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eLITERATURE REVIEW
eCysticFibrosis Review
Presented by The Johns Hopkins University School of Medicine, The Institute of Johns Hopkins Nursing and the Postgraduate Institute for Medicine
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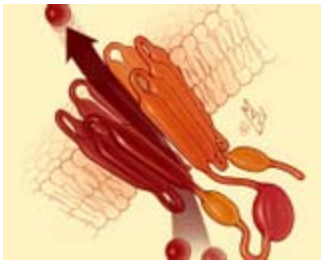

September 2008: VOLUME 1, NUMBER 3

How to Interpret Genetic Tests for Cystic Fibrosis

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In this Issue...

Although caring for patients with cystic fibrosis (CF) has changed significantly in the past few years, one of the strongest emerging trends is the increasing use of molecular testing in all aspects of patient management. While sweat chloride measurement remains the gold standard for diagnosis, many clinicians now consider molecular testing a helpful tool for confirming or excluding the diagnosis of CF, especially in patients with an atypical clinical presentation. This shift has been accompanied by a change in referrals for molecular testing from geneticists to caregivers in specialty CF centers and, more recently, to pediatricians and internists. The latter is likely the consequence of newborn screening and the identification of adults with mild forms of CF. Since most affected individuals now receive molecular testing, it is tempting to turn to genotype for prognostic predictions. Although helpful for depicting some aspects of the phenotype in general terms, patient-specific, comprehensive clinical predictions based on cystic fibrosis transmembrane conductance regulator (*CFTR*) genotype are limited. In this issue, we review recent publications that demonstrate that genetic testing for CF achieves maximum utility when it is interpreted and reported with a full assessment of the clinical implications of the genotype (as known), the test sensitivity, and any residual risk for a *CFTR* mutation in the patient.

THIS ISSUE

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Guest Faculty Disclosures

Garry R. Cutting, MD has disclosed that he receives royalties from licenses involving CF mutations.

Barbara Karczeski, MS has disclosed no relationship with commercial supporters.

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The authors have indicated that there will be references to unlabeled or unapproved uses of drugs or products in this presentation.

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At the conclusion of this activity, participants should be able to:

Newsletter:

- Discuss the role of genetic testing in the diagnosis of cystic fibrosis (CF)
- Identify the clinical context in which genetic testing is most useful
- Describe the limitations of genetic testing for CF

Podcast:

- Outline the important aspects of transmitting genetic information to patients and families
- Explain why some mutations cause disease and some do not
- Summarize the similarities and differences in the use of genetic testing in population and new born CF screening

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COMMENTARY

Genetic testing for cystic fibrosis (CF) became available shortly after the identification of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene 20 years ago. Testing of patients with CF in North America and Europe revealed that one common mutation called ΔF508 and about 15 to 20 less common mutations accounted for approximately 85% of the mutations in Caucasian populations. Over the ensuing years, it was recognized that there are more than 1500 other mutations in the *CFTR* gene, almost all of which are rare. Consequently, minimal clinical information is available on the rare mutations to determine whether they in fact cause disease.

As discussed in the article by Lebo and Grody, CF testing for screening purposes has been restricted to the panel of 23 “common” mutations recommended by the American College of Medical Genetics (ACMG). The availability of methods for analyzing the working parts of the *CFTR* gene (ie, exons) in clinical laboratories enables detection of many of the rare mutations. The article by Kammesheidt and colleagues shows how methods for scanning the *CFTR* gene can be used in CF patients in whom the detection rate for the ACMG-approved panel of mutations is low. However, as noted in the Kammesheidt paper, the disease-causing potential of some of the mutations found in a comprehensive scan cannot be determined. For this reason, as noted in the worldwide consensus statement by Castellani and colleagues, scanning or sequencing of the *CFTR* gene should be restricted to individuals with a diagnosis of CF, so that identified mutations can be interpreted in the clinical context. Indeed, Southern and coworkers indicated that use of genetic information is appropriate in CF newborn screening when mutation information has a high predictive value for disease potential. This issue was investigated in detail by Scotet and associates with respect to R117H, the second most common CFTR mutation. The R117H mutation presents a particular diagnostic problem because it occurs with different versions of a variant, called 5T and 7T, elsewhere in the *CFTR* gene. The combination of R117H paired with 5T causes CF, whereas R117H paired with 7T has been associated with a wide range of phenotypes, including CF, male infertility, pancreatitis, and normal. The interpretative complications associated with R117H led Scotet and coworkers to propose that the R117H mutation should not be included in CF newborn screening testing. In areas of the world in which R117H is not common, one could argue that it may be reasonable to exclude this mutation. However, in populations in which R117H is more common (ie, the United States), the elimination of R117H would cause a reduction in test sensitivity that may negate the gain in test simplification.

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The final paper in the review by McKone and colleagues addresses the use of *CFTR* mutation information for prognostic purposes. The *CFTR* genotype is predictive of pancreatic status (eg, pancreatic insufficiency vs pancreatic sufficiency) but is not useful for predicting pulmonary status—the major cause of morbidity and mortality in patients with CF. Interestingly, McKone and associates showed that the *CFTR* genotype is predictive of survival in patients with CF, specifically beyond 30 years of age. Although additional research is needed, the McKone study hints that testing of the *CFTR* gene and, more likely, of CF gene modifiers, will provide useful prognostic information for patients with CF and their families.

DELIVERY OF GENETIC TESTS FOR CYSTIC FIBROSIS

Lebo RV, Grody, WW. **Testing and reporting ACMG cystic fibrosis mutation panel results.** *Genet Test.* 2007;11(1):11-31.

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Kammesheidt A, Kharrazi M, Graham S, et al. **Comprehensive genetic analysis of the cystic fibrosis transmembrane conductance regulator from dried blood specimens–implications for newborn screening.** *Genet Med.* 2006;8(9):557-562.

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Lebo and Grody consider “the optimal submission of patient samples”, with a focus on testing and reporting using the American College of Medical Genetics minimum mutation panel. A review of reports generated in the clinical experience of the authors serves as the basis for suggesting the reporting of prototypes, with the guiding principle being to provide clinicians with the most informative results possible while still respecting Health Insurance Portability and Accountability Act (HIPAA) medical privacy regulations. Kammesheidt and colleagues consider whether comprehensive cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation identification is possible on dried blood specimens, with the aim being to use this expanded assay in the setting of newborn screening, especially in non-Northern European populations. The investigators obtained 42 archived blood spot specimens from patients with a clinical diagnosis of cystic fibrosis (CF) and performed a mutation scanning technique (temporal temperature gradient gel electrophoresis, followed by bidirectional sequencing of abnormal segments). Patients who did not have 2 identified mutations underwent *CFTR* deletion analysis.

Lebo and Grody begin with a very focused test (a 23-mutation panel) and try to ensure that it is applicable to the broadest possible patient population. They provide template reports for various clinical situations and risk tables for clinicians to use in assessing test sensitivity and residual risks for a specific patient’s ethnicity and clinical status. Of particular note for the clinician, the risk analysis is provided in Tables 6A and 6B of the article (as below).

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Table 6A: After-Test Risks: Negative Test Results on Suspected CF Patients Without Factoring in Clinical Phenotype

Ethnic origin	*Carrier risk before testing*[d]	*Percent total mutations detected*	*Percent affected, 2 mutations detected*	*Percent affected, 1 mutation detected*	*% Affected patient tests negative*	*Likelihood normal patient tests negative*	*Likelihood normal result in normal vs. affected patient*
Northern European Caucasian[a]	1/29 (3.4%)	90%	(81%)	(18%)	(1%)	(96.9%)	97:1
U.S. Caucasian origin unspecified	1/29 (3.4%)	80%	(64%)	(32%)	(4%)	(97.2%)	24:1
Ashkenazi Jewish	1/29 (3.4%)	97%	(94%)	(5.8%)	(0.09%)	(96.7%)	1074:1
Southern European Caucasian[a]	1/29 (3.4%)	72%	(52%)	(40%)	(7.8%)	(97.5%)	13:1
African American	1/65 (1.5%)	69%	(48%)	(43%)	(10%)	(98.9%)	9.9:1
Asian American	1/90 (1.1%)	25%[b]	(6%)[b]	(38%)[b]	(56%)[b]	(99.7%)	1.8:1[b]
Hispanic American[c]	1/46 (2.2%)	57%	(32%)	(49%)	(18%)	(98.8%)	5.5:1

[a]Northern Europe includes the Alps: southern Europe is south of the Alps.
[b]Estimated value. On the one hand, no CF mutations were found in 900 asymptomatic Asians tested in Great Britain (Curtis *et al.* 1993), whereas the standard panel of 23 mutations characterized 4 of 16 mutations (25%) in 8 Asians tested by one American laboratory (Heim *et al.* 2001).
[c]Unless the frequencies from a specific population have been determined, Hispanic risks can be derived most accurately from the proportion of ancestral genes derived from Spain (southern European frequencies), African American, and/or Native American (Asian American frequencies).
[d]this is the likelihood of detecting a mutation in a randomly selected population being screened for cystic fibrosis.

Table 6B: Test Detected One Mutation in Suspected CF Patient: After-Test Risks Without Factoring in Clinical Phenotype

Ethnic origin	Carrier risk before testing	Percent total mutations detected	Percent affected, 2 mutations detected	Percent affected, 1 mutation detected	% Affected patient tests negative	Likelihood 1 mutation detected in random normal patient	Likelihood 1 mutation detected in affected vs. random patient
Northern European Caucasian[a]	1/29 (3.4%)	90%	(81%)	(18%)	(1%)	3.1%	6:1
U.S. Caucasian origin unspecified	1/29 (3.4%)	80%	(64%)	(32%)	(4%)	2.7%	12:1
Ashkenazi Jewish	1/29 (3.4%)	97%	(94%)	(5.8%)	(0.9%)	3.3%	2:1
Southern European Caucasian[a]	1/29 (3.4%)	72%	(52%)	(40%)	(7.8%)	2.5%	16:1
African American	1/65 (1.5%)	69%	(48%)	(43%)	(10%)	1.1%	41:1
Asian American	1/90 (1.1%)	25%[b]	(6%)[b]	(38%)[b]	(56%)[b]	0.28%	136:1[b]
Hispanic American	1/46 (2.2%)	57%	(32%)	(49%) 1/2	(18%)	1.2%	40:1

[a]Northern Europe includes the Alps: southern Europe is south of the Alps.
[b]Estimated value. On the one hand, no CF mutations were found in 900 asymptomatic Asians tested in Great Britain (Curtis *et al.* 1993), whereas the standard panel of 23 mutations characterized 4 of 16 mutations (25%) in 8 Asians tested by one American laboratory (Heim *et al.* 2001).

Using mutation frequency data alone, the authors demonstrate that the risk for having CF after a negative genetic test is 1 in 98 (Table 6A, Caucasian), whereas the likelihood of having CF if 1 mutation is detected is 1 in 7 (Table 6B, Caucasian). Kammesheidt and coworkers begin with a broader focus (a mutation identification test that could reveal many types of changes in the gene) and investigate its potential application to a more narrow patient population. They report the identification of 2 (or even 3) mutations in each of the 40 patients tested, who were mostly of Hispanic ancestry. The sensitivity of their method is significantly higher than that expected in panel-based mutation tests in this ethnic population.

Although choosing the most appropriate test for a particular patient is the responsibility of the referring physician, the laboratory is responsible for selecting the best technical platforms and for developing the most useful clinical tests. Designing tests for the detection of CF is complicated by the high number of mutations, the effect of patient ethnicity on test sensitivity, and the clinical variability of CF or a *CFTR*-related phenotype. Lebo and Grody underscore the importance of referrers providing the laboratory with sufficient information, prior to testing, regarding the reason for testing and the patient's ethnicity. This information is essential in calculating test sensitivity and the residual risk for the patient having an undetected mutation. Residual risk is a concept foreign to most families, and prudent counseling regarding the test results is essential for ensuring that the patient leaves the clinician's office knowing that a negative test does not totally negate the chance that the patient might have a *CFTR* mutation.

The Kammesheidt study highlights the utility of mutation scanning or gene sequencing in a population in whom panel-based testing lacks a high enough sensitivity to provide a diagnostic answer, and also poses 2 challenges faced by laboratories that offer CF testing. First, interpretation of novel sequence variations is exceedingly difficult in a clinical setting. Currently, there are no reliable functional assays for these variants, and bioinformatic tools, although helpful, often fall short of providing overwhelming evidence of disease association. Second, the authors underscore the need for family studies to confirm that 2 mutations are on opposite alleles. This is often a challenge for laboratories, as well as for referrers, in an age of limited health care resources. Unfortunately, several essential elements are missing from this study that would be necessary to judge such an approach feasible in the setting of newborn screening for CF. First, the authors used proprietary methods in their study; therefore, independent replication of test performance is not

possible. Second, although they reported a 100% mutation identification success rate, they failed to include the 2 patients for whom the blood spot sample was inadequate to complete testing—an almost 5% failure rate. Third, although the authors demonstrate 100% sensitivity, this method would entail a sacrifice in specificity (when variants of unknown clinical significance are detected in populations for whom the full spectrum of disease-associated mutations has not been described), and an uncertain diagnosis would only serve to heighten family anxiety. Fourth, the investigators acknowledge that they do not know the impact their protocol would have on the financial viability of newborn screening programs. The latter is a critical issue, as screening is predicated on achieving acceptable sensitivity rates in a cost-effective manner.

References

1. Curtis A, Richardson RJ, Boohene J, Jackson A, Nelson R, Bhattacharya SS (1993) Absence of cystic fibrosis mutations in a large Asian population sample and occurrence of a homozygous S549N in an inbred Pakistani family. *J Med Genet* 30:164–166.
2. Heim RA, Sugarman EA, Allitto BA. Improved detection of cystic fibrosis mutations in the heterogeneous U.S. population using an expanded, pan-ethnic mutation panel. *Genet Med.* 2001 May-Jun;3(3):168-176.

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USE OF GENETIC TESTS FOR THE DIAGNOSIS OF CYSTIC FIBROSIS

Castellani C, Cuppens H, Macek M Jr, et al. **Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice.** *J Cyst Fibros.* 2008;7(3):179-196.

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Castellani and colleagues present a consensus statement on “the use and interpretation of cystic fibrosis (CF) mutation analysis in clinical settings,” to serve as a guide for clinicians integrating these test results into their practice. The consensus statement, the result of a 2007 international conference organized by the European Working Group on Cystic Fibrosis Genetics, addresses both technical and clinical aspects of CF testing.

The statement covers aspects of CF testing from quality control and mutation nomenclature to the recommended report format, with several sections of particular interest to clinicians ordering and integrating molecular CF results into clinical care. Specifically, the emphasis of the consensus statement is to place molecular testing for CF within the context of the clinical situation in which testing is being considered. Molecular testing is not necessary to establish a diagnosis of CF; however, it may be extremely helpful if a patient lacks a definitive phenotypic presentation. Mutation identification is also the only way to facilitate carrier testing for relatives and prenatal diagnosis for parents. The appropriate molecular test may vary based on whether classic or nonclassic CF is suspected, and on the ethnicity of the patient. Cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation panels, mutation scanning, and mutation sequencing have differing strengths and weaknesses, and choice of CF testing should be specific to the clinical context. This report emphasizes that testing may not provide definitive diagnostic information because some mutations in *CFTR* do not cause CF but result instead in a *CFTR*-related disorder, and many rare mutations have unknown or unproven clinical relevance. In addition, it is noted that genotype is not a reliable predictor of patient-specific prognosis. This information may be useful in providing guidance on the likelihood of pancreatic insufficiency, but it is not helpful in predicting the severity of lung disease.

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Although the consensus statement outlines guidelines for ordering and interpreting molecular tests for CF, the reality is that many of these elements are usually omitted, rendering the job of both the clinician and the laboratory more difficult. Practicalities of today's health care system mean that the ordering physician is often several steps removed from the testing laboratory, thus hampering communication efforts. Uncertain findings often muddy the clinical picture instead of clarifying it; therefore, molecular testing for CF in the diagnostic setting is a valuable tool, but "mutation analysis is not the answer to every diagnostic dilemma."

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GENETIC TESTING AND NEWBORN SCREENING

Southern KW, Munck A, Pollitt R, et al; ECFS CF Neonatal Screening Working Group. **A survey of newborn screening for cystic fibrosis in Europe.** *J Cyst Fibros.* 2007;6 (1):57-65.

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Scotet V, Audrézet M-P, Roussey M, et al. **Immunoreactive trypsin/DNA newborn screening for cystic fibrosis: should the R117H variant be included in *CFTR* mutation panels?** *Pediatrics.* 2006;118(5): e1523-e1529.

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Southern and colleagues provide an overview of the cystic fibrosis newborn screening (NBS) programs in operation throughout Europe. Data were collected via questionnaires, with all 26 known programs responding. Programs provided information on testing protocols, quality control, follow-up procedures, and epidemiology. Scotet and coworkers report on the French NBS screening program, which is the largest in Europe. With the belief that "it is of the utmost importance that only mutations that result in classical cystic fibrosis are included in" newborn screening, Scotet and associates assessed the clinical outcomes of children with R117H, a cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation associated with a variable phenotype, to ascertain whether it is an appropriate mutation to include in NBS molecular testing panels. They reviewed NBS records to estimate the frequency of R117H in screen-positive infants and obtained clinical follow-up data.

Currently, of the 26 NBS programs for cystic fibrosis (CF) in Europe, only 7 countries are represented. All of the programs use immunoreactive trypsinogen levels as the first-tier analysis, although subsequent testing tiers (from 2 through 4, in some laboratories) vary significantly. Of the 26 different laboratories, 21 use molecular testing as a second- or third-tier test, and typically attempt to detect the 30 most common *CFTR* mutations reported in patients with CF. As evidence for amending the mutations included in the NBS panel, the French group identified 7.3% of screen-positive patients who were compound heterozygotes for R117H and another *CFTR* mutation. These children (mean age, 7 years at the time of the study) were healthy, and none had developed symptoms consistent with classic CF.

Although DNA analysis is integral to most NBS programs and indeed correlates with an earlier age at diagnosis in screened children (Southern), measurement of sweat chloride concentration remains the gold standard of diagnostic testing for CF. Rather than the molecular evidence of dysfunctional CFTR protein, sweat testing provides direct physiologic proof of dysfunction. Southern and colleagues theorize that this level of proof helps parents come to terms with the reality of a CF diagnosis. Along this vein, the NBS survey highlights a disturbing finding: although most screen-positive children are referred for specialist care, only 21 of 26 programs refer families for genetic counseling. The focus of NBS programs should be the families they aim to assist. Indeed, one of the goals of NBS is to avoid "a long and stressful diagnostic journey" for families (Southern). In this context, inclusion of the *CFTR* mutation R117H represents a model NBS pitfall, prompting Scotet and coworkers to argue that R117H does not meet inclusion criteria for NBS: although frequently identified, R117H-7T does not cause classic CF. Because of its questionable phenotypic consequence, the finding of R117H in a screen-positive child

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presents a stressful situation for both family and referrer. Scotet and associates reasonably argue that R117H should therefore be withdrawn from test panels used in NBS. However, R117H with the 5T variant can cause classic CF and accounts for approximately 0.7% of CF alleles. Population carrier screening panels for CF in the United States have dealt with this issue by reflex testing R117H-positive patients for the 5T variant, which might be an option for NBS. Southern and coworkers concluded that that there is no perfect NBS program, nor will there be, secondary to the heterogeneous nature of both the disease and the patient populations served, as well as constraints of geography and infrastructure. The well-constructed NBS program for CF addresses the "complicated clinical interface between the screening program and the eventual clinical diagnosis" (Southern) through clear protocols, tight quality control, and well-defined follow-up and referral procedures.

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CFTR GENOTYPE AND PROGNOSIS

McKone EF, Goss CH, Aitken ML. **CFTR genotype as a predictor of prognosis in cystic fibrosis.** *Chest.* 2006;130(5):1441-1447.

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McKone and colleagues sought to assess the effect of the cystic fibrosis transmembrane conductance regulator (*CFTR*) genotype on prognosis (as measured by survival) and to determine whether the genotype might be acting through specific phenoptypic parameters. They conducted a retrospective review of more than 15,000 patients in the Cystic Fibrosis Foundation patient registry with known and classifiable (by CF mutation classes I through V) genotypes. Patients were stratified into high-risk (at least 1 mutation from Classes I through III, in which no functional protein is predicted) and low-risk (both mutations from Classes IV or V, in which residual protein function is expected) groups. The authors assessed all-cause mortality during the 10-year period from 1993 through 2002).

A total of 1672 deaths were reported in the cohort over the review period. Mortality was 2.25 times more likely in the high-risk vs low-risk mutation group. Median survival for patients with a high-risk genotype was 36.3 years, vs 50.0 years for those with a low-risk genotype. Of the phenotypic characteristics assessed, lung function, body mass index, and pancreatic sufficiency had the greatest effect on survival, but these alone were not sufficient to explain the difference in survival across the 2 groups. *CFTR* genotype was independently able to predict survival, with the highest positive predictive value and negative predictive value at a cutoff of 30 years at age of death.

The authors concluded that there was a significant difference between the high-risk and low-risk groups in survival and age at death, and that genotype alone could provide some prognostic information, especially in low-risk groups. Although many practitioners are interested in genotype-phenotype information, past approaches have examined the effect of genotype on phenotypic elements. The article presents interesting data that contribute to our understanding of the effects of genotype on the course of CF, but the information is less useful for patient counseling than the authors propose. Clear limitations to the study exist, which the authors address in their discussion. Specifically, they refer to the great range of variation in CF that seems to be independent of, or less dependent on, genotype: degree of medical compliance, genetic modifiers, and environmental and other nongenetic factors are not accounted for in this analysis. Ultimately, a binary system that predicts the likelihood of survival past 30 years of age is not likely to translate into a helpful tool for determining prognosis or counseling families. The development of a more complex algorithm that includes *CFTR* genotype, modifier gene genotype, and other nongenetic factors is needed to provide true prognostic information.

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- Discuss the role of genetic testing in the diagnosis of cystic fibrosis (CF)
- Identify the clinical context in which genetic testing is most useful
- Describe the limitations of genetic testing for CF

Podcast:

- Outline the important aspects of transmitting genetic information to patients and families
- Explain why some mutations cause disease and some do not
- Summarize the similarities and differences in the use of genetic testing in population and new born CF screening

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