Clinical

Laboratory

Improvement

Advisory

Committee

Summary Report

September 16 - 17, 1998

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Clinical Laboratory Improvement Advisory Committee (CLIAC)

September 16 - 17, 1998

Summary

Table of Contents

Record of Attendance

Committee Members
Dr. Morton Schwartz, Chair
Dr. Thomas Bonfiglio
Dr. Lemuel Bowie
Dr. Mary Burritt
Dr. Ronald Cada
Dr. Patricia Charache
Dr. Susanne Gollin
Dr. Verlin Janzen
Dr. Bereneice Madison
Ms. Diana Mass
Ms. Deborah McHugh
Dr. Toby Merlin
Ms. Sharon Radford
Mr. Elliott Segal
Dr. Ulder Tillman

Ex Officio Members
Dr. Carlyn Collins, CDC
Dr. Steven Gutman, FDA
Ms. Judith Yost, HCFA

Liaison Representatives
Ms. Kay Setzer (HIMA)

Executive Secretary
Dr. Edward Baker

Centers for Disease Control and Prevention
Ms. Nancy Anderson
Dr. Rex Astles
Ms. Carol Bigelow
Ms. Diane Bosse
Ms. Cheryl Coble
Ms. Carol Cook
Ms. Sharon Granade
Dr. Ed Holmes
Dr. Adam Manasterski
Ms. Anne O'Connor
Dr. John Ridderhof
Ms. Renee Ross
Mr. Darshan Singh
Mr. Gregory Smothers
Ms. Rhonda Whalen
Dr. Laurina Williams

Clinical Laboratory Improvement Advisory Committee

The Secretary of Health and Human Services is authorized under Section 353 of the Public Health Service Act, as amended, to establish standards to assure consistent, accurate, and reliable test results by all clinical laboratories in the United States. The Secretary is authorized under Section 222 to establish advisory committees.

The Clinical Laboratory Improvement Advisory Committee (CLIAC) was chartered in February 1992 to provide scientific and technical advice and guidance to the Secretary and the Assistant Secretary for Health regarding the need for, and the nature of, revisions to the standards under which clinical laboratories are regulated; the impact on medical and laboratory practice of proposed revisions to the standards; and the modification of the standards to accommodate technological advances.

The Committee consists of 20 members, including the Chair. Members are selected by the Secretary from authorities knowledgeable in the fields of microbiology, immunology, chemistry, hematology, pathology, and representatives of medical technology, public health, clinical practice, and consumers. In addition, CLIAC includes three ex officio members, or designees: the Director, Centers for Disease Control and Prevention; the Commissioner, Food and Drug Administration; the Administrator, Health Care Financing Administration; and such additional officers of the U.S. Government that the Secretary deems are necessary for the Committee to effectively carry out its functions. CLIAC will also include a non-voting liaison representative who is a member of the Health Industry Manufacturers Association and such other non-voting liaison representatives that the Secretary deems are necessary for the Committee to effectively carry out its functions.

Due to the diversity of its membership, CLIAC is at times divided in the guidance and advice it offers to the Secretary. Even when all CLIAC members agree on a specific recommendation, the Secretary may not follow their advice due to other overriding concerns. Thus, while some of the actions recommended by CLIAC may eventually result in changes to the law, the reader should not infer that all of the advisory committee's recommendations will be automatically accepted and acted upon by the Secretary.

Welcome and Introductory Information

The meeting was called to order by CLIAC Chair Dr. Morton Schwartz. The Committee members made self-introductions and disclosure statements of their relevant financial interests as they relate to the topics to be discussed during the CLIAC meeting. Dr. Schwartz explained that Ms. Rhonda Whalen, Senior Health Scientist in the Division of Laboratory Systems (DLS), Public Health Practice Program Office (PHPPO) at the Centers for Disease Control and Prevention (CDC), would be representing Dr. Carlyn Collins, Director of DLS in giving the CDC update on the Clinical Laboratory Improvement Amendments of 1988 (CLIA), and that Dr. Collins would be joining the meeting later in the day.

Presentations and Committee Discussion

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS OF 1988 (CLIA) UPDATE

Centers for Disease Control and Prevention (CDC)

Ms. Rhonda Whalen, DLS, PHPPO, presented a brief status report on two issues relevant to CLIA. First, she informed the CLIAC that the Department of Health and Human Services (HHS) has chartered an advisory committee to facilitate communication and collaboration on policy issues pertaining to genetic testing among HHS workgroups and agencies. She added that selection of members for this committee is underway, and that the CLIAC will be represented. Ms. Sara Carr, of the National Institutes of Health will be leading the HHS advisory group. Ms. Whalen then reported to the CLIAC on the status of the possible transfer of the CLIA test categorization and waiver activities from the CDC to the Food and Drug Administration (FDA), as was intended in the CLIA regulations. She explained that the CDC, FDA, and Health Care Financing Administration (HCFA) are discussing this issue, but that no final decision has been made. The CDC is presently categorizing an average of 2000 test systems per year. A few CLIAC members noted that there are differences in the review processes and categorization criteria used by the CDC and FDA, and expressed opinions that it may be advantageous to look at tests using more than one process.

Health Care Financing Administration (HCFA)

Ms. Judy Yost, Director of Outcomes and Improvement, HCFA, presented an update on CLIA implementation. She did not include statistical information regarding laboratory certification and performance, noting that there had been no significant changes in this data since her last report. Ms. Yost mentioned that their Division has convened a workgroup of HCFA surveyors and other representatives to look at possible indicators of program integrity (i.e. “sink tests”) that would be useful to investigators looking at fraud and abuse. She emphasized that fraud and abuse investigations are not part of CLIA inspections. Ms. Yost then reported on the “Y2K” dilemma regarding the preparation of computer systems for the year 2000. She stated that the CLIA data system has been updated and urged the CLIAC to ensure that their facilities will be in compliance. Next, Ms. Yost informed the Committee that the 1997 registry listing laboratories that, and

individuals who, have been sanctioned under CLIA or have been convicted of fraud and abuse violations will be available on the HCFA home page under the Division of Outcomes and Improvements - CLIA (http://www.hcfa.gov). She explained that HCFA has been updating their validation survey process for accrediting organizations and exempt states, streamlining the process, and adding an option that validation surveys may be performed concurrently with an inspection performed by the organization or exempt state. The 1997 validation report is complete and has been distributed. In all cases, there were fewer than 20% discrepancies between the validation surveys performed by HCFA and the inspections performed by the organization or the state. Some surveys showed no discrepancies. Last, Ms. Yost noted that the CDC and HCFA are working on the final CLIA regulation, and that the HCFA 116 form (CLIA application) has been made more user friendly and is undergoing Departmental review for clearance.

Food and Drug Administration (FDA) **Addendum A**

Dr. Steven Gutman, Director, Division of Clinical Laboratory Devices, Office of Device Evaluation, Center for Devices and Radiological Health, FDA, reported on the changes taking place within the FDA and their effect on the review and classification of clinical laboratory devices and reagents. In making these changes, the FDA is redirecting its resources and efforts to eliminate reviews of products that are low risk, low impact, and to focus evaluations on high risk or high impact products. Dr. Gutman discussed the FDA's regulation on analyte specific reagents (ASR's), dealing with the requirements for in-house (home brew) laboratory tests. He stressed that this regulation recognizes CLIA, and that the intent is to regulate the ASR's in a consistent fashion. The regulation impacts manufacturers of ASR's by including requirements for their manufacturing and labeling practices. It impacts laboratories performing home brew tests, by requiring that they meet the CLIA requirements for high complexity testing. It also requires laboratories to include a disclaimer on reports of results from a home brew test (incorporating an ASR) stating that the reagents have not been reviewed by the FDA.

Dr. Gutman then briefly described several other new initiatives underway at the FDA, and added that there is still work to be done on updating guidance documents and standards for review and classification of devices. He explained that the initiatives are resulting in across the board down-classifications, and that modifications to products now require less FDA oversight. However, the FDA is maintaining its workload despite the exemptions and is maintaining good science in the reviews that are performed.

Following Dr. Gutman's presentation, several CLIAC members asked for clarification of the terms "home brew", "analyte specific reagents", and "replacement reagents". He responded that using another manufacturer's reagents on an instrument or automated system (replacement reagents) is not the same as a home brew (or in-house) assay, where analyte specific reagents, not subject to a premarket review, are obtained as individual ingredients and assembled to perform a test developed by that laboratory. Dr. Gutman also noted that the required disclaimers on home brew tests are labeling requirements for regulation of devices, and should not attempt to regulate the practice of medicine (e.g. make false claims about the interpretation of a test). He stated that the FDA is not aware of situations where such abuse is taking place, but that they would step in if such a situation occurred.

ASSISTED REPRODUCTIVE TECHNOLOGY EMBRYO LABORATORY PROCEDURES

Introduction and CDC Update — Addendum B

Dr. Carlyn Collins asked the CLIAC to recall information presented on May 29, 1998, regarding the potential CLIA applicability to assisted reproductive technology (ART) embryo laboratory procedures. She noted that questions regarding this issue have been raised by professional organizations, individuals, and members of Congress. She summarized the Fertility Clinic Success Rate and Certification Act of 1992 (FCSRCA) and described the model certification program for embryo laboratories containing voluntary standards that the CDC is developing, as mandated in this statute. She also provided the CLIA definition of clinical laboratory testing, and a comparison of the FCSRCA and CLIA pertaining to the regulation of clinical laboratory testing.

CLIAC Discussion

A few CLIAC members asked if there are data showing that laboratory performance or pregnancy success rates improve when embryo laboratories participate in voluntary quality assurance programs, such as the College of American Pathologists Reproductive Laboratory Accreditation Program (CAP RLAP). They stated that they would prefer to evaluate this issue using outcome data, such as the CDC pregnancy success rate report, also part of the implementation of the FCSRCA. Dr. Collins agreed that it would be advantageous to have data when determining appropriate regulation of embryo laboratories, but pointed out that there are many factors affecting pregnancy success rates besides embryo laboratory performance. A major variable is the age of the woman undergoing the ART procedure.

Another issue discussed was the CLIA definition of clinical laboratory testing, and whether embryo laboratory procedures fit this definition. Several members stated that embryo laboratory procedures are analogous to other tests that are currently subject to CLIA, such as semen analyses or blood bank testing. A number of the members agreed that embryo laboratory procedures, especially the microscopic examinations, are examinations of material derived from the human body to provide information for the diagnosis or treatment of an impairment of the health of human beings, that impairment being female infertility. A few members disagreed with this point. Several noted that laboratory examinations in the ART process prior to the stage of evaluating an embryo should be covered under CLIA, but suggested that more deliberation is needed on embryo examination. One CLIAC member questioned why the FCSRCA was passed by Senator Wyden as a voluntary measure for embryo laboratories, rather than including these facilities under the purview of CLIA. Dr. Collins stated that when the CLIA regulations were originally published, several areas were not initially addressed due to the need to move quickly on the implementation process. She explained that at that time, the evaluation of ART focused mainly on the *in vitro* fertilization process, and embryo laboratory procedures were not addressed.

Ms. Yost expressed some concerns and additional points for the CLIAC to consider when discussing the potential applicability of CLIA to embryo laboratory procedures. She explained that CLIA would not cover all procedures performed in ART facilities (e.g. medical treatment,

embryo and gamete storage) and stated that coverage of embryo laboratories under CLIA could mislead the public into thinking that all areas of ART are being monitored. She also noted that CLIA does not cover product evaluations, functional tests or other mechanical procedures. She raised the issue of payment for oversight of additional laboratories under CLIA, and questioned whether the scope and frequency of problems in embryo laboratories was sufficient to warrant Federal oversight. She stated that HHS has received a number of inquiries on this issue, and to date, has not taken a position on CLIA applicability to embryo laboratory procedures.

Public Comments

1. Jacob Mayer, Ph.D., representing the Society for Assisted Reproductive Technology (SART) of the American Society for Reproductive Medicine (ASRM), commented that there is no testing performed in an embryo laboratory, but that the purpose of these facilities is to develop and grow embryos outside of the body. He stressed that the work performed by the laboratory is part of the patient's treatment, and is not designed to provide information regarding infertility. Diagnostic tests are performed prior to the *in vitro* fertilization procedure. He added that there is an advantage to regulation of embryo laboratories and that SART is in favor of certification under an appropriate regulatory authority that recognizes the unique nature of these laboratories.

2. Mary Beth Gerrity, Ph.D., representing the Reproductive Biology Professional Group of the ASRM commented in support of the inclusion of embryo laboratory procedures under CLIA. She stated that as an inspector for the College of American Pathologists Reproductive Laboratory Accreditation Program (CAP RLAP), and an author of it's checklists, she had seen evidence that the voluntary process of certification and regulation was not working. She said that many laboratories do not have a quality assurance program in place, and personnel may not be qualified or are not properly supervised. She has observed a widespread lack of knowledge regarding laboratory practices, including safety and procedures for sample identification and labeling.

3. Tammie Schalue, Ph.D., representing the American Association of Bioanalysts, commented in support of inclusion of embryo laboratory procedures under CLIA, noting that the CLIA regulations are flexible and will work today and in the future. She added that although SART supports laboratory certification, not all ART programs are members of SART. She stressed that diagnoses are made when performing embryo laboratory procedures, and that patient treatment is affected.

4. Brooks Keel, Ph.D., President of the American Association of Bioanalysts, briefly echoed the statements of the previous two commenters. He said that there is a need for mandatory Federal oversight of embryo laboratory procedures, that they are high complexity laboratory tests used in patient diagnosis and treatment. He again made the point that oocyte evaluations are no different from sperm analyses, which are currently subject to CLIA.

CLIAC Recommendation

After hearing the Committee discussion and the public comments, Dr. Schwartz asked whether embryo laboratory procedures should be subject to the CLIA regulations. The CLIAC

recommended that embryo laboratory procedures should be under the purview of CLIA, and that appropriate CLIA coverage should be defined. The Committee suggested that a good starting point for determining what should be covered and how CLIA should be applied to embryo laboratories is the CAP RLAP. Dr. Collins stated that the CAP program was used as a starting point for the model certification program for embryo laboratories, developed under the FCSRCA, and that input on the model program was provided by professional groups, representatives of State and Federal agencies, and technical experts in ART and embryo laboratory procedures. In addition to the CAP, other groups that contributed to the development of the model program included ASRM, SART, and the AAB. Dr. Schwartz asked that the CLIAC be notified when the model program is finalized, and a member commented that excellent progress has been made in this area. Another member noted that CLIA contains minimal standards, whereas the accreditation organizations may have more stringent requirements, and asked that CLIA standards for embryo laboratories be minimal.

GENETIC TESTING

Genetic Testing Workgroup Report — Addendum C

Dr. Wendell O'Neal, Chair of the Genetic Testing Workgroup, summarized the activities of the July 30 - 31, 1998, meeting of the Workgroup. He explained that at the July meeting, the Workgroup completed its discussion of the remaining issues for each phase of genetic testing, and those that applied to all phases of testing (including the genetic test definitions). He added that the Workgroup addressed the topics for which the CLIAC had previously provided input, as well as those topics which neither the CLIAC nor the full Workgroup had covered. Prior to the CLIAC discussion of each of the issues, Drs. O'Neal and Schwartz recognized the Workgroup for their contributions throughout the process, and the CDC staff for their support of the Workgroup activities.

CLIAC Recommendations for Genetic Testing — Addendum D

Dr. O'Neal introduced each topic the Workgroup had considered at their July meeting, and Dr. Schwartz led the Committee discussion for each phase of testing, beginning with the genetic test definitions and the issues that apply to all phases of testing, and then the remaining topics for the pre-analytic, analytic, and post-analytic phases of testing. In many cases, the CLIAC accepted the suggestions made by the Workgroup or made slight modifications to the proposals in the report. For the topics that were previously addressed by the CLIAC, no further changes were recommended. Pertinent discussion and CLIAC recommendations for each topic addressed at this meeting follow. A comprehensive list of the CLIAC recommendations for all genetic testing issues (including those made at this meeting and prior meetings) is found in Addendum D.

Genetic Test Definitions

The CLIAC considered the definitions of a molecular and cytogenetic test, and a biochemical genetic test as presented in the Workgroup report. After several grammatical and organizational changes were suggested, the Committee recommended the definitions below, with no substantial

changes to either definition:

Molecular genetic and cytogenetic test - The analysis of human DNA, RNA, and chromosomes 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.
Biochemical genetic test - The analysis of materials derived from the human body, including human proteins and certain metabolites, predominantly used to detect inborn errors of metabolism, heritable genotypes, or mutations 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. [Tests that are used primarily for other purposes, but may contribute to diagnosing a genetic disease (e.g. blood smear, certain serum chemistries), would not be covered by this definition.]

Topics Applicable to All Phases of Genetic Testing

Informed Consent **-** Although the CLIAC agreed with the suggestions made by the workgroup regarding this topic, there was some concern about the meaning of the terms "*authorized* person" and "*appropriate* informed consent". After discussion, the Committee recommended that these terms be reviewed and clearly defined or explained if used in the CLIA regulations.
Re-use of Tested Specimens **-** The CLIAC accepted the Workgroup proposal, but stressed that there may be valid reasons to retain a specimen in addition to the reasons mentioned [in case test methodology improves, to confirm original diagnosis, for quality control/quality assurance (QC/QA) or new test development] and added that specimens may be kept for education and/or training. In re-using excess material from patient specimens for QC/QA when testing for the same disease, the Committee noted that although this is appropriate use of the material, commercial products should be considered for this purpose when available. The CLIAC also stressed that when using excess material for methods improvement, all patient identifiers should be removed prior to use.
Confidentiality **-** A number of the Committee members expressed the opinion that confidentiality is sufficiently covered by the current CLIA regulations. However, several members stated that there should be a requirement specific to genetic testing of a sensitive nature, and potential language was suggested if such a requirement was added to the regulations.

Topics Applicable to Individual Phases of Genetic Testing

Ordering Additional Tests (pre-analytic) **-** The CLIAC briefly discussed the extent to which the laboratory has a responsibility to assist its clients in ordering appropriate tests, and suggesting follow-up tests, especially in light of rapid medical and technical advances, and increasing specialization. There was concern that if the regulations are too stringent, it may appear that this consultation is required for every testing situation, which would greatly increase the burden on the laboratory. In an effort to address this concern and maintain flexibility, the Committee recommended that the laboratory assist in ordering appropriate tests "when deemed necessary". They accepted the Workgroup proposal regarding non-written requests for new tests.
Specific Quality Control (analytic) **-** The CLIAC accepted the Workgroup proposal.

Specimen Integrity (analytic) **-** The CLIAC accepted the Workgroup proposal.
Proficiency Testing (PT) (analytic) **-** The CLIAC accepted the Workgroup proposal for tests where PT is available, and recommended that where PT does not exist, laboratories use an alternative mechanism to monitor performance. The alternative monitoring should be performed three times per year, on five specimens per event.
Personnel Qualifications (analytic) - The CLIAC reviewed the Workgroup proposal to change the CLIA title for "Technical Supervisor" to "Technical Director", and suggested consideration of whether this is appropriate, not only for genetic testing, but for all areas of the laboratory.
General Supervisor **-** In discussing the personnel qualifications for this category, the Committee focused both on the education and experience required for this position. Several members express the opinion that since this person is on-site and provides immediate oversight of laboratory activities (including troubleshooting), a high degree of education, training, and specific experience should be required. Other members were concerned that as genetic testing becomes more automated, the requirements for this position should not be overly restrictive. The final CLIAC recommendation was to modify the Workgroup proposal slightly, to specify that all degrees must be in a chemical, physical, biological or clinical laboratory science, and that experience must be in high complexity genetic testing, but not necessarily in the relevant subspecialty.
Clinical Consultant **-** The CLIAC accepted the Workgroup proposal, but had questions regarding the qualifications of genetic counselors who have graduated from accredited institutions but are not board certified, and whether or not a "grandfather" clause should be included for this position, to ensure that these people would not be disenfranchised. The Committee tabled a decision regarding this issue and asked that the CDC obtain additional information.
Testing Personnel - The CLIAC recommended that the qualifications for testing personnel in the current CLIA regulations are adequate for genetic testing.
Personnel Responsibilities (analytic) **-** The CLIAC recommended that the personnel responsibilities currently specified in the CLIA regulations be adopted for personnel in genetic testing laboratories and accepted the two additional proposals suggested by the Workgroup.
Validation of Tests (analytic) **-** The CLIAC accepted the Workgroup proposal.
Special Reporting Requirements (post-analytic) **-** The CLIAC accepted the Workgroup proposal with one modification, that being to add that the Technical Supervisor (in addition to the Laboratory Director and Clinical Consultant) must ensure that reports include pertinent information required for specific patient interpretation.
Record/Specimen Retention (post-analytic) **-** The CLIAC accepted the Workgroup proposal.

Public Comments

There were no public comments for the CLIAC regarding genetic testing.

Concluding Remarks

Dr. Schwartz announced that the dates for future CLIAC meeting would be as follows: February 2 - 4, 1999; May 11 - 13, 1999; and September 21 - 23, 1999. For each meeting, the CDC will determine which two days (within the three days noted for each month above) the meeting will be held. He then adjourned the CLIAC meeting.

PLEASE NOTE: The CDC has scheduled the CLIAC meetings for the following dates:

February 3 - 4, 1999
May 11 - 13, 1999 (will be held on either Tues/Wed or Wed/Thurs)
September 22 - 23, 1999

I certify that this summary report of the September 16 - 17, 1998, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.