THE AMERICAN SOCIETY OF HUMAN GENETICS

9650 ROCKVILLE PIKE / BETHESDA MD 20814 / (301) 571-1825 / FAX: (301) 530-7079

January 16, 1992

MEMORANDUM

TO: Ad Hoc Committee on Cystic Fibrosis Carrier Screening

✓Arthur Beaudet	Philip Reilly
✓James Bowman	✓ Peter Rowley
C. Thomas Caskey	Charles Scriver
✓ Francis Collins	Elizabeth Short
✓ Jessica Davis	✓ Ann C.M. Smith
✓Norman Fost	James Sorensen
	✓ Lap-Chee Tsui
	Nancy Wexler

Ben
EG

FROM: ✓Sherman Elias, Chair
✓Michael M. Kaback, Co-Chair

RE: Meeting at Squaw Creek, February 10-11, 1992

Enclosed is a packet with the agenda for the meeting, minutes of our last meeting and other relevant background information. As you know this meeting's focus is to critically review the current ASHG position on the NIH policy statement on cystic fibrosis carrier screening and determine whether it is appropriate to update our position at this time. Please note that a copy of the statement which was published in the New England Journal of Medicine is included in the packet in the green section.

For ease of reference this packet has been color coded as follows:

- Agenda (goldenrod)
- Committee list (pink)
- Minutes of previous meeting (yellow)
- Current policies (green)
- Funded projects in progress (blue)
- Inventory list of printed materials on cystic fibrosis received thus far (orchid)

We are looking forward to a very productive meeting and to seeing you at Squaw Creek.

cc: E. Strass, Executive Director

Eric due back July 8.

NATIONAL ACADEMY OF SCIENCES/INSTITUTE OF MEDICINE STUDY

Purpose: Make recommendations regarding the integration of genetic services into "mainstream medicine".

Current make-up of panel:

Roger Williamson OB / State MSAFP
Bob Greenstein CORN / Reimb.
Ed McCabe AAP / Gen
George Cunningham CA DPH / CORN
John Meaney AZ DPH / CORN
ANN WILLEY NY DPH / CORN
Jessie Davis ASHG / CORN
JAIME FRIAS TEXAS / Consumers
ED Nursing

Governor's Wife
Claudia Weicker

Lawyers/Ethicists
James Childress, PhD
Pat King, JD
Marc Alan Lapp', PhD
Peter Libassi, LLB
Philip Reilly, MD, JD
Mark Rothstein, JD

Economist
Gerald Rosenthal, PhD

Molecular Geneticists
Francis Collins, MD
Helen Donnis-Keller, PhD
Frank Fujimura, PhD

Genetic Counselor
Barb Bowles Biesecker, MS

Psychologist
Nancy Wexler, PhD

Internist/Geneticist
Tom Caskey, MD (spends most time in lab)

Pediatricians/Geneticists
Barton Childs, MD (has given a lot of thought to these issues in past)
Tony Holtzman, MD (also Public Health)
Mike Kaback, MD (also Screening, is leaving post as)

Where are the are the people from "mainstream medicine"...Obstetricians, Family Physicians, Pathologists, the Public Health Professionals, the Nurses, disease specific clinic representation, the disability communities, state and regional genetic service delivery systems, CORN, M/CH communities

Whole regions of the country not represented. Whole segments of the health service delivery community that would necessarily to implement the recommendations. If they want to effect change the recommendations must be relevant. Skewed committee that is unlikely to be able to carry out its mandate in a meaningful way.

INSTITUTE OF MEDICINE

Division of Health Sciences Policy

Committee on Predicting Future Disease: Issues in the Development, Application and Use of Tests for Genetic Disorders

ROSTER

C. Thomas Caskey, M.D. *(Chair)*
Professor and Director
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C. S. Mott Children's Hospital
Division of Pediatric Genetics
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[redacted]

James F. Childress, Ph.D.
Chairman, Department of Religious Studies
Edwin B. Kyle Professor of Religious Studies
University of Virginia
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[redacted]

Barton Childs, M.D.
Emeritus Professor of Pediatrics
The Johns Hopkins University
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[redacted]

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Frank Fujimura, Ph.D.
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Neil Holtzman, M.P.H., M.D.
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Professor of Health Policy
and Management and Epidemiology
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[redacted]

Patricia King, J.D.
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Professor of Health Policy and Ethics
University of Illinois College of Medicine
Department of Medical Education (M/C 591)
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Peter Libassi, LL.B.
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Corporate Communications
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Professor of Pediatrics, Medicine,
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Philip R. Reilly, M.D., J.D.
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Gerald D. Rosenthal, Ph.D.
Director, Economic Studies/Health
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Law Foundation Professor of Law and
Director, Health Law and Policy Institute
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Claudia T. Weicker
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Nancy Sabin Wexler, Ph.D.
Associate Professor of Clinical
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Departments of Neurology and Psychiatry
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[redacted]

MEMORANDUM

DATE: February 11, 1992

TO: Board of Directors, American Society of Human Genetics
FROM: Sherman Elias, M.D.
Chair, Ad Hoc Committee on Cystic Fibrosis Carrier Screening

RE: Consensus Statement

Enclosed please find the consensus report of the ASHG Ad Hoc Committee on Cystic Fibrosis Carrier Screening, which was drafted on February 10-11, 1992 at Squaw Valley. The Board should note that there was considerable discussion about how to handle minority opinions. If the primary purpose of the statement is to educate readers, these opionions are a fact and should be included. On the other hand, including minority opinions in a short report may weaken the impact of the report's effect on policy and practice. The press may focus on the disagreement and the minority opinion so that the message might be "*ASHG Divided*" rather than "*ASHG Reaffirms Policy*" on CF screening. Commercial companies may also use such disagreement as support for marketing activities. In support of the latter view, many organizations report conclusions in their statements without identifying minority opinions.

There was also a suggestion to identify the statement as coming from the ASHG, not just the Committee, to increase its effect.

If in the Board's opinion, the minority position should be included, the following paragraph would have to be included as the second to the last paragraph before the **Recommendations** section:

> " Although most members of the Committtee felt that CF testing should not be offered routinely to individuals or couples *without* a family *history of* CF, a *minority* felt *that* geneticists counseling individuals or couples about reproductive risks should inform them of the benefits and limitations of CF testing. It is recommended that programs choosing to initate screening at this time should compile data on patient decsion-making and outcomes to complement other pilot study data. "

Respectfully submitted,
Ad Hoc Committee on Cystic Fibrosis Carrier Screening

CONSENSUS REPORT:
AD HOC COMMITTEE ON CYSTIC FIBROSIS CARRIER SCREENING
AMERICAN SOCIETY OF HUMAN GENETICS

The identification in 1989 of the cystic fibrosis (CF) gene and its most common mutation immediately raised the possibility of CF carrier detection by DNA analysis. The American Society of Human Genetics (ASHG) issued a statement recommending that CF carrier testing should be made available to individuals with a family history of CF (Am J Hum Genet 1990; 46:393). It was also stated that screening of the general population should not be undertaken until the rate of CF carrier detection improves. An additional prerequisite emphasized the need for the establishment of effective educational and counseling programs consistent with previous widely accepted principles. An NIH workshop, convened in February 1990, reached similar conclusions (N. Eng. J. Med. 1990; 323: 70-71). The statement of the workshop was endorsed by the ASHG.

Since then, substantial progress has been made in defining the mutational basis of the disease and the basic biochemical defect. As recommended by the NIH workshop, pilot projects to study the complex issues involved in general population screening for CF carriers in the United States have been initiated, but substantive results are not anticipated for at least two years. Interest in CF carrier screening has expanded in the medical community, the biotechnology industry and the public. Other pilot projects are underway in Canada and Europe. Accordingly, the ASHG Ad Hoc Committee on Cystic Fibrosis Carrier Screening reassessed the issues surrounding CF carrier detection.

Cystic fibrosis is an autosomal recessive genetic disorder characterized by chronic lung disease and pancreatic insufficiency. There is a broad range of clinical severity. Recent advances in clinical care including postural drainage, pancreatic enzyme replacement, and improved antibiotics have increased survival, although a small fraction of patients still die in the first decade. Even without anticipated improvements in therapy, most individuals born today with CF are expected to survive into their thirties or forties. CF occurs about 1 in 2500 newborns of European ancestry. It is less frequent among other ethnic and racial groups. About 1 in 25 persons of European ancestry is a carrier, having one normal and one abnormal CF gene.

A single mutation, denoted ΔF508, is found in approximately 70% of carriers of European ancestry. Currently, over 160 other mutations have been identified. Many of these are extremely rare, but a few reach frequencies of 1-3% of CF carriers. Current surveys indicate that 85-90% of CF carriers in the North American white population can be detected by testing for 6-12 mutations. The detection rate is even higher in some populations (e.g.,

Ashkenazi Jews), but is substantially lower in blacks, Hispanics and Asians. In view of this mutational heterogeneity, it is unlikely that CF carrier detection rates by DNA testing will exceed 95% in the foreseeable future.

The severity of disease in a given patient is to some extent correlated with the particular mutations present. However, it is difficult to make meaningful predictions about the clinical course of the disease based on DNA testing, because the spectrum of disease for a given genotype is quite broad. Furthermore, for all but the most common genotypes there are insufficient numbers of affected individuals to adequately define the clinical spectrum. A few mutations are associated with phenotypes that are much milder than classical CF.

Analyses of the CF gene and its protein product indicate that the gene encodes a membrane protein, which has properties of a chloride channel. Recent data indicating the ΔF508 mutant protein may have residual activity increase the possibilities of specific drug therapy. Intense efforts also are underway to develop gene therapy strategies to deliver the normal CF gene to the respiratory tract. The success of these approaches to the amelioration or cure of CF is uncertain. The perceived rate of progress of these and other developments will undoubtedly affect the level of public interest in CF carrier screening.

These scientific developments do not in themselves resolve the question of whether CF carrier screening programs should be implemented at present. Population-based screening implies offering a program of carrier testing, with appropriate informed consent and genetic counseling, to potentially millions of healthy people. The primary purpose of such screening would be to allow people to make more informed reproductive decisions

Testing individuals with a family history of CF, or with a blood relative identified as a CF carrier, is straightforward, accurate, and can significantly affect an individual's predicted risk of having a child with CF. Accordingly, there is widespread agreement that testing should be offered in this situation. Hence, it is important for all health professionals to obtain accurate family histories, especially for patients of reproductive age.

It is acknowledged that testing of highly motivated individuals in the general population may occur. As previously stated, testing should only be provided by knowledgeable health care professionals after appropriate education and counseling.

Although the carrier detection rate is approaching 90%, other important prerequisites must be further addressed before widespread screening can be recommended. These include the effectiveness of educational materials, the level of utilization of screening, laboratory aspects

(e.g., quality assurance, proficiency testing), counseling issues, and the beneficial and deleterious effects of screening. Pilot projects currently underway may help to address these issues. Of particular importance are the consequences of screening couples in which one partner has an identified CF mutation and the other partner tests negative but cannot be excluded as carrying a rare CF mutation. Approximately 1 in 15 of all white couples tested will fall into this category and will be left at a modestly increased risk of having a child with CF (approximately 1 in 1000 assuming a 90% carrier detection rate). Finally, CF screening must be viewed within the perspective of available resources and other health care priorities.

The Committee would like to express concern that entrepreneurial motivations, some of which involve real or potential conflicts-of-interest, may be impacting upon these important decisions. All individuals involved in these deliberations should be encouraged to reveal publicly such potential conflicts, and to assiduously avoid clinical situations where recommendations *about* CF carrier screening could be influenced by personal profit motives.

Recommendations:

- Although the sensitivity of carrier testing for CF has improved and pilots studies are underway, CF testing is not recommended at this time for individuals or couples who do not have a family history of CF.

- Individuals with a positive family history of CF, or who have a blood relative identified as a CF carrier, should be offered CF testing, with appropriate education and counseling. Optimally, carrier testing, should be offered prior to conception, to provide a couple the broadest range of reproductive options

- When indicated, CF counseling and testing should adhere to the following guidelines.

  a. Screening should be voluntary, and confidentialty must be ensured.

  b. Screening requires informed consent. Pretest education should explain the benefits and hazards (e.g., stigmatization and possible loss of insurability).

  c. Providers of screening services have the obligation to ensure that adequate posttest counseling is provided.

  d. Quality control of all aspects of the laboratory testing, including systematic proficiency testing, is required

e. As with all indicated health care services, there should be equal access to testing

- Efforts should be expanded to educate health care providers and the public regarding the complexities of CF screening in particular and issues involved in genetic health care services in general.

INSTITUTE OF MEDICINE
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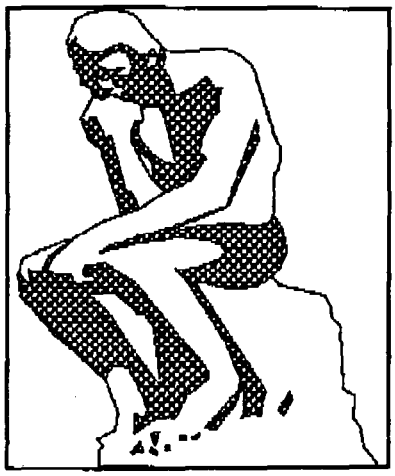
Division of Health Sciences Policy
Committee on Assessing Genetic Risks

Telephone: 202/334-2329
FAX: 202/334-1385

FAX



FROM: ELAINE LAWSON

TO: ELIZABETH THOMPSON

NUMBER OF PAGES: 6

NOTES: Looking forward to seeing you!

—EL

LABORATORY WORKSHOP

SPEAKER	PHONE #	STATUS	ACCEPTED
Arthur Beaudet 1/27	[redacted]	called 12/16,17,20	ACCEPTED
David Blumenthal		called 1/2	ACCEPTED
Jessica Davis, CORN 1/3		called 12/20	ACCEPTED
Nat Goodman, Informatic		called 1/6	ACCEPTED
✓Wayne Grody, CAP		called 12/20	ACCEPTED
✓Frits Hommes		called 12/20	ACCEPTED
Katherine Klinger, Integrated Genetics		called 12/20 and 1/2	ACCEPTED
George Knight, CORN		called 12/20	ACCEPTED
Karla Matteson, SERGG & ASHG/CAP		no answer 12/20 called 12/23	ACCEPTED
✓F. John Meaney, CORN 1/2 (Bio)		called 12/20	ACCEPTED
Patricia Murphy, NYS		called 12/20	ACCEPTED
Debbie Nickerson		called 12/23 & 1/2	ACCEPTED
Sy Perry, Georgetown N/A		called 1/6	ACCEPTED
Hope Punnette 1/27 ASHG com. on Med Genetics		called 1/17	ACCEPTED
Pat Rocha, Roche N/A		called 1/6	ACCEPTED
Joseph Shulman 1/24		called 1/6	ACCEPTED
✓Paul Silverman, Beckman (Bio)		called 12/20	ACCEPTED
M. Anne Spence, ABMG 1/27		called 12/20	TENTATIVE
Anthony Tirone, HCFA (2)		Sent Letter 12/23	TENTATIVE
Tom Tsakeris, FDA		called 12/19	ACCEPTED
Victor W. Weedn, AFIP		called 1/6	ACCEPTED
Ann Willey, NYS		called 12/20	ACCEPTED

✓Mike Connealy
Francis Collins
Tony Holtzman 1/24
Phil Reilly

INSTITUTE OF MEDICINE

COMMITTEE ON ASSESSING GENETIC RISKS: ISSUES AND IMPLICATIONS FOR HEALTH

WORKSHOP ON

LABORATORY ISSUES IN HUMAN GENETICS

February 12-13, 1992, IOM Foundry, Room 2004

February 12, 1992

8:00 am **Continental Breakfast**

8:30 am **Session I - "Overview of Laboratory Issues and Problems"**
Francis Collins, Chair

—Georgetown Forum (4/91) on the Technical, Regulatory and Societal Issues in Biotechnology & the Diagnosis of Genetic Disease

- Seymour Perry, Chair, Community and Family Medicine, Georgetown University School of Medicine

—National Data on Genetic Services

- John Meaney-CORN

—Criteria for Determining When to Move Diagnostic Tests to Clinical Practice (including aspects of costs and effectiveness)

- Art Beaudet, Baylor College of Medicine
- Joe Shulman, Integrated Genetics and IVF
- Pat Rocha, Hoffman-LaRoche on PCR licensing
- Tony Holtzman, Johns Hopkins School of Medicine

9:45 am **Discussion**

10:30 am **Coffee Break**

February 12, 1992 (continued)

10:45 am **Session II - "Voluntary Genetics Laboratory Quality Assurance Efforts"**
Norm Fost, Chair

- George Knight, New England Regional Genetics Network and CORN DNA Voluntary Quality Assurance Committee
- Karla Matteson, Director, Dev. and Genetics Center, University of Tennessee Medical Center, Southeast Regional Network
- Frits A. Hommes, Ph.D., National Biochemical Genetics Laboratory Proficiency Testing Program (voluntary)
- Katherine W. Klinger, Ph.D., Vice President, Research, Integrated Genetics (private laboratory quality assurance initiative)
- Mike Conneally, Huntington's Pilot Program Experience

11:45 am **Discussion**

12:45 pm **Lunch**

1:30 pm **Session III - "Developing Standards and Criteria"**
Mike Conneally, Chair

- Jessica Davis, President, Council of Regional Networks (of Genetic Services)
- Wayne Grody, CAP committee on developing proficiency requirements for DNA testing and personnel
- Hope Punnette, ASHG Committe on Genetic Services
- Karla Matteson, ASHG/CAP Working Group
- M. Anne Spence, ABMG

2:30 pm **Discussion**

3:15 pm **Break**

February 12, 1992 (continued)

3:30 pm **Session IV - Regulation - Existing Authorities and Agencies**
Tony Holtzman, Chair

—Laboratory Regulatory Authority (State)

- Ann Willey, New York State Laboratory Program
- Patricia D. Murphy, Ph.D., New York State DNA Laboratory Licensing Program

3:45 pm **Discussion**

4:15 pm **Session IV - Regulation - Existing Federal Authorities and Agencies**
Tony Holtzman, Chair (continued)

- FDA—Thomas Tsakeris, Director, Division of Clinical Laboratory Devices, Office of Device Evaluation, FDA
- HCFA (CLIA88 Regulations)—Tony Tirone, Director, Surveys & Certification, Health Standards Quality Bureau, HCFA

5:00 pm **Discussion**

5:45 pm **Session V - DNA Banking and DNA Data Banking**

- Phil Reilly, Shriver Center
- Victor Weedn, Armed Forces Institute of Pathology

6:15 pm **Discussion**

6:30 pm **Reception - Georgetown Marbury Hotel**

7:30 pm **Dinner - Georgetown Marbury Hotel**

8:45 pm **Session V - "Laboratories of the Future"**
Frank Fujimura, Chair

—Changes in Laboratory Technology and Informatics

- Paul Silverman, Beckman Instruments
- Nat Goodman, HGP Informatics Working Group

9:15 pm **Discussion**

9:30 pm **Adjourn**

February 13, 1992

8:00 am **Continental Breakfast**

8:30 am **Session V - "Laboratories of the Future" (continued)**
Helen Donis-Keller, Chair

—New Clinical and Laboratory Procedures

- Katherine Klinger, FISH 2-day AFP & CVS results
- Diane Bianchi, Fetal cell separation
- Francis Collins, Other Laboratory Advances and Prospects (e.g., Rapid Sequencing Techniques and Future Probes)
- Debbie Nickerson, Automating Ligation Reactions

9:15 am **Discussion**

10:00 am **Break**

10:15 am **Session VI - "Human Genetics Laboratories and Conflicts of Interest and Commitments"**
Peter Libassi, Chair
(with background reading on Harvard & Hopkins systems; Medicare/Medicaid restrictions on physician ownership of labs and referral practices; excerpt of IOM report "For-Profit Enterprise in Health Care" (1986); and Hillman article on referrals for imaging)

- David Blumenthal, Harvard University

10:45 am **Discussion**

11:45 noon **Working Lunch**

12:00 pm **Session VII - Commentary on Top Priority Laboratory Issues for Future: (5 minutes of remarks each from all remaining speakers-10 here)**

-for the 1990s? for the year 2000? and beyond?

12:50 pm **Discussion**

1:30 pm **Session VII - Commentary (5 minutes each from remaining 6-8 speakers) (continued)**

2:00 pm **Discussion**

2:30 pm **Session VIII - *Committee Executive Session* - Discussion of Policy Implications and Need for Additional Data/Discussion**

4:00 pm **Adjournment**

Marbury
G Burd
Tillman

[redacted]

INSTITUTE OF MEDICINE

COMMITTEE ON ASSESSING GENETIC RISKS: ISSUES AND IMPLICATIONS FOR HEALTH

WORKSHOP ON
HUMAN GENETICS LABORATORIES: ISSUES ON THE PRESENT AND FUTURE
February 12-13, 1992
IOM Foundry, Room 2004

February 11, 1992 (POSSIBLE DINNER DEPENDING ON COMMITTEE TRAVEL PLANS)

February 12, 1992

Room 2004

8:00 am **Continental Breakfast**

8:30 am **Session I - "Overview of Laboratory Issues and Problems" (Francis Collins, Chair)**

—Cancer Diagnostics/Prognostics

- (Jeffrey Sklar, Co-Chair, IOM Research Briefing)

—National Data on Genetic Services

- (John Meaney-CORN)

—Appropriateness

- (Tony Holtzman, Kazazian)

—Cost of Testing

- (Art Beaudet, rep. from Hoffman-LaRoche on PCR licensing)

9:45 am **Discussion**

10:30 am **Coffee Break**

February 12, 1992 (continued)

10:45 am **Session II - "Voluntary Genetics Laboratory Quality Assurance Efforts" (Mike Conneally, Chair)**

- _____, New England Regional Genetics Network Voluntary Quality Assurance Program
- Karla Matteson, Director, Dev. and Genetics Center, University of Tennessee Medical Center, Southeast Regional Network
- Frits A. Hommes, Ph.D., National Biochemical Genetics Laboratory Proficiency Testing Program (voluntary)
- Katherine W. Klinger, Ph.D., Vice President, Research, Integrated Genetics (private laboratory quality assurance initiative)
- Huntington's Pilot Program Experience (Mike Conneally)

11:30 am **Discussion**

12:30 pm **Lunch**

1:30 pm **Session III - "Developing Standards and Criteria" (Tony Holtzman, Chair)**

- Jessica Davis, President, Council of Regional Networks (of Genetic Services)
- James Haddow, CORN DNA Quality Assurance Committee, DNA Testing Subcommittee
- Wayne Grody, M.D., Ph.D., CAP committee on developing proficiency requirements for DNA testing and personnel
- _____?, ASHG/CAP Working Group
- Charles Epstein, ABMG
- Perspectives of Academic Depts. of Pathology, Laboratory Medicine

2:00 **Discussion**

February 12, 1992 (continued)

2:45 **Session IV - Regulation - Existing Authorities and Agencies (Tony Holtzman, Chair)**

—Laboratory Regulatory Authority (State)

- Ann Willey, New York State Laboratory Program
- Patricia D. Murphy, Ph.D., New York State DNA Laboratory Licensing Program

—Role of Public Health Laboratories

- Joseph Josephs, ASTPHLD

-Role of Private Laboratories

- Joseph Shulman, Genetics and IVF, Fairfax, VA

3:45 **Break**

4:00 **Discussion**

4:45 Session V - Regulation - Existing Federal Authorities and Agencies (Peter Libassi, Chair)

- FDA (Jerome Donlon, M.D., Ph.D., Director, Office of Biological Product Review, FDA or
  Freda Yoder, Division of Clinical Lab Devices, FDA
  M. Patricia Cricenti, Scientific Reviewer, FDA
- HCFA (CLIA88 Regulations, Peggy Leoni, Acting Chief, Lab and Home Health Services, HCFA

5:30 **Discussion**

6:30 pm **Reception** Marbury Hotel

7:15 pm **Working Dinner**

8:45 pm Panel Discussion: "Human Genetics Laboratories and Conflicts of Interest" (with background reading on Medicare/Medicaid restrictions on physician ownership of labs and excerpt of IOM report "For-Profit Enterprise in Health Care" (1986)

—David Blumenthal/Mike Stoto (Harvard System)
—Art Beaudet, and ? (current lab testing/problems/costs, etc.) Back at Foundry

9:30 **Adjourn**

February 13, 1992 (continued)

8:00 am **Continental Breakfast**

8:30 am **Session V "Laboratories of the Future"**
(Frank Fujimura, Chair)

—Changes in Laboratory Technology and Informatics

- Paul Silverman, Beckman Instruments
- Rep. from HGP Informatics Working Group
- Francis Collins, Rapid Sequencing Techniques and LCR (Ligase Chain Reaction) Techniques

9:15 am **Discussion**

10:00 am **Break**

10:15 am **Session V (continued)**

—New Clinical and Laboratory Procedures

- Katherine Klinger, FISH 2-day AFP & CVS results
- Diane Bianchi, Fetal cell separation
- Francis Collins, other laboratory/research prospects

11:00 am **Discussion**

11:45 noon **Working Lunch**

12:00 pm **Session VI - Commentary on Top Priority Laboratory Issues for Future:**
(5 minutes of remarks each from all remaining speakers-10 here)

-for the 1990s?
-for the year 2000? and beyond?

12:50 pm **Discussion**

1:30 pm **Commentary (5 minutes each from remaining 6-8 speakers)**

2:00 pm **Discussion**

2:20 pm **Break (brief)**

2:30 pm **Session VII - Committee Discussion of Policy Implications and Need for Additional Data/Discussion**

4:00 pm **Adjournment**

INSTITUTE OF MEDICINE

COMMITTEE ON ASSESSING GENETIC RISKS: ISSUES AND IMPLICATIONS FOR HEALTH
WORKSHOP ON
LABORATORY ISSUES IN HUMAN GENETICS
February 12-13, 1992, Georgetown Marbury Hotel Grand Ballroom

February 12, 1992

8:00 am **Continental Breakfast**

8:30 am **Session I - "Overview of Laboratory Issues and Problems"**
Francis Collins, Chair

- National Data on Genetic Services
  - John Meaney-CORN
- Georgetown Forum (4/91) on the Technical, Regulatory and Societal Issues in Biotechnology & the Diagnosis of Genetic Disease
  - Seymour Perry, Chair, Community and Family Medicine, Georgetown University School of Medicine
- Criteria for Determining When to Move Diagnostic Tests to Clinical Practice (including aspects of costs and effectiveness)
  - Art Beaudet, Baylor College of Medicine
  - Joe Shulman, ~~Integrated~~ Genetics and IVF
  - Douglas McQuilken, Roche Molecular Systems, Inc.
  - Tony Holtzman, Johns Hopkins School of Medicine

9:45 am **Discussion**

10:30 am **Coffee Break**

PCR tech will continue to be avail through Roche for R&D
PCR for service will receive a royalty
9% - non-profit
? - for profit
varies.

February 12, 1992 (continued)

10:45 am **Session II - "Voluntary Genetics Laboratory Quality Assurance Efforts"**
Nancy Wexler, Chair

- George Knight, New England Regional Genetics Network and CORN DNA Voluntary Quality Assurance Committee
- Frits A. Hommes, National Biochemical Genetics Laboratory Proficiency Testing Program (voluntary)
- Mike Conneally, Huntington's Pilot Program Experience
- William Seltzer, Proposed DNA Quality Assurance Program
- Katherine W. Klinger, Ph.D., Vice President, Research, Integrated Genetics (private laboratory quality assurance initiative)

11:30 am **Discussion**
12:30 pm **Lunch**

1:15 pm **Session III - "Developing Standards and Criteria"**
Mike Conneally, Chair

- Jessica Davis, President, Council of Regional Networks (of Genetic Services)
- Wayne Grody, CAP committee on developing proficiency requirements for DNA testing and personnel
- Hope Punnett, ASHG Committe on Genetic Services
- Karla Matteson, ASHG/CAP Working Group amd CORN Southeast Regional Network
- Thaddeus Kelly, Vice Chair, ABMG
- Michael Watson, American College of Medical Genetics

ABMG
– Recertification requirements
– non-MD's excluded
– will no longer certify programs.

2:30 pm **Discussion**

3:15 pm **Break**

3:30 pm **Session IV - Regulation - Existing Authorities and Agencies**
Tony Holtzman, Chair

—Laboratory Regulatory Authority (State)

- Ann Willey, New York State Laboratory Program
- Patricia D. Murphy, Ph.D., New York State DNA Laboratory Licensing Program

3:45 pm **Discussion**

4:15 pm **Session IV - Regulation - Existing Federal Authorities and Agencies**
Tony Holtzman, Chair (continued)

- FDA—Max Robinowitz, M.D., Medical Officer, FDA

5:00 pm **Discussion**

5:45 pm **Session V - DNA Banking and DNA Data Banking**

- Phil Reilly, Shriver Center
- Victor Weedn, Armed Forces Institute of Pathology

6:15 pm **Discussion**

6:30 pm **Reception - Georgetown Marbury Hotel**

7:30 pm **Dinner - Georgetown Marbury Hotel**

8:45 pm **Session V - "Laboratories of the Future"**
Frank Fujimura, Chair

—Changes in Laboratory Technology and Informatics

- Paul Silverman, Beckman Instruments
- Nat Goodman, HGP Informatics Working Group

9:15 pm **Discussion**

9:30 pm **Adjourn**

~~Wendy~~ Seltzer – HCFA uninformed
community should be emphasized
Q A Education should be formal part.
Q. Counselors needed training

Meaney – DATA needed (Gen & BD)
historical DATA may be available through
FBMC & through states

Thad Kelley – original federal $ went to hire Gen couns.
again Seltzer that is still needed
Bissecker no reimbursement for gen counselor
gen counselor / MD signs bill.
goes into.

Karla Matteson – RFLP is illegal? todo??
? Do a lot of DNA work for people – No $
Quality control.
Education of prof & pts.

Fred's Hommes – genotype / phenotype correlations
know mutation – know gene product –
correlation between genotype & clinical
phenotype we are ignorant
phenotype is often multifactorial
theoretical background lacking
teaching & developing these areas is needed

Wayne Grady – Genetic testing / for common diseases
need standing authoritative
list of probes for. doctors.

Jessie Davis – year 2000 objectives
need more genetics.

Hope Punnett genetic makeup should not
exclude people from workplace.

February 13, 1992

8:00 am **Continental Breakfast**

8:30 am **Session V - "Laboratories of the Future" (continued)**
Helen Donis-Keller, Chair

—New Clinical and Laboratory Procedures

- Katherine Klinger, FISH 2-day AFP & CVS results
- Debbie Nickerson, Automating Ligation Reactions
- Francis Collins, Other Laboratory Advances and Prospects (e.g., Rapid Sequencing Techniques and Future Probes)

9:15 am **Discussion**

10:00 am **Break**

10:15 am **Session VI - "Human Genetics Laboratories and Conflicts of Interest and Commitments"**
Arno Motulsky, Chair

- David Blumenthal, Harvard University
- Robert Cook-Deegan, IOM, on Gene-sequence Patent Issues

10:30 am **Discussion**

11:15 am **Session VII - Commentary on Top Priority Laboratory Issues for Future: (5 minutes each of remarks from invited speakers-15 here)**

-for the 1990s? for the year 2000? and beyond?

12:00 pm **Working Lunch and Discussion**

12:45 pm **Session VII - Commentary (5 minutes each from 10+ invited speakers) (continued)**

1:30 pm **Discussion**

2:00 pm **Session VIII - *Committee Executive Session* - Discussion of Policy Implications and Need for Additional Data/Discussion**

4:00 pm Adjournment

Pat Murphy - desires tenable regulatory mechanisms.

Hope Dunnett - testing not an end - must be associated counns. etc.
science separate from $ (eg. ASHG ↔ ACMG)

~~Marie Robertson~~ Paul Silverman - "Ethnic kits" will impact on professionals & society.
social & psychological issues must be addressed.
personal accounts on individual groups eg. Hbs, etc.
important but do not convey value of ethnicity

Debbie Nickerson - automation needs

Victor Weedn - privacy needs
data banks / privacy
autonomy of pts vs family

Ann Willey - need for development / need for controls
need for national standards may not be tenable
regulatory reciprocity is needed.
if HCFA would have expanded cytogenetics regulations to all genetics might have helped

Thad Kelley - Education needs - careers in genetics must be emphas
Consumers must be empowered
regulation to ↑ quality of tests
good labs participate in prof. testing
bad labs may not - no requirement

George Knight - must be humble & seek help from experts for regulation

Joe Schulman - stop paying lip service to profit / non profit debate
outcome will be good in spite of some muddling now.
minimal regs streamline
no substitute for integrity
shortage of counselors - genetics
community should start schools
govt won't do.

Katherine Klinger - genetic testing more than DNA
? protein, metabolite, etc.
standards should not be DNA specific
learn from past (eg. clin. chem)
lab test only one part human component
don't get lost

Mike Watson - must get more focused.
directory of services
Education of professionals & public

CONSENSUS REPORT:
AD HOC COMMITTEE ON CYSTIC FIBROSIS CARRIER SCREENING
AMERICAN SOCIETY OF HUMAN GENETICS

The cloning and characterization in 1989 of the cystic fibrosis (CF) gene and its most common mutation immediately raised the possibility of identification of CF carriers by DNA analysis. The American Society of Human Genetics (ASHG) (Am J Hum Genet 1990; 46:393) issued a statement shortly afterwards that CF carrier testing should be made available immediately to individuals with a family history of CF. It was also stated that screening of the general population should not be undertaken until the detection rate of CF mutations improved, and effective educational and counseling guidelines were established.

An NIH workshop was convened in February 1990 and concurred with this view, publishing its statement (which was also endorsed by ASHG) a few months later (N. Eng. J. Med. 1990; 323: 70-71). In the subsequent interval, substantial progress has been made in defining the mutational basis of the disease and the basic biochemical defect. As recommended by the NIH workshop, pilot projects to study the complex issues involved in general population screening for CF in the United States have been initiated; complete results are not anticipated until 1993. Interest in therapie of CF carrier screening has expanded in the (medical) community, the public and the biotechnology industry. Accordingly, the ASHG Ad Hoc Committee on Cystic Fibrosis Carrier Screening has reassessed the issues surrounding CF carrier detection and has prepared this statement.

Cystic fibrosis is an autosomal recessive genetic disorder characterized by chronic lung disease and pancreatic insufficiency. There is a broad range of clinical severity. Recent advances in clinical care including postural drainage, pancreatic enzyme replacement, and improved antibiotics have led to a steady increase in survival, although a small fraction of individuals affected will die in the first decade with most patients now living into adulthood. Even without further improvements in therapy, most individuals born today with CF are expected to survive, albeit with a broad spectrum of lung impairment, into their thirties or forties. This disease affects about 1 in 2500 newborns of European ancestry at birth. It is less frequent among other ethnic and racial groups. About 1 in 25 persons of European ancestry is a carrier, having one normal and one abnormal CF gene.

A single mutation, denoted dF508, is found in approximately 70% of carriers of European ancestry. To date (as of Feb 1991) currently, over 160 different mutations have been identified. Many of these are extremely rare have been found in only a single family, but a few reach frequencies of 1-3% of CF carriers. Current surveys indicate that 85-90% of European CF carriers in the North American white population can be detected by testing for 6-12 mutations. The detection rate is even higher in some populations (e.g., Ashkenazi Jewish ancestry), but is substantially lower in blacks, Hispanics and Asians. In view of this heterogeneity, it is unlikely that CF carrier detection rates (Ahz) by DNA testing will exceed 95% by DNA testing in the foreseeable future.

The severity of disease in a given patient is to some extent correlated with the particular mutations present. However, it is difficult to make meaningful predictions about the clinical course of the disease based on DNA testing, because the spectrum of disease for a given genotype is quite broad. Furthermore, for all but the most common mutations there are insufficient

numbers of affected individuals to adequately define the clinical spectrum. A few mutations have been identified in the gene which produce a much milder phenotype, including isolated congenital absence of the vas deferens.

Analyses of the CF gene and its protein product indicate that the gene encodes a membrane protein, which has properties of a cyclic AMP-activatable chloride channel. Recent data indicating the dF508 mutant protein may have residual activities have raised the possibility of specific drug therapy. Intense efforts are also underway to develop gene therapy strategies to deliver the normal CF gene to the respiratory tract. Despite the potential of these approaches, however, their successful applications to amelioration or cure of CF are uncertain.

These scientific developments have implications for the issue of CF carrier screening, but do not in themselves resolve the question of whether such programs could or should be implemented at present. Population-based screening implies offering a program of carrier testing, with appropriate informed consent and genetic counseling, to potentially millions of healthy people. The purpose of such screening would be to allow people to make more informed reproductive decisions

Testing of individuals with a family history of CF, or with a blood relative identified as a CF carrier, is straightforward, accurate, and can significantly affect an individual's predicted risk of having a child with CF. Accordingly, there is widespread agreement that testing should be offered in this setting. This emphasizes the importance of obtaining accurate family histories for patients of reproductive age.

Although carrier

~~Despite the fact that~~ the detection rate is approaching 90%, ~~there are~~ still other important prerequisites ~~that need to~~ must further be addressed before widespread screening can be recommended. ~~Remaining issues~~ THESE include the effectiveness of educational materials, the level of utilization of screening, laboratory aspects (e.g., quality assurance, proficiency testing), counseling issues, and the beneficial and deleterious effects of screening. Of particular importance are the consequences of screening couples in which ~~only~~ one partner has an identified CF mutation. Pilot projects currently underway may help to address these issues. Finally, CF screening ~~should~~ must be viewed within the perspective of available resources and other health care priorities.

Although the Ad Hoc Committee on the whole believes that CF carrier screening should not be offered routinely at this time to individuals or couples without a family history of CF, ~~it is acknowledged that~~ some geneticists believe that ~~they~~ should inform such individuals of the benefits and limitations of CF screening. ~~It is recommended that programs choosing to initiate screening at this time~~ should compile data on patient decision making and outcomes to complement other pilot study data.

Recommendations:

- Although the sensitivity of carrier testing for CF has improved and pilots studies are underway, CF testing is not recommended at this time for individuals or couples who do not have a family history of CF.

It is
The Society acknowledged, ~~as in its previous statement~~, that testing of highly motivated individuals may occur. However this ~~should only~~ be provided by knowledgeable

Norm Foss

pt. initiated screening

Conflict of interest issues

We believe it is important to

Disclosure of conflict of interest
of members making recommendation

— Big problem in Entrepreneurial
endeavors

—

Anyone who does offer
should take extra steps
to avoid

- Individuals with a positive family history of CF, or who have a blood relative identified as a CF carrier, should be offered CF testing, with appropriate education and counseling. Optimally, carrier testing, should be offered prior to conception, to provide a couple the broadest range of reproductive options

- When indicated, CF counseling and testing should adhere to the following guidelines.

  a. Screening should be voluntary, and confidentialty must be ensured.

  b. Screening requires informed consent. Educational ~~material to be used before screening~~ should explain the benefits and ~~possible~~ hazards (e.g., ~~untoward psychosocial effects~~, stigmatization and loss of insurability).

  c. Providers of screening services have the obligation to ensure that adequate ~~education and~~ counseling ~~are included~~.

  d. Quality control of all aspects of the laboratory testing, including systematic proficiency testing, is required

  e. As with all indicated health care services, there should be equal access to testing

- Efforts should be expanded to educate health care providers and the public regarding the complexities of CF screening in particular and issues involved in genetic health care services in general.

- Individuals with a positive family history of CF, or who have a blood relative identified as a CF carrier, should be offered CF testing, with appropriate education and counseling. Optimally, carrier testing, should be offered prior to conception, to provide a couple the broadest range of reproductive options

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  e. As with all indicated health care services, there should be equal access to testing.

- Efforts should be expanded to educate health care providers and the public regarding the complexities of CF screening in particular and issues involved in genetic health care services in general.

ADHOC COMMITTEE ON CYSTIC FIBROSIS CARRIER SCREENING
COMMITTEE MEETING MINUTES
October 6, 1991
Washington, D.C.

The meeting was called to order at 4:10 pm by chairman Sherman Elias. Present were M. Kaback (Co-chair), A. Beaudet, J. Bowman, F. Collins, J. Davis, N. Fost, P. Reilly, P. Rowley, C. Scriver, and ACM Smith. Absent were E. Short, J. Sorensen, L. Tsui, N. Wexler.

I. Old Business:

A. Review of Existing Position Statement: The major issue under discussion dealt with re-evaluating the Committee's 1990 position statement. The Committee is on record as accepting the March 1990 NIH statement subsequently published in NEJM. This was communicated to ASHG membership by Past Chairman A. Beaudet at the fall 1990 business meeting. However, no written statement has been published by the Committee.

The NIH statement emphasized the need to meet certain criteria before mass population carrier screening begins. While significant gains have been made with respect to detection rate, pilot screening and education programs are just beginning with NIH funding via ELSI. Some Committee members felt strongly that these pilot projects must be completed before mass screening commences. There was a general consensus of the need to critically evaluate the existing 1990 statement in light of progress made since 1990. The possibility of achieving this via an 2nd NIH workshop versus as a committee meeting was discussed. Since convening a 2nd workshop would take some time, the committee agreed to hold another Committee meeting this winter.

A motion was passed to read the following statement at the membership meeting:

> *"Based on developments in the field of CF screening and testing, the Adhoc Committee on CF Carrier Screening concluded that there is a need to review the current ASHG position. The ASHG orchestrated and subsequently endorsed the statement from the NIH workshop on population screening for cystic fibrosis, which as published in the July 5, 1990 issue of the New England Journal of Medicine. The Adhoc Committee plans to meet within the next 6 months to thoroughly address these issues."*

B. Three additional issues which warrant the Committee's attention were raised by Fost:

1. Conflict of interest and genetic testing, and
2. Cost/resource allocation issues.
3. Need for specific practice guidelines for clinical care.

C. Beaudet announced to the Committee that as of 9/1/91 all prenatal patients seen for counseling by his group are informed about the availability of CF testing and offered testing (using a 2 step model) if they so desire. Also, he will be conducting group counseling/education sessions for the general population and offer screening to the general community. He will not accept samples directly from community physicians.

Kaback appreciated Beaudet's candor, but felt that prenatal patients are a vulnerable target. Without having the outcome of pilot projects, the question of potential "harm" to such couples needs to be discussed.

D. Future meeting: Plans were made to meet in February 1992 in conjunction with another ASHG committee. The morning of Day 1 would be for presentations and discussion; with general consensus on action items reached in the afternoon. A sub-committee (Elias, Collins, Reilly, Beaudet, and Fost; ACM Smith will serve as secretary) will be responsible for writing a draft document that evening to be presented to the full Committee for final review on Day 2. A tentative agenda (no order assigned) for the meeting was drafted as follows:

1. Review technical aspects of testing (L Tsui)
2. Review clinical studies/pilots, European and British experience and funded U.S. projects in progress (Rowley)
3. Proposals for policy (Fost & Reilly)
4. Line by line review of NIH/ASHG statement
5. Quality assurance issues (review CORN position - Davis)
6. Newborn screening for CF (J. Davis, Gen Services Comm)
7. Canvass other societies (ACOG AAP, NSGC, ISONG, AMA, etc) for statements.

E. CF Educational/Counseling Materials: At the last meeting the Committee agreed to attempt to collect all available educational materials pertaining to CF carrier screening. Since this was never officially announced, plans to publish a notice in the ASHG newsletter were made. These will be sent C/O ACM Smith at Executive Office. Smith has already provided a copy of the brochure prepared by the National Society of Genetic Counselors.

II. New Business: none

Given the late hour, the meeting was adjourned at 6:00 pm.

Respectfully submitted,
Ann C. M. Smith, Committee member

wp5.0\data\CFCOMM91.MIN

TO: Members, ASHG Ad Hoc Committee on Cystic Fibrosis Screening

FROM: Philip Reilly

DATE: 22 January 1992

Subject: Draft of Statement to Update ASHG Position (For Discussion)

In November, 1989, in response to the identification of the gene mutations in which cause cystic fibrosis, the ASHG issued a brief statement cautioning that the then available carrier test was not appropriate to screen individuals without a family history of the disorder and emphasizing that pre-test education, post-test counseling and quality assurance of laboratories were critical issues to address before embarking on any large scale screening programs. (1) Six months later an NIH workshop on population screening for cystic fibrosis issued a more comprehensive statement on the subject. It identified four reasons why screening "should not be recommended for individuals and couples without a family history". They were: that the test could only detect 70 to 75 percent of carriers, that the gene frequency varied substantially across ethnic groups (which complicated counseling), that there were limitations on the ability of our health care systems to offer proper pre-test education, and that 1:15 couples tested would face an increased risk (about 1:500) for bearing a child with CF and would not have access to a definitive prenatal test. (2) The ASHG statement and the NIH Special Report called for pilot screening programs to study these and related questions. The ASHG also created a special committee to monitor developments in this area.

Since 1989 many research groups have discovered scores of CF mutations. Although most are "private" (found in a single family), some account for between 1 and 3 percent of the total of CF chromosomes. Involved laboratories have added steadily to the panel of mutations used in screening. During 1991 several labs claimed the ability to identify 85-90% of carriers among persons of northern European ancestry. It is now clear that a multiple mutation test has or will soon surpass the 90% level of detection for northern European and Ashkenazi Jews. Assuming a 90% figure, this means that 81% of all at risk couples will be identified. Those couples in whom one is positive and the other has tested negatively will face about a 1:1000 risk of bearing a CF child. This is higher than their pre-test risk (1:2500).

The advances in testing are welcome but the twin problems of education (of both primary care practitioners and patients) and counseling of individuals and couples in whom one or both spouses test positive have not yet been addressed in a comprehensive manner. The ASHG is hopeful that the results of pilot studies in Europe and the USA will help teach us how best to provide CF screening. Many of these studies are underway and preliminary results may be available in 1993.

We have entered a new, but still early, chapter in CF testing. In that light we suggest the following:

1. All physicians who identify individuals with a family history of CF should inform them about the CF carrier test and explain its benefits and risks, or refer them to physicians or genetic counselors for such information.

2. Clinical geneticists and genetic counselors who are counseling individuals or couples about reproductive concerns should inform them about CF testing, and explain its benefits and limitations.

3. In all circumstances in which a health care provider informs a patient about the availability of CF carrier or diagnostic testing he or she should be prepared to provide or arrange for pre-test education and to provide or arrange for post-test counseling to appropriate persons.

4. ASHG should not attempt to set standards in obstetric practice, but by letter should urge ACOG to closely monitor developments in CF testing and at intervals publish a position statement on this subject.

5. ACOG should decide whether obstetricians who will be performing an amniocentesis or CVS for other reasons should inform women and/or couples about CF testing and explain its benefits and limitations.

References

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

2. Statement from the National Institutes of Health workshop on population screening for cystic fibrosis gene. NEJM 1990; 323:70-71.

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CF comm mtg

Attention anticipated - Wall Street Journal
Black out of mtg results until Brd mtg.
Brd mtg SPRING / LA JOLLA too late
Brd may be asked to approve by FAX / Phone.

Update Lap Tsui
? CFTR - chloride channel
Diff ē CF mutation detection
large gene - multi-exon
PCR based technique
normal SEQUENCE variation
no CONVENIENT functional assay
Some may be buried in introns ??

10 new mutations each month
168 mutations ?

Differentiation between mild / severe mutations
mild → pancreatic sufficient
severe → pancreatic insufficient

mild / mild } → mild
mild / F508 }

F508 / F508
F508 / severe } severe
severe / severe }

Ed - This is really going to complicate counseling
"You are carrier for a "mild" form of CF."

60000 screened
215 positive scr.
14 confirmed

RESORT AT SQUAW CREEK

Cong absence of vas deferens ± CF mutations
No other evidence of CF.

Rowley - nice job reviewing grants
Compl.

Kaback - says not all questions will be answered by these studies
eg. longitudinal studies re:
Education
Results impact
Peter disagreed stated his math long. compares

Beaudet - some other "unfunded" studies with may come out sooner than these.

Fam hx of indiv affected different fam hx of CF carriers.

Davis CORN

NB Screening
WIS. 200,000 screens 350 ↑IRT 40 ± CF
2 tiered testing now ↑IRT → DNA analysis.

Discussion of NB screening

Discussion of other statements

Positions do not support pop based CF screening.

Kobacker feels there is no justification for moving to gen pop.

3 islands of difference - BAYLOR / FAIRFAX / Cooke
Brandt Schulman Gilbert
advocating broadbased screening

Discussion

Duty to inform

Is it providers responsibility to initiate discussion at this time.

Do test, Recommend test, Offer test, Info about test, Dissuade from having Test

National Commission of Consumers

to respond to Experts recommendations re: CF screening.

Consumer opinion is only one opinion.

What about legal opinion, professional opinion etc.

? Rec. Should be done, offered, informed
Disc.

Discussion re disease
I suggested writing committee look at Ben's document

Spectrum of disease must be discussed
DNA analysis has allowed identification of previously unidentified people who were mildly affected.

Incidence 1/2500 → 1/3000
1/25

$\sqrt{160}$
4 | 3000
28
20
20
224
56
784

Expand background in 1st paragraph
160 mutations
7 out of 97 p̄ sequencing no identifiable mutations ? introns

Norm Fost
- Any c̄ fam hx of aff'd or carriers / Duty to offer
- No fam hx no duty to offer or inform

Art Question is... Should people be informed or not!

Mike - ASHG should look at Ed materials & make recommendation
NO - By others in group

#2 statement
Yes Bowman, Davis, Beaudet
No Rowley, Smith, Collins, Kaback, Fost,

Screening standards clear - 20 years old — things have not changed

Is it time to revoke 1990 recommendations

Art - Must report minority opinion
Art, Phil, Tom, Jim, Jessica

Bullets

- Despite recent technologic advances Gen pop screening still not rec. Trials → pilots underway
- People ± relatives ± CF should be educated & couns re test offered

? Optimally
in In order to ~~in~~ provide broadest range of rep. options
PCC is better than PN

- Equal access as with other health services.
- Due to anticipated ↑ in gen. scr.
- Based on Early exp. Prof. Ed of Health Pros as urgently needed.

* De-emphasize 90-95% Reversibility as major ~~issue~~ criteria for implementing screening

* PCC may or may not be optimal
does ↑ options, but may in fact not be optimal.

* Some people would say this committee ~~is not~~ is not a representative sample of the Society.

Ad Hoc Committee on Cystic Fibrosis Carrier Screening

Resort at Squaw Creek
Olympic Valley, CA
February 10-11, 1992

AGENDA

Monday, February 10, 1992

7:30 am - 8:00 am	Continental breakfast	
8:00 am - 8:20 am	Brief review of technical aspects of CF screening	L. Tsui
8:20 am - 9:00 am	Review clinical studies/pilot studies	P. Rowley
9:00 am - 9:15 am	Review CORN position and CF newborn screening	J. Davis
9:15 am - 9:45 am	Discussion of statements from other societies and educational materials	
9:45 am - 10:00 am	Review NIH/ASHG statement	
10:00 am - 10:15 am	Break (Coffee/Soft drinks)	
10:15 am - 12:00 Noon	Proposals for policy	
12:00 N - 5:30 pm	Lunch (provided) and break	
5:30 pm - 7:00 pm	Consideration of ASHG CF statement changes	
Monday evening	Subcommittee to develop a working draft of a new ASHG CF policy statement -- Elias, Collins, Reilly, Beaudet, Fost, Smith (to also serve as Secretary).	

Tuesday, February 11, 1992

7:30 am - 8:00 am	Continental breakfast	
8:00 am -	Discussion and finalization of new ASHG CF statement	

Need Health Economist to review this proposal

* David Ask MS/U of Penn School of Med
Prescriptive Decision Modeling for CF Screening
Specific aim: To guide the development of health policy re: genetic screening, specifically CF screening.
Cost/Benefit Analysis to be carried out
Cost/Effectiveness
Cost-identification
Cost-utility
incremental cost effectiveness

spent: # saved
spent: CF birth prev
look for lowest cost
spent: many outcomes allows Exam of diff strats at one time

3 yr / 440,000

will identify cost from various perspectives
pt/fam; insurance co. & Society

Should CF screening target ΔF508 mutation alone or others as well
Should screening be parallel or serial
Should rescreening occur as new mutations are identified
Id best sequence of testing & treatment following alternative screening results
What is anticipated impact of future innovations in screening / prev. dx / Rx
What are monetary / non-monetary tradeoffs
How will answers vary according to perspectives

Yes Economist no psychol?

David Asch U of Penn School of Med

X How much Info About Risk for CF do Couples Want

Aim: to elucidate the important factors in individual judgments about value of genetic carrier info

Test:

Many Preconception couples prefer less info to more

Many Prenatal couples prefer less to more info

Couples in preconception prefer more info than couples in prenatal.

Will test

Sequential Carrier Testing Strategy

Believe most couples will opt not to test partner if 1st partner is negative. Believe preconception couples will be somewhat more likely to test partner

Psychologist yes

E

Bonnie Barry U of Utah School of Med
CF screening in high & low risk pops

Concerned about depth of application
lack of literature re: other programs
which have tested mechanism
for delivery of services albeit
not for CF.

No statistical analysis.
Anticipate 2000 tests in 3 yrs.
what will approach statistical significance
high personnel effort

psychometrician?

749,000
3 yr
expensive
to answer
these questions

Bob Baughmiller
CF Carrier Testing and the Churches

Not a bad idea. Pretty superficial proposal.
Methodology vague
No outcome measures.
Statistical significance ??

3 yr
496,000

Maimon Cohen — U of MD School of Med.
Previous Screening Experiences: Lessons for CF Screening

Using study groups w previous screening experiences (Jews & Blacks) will assess
- understanding, interest, readiness
- format
- outcomes
  - stigma, discrim, confid.
  - cost effectiveness

3 yr. 655,000

Using Academy of Sciences guide to screening principles

no - psychol ed nurse

Team
?? Anthropologist
psych
Ed

wonder if Caucasian (non-Jewish) group wouldn't add some info to this proposal - those with no past screening exp. for comparison.

Bob Greenstein U of CT School of Med

~~[illegible] NSF Med School~~

Study of CF Screening in Primary Care Settings

Assess & Analyze decision-making re screening for CF

Factors affecting screening vs non-screening

Develop ed programs

639,000
3 yrs

Primary care setting

Interdisciplinary
MS RN & PhD RN
Self efficacy / Health Belief Model

Nursing is involved using validated tools.

Frank Deposito NJ School of Med

Carrier Status in Families.

Assess factors which influence communication re: CF carrier status among family members

Will interview informed family members

? What about bias — those families who choose not to inform family members.

3yr $500,000

Design Ed / counseling strategies

This does not look at Gen pop screening issues.

2 yr
428,000

Sherm Elias U of Tenn Memphis
Client Values in CF Carrier Screening

Wants to develop mechanism to ~~develop~~ provide info within the context of their personal belief or value system.

(support material?)

Inventory form will determine if value system is
Logical
Expert
Spiritual
or Experiential

In Literature didn't see
set.
2 page inventory
1 in set

p. 69 "moral value" based instruction by GC
broad assumption

Four sets of interactive Videodisc Ed materials will be developed & administered to 2000 people (1000 couples)

Sounds interesting - wonder if it can be done in that time for that cost. 41,000
Technology available.
?? Videodisk application to rest of country

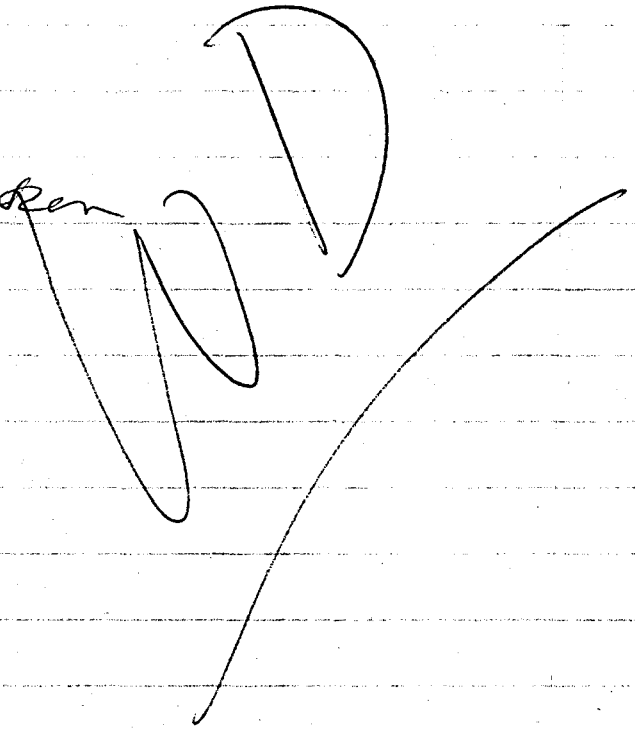
Frank Grad Columbia Law School

1 yr
639,000

expensive
budget justification missing
from my copy.

Legal Research

Conference
Book
? Draft Legislation



Wayne Grody UCLA School of Med
~~Wayne Grody~~ CF mutation screening & Couns

3 yr
685,000

Aims
~~[illegible]~~

Assess interest / acceptance. ethnically diverse pop
Study ethical / social issues
Assess efficacy
ascertain technical feasability / dried blood spot
Gain estimate of allele freq.

12,000
.04
480.00

20,000 women (40% refusal) 12,000 tested
< 100 newborns tested to ~~[illegible]~~ try to ident: false neg. rate
≅ 400 positive "face to face reassurance & counseling" p43.
questionnaires / letters seem pretty "~~[illegible]~~" due to lack of better word, "crude"
assure parents c̄ PD that CF is not present barring "freak" occurrences such as uniparental disomy.

12,000 tested — ≅ 4 expected to be affected if all 12,000 are pregnant
?? 400 women pos.
?? < 20 couples at risk
≅ 10 prenatal dx
2 affected ?

~~No anthropologist~~
~~[illegible]~~ Ed: Eth.

Eugene Pergamenti Northwestern U.
Focus groups designed CF ed services

3 yrs
$00,000 I Review of Lit
Focus groups (10) each 10-12 people ~ CF Exp. pts, fams, health prof etc
Develop focus group interviews
Ed mat devel
Analysis / prep for distrib
II Focus groups (4/6) 10-12 each
people ~ no CF exp, diff settings, diff Ethno cultural background, Regions
III ??

Question whether outcomes of focus groups will be that helpful?
Is staff prepared for this process?
Phase III not developed well

Ho Hum

Richard Erbe Buffalo
Social / Ethical Aspects of CF
Primary care setting, various Ethnocultural pops.*
① Study knowledge, attitudes psycho-social responses 3000 women

3yrs $500,000

* must read English & be able to fill out questionnaires

p to women will receive neg results at next prenatal visit — Assurances?

② Study OB attitudes

Plans use of focus groups although use is unclear
Good Proposal
Consultants Wertz, Rapp Sorenson etc.

Many goals Many hypotheses.

③ Conference of Experts.

Disagree on some of hypotheses. Ot-Web.

experiments not yet developed

believes NIH should pay for test

How about collaboration other funded sites ? Cheaper ?
consider paying for part of test

Lorraine Onean Gaines Valhalla N.Y
CF Counseling & Ed Strategies

Aims
1. Determine knowledge acceptance interest
2. Id optimum method pretest Ed.
3 Determine Effectiveness of 3 modes of info to group, indiv, take home.
4. Effectiveness of post test counsel
5. Effectiveness of Community based Ed workshops

3 yr $40,000

Is there a videotape?? Will they develop one

Lit search - limited to CF & Gen not other issues

Fairly simple proposal

Screening Routinely offered to fams w CF " ??

John Phillips Vanderbilt —
CT Screening: An Alternate Paradigm

OB Office Vanderbilt Self admin.

1. Determine ethically acceptable CT screening program to minimal G.C. Counseling, contact EXCEPT + pos results
2. Self administered? fingerstick method

3 yrs
90 4,000
Offense

Strong team no nurses

Only studying AFSOB

Good design — hours fingersticks unlikely to find many

Anxiety measures??

150
20 | 3000
1%
~150 carriers

Ct's projections (diff from theirs p 53)??
3000 150+ 6 partners also positive

6
500 | 3000
6 couples
++

NON-pregnant women will be recruited

* Excluding non caucasions is that justified?

no cost

Margretta Seashore Yale
Screening for heterozygosity

3 yrs 724,000

- assess knowl. attitudes
- use assess to design ed programs & mat
- use in primary care setting so no more gen prof are needed
- can rapid inexpensive tests be done.

Justification Will enroll 21-45, English speaking, not an undergrd

? Small Anticipate 70% enrollment ~~[illegible]~~ Expect. 544 total

544/22 = 5,140? 22 carriers / 1 couple? is that enough

* No psychologists, nurses, ed spec. consultants will be designed ed tools

Wylie Burke U of Wash
Decision-making in CF Screening.

3 yrs
$14,000

Assess interest in screening in
1. Relatives of CF pts (180) } free test
2. Couples getting prenatal care (180)
3. Primary care pts (400) } ½ free ½ $125
4. Telephone survey (random) (400)
Two groups randomized written / in person

Likert

Determine acceptance rates four groups
Satisf. & retention in person vs written
Id adverse effects — ?? such as

Plan to look for 6 alleles
1150 subjects
no exclusions

Good team
yes Research coord - nurse Ethicist
* no no psych; Ed cons.

Paolo Maria Fontina Childrens Philadelph.

3 yrs
$60,000

This is aimed at furthering technology
Automated procedures for 5 mutations
Method for 40-50 other mutations
Cost effective way to do blood spots

Not reviewed?

Fred Gilbert Cornell Univ.
Studies of Testing & Counseling for CF mutation

3 yrs
900,000

Determine interest and acceptance in different SES groups
Compare pre-test mechanisms & acceptance in different SES groups
Determine post-test info/couns & f.u. needed.
Determine if different settings require more input
Determine limits of disclosure
Compare accuracy & acceptance of two methods blood / mouth rinse
Define costs / reliability of testing
— 6 mutations
Good preliminary work for year

Pregnant women / all races.
Pvt MD office / OB clinic UH / GC clinic.

no psych, Ed, [redacted]

Mark Hughes Baylor
CF Ed

Assess knowl & attitudes pvt OB gyn group
Evaluate Ed programs (health educ
Evaluate videotape & lin couns → carriers
Eval Ed models for recruiting fam memb
Conduct post intervention interview ↑ carriers
to assess psych impact
Cost effectiveness Eval.

3 yrs
955,000

uses focus groups

N = 20,000 OB/GYN
N = 350 focus or 700 car. pat.

OB - preg vs non preg
Cost / No cost
Ed interven Effectiveness

Good team —
Ed. spec nurse yes
no psychol.

Good plan
Big #'s

Stevens Tulsa

Psych Effects of CF Scr. & Couns

2 yrs
64,000

Examine effects of CF carrier testing on psychological functioning (psychiatrists)

Cheap

Examine effects of couns.
Efficacy of methods of couns

N = 75 fairly small sample
? only 3 will be carriers
unlikely

With Kaiser San Jose
CF Screening Pilot
Feasability of Screening
in HMO

2yrs
406,000

N = 5000 . White/ Hisp pregnant

5 mutations

psych.
no Pt Team

Linn Community Health System as Model for Genetic Screening

Metrolab
Portland

3yrs
834,00

① To explore gen knowledge
② To identify factors that predict interest
③ To assess advantages & disadvantages of conveying results of gen testing through primary health care providers.

→ N=400
Expensive

/ mutation

Primary Care Feasibility Study

+ Team

nurse midwife & pract.
psychol.

Parad Boston Childrens
CF Carrier Screening Opt Couns & Testing

3 yrs
968,000

Develop Ed mats written, videos, couns
Focus groups feedback

1800 low risk couples
500 high risk couples

Looks like good proposal

Focus Groups

Team
Psychologist / PhD RN
Nurse
Ed Consultant

Susan Black Gen & IVF
CF counseling & screening
2 yr - compare two pops
614,000 ① upper middle well ed pop (Gen & IVF)
② inner city (Hutzel Detroit)
- Measure comprehension, reactions of pts
- Two different approaches to Ed & Couns.
- MD perceptions

Good genetics team but no one from ed / psych etc.

? N-4000 Gen & IVF — 7 mutations (3 in Jewish 92%)
N-3000 Hutzel
Measure comprehension
simple vs complex couns / mat.
Measure impact on MD
Measure preconception vs post concep
compare Gen & IVF pop vs Detroit
Develop recommendations

Good pilot stuff

Bob Desnick Mt Sinai NY
CF Testing/Counseling in the Ashkenazi Jewish Pop

3yr $92,000

Conduct & evaluate pilot screening program in Jewish pop
90-95% of carriers can be identified
≅5000 couples
will be recruited for screening for Tay Sachs (96%), CF (90%) & Gaucher (93%)

Psychological studies to be [redacted] (directed) out by psychiatrist

Dr Eng (PD) 1/2 time or 1/4 time P-8 ??
$30 000

Good experience ~ screening program
Looks like well written proposal

Rena Falk LA Childrens

Use of Spanish Video / Pamphlet:
A Model for CF Screening
(Testing the Tools only)

3 yrs
617,000

N = 1200

Develop pamphlets & Videotapes
English & Spanish
Administer Video vs pamphlet Evaluate decision
knowledge
& wk fu.

Only pt's CF fam hx will offered testing ??
What about anxiety in the test??
5 mutations

no Education consultant (who has training in ed principles)?
Ethnically Sensitive (appropriate)

Helen Fanos Children's Oakland

Perception of Carrier Status by CF Sibling

3yrs
364,000

Aims ① to identify factors motivating or interfering in CF testing of sibs
② assess CF sib's spouses interest
③ Assess understanding of results
④ Assess psych functioning & Id probs.

Sibs & spouses 102 (N)
sibs 2/3 (50) will be carriers 30 ? 20 not all detected
? only one couple would both carry
N too small ??

Full time salary for N = 102 ?
× 3 yrs ?

Good idea, but ....

Thad Kelley U of VA

Pop Screening for CF carriers: A Pilot Proj.

4 yrs
1.7 million

Hypotheses

① Knowledge & interest is low
② Can be integrated into existing MED GEN services (at a high price)
③ Diff ed programs are differently effective
④ Costs will have a major impact
⑤ GC can prevent negative consequences
⑥ Ideal setting may be schools

they confirmed

Aims:

① Ascertain knowledge & interest
② Develop "variety" of ed mats
③ Post ed/couns. interviews determine what factors determine decisions re testing
④ Evaluate cost as major variable
⑤ Assess impact of carrier testing on self
⑥ Establish working groups ± public school systems

interest

high prenatal 1500
mod GC clinic (800-1000) ½ both present
low Fam Pl clinic 1000

n = ≃ 500 ≃ 500 ≃ 500

Where's budget justification??

high personnel effort & cost

John Mulvihill U of Pittsburg.
Evaluating systems to detect CF carriers

3 yrs
866,000

① Assess existing knowledge & of 700 Health Profs
educate & evaluate impact.

② Recruit 5200 pts measure knowledge
educate, offer testing, & assess impact
evaluate decision process

③ Evaluate various ed models
Assess issues re: confidentiality.

5 mutations to be tested

Good team
Good design

Carole Ober U of Chicago

3 years
$84,000

① Develop computer automated system for calculating modified risks for CF carrier Status.
② Study knowledge & attitudes, effects various ethnic groups
③ Cost benefit / effectiveness analysis

No psychologist
otherwise good team
Arm 1 - Ober Nagylaki Thisted
Arm 2 - Ober Easton Very Burton Krauthoff Boon
Arm 3 -
Herckerling / Very PI's - ~~not in budget~~ consortium?

Jim Sorenson — U of North Carolina

An Eval of Testing & Counseling for CF mutations

3 yrs
$42,000

① Compare effectiveness & cost effectiveness of two CF carrier screening arrangements (no counselor vs counselor)
LMD vs GC clinic

② assess effectiveness & cost effect of video (Video to be developed ? focus input)

③ Compare LCR to PCR techniques

Good psych. components

Pretty good team

Eva Supansky

Model Std Ed & Carrier Testing in Primary Care Offices

3yrs
611,000

① Measure interest & understanding gen pop
② Compare methods of Ed & Effectiveness. brochure, vide, office nurse
③ Blotter pad collection F508 mutation $30 whites only / PCC & PN/OHQ
④ Carriers to gc clinic
⑤ non-carriers letter

Cost effectiveness & minimum standard of car.

F508 only

Whites only

Education consultant

Judy Capra

no psychologist?

use Gen Applications

Course to train nurses