Complete Summary

GUIDELINE TITLE

Cystic fibrosis prenatal screening in genetic counseling practice: recommendations of the National Society of Genetic Counselors.

BIBLIOGRAPHIC SOURCE(S)

Langfelder-Schwind E, Kloza E, Sugarman E, Pettersen B, Brown T, Jensen K, Marcus S, Redman J. Cystic fibrosis prenatal screening in genetic counseling practice: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2005 Feb;14(1):1-15. [90 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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METHODOLOGY - including Rating Scheme and Cost Analysis
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SCOPE

DISEASE/CONDITION(S)

Cystic fibrosis

GUIDELINE CATEGORY

Counseling
Screening

CLINICAL SPECIALTY

Family Practice
Medical Genetics
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

- To provide practice recommendations for genetic counselors whose clients are considering cystic fibrosis (CF) carrier testing or seeking information regarding CF carrier test results
- To supplement the knowledge and understanding of genetic counselors regarding CF mutation analysis
- To compare and contrast approaches to CF prenatal screening
- To provide a framework for genetic counselors who are helping clients make decisions about CF testing, prenatal diagnosis, and pregnancy management, including pregnancy termination
- To highlight the complexities of CF mutation testing, pitfalls of genotype/phenotype correlation, and the nuances of interpreting positive results

TARGET POPULATION

- Pregnant women and their partners
- Individuals who are considering cystic fibrosis (CF) carrier testing or who are seeking information regarding CF carrier results

INTERVENTIONS AND PRACTICES CONSIDERED

1. Prenatal screening for cystic fibrosis (CF)
2. Genetic counseling for CF
3. Offering CF carrier testing

MAJOR OUTCOMES CONSIDERED

- Incidence of cystic fibrosis (CF)
- Residual risk of cystic fibrosis
- Sensitivity of screening tests

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Guidelines and policy statements published by the National Institutes of Health, U.S. Congressional Office of Technology Assessment, American Society of Human Genetics, American College of Medical Genetics, America Society of Urology, American Society of Reproductive Medicine, and the American College of Obstetricians and Gynecologists were reviewed.

The MEDLINE and PubMed databases were searched (using the key words CF carrier testing/ screening, CF mutations, and CF genotyping), to locate relevant English language medical papers published between 1990 and May 2004. Papers were reviewed with attention to genetic counseling and screening issues.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The literature was reviewed and evaluated for quality according to the categories outlined by the U.S. Preventive Services Task Force (1995):

I. Evidence obtained from at least one properly designed randomized controlled trial

II-1. Evidence obtained from well-designed controlled trials without randomization

II-2. Evidence obtained from well-designed cohort or case-control-analytic studies, preferably from more than one center or research group

II-3. Evidence obtained from multiple time series with or without the intervention

III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The authoring subcommittee consisted of genetic counselors with expertise in cystic fibrosis (CF) testing and counseling, prenatal genetic counseling as well as experience working with CF patients and families.

The authors recruited a focus group of practicing genetic counselors with expertise in prenatal, infertility, and/or CF newborn screening counseling.

The focus group was held at the 2003 National Society of Genetic Counselors (NSGC) Annual Education Conference in Charlotte, NC. A semistructured interview guide was prepared in order to elicit opinions regarding the need for NSGC guidelines and recommendations regarding content. Also, the authoring subcommittee queried and reviewed all postings of the archives of the NSGC's listserve, an online discussion group, regarding CF testing to identify areas of ongoing uncertainty regarding these issues. In addition, the authoring committee sought expert review from specialists and consumer groups in North America.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

A draft of the document was made available on the Internet to all members of the National Society of Genetic Counselors (NSGC) for comment. The NSGC Ethics Subcommittee and an attorney for the NSGC reviewed the revised document. No conflicts with the NSGC Code of Ethics were identified in the final document. The NSGC Board of Directors approved the final document in October 2004.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Quality of Life

Genetic counselors should be familiar with the range of severity of cystic fibrosis (CF) symptoms and the basic approach to medical management of CF patients. Clients seeking additional information may be referred to consumer organizations such as the Cystic Fibrosis Foundation.

Genotype/Phenotype Counseling

There is no simple one-to-one relationship between genotype and phenotype and many modifying factors likely exist. Conveying complex information in a sensitive and supportive manner is a necessary skill when counseling about CF.

Genotype alone does not explain the variability of CF clinical presentation. In response to patient requests for prognostic information, genetic counselors should be cautious about estimating clinical severity based on limited data. Genetic counselors should avoid using individual patient experiences or published case reports as a basis for predicting the clinical course of a person or fetus with CF, even when the genotype is similar. General discussions of pancreatic status or prospect for classic versus non-classic presentation may be appropriate.

Complex Alleles

Complex *CFTR* genotypes--where more than one *CFTR* mutation or variant is present in the same copy of the gene (in *cis*) and the presence or absence of that variant affects phenotype--characterize two common *CFTR* mutations, I148T and R117H.

I148T in the absence of 3199del6 appears to be a polymorphism, given its presence in apparently healthy adults who are compound heterozygotes. Further studies would be required to determine whether I148T alone with a *CFTR* mutation on the other chromosome is associated with single-organ or late onset expression of disease. Counseling for I148T positive individuals is therefore best done with knowledge of 3199del6 status. The American College of Medical Genetics (ACMG) Cystic Fibrosis Working Group has recommended the removal of I148T from the ACMG panel because 3199del6 is the pathogenic finding. Genetic counselors reviewing test results issued prior to the implementation of this recommendation may be called upon to clarify older results with patients and/or providers.

The R117H mutation is also a complex allele, occurring on different intron 8 polythymidine ("polyT") backgrounds: 5T or 7T. As with I148T, the background contributes to the phenotypic expression. Therefore, identifying the intron 8 statuses for this mutation provides significant information for counseling purposes.

The R117H mutation has been reported to occur on the same chromosome as the 5T or 7T intron 8 variants. Individuals with a disease-causing CF mutation on one chromosome (such as delta F508) and an R117H mutation on the other have been reported with a variety of clinical presentations: no symptoms, congenital absence of the vas deferens in males, chronic pancreatitis, and non-classic and pancreatic sufficient CF. The likelihood of each of the possible clinical outcomes of a given genotype is currently unknown as there is considerable overlap in clinical presentation among individuals with the same genotype. However, individuals with delta F508 (or another CF mutation) on one chromosome, and R117H/5T in *cis* on the other chromosome, would be expected to have cystic fibrosis (likely pancreatic sufficient), whereas an individual with a CF mutation on one chromosome and R117H in *cis* with 7T or 9T on the opposite chromosome is more likely to be asymptomatic or have milder symptoms, e.g., congenital bilateral absence of the vas deferens (CBAVD) in males. As asymptomatic people with these genotypes are followed over time, the risks for development of CF-related symptoms later in life may be clarified. Current carrier testing recommendations therefore include performing polyT variant analysis reflexively for individuals identified as R117H positive.

Poly T

As *CFTR* variants of variable consequence or unknown significance continue to be identified and reported, genetic counselors should emphasize the distinction between known disease-causing mutations such as delta F508 that lead to classic CF, and *CFTR* variants such as the 5T allele that are not expected to result in classic CF.

Prenatal Ultrasound Findings

Fetal echogenic bowel (FEB) is visualized in approximately 0.6 to 1.4% of pregnancies during routine fetal anatomy scans. An estimated 2% of FEB can be attributable to CF, depending on the brightness of the bowel, the presence of *CFTR* mutations in one or both parents, ethnicity and whether other fetal anomalies have been identified. Thus, CF appropriately remains in the differential diagnoses for fetuses with FEB. Given that there may be time constraints for couples who would consider pregnancy termination, parental carrier testing and/or fetal CF mutation analysis should be discussed when FEB has been identified.

CF Testing Models

One of the basic tenets of medical screening is that its objective be to identify a serious medical condition prior to onset of symptoms, or to identify persons at sufficiently high risk to justify further testing procedures. The term "carrier testing" refers to carrier detection in an individual, whereas "CF screening" refers to the identification of affected individuals (or fetuses) within a population.

Sequential testing (also called *two-step*, or *step-wise* testing), is a common approach in which initially one member of the couple is tested, and only if a CF mutation is identified is the partner then tested. This method is reported to be cost-effective for the Caucasian population. Sequential testing is best applied within the context of a screening program, which can assure that samples from

both members are tested at the same laboratory, and that a (residual) risk for having an affected child is provided. An alternative *couple-based* model involves collecting samples from both members of the couple but testing the second sample only if a mutation is identified in the first. Only couples in which both partners carry mutations are reported as positive. Professional organizations in the United States have favored the sequential screening approach over the couple-based model, because CF carriers are routinely identified, allowing results to be transferred to new relationships and enabling patients to inform family members of their carrier testing results. United States recommendations have endorsed the couple-based approach as long as the results are given to both members of the couple.

Concurrent testing of both partners simultaneously is available for couples in which extenuating circumstances dictate a need to accelerate the testing process. This is the least cost-effective method of screening. However, concurrent testing may be useful for couples anxious about risk due to a family history of CF, following identification of echogenic bowel on ultrasound, or for a couple who is offered CF carrier testing in the second trimester.

Cascade testing describes an approach to testing of additional family members after the identification of an affected individual or CF carrier. It is dependent upon communication of test results to family members, as well as the willingness of these informed family members to pursue testing themselves. Studies have not supported cascade testing as a useful approach to population screening, but this method may have value in identifying some carrier relatives of motivated individuals themselves identified as carriers through population screening programs. While discussion of the implications of a positive carrier test for blood relatives is an important component of post-test counseling for carriers, genetic counselors must adhere to ethical obligations and legal requirements by respecting patients' wishes regarding notification of relatives.

The suitability of the above-described approaches to CF screening needs to be assessed for a given practice. Genetic counselors should work within their institutions to develop approaches to offering CF screening consistent with local/regional practices and customs and the needs of the individual family.

Significance of Ethnic Background

Because it is difficult to determine precisely which ethnic subgroup to assign a patient, and reliable risk data is not available for many populations, genetic counselors are urged to use prevalence and detection rate tables based on studies within several ethnic populations. These data represent "best estimates" and are considered reliable.

The concept of residual risk should be included as part of any discussion of negative CF carrier testing results.

Given the dearth of ethnic-specific risk data, at this time it is appropriate for genetic counselors to use general published guidelines such as Table II in the original guideline document, or specific figures provided by the laboratory, when counseling patients about pre- and posttest CF carrier risks.

The ACMG standard panel of CF disease causing mutations, comprised of mutations with >0.1% frequency among patients with CF, may not include particular mutations known to occur with relatively high frequency in certain populations. Genetic counselors should also keep in mind that even if a mutation is reported to be "ethnic specific," its frequency may not have been studied in the unaffected population of that ethnic group (see previous discussion of "Complex Alleles").

Genetic counselors should work with their genetic and obstetrician/gynecologist (OB/GYN) colleagues as well as their institutional legal department to develop a consistent approach for actively offering CF screening or making information available to patients of certain ethnicities who are at lower risk to be CF carriers or for whom testing is not very sensitive. Genetic counselors should consider "ethnic specific" mutation testing as one factor in selecting a laboratory to send patient samples. Other factors may include insurance reimbursement, institutional contractual arrangements, and state regulatory issues.

Significance of Family History

The approach to carrier testing differs significantly from the general population approach when the client reports a family history of the condition. Interpretation of a negative CF carrier test result is dependent on knowing which specific mutations have been identified in a blood relative who has CF or is a carrier. Medical records to confirm the diagnosis and, whenever possible, the affected person's genotype, are best obtained prior to meeting with a relative of a person with CF or CF carrier. If familial mutations have been identified, then it is important to make sure that the panel used for testing the client includes those mutations. If the affected relative does not have two identifiable mutations, then a negative CF test result on the client may be misleading or falsely reassuring. The process of obtaining proper releases may delay access to the information, and on some occasions, such clinical information may not be available in a timely fashion. When documentation of mutations is not available, it is appropriate to consider testing for a panel of clinically significant mutations to determine if the patient carries a common CF mutation. Testing the partner may provide adequate reassurance to the couple if the partner's result is negative. If the partner is a carrier, additional family studies, including linkage analysis may be necessary before the risk to the pregnancy can be clarified and informative prenatal diagnosis can be offered.

Psychosocial and Counseling Issues

Careful attention to and emphasis on the emotional component of the genetic counseling process are critical to the provision of quality genetic counseling for CF.

Special Circumstances

Children who are born in a state in which newborns are routinely screened for CF may subsequently be identified as CF carriers even if their parents had previously declined to be tested in the prenatal setting. In this situation, one of the parents is an obligate CF carrier, and additional genetic counseling is indicated, so that the

parents may reconsider carrier testing in light of the new, albeit unsolicited, information.

In some circumstances, such as for couples who express a great deal of anxiety about residual risk, or partners of known carriers or affected individuals who are from ethnic groups that have a low detection rate using the standard panel, offering an expanded panel, scanning, or sequencing may provide additional reassurance to clients if the test results are negative. These methodologies have not been endorsed as appropriate for routine CF carrier testing. Genetic counselors should be aware of the possibility of identifying a new sequence variant or result for which clinical predictions cannot be reliably made, and include this possibility in their pretest counseling.

Genetic counselors should inform patients interested in CF carrier testing that they will be tested for a panel of disease-causing mutations. While expanded panels or *CFTR* sequencing may improve the odds of finding a CF mutation if it is there, these methodologies do not detect all CF mutations. In addition, *CFTR* sequencing results may raise unanswerable questions, increase patient anxiety, and possibly lead to termination of unaffected pregnancies, if a novel mutation or polymorphism is identified.

On rare occasions, individuals with CF will be identified through carrier testing. CF carrier testing may also reveal more than one mutation or sequence variant in an asymptomatic individual. In this situation, data from published case reports may be helpful in predicting whether mutations are in *cis* or *trans*, but phase should be determined through *CFTR* analysis of the patient's parents or children whenever possible. Genetic counselors should obtain clinical information from the patient, including personal or family history of infertility, asthma and sinus disease, malabsorption, nasal polyps, etc. When mutations are found to be in *trans*, genetic counselors should also recommend referral to an accredited CF care center for further evaluation.

Patient Education

Patients may be unfamiliar with either CF or deoxyribonucleic acid (DNA) technology when carrier testing is offered. Therefore, patient education plays a vital role in informed decision making. In preparing patients for the range of test results, CF education may also help clients to anticipate their responses.

Genetic counselors should become familiar with the two American College of Obstetricians and Gynecologists (ACOG) patient education pamphlets that have been distributed to all ACOG members, and which OB/GYNs may be purchasing for use with CF screening.

Exceptions/Special Cases

Genetic counselors should use their best clinical judgment regarding situations when it may not be appropriate to offer CF carrier testing within the scope of a particular genetic counseling session. If CF testing is not offered, it is appropriate to recommend to the primary care provider that CF screening be considered at a future visit, and include a notation in the patient record/summary letter regarding

current CF screening recommendations and the reason that screening was not offered.

Conclusions

To some patients, CF screening may provide an opportunity that can give them important information about a current or future pregnancy. To others, it may provoke unwelcome anxiety or require a painful decision about the pregnancy. Genetic counselors will play an important role in providing information and support sufficient to allow people to make choices that are consistent with patient values and based on the best available information.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

All supporting evidence is class III, opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. No supporting literature of categories I and II was identified.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of prenatal cystic fibrosis screening

POTENTIAL HARMS

CFTR sequencing results may raise unanswerable questions, increase patient anxiety, and possibly lead to termination of unaffected pregnancies, if a novel mutation or polymorphism is identified.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The genetic counseling recommendations of the National Society of Genetic Counselors (NSGC) are developed by members of the NSGC to assist practitioners and patients in making decisions about appropriate management of genetic concerns. Each practice recommendation focuses on a clinical or practice issue and is based on a review and analysis of the professional literature. The information and recommendations reflect scientific and clinical knowledge current as of the submission date and are subject to change as advances in diagnostic techniques, treatments, and psychosocial understanding emerge. In addition, variations in practice, taking into account the needs of the individual patient and

the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments, or procedures alternative to the recommendations outlined in this document. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. Genetic counseling recommendations are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Langfelder-Schwind E, Kloza E, Sugarman E, Pettersen B, Brown T, Jensen K, Marcus S, Redman J. Cystic fibrosis prenatal screening in genetic counseling practice: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2005 Feb;14(1):1-15. [90 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Feb

GUIDELINE DEVELOPER(S)

National Society of Genetic Counselors - Medical Specialty Society

SOURCE(S) OF FUNDING

This project was supported by the National Society of Genetic Counselors, Inc.

GUIDELINE COMMITTEE

NSGC Subcommittee on Cystic Fibrosis Carrier Testing

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the National Society of Genetic Counselors Web site.

Print copies: Available from the National Society of Genetic Counselors, 401 N. Michigan Avenue, Chicago, IL 60611; Web site: www.nsgc.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on March 22, 2006. The information was verified by the guideline developer on May 3, 2006.

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