Am. J. Hum. Genet. 51:943–950, 1992

Invited Editorial: Cystic Fibrosis Genotypes and Views on Screening Are Both Heterogeneous and Population Related

Charles R. Scriver*,†,‡ and T. Mary Fujiwara†,‡,§

*De Belle Laboratory, Division of Medical Genetics, McGill University/Montreal Children's Hospital Research Institute; and †Centre for Human Genetics and Departments of ‡Pediatrics and §Medicine, Faculty of Medicine, McGill University, Montreal

An article in this issue of the *Journal* (Abeliovich et al. 1992) and two others elsewhere (Férec et al. 1992; Rozen et al. 1992) describe three different populations, in Israel, Brittany, and Quebec, in which just a few identifiable mutations account for 93%–98% of those causing cystic fibrosis (CF) disease in the region. This level of mutation detection constitutes a threshold, below which one approaches CF disease prevention at the family level, by genetic testing and counseling, and above which one might also approach it at the level of the community, by population screening (ten Kate 1990). (We distinguish here between genetic *screening* and *testing* [U.S. Congress Office of Technology Assessment 1992, p. 4]. The former refers to a test applied to a population, group, or individual to distinguish between persons with the condition and those without it. *Testing* implies the use of specific methods to identify the status of consultands known to be at high risk because of family history.) Whether in the newborn or in carriers of reproductive age, screening for CF has been a controversial topic involving issues such as community structures to support screening, equitable access to health care, and commercial implications, among others.

"Cystic fibrosis of the pancreas" was formally reported for the first time in 1938; in the 1940s the term "mucoviscidosis" was coined to describe the character of CF disease; autosomal recessive inheritance was recognized in the mid-1940s; a test for diagnosis of suspected cases by means of sweat electrolyte content appeared in the 1950s. This knowledge, combined with aggressive therapy (chest percussion, antibiotics, and digestive-enzyme replacement), significantly improved quality of life and longevity for CF patients (Boat et al. 1989; Collins 1992; U.S. Congress Office of Technology Assessment 1992, pp. 5–6). Median survival age, once less than 2 years, is now 31.8 years (27.5 years for females and 36.6 years for males) for the 5-year period 1986–1991 in Canada, for example (Canadian Cystic Fibrosis Foundation 1992). Meantime, studies describing the patient's view of CF disease are noticeable by their rarity (this is true, of course, for most diseases). One report tells of adult-age patients with typical CF who function on a par with their healthy peers in nearly all aspects (Shepherd et al. 1990). All of this clearly represents better news for the CF patient than was the case 50 years ago. Yet there are shadows; median life span is not equal to that of persons without CF; the disease shows considerable variation in severity among patients, which is not entirely explained by CFTR genotype; the definition of CF disease has broadened; and prognosis seems not to have been improved yet by newborn screening for earlier diagnosis and onset of treatment.

Then, in the late 1980s, the gene that is mutant in CF patients was isolated by positional cloning (Rommens et al. 1989) and was characterized and named the "cystic fibrosis transmembrane conductance regulator" (gene symbol CFTR) (Riordan et al. 1989), and analyzed for mutations (Kerem et al. 1989). It had already been settled that mutation at only one locus was sufficient to explain inheritance of CF (Romeo et al. 1985; Beaudet et al. 1986; Tsui and Buchwald 1988). Mutation and haplotype analysis revealed that, whereas allelic heterogeneity in CF (Cutting et al. 1989; Kerem et al. 1989; Lemna et al. 1990) might explain some of the phenotypic heterogeneity and refine prognosis (Kerem et al. 1989, 1990; Cutting et al. 1990; Kobayashi et al. 1990; Hamosh et al. 1992; Kristidis et al. 1992; Santamaria et al. 1992; Wine

Received August 25, 1992.

Address for correspondence and reprints: Dr. Charles R. Scriver, Room A707, Montreal Children's Hospital, 2300 Tupper Street, Montreal, Quebec H3H 1P3 Canada.

This article represents the opinion of the authors and has not been peer reviewed.

0002-9297/92/5105-0001$02.00

1992), at the same time it complicated the use of a DNA test. These developments catalyzed studies to document the distribution of mutant alleles in human populations (Cystic Fibrosis Genetic Analysis Consortium 1990; European Working Group on CF Genetics 1990); to discover that one allele (ΔF508) accounts for 70% of mutations detected in northern Europeans but accounts for a lower percentage in southern Europeans; and to address questions about the putative mechanisms (Meindl 1987; Jorde and Lathrop 1988; Romeo et al. 1989; Tsui 1989) underlying the polymorphic frequency (up to .02) of CF alleles in Caucasian populations of European descent. Over 200 mutations have been reported to the Cystic Fibrosis Genetic Analysis Consortium.

Knowledge about mutant CFTR genotypes is pertinent to screening; so is the new knowledge about the CFTR protein. The gene product is an ATP-dependent membrane transporter (Riordan et al. 1989), functioning as a small-conductance chloride channel (Anderson et al. 1991; Bear et al. 1992; Welsh et al. 1992). Malfunction of this channel in respiratory (Knowles et al. 1983), sweat-gland (Quinton 1983), pancreatic (Bradbury et al. 1992), and reproductive-tract epithelium (Trezise and Buchwald 1991) and in the acidification-dependent mechanisms for sialylation and sulfation of mucus proteins (Barasch et al. 1991) could explain many components of the CF disease phenotype. With this knowledge, the possibilities for somatic gene therapy (Rosenfeld et al. 1992) and for drug therapy with amiloride (Knowles et al. 1990), aerosolized α1-antitrypsin (McElvaney et al. 1991), aerosolized ATP or UTP (Knowles et al. 1991), and human DNAase (Hubbard et al. 1992) are now tangible (Collins 1992).

The absence, up to now, of both a simple method to detect all CFTR mutations at once and a phenotype test analogous to the ones used to screen carriers for Tay-Sachs or β-thalassemia mutations, for example, signifies reduced sensitivity of the CF screening test; and these circumstances also compromise the effectiveness of mutation analysis for diagnosis and counseling of individuals or couples at high risk. Accordingly, The American Society of Human Genetics (ASHG) issued a statement (Caskey et al. 1990)—and the *Journal* published an editorial (Beaudet 1990)—urging the community to "proceed with caution," a message widely echoed (Colten 1990; Cystic fibrosis: prospects for screening and therapy 1990; Workshop on Population Screening for the Cystic Fibrosis Gene 1990). At the time, there was a broad consensus on these points: mass screening should not be implemented; couples should be informed about available tests when a partner had a close relative affected with CF; there should be follow-up to counseling and interpretation of the test result; access to the appropriate health-care resources should be equitable; there should be quality control of tests; and any population-oriented initiatives should reflect findings in pilot studies. Those positions are retained in a forthcoming statement from the ASHG Ad Hoc Committee on Cystic Fibrosis Carrier Screening, and they are reiterated elsewhere (Biesecker et al. 1992). The result is that current knowledge about CF genotypes and phenotypes is not yet being translated into programs in a way corresponding to that experienced with phenylketonuria (newborn screening), Tay-Sachs disease, and β-thalassemia (carrier screening). The reasons why will make an interesting topic for research by social scientists and historians of science.

The medical and social implications of DNA-based population screening for CF carriers, notably for users of American health-care systems, were examined in a widely cited article (Wilfond and Fost 1990). The issues were recently summarized in this way:

> Prospects for routine CF carrier screening are viewed with mixed feelings. Invariably, discussions about CF carrier screening focus on how health insurers use, or might use, genetic information and they become linked to the broader debate about health care access in the United States. Some also question the adequacy of quality assurance for DNA diagnostic facilities and the tests themselves. Today's tests detect 85 to 95 percent of CF carriers depending on a person's race and ethnicity. This lack of perfection troubles those who would like more sensitive detection rates before the tests are put to widespread use. Some also wonder whether the current number of genetic specialists can handle a swell of CF carrier screening cases, let alone cases for tests for other genetic conditions made possible by the Human Genome Project. And fundamental to consideration of CF carrier screening is the issue of genetic counseling and abortion. [From the Report Brief on the OTA report on cystic fibrosis screening (U.S. Congress Office of Technology Assessment 1992)]

Many opinions opposing population screening for CF carriers were published, but only one important fact emerged relevant to screening for this or any other autosomal recessive condition; it concerned sensitivity of the DNA test in relation to the corresponding frequencies of the allele(s) detected by the screening test

(ten Kate 1989, 1990). If one screens only for the most prevalent allele(s), there will be couples where only one partner has been identified as a carrier but where the other partner has not been excluded from carrier status. This means that the postscreening risk that this couple will have an affected child may not be less than the prescreening risk. In a population where incidence of the target disease is 1/2,500 and the carrier frequency is 1/25, the threshold (sensitivity) value at which postscreening risk, ascertained by the DNA test, is less than prescreening risk is about 96% mutation detection (ten Kate 1989). The sensitivity threshold can drop to about 90% if one chooses for the couple an arbitrary risk below 1/1,000 (ten Kate 1990). The threshold value will, of course, change according to the precise incidence of CF disease in a given population. *In three different populations, detection rates above 92% have now been reported for small subsets of known CF mutations* (table 1). In Denmark and northwestern England (Cutting et al. 1992; Ferrie et al. 1992), detection rates exceed 90%. If population screening began in such regions, what would be the purpose?

Genetic screening has three rationales (National Academy of Sciences 1975): (1) early treatment to prevent disease, (2) genetic counseling to avoid disease, and (3) research. In CF, the second and third rationales are relevant, and, if treatment improves dramatically (see above), the first rationale will become important. Newborn screening by the dried-blood-spot immunoreactive assay for trypsinogen excess (an indirect test for CF; see Rock et al. 1990; Hammond et al. 1991) is considered by some to be suitable for mass screening. It has an apparent false-positive rate of 0.3%, a sensitivity of .88 (when CF infants presenting with meconium ileus are excluded), and a reasonable cost (approximately $2.50/infant screened) (Hammond et al. 1991). Others (Holtzman 1991) are skeptical that this or any other mode of newborn screening for CF will, at present, confer a significant benefit either to the CF patient or to society. Providers of newborn screening are themselves cautious about the overall benefits (now) of an early diagnosis (Hammond et al. 1991). On the other hand, newborn screening (in a research mode) has revealed that a significant proportion of CF infants begin postnatal life with pancreatic sufficiency and then develop insufficiency (Waters et al. 1990). If early diagnosis combined with new forms of drug therapy (see above) could prevent deterioration of pancreatic function, that would be a benefit. It is worth giving consideration to aspects of CF such as this when one is designing the randomized controlled trials of newborn CF screening, which are recommended (Holtzman 1991). In the research mode, population screening for carrier detection will provide a third method to estimate gene frequencies and to compare these estimates with those from case findings in epidemiologic studies (see Abeliovich et al. 1992) and from newborn screening (see Boat et al. 1989; table 108-7).

Another product of CF screening research is likely to be more information about the expanding continuum of associations between clinical disease and CFTR mutations—e.g., the associations between CFTR mutations and (1) chronic bronchial hypersecretion (Dumur et al. 1990) and (2) males with infertility due to congenital absence of the vas deferens, in whom the frequency of having a mutant CFTR allele is 10–16 times normal (Rigot et al. 1991; Anguiano et al. 1992). The major rationale in screening for carriers of recessive alleles is to provide genetic counseling. Suppose that the technical criteria for CF screening are met, as they are now in three populations (table 1); does one establish screening programs there for the purpose of counseling heterozygotes? The answer depends in part on where one lives, the social values of the population, and the type of health-care system in effect. The latter is a determinant of both access to genetic screening services (National Academy of Sciences 1975) and the resources the community can provide to make the process equitable (Modell 1990). CF carrier screening is likely to be instituted earlier in regions with this form of insurance than in those without national health insurance. Nonetheless, there are abiding concerns about CF screening—concerns that did not emerge (or persist) to the same extent in Tay-Sachs and β-thalassemia carrier screening programs; among these concerns are those mentioned above, as well as potential competition, between contending strategies (cure, treatment, and avoidance), for limited resources; insufficiently informed public and private opinion; and confidentiality of the information obtained by testing. There has been no shortage of opinion about the potential harm arising from population screening for CF. There is a comparative dearth of information on the views of the potential clients. The latter is now beginning to appear; it is interesting, and it originates from patients, their families, unaffected couples, pregnant women, adolescent-age students, and the community at large.

An Australian survey (Turner et al. 1991), distributed to members of the New South Wales Cystic Fibro-

Table 1

Distribution of Mutations in CF Patients

Population (reference [no. of CF chromosomes]) and Mutation	Distribution (%)	
Askhenazi from Israel (Abeliovich et al. 1992 [94]; Shoshani et al. 1992 [95]):		
W1282X	48	60
ΔF508	30	22
G542X	12	4
3849 + 10 kb, C→T	4	0
N1303K	3	4
Total	97	92[a]
Celtic Bretons from France (Férec et al. 1992 [365]):		
ΔF508	82	
1078delT	5	
G551D	4	
1717-1 G→A	1	
W846X	1	
G91R	1	
Three alleles at 0.55% each	2	
Ten alleles at 0.27% each	3	
Total	98[a]	
French Canadians from northeastern Quebec (Rozen et al. 1992 [181]):		
ΔF508	58	
621 + 1 G→T	23	
A455E	8	
G85E	1	
711 + 1 G→T	1	
G542X	1	
Y1092X	1	
N1303K	1	
Total	93[a]	

[a] Because of rounding, individual values do not sum to the total.

sis Foundation, elicited replies both from patients and from parents. Prenatal diagnosis was perceived as an acceptable option by the patients and by the great majority of parents; virtually all respondents supported the option of carrier detection. An American survey (Wertz et al. 1991) elicited from CF parents (68% participation) opinions about abortion for various medical conditions; CF ranked fifth among 12 fetal characteristics considered cause for a voluntary first-trimester legal abortion; only 20% would themselves abort because of CF. An English survey of CF parents found strong support for carrier screening and for opportunities to avoid the disease (Watson et al. 1992*a*).

Women and couples have been asked about intrapartum tests for CF carrier status. Pregnant Scottish women approved of both the information given to them (in written form) about CF and the availability of tests (Mennie et al. 1992*b*); 73% of 4,348 women in the prenatal clinic were then tested for the CF alleles that accounted for 85% of the CFTR mutations in the population (Shrimpton et al. 1991). The observed carrier rate was 1/29; there were four carrier couples, all of whom asked for prenatal diagnosis, and the single affected fetus was terminated (Mennie et al. 1992*a*).

An American study, of attitudes only (Botkin and Alemagno 1992), surveyed pregnant Caucasians; 98% of the respondents preferred that CF carrier screening be done before pregnancy, but 69% would accept it during pregnancy; only 29% would consider terminating an affected CF fetus (compare with the data in Wertz et al. 1991); 91% thought carrier status would not influence choice of partner, and 67% would seek prenatal diagnosis if both partners were carriers. Another American study, in Amish, Mennonite, and Hutterite CF kindreds and in families from the general population, noted the strong influence of cultural factors on attitudes toward genetic testing and counseling for CF (Miller and Schwartz 1992).

Couples in England who had recently become parents were surveyed for attitudes about both CF carrier screening in particular and genetic screening in general (Green 1992). The respondents were not swayed by the argument that genetic screening costs would diminish other health-care resources; advantages perceived outweighed disadvantages perceived; they showed concern that "the wrong people might get hold of the information and use it to discriminate against carriers"; the majority (60% "definitely" and 22% "possibly") thought a population-based test for CF carriers was worth having, despite its current difficulties, and that it should be made available. As for the timing of the test, 34% favored school leavers (high school students), and 48% favored it at the start of pregnancy. Respondents were overwhelmingly positive about their own participation if CF screening should become available.

A survey of new mothers in Holland found 80% in favor of CF screening (ten Kate and Tijmstra 1990). Perceptions and attitudes among the general public (students, newspaper readers, and new mothers) in Holland favored (96%, 90%, and 80%, respectively) offering a CF screening test; 54%, 77%, and 63%, respectively, said they would make use of the test themselves (ten Kate and Tijmstra 1990). In Belgium,

over 75% of adults favored being informed about the availability of voluntary population screening for CF carriers, but they were not generally well informed as to the nature of CF disease: 63% wanted to know their own carrier status, and 75% would, under the appropriate conditions, consider prenatal diagnosis (Decruyonaere et al. 1992).

Retrospective opinions after uptake of the CF-testing option might be different from prospective attitudes and perceptions. Is there evidence that the experience quells the support for screening? Uptake was high (86%) among the eligible pregnant Scottish women in the clinic (Mennie et al. 1992*a*). In England it was 66% in general practice and 87% in the family-planning clinics; of persons offered the same option by letter, only 10% were tested (Watson et al. 1991). (Higher participation rates in the opportunistic setting are also seen in Tay-Sachs and thalassemia carrier screening programs.) Use of mouthwash samples instead of blood samples facilitates uptake (Watson et al. 1991; Kaplan et al. 1992). Follow-up of 3,176 persons screened in primary-health-care settings in the United Kingdom (Watson et al. 1992*b*) showed that 100 carriers of mutant CFTR alleles had been detected, all with no previous family history; the anxiety initially experienced was soon allayed, and 87% of their informed partners were subsequently tested; carriers and noncarriers alike strongly approved of testing, on the basis of their own experience; they said it increased their knowledge of CF.

Scottish students (high school level) surveyed for their prospective opinions about CF screening favored carrier detection (86%) (Cobb et al. 1991). Retrospective opinions were obtained from high school students in Montreal (Kaplan et al. 1991, 1992) after they had voluntarily participated in a project that offered mutation analysis, evaluated understanding of test sensitivity, and estimated unconditional CF allele frequencies. Students understood and accepted the limitations of a DNA test that had imperfect sensitivity; they participated voluntarily at higher rates when the sample was a mouthwash (vs. a blood sample), and they approved of testing, regardless of whether they had themselves participated (at rates up to 70%); findings were not influenced by their ethnicity. Adolescent carriers of mutations for CF, Tay-Sachs (Zeesman et al. 1984), and β-thalassemia (Scriver et al. 1984) were alike in their reception and intended use of the information obtained by a screening test.

One way to find out how society will react to CF carrier screening is to try it and see (Green 1992). However, the advantages and disadvantages of trying to find out have yet to be evaluated fully (Screening for cystic fibrosis 1992; Davies 1992). "We still need to think very carefully about whether nationwide programmes are what we really want and what the aims and ethical base of such an approach might be" (Screening for cystic fibrosis 1992, p. 210). We agree. Meantime, rates of voluntary uptake of the CF carrier screening option—and citizens' views, both prospective and retrospective, of the experience—suggest that the experiment can continue in some communities, if not everywhere. No doubt, improvement in the technology of mutation detection will facilitate testing and screening for CF carriers (Chehab and Wall 1992; Ferrie et al. 1992; Gasparini et al. 1992). Possible adverse consequences of genetic screening, such as diminished self-perception (Marteau et al. 1992) and discrimination (Billings et al. 1992; Green 1992; Holtzman and Rothstein 1992), will have to be monitored and, if identified, averted. The issues of accessibility and equitability, the health-care context, and the impact of commercialization of CF tests are all brought into sharp focus by the prospect of testing and screening for CF mutations.

"Seeking to learn what the future holds is an enduring human quality. . . . Some people want and seek this information; others do not" (U.S. Congress Office of Technology Assessment 1992, p. 3). The evidence suggests that in some societies the number of citizens who want information about their CFTR locus now exceeds those who say the time has not yet arrived for CF carrier screening. Whose opinion do we heed, and what is to be done?

Acknowledgments

This work was supported in part by the Canadian Genetic Diseases Network (Networks of Centers of Excellence). We thank Loy Denis and Lynne Prevost for preparing the manuscript, and we thank the Cystic Fibrosis Genetic Analysis Consortium for unpublished information. Reviews of the manuscript by Feige Kaplan, John Mitchell, and Ken Morgan made it better; its failures are the authors' responsibility. Intimate personal knowledge of CF (Scriver 1991) has been an influence.

References

Abeliovich D, Lavon IP, Lerer I, Cohen T, Springer C, Avital A, Cutting GR (1992) Screening for five mutations detects 97% of CF chromosomes and predicts a carrier frequency

of 1:29 in the Jewish Ashkenazi population. Am J Hum Genet 51:951–956

Anderson MP, Gregory RJ, Thompson S, Souza DW, Paul S, Mulligan RC, Smith AE, et al (1991) Demonstration that CFTR is a chloride channel by alteration of its anion selectivity. Science 253:202–205

Anguiano A, Oates RD, Amos JA, Dean M, Gerrard B, Stewart C, Maher TA, et al (1992) Congenital bilateral absence of the vas deferens: a primarily genital form of cystic fibrosis. JAMA 267:1794–1797

Barasch J, Kiss B, Prince A, Saiman L, Gruenert D, Al-Awqati Q (1991) Defective acidification of intracellular organelles in cystic fibrosis. Nature 352:70–73

Bear CE, Li C, Kartner N, Bridges RJ, Jensen TJ, Ramgeesingh M, Riordan JR (1992) Purification and functional reconstitution of the cystic fibrosis transmembrane conductance regulator (CFTR). Cell 68:809–818

Beaudet AL (1990) Carrier screening for cystic fibrosis. Am J Hum Genet 47:603–605

Beaudet A, Bowcock A, Buchwald M, Cavalli-Sforza L, Farrall M, King M-C, Klinger K, et al (1986) Linkage of cystic fibrosis to two tightly linked DNA markers: joint report from a collaborative study. Am J Hum Genet 39: 681–693

Biesecker L, Bowles-Biesecker B, Collins F, Kaback M, Wilfond B (1992) General population screening for cystic fibrosis is premature. Am J Hum Genet 50:438–439

Billings PR, Kohn MA, de Cuevas M, Beckwith J, Alper JS, Natowicz MR (1992) Discrimination as a consequence of genetic testing. Am J Hum Genet 50:476–482

Boat TJ, Welsh MJ, Beaudet AL (1989) Cystic fibrosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic basis of inherited disease, 6th ed. McGraw Hill, New York, pp 2649–2680

Botkin JR, Alemagno S (1992) Carrier screening for cystic fibrosis: a pilot study of the attitudes of pregnant women. Am J Public Health 82:723–725

Bradbury NA, Jilling T, Berta G, Sorscher EJ, Bridges RJ, Kirk KL (1992) Regulation of plasma membrane recycling by CFTR. Science 256:530–532

Canadian Cystic Fibrosis Foundation (1992) Canadian Patient Data Registry Reports of 1990. Canadian Cystic Fibrosis Foundation, Toronto

Caskey CT, Kaback MM, Beaudet AL (1990) The American Society of Human Genetics statement on cystic fibrosis screening. Am J Hum Genet 46:393

Chehab FF, Wall J (1992) Detection of multiple cystic fibrosis mutations by reverse dot blot hybridization: a technology for carrier screening. Hum Genet 89:163–168

Cobb E, Holloway S, Etlon R, Raeburn JA (1991) What do young people think about screening for cystic fibrosis? J Med Genet 28:322–324

Collins FS (1992) Cystic fibrosis: molecular biology and therapeutic implications. Science 256:774–779

Colten HR (1990) Screening for cystic fibrosis: public policy and personal choices. N Engl J Med 322:328–329

Cutting GR, Antonarakis SE, Buetow KH, Kasch LM, Rosenstein BJ, Kazazian HH Jr (1989) Analysis of DNA polymorphism haplotypes linked to the cystic fibrosis locus in North American black and Caucasian families supports the existence of multiple mutations of the cystic fibrosis gene. Am J Hum Genet 44:307–318

Cutting GR, Curristin SM, Nash E, Rosenstein BJ, Lerer I, Abeliovich D, Hill A, et al (1992) Analysis of four diverse population groups indicates that a subset of cystic fibrosis mutations occur in common among Caucasians. Am J Hum Genet 50:1185–1194

Cutting GR, Kasch LM, Rosenstein BJ, Tsui L-C, Kazazian HH Jr, Antonarakis SE (1990) Two patients with cystic fibrosis, nonsense mutations in each cystic fibrosis gene and mild pulmonary disease. N Engl J Med 323:1685–1689

Cystic Fibrosis Genetic Analysis Consortium (1990) Worldwide survey of the ΔF508 mutation—report from the Cystic Fibrosis Genetic Analysis Consortium. Am J Hum Genet 47:354–359

Cystic fibrosis: prospects for screening and therapy (1990) Lancet 335:79–80

Davies K (1992) Genetic screening for cystic fibrosis. Nature 357:424

Decruyonaere M, Evers-Kiebooms G, Denayer L, Van den Berghe H (1992) Cystic fibrosis: community knowledge and attitudes towards carrier screening and prenatal diagnosis. Clin Genet 41:189–196

Dumur V, Lafitte J-J, Gervais R, Debaecker D, Kesteloot M, Lalau G, Roussel P (1990) Abnormal distribution of cystic fibrosis ΔF508 allele in adults with chronic bronchial hypersecretion. Lancet 335:1340

European Working Group on CF Genetics (1990) Gradient of distribution in Europe of the major CF mutation and of its associated haplotype. Hum Genet 85:436–441

Férec C, Audrezet MP, Mercier B, Guillermit H, Moullier P, Quere I, Verlingue C (1992) Detection of over 98% cystic fibrosis mutations in a Celtic population. Nature Genet 1:188–191

Ferrie RM, Schwarz MJ, Robertson NH, Vaudin S, Super M, Malone G, Little S (1992) Development, multiplexing, and application of ARMS tests for common mutations in the CFTR gene. Am J Hum Genet 51:251–262

Gasparini P, Bonizzato A, Dognini M, Pignatti PF (1992) Restriction site generating-polymerase chain reaction (RG-PCR) for the probeless detection of hidden genetic variation: application to the study of some common cystic fibrosis mutations. Mol Cell Probes 6:1–7

Green JM (1992) Principles and practicalities of carrier screening: attitudes of recent parents. J Med Genet 29: 313–319

Hammond KB, Abman SH, Sokol RJ, Accurso FJ (1991) Efficacy of statewide neonatal screening for cystic fibrosis by assay of trypsinogen concentrations. New Engl J Med 325:769–774

Hamosh A, King TM, Rosenstein BJ, Corey M, Levison H,

Durie P, Tsui L-C, et al (1992) Cystic fibrosis patients bearing both the common missense mutation Gly→Asp at codon 551 and the ΔF508 mutation are clinically indistinguishable from ΔF508 homozygotes, except for decreased risk of meconium ileus. Am J Hum Genet 51:245–250

Holtzman NA (1991) What drives neonatal screening programs? N Engl J Med 325:802–804

Holtzman NA, Rothstein MA (1992) Eugenics and genetic discrimination. Am J Hum Genet 50:457–459

Hubbard RC, McElvaney NG, Birrer P, Shak S, Robinson WW, Jolley C, Wu M, et al (1992) A preliminary study of aerosolized recombinant human deoxyribonuclease I in the treatment of cystic fibrosis. N Engl J Med 326:812–815

Jorde LB, Lathrop GM (1988) A test of the heterozygote-advantage hypothesis in cystic fibrosis carriers. Am J Hum Genet 42:808–815

Kaplan F, Clow C, Scriver CR (1991) Cystic fibrosis carrier screening by DNA analysis: a pilot study of attitudes among participants. Am J Hum Genet 49:240–242

Kaplan F, Mitchell J, Ravone G, Fernandes L, Clow C, Scriver CR (1992) Cystic fibrosis carrier detection by DNA test: a population study: carrier frequencies and attitudes toward a test with imperfect sensitivity. Am J Hum Genet Suppl 51 (in press)

Kerem B-S, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, et al (1989) Identification of the cystic fibrosis gene: genetic analysis. Science 245:1073–1080

Kerem E, Corey M, Kerem B-S, Rommens J, Markiewicz D, Levison H, Tsui L-C, et al (1990) The relation between genotype and phenotype in cystic fibrosis: analysis of the most common mutation (ΔF508). N Engl J Med 323:(22) 1517–1522

Knowles MR, Church NL, Waltner WE, Yankaskas JR, Gilligan P, King M, Edwards LJ, et al (1990) A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. N Engl J Med 322:1189–1194

Knowles MR, Clarke LL, Boucher RC (1991) Activation by extracellular nucleotides of chloride secretion in the airway epithelia of patients with cystic fibrosis. N Engl J Med 325:533–538

Knowles MR, Stutts MJ, Spock A, Fischer N, Gatzy JT, Boucher RC (1983) Abnormal ion permeation through cystic fibrosis respiratory epithelium. Science 221:1067–1069

Kobayashi K, Knowles MR, Boucher RC, O'Brien WE, Beaudet AL (1990) Benign missense variations in the cystic fibrosis gene. Am J Hum Genet 47:611–615

Kristidis P, Bozon D, Corey M, Markiewicz D, Rommens J, Tsui L-C, Durie P (1992) Genetic determination of exocrine pancreatic function in cystic fibrosis. Am J Hum Genet 50:1178–1184

Lemna WK, Feldman GL, Kerem B-S, Fernbach SD, Zevkovich EP, O'Brien WE, Riordan JR, et al (1990) Mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis. N Engl J Med 322:291–296

McElvaney NG, Hubbard RC, Birrer P, Chernick MS, Caplan DB, Frank MM, Crystal RG (1991) Aerosol α1-antitrypsin treatment for cystic fibrosis. Lancet 337:392–394

Marteau TM, van Duijn M, Ellis I (1992) Effects of genetic screening on perceptions of health: a pilot study. J Med Genet 29:24–26

Meindl RS (1987) Hypothesis: a selective advantage for cystic fibrosis heterozygotes. Am J Phys Anthropol 74:39–45

Mennie ME, Gilfillan A, Compton M, Curtis L, Liston WA, Pullen I, Whyte DA, et al (1992*a*) Prenatal screening for cystic fibrosis. Lancet 340:214–216

Mennie ME, Liston WA, Brock DJH (1992*b*) Prenatal cystic fibrosis carrier testing: designing an information leaflet to meet the specific needs of the target population. J Med Genet 29:308–312

Miller SR, Schwartz RH (1992) Attitudes toward genetic testing of Amish, Mennonite, and Hutterite families with cystic fibrosis. Am J Public Health 82:236–242

Modell B (1990) Cystic fibrosis screening and community genetics. J Med Genet 27:475–479

National Academy of Sciences (1975) Genetic screening: programs, principles and research. National Academy of Sciences, Washington, DC

Quinton PM (1983) Chloride impermeability in cystic fibrosis. Nature 301:421–422

Rigot J-M, Lafitte J, Dumur V, Gervais R, Manouvrier S, Biserte J, Mazeman E, et al (1991) Cystic fibrosis and congenital absence of the vas deferens. N Engl J Med 325: 64–65

Riordan JR, Rommens JM, Kerem B-S, Alon N, Rozmahel R, Grzelczak Z, Zielenski et al. (1989) Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 245:1066–1073

Rock MJ, Mischler EH, Farrell PM, Wei L-J, Bruns T, Hassemer DJ, Laessig RH (1990) Newborn screening for cystic fibrosis is complicated by age-related decline in immunoreactive trypsinogen levels. Pediatrics 85:1001–1007

Romeo G, Bianco M, Devoto M, Menozzi P, Mastella G, Giunta AM, Micalizzi C, et al (1985) Incidence in Italy, genetic heterogeneity, and segregtion analysis of cystic fibrosis. Am J Hum Genet 37:338–349

Romeo G, Devoto M, Galietta LJV (1989) Why is the cystic fibrosis gene so frequent? Hum Genet 84:1–5

Rommens JM, Iannuzzi MC, Kerem B-S, Drumm ML, Melmer G, Dean M, Rozmahel R, et al (1989) Identification of the cystic fibrosis genes: chromosome walking and jumping. Science 245:1059–1066

Rosenfeld MA, Yoshimura K, Trapnell BC, Koneyama K, Rosenthal ER, Dalemans W, Fukayama M, et al (1992) In vivo transfer of the human cystic fibrosis transmembrane conductance regulator gene to the airway epithelium. Cell 68:143–155

Rozen R, De Brackeleer M, Daigneault J, Ferreira-Rajabi L, Gerdes M, Lamoureux L, Aubin G, et al (1992) Cystic fibrosis mutations in French Canadians: three CFTR mutations are relatively frequent in a Quebec population with an elevated incidence of cystic fibrosis. Am J Med Genet 42:360–364

Santamaria F, Salvatore D, Castiglione O, Raia V, de Ritis G, Sebastio G (1992) Lung involvement, the ΔF508 mutation and DNA haplotype analysis in cystic fibrosis. Hum Genet 88:639–641

Screening for cystic fibrosis (1992) Lancet 340:209–210

Scriver CR (1991) Public and private views of identity: acceptance of the 1990 Ross Award. Clin Invest Med 14: 167–175

Scriver CR, Bardanis M, Cartier L, Clow CL, Lancaster GA, Ostrowsky JT (1984) β-Thalassemia disease prevention: genetic medicine applied. Am J Hum Genet 36:1024–1038

Shepherd SL, Hovell MF, Harwood IR, Granger LE, Hofstetter CR, Molgaard C, Kaplan RM (1990) A comparative study of the psychosocial assets of adults with cystic fibrosis and their healthy peers. Chest 97:1310–1316

Shoshani T, Augarten A, Gazit E, Bashan N, Yahav Y, Rivlin Y, Tal A, et al (1992) Association of a nonsense mutation (W1282X), the most common mutation in the Ashkenazi Jewish cystic fibrosis patients in Israel, with presentation of severe disease. Am J Hum Genet 50:222–228

Shrimpton AE, McIntosh I, Brock DJH (1991) The incidence of different cystic fibrosis mutations in the Scottish population: effects on prenatal diagnosis and genetic counseling. J Med Genet 28:317–321

ten Kate LP (1989) Carrier screening in CF. Nature 342:131

——— (1990) Carrier screening for cystic fibrosis and other autosomal recessive diseases. Am J Hum Genet 47:359–361

ten Kate LP, Tijmstra T (1990) Community attitudes to cystic fibrosis carrier screening. Prenat Diagn 10:275–276

Trezise AEO, Buchwald M (1991) *In vivo* cell-specific expression of the cystic fibrosis transmembrane conductance regulator. Nature 353:434–437

Tsui L-C (1989) Tracing the mutations in cystic fibrosis by means of closely linked DNA markers. Am J Hum Genet 44:303–306

Tsui L-C, Buchwald M (1988) No evidence for genetic heterogeneity in cystic fibrosis. Am J Hum Genet 42:184

Turner G, Wilcken B, Griffiths H (1991) Cystic fibrosis screening and community genetics. J Med Genet 28:575

U.S. Congress Office of Technology Assessment (1992) Cystic fibrosis and DNA tests: implication of carrier testing. OTA-BA-532. U.S. Government Printing Office, Washington, DC

Waters DL, Dorney SFA, Gaskin KJ, Gruca MA, O'Halloran M, Wilcken B (1990) Pancreatic function in infants identified as having cystic fibrosis in a neonatal screening program. N Engl J Med 322:303–308

Watson EK, Marchant J, Bush A, Williamson R (1992*a*) Attitudes towards prenatal diagnosis and carrier screening for cystic fibrosis among the parents of patients in a pediatric cystic fibrosis clinic. J Med Genet 29:490–491

Watson EK, Mayall E, Chapple J, Daiziel M, Harrington K, Williams C, Williamson R (1991) Screening for carriers of cystic fibrosis through primary health care services. Br Med J 303:504–507

Watson EK, Mayall ES, Lamb J, Chapple J, Williamson R, (1992*b*) Psychological and social consequences of community carrier screening programme for cystic fibrosis. Lancet 340:217–220

Welsh MJ, Anderson MP, Rich DP, Berger HA, Denning GM, Ostegaard LS, Sheppard DN, et al (1992) Cystic fibrosis transmembrane conductance regulator: a chloride channel with novel regulation. Neuron 8:821–829

Wertz DC, Rosenfield JM, Janes SR, Erbe RW (1991) Attitudes toward abortion among parents of children with cystic fibrosis. Am J Public Health 81:992–996

Wilfond BS, Fost N (1990) The cystic fibrosis gene: Medical and social implications for heterozygote detection. JAMA 263:2777–2783

Wine JJ (1992) No CFTR: are CF symptoms milder? Nature Genet 1:10

Workshop on Population Screening for the Cystic Fibrosis Gene (1990) Statement from the National Institutes of Health workshop on population screening for the cystic fibrosis gene. N Engl J Med 323:70–71

Zeesman S, Clow CL, Cartier L, Scriver CR (1984) A private view of heterozygosity: eight-year follow-up study on carriers of Tay-Sachs gene detected by high school screening in Montreal. Am J Med Genet 18:769–778