

Lessons Learned from Carrier Screening Cystic Fibrosis

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**Population-Based Carrier Screening for Single-Gene Disorders
Lessons Learned and New Opportunities
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Cystic Fibrosis

Cloning
and
Genetics



NIH Consensus Development Conference



GENETIC
TESTING FOR
CYSTIC FIBROSIS

April 14-16,
1997
Natcher
Conference
Center
National
Institutes of
Health
Bethesda
Maryland

NIH Consensus Statement: Genetic Testing for Cystic Fibrosis 1997

- **Objective:** To provide health care providers, patients and the general public with a responsible assessment of the optimal practices for genetic testing for cystic fibrosis (CF)
- **Participants:** A non-Federal, nonadvocate, 14-member panel representing the fields of genetics, obstetrics, internal medicine, nursing, social work, epidemiology, pediatrics, psychiatry, genetic counseling, bioethics, health economics, health services research, law, and the public. In addition, 21 experts from these same fields presented data to the panel and a conference audience of 500

Predefined Questions Presented to Panel

- **What is the current state of knowledge regarding natural history, epidemiology, genotype-phenotype correlations, treatment and genetic testing of cystic fibrosis in various populations?**
- **What has been learned about genetic testing for cystic fibrosis regarding (public and health professional) knowledge and attitudes, interest and demand, risks, and benefits, effectiveness, cost and impact?**
- **Should cystic fibrosis carrier testing be offered to (1) individuals with a family history of cystic fibrosis; (2) adults in the preconception or prenatal period; and/or (3) the general population?**

Predefined Questions Presented to Panel

Continued

- **What are the optimal practices for cystic fibrosis genetic testing (setting, timing, and the practices of education, consent, and counseling)?**
- **What should be the future directions for research relevant to genetic testing for cystic fibrosis, and more broadly, for research and health policies related to genetic testing?**

NIH Consensus Statement: Genetic Testing for Cystic Fibrosis- 1997

- **Evidence:** The literature was searched through Medline, and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.
- **Consensus Process:** The panel, answering predefined questions, developed its conclusions based on the scientific evidence presented in the open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference.

NIH Consensus Statement: Genetic Testing for Cystic Fibrosis 1997

- **Conclusions**

Genetic testing for CF should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy and to couples seeking prenatal testing

Comprehensive educational programs targeted to health care professionals and the public should be developed using input from people living with CF and their families and from people from diverse racial and ethnic groups

Genetic counseling services must be accurate and provide balanced information to afford individuals the opportunity to make autonomous decisions

It is essential that the offering of CF carrier testing be phased in over a period of time to ensure that adequate education and appropriate genetic testing and counseling services are available to all persons being tested

A variety of recommendations were made concerning the importance of additional research, protection of individual rights and privacy among others

History of CF Carrier Screening

- 1989: CFTR gene & common mutation identified in CF patients
- 1997: NIH Consensus Development Conference
 - First call for population-based screening
- 1997: NIH workshop
 - Recommend development of guidelines, educational material, informed consent, laboratory standards
- 2001: ACOG/ACMG Clinical & Laboratory Guidelines

SUMMARY OF ACMG RECOMMENDATIONS FOR POPULATION-BASED CYSTIC FIBROSIS CARRIER SCREENING

1. Testing should be offered to Caucasians and Ashkenazi Jews, and made available to all other ethnic groups.
2. Either simultaneous or sequential couple screening may be used, as long as results are given to both partners.
3. A universal, pan-ethnic core mutation panel should be used, consisting of:
 - 25 mutations
 - 3 exonic polymorphisms as reflex tests
 - 5/7/9T intronic polymorphism as reflex test only if R117H is positive

SUMMARY OF ACMG RECOMMENDATIONS FOR POPULATION-BASED CYSTIC FIBROSIS CARRIER SCREENING (cont'd.)

4. Extended mutation panels for positive-negative couples should not be offered or encouraged.
5. Reporting of results and residual risks should be based on the detection rates and model report forms developed by the committee.
6. Primary care providers not comfortable with the complexities of these reports should refer the couple to a genetics professional.
7. Quality assurance standards should adhere to the guidelines of ACMG, CAP, and the NIH-DOE Task Force on Genetic Testing.

Initial Experience with CF Carrier Screening

- CF carrier testing in major labs in U.S. increased 7-10 fold within first 18 months
- Concerns raised about the mutation panel
 - Mutation frequencies differ in general population
 - I148T 50-100 times more common
 - Identified “milder mutations”
 - R117H
 - Identified new variants that influence severity of mutations
 - 3199del6

CF Carrier Screening Practice Patterns of Ob/Gyns

- Questionnaire mailed to 1165 ACOG fellows in Sept. 2003
 - 600 randomly selected
 - 565 Collaborative Ambulatory Research Network (CARN)
- 64% response rate (57.9% CARN)
- Analysis
 - Mann Whitney U test for group differences on ordinal measures
 - Univariate analysis of variance with gender and residency as fixed factors for group differences of continuous measures
 - Descriptive statistics reported as mean \pm SEM

CF Carrier Screening Practice Patterns of Ob/Gyns

- Routinely inquire about family history of CF
 - Pregnant 88.7%
 - Non-pregnant 13.5
 - Only if attempting pregnancy (36.4%)
- Always provide information regarding screening
 - Pregnant 86.6%
 - Non-pregnant 6.3
 - Only if attempting pregnancy (38.4%)

CF Carrier Screening in Pregnancy

Practice Patterns of Ob/Gyns

- **Offer to all patients** **65.8%**
- **Offer to some patients** **32**
 - At patient's request 67.1
 - Family history 61.8
 - Partner with CF 51.2
 - Ethnicity 46.7
 - All of above 27.4
- **Never offer** **2.2**

CF Carrier Screening Prior to Conception

Practice Patterns of Ob/Gyns

- **Offer to all patients** **13%**
- **Offer to some patients** **67.7**
 - At patient's request 80.1
 - Family history 54.7
 - Partner with CF 43.6
 - Ethnicity 25.2
 - All of above 18
- **Never offer** **19**

How familiar are ObGyns with CF carrier screening guidelines?

Does this impact their knowledge and practice behavior?

ObGyns Familiarity with CF Carrier Screening Guidelines

- Read 19.2%
- Skimmed 44.5
- Heard of/not read 27.6
- Never heard of 8.8

ObGyns Familiarity with CF Carrier Screening Guidelines

- Majority (82%) aware of recommendations to offer CF carrier testing
- Majority admitted their practice pattern had changed esp the readers and skimmers
- Individuals who read the document more likely to answer correctly except on more complex scenarios such as interpretation of results/risk assessment

Factors that may influence patient acceptance of CF carrier screening test

- Family history or partner with CF (97.5%)
- Out of pocket cost (71.2)
- Acquaintance with CF (67.6)
- Perception of having child with CF (54.8)
- Attitudes towards termination (50.6)
- Desire for good outcome (50.1)
- Perception screening is routine (43.1)
- Perception CF chronic disease burden (39.5)

Lessons Learned

- Majority of ObGyns are offering CF carrier screening in prenatal setting
- Not using selection criteria
- ObGyns do not routinely offer preconception carrier screening unless patient requests, family history or affected partner
- Educate public and practitioners about the benefits of preconception screening

Lessons Learned

- Guidelines influence practice behavior
- Guidelines important source of information
- Keep guidelines simple
- Continuing medical education on genetics and CF needed to increase comfort level
- Utilize alternative venues to reach all providers about new guidelines

Lessons Learned

- Complexity leads to confusion
 - Different panels
 - Number of mutations
 - Significance of mutation (mild vs classic CF)
 - Variable severity and inability to predict phenotype
- Ongoing monitoring of findings in general population and laboratory practice is important
- Consistent and clear reporting of lab results is important to avoid misinterpretation

The Cystic Fibrosis mutation “arms race”: when less is more

Wayne W. Grody, MD, PhD¹, Garry R. Cutting, MD², and Michael S. Watson, PhD³

The implementation of population-based cystic fibrosis carrier screening in late 2001 represented the first application, at an all-inclusive, whole-population level, of molecular genetic testing. It also represented the product of 12 years of research, pilot studies, deliberation, and consensus building by the National Institutes of Health, the American College of Medical Genetics (ACMG), and the American College of Obstetricians and Gynecologists (ACOG). That long developmental timespan owed to the complexity of the gene, the large number (>1500) and heterogeneity of its mutations and variants, and ethical concerns about clinical variability of the disease and potential adverse psychosocial impacts.¹ Yet, its eventual launch was seen as a model for the thoughtful integration of preventive molecular medicine into routine primary care (in this case, predominantly obstetrics and family medicine) and an early fruit of the investment in genomic research. Indeed, it was both fitting and significant that the seven pilot studies, conducted in the mid-1990s, were funded by the National Center for Human Genome Research (now the National Human Genome Research Institute [NHGRI]) under the sponsorship of the Ethical, Legal and Social Implications program. These studies culminated in a consensus conference at NIH in 1997, which recommended offering cystic fibrosis (CF) carrier screening to all pregnant couples and those planning a pregnancy.^{2,3} Details of exactly how such a program should be implemented were considered at a second consensus conference held in 1998⁴ and then worked out by a steering committee comprised of representatives from ACMG, ACOG, and NHGRI.⁵ Subcommittees were formed to work out the three essential prongs of the effort: (1) patient education and informed consent; (2) laboratory testing (including the minimum core panel of mutations to be screened), interpretation, and reporting; and (3)

subcommittees recommended a universal (pan-ethnic) screening panel of 25 *CFTR* mutations, which met the dual criteria of known association with CF and having an allele frequency in the affected US population of $\geq 0.1\%$, based on data maintained by the Cystic Fibrosis Foundation and others. The detection rate of this panel in Caucasians of European descent (80%) and the other major racial and ethnic groups was presented in an appendix to the subcommittee's report⁶ for use in calculating residual risks in those who test negative, and other aspects of genetic counseling.

Recognizing that before these recommendations there was wide disparity in the number and identity of *CFTR* mutations tested by individual laboratories,⁷ with no single laboratory offering this precise panel, testing laboratories and reagent vendors were given several months to “ramp up” to this minimal requirement. Even then, there were challenges. With no FDA-cleared molecular test kits available at that time for any genetic disease, much less one as complex as CF, laboratories had been developing their own in-house methods. But, although these may have been adequate for four or six mutations, the prospect of developing a “home brew” assay for as many as 25 mutations (and corresponding normal allele sequences) was beyond the capabilities of most facilities. In addition, positive control samples for most of the recommended mutations, ostensibly required under Clinical Laboratories Improvement Amendment (CLIA) regulations for use in quality control, were not to be had for love or money; they were simply not available, even in the laboratories already testing for them.

Fortunately, the law of supply-and-demand soon intervened to provide solutions to both of these impediments. Perceiving a large market as CF screening was declared standard of

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