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Ordering Molecular Genetic Tests and Reporting Results

Practices in Laboratory and Clinical Settings

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Previous studies have suggested that patient care may be compromised as a consequence of poor communication between clinicians and laboratory professionals in cases in which molecular genetic test results are reported. To understand better the contributing factors to such compromised care, we investigated both pre- and postanalytical processes using cystic fibrosis mutation analysis as our model. We found that although the majority of test requisition forms requested patient/family information that was necessary for the proper interpretation of test results, in many cases, these data were not provided by the individuals filling out the forms. We found instances in which result reports for simulated diagnostic testing described individuals as carriers where only a single mutation was found with no comment pertaining to a diagnosis of cystic fibrosis. Similarly, reports based on simulated scenarios for carrier testing were problematic when no mutations were identified, and the patient's race/ethnicity and family history were not discussed in reference to residual risk of disease. Remarkably, a pilot survey of obstetrician-gynecologists revealed that office staff, including secretaries, often helped order genetic tests and reported test results to patients, raising questions about what efforts are undertaken to ensure personnel competency. These findings are reviewed in light of what efforts should be taken to improve the quality of test-ordering and result-reporting practices. ***(J Mol Diagn 2008, 10:459–468; DOI: 10.2353/jmoldx.2008.080050)***

Discoveries emanating from the Human Genome Project, better understanding of the genetic basis of disease, and the ever-growing number of molecular genetic tests that are clinically available and that are perceived to have value to patient care are prompting clinicians to integrate genetic medicine into medical practice.[1,2] Genetic testing is no longer limited to rare disease testing performed in specialty clinical and laboratory settings. Tests for disorders such as cystic fibrosis (CF), fragile X syndrome, and factor V Leiden are commonly used by primary care clinicians including internists, family physicians, obstetrician-gynecologists (OB-GYNs), and pediatricians.[3,4] Specialists, other than medical geneticists, also use genetic tests to aid in diagnosis and patient management. For example, neurologists may order tests to differentiate the various forms of spino-cerebellar ataxia.[5] With more than 1200 genetic tests currently available in clinical laboratories and with ongoing advances in gene discovery and testing methods, we anticipate that the integration of genetics into clinical practice will continue at a rapid pace.[6]

The pre- and postanalytic components of the genetic testing process represent challenges to laboratory medicine; clinicians must order the correct test and receive a

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Standard of practice is not being defined by this article, and there may be alternatives.

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test result interpretation appropriate for their patient's clinical findings and family history. Previous studies have demonstrated variation in how laboratories report and interpret molecular genetic test results, clinician dissatisfaction with genetic test reports, and poor understanding of the interpretive comments for selected examples.[7–12] Further evidence of challenges for communicating molecular genetic test results was reported in a 2003 study in which 83% of genetic counselors surveyed nationwide indicated that they needed to have follow-up contact with the laboratory to clarify the interpretation of the test result.[11]

Professional guidelines and educational efforts have been developed to disseminate best practices for genetic testing. However, questions have been raised about how well such guidance is implemented in practice and few studies exist addressing this concern. In one study, Morgan and colleagues[12] reported in 2005 that whereas a majority of OB-GYNs surveyed knew of the American College of Obstetricians and Gynecologists/American College of Medical Genetics guideline for preconceptual CF carrier screening, only 22.2% of those surveyed were able to correctly answer a question about the relevance of race/ethnicity for determining residual risk, a topic discussed in the published guideline and included in supporting education materials for OB-GYNs.

In 2003, a national workshop was held to consider the importance, challenges, shortcomings, and potential efforts needed to promote and develop best practices for the ordering of molecular genetic tests and reporting of test results. This workshop was attended by clinicians, laboratory directors, policy makers, educators, information technology specialists, third-party payers, and others. Two recommendations emerged. The first was the need to enhance effective communication between the laboratory and clinical settings. This recommendation supported previous studies that had shown variability in laboratory reporting of test results and difficulty among clinicians in understanding their clinical implications.[7–10] The second recommendation was to collect data about laboratory and clinical practices relevant to how genetic tests are ordered and results are reported. Such an activity is essential for identifying gaps and developing efforts, based on evidence, for promoting efficacy and appropriate use of genetic testing services. After the workshop, participants remained engaged and continued to provide input into the multifaceted study described herein.

In this study, laboratory requisition forms and reports were evaluated for content and short surveys of laboratory directors and OB-GYNs were undertaken. We used CF (MIM 219700) mutation analysis as our primary model for investigating clinical and laboratory practices. We anticipate that results from this study will stimulate research and practice guidelines to improve the quality of the pre- and postanalytic phases of genetic testing particularly regarding the communication of clinically relevant information between the laboratory and clinical settings.

DNA-based testing for CF was chosen as the model for this study for the following reasons: first, established guidelines for offering prenatal CF carrier testing have been available since 2001 through a joint effort of the American College of Obstetricians and Gynecologists and the American College of Medical Genetics.[13] Second, DNA-based testing for CF carrier detection is one of the most frequently ordered molecular genetic tests.[14,15] Third, the multiple indications for testing include issues related to both patient care (ie, diagnosis of symptomatic persons and newborn screening to facilitate early diagnosis and treatment) and reproductive decision-making (carrier testing and prenatal testing). Fourth, the most prevalent disease-associated mutations are known and are amenable to laboratory analysis as a panel of mutations, as is the case for many other molecular genetic tests.[16] Fifth, race/ethnicity, family history, and test method are important factors in determining the mutation detection rate and calculating residual risk when no mutations are identified. Sixth, in CF as for many other disorders, genotype-phenotype correlations are not sufficiently established to make accurate predictions of disease severity based on molecular genetic test results.

Materials and Methods

The study was guided by an advisory group identified in the Acknowledgments section. Participants in the study including laboratory directors, clinicians, and other professionals, were assured confidentiality, and that only aggregate data would be reported. A laboratory practice survey was undertaken by Wadsworth Center, New York Department of Health. The second survey of OB-GYNs was developed and implemented under the direction of Mount Sinai School of Medicine under contract to Wadsworth Center, New York Department of Health, and approved by the institutional review board at the Mount Sinai School of Medicine.

Phase 1. Assessment of Test Requisition and Result Reporting Forms

Initial work was undertaken from mid-2003 to mid-2004. Laboratories offering DNA-based testing for CF were identified by: contacting those listed in the GeneTests database (*http://www.genetests.org*, accessed 2003) ($n = 70$ at that time); posting the opportunity to participate on the Association for Molecular Pathology listserv; and inviting participation by others who became known to the co-authors of the study. Laboratories were contacted and invited to submit their test requisition forms and to prepare reports for the simulated cases that had been developed in consultation with the advisory group (Table 1). Initially, 32 laboratories responded but only 26 provided a complete response consisting of test requisition forms populated with information presented in the case scenarios and test result reports based on the case scenarios and a mock test result. The content and format of these requisition forms and result reports were analyzed by several of the co-authors; findings are presented here as aggregate data.

Laboratory Practices Survey

A laboratory practice survey was sent to participating laboratories in mid-2004 (a copy of the survey is available

Table 1. Clinical Case Scenarios

Carrier test scenarios
Case 1: Georgia P. is a 22-year-old primigravida at ~8 weeks in the office for her first prenatal visit. She reveals that her maternal uncle had cystic fibrosis and passed away from pulmonary complications at the age of 30. Her grandparents are both deceased. Both of Georgia's parents are of African-American origin. The CF carrier screen for Georgia on the standard panel reveals no mutation found.
Case 2: Carol C. is a 36-year-old primigravida at 10-weeks gestation by dates and physical exam. She is Caucasian, of Cajun descent, and her husband is Caucasian of Scottish descent. She denies a family history of cystic fibrosis or any genetic conditions for her family, yet is uncertain of her husband's family. She requests carrier testing for CF when offered. Her test results reveal no mutation found.
Diagnostic test scenarios
Case 1: Tom E. is a 3-month-old Caucasian male who was delivered vaginally. He is breastfed and has demonstrated poor weight gain, with frequent, loose stools and his mother states that he is "gassy" and irritable and "always hungry." He was hospitalized with pneumonia at 1 month of age and an upper respiratory infection (URI) at 2 months of age. As part of the diagnostic process, sweat testing revealed an elevated value at 80 mmol/L sweat chloride. The test was repeated on a separate occasion (75 mmol/L) and the DNA-based test for CF was ordered at the same time. The results indicate that Tom has two copies of F508del.
Case 2: A 9-month-old Hispanic boy, Bobby, is noted to be falling off his growth curve for weight during the past two health maintenance visits. Bobby's parents, Maria (24 years old) and Julio (26 years old), are both of Hispanic descent. Bobby has had a series of respiratory infections with intermittent diarrhea and chronic wheezing. His mother now reports that he has begun to have foul smelling bulky stools. Laboratory tests reveal a normal CBC and urinalysis; however, sweat testing reveals a positive test result (61 mmol/L sweat chloride, 65 mmol/L repeat). The results of CF diagnostic testing show that Bobby has one copy of the 3849 + 10 kb C > T mutation within the CFTR gene. No prenatal carrier testing was performed on the parents.

from the corresponding author). The survey queried the laboratories about several issues including number of tests performed, who ordered the test, handling of information missing from the requisition form, and personnel responsibilities. Of the 26 laboratories that participated in the ordering and reporting activities of the project, 24 responded to the practice survey.

Phase 2. OB-GYN Physician Survey

In October 2005, a pilot study surveyed OB-GYNs in New York City to collect data relevant to office practices (ie, which staff ordered tests and reviewed test results) and satisfaction with the interpretation section of the test result report. To gauge physician satisfaction, excerpts from laboratory test reports received from phase 1 of this study were provided to OB-GYNs participating in the survey. They were asked to score their perception of satisfaction using a Likert scale from 1 to 5 with a score of 5 being an indication of a high level of satisfaction. Of the 200 surveys sent, 84 (42%) were completed and returned.

Results

Participating Laboratories

The 26 participating laboratories varied in setting and location. Of these, seventeen laboratories were located in universities or medical schools, seven were independent clinical laboratories, and two did not associate themselves with either of these settings. Laboratories were dispersed geographically with the greatest concentration (14 laboratories) located within states bordering the east coast. Three laboratories were located within states bordering the west coast and the remainder were located inland. All laboratories used mutation analysis of a panel comprising common mutations in their standard test offering. No reports were received indicating use of sequence analysis or mutation scanning assays. All 26 laboratories provided carrier testing for CF; 25 laboratories provided diagnostic testing for CF.

Test Requisition Forms

Requisition forms used by the laboratories varied in both complexity and the information requested. Seventeen laboratories used a form developed specifically for the ordering of molecular genetic tests that included CF testing as a testing option. Seven laboratories used forms specific for CF testing. The remaining two laboratories used requisition forms containing a large menu of tests that encompassed molecular pathology, clinical chemistry, and other types of tests. The evaluation was limited to paper forms; electronic requisition processes were not evaluated in this study.

Table 2 summarizes elements requested on the requisition forms. Formats varied, particularly in the manner in which family history and race/ethnicity information was requested. Requisitions provided between 3 and 11 choices for race/ethnicity (eg, Caucasian, African-American, Hispanic, and so forth) and/or an open field. The majority provided an open field for family history information. Eight of these forms requested a pedigree; however, no guidance was provided for pedigree construction.

Table 2. Information Requested on Requisitions

Inquiry from requisition	Number of laboratories (n = 26 laboratories)
Is test diagnostic or for carrier screening?	17 (65%)
Is patient affected?	10 (38%)
Is test for a fetus?	16 (62%)
What clinical symptoms are observed?	6 (23%)
Is there a family history?	20 (77%)
What family member is affected?	16 (62%)
What is the family-specific mutation?	8 (31%)
What is the patient's race/ethnicity?	26 (100%)

Laboratory Reports for Simulated Cases

Test result reports generated by participating laboratories were evaluated for format, content, and use of language. Reports typically were organized as follows: i) laboratory identifier, ii) patient/family information, iii) indication for testing, iv) result, v) interpretation, and vi) comments. We observed several features that potentially affect the communication of information. First, we noted that interpretation and comments were usually provided as short paragraphs of text. Second, not all reports included the indication for the test (73%, $n = 19$). Third, although all reports indicated the specific mutations tested, the nomenclature used for reporting mutations varied with most reports using common mutation names, eg, ΔF508 instead of or along with formal naming conventions (see *http://www.hgvs.org/rec.html*, accessed March 2008). Fourth, the language used to describe a finding of one or no mutations within diagnostic and carrier test reports varied. Descriptive language included use of the following terminology: "negative," diagnostic and carrier results; "no mutations found," diagnostic and carrier results; "positive for one copy," diagnostic test result results; "heterozygous," diagnostic test results; "carrier," diagnostic and carrier results. Two of twenty-six laboratories described the mechanism of inheritance for CF within their reports whereas the remaining 24 did not.

Interpretive comments for carrier testing were evaluated to determine how the residual carrier risk was conveyed in the simulated reports (Table 3). Two of the case studies were similar in that they reported negative findings (ie, no mutation was identified); however, the cases differed in that one had a positive family history of CF whereas the other did not. Findings that may affect the means by which information is communicated and understood included the following: first, residual risk was provided numerically by 24 of 26 laboratories. The remaining two laboratories provided a written explanation stating that the result indicated a reduced risk of having a disease-associated mutation. Second, 8 of 26 laboratories addressed the issue of the risk to the tested person of having an affected child; two provided numerical risk estimates taking into consideration variations associated with the partner's carrier status and race/ethnicity. Third, 23 of 26 laboratories noted the importance of family history in the test result interpretation. Fourth, 13 of 26 laboratories integrated information about the existence of an affected family member into their test result interpretation and 12 of these noted the benefit of knowing the family-specific mutation when family history was positive. Fifth, 21 laboratories provided the detection rate for their mutation panel for both simulated cases (one with a positive family history and one with a negative family history), whereas only 4 laboratories provided the mutation detection rate when the family history was negative. Sixth, recommendations for genetic counseling varied: 15 laboratories recommended genetic counseling for both carrier case scenarios, whereas only 8 provided such guidance for the simulated case in which the family history was positive.

Table 3. Information Provided in Carrier Test Reports

Information element	Number of laboratories ($n = 26$)
Numerical risk assessment for being a carrier	24 (92%)
Descriptive risk assessment for being a carrier	2 (8%)
Comment (nonnumerical) regarding risk for having an affected child	8 (31%)
Numerical risk for having an affected child	2 (8%)
Comment for usefulness of family history	23 (88%)
Included information about affected uncle	13 (50%)
Comment for usefulness of identifying family-specific mutation	12 (46%)
Detection rate (each laboratory, both case studies)	21 (81%)
Detection rate (each laboratory, only for report where family history exists)	4 (15%)
Genetic counseling (each laboratory, both case studies)	15 (58%)
Genetic counseling (each laboratory, only for report where family history exists	8 (31%)

In contrast to carrier tests, in which only one mutation is usually identified, CF mutation analysis for symptomatic patients seeks to identify two mutations in the tested person. Diagnostic test result reports were evaluated with respect to information provided pertinent to establishing a diagnosis (Table 4). Twenty-five laboratories provided mutation analysis for this purpose. Findings included the following. First, only 17 of 25 laboratories reporting heterozygous results noted within the report that the patient was symptomatic despite the fact that this had been indicated on all requisition forms returned to the laboratories. Of these 17, 7 specifically noted that the patient tested had a positive sweat test. Second, interpretation of test results varied, particularly with respect to the patient in whom only a single mutation was identified. Seventeen laboratory reports specified that the result was consistent with the diagnosis of CF and 16 commented that a second mutation had not been detected. Fifteen reports additionally noted that the test result establishes that the patient is at least a carrier. One report noted that the symptomatic patient could be a compound heterozygote for a known mutation and a rarer allele not included in the testing panel or, alternatively could be an unaffected carrier. Five reports provided no comment regarding the result and its implications for a diagnosis of CF. A single report specified that the patient was a carrier for a disease-associated mutation, but made no reference of the relevance of this finding to establishing the diagnosis of CF.

Some differences were apparent in the diagnostic test result reports for the simulated case with two mutations identified and the simulated case with one mutation identified. First, reports in which two mutations were identified all stated that the result was consistent with the diagnosis of CF. Second, in the case in which only one mutation was identified, 17 of 25 reports commented that the finding may be consistent with the diagnosis of CF. Nineteen specified the detection rate of the mutation panel used,

Table 4. Features of Homozygous and Heterozygous Test Result Reports

	Allele 1: delF508/delF508; allele 2: delF508/delF508; number of reports (n = 25)	Allele 1:3849 > 10 kb C > T; allele 2: no findings; number of reports (n = 25)
Note patient is symptomatic	25 (100%)	17 (68%)
Specify specific symptoms (ie, positive sweat test)	7 (28%)	7 (28%)
How does the report describe association with CF disease?		
States consistent with diagnosis	25 (100%)	17 (68%)
States consistent with clinical indications	12 (48%)	15 (60%)
States carrier status	n/a	15 (60%)
States second mutation not detected	n/a	16 (64%)
Does not comment	0 (0%)	5 (20%)
Is the detection rate provided?	7 (28%)	19 (76%)
Are limitations stated?		
Ethnicity/race	7 (28%)	20 (80%)
Family history	9 (36%)	7 (28%)
Mutation panel listed	25 (100%)	25 (100%)

whereas only seven reports provided this information when two mutations were identified. Third, race/ethnicity was mentioned in 20 of the reports for the patient with a single mutation identified and in 7 of the reports for the patient with two mutations identified. Fourth, other information provided appeared comparable between the reports based on the two diagnostic clinical simulations.

Laboratory Practices Survey

The 24 responding laboratories reported the following characteristics. First, laboratory settings varied: 62% (n = 15) were within hospital/academic settings, 29% (n = 7) were independent clinical laboratories, and 8% (n = 2) were in other settings that were not defined. Second, the number of DNA-based CF tests performed varied from <100 to >5000 per month. The mean laboratory number of tests performed was <500 samples per month; however, three laboratories reported testing volume >1000 samples per month. As an aggregate, 95% of the tests were performed for carrier testing. Third, ~25% of requisition forms received did not contain requested information essential for providing a comprehensive interpretation of the result, such as the indication for testing, race/ethnicity, and family history. Laboratories reported spending between 0.5 and 30 hours (mean, 6 hours; median, 3 hours) per month attempting to collect missing information among all CF requisitions received. We did not assess how successful laboratories were in this endeavor. Fourth, 79% (n = 19) of the laboratories indicated they track the mutations identified in their client population and 29% (n = 7) indicated they perform testing for additional mutations for some patient ethnicities. Fifth, 75% (n = 18) of laboratories indicated tests were ordered through paper requisitions as opposed to electronic submissions.

Laboratories also were queried as to who ordered the tests (Table 5). Differences were noted between ordering of carrier testing and diagnostic testing. Not surprisingly, physicians ordered the majority of tests. However, midwives, nurse practitioners, genetic counselors, and patients also ordered tests. Fifty-eight percent (n = 14) of the laboratories reported receiving requisitions for carrier testing from patients. The survey did not ask about the circumstances surrounding the ordering of tests by patients. These data do not discount the involvement of a physician or other medical professional in the test ordering process because the task may have been delegated to the patient within the context of a medical practice setting.

OB-GYN Survey

Of the 84 physicians responding: i) 81% (n = 68) worked in private sector settings and 19% (n = 16) were from academic settings; ii) the median time in practice for responding clinicians was 13 years (range, 4 to 55 years); iii) 77% (n = 65) offered CF testing in their practice and 94% (n = 79) take no further action when the test result is negative; and, iv) 92% (n = 52) recommend partner testing when the test result is positive. Responding physicians reported that several individuals within their practices were responsible for completing test requisitions, reviewing test results, communicating results to the patient, and providing follow-up recommendations to patients (Table 6). Most notably, 86% (n = 72) of the respondents indicated that secretaries communicated test results to the patient over the phone.

Using a Likert scale (1 to 5 with 5 expressing a high level of satisfaction), clinicians were asked to express their level of satisfaction with sample test reports and interpretive comments generated by the laboratories participating in the study (Table 7). Mean scores for the three

Table 5. Who Orders DNA-Based Tests for CF as Reported from the Laboratories?

	Number of laboratories (%): total laboratories surveyed (n = 24)	
Requester	Carrier testing	Diagnostic testing
Physician	23 (96%)	20 (83%)
Midwife	11 (46%)	2 (8%)
Counselor	20 (83%)	15 (62%)
Nurse practitioner	14 (58%)	7 (29%)
Patient	14 (58%)	0 (0%)

Table 6. Professional Roles: Ordering Tests and Receiving Result Reports in the OB-GYN Setting

	Responsibility (number of clinicians, %: total surveyed, n = 84)			
Title	Fills out requisition	Review results	Communicates results	Recommends additional testing
Physician	11 (13%)	7 (8%)	2 (2%)	13 (15%)
Nurse	23 (27%)	21 (25%)	4 (5%)	60 (71%)
Genetic counselor	0% (0%)	0 (0%)	6 (7%)	7 (9%)
Secretaries	37 (44%)	49 (59%)	72 (86%)	4 (5%)
Patient	9 (11%)	n/a	n/a	n/a
Others	4 (5%)	7 (8%)	n/a	n/a

questions regarding test ordering, were 3 or less. Mean scores for the interpretive component of reports, ranged from 1.2 to 3.6. However, in general, mean scores reflected a low level of satisfaction with the laboratory interpretations provided.

Discussion

Genetic testing is a rapidly evolving field that is being integrated into patient care in both primary and specialty care settings. Test selection and integrating results into patient management can be challenging for the physician and all persons tasked with using genetic tests and results for patient care. Effective communication between health care and laboratory service providers is crucial to this process. Effectively managing and applying genetic knowledge relevant to patient care, will certainly influence the practice of medicine in the near future.[17]

Genetic laboratory testing services are typically offered in specialty settings with staff that has expertise in genetics. Those directing or otherwise overseeing the operations of molecular genetic testing laboratories are often certified by either the American Board of Medical Genetics or hold a subspecialty certification in Molecular Genetic Pathology from the American Board of Pathologists.[18] Several professional and standards setting organizations including the American College of Medical Genetics, the Clinical and Laboratory Standards Institute, and the College of American Pathology have developed standards and guidelines to promote high quality in laboratory practice.[19–24] As such, services offered by genetic testing laboratories are likely equal or superior to other disciplines of laboratory medicine that have developed a similar professional support structure. However, analysis of the data reported herein suggests shortcomings in the communication of critical information pertinent to testing between the laboratory and clinical settings. In addition, technology has become available and at a cost amenable to laboratory settings that do not specialize in genetic testing and as a consequence, do not have onsite experts in molecular genetics. Nonetheless, in these instances, means must be found to assure that clients have access to expert consultation regarding questions about test ordering and the interpretation of test results.

This study focuses on present practice, particularly the pre- and postanalytic phases of testing, that rely on ex-

Table 7. OB-GYN Satisfaction with the Test Requisition and Report Interpretive Language

	Mean Likert scores, range 1 to 5 (5 represents strong satisfaction)*
Requisition statements	
Genetic test requisition forms are clear in noting which information is important to provide	2.1
It is important to provide requested family history for proper interpretation of the test result by the laboratory	3.0
It is important to provide the patient's ethnicity for proper interpretation of the test result by the laboratory	1.8
Satisfaction with interpretive language extracted from test reports	
Scenario 1: Carrier testing/no mutations found/no family history	
Interpretive comments	
A negative result reduces the risk of being a CF carrier from 1 in 25 to 1 in 250	3.2
Testing indicates a normal result for all 32 mutations analyzed. This does not rule out the possibility of being a carrier but does reduce the carrier risk	3.6
Based on the negative screening result, this couple is not at a high risk (<1 in 4) of having a baby born with cystic fibrosis.	2.4
Scenario 2: Carrier testing/no mutations found/affected uncle	
Using a Bayesian calculation and taking into account family history of an uncle affected with CF, the remaining carrier risk for this individual is 13.4%. This risk could be further modified if known CF carriers in the family are analyzed.	1.2
Based on the pedigree provided, this patient has an *a priori* risk of 25%. This testing reduces that risk by ~70% resulting in a residual risk of ~8%.	1.4
The test sensitivity in African-Americans is ~69% using this panel of mutations. This individual's carrier risk prior to testing was 1 in 3, and after a negative test, is estimated to be 1 in 75. Additional testing of a larger panel is available.	1.3

*Data from 84 surveys completed.

change of information between clinical and laboratory settings for test ordering and test result reporting. Our findings of the complexities associated with the test requisition form and processes that may affect proper ordering of tests are consistent with previous reports.[25] To interpret tests properly, laboratories must consider information such as the patient's clinical findings and family history, and the influence of race/ethnicity and test methods used in determining the mutation detection rate.[19,21] For instance, in the example of DNA-based carrier testing for CF, to provide an accurate residual carrier risk after no mutations are found on mutation analysis, the laboratory should consider both race/ethnicity and family history of the patient. Failure of the clinical setting to provide or the laboratory to collect this information compromises interpretation of the test result. In such cases, it may be essential for the laboratory to state this on their test result report. For example, when both race/ethnicity and family history are missing, a laboratory may state "The laboratory can only state that no CFTR mutation was detected using the (fill in blank) panel; because this panel does not detect all CFTR mutations, a non-zero risk remains that the patient is a CF carrier. The magnitude of the risk cannot be determined because neither race/ethnicity nor family history for this patient was provided." The consequences of not clearly communicating this limitation can potentially lead to errors in judgment regarding reproductive decision-making, a differential diagnosis, and risk to other family members of having a disease-associated mutation.

The use of common versus standard naming conventions for mutations may be confusing to both laboratories and clinicians in knowing when a given mutation is similar to or different from mutations described in literature references, professional guidance documents, and results from other laboratories. The Human Genome Variation Society (*http://www.hgvs.org*, accessed March 2008) is an international effort to develop and promote use of standard nomenclature for designating sequence variations, including mutations. Until such a standard becomes more broadly accepted and used, it may be best to include both the common and standard name of mutations in test result reports. This is recommended by an international guideline for quality assurance in molecular genetic testing developed under the auspices of the Organization for Economic Cooperation and Development and supported by the College of American Pathologists Checklist for Molecular Pathology that requires the use of standard nomenclature universally understandable to the genetics community.[23,26]

Requisition forms varied in the number of categories provided for race/ethnicity. This may be confusing to clinicians who may use multiple laboratories as a consequence of contractual arrangements of third party payers and other factors. Because calculation of residual risk can vary based on the mutation panel and source of data for the population prevalence used, it may be useful for laboratories to note in their reports the basis for their calculations; for instance, use of the American College of Obstetricians and Gynecologists/American College of Medical Genetics and revised American College of Medical Genetics guideline for CF.[13,27]

Requisition forms provided little or no guidance for the collection of family history information. Laboratories are positioned to emphasize the importance of family history by emphasizing its importance for interpretation of test results and as helpful in identifying other family members at increased risk for inheriting a disease-associated mutation. At this time, several excellent family history tools have been developed and it may be useful to refer clinicians to these.[28] In fact, the US Surgeon General's Office has launched a national public health campaign to encourage all families to learn more about their family history and has created a computerized tool for the collection of family health information (*http://www.hhs.gov/familyhistory/*, accessed March 2008). Looking to the future, it will be useful to explore how these tools can be adapted to the laboratory requisition process to simplify the collection and presentation of family history information for the purpose of test ordering.

Notably, laboratories reported a mean of 25% of requisitions received were missing information considered important for interpretation of the test result. For requisitions that list multiple tests, it may not be clear to the person filling out the form that specific information is applicable and important to provide. Such information may be more effectively collected by laboratories that use secondary forms specific to DNA-based testing for heritable conditions. A guided requisition process, either paper or electronic, may be helpful in addressing this shortcoming; laboratories already engaging in this practice should share their experiences broadly. In our study, 75% ($n = 20$) of the laboratories indicated their ordering was paper-based. However, electronic forms may be superior with regards to their capacity to provide prompts for both general and patient-specific information, along with explanations, when requested by the user. Although such systems are in place in several settings, primarily within integrated medical systems, developing and implementing such tools across a nonintegrated health care system poses a significant challenge.[29]

An important component of quality assurance is laboratory review of the test requisition to assure that the test ordered was consistent with the indication for testing and patient data provided.[19,21,30] Such a review can also assist the laboratory in applying an appropriate test method if more than one is available. For instance, in our study group, eight laboratories reported that they add race/ethnic-specific mutations to their test panel, based on information provided on the requisition form. With respect to this observation, it may be useful for laboratories to review how the presence and absence of information provided on the test requisition form influences the choice of test method and the interpretation of the test result. Such an exercise may be useful in identifying changes to the requisition form that may be useful for enhancing the collection of information by the laboratory from the health care setting. This may also present an opportunity for educating clients about the importance of providing key information on the laboratory requisition form.

In reviewing the features of test reports prepared by laboratories based on simulated clinical scenarios for carrier testing, none used the complete format from the model reports provided within the American College of Obstetricians and Gynecologists/American College of Medical Genetics guideline, although most used a similar format for patient identifiers, test result, interpretation, comments, and disclaimer.[13] It is important to recognize that this guideline was developed to specifically address carrier testing of persons before or during pregnancy and a comparable guideline for the diagnostic setting has not been put forward. From our data and those from a previous study, information content, nomenclature, and terminology varied on laboratory result reports.[7] Although the majority of mutation-negative carrier testing results from our simulated cases provided a numerical residual risk, discussion of the influence of race/ethnicity, family history, and other factors in deriving the residual risk varied. Considering these factors, it may be useful for professional groups to consider developing and adopting a uniform framework for the presentation of residual risk in carrier testing when the sensitivity of the test varies by test method used by the laboratory and the race/ethnicity of the person being tested. Reporting of uncertainties in a diagnostic test result also varied among laboratories. In the instance of detecting only one mutation in a symptomatic person, several test result reports commented on the person's carrier status with only 17 of 25 directly commenting on relevance to a diagnosis for CF. We also noted that few laboratories (2 of 26) specified the mechanism of inheritance for CF on their test result reports. Inclusion of this information may be useful for understanding the interpretation of the result when it can be associated in a meaningful way with a clinical context and/or pedigree analysis. In considering these factors, a critical issue to address within the interpretation is the relationship of the test result to the reason for testing in terms of the patient's clinical findings and the family history.

We found that recommendations for follow-up provided on the simulated test reports varied. Many of the reports reviewed did not have a recommendation for genetic counseling. In reviewing several of the professional guidance documents, it was apparent that the recommendation for genetic counseling is strongly recommended when test results can influence health care and/or personal/family decision-making (eg, reproductive decision making).[13,19,21–23] For instance, genetic counseling should be recommended for a test result that establishes a person as a carrier for a CF-associated mutation. However, a laboratory may choose not to provide a recommendation for genetic counseling to an asymptomatic individual of known race/ethnicity and no family history of CF when no CF associated mutations are detected because these results are not expected to have an impact on reproductive decision making. We also noted that most of the reports providing a recommendation for genetic counseling gave little or no context for its usefulness raising the question as to whether an unsubstantiated recommendation for genetic counseling discourages its use.

Where can clinicians seek help when they have questions about the test or result? Less than half of the laboratories submitted reports with a recommendation for contacting the laboratory for additional consultation. We did not investigate the level of assistance otherwise available from the laboratory but recognize that this varies with some laboratories having extensive on-line and written resources. However, no reports explicitly mentioned the availability of public resources such as GeneTests (*http://www.genetests.org*, accessed March 2008), which is a publicly funded medical genetics information resource that provides authoritative information on genetic testing.[6] Inclusion and emphasis within the test report for the role of genetic counseling and availability of information resources may be useful to the clinician for informing their patient care decisions.

In addition to identifying concerns about the user-friendliness of test requisition forms and capacity of the result report to inform clinical decision-making, the results of the OB-GYN pilot survey revealed a broad range of personnel in the clinical setting tasked with responsibility for ordering tests, reviewing results, communicating the test results to patients, and making recommendations for follow-up testing. Consistent with this observation, the laboratory practice survey indicated that test requisitions were received from persons with varying roles in the clinical setting. It was noteworthy that the OB-GYNs identified secretaries among those tasked with these responsibilities, and to a significant extent. This observation raises concerns about personnel competency, and particularly of those lacking formal medical training, with regard to tasks that affect medical management and patient understanding. Certainly, the quality of care is a reflection of the competency of all involved in the genetic testing process.

It is important to consider to what extent the data presented in this study are valid, can be generalized, and are free from bias. Although data were collected from 2003 to 2005, it is unlikely that practices have changed substantively, particularly because no concerted large-scale efforts have been undertaken to address the issues raised in the study reported. The number of laboratories participating was low considering that ~70 laboratories offering CF testing were listed in the GeneTests directory at the time of the study. Because participation in the GeneTests Laboratory Directory is voluntary, the number of laboratories offering DNA-based CF testing is likely higher than the number listed. Nonetheless, participating laboratories represented a cross section of large to small laboratories that varied geographically. We would argue that participating laboratories were motivated, in part, to contribute to improvement in the quality of genetic testing and as such may represent those seeking to provide higher quality services. Nonetheless, whereas the data are indicative of contemporary practices, they cannot be construed to specify the extent to which the population of laboratories within the US exhibits a similar distribution of practices. The pilot survey of OB-GYNs, on the other hand, was geographically restricted and is biased in this regard. The 44% response rate, although lower than desired, is similar to what is typically reported for physician surveys.[31] A broader national survey is underway to determine whether findings reported herein can be corroborated and whether demographic or practice relation-

ships might exist. Because OB-GYNs primarily order carrier tests for their patients, comparable data for the diagnostic setting are lacking. An assessment of pediatric practices relevant to test ordering and result reporting may address this gap.

In this study, we have identified variations in practice that affect the content and quality of information made available to laboratories and clinicians and likely affect patient management and outcomes. To improve communication between the genetic testing laboratories and clinicians, we have identified several areas for further efforts: making existing guidelines more specific regarding content and process of communication of clinically relevant information and concepts, and exploring ways to increase the competency of all staff working in clinical settings regarding ordering of genetic tests and understanding of test results.

In moving forward, it is likely that electronic clinical decision support systems will become increasingly important for managing and updating knowledge, improving practitioner performance and patient outcomes. A systematic review by Garg and colleagues[32] of such systems noted that whereas data show such systems can improve practitioner performance, far less data are available relevant to the effect of such systems on patient outcomes and this remains a challenge as this field evolves. In addressing these issues, it is critical that both the clinical and laboratory settings continue to work together and evaluate outcomes from evolving practices. There has been some work undertaken in this regard. In studies related to coagulation testing, physicians reported the presence of a patient-specific interpretive narrative improved the usefulness of the test report.[33] Another strategy has been the use of a synoptic reporting framework that uses standardized fields in the reporting of clinically relevant information.[34,35] In a key study, Hammond and Flinner[34] implemented such a process to improve communication between surgical oncologists and pathologists and demonstrated process improvement. We propose that developing such a framework for reporting results should be evidence-based, outcome-oriented, and evaluated in terms of the capacity to benefit clinical decision making. Indeed, until this is accomplished it is likely that actual practice will rely on a combination of professional guidance, expert opinion, personal experience, and preferences of which examples exist in the peer-reviewed literature.[36] In this regard, we have completed a follow-up study that elicited feedback from the clinical community useful for the development of model genetic test reports that promote the communication of clinically relevant information and amenable to a synoptic reporting framework. We anticipate that integrating such a framework into practice will improve the quality of patient care by assisting clinicians in ordering the correct tests and appropriately integrating the test result into health care management, and will improve laboratory performance by reducing the time personnel take to recover essential information missing from test requisition forms and promoting effective communication between laboratory professionals and health care providers.

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