Clinical

Laboratory

Improvement

Advisory

Committee

Subcommittee Meeting on Genetic Testing

Summary Report

January 27-28, 1998

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Subcommittee Meeting on Genetic Testing

January 27 - 28, 1998

Summary

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Record of Attendance

Committee Members

Dr. Patricia Charache
Dr. Susanne Gollin
Dr. Paul Ing
Dr. Katherine Klinger
Dr. Edward McCabe
Dr. Margaret McGovern
Dr. Toby Merlin
Dr. Wendell O'Neal
Dr. Kenneth Pass
Mr. Mark Rothstein
Dr. Morton Schwartz
Dr. Lawrence Silverman

Ex Officio Members

Dr. Carlyn Collins, CDC
Ms. Judith Yost, HCFA

Executive Secretary

Dr. Edward Baker

Centers for Disease Control and Prevention

Ms. Nancy Anderson
Dr. Rex Astles
Ms. Annette Baird
Ms. Rosemary Bakes-Martin
Ms. Carol Bigelow
Dr. Joe Boone
Ms. Gail Bosley
Ms. Diane Bosse
Ms. Cheryl Coble
Ms. Sharon Granade
Dr. Thomas Hearn
Dr. Ed Holmes
Dr. Richard Keenlyside
Dr. John Krolak
Dr. Harvey Lipman
Mr. Kevin Malone
Dr. Adam Manasterski
Dr. John Ridderhof
Ms. Renee Ross
Mr. Darshan Singh
Dr. Shahram Shahangian
Mr. Gregory Smothers
Dr. Steven Steindel
Dr. Roger Taylor
Ms. Julie Wasil
Ms. Glennis Westbrook
Ms. Rhonda Whalen
Ms. Laurina Williams

Welcome and Introductory Information

The meeting was called to order by Genetic Testing Subcommittee Chairman Dr. Wendell O'Neal. Mr. Kevin Malone, Office of the General Counsel at the Centers for Disease Control and Prevention (CDC), explained that the Genetic Testing Subcommittee will provide technical advice to the Clinical Laboratory Improvement Advisory Committee (CLIAC), which will then advise the CDC. In addition, Mr. Malone discussed conflicts of interest as related to an individual's participation in the Genetic Testing Subcommittee. Members then made self-introductions and disclosure statements as they relate to the topics to be discussed during the Genetic Testing Subcommittee meeting.

Charge to the Subcommittee:

Dr. Edward L. Baker, Director of the Public Health Practice Program Office at CDC, welcomed the Subcommittee and explained that CDC had selected Subcommittee members with technical and policy expertise who could advise CLIAC on the challenging issues related to genetic testing. Dr. Baker acknowledged the range of expertise represented by the Subcommittee members and noted that the CDC expected varying thoughts and opinions relative to the issues discussed. Dr. Baker then presented the following charge to the Genetics Subcommittee:

(1) Provide recommendations to the full CLIAC on genetic testing;
(2) Define genetic testing as related to the Clinical Laboratory Improvement Amendments of 1988 (CLIA); and
(3) Determine the applicability and scope of CLIA with respect to all phases of genetic testing, including the pre-analytic, analytic, and post-analytic phases.

Presentations and Subcommittee Discussion

Results of Mount Sinai Genetic Testing Survey — Addendum S-1

Dr. Margaret McGovern, Vice Chair of the Department of Human Genetics, Mount Sinai School of Medicine, presented the results of a survey on quality assurance practices in molecular genetics testing laboratories in the United States. The survey was administered as a questionnaire, and was completed by molecular genetics laboratory directors. Surveys were distributed to 746 individuals who were potentially laboratory directors for molecular genetics laboratories. There was a 68% response rate to the survey. The survey included questions on qualifications of laboratory personnel, laboratory licensing and proficiency testing, number and types of tests performed, quality assurance practices, and policies regarding access to genetic counseling, informed consent, and confidentiality.

Subcommittee Discussion:

Subcommittee members discussed whether the survey data were representative of all genetic

testing laboratories. Specific issues covered in the survey that were also discussed by the Subcommittee included quality control practices, informed consent for testing, and laboratory policies related to obtaining or verifying informed consent.

National Institutes of Health - Department of Energy (NIH/DOE) Genetic Testing Task Force Recommendations **Addendum S-2**

Dr. Michael Watson, Co-Chair, American College of Medical Genetics, presented issues addressed by the NIH/DOE Task Force on Genetic Testing, including Federal regulation of testing, problems and concerns specific to genetic testing, the charge to the Task Force, and the NIH/DOE definition of a genetic test. He listed the components of a genetic test (including quality issues for each phase of testing), and the stages through which a test evolves from research, to the investigative stage, to that of accepted clinical use, describing the scientific validation that must be performed for each test. Dr. Watson gave the following recommendations from the Task Force relative to CLIA: establish a genetic testing specialty; form a genetic testing Subcommittee to advise CLIAC; require formal training in human and medical genetics for laboratory directors and technical supervisors; and mandate genetic proficiency testing. He then concluded with additional Task Force recommendations to: establish an advisory body to the Department of Health and Human Services to coordinate genetic testing issues; develop a genetic testing services accreditation program; develop educational materials to be used by patients and physicians prior to and after testing; and establish standards for transition of a test from research into service.

Department of Health and Human Services (HHS) Genetics Workgroup

Dr. William Raub, Office of the Secretary (OS), HHS, described the OS workgroup that has been considering recommendations of the NIH/DOE Task Force on Genetic Testing, including regulatory issues and the creation of a Department-wide advisory committee or process. Relative to regulation of genetic testing, the workgroup is committed to determining the best mechanism to protect the public without stifling creativity and innovation in research. To do this, the workgroup is considering how to integrate the existing regulation of medical devices and human testing, currently covered by the Medical Device Rules (FDA), CLIA (HCFA, CDC) and Human Subjects Rules (NIH, FDA). The workgroup is also considering how an advisory committee or process would function, and has addressed the following genetic testing issues as important for consideration: (1) the categorization of tests to determine which require the most stringent scrutiny; (2) the need for a data repository or central archive of information; (3) the need for professional and public education; and (4) the opportunity for governmental, private industry and public involvement and cooperation in oversight of this evolving area.

Subcommittee Discussion:

As the Subcommittee began to address the applicability of CLIA to the various types and phases of genetic testing, Dr. Collins emphasized that the CLIA standards are based on the complexity of the test methodology, and do not depend on the context or utility of testing. However, she pointed out that the regulations are flexible, and include specialty requirements for certain areas of testing. Subcommittee members agreed that some aspects of CLIA can easily be applied to genetic testing,

especially the analytic phase. Other issues that are primarily part of the pre- and post-analytic phases of genetic testing may not be addressed appropriately in the current CLIA framework, and need consideration. Some of these include the decision to test, test selection, informed consent, specimen collection, genetic counseling, and personnel qualifications.

Definition of Genetic Testing **Addendum S-3**

Dr. Carlyn Collins reviewed six definitions of genetic testing (or closely related terms), and asked for discussion and recommendations as to the definition appropriate for CLIA purposes. She added that what is needed is a working definition, which can be further refined or modified. The definitions provided were a compilation of those used by advisory groups, professional organizations, and governmental agencies for the purposes of dealing with genetic testing or information.

Subcommittee Discussion:

The Subcommittee asked for clarification as to which of the different types of genetic tests would be covered by CLIA, and Dr. Collins pointed out that CLIA covers all clinical laboratory tests. Dr. Baker then asked that the Subcommittee define the domain of testing to be included in genetic testing, which led to a discussion of the potential groups of tests that could be included. Several subcommittee members stated that molecular and biochemical genetic tests may need special requirements in the regulations, such as those currently included for cytogenetics.

In considering the definitions for genetic testing provided to the Subcommittee, it was decided that the definition developed by the NIH/DOE Task Force on Genetic Testing was the most appropriate to use as a starting point for CLIA purposes. (Other definitions were eliminated because they focused on genetic information, or because they excluded certain elements such as cytogenetics.) Several Subcommittee members suggested that the definition be limited to the first two sentences of the NIH/DOE Task Force definition. Dr. Schwartz recommended that the language be modified to correspond with the language used in the CLIA statute for a laboratory test. The Subcommittee agreed that the definition should be written in a manner to exclude non-human genetic material, but there was extensive discussion about whether or not to include several of the phrases or concepts implied by the NIH/DOE Task Force definition. In an effort to establish a broad preliminary definition that would be flexible and could be modified, the Subcommittee agreed to use the following as a proposed working definition (phrases in italics are subject to further discussion and potential revision):

- Genetic test - the analysis of materials derived from the human body, including human DNA, RNA, chromosomes, *proteins, and certain metabolites* in order to detect *heritable or acquired* disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations.

Genetic Testing Issues for Each Phase of Testing **Addendum S-4**

Dr. Collins asked the Subcommittee for input on specific issues pertaining to each phase of genetic testing. She began the discussion of each phase by listing several relevant factors, and asked the Subcommittee to identify additional factors to be considered. Dr. Baker added that in their deliberations, the Subcommittee members should not limit their thinking to only those issues within the boundaries imposed by the CLIA regulations, but should include all that they consider critical for genetic testing. In the discussions of each phase of testing that followed, the Subcommittee agreed that the factors listed by Dr. Collins were important to consider and proposed additional issues to be addressed.

Subcommittee Discussion:

Pre-analytic Factors

In discussing the pre-analytic factors of appropriateness of testing, and informed consent, several Subcommittee members raised the issue of whether genetic counseling prior to testing should be addressed by CLIA. This includes the responsibility to educate the physician or user of the test results about test ordering relative to the type of tests being performed by the laboratory for a specific disease or condition. Pre-analytic genetic counseling would also cover education of family members about the testing process. Confidentiality of testing was also mentioned. In discussing sample handling and preparation as well as informed consent, a Subcommittee member asked about consent to re-use specimens, and it was agreed that this issue should be addressed. These factors (genetic counseling, confidentiality, and consent to re-use specimens) were added to the list presented by Dr. Collins.

Analytic Factors

For the analytic phase of testing, especially the areas of quality assurance and quality control, the Subcommittee noted that many of the CLIA standards currently in place can directly be applied to genetic testing. There are specialty requirements for cytogenetics; these may also be needed for biochemical and molecular testing. Other areas of quality control that the Subcommittee members recommended be specifically addressed are control of contamination in the laboratory, the laboratory environment in general, and validation of tests. These items were added to the factors for consideration.

The two biggest areas of concern for the analytic phase were personnel requirements and proficiency testing (PT). Ms. Rhonda Whalen reviewed the current personnel categories and qualifications for high complexity testing under CLIA, and the Subcommittee agreed that the current structure and categories are sufficient for genetic testing. They suggested, however, that the qualifications for each of the personnel categories be evaluated to determine if they are appropriate for the genetic testing laboratory. Dr. Collins reminded the Subcommittee to consider access to testing when developing recommendations pertaining to personnel requirements. There was also discussion regarding proficiency testing requirements, and PT programs currently available for genetic testing. The Subcommittee asked the CDC to provide them with information regarding available PT programs for genetic testing.

Post-analytic Factors

The Subcommittee began discussion of the post-analytic factors by addressing the issue of a gene registry. Several members stated that although it may not be appropriate for a gene registry to be specifically addressed by CLIA, special issues of confidentiality should be covered under the post-analytic phase of testing. One member suggested that the development of gene reference standards could potentially be an issue. Another member noted that the use of previously tested specimens and maintenance of the data related to them should be addressed. These issues were added to the list of factors presented by Dr. Collins.

The Subcommittee discussed special reporting requirements in conjunction with consultation to non-geneticist care givers (professional healthcare providers), and the role of the laboratory in genetic counseling. The members agreed that the wording of test report information is critical for correct interpretation, and stated that CLIA does not currently address this sufficiently. After reviewing the responsibilities of the Laboratory Director and Clinical Consultant as specified in CLIA, the Subcommittee determined that these are written adequately to cover the consultative role that the genetic testing laboratory must play in providing assistance and interpretive information to physicians and other providers. The Subcommittee recommended that the laboratory not take a direct role in genetic counseling, and that CLIA not require a genetic counselor as a personnel category. Dr. Baker stressed that as the Subcommittee considers the issues relative to reporting and interpretation of genetic information, the members should seek to develop policies that will protect the public from misuse of the information, and facilitate its appropriate use.

Summary of Genetic Testing Issues

Subcommittee Discussion:

The Subcommittee designated workgroups (consisting of representatives from the Subcommittee and the full CLIAC) for the pre-analytic, analytic, and post-analytic phases of testing to address the relevant issues, as outlined by Dr. Collins, and supplemented during the discussion. This concept will be presented to the full CLIAC. After input by the full CLIAC, the workgroups will consider the factors and work to bring recommendations regarding each phase of genetic testing to future Subcommittee meetings.

In an effort to focus the thinking on issues specific to genetic testing, the Subcommittee briefly discussed factors that the members felt make genetic tests different from other types of clinical laboratory tests. These included: rapidly developing technology and the discovery of new tests or genes; labile samples that could be difficult to recollect; legal and ethical issues related to specimen storage, confidentiality and patient anonymity; variation in testing and information reported by laboratories; impact of test results on families and the public; and uninformed or misinformed clinical users.

Public Comments

There were no public comments for the Subcommittee.

Concluding Remarks

It was decided that the Genetic Testing Subcommittee would meet next on May 27 - 28, 1998, preceding the full CLIAC meeting on May 29. Dr. O'Neal then adjourned the Subcommittee meeting.

I certify that this summary report of the January 27 - 28, 1998, meeting of the Genetics Subcommittee of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.

/S/ Wendell R. O'Neal, Ph.D.
Chairman

Addendum S-1

Addendum S-2

Addendum S-3

Addendum S-4