education, consent, and sample management
- Analytic activities occur at the laboratory and include sample processing, testing and reporting. A minimum of 60 laboratories are likely to be needed to manage 1,000,000 couples tested annually. Between 100 and 500 new DNA clinical technologists in the United States will need to be available.
- Post-analytic activities occur at clinical referral sites and can include counseling of carrier individuals as well as couples where both partners have positive test results. Only 3 full time counselor equivalents would be needed to provide services to couples where both are carriers (assuming 1,000,000 couples tested annually). Between 50 and 100 additional full time counselor equivalents would be needed if all carrier individuals identified are also provided services.

Facilities for managing prenatal cystic fibrosis screening can be developed in the same manner as existing prenatal screening programs and may be superimposed upon existing infrastructure.

In order for a prenatal screening program to be properly implemented, appropriate facilities (e.g., laboratory space, equipment, and computers) and staff are required. Prenatal screening for cystic fibrosis needs to be viewed in the context of a combined laboratory and patient service program. That is, a centralized administrative function oversees all aspects of the screening program. This includes educational materials and consent, laboratory testing and interpretation, and finally, genetic counseling and diagnostic testing. Existing prenatal screening models indicate that the Laboratory Directors is likely to be responsible for program administration, along with other genetics professionals. Screening activities can be divided into three phases, and the facilities and personnel for each of these phases is discussed below.

Pre-analytic activities
These activities performed at the primary care sites and include physician and patient education, obtaining consent, obtaining an appropriate sample, completing the requisition slip, and ensuring that the sample reaches the testing laboratory. The program needs to ensure that primary care providers have the necessary information by providing physician educational materials, in-service training, and face-to-face meetings. Patient educational materials also need to be made available (the content and type of materials are covered in more detail in Questions 39 and 40). A program staff member should be available to answer questions by phone. Sample collection materials should be clearly specified or provided. A simple and clear test requisition slip for screening should be provided (Question 34). Based on results from pilot trials, primary care providers should be informed that, on average, 5 to 10 minutes of time should be allocated per patient for educational/consent activities.

Analytic activities

The laboratory facilities and resources that are needed can be estimated from published information concerning prenatal screening for Down syndrome and open neural tube defects. There are approximately 4 million pregnant women per year in the United States, and prenatal serum screening for Down syndrome and neural tube defects is chosen by over half (Palomaki *et al.*, 1997). That testing is performed in about 200 laboratories. Within a few years of cystic fibrosis prenatal screening being made a standard of care, as many as 1 million pregnancies might be screened annually. How many laboratories might be expected to perform such screening, and what might their characteristics be? Molecular testing for cystic fibrosis is highly complex and requires expert interpretation. This limits the number of laboratories capable of delivering this service. Existing laboratories that offer cystic fibrosis testing include for-profit laboratories, not-for-profit laboratories and academic institutions. Some states may choose to oversee and manage such testing (as is the case in California for second trimester maternal serum screening for Down syndrome and open neural tube defects). According to the latest American College of Medical Genetics/College of American Pathologists' External Proficiency Testing Program, 36 laboratories now offer cystic fibrosis testing. However, some of these may not pursue mass screening. If 30 laboratories were to provide services to 1 million pregnancies, they would test an average of over 30,000 couples per year. This would currently be difficult, given the limited level of automation available (high-throughput automated systems are not readily available). Realistically, the number of qualified laboratories would need to at least double and could expand to as many as 150. Assuming that one laboratory technician can log-in, process, test and report 2,000 samples per year, an estimated 500 new DNA clinical technologists would be required. Were automated systems available, this number might be reduced considerably, to perhaps 100 to 200 technologists. The number of new technologists may be further reduced if some were currently underutilized or engaged in research.

Post-analytic activities

Post-analytic activities center around the counseling of screen positive individuals (two-step or expanded one-step models only) or screen positive couples (all models). Screen positive couples are usually offered a comprehensive genetic counseling session estimated to take between one-half and one hour. Only about 1:850 couples will require this level of counseling (this rate is for the non-Hispanic Caucasian and Jewish populations; screen positive couples occur less frequently in other racial/ethnic groups – Question 20). In a hypothetical population of 1,000,000 couples screened, the one hour per couple counseling time is equivalent to about 2 or 3 full-time genetic counselors. Were programs to utilize the two-step approach and offer a one-half hour genetic counseling session to all screen positive women (about 1 in 30), the genetic counselor time would be much higher, equivalent to 45 or 50 full-time genetic counselors. Were a half-hour counseling session to be offered to all screen positive individuals in an expanded one-step program (about 1 in 15), the genetic counselor time would total nearly 100 full-time genetic counselors. To put these numbers in perspective, between 90 and 100 genetic counselors graduate from training programs each year. At most, 340 fetuses affected with cystic fibrosis would be identified among the 1,000,000 couples tested, and couples in this situation would need another level of counseling and support to help them reach a course of action which would be most appropriate for them.

Will adequate facilities be available for prenatal cystic fibrosis screening?

Some information concerning the answer to this question can be found in the history of prenatal screening for open neural tube defects, beginning in the late 1970's and early 1980's. At that time, successful pilot trials had been reported from both the United Kingdom and the United States, but wide implementation in the United States was considered to be difficult, due the variety of health delivery mechanisms. A few qualified laboratories began offering testing, and their success encouraged others to begin. With the statement from the American College of Obstetricians and Gynecologists in 1985 suggesting that such testing should become routine, resources were found to train, implement and oversee widespread screening for neural tube defects in the United States. A similar path is likely to be followed now that the policy recommendations from the Joint Committee on Prenatal Cystic Fibrosis Testing (American College of Medical Genetics/American College of Obstetricians and Gynecologists) have been issued (Grody *et al.*, 2001). One factor that makes the introduction of prenatal screening for cystic fibrosis less demanding is that mechanisms are already in place for widespread delivery of other prenatal screening services. In many instances, the new screening protocols can be superimposed on existing infrastructure.

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CLINICAL UTILITY

Question 38: What educational materials have been developed and validated and which of these are available?

Summary
The components of educational materials for both providers and patients have been published
Approximately 5-10 minutes of provider time was spent in direct educational contact with the patients
Four examples of patient educational material have been reviewed and found to

- satisfy most, but not all, content criteria
- rate either 'adequate' or 'superior' using objective readability and presentation standards

Introduction

Prenatal screening program need educational materials appropriate for two separate but overlapping audiences: providers and patients. Because screening will be implemented at primary care settings, where expertise in genetics and genetic testing may be limited it is important that providers have access to information about how to offer and interpret prenatal cystic fibrosis testing. In addition, they should be able to answer most of the patient questions that will arise. There also needs to be access to expert genetic resources in the event that difficulties arise. Equally important, there need to be high quality, validated educational materials for patients to help them make informed decisions.

Provider education

The Secretary's Advisory Committee on Genetic Testing (SACGT) has recently suggested a genetic test template to inform and educate health professionals (Federal Register, 2000). The seven elements are summarized in Table 4-25. The first six of these are likely to be similar in any laboratory offering prenatal cystic fibrosis testing, except for minor differences in the laboratory procedures. The seventh component, billing and reimbursement, is laboratory-specific. Answers to some of the elements are not yet readily available (e.g., analytic versus clinical laboratory performance).

Table 4-25. Components of a Genetic Test Information Sheet for Health Care Providers

Component	Description
Purpose of the test	The purpose and setting for testing (e.g., predictive, newborn)
Clinical condition	Description including prevalence, manifestations and prognosis
Definition of test	Specific laboratory measurements
Analytical validity	How accurately the test measures the intended analyte
Clinical validity	Accuracy with which measurement predicts clinical condition
Clinical utility	Contribution of the test results to improved outcome
Cost of testing	Costs, billing information and reimbursement policies (e.g., CPT code)

Developing educational materials for health care providers

At least 13 centers have developed educational materials of this type as part of pilot studies of prenatal cystic fibrosis screening (Question 35). It would be helpful if these materials were to be reviewed before any new material is created. For providers, educational material should cover at least the first six

components of the SACGT genetic test template. Reviewers should be drawn from professional organizations and work with professional educators involved in adult education and continuing education for health care professionals. If existing materials do not meet the SACGT criteria, laboratories could create and make available their own provider education materials. Any such newly created materials need to be formally validated. Methods of validation include: 1) the use of focus groups, and 2) field-testing the educational materials with health care providers and their staffs, followed by evaluative surveys. Such surveys should be designed and carried out by professional evaluators. The American College of Obstetricians and Gynecologists has recently produced a Clinical and Laboratory Guideline on this subject for its members (ACOG Guidelines, 2001). The American College of Medical Genetics has also published Laboratory Standards and Guidelines on this topic and much of that information would be useful in provider educational materials (Grody *et al.,* 2001).

Gap in Knowledge: Content of Provider Educational Material. Missing in Table 4-25 are other laboratory-specific instructions to the health care provider. Examples of additional provider education topics are listed in Table 4-26. Many laboratories include this type of information as part of a 'Resource Guide', and it is often covered again in face-to-face encounters between laboratory outreach personnel and primary care providers (e.g., rounds, seminars and office visits). Lack of knowledge about, or failure to follow, these instructions is a major cause of pre-analytic errors identified in studies of prenatal screening for cystic fibrosis (Dequeker *et al.*, 2000).

Table 4-26. Other Laboratory-specific Information that Ought to be Included in Provider Education

Component	Description
Sample collection	Description of sample type, volume, and labeling requirements
Shipping instructions	Packaging and addressing
Time requirements	Type of shipper, turn-around-time
Requisition slip	Description, ordering and justification of fields
Consent	Who is responsible for collecting and maintaining consent
Reporting	How reports are transmitted and interpreted. Model used.
Confidentiality	How it will be maintained
Certification	Certifications/licenses for specific genetic testing
Further testing	What further testing might be suggested/required
Urgent Action	What results require immediate physician contact

The teachable moment

For both providers and patients, effective provision of information involves two critical elements: timing and types of materials. Effective timing makes use of the "teachable moment", that point in a learning experience when the learner is more receptive to accepting and using new information, accepting new attitudes, or learning new skills (Woods *et al.,* 1996). Fr the health care provider, the teachable moment comes at the time when an issue arises with a patient. For that reason, written material that the provider can use at the time of the patient visit are far more effective than didactic sessions that may take place days, weeks, or even longer before the issue actually arises with the patient. For the patient, that moment occurs when required information is provided precisely at the time it is needed to help that patient make a decision (Leist *et al.,* 1990). It is, therefore, important that appropriate educational/informational materials be readily available to providers and patients at the time when the materials will be most useful.

Patient education

Educating pregnant women about prenatal screening for cystic fibrosis has been described as providing relatively complex genetic information to large populations in order that couples make informed choices. In reality, the aim of patient educational is more limited. Several key points need to be clearly stated so that those involved feel that they can make an informed decision about whether or not they want to have their pregnancy screened. In addition, it is important to ensure that ample time is available for questions and answers between the provider and patient, without placing a burden upon the office. Table 4-27 summarizes data from published pilot studies showing the type of patient educational materials and average time needed for transmitting the information. All studies utilized printed pamphlets and most also reported verbal interactions with the health provider/staff. Two studies also included videotapes. Most providers found that an average of 5-10 minutes was spent in direct educational contact (e.g., time spent reading the pamphlet or watching the video were not included).

Table 4-27. Summary of Patient Educational Materials Used in Prenatal Cystic Fibrosis Pilot Studies

Screening Center	Pamphlet/ Brochure	Videotape	Verbal Explanation/ Questions	Estimated Minutes Spent
Edinburgh, Scotland	✓		✓	NR
Copenhagen, Denmark	✓			NR
Manchester, England	✓		✓	10
Oxford, England	✓			NR
East Berlin, Germany	✓		✓	NR
Maine, USA	✓		✓	10
Aberdeen, Scotland	✓		✓	NR
Rochester, NY	✓		✓	5
N California, USA	✓	✓	✓	10
Leeds, England	✓		✓	11
Milan, Italy	✓		✓	10-15
Los Angles, USA	✓	✓	✓	30
New York, USA	✓		✓	3-5[1]

NR – Not Reported

[1] Group counseling session for 12 couples lasted 40 minutes

Evaluation of patient and provider educational materials

Several formal evaluations of existing written patient and provider educational materials for genetic testing have been reported (Loeben *et al.*, 1998). The materials were evaluated for content, using 10 criteria for minimal content drawn from published recommendations by policy-making bodies (Table 4). The content overlaps with that presented in Table 1. The authors analyzed 115 pamphlets (20 of these were for cystic fibrosis testing), most of which (65 percent) were developed by the organizations offering testing, or in collaboration with other groups (27 percent). The remainders were from disease-specific support groups or the March of Dimes. As shown in Table 4-28, most of the materials failed to address

many of the criteria listed. The authors concluded that the patient pamphlets were more complete and that provider materials seemed more aimed at identifying patients for testing than for providing information to evaluate the tests. It was not possible to obtain separate information for the 20 cystic fibrosis pamphlets from the published report. Little, if any, information was available about reading level or patient response to the material.

Table 4-28. Criteria for Content Analysis of Genetic Test Educational Materials

Criterion	Description	Specified Pamphlet Addresses Criteria (%)	
		Provider	Patients
Intended purpose	Screening, diagnostic or predictive testing	28	36
Test performance	Sensitivity, specificity and predictive values	38	54
Risks, limits, benefits	Medical or social benefits or risks	7	13
Rights of patients	Voluntary nature, confidentiality, consent	3	27
Candidates for testing	Any medical or family history criteria	52	77
Description of condition	Symptoms, characteristic and incidence	45	100
Genetic counseling	Counseling is available or necessary	52	67
Interpretation of test	Risk of disease for positive and negative results	21	36
Treatment options	Treatment, prevention or medical management	7	62
Cost	Cost to the patient	52	31

Availability of patient education material

Patient educational materials are already available from several sources, including some that have been published as part of reports of prenatal cystic fibrosis pilot studies (Mennie *et al.,* 1992; Loader *et al*., 1996). Other patient educational materials are available on-line. In addition to these, two patient educational pamphlets have recently been produced by the American College of Obstetricians and Gynecologists and the American College of Medical Genetics. These pamphlets are available in English only and are now available for purchase.

Objective methods for evaluating patient educational materials

Cystic fibrosis screening programs should be aware that it is not ordinarily necessary to develop patient education materials from scratch. Several evaluation tools have been developed that will allow assessment of existing materials and provide suggestions for improving them, if necessary. In evaluating materials, two critical elements need to be considered: content and patient comprehension. Among the published guidelines for evaluation are Loeben's criteria for content analysis of educational materials (Loeben *et al.*, 1998), listed in Table 4-28 above; and Suitability Assessment of Materials (SAM) for evaluation of materials for patient comprehension (Doak *et al.*, 1995). Because the average literacy level of the population in the United States is between the 6^{th} and 8^{th} grades, one of the most important considerations in evaluating materials is reading level. Simple and clear language is necessary so that the message is understood. SAM criteria address this, along with other factors, including purpose, scope, inclusion of summary, behavior-oriented content, reading grade level, use of active voice and commonly used words, cover graphic that shows purpose, simple line drawings, relevance of illustrations, lists, explanation of tables, captions used for graphics, material layout factors, typography, number of items under subheadings, and cultural appropriateness. The SAM evaluation takes 45 minutes and provides a

numerical measure of a document's suitability. There are many published tools for estimating the 'readability' of written materials including the widely used and accepted Fry formula (Fry, 1977). There are also several computerized formulae, such as the Fog Index, the Flesch Reading Ease (Tefki, 1987) or the Flesch Grade Level. Although most of the educational materials used in the prenatal cystic fibrosis pilot studies were originally written in English, alternative languages and cultural approaches should be considered, depending on the population being served. It is always important to involve consumers in the planning and review of patient educational materials (Myers *et al.*, 1994).

Table 4-29 gives summary ratings of four available sets of patient materials. The ratings for the materials are based on the Loeben, *et al.* (1998) and SAM guidelines. A SAM "superior" rating indicates that the materials satisfy 70-100 percent of the SAM criteria, an "adequate" rating satisfies 40-69 percent, and a "not suitable" rating satisfies 0-30 percent of the criteria.

Table 4-29. Summary Ratings for Four Available Sets of Patient Educational Materials

Material	Content Criteria	SAM Rating
Cystic Fibrosis Carrier Testing: The Decision is Yours (ACOG, 2001)	Meets Most [1]	Adequate [5,7]
Cystic Firosis Testing: What Happens if Both My Partner and I Are Carriers (ACOG, 2001)	Meets most [2,3,4]	Adequate [6,7]
Cystic Fibrosis: It's Your Choice (Loader *et al.*, 1991)	Meets most [2]	Superior
Information About Cystic Fibrosis (CF) and CF Carrier Testing (Clayton *et al.*, 1995)	Meets most [1,2,4]	Superior

Notes
1. does not address test performance
2. does not address confidentiality or consent
3. does not address availability of counseling
4. does not address cost to the patient
5. literacy demand is somewhat high
6. literacy level is above grade 9
7. few or no illustrations, graphics not relevant or not explained

Readability scores are based on the Fry Readability Graph (Fry, 1977).

In another published review that concentrated on 28 provider and/or patient pamphlets containing educational materials directed at cystic fibrosis testing, the authors concentrated on three content areas: description of cystic fibrosis, life expectancy and reproductive options (Loeben *et al.*; 1998). Each sentence in the pamphlet was classified as expressing "Optimism/Hope", "Neutral" or "Pessimism/Caution". The results were stratified based on geography (United States and the United

Kingdom), the type of laboratory (non-commercial and commercial), and whether the setting was prenatal or other. There was a wide variation in the number of sentences describing cystic fibrosis (median 6.5, range 1 to 37) with neutral sentences being far more common than negative or positive ones. Fewer sentences dealt with life expectancy (median 4, 0-7) and in the UK and US commercial pamphlets, positive sentences were rare. When a carrier couple was identified, most (24/28) discussed prenatal diagnosis, but only about half (15/28) mentioned selective termination (or a similar term). Termination was mentioned more often in pamphlets from the UK than from the US (8/9 versus 7/19). In the United States, termination was never mentioned by commercial laboratories (0/7) but by more than half of non-commercial laboratories (7/12). The authors concluded that for information to be truly 'balanced', it should contain both positive and negative comments intermixed with neutral comments.

Other evaluation criteria

Because the average literacy level of the population in the United States is between the 6th and 8th grade, it is important to consider reading level for patient materials. Simple and clear language is necessary so that the message is understood. The Suitability Assessment of Materials (SAM), a well-tested evaluation system for health-related educational materials for patients, is now in widespread use. It provides ratings based on 22 factors in six categories: content, literacy demands, graphics, layout and typography, learning stimulation and cultural appropriateness (Doak *et al.*, 1995). The evaluation takes 45 minutes and provides a numerical measure of a document's suitability. Other tools are available for calculating 'readability' of written materials, the most highly recommended and widely accepted of which is the Fry Formula (Fry, 1977). There are also several computerized formulae such as the Fog Index, the Flesch Reading Ease (Tefki, 1987) or the Flesch Grade Level. In addition to literacy level, it is important that patient materials be made available in languages other than English. Although most of the materials used in the pilot trials were originally written in English, alternative languages should be considered, depending on the population being served. It is always important to involve consumers in the planning and review of patient educational materials (Myers *et al.*, 1994).

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The Fog Index can be computed at www.fpd.finop.umn.eu/Related/Writing_tips/Writing_tips.html

CLINICAL UTILITY

Question 39: What are the informed consent requirements?

Informed consent for cystic fibrosis prenatal screening is recommended by the American College of Medical Genetics, due to the vulnerability of the screened population (Question 6). In addition, there is no available treatment for cystic fibrosis prenatally. Therefore, the only option available to parents who test positive and wish to avoid the birth of an affected child, is to terminate the pregnancy. Since this option will be morally unacceptable for some, and emotionally difficult for many, it is important that women/couples fully understand the lack of other preventive options before entering the testing pathway. To accomplish this, the health provider or screening program should provide a simple and clear booklet to be given to eligible women/couples at the earliest stages of their pregnancy (Question 8). It is also considered standard of care that a carrier couple who choose to have amniocentesis are offered genetic counseling before the procedure. General recommendations about informed consent for genetic tests vary. New York State regulations that the laboratory make a reasonable effort to document consent prior to testing. This can be in the form of a patient or physician signature. Existing CLIA regulations do not require that laboratories document informed consent, but current CLIAC recommendations do include this requirement. The NCCLS Molecular Guidelines state that the referring clinician has the primary responsibility for informing patients of the risks, costs and benefits of testing. Whether or not the laboratory is required to document consent is left to the discretion of the laboratory and any applicable federal, state or local requirements.

CLINICAL UTLITY

Question 40: What methods exist for long-term monitoring?

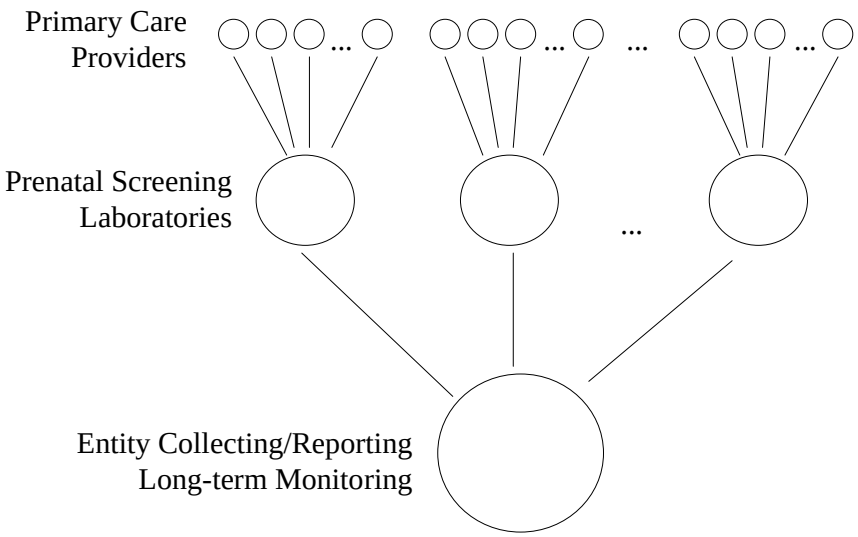
Summary
Long-term monitoring helps to
- document, and ensure, quality of service delivery
- assess public health impact
- identify areas of concern

The process requires cooperation between health care providers and screening laboratory personnel.
Oversight by professional organizations and/or governmental agencies would be beneficial.
A successful monitoring strategy involves ensuring that the data collected are useful.

Methods for organizing and conducting a practical evaluation of public health programs have been published (Loc *et al.*, CDC Handbook). Cystic fibrosis screening is now becoming available as part of routine prenatal care. Long term monitoring of the screening process can be valuable in helping to assure quality and assess public health impact. Long term monitoring also provides a framework for the collection of further information about clinical validity and utility, as well as ethical, legal, social and financial issues. Areas of concern in the screening process can also be identified by this mechanism. In conjunction with the introduction of routine screening, decisions should be made as to the questions of interest, as well as the strategies to be employed to collect, analyze and report relevant information. Specific goals could also be established at that time. Priorities for studying long term monitoring issues might be based on feedback from providers, laboratories, and those being offered screening. Stakeholders, including the general pregnancy population, public health officials, cystic fibrosis screening laboratory directors, health care providers, third party payers and advocacy groups are appropriate to include in the process. Long term monitoring can provide answers to the following types of questions:

- Are providers and patients properly educated to make informed decisions?
- Is the quality of laboratory service adequate?
- In aggregate form, what are the results of laboratory testing?
- Is the panel of recommended mutations appropriate?
- How are laboratory test results reported to the provider/patient?
- What actions are taken based on the laboratory results?
- Is there a discernable impact on birth prevalence of cystic fibrosis?
- Is reimbursement being routinely provided?
- Are there further ethical, legal or social implications that need to be addressed?
- Should the screening process be modified or discontinued?

Based on previous collection efforts of this type, long term monitoring data will be most successful when all of those engaged in the effort find the information to be useful. Figure 4-3 shows a schematic of the groups involved in the process. One example of how this could occur in prenatal cystic fibrosis screening is to address the problem of collecting ethnic/racial data on the laboratory requisition slip. This information is necessary for accurate computation of residual risk. In order to encourage the collection of this important information, primary care providers need to be convinced that the laboratory interpretation of test results will take this into account and that their patients will directly benefit. The American



College of Obstetricians and Gynecologists (ACOG) could be helpful in informing their membership about this and similar types of issues. The laboratory can then use of this information in its interpretation. Monitoring the racial/ethnic mix of samples arriving for testing could help in ensuring that the test is being offered appropriately. Lastly, those responsible for providing oversight of long term monitoring might periodically survey laboratories and provide feedback and recommendations.

Figure 4-3. A Schematic Representing the Groups Involved In Collecting, Evaluating and Using Long Term Monitoring Information

Laboratory information could be obtained through surveys distributed to participants of external proficiency testing programs (e.g., the ACMG/CAP MGL survey). An existing example of a nationwide survey of this type involves the collection of information concerning prenatal screening for Down syndrome. (Palomaki *et al.*, 1997). Some of the success of this survey was due to ACOG Technical Bulletins directed specifically to this topic, outlining the responsibilities of the primary care provider to supply necessary demographic and pregnancy-related information to the laboratory. Data collection on the part of screening laboratories could also be required as part of the accreditation process by CLIA or CAP, or as part of the proposed FDA review process. There are some types of information that can be gathered without involving laboratories directly. Targeted studies could evaluate specific topics in depth at an individual screening site. Long term monitoring of the birth prevalence could be accomplished by a non-profit organization such as the Cystic Fibrosis Foundation. Much of the needed information is already being collected by that organization. Ethical, legal, and social issues are most appropriately examined by individual studies or surveys. This approach may allow important questions to be answered in the areas of discrimination, stigmatization, and barriers to access. Table 4-1 contains selected data elements, stratified according to screening stage, that could be addressed as part of a long-term monitoring effort.

Table 4-30 presents the data that might be collected by each screening laboratory. The laboratory needs to distinguish whether the sample to be tested is for screening or diagnostic purposes, by including an 'indication' field on the requisition slip. Examples of indications other than general population screening include: family history of cystic fibrosis, clinical suspicion of cystic fibrosis, and prenatal diagnosis.

Table 4-30. Possible Topics to be Addressed for Prenatal Cystic Fibrosis Screening as Part of a Long Term Monitoring Effort

Pre-analytic

Completeness of patient information on the requisition slip
Sample rejection rate
Indication for testing (restrict to prenatal screening)

Analytic

Number of mutations tested
Assay and test failure rates
Number of women/couples screened
(stratified by race/ethnicity, socioeconomic status, region and gestational age)
Turn-around time
Carrier frequencies (stratified by race/ethnicity)
Partner uptake rates for programs using two-step model (stratified by race/ethnicity)
Number and rate of carrier couples (stratified by race/ethnicity)
Number and rate of affected pregnancies (termination rate optional)
Methods of payment

Post-analytic

Software used and contents of report
Long term knowledge of women/couples
Impact on birth prevalence (stratified by race/ethnicity)
Patient/health care provider satisfaction
Miscellaneous ethical, legal or social issues

Table 4-31. Specific Information that a Laboratory Offering Prenatal Screening for Cystic Fibrosis Might Have Available to Satisfy Requests for Long Term Monitoring Information

General Laboratory Information

Completeness of filling out requisition slips
Sample rejection and assay failure rates
Source of interpretative software/sample reports
Turn-around time (from arrival to reporting)

Specific Information for Each Woman/Couple Screened

Date of test
Geographic location where the woman's sample was obtained
Race/ethnicity
Gestational age at initial sampling
Result of test (i.e., positive, negative, failure)
For positive tests, the mutation detected

Specific Information for Each Woman/Couple Testing Positive

Whether partner accepted
If yes, partner test result (if positive, mutation detected)
Was genetic counseling offered/accepted
Was prenatal diagnostic testing of the fetus offered/accepted
Results of prenatal diagnostic testing
Date result transmitted to couple
Pregnancy outcome (i.e., termination vs. continuation)

Reference laboratories providing services to distant programs may find it difficult to collect information in the third section of Table 4-31. In some instances, when a woman is found to have a mutation and the partner's sample is requested, that sample may go to another laboratory because of insurance requirements (each partner has a different insurance company that utilizes a different laboratory). This could make identifying positive couples difficult. Further, counseling may be handled locally, and diagnostic testing may be directed to another laboratory. Given the relatively infrequent occurrence of a couple testing positive, methods need to be found to collect this information in order to document whether the screening process is functioning properly. Some laboratories may find it difficult to identify the resources necessary for the data collection. In order to encourage data collection, it is important to provide feedback. For example, The European Quality Assessment Schemes reported that 31 percent of cystic fibrosis reports contained errors (Dequeker *et al.,* 2000). These findings from Europe suggest that it will be important to monitor laboratory reports in the United States, as well. If this were to be done, it could: 1) document the overall status of cystic fibrosis reporting in the United States, 2) identify specific errors that could be corrected, and 3) identify the characteristics of a standard clinical report. Reports from pilot trials (Question 33) contain summaries for much of the laboratory-based information suggested in Table 4-31. However, these reports often leave out crucial details, are active over only a short time period, or cover only a small geographic area. Since prenatal screening for cystic fibrosis is still not widespread in the United States, there have been no comprehensive reports documenting screening services as described in this section.

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CLINICAL UTILITY

Question 41: What guidelines have been developed for evaluating program performance?

Summary
No specific guidelines for long term program evaluation have been published
In the absence of guidelines and oversight requirements, it is suspected that many screening laboratories are not collecting the type of information necessary for such monitoring

No specific guidelines for long-term program evaluation of prenatal cystic fibrosis screening have been published. A collaborative effort of the American College of Medical Genetics and American College of Obstetricians and Gynecologists has resulted in clinical and laboratory guidelines for such screening, but these guidelines do not include program evaluation (Grody *et al*., 2001; Grody and Desnick, 2001). These two organizations are the logical groups to develop cystic fibrosis program evaluation guidelines, or to delegate this task to a third party.

> **Gap in Knowledge: Guidelines for Long Term Program Evaluation.** Currently there are no guidelines for the evaluation of prenatal cystic fibrosis screening programs. Many clinical laboratories providing such services are not collecting the necessary information for an appropriate evaluation.

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