

ACCE

A CDC Sponsored Project

Population-Based Prenatal Screening for Cystic Fibrosis via Carrier Testing

Editors

James E. Haddow, M.D., Glenn E. Palomaki, B.S., B.A.

Foundation for Blood Research

Scarborough, Maine 04074

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DRAFT

The following individuals contributed original material to this report:

Linda A. Bradley, Ph.D.

Clinigene Laboratories, Hauppauge, New York

Scott Grosse, Ph.D.

Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, Atlanta, Georgia

James E. Haddow, M.D.

Foundation for Blood Research, Scarborough, Maine

James B. Haddow, Esq.

Petrucelli, Martin, & Haddow, LLP, Portland, Maine

Glenn E. Palomaki, B.A.

Division of Biometry, Foundation for Blood Research, Scarborough, Maine

Nancy A. Press, Ph.D.

Division of Medical Genetics, Oregon Health Sciences University, Portland, Oregon

Carolyn Sue Richards, Ph.D.

Dept. of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

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Members of the ACCE Core Group during the time this report was conceived and executed include:

James E. Haddow, M.D., Principal Investigator

Foundation for Blood Research, Scarborough, Maine

Linda A. Bradley, Ph.D.

Clinigene Laboratories, Hauppauge, New York

Wylie Burke, M.D., Ph.D.

Dept. of Medical History and Ethics, University of Washington, Seattle, Washington

Marta Gwinn, M.D., M.P.H.

Division of Genomics and Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Muin J. Khoury, M.D., Ph.D.

Division of Genomics and Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Glenn E. Palomaki, B.S., B.A.

Division of Biometry, Foundation for Blood Research, Scarborough, Maine

Nancy A. Press, Ph.D.

Division of Medical Genetics, Oregon Health Sciences University, Portland, Oregon

Carolyn Sue Richards, Ph.D.

Dept. of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

Paula Yoon, ScD, M.P.H.

Division of Genomics and Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Reviewers of Population-Based Prenatal Screening for Cystic Fibrosis via Carrier Testing, along with a summary of their comments and responses, are listed at the end of this report (Section 7, Glossary and Comments).

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ELSI

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Introduction to ACCE

The ACCE project is funded by the Centers for Disease Control and Prevention (Cooperative Agreement UR3/CCU119356-01) and administered by the Foundation for Blood Research in Scarborough Maine. The aim of the project is to assess the availability, quality, and usefulness of existing data on DNA-based tests and testing algorithms. It is intended that the methods developed as part of this project be suitable for use by others involved in this type of analysis. The final data summaries and interpretations will be presented in forms that can be used by policy-makers, health providers and consumers. Genetic Test Briefs will be a condensation of important points for each disorder and clinical setting evaluated. Gaps in knowledge will also be highlighted.

The ACCE evaluation process requires that many groups work together. Figure 1 displays the groups involved in developing the draft reports (within the large circle), along with those that review and suggest modifications and/or extensions. A representative list of “Reviewers” is also displayed, to give a sense of the type of input that the project is seeking. One important function is to keep federal policy making groups informed of the ongoing process (upper left corner).

Groups To Keep Informed

HHS Interagency Genetics Working Group
CLIAAC Genetics Working Group
Genetics Oversight Committee
CDC Genetics Lab Forum
SACGT
FDA

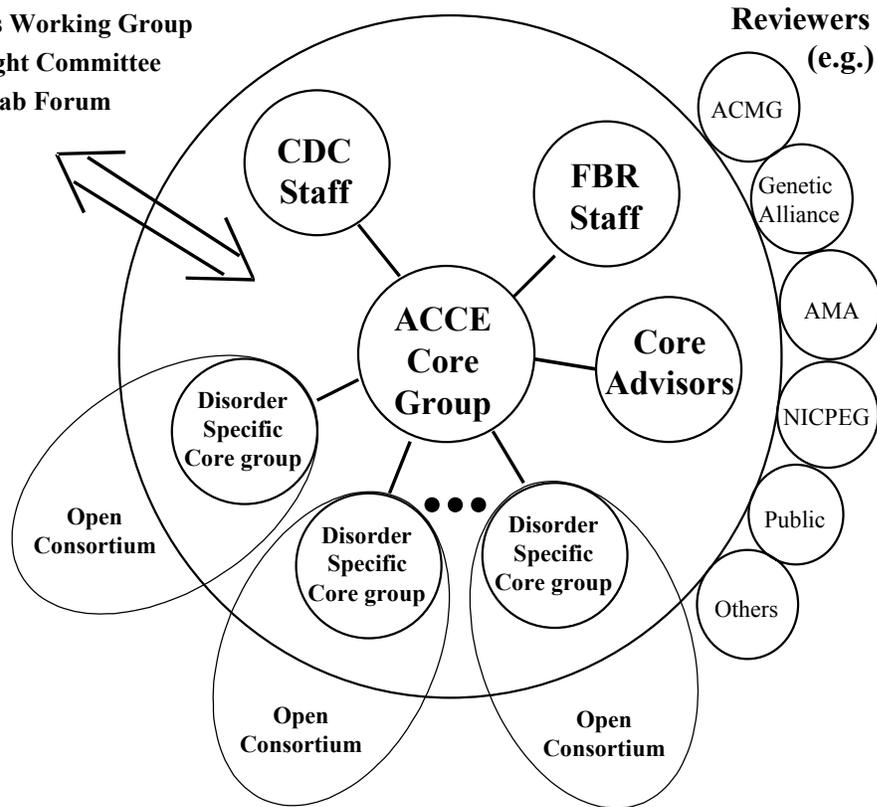


Figure 1. Groups Involved in the ACCE Project

ACCE is derived from the four components of evaluation: Alytic validity, Clinical validity, Clinical utility and Ethical, legal and social implications. The ACCE wheel (Figure 2) summarizes the elements that comprise each of these components. The hub lists the clinical disorder being evaluated, along with the clinical setting in which testing is done (e.g., cystic fibrosis in the setting of prenatal screening). The evaluation process begins only after the clinical disorder and setting have been clearly established. Specific questions 1 through 7 (Table 1) help to define the disorder, the clinical setting and the type of laboratory testing.

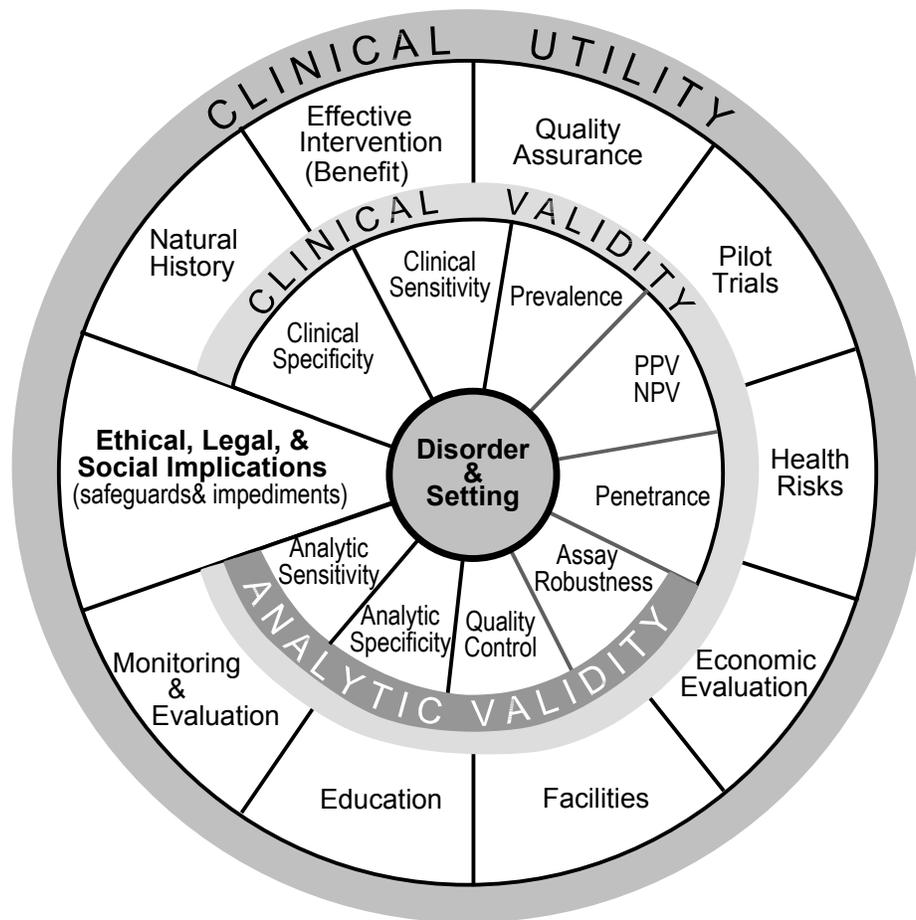


Figure 2. The ACCE Evaluation Process. The figure summarizes the five components for evaluating a genetic test.

Analytic validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest. This aspect of evaluation focuses on the laboratory component. The four specific elements of analytic validity include analytic sensitivity (or the analytic detection rate), analytic specificity (or the analytic false positive rate), laboratory quality control, and assay robustness. Analytic sensitivity defines how effectively the test identifies specific mutations that are present in a sample. Analytic specificity defines how effectively the test correctly classifies samples which do not have specific mutations (although the term ‘mutation’ is used here, the terms polymorphism or variant may be more appropriate for certain situations). Quality control assesses the procedures for ensuring that results fall within specified limits. Robustness

measures how resistant the assay is to changes in pre-analytic and analytic variables. Specific questions 8 through 17 (Table 1) help organize the information available to document analytic validity.

Clinical validity of a genetic test defines its ability to detect or predict the associated disorder (phenotype). The four elements of analytic validity are all relevant to assessing clinical validity, along with six additional elements. These include clinical sensitivity (or the clinical detection rate), clinical specificity (or the clinical false positive rate), prevalence of the specific disorder, the positive and negative predictive values, penetrance, and modifiers (gene or environmental). Penetrance defines the relationship between genotype and phenotype and allows the frequency of the clinical expression of a genotype (expressivity) to be determined. Clinical sensitivity is the proportion of individuals who have, or will develop, the phenotype who also have positive test results. Clinical specificity is the proportion of individuals who do not have, or will not develop, the phenotype who also have negative test results. Prevalence measures the proportion of individuals in the selected clinical setting who have, or will develop, the phenotype. The positive and negative predictive values more meaningfully define the test performance by combining clinical sensitivity, clinical specificity and prevalence. Specific questions 18 through 25 (Table 1) help organize the information available to document clinical validity.

Clinical utility of a genetic test defines the elements that need to be considered when evaluating the risks and benefits associated with its introduction into routine practice. Specifically, clinical utility focuses on the health outcomes (both positive and negative) associated with testing. The natural history of the specific disorder needs to be understood, so that such considerations as optimal age for testing might be taken into account. It is necessary to determine the availability and effectiveness of interventions aimed at avoiding adverse clinical consequences (if no interventions are available, for example, testing may not be warranted). Quality assurance assesses procedures in place for controlling pre-analytic, analytic, and post-analytic factors that could influence the risks and benefits of testing. Pilot trials assess the performance of testing under real world conditions, including the psychologic and social risks and benefits of testing. Health risks define adverse consequences of testing or interventions in individuals with either positive or negative test results. Economic evaluation helps define financial costs and benefits of testing. Facilities assess the capacity of resources to manage all aspects of the service. Education assesses the quality and availability of informational materials and expertise. Monitoring and evaluation assess a program's ability to maintain surveillance over its activities and make adjustments. Specific questions 26 through 41 (Table 1) help organize the information available to document clinical utility.

Ethical, legal and social implications surrounding a genetic test refer to two types of concerns: those inherent in any medical technology, and those that are particularly germane to genetic testing. The latter concerns include: implications for relatives of the individual undergoing genetic testing, the possibility of insurance discrimination, stigmatization based on genotype (disease risk) rather than phenotype (actual disease), and the 'invisible' nature of genetic testing (i.e. that it pertains to the provision of information rather than the conduct of an invasive medical procedure). The degree and the precise nature of these risks, however, depend to a great degree on the preceding three components. Thus, ELSI concerns are represented in Figure 2 by a penetrating pie slice, implying that the safeguards and impediments should be considered in the

context of the other components. Questions with ELSI relevance are contained in each section of Table 1 while questions 42 through 44 (Table 1) help organize the information available to document specific ELSI issues.

Table 1. The ACCE Model’s List of Targeted Questions Aimed at a Comprehensive Review of DNA Testing

| Element | Component | Specific Question | |
|--------------------------|--------------------------|---|---|
| Disorder/Setting | Disorder | 1 What is the specific clinical disorder to be studied? 2 What are the clinical findings defining this disorder? | |
| | Setting | 3 What is the clinical setting in which the test is to be performed? | |
| | Testing | 4 What DNA test(s) are associated with this disorder? 5 Are preliminary screening questions employed? 6 Is it a stand-alone test or is it one of a series of tests? 7 If it is part of a series of screening tests, are all tests performed in all instances (parallel) or are only some tests performed on the basis of other results (series)? | |
| | Analytic Validity | Sensitivity | 8 Is the test qualitative or quantitative? 9 How often is the test positive when a mutation is present? |
| | | Specificity | 10 How often is the test negative when a mutation is not present? |
| | | Quality Control | 11 Is an internal QC program defined and externally monitored? 12 Have repeated measurements been made on specimens? 13 What is the within- and between-laboratory precision? 14 If appropriate, how is confirmatory testing performed to resolve false positive results in a timely manner? |
| | | Robustness | 15 What range of patient specimens has been tested? 16 How often does the test fail to give a useable result? 17 How similar are results obtained in multiple laboratories using the same, or different, technology? |
| Clinical Validity | Sensitivity | 18 How often is the test positive when the disorder is present? | |
| | Specificity | 19 How often is the test negative when the disorder is not present? 20 Are there methods to resolve clinical false positive results in a timely manner? | |
| | Prevalence | 21 What is the prevalence of the disorder in this setting? 22 Has the test been adequately validated on all populations to which it may be offered? | |
| | PPV,NPV | 23 What are the positive and negative predictive values? | |
| | Penetrance | 24 What are the genotype/phenotype relationships? 25 What are the genetic, environmental or other modifiers? | |

Clinical Utility

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

ELSI

- | | |
|-------------|---|
| Impediments | 42 What is known about stigmatization, discrimination, privacy/confidentiality and personal/family social issues? 43 Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements? |
| Safeguards | 44 What safeguards have been described and are these safeguards in place and effective? |

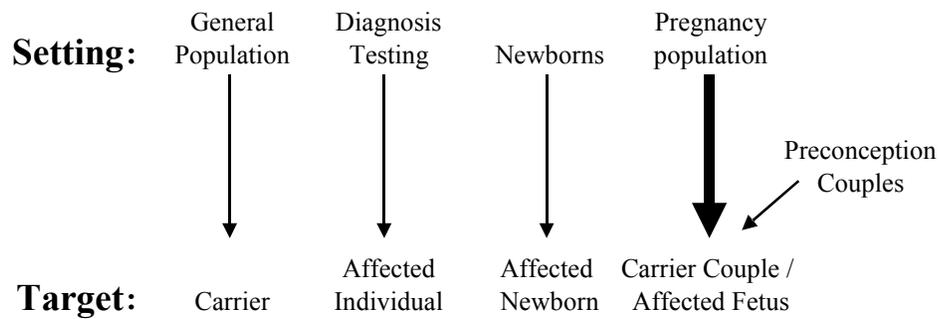
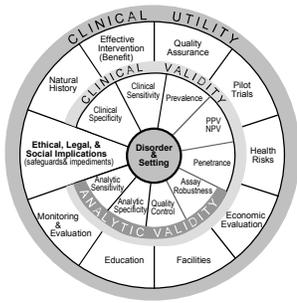


Figure 3. Possible Clinical Settings for Cystic Fibrosis Testing

The ACCE project's purpose is to develop a model system for assessing available information about specific genetic tests and test protocols. The first disorder to undergo an ACCE review is cystic fibrosis in the prenatal setting. Figure 3 shows several possible settings for cystic fibrosis testing. Some of these employ only DNA based testing (e.g., prenatal), while others may utilize both DNA and biochemical testing (e.g., IRT measurements in newborn screening). The target of a cystic fibrosis testing program can vary by clinical setting. In the diagnostic setting, an individual with symptoms or family history might be tested to confirm a diagnosis. In the setting of prenatal screening, the final goal is to identify a fetus with two cystic fibrosis mutations. As steps in this process, both carrier individuals, carrier couples and, occasionally, carrier fetuses, would be identified. This report is aimed at assembling the available data, assessing their reliability, creating summary data reports when possible, identifying gaps and providing interpretations. The intent of this report is to provide policy makers with accurate, up-to-date information for use in their deliberations.

James E. Haddow, M.D.
ACCE Principal Investigator



ACCE

A CDC-Sponsored Project

Genetic Test Brief: Population-Based Prenatal

Screening for Cystic Fibrosis via Carrier Testing

(Q indicates the question number where further information can be found)

Disorder/Clinical Setting – Cystic Fibrosis/Prenatal Screening

- Disorder (Q2, Q3 and Q26)
 - ◆ is autosomal recessive and is caused by mutations in the *CFTR* gene
 - ◆ is associated with major health problems
 - ◆ primarily involves the lungs and gastrointestinal tract
 - ◆ is currently associated with a median survival of 24 years
 - ◆ is projected to have a median survival of 32 years for those born in 2000
- Treatment (Q26)
 - ◆ is aimed at slowing progression of the disease
 - ◆ may be improved in the future by advances such as gene therapy
- Screening process involves (Q4, Q5, Q28, Q38, Q39)
 - ◆ DNA testing with a panel of mutations (25 are currently recommended by ACMG)
 - ◆ informing pregnant women and their partners (or couples planning pregnancy) of the availability of testing
 - ◆ engaging in an education and informed consent process
 - ◆ offering counseling when both partners are carriers
 - ◆ offering diagnostic testing of fetal cells (obtained via amniocentesis or chorionic villus sampling) when both partners are carriers
 - ◆ offering information to couples with an affected fetus regarding planning for management of the disease and about the option of pregnancy termination
- Prevalence (up to 1:2300) and proportion of detectable carriers (up to 94%) (Q5, Q21)
 - ◆ vary considerably by race/ethnicity
 - ◆ can be determined by a preliminary screening question and be used to help inform couples about the usefulness of this testing process to them

Analytic Validity

- The analytic process is qualitative; the mutation is either present or absent (Q8)
- The only currently available reliable source of data for determining analytic sensitivity and specificity is from external proficiency testing (Q9,Q10)
- External proficiency testing schemes are not the optimal source for these data and interpretation is complicated (Q9,Q10)

- Data from the ACMG/CAP external proficiency testing program show that (Q9, Q10)
 - ◆ on average, participating laboratories will correctly identify a mutation about 97.9% of the time (95 percent CI 96.9-98.7%) (analytic sensitivity)
 - ◆ when a mutation is not present, laboratories will, on average, provide the correct answer about 99.4% of the time (95 percent CI 98.7-99.9%) (analytic specificity)
- Data from an external proficiency testing program in Europe show similar overall error rates to those found in the ACMG/CAP survey(Q9,Q10)
- Analytic performance for a given mutation is not likely to differ by race/ethnicity (Q22)
- Internal quality control procedures are well described, and adherence is externally monitored by accrediting organizations (Q11)
- Few laboratories report assay repeatability and failure rates (in the pre-analytic and analytic phases). This information is often on file within the laboratory but is not published (Q16)
- Confirmatory testing (additional testing to verify the initial positive result) (Q14)
 - ◆ should be considered when a carrier, carrier couple, or affected fetus is identified
 - ◆ should improve analytic specificity, but few data are available to estimate the impact
 - ◆ is not routinely performed in all laboratories currently offering prenatal screening
- Sample types successfully used for screening purposes in pilot trials include: (Q15)
 - ◆ whole blood (purified DNA and lysates)
 - ◆ buccal lysates (cheekbrush and mouthwash)
- Available DNA assays for the *CFTR* mutations all appear to perform reliably (Q17)

Clinical Validity

- Taking the non-Hispanic Caucasian population (the main target of screening) as an example: (Q18, Q19, Q21, Q23)
 - ◆ the prevalence is about 1:2500, based on prenatal and newborn screening trials and population registries
 - ◆ 78 of 100 carrier couples will be detected (25 mutation panel) but of these, only 75 will have a positive test result correctly reported (clinical sensitivity 75%)
 - ◆ Clinical specificity is projected to be high (based on several assumptions) meaning that nearly all non-carrier couples will be correctly classified
 - ◆ the positive predictive value for a carrier couple is at least 99.0%
 - ◆ in couples where no mutation is identified, the residual risk (1-negative predictive value) is considerably lower than the birth prevalence
 - ◆ in couples where only one partner is a carrier, the residual risk is always higher than the birth prevalence
- Self-reporting is the usual method of identifying race/ethnicity and can be associated with misclassification. (Q18, Q19, Q21)
- Among other racial/ethnic groups in the United States, the proportions of carrier couples that have detectable mutations using the recommended panel are: (Q18)
 - ◆ 88 of 100 among Ashkenazi Jewish couples (94% of mutations identifiable)
 - ◆ 52 of 100 among Hispanic Caucasian couples (72% of mutations identifiable)
 - ◆ 42 of 100 among African American couples (64.5% of mutations identifiable)
 - ◆ 24 of 100 among Asian American couples (49% of mutations identifiable), but this rate is likely to be confounded by self-reporting

- The birth prevalence of cystic fibrosis is about: (Q21)
 - ◆ 1:2,500 in non-Hispanic Caucasian births
 - ◆ 1:2,300 in Ashkenazi Jewish births
 - ◆ 1:13,500 in Hispanic Caucasian births
 - ◆ 1:15,000 in African American births, but is much lower in native Africans
 - ◆ 1:31,000 in Asian American births, but is much lower in native Asians
- Nearly all fetuses identified with two mutations in the recommended panel will develop clinical manifestations of cystic fibrosis. The exceptions are R117H and I148T (both included in the panel) and D1152H (not in the panel, but in some commercial reagents). These three mutations are often not associated with cystic fibrosis. (Q23, Q24)
- Knowing a specific genotype does not accurately predict the presence or severity of specific clinical manifestations such as pancreatic insufficiency, the time of onset, or rapidity of progression (Q24)
- Environmental and genetic modifiers (Q25)
 - ◆ are likely to play a role in the natural history, but little information is known
 - ◆ may, in the future, provide information about prognosis or response to treatment

Clinical Utility

- The natural history is well described (Q26)
- To some extent, the impact of a positive test depends upon the screening model (Q27)
- Three models have been used for prenatal screening and the following characteristics are important to keep in mind: (Q27, Q33)
 - ◆ all have the same clinical sensitivity (detection rate) but differ as to the number of individuals made aware of their carrier status and offered counseling
 - ◆ all call for offering counseling and fetal diagnostic testing when both partners are found to be carriers, to allow informed decision-making
 - ◆ the decision about which model to use will depend upon characteristics of the health provider and patient population
 - ◆ ethical, financial, and social concerns differ depending upon the model chosen
- When cystic fibrosis is identified in the fetus, the couple may begin planning for early treatment after birth, or choose to terminate the pregnancy (Q28, Q29)
- An adequate process of education and consent will help ensure that women/couples fully understand the process and options prior to agreeing to testing (Q31, Q39)
- Thirteen original pilot trials (5 in the U.S.) can be summarized as follows: (Q33)
 - ◆ many of the trials superimposed cystic fibrosis screening upon existing prenatal screening services
 - ◆ over 55,000 women/couples were screened (uptake rates of 60-90%)
 - ◆ 54 positive couples were identified, and 85% to 100% chose diagnostic testing
 - ◆ 18 affected fetuses were identified, and 15 (83%) were selectively terminated
- Health risks for follow-up testing include the well-defined complications of amniocentesis and chorion villus sampling that can be minimized through the use of experienced health personnel (Q34)
- The lack of effective treatment or action other than pregnancy termination is the major ethical and psychosocial issue

- Key components of financial costs associated with screening have been identified and reasonable estimates based on the literature have been assigned as follows: (Q35, Q36)
 - ◆ the cost per case of cystic fibrosis identified prenatally is about \$400,000 in the main target population. Costs in some other racial/ethnic groups are much higher.
 - ◆ this cost is reduced considerably if subsequent pregnancies are taken into account
 - ◆ the total costs of offering screening per couple range from \$120 to \$240, depending on the screening model chosen
 - ◆ the direct annual medical costs for the average individual with cystic fibrosis are between \$15,000 and \$20,000
 - ◆ based on consensus estimates of annual medical costs, expected lifetime and recommended discount rates, the total lifetime direct medical costs are between \$300,000 and \$500,000
- External proficiency testing programs are in place for laboratory testing (Q32)
- Quality assurance guidelines have been produced by regulators and by professional organizations (Q32)
- Testing facilities can be developed in the same manner as existing prenatal screening programs and may be superimposed upon existing infrastructure (Q37)
- A total of 30 or fewer laboratories are currently providing screening services in the U.S. If screening were to be widely accepted, it would likely lead to: (Q37)
 - ◆ more laboratories offering prenatal screening
 - ◆ an increase in the number of DNA clinical technologists required
 - ◆ an increase in the number of genetic counselors
- Patient educational materials are available. They meet most content criteria and have been rated adequate or superior using objective readability standards (Q38)
- More attention needs to be given to defining the content of informational materials for providers. Critical components of this information that can improve patient service have been identified but are not always included (Q38)
- General methodologies for long term monitoring of program effectiveness exist, but: (Q40, Q41)
 - ◆ national guidelines have not been developed
 - ◆ many laboratories are not collecting the information necessary to document effectiveness

Ethical, Legal and Social Implications (ELSI)

- Many ELSI issues are similar to those already encountered with existing prenatal screening programs for neural tube defects and Down syndrome, such as programmatic support to assure:
 - ◆ an education and informed consent process which helps couples understand their personal values with regard to decision-making prior to beginning the prenatal screening process
 - ◆ balanced information for decision-making, including the opportunity to learn about the medical and non-medical issues involved with parenting a child with cystic fibrosis and the availability of support groups
 - ◆ opportunities for opting out at all stages

- ◆ ready and accessible expert services for counseling, diagnosis, and pregnancy termination for all those to whom prenatal screening is offered
- ◆ consideration of under-served populations
- ◆ collection of data on insurance discrimination that might result if widespread prenatal screening is instituted (e.g., are carriers being incorrectly classified as being at increased risk for health problems)
- Some examples of issues more specific to prenatal screening for cystic fibrosis include:
 - ◆ potential stigmatization of carrier individuals and couples
 - ◆ appropriate management of leftover DNA samples
 - ◆ how to offer screening to diverse population groups with varying gene frequencies and prevalences
- Civil liability risks to prenatal care providers include: (Q43)
 - ◆ failure to offer (or make available) prenatal cystic fibrosis screening
 - ◆ testing without patient consent
 - ◆ referring tests to a laboratory known or suspected to not be qualified
 - ◆ breaching patient confidentiality
- Civil liability risks to the testing laboratory include: (Q43)
 - ◆ failure to perform the test according to current standards and guidelines
 - ◆ failure to communicate with the physician/patient about the test's performance
 - ◆ breaching patient confidentiality or inappropriate use of left-over samples
 - ◆ not obtaining appropriate licensing for applicable patents

Specific Issues or Gaps in Knowledge that Need to be Addressed:

Disorder/Setting

- When prenatal cystic fibrosis screening guidelines are being developed, they should emphasize the need for maintaining a focus on the primary disorder being screened for. Secondary conditions (such as CBAVD) draw attention away from the primary focus and unnecessarily complicates the process.

Analytic Validity

- There is no agreement as to how the finding of a wrong mutation should influence the computation of analytic validity (Q9, Q10)
- Reliable, method-specific (and, possibly, mutation-specific) estimates of analytic performance are not available (Q9, Q10, Q17)
- Analytic performance estimates are available for only a minority of the 25 recommended mutations (Q9, Q10)
- The relationship between panel size and analytic performance is not known (Q9, Q10)
- Control material needs to be available for all tested mutations (Q11)
- There are no guidelines that define the circumstances in which confirmatory testing should be performed, and the type of confirmatory testing to be used (Q13)
- Overall, and method-specific assay failure rates are not usually published (Q16)

Clinical Validity

- The extent to which confirmatory testing can increase analytic specificity is not known. (Q19)
- Genotype/phenotype relationships for some low penetrant mutations (e.g., I148T and D1152H) are not known at the population level (Q20)
- It is not clear how the self-reporting of race/ethnicity will affect the screening process (Q21)
- Variation in polymorphism frequency by race/ethnicity has not been evaluated (Q22)
- The reliability of prenatal diagnostic testing is not well documented, especially in the presence of maternal cell contamination (Q23, Q28)
- Although the recommended testing process associated with the finding of an R117H mutation is well defined, the implications for counseling are not (Q24)
- The clinical complexities of routinely testing all screened individuals for the 5T/7T/9T polymorphism have not been well defined (Q24)

Clinical Utility

- Appropriate information is not available for counseling a couple, when the fetus has two *CFTR* mutations, one of which is a low penetrant allele (e.g., I148T or D1152H). (Q28)
- Access to pregnancy termination is limited by both geography and reimbursement (Q30)
- Guidelines for long-term program evaluation are not available, and screening laboratories are not yet collecting the necessary information for an appropriate evaluation (Q40, Q41)