

Genetic testing and quality control in diagnostic laboratories

To evaluate the quality of genetic testing for cystic fibrosis, 136, 145 and 159 laboratories participated in a European study in 1996, 1997 and 1998, respectively. We sent six purified DNA samples carrying the more common *CFTR* mutations with the request to test them using routine protocols. A panel of experts reviewed the results together with the raw data.

We assigned the samples as 'correctly genotyped' when the result was correct or when a laboratory did not test for this mutation and assigned it as wild type. For a total of 1,632, 1,740 and 1,908 alleles

tested in the three schemes, we identified 63, 49 and 36 errors, respectively.

Apart from incorrect results due to technical reasons or to misinterpretation of the (technically correct) results (on average 90%), administrative (reporting) mistakes (on average 10%) were frequent. In the last two quality assessment (QA) schemes, all the commercial kits had problems in identifying samples heterozygous for G551D and R553X. Over the three-year period, the quality improved but the error rate remained high (Fig. 1). Less than half (48%) of the 114 laboratories who partici-

pated in the three trials made no mistakes. Thirty-nine percent made a mistake only once, whereas 2% failed in each trial. This challenges the notion that only a small number of laboratories are responsible for the mistakes in (consecutive) QA schemes. An effect of throughput volume on accuracy could be discerned. In 1998, 30% of the laboratories with less than 100 routine cystic fibrosis (CF) tests per year made one or more mistakes, whereas those handling 100–300 tests or more, 10% and 17%, respectively, made errors. In the best of three QA trials, more than 20% of the participants failed to type at least one of six DNA samples correctly. This number might, however, underestimate the frequency of mistakes made in routine work. Table 1 summarizes the mutation detection methods used. A clear shift towards commercial kits exists. In the 1998 scheme, almost 50% of the participants used commercial kits as the primary testing tool, compared with 28% in 1996.

As a positive consequence of the first QA scheme, many laboratories successfully adapted their protocols to prevent future mistakes. The use of a commercial kit alone, however, does not ensure high accuracy of mutation analysis, which again stresses the importance of validating all genetic tests in the laboratory¹. Although a mutation detection rate superior to 95% would be desirable, the heterogeneity of the *CFTR* mutations in Europe and the United States^{2–4} makes this goal not achievable for all regions with the current technology. The European concerted action on CF therefore advises the organization of genetic diagnostic services at two levels: one local, testing only frequent mutations (85% of the patients), and a limited number of regional expert laboratories testing for less frequent mutations using more sophisticated technologies and providing support and training⁵.

In conclusion, proficiency testing is part of the mandatory certification procedure in some countries such as the US and the UK (refs 6,7). Most research laboratories, and most diagnostic laboratories, however, do not have such certification⁸. Combined with the risk of errors in the pre-test phase (appropriateness) and post-test phase (clinical interpretation), which is considered to be very high, particularly for predictive tests⁹, these error rates could have serious consequences for the testees. The European QA scheme for Huntington disease also identified unacceptable errors¹⁰. It is clear that the implementation of recommendations for testing as proposed by Holzman¹¹, by our European concerted action⁵ and by the UK Quality Network¹² can have an important role in improving

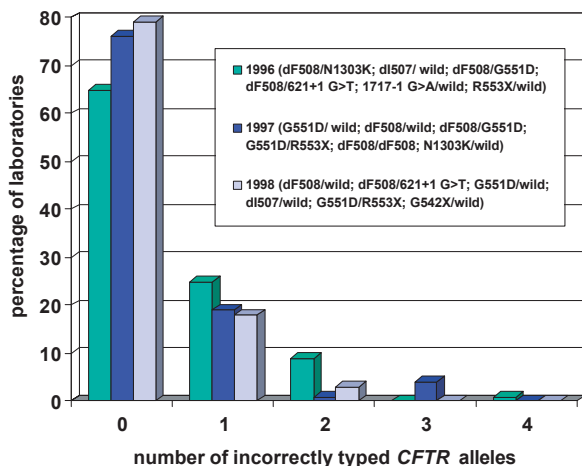


Fig. 1 Results of the QA schemes.

Table 1 • Evolution of testing strategies

	Primary testing (%) [total (%)]		
	1996 (132 labs)	1997 (139 labs)	1998 (151 labs)
Heteroduplex	48 [48]	31 [34]	36 [40]
Reverse dot blot	27 [37]	27 [37]	24 [41]
non-commercial	9 [14]	8 [13]	6 [10]
INNO-Lipa*	18 [23]	19 [24]	18 [31]
ARMS	14 [22]	19 [25]	15 [21]
non-commercial	4 [10]	5 [9]	2 [6]
Elucigene CF(4)*	6 [6]	3 [3]	1 [1]
Elucigene CF(12)*	4 [5]	11 [12]	12 [14]
Restriction enzyme	1 [65]	9 [50]	2 [45]
Sequencing	1 [12]	1 [11]	2 [11]
DGGE	2 [11]	2 [10]	2 [9]
SSCP	2 [9]	3 [5]	1 [6]
OLA*	0 [0]	5 [7]	18 [21]
Other methods	4 [19]	3 [4]	0 [6]
*All commercial kits	28 [34]	38 [46]	49 [67]

*Elucigene CF12, AstraZeneca, Abingdon, Oxfordshire, U.K.; OLA CF assay, PE Applied Biosystems, New Jersey, U.S.A.; INNO-Lipa CF2, Innogenetics, n.v., Gent, Belgium.

the safety and efficacy of genetic testing. The gradual reduction in the error rates of the successive QA schemes for *CFTR* testing described here already illustrates the benefit of these schemes.

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