Clinical

Laboratory

Improvement

Advisory

Committee

Summary Report

April 5 - 6, 2000

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Clinical Laboratory Improvement Advisory Committee (CLIAC)

April 5 -6, 2000

Summary Report

Table of Contents

Record of Attendance

Committee Members
Dr. Toby Merlin, Chair
Dr. George Birdsong
Dr. Thomas Bonfiglio
Dr. Mary Burritt
Dr. Ronald Cada
Dr. Joseph Campos
Dr. Patricia Charache
Dr. Brenta Davis
Dr. Andrea Ferreira-Gonzalez
Dr. Susanne Gollin
Dr. Edward Hook
Dr. Verlin Janzen
Ms. Diana Mass
Dr. Timothy O'Leary
Ms. Sharon Radford
Dr. Larry Silverman

Ex Officio Members
Dr. Steven Gutman, FDA
Dr. Robert Martin, CDC
Ms. Judith Yost, HCFA

Liaison Representative
Ms. Kay Setzer, HIMA

Executive Secretary
Dr. Edward L. Baker, CDC

Centers for Disease Control and Prevention
Ms. Nancy Anderson
Dr. Rex Astles
Dr. Joe Boone
Ms. Gail Bosley
Ms. Diane Bosse
Ms. Sharon Granade
Dr. Thomas Hearn
Dr. Ed Holmes
Dr. Devery Howerton
Dr. Ira Lubin
Dr. Adam Manasterski
Ms. Renee Ross
Mr. Darshan Singh
Ms. Rhonda Whalen

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 regulations, the reader should not infer that all of the advisory committee's recommendations will be automatically accepted and acted upon by the Secretary.

CALL TO ORDER AND INTRODUCTORY INFORMATION

Dr. Toby Merlin, CLIAC Chair, called the meeting to order and presented a brief overview of the agenda for the meeting. 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. Robert Martin, Director, Division of Laboratory Systems (DLS), Public Health Practice Program Office (PHPPO), Centers for Disease Control and Prevention (CDC) welcomed the CLIAC and emphasized the importance of their input on the role of CLIA in addressing critical issues such as specimen types and test systems not currently regulated and the CLIA-related research agenda.

PRESENTATIONS AND COMMITTEE DISCUSSION

CLIA Update

Centers for Disease Control and Prevention (CDC) **Addenda A-D**

Dr. Devery Howerton, Chief, Laboratory Practice Standards Branch (LPSB), DLS, PHPPO, CDC, announced the publication of the Cytology Proficiency Testing withdrawal notice followed by a brief history of events leading to this notice. She proceeded with a summary of test systems categorized and approved for waiver by the CDC.

There was a brief discussion among the members on the transfer of the test categorization program to the FDA. The FDA emphasized that prior to publishing a final rule, the waiver process would be reviewed and individuals would have an opportunity to provide comments on the waiver process at a public meeting FDA is having on August 14-15, 2000 in Gaithersburg, Maryland. Dr. Howerton then presented an update on the laboratory workforce shortage including data on vacancy rates, changes in medical technology and medical laboratory technician programs, numbers of graduates, factors affecting turnover within laboratories, and projections for laboratory personnel shortages in the future.

Dr. Robert Martin presented an update (Addendum B) on the March 30-31, 2000 National Electronic Disease Surveillance System (NEDSS) National Stakeholders meeting. He reviewed the long-term vision for NEDSS, discussed actions taken in FY99 and announced President Clinton's plans to provide funding for a National Surveillance System. Another project under development in DLS is the National Laboratory System. This is an attempt to better integrate hospital, independent, public health and federal laboratories. Dr. Martin discussed the steps taken in FY99 to implement the National Laboratory System and the next steps including the laboratory demonstration projects.

Dr. Joe Boone, Assistant Director for Science, DLS, PHPPO, CDC reported on several topics in genetics (Addendum C). First, he discussed the genetic testing Notice of Intent (NOI) being developed by the CDC which had been submitted to the Department for clearance and was awaiting the resolution of a few procedural matters (the NOI was published May 4, 2000). He

also mentioned the genetic testing training, Genetic Training for Primary Care Providers, project and alerted the Committee to the genetic laboratory testing web site (http://www.phppo.cdc.gov/dls/genetics). He concluded with a report on the February 23, 2000 CDC Genetic Forum Laboratory Workgroup meeting. The purpose of the Genetic Testing Laboratory Forum is to assure that laboratory issues related to the quality of genetic testing are appropriately addressed. Dr. Boone discussed the first steps of the Forum and the future development of a regulatory paradigm for genetic tests. One of the major issues to be considered by the Forum is the determination of when a test is ready to be used for patient care. The Genetic Forum will be meeting on June 2, 2000 in Atlanta.

Dr. Patricia Charache reported on the Secretary's Advisory Committee on Genetic Testing (SACGT) (Addendum D), established as a result of a recommendation made by the National Institutes of Health/Department of Energy Task Force on Genetic Testing. Dr. Charache is a member of the SACGT and is the CLIAC liaison to the Committee. On December 1, 1999, the SACGT published a notice in the Federal Register seeking comments on the current oversight of genetic testing. Following receipt and analysis of the comments, the SACGT is developing options for oversight. The SACGT meeting on February 24-25, 2000 focused on the assessment of the adequacy of oversight of genetic tests and considered four issues: Benefit and Risk Criteria; Test Categorization; Data Collection, Evaluation and Dissemination; and Appropriate Levels of Oversight. The SACGT developed preliminary draft recommendations for oversight of genetic tests and is currently soliciting public comments on these recommendations. The SACGT will consider these comments at their next meeting on June 5-7, 2000.

CLIAC discussed the FDA review of genetic tests and noted that while the review must not be superficial, it should not delay the availability of tests. Various review options were discussed including surrogate reviews by a third party and a decentralized review process for better utilization of resources.

Committee Discussion

The CLIAC members agreed there were various factors contributing to the laboratory workforce shortage, one of which is a decline in the number of people entering laboratory training programs. They attributed this decrease in students to:

- Inadequate salaries
- A poor professional image of laboratory science
- Stressful working conditions caused in part, by an emphasis on error- free performance while fewer people are available to do the work
- Concerns with potential exposure to infectious disease and safety issues
- Changes in the roles of women. Formerly, most medical technologists were women, but now women have other professional opportunities in other fields. Men have not been recruited to compensate for this loss
- Loss of funds for training. Medicare previously subsidized training; however, these funds are no longer available.

Another factor cited was turnover of employees.

The members talked about solutions to the workforce shortages. One member said in order to attract more people to the field, the jobs must be more attractive. Another member commented that while people with a bachelor's degree in science could be hired, this is not a long term solution because these individuals often leave the laboratory field quickly. Another member said that distance learning could be of assistance in providing access to training but that most programs don't have this capability.

The CLIAC agreed it is important to monitor the impact of these shortages, and suggested private sector databases be investigated to measure the workforce and the link between laboratory performance and patient outcome. They also agreed a systematic mechanism for collecting accurate data is needed. The CLIAC ended the discussion by suggesting a workgroup be established to develop specific recommendations on laboratory workforce shortages and report to CLIAC in September. The Committee also recommended a letter be sent to the Secretary of Health and Human Services to alert her of the crisis in the laboratory workforce.

Public Comments

James T. Griffith, Ph.D., Chancellor Professor and Chairperson, Department of Medical Laboratory Science, University of Massachusetts, President of the American Society for Clinical Laboratory Science (ASCLS) announced a summit meeting in June 2000 with attendance of eighteen laboratory organizations to evaluate laboratory workforce shortages and offered to share information from this meeting with CLIAC. In addition, he offered the assistance of the ASCLS to the CLIAC workgroup on laboratory personnel shortages.

Health Care Financing Administration (HCFA) **Addenda E**

Ms. Judy Yost, Director, Division of Laboratories and Acute Care Services, Center for Medicaid and State Operations, HCFA, reviewed HCFA's CLIA implementation activities. She presented data from January 2000 on laboratory certification, CLIA-exempt states, accreditation organizations, survey deficiencies, and enforcement. She noted the Government Accounting Office report determined that the fee increase for exempt states was warranted. Ms. Yost said a HCFA solvency committee has been formed to provide advice on maintaining a fiscally viable CLIA program.

Food and Drug Administration (FDA) **Addenda F-G**

Ms. Clara Sliva, CLIA Coordinator (Acting), Division of Clinical Laboratory Devices (DCLD), Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), FDA, updated the CLIAC on the transfer of the test categorization and waiver processes to the FDA. (Addendum F). A guidance document for manufacturers is being compiled. She advised the Committee that the FDA may revisit the proposed rule on the waiver process and emphasized FDA's plans to convene a public meeting in August to discuss the waiver process. Compliments were extended to the CDC staff for their past work and current cooperation and consultation.

Dr. Steven Gutman, Director, DCLD, ODE, CDRH, FDA, reviewed the FDA process for pre-market approval/clearance of medical devices (Addendum G). He said the major review activity is the 510(k) program, and mentioned three new review programs: special 510(k), abbreviated 510(k) and third party reviews. Last, he described the fine tuning of the process (replacement reagent process, re-examining labeling issues and opening the new/old guidelines to public comment) which is currently taking place.

A CLIAC member asked about the impact of the proposals for oversight of genetic tests. Dr Gutman responded that it was unpredictable. Another member inquired about the off-label use of waived tests. Dr. Gutman replied that the FDA has concerns but is restricted to what the law allows. There is no law that prevents a product from being misused. However, under CLIA, laboratories performing waived tests must follow the manufacturer's instructions for testing. If the instructions are not followed, the test is no longer waived; it is uncategorized and, as such, is considered high complexity.

Specimens and Test Systems Not Currently Regulated

CLIA Considerations **Addendum H**

Ms Rhonda Whalen, Health Scientist, LPSB, DLS, PHPPO, CDC, introduced the topic of specimens and test systems not currently regulated. She reminded the Committee that CLIA applies to laboratories and the term laboratories is defined in the law as facilities for the "examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings." She pointed out this broad language permits various interpretations which may allow certain additional tests to be regulated under CLIA, but technical concerns need to be addressed for appropriate decision making. These include: the type of testing/specimens involved; the appropriateness of the standards; and current oversight of non-regulated tests.

Representative Test Systems Not Currently Considered Under CLIA **Addendum I**

Dr. Rex Astles, Health Scientist, LPSB, DLS, PHPPO, CDC, presented an overview of representative test systems not currently regulated under CLIA covering both non-invasive and invasive/minimally invasive testing. He discussed issues unique to these test systems which must be considered. They are: 1) testing context; 2) testing does not involve a separable specimen; 3) inability to calibrate or adjust some test systems and; 4) biocompatibility issues with invasive test systems. The presentation concluded with examples of the various test systems.

FDA Review Process for Alternative Devices **Addendum J**

Dr. Gutman gave an overview of the FDA policy for review and clearance of these test systems which test different specimen matrices. He noted that these devices are treated the same as other medical devices (Tier III 510(k) or PMA process).

American Association for Respiratory Care (AARC) **Addendum K**

Mr. Carl Mottram, B.A., R.T., RPFT, Mayo Clinic, reviewed the AARC Clinical Practice Guidelines and other professional standards and guidelines for testing exhaled breath. He discussed the various uses of measurements on exhaled breath showing that the results are used both diagnostically and for monitoring and discussed calibration of the various instruments. In addition, Dr. Mottram discussed the in vivo/ in vitro sensors used for blood gas monitoring or diagnostic testing, their uses and calibration methods.

Redefining Laboratory Testing **Addendum L**

Dr. Glen Hortin, Chief of Clinical Chemistry, Warren Magnusson Clinical Center, NIH, and Chair, Point-of-Care testing committee, College of American Pathologists (CAP) began his presentation by posing the question "Where is the lab?" He said at this time, CAP has not developed an official position on standards for testing devices not covered by CLIA; however, CAP applies the same basic standards regardless of test setting. He pointed out that Florida regulations apply to intermittent access analyzers and that the Department of Transportation requires quality assurance programs with external calibration checks for breath alcohol analyzers. He reviewed the various types of devices and discussed whether it was appropriate to distinguish between *in vivo* and *in vitro* tests or between monitoring versus diagnostic laboratory tests.

Committee Discussion

To open the discussion on unregulated testing, Dr. Martin presented a slide composed of the following five discussion questions:

- Should testing using breath specimens be regulated under CLIA?
- Should any of the types of test systems described (in the CLIA presentations) be regulated under CLIA?
- If yes, which ones and why?
- What standards should apply (QC, QA, PT, personnel qualifications)?
- How would compliance with standards be evaluated?

He reviewed the slide and suggested the discussion focus first on whether breath testing should be regulated under CLIA. One member noted that breath is expelled from the body and breath testing should be regulated the same as testing performed on other specimens. In general, the Committee was in agreement that testing using breath specimens should be regulated under CLIA, although one member said that in-line measurements and spirometry should not be included under CLIA. One member stated that States and courts should determine the requirements for regulation rather than CLIA.

With respect to other testing not currently regulated under CLIA, some CLIAC members indicated that some tests may need to be exempt from regulation. Others said that in-line monitors should not be regulated and that only tests performed in the laboratory should be regulated. It was noted that these tests may require standards that differ from the current CLIA regulations. One member suggested that tests could be tiered based on possible harm to the patient, but it will be necessary to determine if CLIA is the appropriate regulatory program. A second member commented that you cannot rely on any test not causing harm. A third member asked if patient harm wasn't the main consideration for CLIA and the FDA. Dr. Gutman

responded that the FDA considers patient harm the central purpose in enforcing its regulations. Ms. Yost commented that surveyors are concerned about limited quality control (QC) for these tests as these tests are frequently not performed in laboratories and in these settings, QC may not be required. She also pointed out that although the CLIA law is broad enough to cover these tests, regulations would have to be developed to address such testing.

The Committee discussed whether any of the types of test systems described in the presentations should be regulated under CLIA. The point was made that although the issue is complicated, it will become more important in the future as testing moves toward more non-invasive and in vivo methods, and broad input is needed. Another opinion was that CLIA may be applicable to some tests but not to others and these tests should be considered individually. One member felt the devices should be categorized based on technology and then a decision could be made as to which would be appropriate for CLIA regulation. The CLIAC agreed these tests need to be monitored but expressed concern about how oversight would impact patient care, for example whether inspections would be conducted in operating rooms. One member said all of these systems should be included in a quality assurance program and be subject to some regulation under CLIA. In general, the Committee suggested more information is needed and asked the CDC to formulate some options for CLIAC consideration. Also, CLIAC members were interested in whether other countries regulate these devices and asked that this information be presented at a future meeting. Finally, the Committee suggested seeking consultation from the related medical specialties (e.g. anesthesiologists) and reviewing pertinent practice guidelines for this testing.

CDC Research Agenda for Improving Laboratory Testing Practices **Addendum M**

Dr. Thomas Hearn, Deputy Director, DLS, PHPPO, CDC briefly reviewed the government's six main roles in laboratory testing. He emphasized the CLIA studies are defined in the law and that there are three areas of research: quality, access, and cost. Dr. Hearn gave a brief review of the history of Evaluation of Quality in Laboratory Practices and Standards (EQLPS) listing areas of research for this program. He summarized research carried out from inception to the present and posed a number of questions relevant to laboratory practice/standards research. He explained the strategy for future work, and he ended his talk with a slide on the new challenges facing EQLPS.

Committee Discussion

One CLIAC member noted that although there is a wealth of information available in laboratory databases, the knowledge of how to use the tools for data analysis is lacking. Another member agreed and said laboratorians must be educated on how to use their own data. One member asked if there were plans to study the effects of laboratory errors. Dr. Hearn replied that an Ambulatory Sentinel Practice Network study collected data on laboratory test errors and their consequences which showed that although errors were rare, they were significant when they occurred. Dr. Boone commented that CDC had conducted a project with a local hospital to evaluate laboratory errors; however, concerns about liability prevented publishing the article documenting the errors. Dr. Hearn commented that informatics and medical errors are important issues at NCCLS. Several members commented that more laboratories are adopting International

Standards Organization (ISO) standards to improve quality through process control.

How Should the Nation's Agenda for CLIA-Related Research be Set **Addendum N**

Dr. Joe Boone, Assistant Director for Science, DLS, PHPPO, CDC gave an overview of CLIA research. He explained that past research had focused on CLIA studies, present research is focused on laboratory practice and performance, and asked the question "Where should the future focus be directed?" He also reviewed the scope of EQLPS and the research objectives.

Committee Discussion

Dr. Martin asked the Committee for input on where CLIA research should be focused. One CLIAC member said the bottom line for setting priorities should be improving patient care. Another member said further regulation probably will not result in better test performance; regulations are not the solution, other approaches are needed. Another member said that quality systems is a trend; laboratories will need to decide about adoption of ISO standards for certification under ISO 9000. A member commented that health care is being pressured to perform as an industry that produces care and this forces new thinking. It is necessary to focus on more than the analytic process. Another member commented that the key is to address where clinical medicine and the laboratory intercept and how they can help each other. Another member said that public health testing should be considered. There is a need to improve communication to the physician, as well as the patient, and a need to optimize the use of funds. Another member said there needs to be better interface between the laboratory and clinician but there are individuals using the laboratories today who have even less information about the laboratory than the clinician. Dr. Boone commented that laboratories and physicians have different perspectives. Physicians are willing to use an imperfect test if it provides rapid results so that they may proceed with patient treatment. A member agreed and said the need for rapid tests is increasing. Another member said that the post-analytic process is very important to patient outcome and there should be some focus on communication and turn around time. Another member said interfaces are critical, the results don't always get to the care-giver and the focus should be on how the system can be improved to work better. A member commented that it is difficult to get people to look at this as a system. Several CLIAC members felt that research is needed relating to the interfaces between the laboratory and the users (clinical practice), as well as the purpose for testing.

In summary the CLIAC discussion generated the following ideas for future research:

Studies on development of information management tools concerning

- the interface between the laboratory and physicians
- effective ways to educate patients, public, physicians about laboratory testing

Studies showing impact/effect of off-site laboratory testing (i.e. home use, POC)

Studies on evidence-based testing

Economic Studies

- impact of CLIA on patient care
- relationship of test outcome to patient care
- impact of reimbursement systems on laboratory practice

Outcome research

- whether the type of information physicians receive affects the patient outcome
- whether the size of the testing laboratory affects testing
- the impact of sending specimens to multiple laboratories has on patient care (insurance-directed laboratory usage)

Dr. Martin asked CLIAC for advice on who should be involved in setting the research agenda. CLIAC members said external advice and information should be sought but CDC should determine internally how the projects fit into the CDC mission and whether there are resources and partners available. A member said that input on selecting types of study design would be useful.

Introduction to Proficiency Testing Issues **Addendum O**

Ms. Nancy Anderson, Health Scientist, LPSB, DLS, PHPPO, CDC presented an introduction to CLIA proficiency testing issues. She reviewed the CLIA law pertaining to proficiency testing (PT), the CLIA regulatory requirements for PT (including consensus requirements for scoring), and CLIAC's previous recommendations for PT consensus. She discussed the process for revising the PT regulations and the considerations in the CLIA law for adding analytes. She ended her talk by listing potential criteria for adding analytes, and asked the committee what type of information or data they would need for future discussion on revising the PT regulations with respect to :

- adding required analytes
- changing consensus or scoring requirements
- other revisions

Committee Discussion

One CLIAC member asked if there are studies to determine thresholds for pass/fail criteria. Dr. Boone replied that the performance limits in the current CLIA regulations were established in 1986 and need to be reviewed and modified. Another member commented if performance is good for some currently regulated analytes, perhaps these analytes need not continue to be tested. One member questioned whether laboratory errors have been identified through the use of PT. One member observed it would not make sense to expand PT (and costs) unless it leads to improved patient care. Another member said that the context in which a test is used must be considered. For example, although physicians know that glucose monitoring devices are not as accurate as traditional laboratory glucose tests, the physicians feel they are clinically sufficient. If these tests

have some systematic bias, this may be a problem to evaluate through PT. A Committee member said that genetic testing should definitely be added to the list of regulated analytes. It was suggested that tests be added to regulated PT analytes based on clinical significance, problems with testing and cost/benefit considerations. Several members specifically suggested adding PT for "black box" testing, glucose meters, etc. and pointed out the need to evaluate PT for POLS. One member observed that PT in microbiology has become easier and does not discriminate between good and bad performance. A Committee member noted that although the list of regulated tests is short, CAP accredited laboratories are required to participate in all available PT for all analytes. One Committee member commented that a large amount of information from voluntary PT programs (CAP and other programs) could be used to indicate "problem" analytes. Judith Yost mentioned measures of evaluating laboratory performance other than PT. A Committee member agreed with Ms Yost, that other ways of evaluating laboratory performance are available but noted that the current HCFA data base only contains pass/fail scores and does not capture PT results which are needed to evaluate PT performance. One member commented that PT programs drive laboratorians to get the same answer, regardless of the heterogeneity of different methods for the same analyte. Another member suggested an evaluation of how PT programs assess performance using different methodologies.

The CLIAC agreed that more information should be provided to the Committee to facilitate future discussions on PT. At this time, their suggestions for potential criteria for adding analytes included:

- impact on patient care
- testing problems
- cost/benefit to laboratories

Dr. Boone introduced Dr. Mike Noble, who is serving as a consultant on PT to DLS. Dr. Noble said PT samples are an important educational tool in small labs and that Canadian Microbiology PT found that the "critiques" are the single most useful educational tool. The members agreed PT has many uses other than measuring performance - it is an unmatched educational tool and PT data can be used to evaluate new instruments.

Date for the next CLIAC meeting: September 27 - 28, 2000.

I certify that this summary report of the April 5-6, 2000, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.

/S/ Toby L. Merlin, M.D.
Chairman