CONFERENCE SUMMARY

Communication: Key to Appropriate Genetic Test Referral, Result Reporting and Interpretation

May 2-3 2003, Mt. Sinai School of Medicine, New York, New York

(Hosted by Mt. Sinai School of Medicine and the Centers for Disease Control and Prevention)

Meeting Objectives:

The conference was convened to explore communication issues among professionals relevant to the ordering, reporting, and interpretation of genetic tests that impacts health care decision-making. **Cystic fibrosis** DNA-based testing served as a model for discussion.

Meeting Outcomes:

1. Problems and challenges were identified in the process of ordering, reporting, and using genetic tests. There is a lack of quantifiable data relating these to patient outcomes and other costs associated with the testing process.
2. Opportunities were identified for improving practices and professional competencies. General and specific strategies to address (resolve) current problems (bridging communication gaps) were provided.
3. In considering next steps, the ordering and reporting of genetic tests needs to be considered as a process with internal and external quality control and provisions for assuring professional competencies.
4. The multidisciplinary format of this conference and resulting recommendations strongly support the need for enhanced interdisciplinary interactions toward assuring the safe and effective use of genetic tests.

Participants:

1. Approximately 60 invited professionals participated.
2. Professionals represented included physicians, nurses, physician assistants, laboratory directors, genetic counselors, medical geneticists, policy makers, patient advocates, payers, public health professionals, and others who order genetic tests, receive and use test result reports, or otherwise are involved in providing genetic testing services to the public.
3. Attendees were affiliated with individual and group clinical practices, academic entities, foundations, professional organizations, and government agencies.

Meeting format:

1. The processes of ordering, reporting, interpretation, and use of Cystic fibrosis diagnostic and carrier testing were used to form the basis of discussions about general genetic testing issues, shortcomings, and solutions.
2. The conference took place over the course of one and a half days.
3. Participants were initially provided background in the form of a half-day program that included three short talks highlighting cystic fibrosis test ordering and reporting issues followed by a panel discussion. The second day comprised workgroup deliberations.
4. Workgroups were structured to be multidisciplinary in composition.
5. Each attendee was assigned to one of five multidisciplinary workgroups.
6. Each workgroup met for two sessions. The first focused on pre- and the second on post-test issues.
7. Workgroup discussions were based around five different case studies with requisitions and reports provided, as appropriate. The case studies were designed to highlight various aspects of genetic testing such as patient-specific data collection, test selection, communication of results and other issues.
8. Workgroups reported back to the full meeting for discussion and further development of recommendations.
9. Participants also had the opportunity to hear a presentation from the coordinator of the European Cystic Fibrosis Thematic Network about cystic fibrosis testing in the European community.

Major Findings (a culmination of the panel and workgroup discussions)

General Issues

1. There is limited data to quantify the problems discussed related to the ordering, reporting, and interpretation of genetic tests.
2. Current practices in the ordering and reporting of genetic tests are variable and unevenly implemented. When implemented with an insufficient knowledge base, practice is likely to contribute to unnecessary costs and increase the potential for adverse patient outcomes.
3. Any efforts to improve the process must involve those who use (including patients/clients and health care professionals), perform, and pay for genetic testing services.
4. Practice-specific implementation plans are often absent when recommendations or policies are crafted in the ordering, reporting, and interpretation of genetic tests.
5. Genetic terminology and jargon contained within test requisitions and reports is often unclear to health care providers and has led to poor collection of patient-specific information, miscommunication of information, and reporting and interpretation of results (see JAMA 289:2923-2924).

6. There are no standard data formats for either test requisitions or reports. Recommendations made by ACMG, NCCLS, and others provide recommended data categories, some of which are not well defined. For instance, standard ethnicity groups for inquiry are not established.
7. Specialty genetic services, including genetic counseling, are provided by a number of disciplines including physicians (general and specialty), geneticists, advanced practice nurses, physician assistants, certified midwives, and others. Services are provided with varying levels of competency about specific genetic disorders and tests.
8. The lack of basic CF/genetic knowledge on the part of providers, incorrect or missing data on requisitions is not the result of laziness or carelessness, but rather not knowing what is critically necessary to assure the best patient care.
9. Standards do not exist for communicating information on the requisition form to the performing laboratory or on the report form back to the health care provider. Such information may pass through several intermediate facilities and in the process be copied and edited. This introduces a potential for error.
10. Clinicians learn through several mechanisms, one of which occurs when seeing their patients. The ordering and reporting of tests and results require requisition and report forms. Properly structured, these forms may provide "teachable" moments for users of these forms (Users can include physicians, physician assistants, advanced practice nurses, and other office staff).
11. The test result report needs to be easy to understand yet sufficiently comprehensive to be useful for appropriate clinical decision making.
12. The requisition and reporting form need to be written in a format that can be understood by all who will use it. The original requisition should contain all the information required by the laboratory performing the test, which may not be the laboratory to which the initial order was sent, to evaluate the appropriateness of the referral and prepare an accurate and complete interpretation.
13. There is a need for requisitions and reports to specify resources from which health care providers can learn more about the test and its clinical implications (i.e. information regarding the consultative role of the laboratory, disease specialists, or specialty centers).
14. Payers focus on reimbursement for services related to medical necessity and for diagnosis and treatment of existing disease. Predictive and carrier testing for asymptomatic individuals is often difficult to justify by these definitions. Certain diagnostic tests for symptomatic individuals are sometimes difficult to justify (i.e. microsatellite instability analysis for colon cancer) because of uncertainty about the clinical significance.
15. Genetic tests are often reimbursed only once - follow up testing using an expanded panel or sequencing usually is not covered by payers without special justification.
16. The genetic testing laboratory should serve a "consultative" role rather than simply being a "provider" of test results. Most laboratories have one or more board-certified professionals able to act in this capacity.
17. Test results are often phrased as "positive" or "negative" findings (i.e. positive for disease-associated mutations, negative for being a carrier based on the mutations tested). These connotations are confusing and can give a false impression about how the result relates to the condition for which the test was ordered.
18. The GeneTests resource is an appropriate venue to provide important information and educational material to users of genetic tests and their results.(GeneTests is a federally sponsored genetic testing database and resource - see attachment A3).

19. There is confusion regarding the implementation of the HIPAA requirements to the collection and use of family history.
20. This conference/workshop was a model that worked and should be considered again for addressing the issues discussed.
21. Time constraints, professional expertise available, and ability to refer need to be carefully considered as genetics enters into primary care practice. It will be important to consider these issues as to what is in the best interest of the patient and the effective use of available resources.
22. Appropriate use of genetic tests is ultimately based on our knowledge of the association of genes, environment, and populations. The clinical validity of genetic tests is determined, to a great extent, through observed outcomes. Public health efforts to collect, evaluate, and disseminate data relevant to these needs is critical toward assuring the safe and effective use of genetic tests.
23. Informed consent remains a confusing topic. Questions that arise include:
    1. What "level" of informed consent should be required from the patient and under what circumstances?
    2. Who is responsible?
    3. What measures are appropriate to assure the usefulness of an informed consent process?

Ordering Tests (common issues regarding ordering and reporting are covered above)

1. Requisition forms differ in what and how patient-specific information is requested. Since information collected during the requisition process is often critical in developing an appropriate interpretation of the test result, there are concerns about the availability of this information to the laboratories attempting to interpret the test results.
2. Health care providers need to better understand what information the laboratory needs. This is important to assure the appropriate test methodology is chosen and an accurate and useful interpretation can be prepared. For example, many laboratories offering cystic fibrosis testing provide family-specific mutation assays, sequencing and mutation panels with and without reflex testing. Some laboratories offer an expanded mutation panel and several offer sequence analysis. The methodology chosen should depend on the reason for referral and what information is provided about the patient.
3. Beyond providing laboratory contact information, requisition forms do not typically provide guidance in the collection and reporting of certain information (i.e. ethnicity and family history)
4. For cystic fibrosis and many other genetic tests, no standard algorithms exist for selecting the appropriate test to order.
5. Requisitions typically are used to order one or more tests. As such, requisition forms often times do not emphasize the particular information needed for a particular test (i.e. cystic fibrosis) or for the reason a test is ordered (i.e. diagnostic versus carrier testing). Better clarity regarding these.
   issues may also be useful toward assuring appropriate reimbursement.
6. The laboratory often receives incomplete information about the patient for whom the test is ordered. Often times, the requisition form is incomplete and efforts on the part of the laboratory are not successful in collecting the missing information.
7. Prompts on the requisition form that specify the most common indications for testing may be useful for those ordering tests.
8. It is important for health care providers to collect and have available information about the patient's partner for some tests (i.e. CF carrier screening). This information can be critical for both the health care provider and the laboratory in calculating risk for disease in a current

pregnancy or future child.

Reporting and interpretation of test results (common issues regarding ordering and reporting are covered above)

1. The test result should be clearly stated and the laboratory interpretation written to be easily understood and sufficiently comprehensive. When appropriate, the interpretation should describe the result in terms of the context of the patient's clinical condition, family history, partner information, and reason the test was requested.
2. Sufficient information should be present to allow for future re-interpretation based on new knowledge.
3. Laboratory professionals should seek input from health care providers, health care payers, and others in developing their reports.
4. Reports should clearly state that, in most cases, the absence of a detectable mutation is not synonymous with zero risk for being a carrier or definitively ruling out a diagnosis.
5. Counseling recommendations, when appropriate to include, should be explicit. Counseling recommendations for the health care provider serve to aid their interactions with the patient (educating the patient and providing them with the tools to make informed decisions) or provide an appropriate referral. The role of counseling in reaching medical management decisions should be made clear.
6. For some laboratory test reports, an executive summary for physicians of the test results and interpretation may be useful. For laboratory records, a methods summary may be useful as well. Such a summary may also be useful to those more familiar with the test ordered and its implications.
7. The laboratory test result report can be useful as an educational tool as well as guiding patient management.
8. Regulatory mandates (CLIA) and voluntary guidelines (i.e. ACMG, ACOG, NCCLS, and CAP) have specific recommendations regarding elements to be included within genetic test reports (i.e. test result, methodology, adjusted risk). How to clearly present these items to those not generally familiar with genetic tests has not been addressed.
9. There is a need to address the potential clinical impact related to linkage of patient and partner results. This has clinical, reimbursement, and socio-legal consequences.

Recommendations for next steps (a culmination of the panel and workgroup discussions)

(The best chance for success in addressing these recommendations is through the formation of strategic partnerships that provide for multidisciplinary approaches to be developed. Efforts should be evaluated by determining benefits to clinical and laboratory practices, changes in time expenditures, patient outcomes, and costs.)

1. Develop strategies to quantify impact of current / proposed practices on patient outcomes and other clinical/laboratory costs. For example:
    1. Measure current efforts laboratory spend on time collecting patient information and how changing the requisition process may alter this.
    2. Measure medical decision-making practices based on use of available reports and how changing the reporting process may alter practices or improve provider knowledge base.
2. Explore the concept of health care provider/resource expert teams accessible for clinical consultations in the use of genetic tests. Resource experts may be laboratory professionals or other academic or commercial entities able to serve in this capacity.

3. Develop and evaluate the use of standard formats (data fields and terminology) for test requisition and result reports. Such formats should satisfy the following criteria:
    1. Content should reflect requirements and recommendations from regulatory and professional organizations.
    2. For requisitions, standards should be considered for describing the types of tests available for the clinical indication, and the collection of clinical information, ethnicity and family history (Standard requisition formats for describing ethnicity and the collection of family history are lacking).
    3. For reports, standards should be considered for reporting the analytic test result (and avoiding the ambiguous connotations of a positive and negative test result), interpretation (including description of risks), guidance for clinical management (i.e. follow up testing, genetic counseling, when appropriate), and limitations of the test performed.
    4. Mention of resources useful for obtaining information about the test or condition being tested should be included on both requisition and reporting forms.
    5. Requisitions and reports should be developed not just to report results but also as a teaching tool and to assist in the clinical management of the patient.
    6. In developing these formats, consider mechanisms for collecting follow-up data on patients who have unusual or atypical results.
4. Develop and evaluate a standard process for assuring information collected for the test requisition is accurately communicated to the performing laboratory. A similar process should be explored to assure the test result and interpretation are appropriately communicated back to the ordering health care provider or others, as appropriate.
5. Develop guidance for genetic counseling applicable for use by health care providers in different practice settings. Guidance is also needed for counseling recommendations that are appropriate to include on requisition forms and test result reports.
6. Explore the concept of developing decision-making aids to assist clinicians in selecting the appropriate test and guiding management decisions once test results are returned. Decision-making aids should, in part, focus on knowledge management tools. It may be useful to benchmark other industries (i.e. banking, retail sales) that have developed such tools.
7. Establish a working group of payers and clinical and laboratory professionals (including primary, specialty, and allied health professionals) to consider reimbursement models for genetic tests Issues to be discussed include:
    1. The medical necessity of genetic tests (specifically for new tests and non-diagnostic tests.
    2. The laboratory as a consultant.
    3. When is follow up testing necessary?
    4. Can reimbursement requirements improve the collection and appropriate use of patient-specific information and standards for ordering, reporting, and using genetic tests?
8. The development and implementation of guidelines and recommendations need to follow a more orderly process. This process should include:
        1. Development of evidence-based guidelines and recommendations.
        2. A practice-based implementation plan.
        3. An evaluation plan that uses data to support continued adoption, change, or removal for each guideline or recommendation.
9. Develop a partnership with the legal profession to provide guidance for practice-specific issues (i.e. with regards to HIPAA and other emerging issues).
10 Those who provide public health services need to be responsive to media reports and public

demands and take responsibility for disseminating balanced and accurate information about genetic tests.

11. Efforts undertaken should be assessed to their anticipated and realized costs and benefits. Potential benefits include improved patient outcomes, savings of time and or money, CEUs, or improved reimbursement.
12. Public Health has traditionally taken a role in assuring safe and effective use of medical testing and, in general, addressing patient safety issues. Public health should evaluate the impact of genetics in terms of expanding their assurance efforts to assure access to high quality genetic testing services.

Disclaimer: This document strives to accurately represent what was discussed during the course of the conference and is not meant to imply endorsement for this report by the Public Health Service, the United States Department of Health and Human Services or organizations represented at this conference through their attendees. Use of trade names and commercial sources are for identification only and do not imply endorsement by the Public Health Service or by the United States Department of Health and Human Services.

Attachment A1 - Specific observations and recommendations from workgroups

Workgroup #1: Prenatal Diagnosis

General Comments

1. The requisition and report are opportunities for communication between the diagnostic laboratory and the clinicians they serve.
2. Clinical laboratory directors (and other laboratory clinical genetics staff - often times having medical board certification) are an underutilized resource. Requisitions and reports should not only provide a phone number for contact, but should encourage calls to the laboratory, which can then assist the clinician to properly prepare the requisition and to understand the report.
3. Both the requisition and the report may be retyped, edited, or completely rewritten by intermediate referral sites and laboratories. This often removes information critical to test selection and interpretation and introduces a potential for error.

Pre-test

1. Additional guidance in the use of ultrasound findings as part of a differential diagnosis for CF is needed.
2. A maternal fetal medicine specialist familiar with CF and other clinical possibilities should be available for consultation when there is a finding of an echogenic bowel. The group recognized direct referrals may not be available or practical in many practice settings and suggested telemedicine may be an option. It was commented that some maternal fetal medicine specialist are not familiar with CF and efforts needs to be developed to assure such specialists have the resources to keep up to date on such topics.
3. The following was suggested as a basic list of actions needing follow up to the finding of an echogenic bowel:
    1. Prenatal DNA-based testing for cystic fibrosis (using an expanded panel).
    2. Review ethnicity and family history for cystic fibrosis and associated conditions (this is for both partners).
    3. Counseling (both genetic and general medical) of patient to discuss process and potential outcomes.
    4. Collect parent's blood for DNA-based CF testing (would not expect to do this if prenatal testing is performed).
4. Health care providers need to recognize that chromosomal abnormalities may be present even if the karyotype showed no unusual findings.
5. A glossary, provided on or with the requisition form, would be useful in understanding the information sought. Examples of terms that are potentially ambiguous needing explanation include" indication for testing" and "family history",
6. CF DNA-based testing is available in three formats; the basic panel, expanded panel, and sequencing. Requisitions do not do a good job of differentiating among these formats and health care providers are not likely aware of the implications for their patients when one format is used over another. Key issues include:
    1. The ACOG/ACMG panel has only been recommended for preconception and prenatal carrier screening. For diagnostic testing, it is often not appropriate to use this test format when expanded mutation analysis or sequencing is available.

2. Not all laboratories offer all three of the test formats described above. Those who refer for CF testing need to be aware of the uses, benefits and limitations of each format.
3. The ACOG/ACMG recommended mutation panel is often applied to both carrier and diagnostic

test referrals (contrary to the recommendations). or both carrier and diagnostic tests, and when either none or one mutation is found; an expanded panel or sequencing is recommended. Insurers have been reluctant to pay for the follow up testing in some cases.

7. The workgroup noted that sequence analysis was probably not appropriate for this case/example of late presentation during pregnancy (for reasons of time-urgency, cost and findings of sequence variants of unknown significance). Some suggested an expanded panel would be most appropriate because this case study addresses a diagnostic, not a carrier, concern. Others argued that the basic panel recommended by ACOG/ACMG would be appropriate if both the mother-to-be and her partner are known to be from specific population for which the basic panel has a high detection rate.

Post-test

1. Standard terminologies are needed. For instance, the terms "one copy of mutation," "heterozygous," and "carrier" can be confusing. It is critical that the terminology used be clear as to its relevance to the condition for which the test was ordered.
2. No guidance is provided regarding the residual risk table included in the report. Some clinicians will recognize the table, which is routinely used to calculate residual chance to be a carrier if a sample tests negative on a panel of CF mutations. This same data is used. for determining residual risk for the fetus to be affected when only one deleterious mutation is found. If we know the ethnicity of both parents, the table is used to calculate the chances that the gene which is not observed to have a specific deleterious mutation nevertheless has a mutation as well.
3. It is critical that the test result report integrate both the clinical and mutation findings into an interpretation that clearly specifies any limits on the interpretation that result from lack of certain clinical information and to make it clear if provision of additional information to the laboratory has potential to lead to revision of the interpretation of the result. Collecting such information after the test is performed is often problematic and time-consuming. It is also important to note that if additional clinical information collected after the test is completed suggests that a different testing strategy would have been more appropriate, there may be insufficient time or sample for retesting.
4. The capacity of the laboratory to develop the most useful interpretation of the test results often depends on the patient/family-specific information available.
5. The report needs to emphasize that results have broad impact; extending beyond the patient to the family.
6. Negative findings are particularly confusing in that they do not necessarily rule out disease or the presence of other mutations not detected by the test used. These limitations should be explicitly described in the interpretation.
7. When partner or family information is used, it should be made clear that the interpretation assumes correct reporting of paternity or family relationships (We should recognize that there are circumstances where paternity is not an issue in the interpretation - if the fetus has two deleterious mutations that cannot possibly be in cis, we know the fetus is affected regardless of the father's ethnicity or DNA).
8. Standards do not exist for communicating information on the requisition form to the performing

laboratory. Such information may pass through several intermediate facilities and in the process be copied and edited. This introduces a potential for error.

9. Some workgroup members suggested diagnostic test result reports should have a different format than carrier test result reports.
10. Genetic counseling is often recommended but the recommendation needs to clearly reflect this service as a tool for health management and not just patient education. This may help in better defining the role of genetic counseling in the medical context and provide for improve reimbursement. Two proposals for wording were made: "Genetic counseling is recommended as a tool to evaluate and consider the medical and other implications of these test results." Alternatively, the following wording was proposed, "We recommend consultation with a genetic specialist provider to evaluate the implications of these test results for your health and health care decisions."
11. An executive summary should be included as apart of a more comprehensive report. The idea is that a practitioner well versed in the test will only want the basic information whereas others may want additional details.
12. Current interpretation of a genetic test result may change as a consequence of new research findings. Although the results from a molecular genetic test assessing a patient's genotype is not expected to change (assuming no errors were made in the testing process), the interpretation may need to be revised at a later time. For this reason, although merits of a short and simple report for immediate use are obvious, the report must include all necessary information (e.g., methods used, specific mutations tested, detailed results) to permit future reinterpretation as needed in light of new knowledge.. Laboratory Geneticists or others health care professionals with expert knowledge for the test under question should be consulted to determine if new findings have occurred and are relevant to the test under question.

Workgroup #2: Carrier testing for cystic fibrosis without a family history

General comments

1. Both the test requisition and report provide teachable moments for users of these forms.
2. In terms of this case study, questions remain as to who filled out the requisition and who was contacted in the health care provider's office to gather additional information. It is not clear to what extent those contacted understood what was needed and why.
3. There should be an on-line system that would provide both standard requisitions and reporting forms as well as provide education for providers.

Pre-test

1. The requisition form should be better formatted to emphasize why the information requested is needed and, when appropriate, instructions should be provided or available (i.e. for collecting relevant family history)
2. The process of informed consent varies in practice. Some of this variation is due to differences in State-to-State regulatory requirements.
3. Laboratory follow-up to ascertain missing or incorrect information costs time and money.

Post-test

1. Laboratory follow-up to ascertain missing or incorrect information costs time and money.
2. The test result and interpretation should be clear and appear prominently within the report.

3. Methodological information, including which mutations were tested, should be indicated on the report but need not appear prominently.
4. Test result reports should indicate what information is missing and to what extent this impacts on test interpretation.

Workgroup #3: Carrier testing with a family history

General

1. Implementation of the HIPAA regulations has led to significant confusion especially with regards to what information can be collected from patients about other family members. Being relatively new, it is expected these issues will resolve as the practice community gains a better understanding of the intent of the law.
2. Laboratory contact and clinical-information information resources should be provided on the requisition form and test result report.
3. Lack of standard terminologies and data fields is a significant problem likely contributing to misunderstanding on the part of health care professionals and payers about the test performed.

Pre-Test

1. For this case study, there are gaps in the family history collected (missing or incorrect information). It would be appropriate to contact the cousin's medical care provider to confirm the diagnosis of cystic fibrosis (for the cousin) and whether mutation testing was performed.
2. Recommendations to change the requisition form will be resisted because this is a costly process. There needs to be clear cost-benefit justification.
3. Genetic tests can be complex, as is for cystic fibrosis. As such, there should be algorithms tailored for clinical practice useful for clinicians in making decisions about the offering and ordering of genetic tests.

Post-test

1. The laboratory report is in error for the couple's risk. The partner's risk was incorrectly assigned based on the assumption that he has been tested for the mutation panel cited and no mutations were found. This is opposed to a risk based only on his ethnicity. Improper use of residual risk tables can contribute to such errors and the report should make clear the assumptions that went into risk calculations.
2. There is a tendency to mix both genes and diseases in describing tests and results (i.e. cystic fibrosis versus testing for mutations in the CFTR gene). This makes for confusing situations when mutations lead to atypical disease (i.e. test requested for CF with interpretation addressing male infertility).
3. The result report provides an opportunity to "educate" health care professionals about the appropriate use of genetic tests and results.

Workgroup #4: Diagnostic testing for cystic fibrosis - infant with failure to thrive

Pre-test

1. An interactive guide for test order selection would be useful.
2. Tests should be named in a more descriptive fashion (i.e. ' "CF Standard Panel", "CF Expanded

Panel", "CF Sequencing").

3. Peer-reviewed algorithms should be created to help health care professionals in deciding which test to order. For DNA-based cystic fibrosis testing, an algorithm may be useful in deciding whether to order a particular mutation panel or request sequence analysis. GeneTests (A federally sponsored genetic testing database and resource - see attachment A3) may be a venue to post such algorithms.

Post-test

1. For this case study, the use of the detection rate table is probably not obvious and no guidance is included. An explanation would be helpful.
2. A one-page "ideal" report was developed by this workgroup. The format proposed includes:
   a. patient information / what test was ordered and why
   b. result (this was boxed)
   c. interpretation
   d. mutation panel, methodology, and disclaimers need to be included but can be in small font at bottom of page
3. Clinical Utility should be assessed from outcomes data collected and analyzed by a not-for-profit group. Both the data and analysis should be available to health professionals. This should be an iterative process able to define trends and opportunities for improving outcomes and using resources efficiently and appropriately.
4. The result report provides an opportunity to "educate" health care professionals about the appropriate use of genetic tests and results.

Workgroup #5: Carrier testing for cystic fibrosis with a relative with CBAVD

General

Peer reviewed algorithms for selecting appropriate tests to order and as aids in considering follow up to test results would be helpful. These should be developed jointly by insurers, regulators, and other users of genetic tests and results.

Pre-test

The requisition form provided with this case study does not contain sufficient guidance for selecting the appropriate test.

Post-test

1. This is a complex case where referral to a specialist, at some point, is advisable. Understanding when this should happen and what resources are available can be critical in assuring the patient receives appropriate counseling and health management. The report should address these issues (an opportunity for educating the provider).
2. Primary care physicians/allied health professionals are not conversant in genetic terminology and reports do a poor job in explaining the terminology often used. Use of terminologies such as "homozygous," "7T variant," "phenotypic expression" is confusing without further explanation.
3. The test result should be at the top of report, in big letters, and obvious.
4. The methods section is far too detailed. The benefits and limitations of the methodology used is not clear.

5. The interpretation needs to include patient-specific information in its derivation. Limitations of the interpretation based on what information is available should be clearly stated.
6. The report provided for this case study is too long. A one-page report is preferred.
7. The report must make clear the significance of mutation findings. The American College of Medical Genetics has developed guidelines regarding the description of mutation findings. It is particularly important to differentiate among disease-associated mutations, mutations that modify the expression of primary disease-associated mutations, and benign mutations. Recently, CF carrier test reports of 5T status without an R117H finding have led to unnecessary amniocenteses being performed.
8. Although the genotype of Bob's brother is stated in this case study, we should recognize that such information is often not available. Since this information can be very useful, the laboratory should try to secure it. This can involve time and cost for both the laboratory and clinical practice. If Bob's brother has not been tested, questions arise as to whether testing is recommended and who will pay.

Other Observations:

A bullet list of "truisms" that health care professionals can read quickly to help guide his/her thinking may be useful. These truisms might be set side in a box so it is easily visualized and digested; if it is put in a prose paragraph, it is less likely to be read. Examples of "truisms" include 1) failure to identify a mutation does not rule out the presence of a disease, and 2) a mutation may or may not be predictive of disease.

Attachment A2: Discipline Specific Issues and Needs

Health care professionals providing clinical care directly to patients (i.e. physicians, physician assistants, nurses, midwives):

1. Professional standards of practice or protocols describing what information is critical to collect, why it is important, and how to interact with the client and other health care professionals would be useful.
2. There is a need to understand what and why certain clinical and patient demographic information is required (i.e. ethnicity for CF carrier testing) by all who review and use test result reports. This is useful for assuring the requisition form is properly prepared and that useful or missing information on the test result report is appropriately noted prior to the patient visit.
3. It would be useful to have tools to assist in the appropriate collection and reporting of patient information.
4. It would be useful to have tools to assist in understanding and communicating risk information.
5. There is a need for a common terminology and process in the ordering of genetic tests and reporting of results.
6. There is a need to promote health care professional/laboratory partnerships toward the development of useful protocols.
7. It would be useful to include checklists for the most common indications for screening or testing on the requisition form or be otherwise available to health care professionals..
8. Regularly updated practical information about dealing with the legal and privacy issues should be available.
9. Regularly updated and accessible educational material should be available.
10. All health care professionals who participate in the provision of genetic testing and counseling should meet educational/training recommendations that strive to achieve established competencies (e.g., NCHPEG).
11. Since education and counseling about genetic issues and concerns is within the purview of health care professionals, access to reimbursement for these services needs to be developed. Reimbursement should include physicians, physician assistants, nurses, counselors, and others who fulfill this role.
12. Reimbursement schedules should differentiate between services provided by clinical genetics practitioner (i.e. medical geneticist, advanced practice genetics nurse) and non-geneticist practitioners. Presently, for non-geneticists, patient counseling and educational efforts are difficult to have reimbursed.

Other health care professionals involved in the patient clinical care process (i.e. medical assistants)

Anyone involved in collecting patient information or reviewing requisitions and reports needs to understand what information is important and why. As with other professionals considered, these individuals can be helpful in highlighting what critical information is available, already collected, or missing.

Laboratory Professionals

1. Laboratories should revisit their requisition and reporting process to consider standard terminology and formats useful and informative to all potential users.

2. The requisition and test report provide educational moments for health care professionals. This educational piece should be structured into the requisition and reporting forms.
3. Laboratory directors, many of whom are board certified, provide a ready source of expertise regarding the genetic tests they provide. Therefore, the laboratory should take more of a consultative role in the testing process as opposed to being "a provider of test results."
4. Laboratories should enhance their efforts to work with clinical practices in developing processes to improve communication and understanding.

Counseling (includes certified genetic counselors and other genetic and non-genetic health care professionals who provide patient counseling)

1. Certified genetic counselors are not always available or access to their services is limited in certain geographic areas. Outreach programs should continue to be explored.
2. Novel mechanisms for access to reimbursable genetic counseling services should be considered. Factors to consider in creating such mechanisms are the complexity of counseling being delivered and the training/expertise/certification of the person providing the service.
3. Appropriate genetic counseling is important, whether provided by a certified genetic counselor or other health care professional. In many cases, genetic counseling can be handled by most health care professionals having the appropriate training. For complex cases, genetic counseling should be provided by either a certified genetic counselor or a specialist with the appropriate genetics knowledge and counseling skills.
   practitioners with complex issues being best handled by those certified or specially trained.
4. Genetic counselors should partner with other genetic specialists and health care providers to educate health care professionals who are likely to order genetic tests, review and use the results.
5. Genetic counselors should enhance their efforts to improve awareness of their specialty and assist health care providers in finding and making use of genetic counseling services.

Public Health Professionals

1. The impact for public benefit and harm is so large that the public health community must play a role. There are at least two major roles.
   1. Assure access to valid testing (this covers access and test validity issues)
   2. Assure both professionals and the public are informed so appropriate decisions can be made about using genetic tests.
2. Public Health should play a pivotal role in supporting the delivery of genetic services. Simply put, the utility of genetic testing depends on its impact on the population to which it is offered (i.e. benefits of newborn screening programs).
3. Public health professionals need to facilitate the collection, review, and dissemination of population-based data relevant to genetic tests.
4. Public Health professionals need to be actively engaged in discussion about the potential role genetics may have in their work beyond that of newborn screening. These discussions need to be held with the clinical practice, manufacturer, and pharmaceutical community.
5. There are several areas in which genetics may soon have a role. These include: chronic disease, identification of populations most likely to benefit from vaccines, and defining at-risk populations for disease or environmental exposures.

General Comments

1. Our current educational model needs to be reviewed since it is becoming increasingly difficult, for generalists and specialists, to keep up with the pace of new knowledge coming available (i.e. health care providers are struggling as it is to keep up with what drugs to use for hypertension). Therefore a new model needs to be considered to better manage this knowledge. This concept has a significant implication for the development of future resources and the role of continuing education (i.e. continuing education may focus more on managing knowledge rather than teaching specific knowledge).

2. A lab test ordering manual or lab website should include (some already do) educational information regarding ordering tests and the implications for potential findings. Additional references or links may also be useful to include. Legal and privacy issues, as well as information about the potential for discrimination should be included in this information.

Attachment A3 - Highlighted Resources and Presentations

These are examples of some excellent efforts underway. There are other efforts of similar excellence and impact that time did not allow us to present.

1. **March of Dimes Foundation**: Genetics & Your Practice *Online*
   (http://www.marchofdimes.com/gyponline)
   (Presenters: Nancy Green, MD, Medical Director; Terri Creeden, MS, MPH, CGC, Director, Professional Genetics Education)

This resource, under development and planned for release in Fall 2003, will provide tools and guidance to assist health care and social science professionals in integrating genetics into their patient services. This web-based program is being developed to be practical, process-oriented, and resource rich. Of particular interest was the needs assessment that revealed what does and does not work in a training program. For instance, training programs that provide practical practice-based information have been successful. On the other hand, presenting guidelines of a general nature leads to confusion about implementation into ones practice. The needs assessment also indicated that providers are generally willing to perform such tasks as collecting a family history, offer genetic tests, and provide patient support. In contrast, health care providers reported that they were not willing to become genetic experts or deal with complex risk assessments.

2. **GeneTests** (http://www.genetests.org)
   (Presenter: Roberta A. Pagon, MD, Principal Investigator, University of Washington)

GeneTests is a publicly funded medical genetics information resource developed for physicians, other healthcare professionals, and researchers. The following resources are contained within GeneTests:

1. *GeneReviews*: an online publication of expert-authored disease reviews. As of April 2003, more than 190 reviews with one new review on the average being added each week. these reviews contain current information on genetic test use in health management and counseling. Links are provided to genomic databases, patient resources, PubMed citations, and policy statements and guidelines.
2. *Laboratory Directory*: an international directory of genetic testing laboratories. Approximately 550 clinical and research laboratories are listed that test for greater than 950 inherited conditions.
3. *Clinic Directory*: an international directory of genetic and prenatal diagnosis clinics. Approximately 1100 clinics are listed of which about 1000 are within the US.
4. *Educational Materials*: an illustrated glossary, information about genetic testing services, and teaching tools. The teaching tools include PowerPoint™ teaching modules.

3. **The National Coalition for Health Professional Education in Genetics** (NCHPEG)
   (http://www.nchpeg.org) (presenter: Joseph D. McInerney, MA, MS, Executive Director)

Established in 1996 by the American Medical Association, the American Nurses Association, and the National Human Genome Research Institute, the National Coalition for Health Professional Education in Genetics (NCHPEG) is a national effort to promote health professional education and

access to information about advances in human genetics. NCHPEG members are an interdisciplinary group of leaders from approximately 100 diverse health professional organizations, consumer and voluntary groups, government agencies, private industry, managed care organizations, and genetics professional societies. By facilitating frequent and open communication between stakeholder groups, NCHPEG seeks to capitalize on the collective expertise and experience of members and to reduce duplication of effort.

NCHPEG endorsed a set of core competencies in genetics on 14 February 2000 for health professionals from all disciplines (medicine, nursing, allied health, public health, dentistry, psychology, social work, etc.) to provide patient care that involves awareness of genetic issues and concerns. These competencies enable professionals to integrate genetics effectively and responsibly into their current practice.

NCHPEG has a number of other projects underway in partnership with its members. For instance, The Association of Women's Health, Obstetric and Neonatal Nurses in collaboration with NCHPEG is surveying its members to gauge their understanding of CF and the ACOG/ACMG guidelines. Also being collected is some basic information on participants' involvement in the clinical application of the guidelines. A revised survey is being prepared for the American Association for Respiratory Care.

Recently, NCHPEG released the first issue of an on-line newsletter devoted to addressing important concepts in taking a family history. Family history is being revisited on several fronts as an important tool for identifying persons at higher risk for medical conditions that may benefit from specific interventions.

4. **Health Resources and Services Administration (HRSA)**
(http://mchb.hrsa.gov/programs/default.htm)
(Presenter: Michele Puryear, MD, PhD, Chief, Genetic Services, Maternal and Child Health Bureau)

The Maternal and Child Health Bureau supports newborn screening and efforts to increase professional and public knowledge of how genetic diseases affect health. Several efforts were described:

1. The Genetics in Primary Care Project was established in 1998, with the National Institutes of Health and Health Resources and Services Administration's Bureau of Health Professionals. The project involves 20 medical schools across the country and was established to help plan, implement, and evaluate faculty-training programs in genetics for primary care providers, including those working in family medicine, general internal medicine, and general pediatrics.
2. The Genetics through a Primary Care Lens was initiated in 2001 and is a collaborative effort between the Genetic Services Branch and the University of Washington. The purpose of this project is to develop a written, evidence-based curriculum for primary care physicians that builds on the Genetics in Primary Care Project. The curriculum will be distributed to medical schools and residency training programs across the country.
3. A work force analysis was initiated in 2001 and is co-funded by HRSA (the Maternal and Child Health Bureau and the Bureau of Health Professionals) and the National Institutes of Health. The purpose of this study is to evaluate the genetic and non-genetic public health and health care workforce that will be needed to translate genetics into practice.

Attachment A4: Case Studies, Requisitions, and Test Result Reports

CASE 1: Carrier testing for cystic fibrosis with a relative with CBAVD

Mary Patient, a 23-year-old Caucasian woman has come to your practice to discuss family planning prior to pregnancy for their first child. During her visit, you offer Mary CF carrier testing, she accepts, and blood is drawn and sent off. Prior to collecting the sample, you learn that Mary and her husband trace their ancestry back to England and to Mary's knowledge no one her or her husband's family has had CF. Results from Mary's test show that she is a carrier for a ?F508 mutation. Mary returns with her husband, Bob, to a follow up appointment to discuss the results and testing for Bob. During the conversation, you learn that Bob's brother's child was conceived by assisted reproductive technology and this had to do with CBAVD for which Bob's brother was diagnosed. Neither Mary nor Bob know about CBAVD.

Documents provided

Pre-test discussion (morning)

1. Mary's test result
2. Requisition form for Bob's CF test

Post-test discussion (afternoon)

1. Bob's test result

Start morning discussion: Next steps - what steps need to be taken prior to ordering a CF carrier test for Bob?

End morning discussion: Laboratory is ready to perform CF carrier test

Start afternoon discussion: Test result report received

End afternoon discussion: Physician, Mary, and Bob are sufficiently informed to consider next steps

CASE 1: Carrier testing for cystic fibrosis with a relative with CBAVD

Case 1: CBAVD

MOLECULAR GENETICS LABORATORY
COMMUNITY HOSPITAL
ANY CITY, USA
TELEPHONE: 555-999-1234
FAX: 555-999-5678

Test:	Cystic Fibrosis Carrier Test	Specimen:	Blood
Name:	Mary Patient	Date of Specimen:	01-02-2003
Sex:	F	Date Received:	01-03-2003
Ethnicity:	Caucasian	Ordering M.D.:	Dr. Doctor
DOB:	5/03/79	Date of Report	01-16-2003

INDICATION FOR STUDY: Carrier testing for cystic fibrosis.

METHOD: DNA was extracted from blood, amplified by PCR and hybridized using allele specific oligonucleotides in the reverse dot blot format. This test is greater than 99% sensitive and specific for the mutations tested.

POS indicates presence of mutation, NEG indicates absence of mutation

Mutation	***Result***	***Mutation***	***Result***	***Mutation***	***Result***
?F508	**POS**/NEG	621+1 G? T	NEG/NEG	R560T	NEG/NEG
711+1 G? T	NEG/NEG	A455E	NEG/NEG	R347P	NEG/NEG
I148T	NEG/NEG	2789+5 G? A	NEG/NEG	R334W	NEG/NEG
G551D	NEG/NEG	R553X	NEG/NEG	3659?C	NEG/NEG
G542X	NEG/NEG	1898+1 G? A	NEG/NEG	R1162X	NEG/NEG
G85E	NEG/NEG	?I507	NEG/NEG	I506V*	NEG/NEG
N1303K	NEG/NEG	W1282X	NEG/NEG	1507V*	NEG/NEG
R117H	NEG/NEG	1717-1 G? A	NEG/NEG	F508C*	NEG/NEG
1078?T	NEG/NEG	3849+10kb C? T	NEG/NEG	5T	NEG/NEG
2184?A	NEG/NEG	N3120+1 G? A	NEG/NEG	7T	POS/NEG
				9T	POS/NEG

*Benign variant

RESULT
Mary is heterozygous for ?F508.

INTERPRETATION
The patient has one copy of the ΔF508 allele and is a cystic fibrosis carrier. If Mary has a child, there is a 50% risk for the child inheriting the ΔF508 allele. The risk for child inheriting a second CF associated allele from her partner depends on his carrier status, family history, and ethnicity. Knowing Mary's husband is Caucasian, we can estimate a risk of 1 in 560 for having a child with two CF alleles and

affected. This risk may be further modified based on the husband's CF carrier test and the presence of a family history relevant to CF.

COMMENTS

Cystic fibrosis is an autosomal recessive disease requiring two CF associated alleles. If considering pregnancy, testing the patient's spouse will be important to determine the risk of having a child affected by CF. Genetic counseling is recommended to help the patient understand implications of the test result for themselves and their family and as an aid in making informed health-related decisions.

DNA studies do not constitute a definitive test for the presence of all CF-associated mutations or disease. The appropriate interpretation of test results requires consideration of other clinical information, family history, and current knowledge about the mutations identified.

This test was developed and its performance characteristics determined by this laboratory. It has not been cleared or approved by the Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. The Clinical Laboratory Improvement Act of 1988 regulates clinical laboratory practice.

Lab Director

Lab Director Ph.D.
Director, Molecular Genetics Lab
CLIA ID#55D5555555
CAP ID#55555-55

Attending L. Physician

Attending L. Physician M.D.
Clinical Geneticist, Dept. of Human Genetics

LABORATORY
Requisition Form - case #1
(Carrier testing for cystic fibrosis with a relative with CBAVD)

1-02-03
Current Date

Patient: Bob Patient
First Last MI

Home address:
XXXXXX
Street
XXXX XXXX XXXX
City State Zip Code
XXX-XXXX
Home Number Alternate Number

Gender: ☑M ☐F DOB: 02/04/1975
MM/DD/YYYY

Is the patient pregnant: ☐Y ☑N

If yes, current gestational age: _____

Genetic test(s) being performed:
- ☑ Cystic Fibrosis
  - ☑ Mutation panel
  - ☐ Sequencing
- ☐ Fragile X
- ☐ Factor V Leiden
- ☐ Hemachromatosis

Reason for requesting genetic test:
- ☑ Carrier screening
- ☐ Diagnosis
- ☐ Family history
- ☐ Mutation typing
- ☐ Male infertility
- ☐ Prenatal
- ☐ Other _____

Current patient symptoms: None

Relevant patient history: _____

Please provide pedigree:
(attach pedigree if not enough room is provided)

Physician: Doctor
First Last MI

Contact Number: XXX-XXXX

Physician signature:
Doctor

Person completing form: XXXXXX XXXX
First Last

Title: Physician

Patient SS # XXX-XX-XXXX

Insurance Name: XXXX

Policy Holder: XXXX

Policy #: XXXX

Sample type:
- ☑ Blood
- ☐ Cheek cells
- ☐ Amnio
- ☐ CVS

Date Collected: 01/02/2003 1:30 PM
MM/DD/YYYY TIME

Patient ethnicity: (mark all that apply)
- ☐ Ashkenazi Jewish
- ☐ Jewish
- ☐ Asian
- ☐ African American
- ☐ Hispanic
- ☑ Caucasian
- ☐ Other: _____

Family history/ affected members:
Brother, CBAVD, Wife, carrier for ΔF508

**The clinical information requested is necessary for the performance of those tests.
Please include a copy of the individual's insurance card.

CASE 1: Carrier testing for cystic fibrosis with a relative with CBAVD

Case 1: CBAVD

MOLECULAR GENETICS LABORATORY
COMMUNITY HOSPITAL
ANY CITY, USA
TELEPHONE: 555-999-1234
FAX: 555-999-5678

Test:	Cystic Fibrosis Carrier Test	Specimen:	Blood
Name:	Bob Patient	Date of Specimen:	01-02-2003
Sex:	M	Date Received:	01-03-2003
Ethnicity:	Caucasian	Ordering M.D.:	Dr. Doctor
DOB:	5/03/80	Date of Report	01-16-2003

INDICATION FOR STUDY: Family history of CBAVD in a brother who has been genotyped and found to have a ΔF508 / R117H / 5T / 9T.

METHOD: DNA was extracted from blood, amplified by PCR and hybridized using allele specific oligonucleotides in the reverse dot blot format. This test is greater than 99% sensitive and specific for the mutations tested.

POS indicates presence of mutation, NEG indicates absence of mutation

Mutation	***Result***	***Mutation***	***Result***	***Mutation***	***Result***
?F508	NEG/NEG	621+1 G? T	NEG/NEG	R560T	NEG/NEG
711+1 G? T	NEG/NEG	A455E	NEG/NEG	R347P	NEG/NEG
I148T	NEG/NEG	2789+5 G? A	NEG/NEG	R334W	NEG/NEG
G551D	NEG/NEG	R553X	NEG/NEG	3659?C	NEG/NEG
G542X	NEG/NEG	1898+1 G? A	NEG/NEG	R1162X	NEG/NEG
G85E	NEG/NEG	?I507	NEG/NEG	I506V*	NEG/NEG
N1303K	NEG/NEG	W1282X	NEG/NEG	1507V*	NEG/NEG
R117H	**POS**/NEG	1717-1 G? A	NEG/NEG	F508C*	NEG/NEG
1078?T	NEG/NEG	3849+10kb C? T	NEG/NEG	5T	NEG/NEG
2184?A	NEG/NEG	N3120+1 G? A	NEG/NEG	7T	**POS/POS**
				9T	NEG/NEG

*Benign variant

RESULT
Bob is heterozygous for R117H and is homozygous for the 7T variant.

INTERPRETATION
The patient has one copy of the R117H mutation and two copies of the 7T variant. Therefore, the R117H allele is present on a 7T background. Bob's spouse has previously been found to have one copy of the ΔF508 allele. The risk for having a child that inherits both CFTR alleles

(ΔF508 and R117H) is 25%. The phenotypic expression of the R117H/7T/ ΔF508 is variable from solitary CBAVD to a more classical CF presentation.

COMMENTS
Cystic fibrosis is an autosomal recessive disease requiring two CF-associated alleles. Genetic counseling is recommended to help the patient understand implications of the test result for themselves and their family and as an aid in making informed health-related decisions.

DNA studies do not constitute a definitive test for the presence of all CF-associated mutations or disease. The appropriate interpretation of test results requires consideration of other clinical information, family history, and current knowledge about the mutations identified.

This test was developed and its performance characteristics determined by this laboratory. It has not been cleared or approved by the Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. Clinical laboratory practice is regulated by the Clinical Laboratory Improvement Act of 1988.

Lab Director
Lab Director Ph.D.
Director, Molecular Genetics Lab
CLIA ID#55D5555555
CAP ID#55555-55

Attending L. Physician
Attending L. Physician M.D.
Clinical Geneticist, Dept. of Human Genetics

CASE 2: Carrier testing for cystic fibrosis without a family history

The laboratory receives a test requisition from "The Medical Practice" requesting carrier testing for cystic fibrosis to assess the risk for having an affected child. No other information about the patient, Janice Patient, is provided. After some effort, the laboratory learns the patient is an 11 week pregnant female who is 25 years old and of unknown ethnicity according to the physician's office. The physician's office is not able to provide any family history but insists the test be performed.

Documents provided

Pre-test discussion (morning)

1. Requisition form for Janice Patient

Post-test discussion (afternoon)

1. Janice's test result and interpretation

Start morning discussion: Laboratory receives requisition - next steps

End morning discussion: Laboratory is ready to perform CF carrier test

Begin afternoon discussion: Test result report received

End afternoon discussion: Readiness to speak with Janice about next steps.

LABORATORY
Requisition Form - case #2
(Carrier testing for cystic fibrosis without a family history)

2-01-03
Current Date

Patient: Janice Patient
First Last MI

Home address:
XXXXXX
Street
XXXX XXXX XXXX
City State Zip Code
XXX-XXXX
Home Number Alternate Number

Gender: ☐M ☑F DOB: 3/01/77
MM/DD/YYYY

Is the patient pregnant: ☐Y ☐N

If yes, current gestational age: _____

Genetic test(s) being performed:
- ☑ Cystic Fibrosis
  - ☑ Mutation panel
  - ☐ Sequencing
- ☐ Fragile X
- ☐ Factor V Leiden
- ☐ Hemachromatosis

Reason for requesting genetic test:
- ☑ Carrier screening
- ☐ Diagnosis
- ☐ Family history
- ☐ Mutation typing
- ☐ Male infertility
- ☐ Prenatal
- ☐ Other _____

Current patient symptoms: _____
_____
_____
_____

Relevant patient history: _____
_____
_____

Please provide pedigree:
(attach pedigree if not enough room is provided)

Physician: Doctor
First Last MI

Contact Number: XXX-XXXX

Physician signature:
Doctor

Person completing form: XXXXXX XXXX
First Last

Title: Physician

Patient SS # XXX-XX-XXXX

Insurance Name: XXXX

Policy Holder: XXXX

Policy #: XXXX

Sample type:
- ☑ Blood
- ☐ Cheek cells
- ☐ Amnio
- ☐ CVS

Date Collected: 02-01-2003 1:45 PM
MM/DD/YYYY TIME

Patient ethnicity: (mark all that apply)
- ☐ Ashkenazi Jewish
- ☐ Jewish
- ☐ Asian
- ☐ African American
- ☐ Hispanic
- ☐ Caucasian
- ☐ Other: _____

Family history/ affected members:
_____
_____
_____

**The clinical information requested is necessary for the performance of those tests.
Please include a copy of the individual's insurance card.

CASE 2: Carrier testing for cystic fibrosis without a family history

MOLECULAR GENETICS LABORATORY
COMMUNITY HOSPITAL
ANY CITY, USA
TELEPHONE: 555-999-1234
FAX: 555-999-5678

Test:	Cystic Fibrosis Carrier Screening	Specimen:	Blood
Name:	Janice Patient	Date of Specimen:	02-01-2003
Sex:	F	Date Received:	02-02-2003
Ethnicity:		Ordering M.D.:	Dr. Doctor
DOB:	3/1/77	Date of Report	02-17-2003

INDICATION FOR STUDY: carrier testing during pregnancy

METHOD: DNA was extracted from blood, amplified by PCR and hybridized using allele specific oligonucleotides in the reverse dot blot format. This test is greater than 99% sensitive and specific for the mutations tested.

POS indicates presence of mutation, NEG indicates absence of mutation

Mutation	***Result***	***Mutation***	***Result***	***Mutation***	***Result***
?F508	NEG/NEG	621+1 G? T	NEG/NEG	R560T	NEG/NEG
711+1 G? T	NEG/NEG	A455E	NEG/NEG	R347P	NEG/NEG
I148T	NEG/NEG	2789+5 G? A	NEG/NEG	R334W	NEG/NEG
G551D	NEG/NEG	R553X	NEG/NEG	3659?C	NEG/NEG
G542X	NEG/NEG	1898+1 G? A	NEG/NEG	R1162X	NEG/NEG
G85E	NEG/NEG	?I507	NEG/NEG	I506V*	NEG/NEG
N1303K	NEG/NEG	W1282X	NEG/NEG	1507V*	NEG/NEG
R117H	NEG/NEG	1717-1 G? A	NEG/NEG	F508C*	NEG/NEG
1078?T	NEG/NEG	3849+10kb C? T	NEG/NEG	5T	NOT TESTED
2184?A	NEG/NEG	3120+1 G? A	NEG/NEG	7T	NOT TESTED
				9T	NOT TESTED

*Benign variant

RESULT
Negative finding for mutations tested

INTERPRETATION
These results do not rule out the possibility that this individual could be a carrier of a mutation not detected by the mutation panel applied. The following table provides data to be used in the genetic counseling for this individual when ethnicity is known. Limited information is available for individuals from ethnic populations not listed. This risk after a negative test may be further modified based on the presence of any family history of CF.

CASE 2: Carrier testing for cystic fibrosis without a family history

Ethnic group	Detection rate	Before test	After negative test
Ashkenazi Jewish	97%	1/29	~1 in 930
European Caucasian	80%	1/29	~1 in 140
African American	69%	1/65	~1 in 207
Hispanic American[a]	57%	1 /46	~1 in 105
Asian American	[b]	1/90	[b]

[a]This is a pooled set of data and requires additional information to accurately predict risk for specific Hispanic populations.
[b]No data available.
Note: Residual carrier risk after a negative test is modified by the presence of a positive family history of CF (i.e., having a first, second, or third degree relative affected with CF) and/or by admixture of various ethnic groups. For these specific situations, accurate risk assessment requires standard Bayesian analysis and genetic counseling.

COMMENTS
Cystic fibrosis is an autosomal recessive disease requiring two CF associated alleles. Genetic counseling is recommended to help the patient understand implications of the test result for themselves and their family and as an aid in making informed health-related decisions.

DNA studies do not constitute a definitive test for the presence of all CF-associated mutations or disease. The appropriate interpretation of test results requires consideration of other clinical information, family history, and current knowledge about the mutations identified.

This test was developed and its performance characteristics determined by this laboratory. It has not been cleared or approved by the Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. The Clinical Laboratory Improvement Act of 1988 regulates clinical laboratory practice.

Lab Director
Lab Director Ph.D.
Director, Molecular Genetics Lab
Genetics
CLIA ID#55D5555555
CAP ID#55555-55

Attending L. Physician
Attending L. Physician M.D.
Clinical Geneticist, Dept. of Human

CASE 3: Carrier testing with a family history

Nancy is a 27-year-old Caucasian woman visits her OB-GYN for her annual exam; Nancy mentions that she and her husband are trying to become pregnant for the first time. During the discussion, you learn that Nancy has a first cousin, on her side of the family that has been diagnosed with cystic fibrosis. Nancy knows little about her husband's family's history except that they originated in Denmark. You advise that a number of tests can be ordered including one for the CFTR gene. She insists on having the test so she will know that her baby will be normal.

Documents provided

Pre-test discussion (morning)

1. Requisition form for Nancy Patient

Post-test discussion (afternoon)

1. Nancy's test result and interpretation

Start morning discussion: Steps leading to a test referral after learning of Nancy's family history of CF.

End morning discussion: Laboratory is ready to perform CF carrier test

Start afternoon discussion: Receive Nancy's test result report

End discussion: Readiness to speak with Janice about next steps.

LABORATORY
Requisition Form - case #3
(Carrier testing with a family history)

2-02-02
urrent Date

Patient: Nancy Patient
First Last MI

Home address:
XXXXXX
Street
XXXX XXXX XXXX
City State Zip Code
XXX-XXXX
Home Number Alternate Number

Gender: ☐M ☑F DOB: 10/01/74
MM/DD/YYYY

Is the patient pregnant: ☐Y ☑N

If yes, current gestational age: _____

Genetic test(s) being performed:
- ☑ Cystic Fibrosis
  - ☑Mutation panel
  - ☐ Sequencing
- ☐ Fragile X
- ☐ Factor V Leiden
- ☐ Hemachromatosis

Reason for requesting genetic test:
- ☑ Carrier screening
- ☐ Diagnosis
- ☐ Family history
- ☐ Mutation typing
- ☐ Male infertility
- ☐ Prenatal
- ☐ Other _____

Current patient symptoms: None

Relevant patient history: _____

Please provide pedigree:
(attach pedigree if not enough room is provided)

Physician: Doctor
First Last MI

Contact Number: XXX-XXXX

Physician signature:
Doctor

Person completing form: XXXXXX XXXX
First Last

Title: Physician

Patient SS # XXX-XX-XXXX

Insurance Name: XXXX

Policy Holder: XXXX

Policy #: XXXX

Sample type:
- ☑ Blood
- ☐ Cheek cells
- ☐ Amnio
- ☐ CVS

Date Collected: 02-01-2003 1:30 PM
MM/DD/YYYY TIME

Patient ethnicity: (mark all that apply)
- ☐ Ashkenazi Jewish
- ☐ Jewish
- ☐ Asian
- ☐ African American
- ☐ Hispanic
- ☑ Caucasian
- ☐ Other: _____

Family history/ affected members:
Diagnosis of Cystic Fibrosis of First Cousin

**The clinical information requested is necessary for the performance of those tests.
Please include a copy of the individual's insurance card.

CASE 3: Carrier testing with a family history

MOLECULAR GENETICS LABORATORY
COMMUNITY HOSPITAL
ANY TOWN, USA
TELEPHONE: 555-999-1234
FAX: 555-999-5678

Test:	Cystic Fibrosis Carrier Testing	Specimen:	Blood
Name:	Nancy Patient	Date of Specimen:	02-02-2002
Sex:	F	Date Received:	02-03-2002
Ethnicity:	Caucasian	Ordering M.D.:	Dr. Doctor
DOB:	10/1/74	Date of Report	02-16-2002

INDICATION FOR STUDY: Contemplating pregnancy, Family history of a first cousin with Cystic Fibrosis.

METHOD: DNA was extracted from blood, amplified by PCR and hybridized using allele specific oligonucleotides in the reverse dot blot format. This test is greater than 99% sensitive and specific for the mutations tested.

POS indicates presence of mutation, NEG indicates absence of mutation

Mutation	***Result***	***Mutation***	***Result***	***Mutation***	***Result***
?F508	NEG/NEG	621+1 G? T	NEG/NEG	R560T	NEG/NEG
711+1 G? T	NEG/NEG	A455E	NEG/NEG	R347P	**POS**/NEG
I148T	NEG/NEG	2789+5 G? A	NEG/NEG	R334W	NEG/NEG
G551D	NEG/NEG	R553X	NEG/NEG	3659? C	NEG/NEG
G542X	NEG/NEG	1898+1 G? A	NEG/NEG	R1162X	NEG/NEG
G85E	NEG/NEG	?I507	NEG/NEG	I506V*	NEG/NEG
N1303K	NEG/NEG	W1282X	NEG/NEG	1507V*	NEG/NEG
R177H	NEG/NEG	1717-1 G? A	NEG/NEG	F508C*	NEG/NEG
1078? T	NEG/NEG	3849+10kb C? T	NEG/NEG	5T	NOT TESTED
2184? A	NEG/NEG	N3120+1 G? A	NEG/NEG	7T	NOT TESTED
				9T	NOT TESTED

*Benign variant

RESULT
Nancy Patient is heterozygous for the R347P mutation.

INTERPRETATION
One copy of the R347P mutation was identified, indicating that this individual is a carrier for one allele associated with cystic fibrosis (CF). If Nancy has a child, there is a 50% risk for the child to inherit the R347P allele. The risk for an affected child depends on the carrier status of her partner. If the patient's husband is Caucasian, the risk of having

an affected child with two CF alleles is estimated to be 1 in 560. This risk may further be modified based upon findings from CF carrier testing for her husband and learning of additional relevant family history.

COMMENTS
Cystic fibrosis is an autosomal recessive disease requiring two CF associated alleles. The interpretation of this test depends upon accurate diagnosis of affected individuals and correct reporting of familial relationships. Genetic counseling is recommended to help the patient understand implications of the test result for themselves and their family and as an aid in making informed health-related decisions.

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Lab Director

Lab Director Ph.D.
Director, Molecular Genetics Lab
Genetics
CLIA ID#55D5555555
CAP ID#55555-55

Attending L. Physician

Attending L. Physician M.D.
Clinical Geneticist, Dept. of Human

CASE 4: Diagnostic testing for cystic fibrosis--infant with failure to thrive

A nine month old Hispanic boy, Bobby, son of Alice and John, 24 and 26 years old, respectively, is noted to be falling off his growth curve for weight during the past two health maintenance visits at the pediatrician's office. Bobby has had a series of respiratory infections and his mother now reports that he has begun to have foul smelling bulky stools. A complete blood count and urinalysis was performed and both are normal. Sweat testing is performed and a positive test result is reported and confirmed. Alice and John are contemplating having another child and indicate they would be interested in prenatal diagnosis. The nearest CF center is over a 2-hour drive away.

Documents provided

Pre-test discussion (morning)

1. Requisition form for Bobby Patient

Post-test discussion (afternoon)

1. Bobby's test result and interpretation

Start morning discussion: Deciding on next steps.

End morning discussion: Laboratory is ready to perform CF diagnostic test

Start afternoon discussion: Receiving test result report.

End afternoon discussion: Readiness to consider next steps.

LABORATORY
Requisition Form - case #4
(Diagnostic testing for cystic fibrosis--infant with failure to thrive)

2-01-03
Current Date

Patient: Bobby (First) Patient (Last) _____ (MI)

Home address:
XXXXXX
Street
XXXX (City) XXXX (State) XXXX (Zip Code)
XXX-XXXX (Home Number) _____ (Alternate Number)

Gender: ☑M ☐F DOB: 04/30/02 (MM/DD/YYYY)

Is the patient pregnant: ☐Y ☑N

If yes, current gestational age: _____

Genetic test(s) being performed:
- ☑ Cystic Fibrosis
- ☐ Fragile X
- ☐ Factor V Leiden
- ☐ Hemachromatosis

Reason for requesting genetic test:
- ☐ Carrier screening
- ☑ Diagnosis
- ☐ Family history
- ☐ Mutation typing
- ☐ Male infertility
- ☐ Prenatal
- ☐ Other _____

Current patient symptoms: _____
falling off growth curve during past two health maintenance visits, series of respiratory infections, foul smelling bulky stools

Relevant patient history: _____

Please provide pedigree:
(attach pedigree if not enough room is provided)

Physician: Doctor (First) (Last) (MI)

Contact Number: XXX-XXXX

Physician signature:
Doctor

Person completing form: XXXXXX (First) XXXX (Last)

Title: _____

Patient SS # XXX - XX - XXXX

Insurance Name: XXXX

Policy Holder: XXXX

Policy #: XXXX

Sample type:
- ☑ Blood
- ☐ Cheek cells
- ☐ Amnio
- ☐ CVS

Date Collected: 02/01/2003 (MM/DD/YYYY) 1:30 PM (TIME)

Patient ethnicity: (mark all that apply)
- ☐ Ashkenazi Jewish
- ☐ Jewish
- ☐ Asian
- ☐ African American
- ☑ Hispanic
- ☐ Caucasian
- ☐ Other: _____

Family history/ affected members:
_____

**The clinical information requested is necessary for the performance of those tests.
Please include a copy of the individual's insurance card.

CASE 4: Diagnostic testing for cystic fibrosis--infant with failure to thrive

MOLECULAR GENETICS LABORATORY
COMMUNITY HOSPITAL
ANY TOWN, USA
TELEPHONE: 555-999-1234
FAX: 555-999-5678

Test:	Cystic Fibrosis diagnostic testing	Specimen:	Blood
Name:	Bobby Patient	Date of Specimen:	02-01-2003
Sex:	M	Date Received:	02-02-2003
Ethnicity:	Hispanic	Ordering M.D.:	Dr. Doctor
DOB:	4/30/02	Date of Report	02-18-2003

INDICATION FOR STUDY: Infant with failure to thrive

METHOD: DNA was extracted from blood, amplified by PCR and hybridized using allele specific oligonucleotides in the reverse dot blot format. This test is greater than 99% sensitive and specific for the mutations tested.

POS indicates presence of mutation, NEG indicates absence of mutation

Mutation	***Result***	***Mutation***	***Result***	***Mutation***	***Result***
?F508	**POS**/NEG	621+1 G? T	NEG/NEG	R560T	NEG/NEG
711+1 G? T	NEG/NEG	A455E	NEG/NEG	R347P	NEG/NEG
I148T	NEG/NEG	2789+5 G? A	NEG/NEG	R334W	NEG/NEG
G551D	NEG/NEG	R553X	NEG/NEG	3659? C	NEG/NEG
G542X	NEG/NEG	1898+1 G? A	NEG/NEG	R1162X	NEG/NEG
G85E	NEG/NEG	?I507	NEG/NEG	I506V	NEG/NEG
N1303K	NEG/NEG	W1282X	NEG/NEG	1507V	NEG/NEG
R177H	NEG/NEG	1717-1 G? A	NEG/NEG	F508C	NEG/NEG
1078? T	NEG/NEG	3849+10kb C? T	NEG/NEG	5T	NOT TESTED
2184? A	NEG/NEG	N3120+1 G? A	NEG/NEG	7T	NOT TESTED
				9T	NOT TESTED

RESULT
Bobby Patient is a heterozygote for ?F508.

INTERPRETATION
One copy of the ?F508 mutation was found in this test, indicating that Bobby Patient is a carrier for this mutation. This is consistent with a diagnosis for cystic fibrosis recognizing that a second CF-associated allele may be present but was not detected by this assay. Follow-up testing using a more extensive panel or sequencing of the CFTR gene is recommended.

Ethnic group	Detection rate	Before test	After negative test
Ashkenazi Jewish	97%	1/29	~1 in 930
European Caucasian	80%	1/29	~1 in 140
African American	69%	1/65	~1 in 207
Hispanic American[a]	57%	1 /46	~1 in 105
Asian American	[b]	1/90	[b]

[a]This is a pooled set of data and requires additional information to accurately predict risk for specific Hispanic populations.
[b]No data available.
Note: Residual carrier risk after a negative test is modified by the presence of a positive family history of CF (i.e., having a first, second, or third degree relative affected with CF) and/or by admixture of various ethnic groups. For these specific situations, accurate risk assessment requires standard Bayesian analysis and genetic counseling.

(Data taken from: The American College of Obstetricians and Gynecologists and American College of Medical Genetics. Preconception and Prenatal Carrier Screening for Cystic Fibrosis, Clinical and Laboratory Guidelines, Washington DC: 2001.)

COMMENTS
Cystic fibrosis is an autosomal recessive disease requiring two CF associated alleles. The interpretation of this test depends upon accurate diagnosis of affected individuals and correct reporting of familial relationships. Genetic counseling is recommended to help the patient understand implications of the test result for themselves and their family and as an aid in making informed health-related decisions.

DNA studies do not constitute a definitive test for the presence of all CF-associated mutations or disease. The appropriate interpretation of test results requires consideration of other clinical information, family history, and current knowledge about the mutations identified.

This test was developed and its performance characteristics determined by this laboratory. It has not been cleared or approved by the Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. The Clinical Laboratory Improvement Act of 1988 regulates clinical laboratory practice.

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CLIA ID#55D5555555
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Attending L. Physician
Attending L. Physician M.D.
Clinical Geneticist, Dept. of Human

CASE 5: Prenatal diagnosis

Melissa Patient, a 37 years old Ashkenazi Jewish woman, visits her obstetrician to discuss results from a follow-up ultrasound showing persistence of a hyperchoic (echogenic) bowel in her unborn child Melissa is in her 22nd week of gestation. No carrier testing for Melissa or her husband had been performed. Other than this observation, her pregnancy has been normal. An amniocentesis was performed earlier and revealed no chromosomal abnormalities. Before speaking to Melissa and her husband, you find out that the laboratory that performed the amniocentesis has cell pellets remaining that can be used for DNA testing.

Documents provided

Pre-test discussion (morning)

1. Requisition form for Melissa's fetus

Post-test discussion (afternoon)

1. Melissa's fetus test result and interpretation—ACMG recommended panel
2. Melissa's fetus test result and interpretation—sequence analysis

Start morning discussion: Consider how best to follow up an abnormal prenatal finding with one outcome being a referral for CF testing.

End morning discussion: Laboratory is ready to perform CF diagnostic test

Start afternoon discussion: Receive test result report(s)

End discussion: Readiness to communicate findings to patient

LABORATORY
Requisition Form - case #5
(Prenatal diagnosis)

2-01-03
Current Date

Patient: Fetus of Melissa Patient
First Last MI

Home address:
XXXXXX
Street
XXXX XXXX XXXX
City State Zip Code
XXX-XXXX
Home Number Alternate Number

Gender: ☐M ☐F DOB: _____
MM/DD/YYYY

Is the patient pregnant: ☑Y ☐N

If yes, current gestational age: 22 weeks

Genetic test(s) being performed:
- ☑ Cystic Fibrosis
- ☐ Fragile X
- ☐ Factor V Leiden
- ☐ Hemachromatosis

Reason for requesting genetic test:
- ☐ Carrier screening
- ☑ Diagnosis
- ☐ Family history
- ☐ Mutation typing
- ☐ Male infertility
- ☐ Prenatal
- ☐ Other _____

Current patient symptoms:
hyperchoic (echogenic) bowel

Relevant patient history: _____

Please provide pedigree:
(attach pedigree if not enough room is provided)

Physician: Doctor
First Last MI

Contact Number: XXX-XXXX

Physician signature:
Doctor

Person completing form: XXXXXX XXXX
First Last

Title: _____

Patient SS # XXX-XX-XXXX

Insurance Name: XXXX

Policy Holder: XXXX

Policy #: XXXX

Sample type:
- ☐ Blood
- ☐ Cheek cells
- ☑ Amnio
- ☐ CVS

Date Collected: 03/02/2003 1:30 PM
MM/DD/YYYY TIME

Patient ethnicity: (mark all that apply)
- ☑ Ashkenazi Jewish
- ☐ Jewish
- ☐ Asian
- ☐ African American
- ☐ Hispanic
- ☐ Caucasian
- ☐ Other: _____

Family history/ affected members:
_____

**The clinical information requested is necessary for the performance of those tests.
Please include a copy of the individual's insurance card.

CASE 5: Prenatal diagnosis - alternate report #1

MOLECULAR GENETICS LABORATORY
COMMUNITY HOSPITAL
ANY TOWN, USA
TELEPHONE: 555-999-1234
FAX: 555-999-5678

Test:	Cystic Fibrosis diagnostic testing	Specimen:	Amniotic Fluid
Name:	Fetus of Melissa Patient	Date of Specimen:	03-02-2003
Sex:		Date Received:	03-03-2003
Ethnicity:	Ashkenazi Jewish	Ordering M.D.:	Dr. Doctor
DOB:	22^{nd} week gestation	Date of Report	03-15-2003

INDICATION FOR STUDY: Prenatal diagnosis

METHOD: DNA was extracted from the amniocytes, amplified by PCR and hybridized using allele specific oligonucleotides in the reverse dot blot format. This test is greater than 99% sensitive and specific for the mutations tested.

POS indicates presence of mutation, NEG indicates absence of mutation

Mutation	***Result***	***Mutation***	***Result***	***Mutation***	***Result***
?F508	**POS**/NEG	621+1 G? T	NEG/NEG	R560T	NEG/NEG
711+1 G? T	NEG/NEG	A455E	NEG/NEG	R347P	NEG/NEG
I148T	NEG/NEG	2789+5 G? A	NEG/NEG	R334W	NEG/NEG
G551D	NEG/NEG	R553X	NEG/NEG	3659?C	NEG/NEG
G542X	NEG/NEG	1898+1 G? A	NEG/NEG	R1162X	NEG/NEG
G85E	NEG/NEG	?I507	NEG/NEG	I506V	NEG/NEG
N1303K	NEG/NEG	W1282X	NEG/NEG	1507V	NEG/NEG
R117H	NEG/NEG	1717-1 G? A	NEG/NEG	F508C	NEG/NEG
1078?T	NEG/NEG	3849+10kb C? T	NEG/NEG	5T	NOT TESTED
2184?A	NEG/NEG	N3120+1 G? A	NEG/NEG	7T	NOT TESTED
				9T	NOT TESTED

RESULT
The fetus of Melissa is heterozygous for ?F508.

INTERPRETATION
One copy of ?F508 was found. The ACMG panel provides a 97% detection rate for mutations occurring in Ashkenazi Jews. Therefore, this does not rule out the presence of a second CF-associated allele. The finding of an echogenic bowel together with the

presence of a ?F508 raises the risk for the fetus being affected with cystic fibrosis. Additional testing using a more extensive panel or sequence analysis is recommended.

Ethnic group	Detection rate	Before test	After negative test
Ashkenazi Jewish	97%	1/29	~1 in 930
European Caucasian	80%	1/29	~1 in 140
African American	69%	1/65	~1 in 207
Hispanic American[a]	57%	1 /46	~1 in 105
Asian American	[b]	1/90	[b]

[a]This is a pooled set of data and requires additional information to accurately predict risk for specific Hispanic populations.
[b]No data available.
Note: Residual carrier risk after a negative test is modified by the presence of a positive family history of CF (i.e., having a first, second, or third degree relative affected with CF) and/or by admixture of various ethnic groups. For these specific situations, accurate risk assessment requires standard Bayesian analysis and genetic counseling.

Table 3. Risk of Offspring Having Cystic Fibrosis*

Racial or Ethnic Group of Both Partners†	No Test	One Partner Negative, One Partner Untested	One Partner Positive, One Partner Negative	One Partner Positive, One Partner Untested	Both Partners Negative
Askenazi Jewish	1/3,300	1/107,880	1/3,720	1/116	1/3,459,600
European Caucasian	1/3,300	1/16,240	1/560	1/116	1/78,400
Hispanic American	1/8,464	1/19,320	1/420	1/184	1/44,100
African American	1/16,900	1/53,820	1/828	1/260	1/171,396
Asian American	1/32,400	‡	‡	1/360	‡

*Estimates based on sensitivity of carrier test and frequency of carriers given in Table 2. If both partners are positive, risk is 1/4 (25%) irrespective of ethnic or racial group.

†Calculation of risk for couples of different racial or ethnic background can be based on data in Table 2 as follows:

No test: Carrier risk of one partner × carrier of other partner × 1/4

One partner negative, one partner untested: Carrier risk after negative test of one partner × carrier risk of other partner without test × 1/4

One partner positive, one partner negative: Carrier risk of negative partner after testing × 1/4

One partner positive, one partner untested: Carrier risk of untested partner × 1/4

Both partners negative: Carrier risk of one partner after negative test × carrier risk of other partner after negative test × 1/4

‡Data not available.

(Data taken from: The American College of Obstetricians and Gynecologists and American College of Medical Genetics. Preconception and Prenatal Carrier Screening for Cystic Fibrosis, Clinical and Laboratory Guidelines, Washington DC: 2001.)

COMMENTS

Cystic fibrosis is an autosomal recessive disease requiring two CF associated alleles. The interpretation of this test depends upon accurate diagnosis of affected individuals and correct reporting of familial relationships. Genetic counseling is recommended to help the patient understand implications of the test result for themselves and their family and as an aid in making informed health-related decisions.

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Attending L. Physician

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Clinical Geneticist, Dept. of Human

CASE 5: Prenatal diagnosis - alternate report #2

MOLECULAR GENETICS LABORATORY
COMMUNITY HOSPITAL
ANY TOWN, USA
TELEPHONE: 555-999-1234
FAX: 555-999-5678

Test:	Cystic Fibrosis diagnostic testing	Specimen:	Amniotic Fluid
Name:	Fetus of Melissa Patient	Date of Specimen:	03-02-2003
Sex:		Date Received:	03-03-2003
Ethnicity:	Ashkenazi Jewish	Ordering M.D.:	Dr. Doctor
DOB:	22nd week gestation	Date of Report	03-15-2003

INDICATION FOR STUDY: Prenatal diagnosis

METHOD: DNA was extracted from the amniocytes. Sequence analysis was performed on all exons and selected regions of certain introns. This test is greater than 99% sensitive and specific for the mutations tested.

RESULT

Two mutations were identified ΔF508 and D1152H.

INTERPRETATION

The finding of two CF-associated mutations is consistent with a prenatal diagnosis for cystic fibrosis.

COMMENTS

Cystic fibrosis is an autosomal recessive disease requiring two CF associated alleles. The interpretation of this test depends upon accurate diagnosis of affected individuals and correct reporting of familial relationships. Genetic counseling is recommended to help the patient understand implications of the test result for themselves and their family and as an aid in making informed health-related decisions.

DNA studies do not constitute a definitive test for the presence of all CF-associated mutations or disease. The appropriate interpretation of test results requires consideration of other clinical information, family history, and current knowledge about the mutations identified.

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Attending L. Physician

Attending L. Physician M.D.
Clinical Geneticist, Dept. of Human

Attachment A5: Organizational Affiliation of Attendees (presented for information only - attendance at the meeting does not imply support for this report by the groups listed below)

Federal Government Agencies

Centers for Disease Control and Prevention, Department of Health and Human Services
Centers for Medicare & Medicaid Services, Department of Health and Human Services
Health Resources Services Administration, Department of Health and Human Services
Office of Science and Data Policy, Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services

Professional Organizations, Academics, and State entities

American Academy of Family Physicians
American Academy of Physician Assistants
American Academy of Pediatrics
American College of Obstetricians and Gynecologists
American College of Medical Genetics
American College of Nurse Midwives
American Medical Association
Association of Molecular Pathologists
Association of Public Health Laboratories
Association of Family Practice Residency Directors
Association of Women's Health, Obstetric, and Neonatal Nursing
Blue Cross and Blue Shield Association
GeneTests
Genetic Alliance
Genetics and Public Policy Center, Johns Hopkins University
International Society of Nurses in Genetics
March of Dimes Foundation
Minnesota Department of Health - Minnesota Children with Special Health Needs
Mount Sinai School of Medicine
National Coalition for Health Professional Education in Genetics
National Society of Genetic Counselors
New England Newborn Screening Program
St. Vincent's Hospital Cystic Fibrosis Center
Tulane University Health Sciences Center
Wadsworth Center, New York State Department of Health

International participation

Cystic Fibrosis Thematic Network
Organization for Economic Cooperation and Development

Attachment A6: Relevant Publications

1. National Institutes of Health. Genetic Testing for Cystic Fibrosis. NIH Consensus Statement (1999) Archives Int Med 159:1529-1539.

2. The American College of Obstetricians and Gynecologists and American College of Medical Genetics. Preconception and Prenatal Carrier Screening for Cystic Fibrosis, Clinical and Laboratory Guidelines, Washington DC: 2001.

3. McGovern MM, Benach, M, Wallenstein, S, Desnick RJ, Keenlyside R (1999) Quality Assurance in Molecular Genetic Testing Laboratories. JAMA 281:835-840.

4. Andersson HC, Krousel-Wood MA, Jackson KE, Rice J, Lubin IM (2002) Medical Genetic Test Reporting for Cystic Fibrosis (ΔF508) and Factor V Leiden in North American Laboratories. Genet Med 5:324-327.

5. Krousel-Wood M, Andersson HC, Rice J, Jackson KE, Rosner ER, Lubin IM (2003) Physicians' Perceived Usefulness of and Satisfaction with Test Reports for Cystic Fibrosis (ΔF508) and Factor V Leiden. Genet Med 5:166-177.

6. Sandhaus LM, Singer ME, Dawson NV, Wiesner GL (2001) Reporting BRCA test results to primary care physicians. Genet Med 3:327-334.

7. Vastag B (2003) Cystic Fibrosis Gene Testing a Challenge: Experts Say Widespread Use is Creating Unnecessary Risks. JAMA 289:2923-2924.

8. NCCLS Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline. NCCLS document MM1-A [ISBN 1-56238-395-7] NCCLS, 940 West Valley Road, Suite 1400, Wayne Pennsylvania 19087-1898 USA, 2000

9. Grody WW, Cutting GR, Klinger KW, Richards CS, Watson MS, Desnick RJ (2001) Laboratory Standards and Guidelines for Population-Based Cystic Fibrosis Carrier Screening. Genet Med 3:149-154.

10. Dequeker E, Cuppens H, Dodge J, Estivill X, Goossens M, Pignatti PF, Scheffer H, Schwartz M, Schwarz M, Tummler B, Cassiman J-J (2000) Recommendations for Quality Improvement in Genetic Testing for Cystic Fibrosis European Concerted Action on Cystic Fibrosis. Eur J Hum Genet 8:S2-S24.

11. Ciske DJ, Haavisto A, Laxova A, Zeng L, Rock M, Farrell PM (2001) Genetic Counseling and Neonatal Screening for Cystic Fibrosis: An Assessment of the Communication Process. Pediatrics 107:699-705.

12. Fernbach SD, Thomson EJ (1992) Molecular Genetic Technology in Cystic Fibrosis: Implications for Nursing Practice. J Pediatr Nurs 7:20-25.