DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
Building : 38A
Room : 614
(301) 496-7531

August 24, 1990

Dr. James Watson
Director
Cold Spring Harbor Laboratory
P.O. Box 100
Cold Spring Harbor, NY 11742

Dear Dr. Watson:

I am pleased that you will be able to attend the upcoming workshop of the NIH-DOE Working Group on the Ethical, Legal and Social Implications of Human Genome Research. The purpose of the meeting is to hold an informal discussion of the social and professional issues involved in the integration of genetic testing into mainstream medical practice, taking our unfolding experience with cystic fibrosis testing as a starting point. We look to you for guidance with respect to the activities of the National Center for Human Genome Research and the role of the community at large in responding to the challenges of these emerging genetic tools.

The workshop will take place from 9:00 a.m. to 5:00 p.m. on Monday, September 10. Reservations for those participants who are staying overnight remain at the Holiday Inn Crowne Plaza. Due to ongoing renovations at the Holiday Inn Crowne Plaza, the meeting room will be across the street at the Days Inn, 1775 Rockville Pike, Rockville, MD. The Days Inn is two blocks west of the Twinbrook Metro Station.

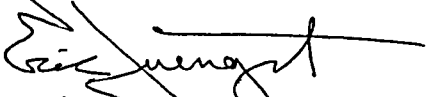
The ELSI Working Group members who are participants in this workshop will be staying through 5:00 p.m. on September 11, to discuss the implementation of ideas raised at the workshop, and to assist the Center with program planning.

Some of you have already sent to the office a brief biography or curriculum vitae. If you have not already done so, we would very much appreciate receiving this information.

Enclosed is a list of participants who are attending the workshop, and some reading material relevant to our discussion.

If you have any questions or suggestions, please do not hesitate to contact me or our Program Assistant, Ms. Elinor Langfelder (301-496-7531).

Sincerely,



Eric T. Juengst, Ph.D.
Program Director
Ethical, Legal an Social Implications Program
National Center for Human Genome Research

cc: Nancy Wexler, Ph.D.
Benjamin Barnhardt, Ph.D.
Elke Jordan, Ph.D.

Enclosures

NIH-DOE Working Group on
Ethical, Legal, and Social Implications of Human Genome Research

Workshop on the Introduction of New Genetic Tests
September 10-11, 1990

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

October 23, 1990

To: James D. Watson, Ph.D.

Re: Information on CF Testing Trials for Meeting with Dr. Gordon, NIDDK

There is a growing recognition within the human genetics community of the need for careful clinical studies of genetic testing for cystic fibrosis. The way in which the cystic fibrosis test is developed, evaluated and introduced clinically is seen to be an important precedent for future genetic tests, because of the comparatively higher incidence of CF within the U.S. population.

Reports from the American Society of Human Genetics (Nov., 1989), the NIDDK Workshop on Population Screening for the Cystic Fibrosis Gene (March, 1990), the NCHGR Workshop on the Introduction of New Genetic Tests (Sept., 1990), and the medical literature have all identified comparative clinical studies of CF testing protocols as the highest priority prerequisite to integrating this test effectively into clinical practice. Such trials are necessary to evaluate the **test sensitivity and specificity levels** required for effective testing, the **optimum setting and design for testing** programs, the **psycho-social impact of testing** on patients, and the **professional infrastructure** required for wider-spread testing.

The NCHGR is currently exploring a number of possible sources of federal support for such clinical studies, including the HHS Agency for Health Care Policy and Research (Dr. Jarrett Clinton, 301-443-5650), the Genetic Services Branch of the HRSA Division of Maternal and Child Health (Dr. Jane Lin-Fu, 301-443-1080), NICHD (Dr. Felix De La Cruz, 301-638-5042) and NIDDK.

The NCHGR, through its program on the Ethical, Legal and Social Implications of Human Genome Research, is already soliciting proposals for studies that attempt to assess the psycho-social, professional ethical, and legal parameters of different genetic testing protocols, in order to help prepare for future tests. These studies could be natural complements to or components of a comprehensive clinical study of CF testing, and NCHGR would like to collaborate with other funding sources to make such combined assessments possible.

Please let me know if there is further information I can provide. I have enclosed, FYI, a copy of the draft report from the Sept. ELSI Working Group Workshop, which is still under review by Nancy Wexler.

Sincerely,

Eric T. Juengst, Ph.D.

cc: Elke Jordan

Faxed to JDW on 10/24/90

DRAFT

Working Group on Ethical, Legal, and Social Issues in Human Genome Research
National Center for Human Genome Research and Department of Energy

WORKSHOP ON THE INTRODUCTION OF NEW GENETIC TESTS

Rockville, Maryland
10 September 1990

In 1983, a presidential commission concluded that

> "Within the next decade screening for cystic fibrosis may be possible. This could be of great benefit. If adequate preparation for its introduction is not made, however, it could also create? serious problems... The possible demand for millions - or tens of millions - of tests in a short period of time, and the consequent need for follow-up diagnostic studies and counseling, is daunting in itself. The Commission ... encourages continued attention to this area by government officials, as well as by people knowledgeable about relevant scientific, ethical, social, and legal concerns" [President's Commission, 1983].

The technical capacity foreseen by the President's Commission is nearly upon us. In August 1988, the discovery of the gene causing cystic fibrosis (CF) was announced. Discovery of the gene led quickly to isolation of the protein whose malfunction causes the disease [Kerem, Rommens, Buchanan, et al., 1989; Riordan, Rommens, Kerem, et al., 1989; Rommens, Iannuzzi, Kerem, et al., 1989], and ushered in a new era of hope for children and young people afflicted with the disease. Further understanding of exactly how the disease is caused might lead to new treatments in the next decade. Identifying the gene also raised the prospect of developing a genetic test, at least for some individuals.

The ability to test for cystic fibrosis raises many public policy issues. This is, in large part, because CF is among the most common single gene defects in Caucasian populations. Demand for CF testing may well swamp a system of genetic services already short-handed and underfunded. Because of this, professional practices and public policies established with respect to CF testing will provide important precedents for the introduction of the new genetic tests that the Human Genome Project is expected to produce.

Soon after the cystic fibrosis gene was discovered professional groups warned that any significantly increased testing required that substantial technical and logistical obstacles be overcome. The American Society for Human Genetics issued a statement in November 1989 [Caskey, Kaback and Beaudet, 1990]. A March 1990 consensus development conference convened by the National Institutes of Health concurred [Workshop on Population Screening for the Cystic Fibrosis Gene, 1990]. Wilfond and Fost wrote about the policy issues remaining to be faced in even greater detail in the Journal of the American Medical Association in May 1990 [Wilfond and Fost, 1990].

To analyze the implications of these issues for genome research, the NIH-DOE Working Group on Ethical, Legal, and Social Issues in Human Genome Research convened a workshop on issues involved in the clinical introduction of new genetic tests on 10 September 1990.

The Working Group invited 12 experts from various sectors of genetic services to discuss the technical status of CF testing and to outline the policy issues facing the nation in the near future. The remaining sections of this document summarize discussion at that workshop.

The disease. Cystic fibrosis affects several organ systems, especially the pancreas and lungs. Most symptoms trace to plugging of pancreatic and lung ducts by viscous material, caused by aberrant secretions from nearby tissues. The dysfunction of membrane proteins apparently alters the composition of material secreted into these channels, and the material cannot be cleared.

The plugged channels isolate lung spaces which then become fertile ground for infection. The path for secretion of pancreatic enzymes into the intestines is blocked, resulting in poor digestion of fats and other foodstuffs. Diagnosis is usually made in childhood because of recurrent lung infections or digestive problems. The disease was often fatal in childhood until recent years, but survival has now been extended well into the twenties by improved treatment of infections and better management of other common clinical problems.

Clinical variability. The severity of cystic fibrosis varies dramatically from case to case. Some children die even now, despite advances in treatment. Other cases are relatively mild and are not noticed until the teens or even later. This variability makes genetic counseling difficult. The experience of the disease reported by families with affected children reflects this clinical variability.

The molecular defect. Cases of CF studied to date trace the cause to a gene that produces a single protein. There many different ways to disrupt protein function, however, and dozens of CF mutations (alterations of DNA) have surfaced in the year since the gene's discovery. The plethora of different mutations may help explain the variations in severity of the disorder. If so, genetic tests may help predict the severity of disease, and the need for increased clinical surveillance.

Genetics of CF. Cystic fibrosis is a **recessive** trait - it is inherited when a child receives defective copies of the CF gene from ?0?? parents. Approximately one in twenty-five Caucasians has one such defective CF gene. Such individuals are called **carriers.** Couples are at high risk of having a child with CF only if both parents are carriers (roughly one in six hundred couples). In such couples, the risk of having an affected child is one in four with each pregnancy.

Variable prevalence in different population groups. The prevalence of CF differs markedly among different population groups. It is relatively rare in most African and Asian populations studied to date, and relatively common among Caucasians. In some populations, especially northern European populations, a single mutation causes the vast majority of cases. In Denmark, for example, 88 percent of cases are caused by a single mutation, called DF508. In other regions, however, as few as 30 or forty percent of CF cases are due to this particular mutation [The Cystic Fibrosis Genetic Analysis Consortium, 199(?].

Testing is already underway. Some countries have already initiated screening programs. In the United States, individual doctors, usually obstetricians, offer the CF test to their patients. Estimates from a series of 500 tests submitted to Houston from around the nation that by testing for the major mutation and the four next most common ones known, 84 percent of carriers are detected.

Most tests are done during pregnancy. Approximately twenty-four of twenty five tests are negative. When a woman is identified as a carrier, then her spouse (or mate if not married) must also be tested. If both are positive, then they are a high risk couple, and have a one in four risk of having a CF baby with each pregnancy. If the man is negative and the woman positive, the risk is approximately 1 in 600, higher than the general population. These couples and those at high risk need genetic counseling to explain the risks and to describe CF so that the couples can make an informed choice about whether to seek prenatal testing.

In Denmark, 95 percent of CF patients receive their health care from a single hospital, the Rigshospitalet in Copenhagen, where they are seen monthly. This ready access to care, combined with a robust national health program and the high prevalence of a single mutation make introduction of genetic tests desirable. Using national health service funds, the Rigshospitalet now offers CF testing.

Early testing has centered on two groups: those with an affected child already, and therefore at 1/4 risk with each new pregnancy, and carrier testing among those of reproductive age. Among families whose risk is known to be 1/4, 80 percent take the test for new pregnancies. Of 50 tests in this group, 12 affected fetuses were detected. Families chose abortion in ten cases and chose not to abort in the other two.

The Rigshospitalet is also offering carrier testing. By testing for the most common mutation and the next most common one, it is estimated that the Danish group is detecting roughly 90 percent of carriers. Of four hundred women offered the test, all but two have taken it. This identified 70 couples in which the spouse was tested (to see if he also was a carrier). Three couples at 1/4 risk have been discovered. Two children from these couples tested positive for CF, and both were aborted. The Danish group will now be continually evaluating the benefits, costs, and reactions to the CF testing service.

In the United Kingdom, there are five pilot studies underway, offering CF testing under a variety of circumstances to different populations. By testing for the major mutation and the three next most common one, it is estimated that the British groups are detecting 85 percent of carriers. In surveys of families, 95 percent of CF families wanted the test available, and 90 percent believed abortion should be available to those at high risk of having affected children. The UK pilot programs focus on different test approaches. One tests all single individuals of reproductive age, another tests couples at the time of marriage and couples entering pregnancy, one is offered through general practitioners, and two test during pregnancy and are linked to obstetrical care.

The UK testing pilots are budgeted for $2 per test, for an projected 50,000 tests this year. Costs are much lower because of the general framework for delivery of health care provides many of the

educational, counseling, and follow up services that must be separately budgeted in the United States. Another major factor is the high volume of standard samples from a single source, which contrasts markedly with the standard American laboratory that receives different kinds of samples from around the country. Most laboratories in the United States do duplicate tests, print formal reports to the referring physician, and carry significant administrative costs associated with widely disparate reimbursement sources and practices. A CF test generally costs $300 in the United States as a consequence of these technical and logistical differences.

The current state of knowledge makes CF testing complex. The CF test has proved far more complicated than imagined before the gene was discovered. The fact that many different mutations cause the same disease means that no single DNA-based test is adequate to the task of reliably detecting carriers or affected children. In the future, it may be possible to develop tests that detect many different mutations in a single test; or it may become possible to test the function of the membrane protein directly, so it would not be necessary to sort through genetic differences. Improving the detection of CF is an immediate urgent scientific priority, being pursued in dozens of laboratories around the world.

Until more sensitive and specific tests become available, however, it is clear that there will be CF testing. The question is how much, how good, and how costly such testing will be.

Policy Issues

Urgent need for trial testing and screening programs. Both previous policy statements have noted an urgent need for trial testing programs. Such programs are already underway in other nations. In the United States, however, the situation is much less amenable to study, and the data are spotty. Some doctors offer the CF test to some people. There is no systematic evaluation of how the services

are offered, how the information is channeled, how well tests are being performed and interpreted, or even whether those availing themselves of the test are helped or harmed. There are 3.5 to 4 million births in the United States each year. If even a small fraction of those requested CF testing, the system would be overwhelmed, from laboratory testing to genetic counseling. There has been restraint to date among companies offering testing services, doctors, and genetic clinics. As the general public becomes more aware of the availability of CF and CF testing, however, the demand will certainly escalate. There is a limited time to gather the information necessary to ready genetic services for this demand. Trial testing program are essential to anticipate future problems and to make testing efficient, fair, and reliable.

Need to assess how genetic tests are paid for by private insurers and prepaid health care providers. Payment for genetic tests varies widely in the United States. In some cases, tests done during pregnancy are reimbursed, but those done to detect carrier status (e. g. , when deciding whether or not to become pregnant) are not. Testing for CF, for example, is not routine, as noted by the public policy statements to date. Some payers reimburse only for services that are "standard care," in which case CF testing would still be excluded, with the exception of families with an affected child, and thus known to be at high risk. Information on reimbursement practices is needed to devise and to decide among policy options. A distillation of criteria on which reimbursement decisions are now made, and how they are likely to be made in the future would be particularly valuable.

Need for improved professional education of physicians, genetic counselors, and others who will provide genetic testing services. Medical genetics has until recently been largely an academic specialty concerned largely with diseases affecting specific populations or rare disorders. An expanding array of new tests like the CF test may well change the complexion of medical genetics, because so many Americans will be directly at risk, and may wish to avail themselves of new genetic

tests. Previous policy statements have noted the need to ensure that any testing be performed only where there can be adequate education, counseling, and clinical follow up. There are approximately 800 genetic counselors and 500 clinical geneticists in the United States, and perhaps another 200 trained individuals offering similar services. They are already strained by current demands, and training is not keeping pace with opportunity. Only 75 new Master' s level genetic counselors are trained each year nationwide. New graduates typically have five or six job offers, and many slots remain unfilled. Yet the anticipated demand for genetic testing has barely begun to be felt. To meet the demand for future genetic services, professional training must be broadened into mainstream medicine and deepened to accommodate the deluge of new information flowing out of molecular genetics.

Need for broad public education at all levels. Genetic diseases are still largely mysterious to most of the general public. The flurry of publicity surrounding discovery of the CF gene has cast some light on that disease, but general awareness is still quite low. Beyond CF, a general understanding of genetics and genetic factors in health and disease will be increasingly important in the future. The conceptual base of medicine is shifting towards genetics; public knowledge must follow.

Need for laboratory quality control among centers performing genetic tests. For example, at present, only a dozen or so laboratories in the United States offer the CF test. As demand increases, however, this number will increase. With the increased number of testing centers, serious issues about the quality of laboratory services may arise. Given the complexity of testing for the multiple mutations and the state-of-the-art expertise in molecular genetics necessary to perform and interpret the tests, these problems may be even worse for CF than for previous genetic tests. Quality control standards for genetic tests must be devised, and revised on an ongoing basis as technology improves and

knowledge accumulates. A system for checking test accuracy, adequacy of documentation and other factors among different laboratories must be developed.

Informed consent. Confidentiality of test results. Previous policy statements have noted the need for all genetic testing to be voluntary and the results to be held confidential. Test results should not be disclosed to third parties without permission of the person tested, unless such disclosure can prevent impending harm to an identified person [President's Commission, 1983]. Tests should thus be administered only when made in response to an educated request by an individual. Results should be reported to the individual, and held confidential in the medical record. There are some ambiguities about how to communicate laboratory results in the American context, however. Laboratories typically report back to referring physicians. It is then the physicians' responsibility to inform the person tested. In some cases, there is a break in the chain. Some laboratories contact both referring physicians and the person tested, but this can lead to misinterpretation of the result, and in some states disclosure of results to anyone other than the physician is barred. The proper referral and notification strategies should be assessed, as part of the trial testing programs noted above.

There is also uncertainty about who now has access to medical records, including genetic data Whether protections are needed specifically for personal genetic data in medical records and in government files remains an open question. The range of alternatives is much more complicated that only mandatory testing or voluntary testing. For an individual seeking private insurance, for example, disclosure of medical records is necessary to obtain the desired insurance. Disclosure of the information may harm the individual, but this may be an unavoidable harm. Moreover, if private insurers learn that individuals are routinely withholding genetic test results from their medical records, then the insurer would consider specifically requesting such tests. This is neither a purely mandatory nor a completely free choice. Sifting through policy alternatives for these and similar cases will

require further information about current practices, and greater understanding about how private employers and insurers might use such information. The Working Group identified this topic for future consideration at a public forum.

Discrimination against families at genetic risk. The potential for discrimination against those who carry disease-related genes must be further assessed. The workshop discussed a case in which a couple was tested for CF, was found to be at risk. Their child tested positive for CF. A physician then told the couple that their prepaid health care would not cover the infant if they chose not to abort. The decision was reversed by management in the Health Maintenance Organization. Several similar cases have turned up, but in all cases the initial discriminatory decisions of lower level employees have been reversed. The Working Group believes that the potential for discrimination against CF carriers merits ongoing attention, followed by possible legislative action if abuses are identified.

References

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8. 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. New England Journal of Medicine, 323(July 5): 70-71.