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Original Article

Carrier screening for cystic fibrosis in US genetic testing laboratories: a survey of laboratory directors

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Initial guidelines for cystic fibrosis (CF) carrier screening were issued in 2001 by the American College of Medical Genetics and the American College of Obstetricians and Gynecologists and updated in 2004. It is unknown how these guidelines have influenced laboratory practice. This study examined the uptake of two components of these guidelines for CF screening in genetic testing laboratories. A survey of directors of US genetic testing laboratories was conducted. Of 190 respondents, 178 answered questions about CF testing. Nearly half (49%) performed some type of DNA testing for CF; most of these (92%) performed CF carrier screening. Ten percent used a 23-mutation panel for CF screening. The results of 5T tests were reported as a reflex test by 79% of laboratories, while 8% always returned 5T results and 7% never returned them. Seven percent of laboratories adopted both guidelines, 80% adopted one of the two guidelines, and 13% had not adopted either recommendation, suggesting that factors other than clinical guidelines may influence laboratories' CF screening practices. Further studies are needed to determine whether the adoption of CF screening guidelines has significant clinical or economic effects on population-based CF screening programs.

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Cystic fibrosis (CF) is one of the most common inherited disorders: 1 in 31 Americans carries a *CFTR* mutation (1), and 800 new cases were recorded in the United States CF registry in 2005 (2). More than 1300 disease-causing mutations have been identified in *CFTR* (3). In 1997, after assessing various CF screening modalities (4, 5), the National Institutes of Health (NIH) concluded that CF carrier screening should be offered to all couples planning a pregnancy or seeking prenatal testing but did not specify the mutations that should be tested (6). A 1998 survey found that 43 laboratories offering CF screening were assaying between 1 and 70 mutations, with a median of 13 (7).

In 2001, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) jointly issued guidelines to improve and standardize population-based CF carrier screening (8). According to the ACMG, these are 'guidelines for optimal laboratory testing, interpretation and counseling' (8) and 'are not to be interpreted as restrictive or the only approach' (9). They recommended using a minimum pan-ethnic panel of 25 CF mutations with additional reflex testing of 6 others contingent on the initial screen.

The 25-mutation panel was designed as a cost-effective screening tool to reduce the incidence of newborns with CF by detecting ~80% of disease-causing *CFTR* mutations in Caucasian Americans, 69% of mutations in Black non-Hispanic Americans, and 57% of mutations in Hispanic Americans (10, 11). The guidelines recognized that the mutation panel might be expanded to increase sensitivity in ethnically diverse patient

populations but recommended against routine use of expanded panels due to their low additional yield (8).

Included in the recommended panel of mutations was the R117H allele, which leads to CF when found in *cis* with five thymidines (referred to as the 5T allele) in intron 8 and in *trans* with another *CFTR* mutation. A 5T allele in intron 8 that is not in *cis* to R117H but is in *trans* with another *CFTR* mutation does not cause classic CF but has been associated with other phenotypes including congenital bilateral absence of the vas deferens (12, 13), pancreatitis (14), and atypical mild CF symptoms (15). Therefore, the guidelines recommend that prospective parents be screened for the 5T allele only as a 'reflex' after a R117H mutation has been identified (8, 16). Because the carrier frequency of the 5T allele in the general population is between 5% and 9% (1, 8), testing for the 5T allele in the initial CF screening panel might identify a large number of individuals not at risk of having a child with classic CF and could provoke unnecessary invasive prenatal testing (1, 8, 16).

In the year after the initial guidelines were issued, CF carrier screening increased by as much as fivefold in some large laboratories (17). Some laboratories routinely reported results of the 5T test in the absence of the R117H mutation (17, 18), resulting in some unnecessary prenatal testing (1). Laboratories continued to offer CF carrier screening panels with varying numbers of mutations. New tests for CF carrier screening for 32–200 mutations continued to be reported in the literature (19, 20).

In 2004, the ACMG guidelines were updated. Two mutations were removed from the panel leaving 23 mutations for carrier screening. The importance of testing for the 5T allele only as a reflex was also reiterated (21). The ACMG also considered the addition of six mutations to the panel that were discovered in frequencies $<0.1\%$ in CF patients. It was determined that the decision to add mutations should be 'focused on clinical utility' and that 'the incremental gain that would be achieved' by adding mutations should be weighed 'against the potential increase in cost and errors associated with the changes' (21). Based on these criteria and the available data, the mutations were not added.

While there has been some empirical research regarding the uptake of CF screening guidelines by healthcare providers (22, 23), there has been limited study of laboratories' adoption of the guidelines. A 2002 survey evaluated CF laboratory reports and concluded that the indication for testing should appear on all reports of 5T test results (24). Another study of one CF screening laboratory found that after the 2001 guidelines were issued, 46% of the prenatal CF tests performed as a result of positive parental screening occurred unnecessarily in situations where one or both parents carried a 5T allele but neither parent carried additional *CFTR* mutations (16).

To assess the influence of ACOG and ACMG guidelines on practices of laboratories performing CF carrier screening, we conducted a survey of directors of genetic testing laboratories in 2006. The survey aimed to define the types of CF testing being offered by US laboratories and the fraction of CF carrier screening programs that have adopted guidelines on the use of the 5T allele test and implemented the recommended minimum 23-mutation panel. The questions about CF testing were part of a comprehensive survey of genetic testing laboratory directors' practices and attitudes (25).

Materials and methods

Survey administration

In the absence of a comprehensive directory of US genetic testing laboratory directors, our search strategy for potential participants was designed to cast a wide net and capture as many genetic testing laboratory directors as possible. A total of 680 potential participants was identified using a set of laboratory directories that have been described elsewhere (25).

All 680 potential participants were mailed an initial invitation to participate in an online survey, followed several days later by an e-mail invitation. Up to eight periodic mail, e-mail, and phone call reminders were made to non-responders over a 3-month period.

A 65-question comprehensive survey, qualified by the Johns Hopkins University Institutional Review Board as exempt (application number NA_00001533), was developed to collect data on the current laboratory practices and opinions of molecular and biochemical genetic testing laboratory directors in the United States. Feedback from six genetic testing laboratory directors was collected in a pretest and incorporated into the final survey instrument. The comprehensive survey collected data about the laboratory setting, types of testing performed (molecular or biochemical or both; research or clinical or both), certification of the laboratory and its director, test volume, and menu.

Knowledge Networks, a survey research firm, fielded the web-based survey instrument from December 2005 through March 2006. The data

provided to the Genetics and Public Policy Center did not include respondents' identifying information. Participants were told that data would be reported only in aggregate and that analyses would not identify any particular laboratory or director. An incentive in the form of a $25 donation to one of four organizations (College of American Pathologists Foundation, ACMG Foundation, American Red Cross, or America's Second Harvest) was offered in exchange for participation.

To be eligible for the comprehensive survey, a potential participant had to identify himself or herself as the director of a molecular or biochemical testing laboratory that reports test results to patients or providers. Only directors of those laboratories conducting molecular genetic testing were asked questions about CF testing. Having identified CF testing laboratories, we then identified which laboratories perform carrier screening for CF and asked that the remaining questions be answered with respect to carrier screening practices.

Potential participants were excluded if they were not laboratory directors, were directors of laboratories that did not provide results, or were directors of laboratories that test only for paternity, identity, ancestry, cytogenetics, infectious diseases tissue typing, or newborn screening. Survey results pertaining to laboratory directors' attitudes and practices with respect to proficiency testing, certification, regulation under the Clinical Laboratory Improvement Act (CLIA), and the value of a genetic testing specialty have been published elsewhere (25). The survey questions used in this study can be found online at http://www.dnapolicy.org/resources/CF_Survey_Instrument.pdf.

Data analysis

We examined the relationship between laboratory characteristics and CF testing practices, including whether laboratories perform CF testing and for what purposes, how many mutations were tested as part of CF carrier screening, and under what circumstances they perform and report the results of the 5T test in intron 8 of *CFTR*.

Laboratory characteristics ascertained included the setting of the laboratory; whether the laboratory performed molecular tests, biochemical tests or both; whether genetic tests were performed for clinical or research purposes; the size of the test menu offered; the annual volume of tests performed; and the organizations that certify the laboratory. The total annual testing volume for each laboratory was estimated using responses to two questions that asked about the number of molecular and biochemical tests performed annually (25). The number of CF screening tests performed annually was not ascertained. Observations based on annual test volume should be interpreted with the understanding that they are estimates of laboratory volume.

To assess the relationship between laboratory characteristics and CF screening practices, general linear and logistic regression models were implemented using SAS version 9.1. Independent variables used in all regression models included all the laboratory characteristics described above.

Results

Of the 680 potential participants, 404 responded. Of the 404 respondents, 199 did not meet the eligibility requirements, while 190 were eligible and completed the survey. Fifteen additional eligible laboratory directors began the survey but did not complete it and were excluded from the analyses. We estimated the total number of eligible laboratory directors in our list of 680 potential participants by extrapolating the proportion of the 404 respondents who were eligible to the 276 nonrespondents (26). In this way, we estimated that 345 potential participants were eligible for the general survey, yielding a valid response rate of 190/345 or 55%.

Of 190 respondents, only the 180 (95%) laboratory directors whose laboratories perform molecular genetic tests were asked about their CF testing practices. Of these, 178 (99%) responded to questions about CF testing and were used for this analysis. Characteristics of these laboratories are found in Table 1.

Prevalence of CF testing

Nearly half of the 178 laboratory directors surveyed about CF testing (49%, $n = 88$) performed some type of DNA testing for CF in their laboratories. Directors in higher-volume laboratories ($p = 0.002$) were significantly more likely to offer CF testing after adjusting for the factors listed in the Materials and methods section (Table 1). Seventy-one percent of commercial laboratories offered CF testing compared with 50% of academic laboratories ($p = 0.89$) and 29% of those in other non-academic hospitals ($p = 0.01$).

Among laboratories that performed CF testing, 99% were certified by CLIA or one of three 'deemed' accrediting organizations (the Joint Commission on Accreditation of Healthcare Organizations, the College of American Pathologists Laboratory Accreditation Program, or the Commission on Office Laboratory Accreditation). All

Table 1. CF testing by US molecular genetic testing laboratories[a]

	Number of molecular testing labs ($n = 178$)	Percent of molecular labs that perform CF testing ($n = 88$)	Percent of laboratories performing CF testing that offer the CF test for			
			carrier screening	diagnostic testing	prenatal testing	mutation confirmation
All	178	49	92	81	63	47
Setting						
Commercial	42	71	87	73	73	43
University or medical school	91	50	93	82	58	44
Other non-academic hospitals	45	29[b]	100	92	54	62
Estimated annual volume of tests (one missing)						
1–1999	63	19	83	67	25	33
2000–5999	66	58[b]	92	84	53[b]	42
6000–14,999	31	71[b]	91	73	77[b]	41
15,000+	17	94[b]	100	94	94[b]	75[c]
Number of distinct tests laboratory offers (one missing)						
1–4	45	27	92	50	33	8
5–19	72	53	92	82[b]	50[b]	39[b]
20+	60	62	92	92[b]	86[b]	68[b]

CF, cystic fibrosis.
[a]$n = 178$; two refused to answer CF questions.
[b]$p \leq 0.01$, adjusted for setting, annual volume, test menu size, genetic testing for clinical/research/both purposes, performance of biochemical and molecular tests or molecular tests only.
[c]$p = 0.04$, adjusted as above.

CF laboratories that were CLIA certified were also certified for high-complexity testing. More CF laboratories reported being CLIA certified compared with the molecular laboratories that did not offer CF testing (91%, $p = 0.03$). Directors of laboratories that performed CF testing were also more likely to be certified by the American Board of Medical Genetics than directors of laboratories not offering CF testing (71% *vs* 45%, $p = 0.03$).

The indications for which laboratories perform CF testing are summarized in Table 1. CF carrier screening was offered by 92% ($n = 81$) of laboratories that performed CF testing.

Carrier screening for the 5T allele in intron 8 of *CFTR*

Directors whose laboratories performed CF carrier screening were asked under what circumstances their laboratory performs a test for the 5T allele in intron 8 and under what circumstances they report the results of the 5T test. Seventy-two percent performed the 5T assay and returned the results only when it was indicated as a reflex test (Fig. 1). Additionally, 8% of laboratories always performed the 5T assay but only returned the results to patients and providers when the reflex test was indicated, so a total of 79% (due to rounding) were returning 5T results to patients only as a reflex test. A total of 15%, or one in seven, CF screening laboratories either did not test for the 5T allele or always performed and reported 5T results (Fig. 1); 8% of CF screening laboratories performed the 5T assay on all screening samples and include 5T results on all CF laboratory reports, while 7% said that they never test for 5T. Another 3% performed the 5T test only when a healthcare provider requested it.

Lower-volume laboratories and those in commercial or non-academic hospital settings were significantly more likely to always include 5T results on CF test reports ($p = 0.02$, 0.03, respectively), adjusting for the other regression variables. Adoption of the 5T reflex guideline was not related to directors' certification by the American Board of Medical Genetics (ABMG).

Number of *CFTR* mutations included in carrier screening

The 81 laboratory directors whose laboratories performed CF carrier screening were asked 'For how many mutations does your laboratory test when performing CF carrier testing?' and asked to fill in a blank with their response. An alternate response 'We perform complete gene sequencing for CF carrier testing' was also made available based on the suggestion of one of the pretest reviewers. One in 10 used a 23-mutation panel. The remainder tested for more mutations, including

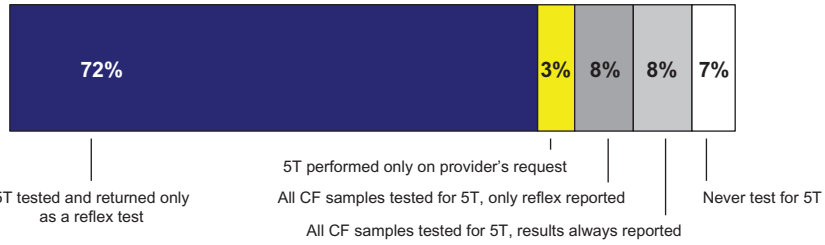

Fig. 1. Circumstances under which laboratories offering cystic fibrosis (CF) screening perform a test for the 5T allele in intron 8 of the *CFTR* gene and return 5T test results ($n = 81$); 2% did not respond.

15% who tested 24 or 25 mutations, 51% who tested between 26 and 40 mutations, 9% who tested between 41 and 50 mutations, and another 9% who tested between 51 and 150 mutations. Four percent responded that they sequence the coding regions of *CFTR*. Excluding the laboratories that said they sequence *CFTR*, the median number of mutations screened was 32. Adoption of the 23-mutation guideline was not related to directors' ABMG certification. We did not ascertain which mutations laboratories include on their laboratory reports or which platforms laboratories were using for CF screening, nor did we verify that laboratories testing 23-mutation panels were testing those recommended in the guidelines.

Discussion

The implementation and uptake of the CF carrier screening guidelines can provide important lessons about the future development, dissemination, and adoption of genetic testing guidelines for other conditions. While CF screening is a complex case in which penetrance and expressivity vary widely across a large number of mutations, genetic tests currently in development for complex diseases and pharmacogenetic applications may prove to be even more complicated to administer.

The data collected in this study quantify the extent to which laboratories have adopted two aspects of the CF screening guidelines but do not explain the reasons laboratories make other choices and do not assess whether there are differences in health outcomes or cost implications associated with adopting either of the suggested practices. Measuring laboratory uptake of the guidelines is not intended to serve as an assessment of the current quality of laboratory testing for *CFTR* mutations but as a measure of the degree to which guidelines have influenced the laboratory component of CF screening programs. As new guidelines for other population-based genetic tests emerge, it will be useful and important to understand the extent of their influence on practice. Measuring laboratory and provider uptake of guidelines is a necessary first step in understanding the effectiveness of developing such guidelines, the realities and barriers that may limit uptake, and whether adoption of guidelines (or the lack thereof) has any serious consequences for genetic screening programs.

We evaluated genetic testing laboratories' adoption of two major components of the CF carrier screening guidelines:

(1) The circumstances under which 5T test is performed and the 5T test results are returned (8).
(2) How many *CFTR* mutations are included in initial carrier screening tests (8, 21).

Four of five CF screening laboratories reported 5T testing results only as a reflex test result. Ten percent tested for 23 mutations. Testing for 23 mutations was not associated with adoption of the guideline on reflex testing for the 5T variant ($p = 0.67$). Seven percent of CF screening laboratories adopted the 5T screening guideline and tested for 23 mutations, while 13% of CF screening laboratories had not adopted the 5T guideline and were testing for more than 23 mutations.

These guidelines are not enforceable standards but recommendations for laboratory directors implementing CF carrier screening. There are likely several factors contributing to a laboratories' decision to adopt the recommendations. A laboratory director's choice to always screen for the 5T allele or to screen for more than 23 mutations may be strongly influenced by market forces and the platforms available. The platforms that a laboratory director has at his or her disposal may limit which CF testing kit a laboratory chooses to use. Although it is beyond the scope of this paper to evaluate the range of commercially available CF testing kits, many test for more than 23 mutations and others may test the 5T allele as part of the initial mutation screen, making masking of a 5T result difficult (18, 27). However, although clinical and legal uncertainties about a laboratory's obligation to report on a tested mutation exist, and obligations may vary according to state law (21), laboratories do maintain some control over which

test results are reported back to providers and patients (21). It should be noted that a major limitation of this study is that directors were not asked about their choice of platform for CF screening or the reasons for this choice. Additional survey work could be performed to explore the influences of assay cost, platform, market pressures, and other factors on directors' adoption of the guidelines.

Given the widespread heterogeneity of the US population, laboratory directors and healthcare providers with significant numbers of minorities in their patient populations may also legitimately seek expanded mutation panels with increased sensitivity for non-Caucasian mutations (28). Ethnic-specific mutations may account for some, all, or none of the additional mutations tested for in different expanded panels.

Finally, as one of the most commonly ordered genetic tests (4), CF carrier testing also represents a growing source of revenue for laboratories. Laboratories may experience pressure from providers and patients to offer expanded mutation panels. Obstetricians and gynecologists may seek out laboratories that test for as many mutations as possible to minimize perceived issues of liability. Both patients and providers may also believe that screening for more *CFTR* mutations always ensures a more effective test. In the competitive marketplace of laboratory testing, these demands could make it more difficult to maintain a CF screening program based on the 23-mutation panel, even if a director feels it is the best approach. However, reports of unnecessary prenatal testing performed in CF screening programs (1, 17, 29) may have increased laboratory directors' attention to and adoption of the 5T testing guidelines.

Based on the uptake of guidelines in other areas of clinical medicine (30–32), it is unreasonable to expect universal adoption of the CF screening guidelines; for example, one review of 143 practice recommendations in 70 different aspects of clinical medicine found a mean uptake of 55% (32). In this context, 80% uptake of the 5T recommendation may be viewed as exceptionally high. However, regardless of whether uptake of the CF screening guidelines is high compared to uptake of other guidelines, the effect of different CF screening practices should be assessed.

Uptake of guidelines for CF screening will be most valuable if other screening practices adversely affect patient outcomes (33) or arrive at the same outcomes at substantially greater cost. Our finding of variable CF screening practices suggests that a natural opportunity exists to examine whether laboratories' uptake of the CF guidelines is associated with lower frequency of procedures such as unnecessary invasive prenatal testing or adverse outcomes from such testing. Additional research may also determine whether more extensive test panels and panels that always return 5T results lead to additional genetic counseling and follow-up care and if so, whether this additional resource use alters the cost/benefit ratio of CF screening programs. Collecting high-quality accurate outcomes data to answer these types of questions may be challenging (1, 34) but may also be important in shaping guidelines for CF screening as well as other genetic tests that lay just over the horizon.

In addition to measuring the effects of implementing the guidelines, the guidelines themselves should be assessed to determine whether they are appropriate, useful, and reasonable given the most current evidence and technologies. One of the most common reasons clinicians do not adopt clinical guidelines is because the recommendations become obsolete; practices may change in response to new evidence or tools before guidelines are revised (33). Thus, the development and implementation of guidelines for genetic screening programs must be an ongoing iterative process that incorporates new evidence about the penetrance and expressivity of particular mutations (8). This has already been demonstrated once in the case of CF screening where, within 3 years of publishing the 25-mutation panel, evidence was collected to determine that two of the mutations provided no clinical utility.

If the guidelines are clinically useful and cost-effective, then finding ways to overcome barriers to their adoption is critical (35). Mechanisms that put decision-making tools into providers' hands at the point of care or that link the adoption of guidelines to reimbursement should be evaluated. Electronic medical record systems that embed practice guidelines in algorithms used to support decision making among healthcare providers, including laboratory staff, may improve appropriate ordering and interpretation of genetic tests.

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