Oversight for Genetic Testing – MMWR Report Development and Issues Needing Input

Bin Chen, Ph.D., FACMG
Division of Laboratory Systems, NCDPCID
Centers for Disease Control and Prevention

Sept. 5-6, 2007
CLIAC Meeting

Outline

- Background
  - Notice of Intent (NOI), May 2000
  - CLIAC recommendations, 2001
  - Evaluation of oversight options for genetic testing (GT) and analysis of potential impact
- Development of MMWR R&R publication
  - Goals
  - Issues to be addressed
  - Publication plan
- Issues needing CLIAC input

Current QA Landscape for GT

- CLIA regulations
  - General requirements for non-waived testing as applicable
  - Specialty of clinical cytogenetics
    - Specific QC requirements
    - Qualification requirements for technical supervisor
  - Requirements for molecular amplification procedures
- FDA requirements for IVD products
- State requirements (e.g., New York and Washington state programs)
- Voluntary professional practice and accreditation guidelines (e.g., ACMG, CAP, CLSI)
- Good laboratory practices

May 2000 Notice of Intent (NOI)

- Included CLIAC recommendations for establishing specific requirements for GT since 1997
- Sought public comments on:
  - Definition and categories of GT
  - Clinical validity
  - Authorized person
  - Informed consent
  - Confidentiality
  - Genetic counseling
  - Pre-analytic, analytic, and post-analytic issues
    - Test requisition, retention and use of tested specimens
    - Quality control, test validation, and proficiency testing
    - Test report and record retention
    - Personnel qualifications and responsibilities

Public Comments on NOI

- Received 57 comment letters containing over 800 comments
- Issues receiving a wide range of comments:
  - Definition and subspecialties of GT
  - Documentation of clinical validity
  - Authorized individuals to order genetic tests
  - Informed consent
  - Laboratory's role in providing consultation and genetic counseling
  - Requirements related to the pre-analytic phase
  - Personnel qualifications and responsibilities

Revised CLIAC Recommendations

- CLIAC review of NOI comment analysis – 9/2000
- Formation of the Second CLIAC Genetics Workgroup
- Genetics Workgroup meeting – 12/2000
- Revised CLIAC recommendations – 2/2001
- Summary crosswalk provided to CLIAC (see handouts)

Challenges in Considering Oversight

- Definition of genetic tests
  - Heritable vs. acquired variations
  - Biochemical genetic tests
- Integration of molecular methods in many specialties and subspecialties
- Lack of PT and QC materials
- Evolving technology
- Lack of national comprehensive and baseline data from available information sources
  - Literature references
  - Information from state programs: NY, WA, NE NBS Program
  - CDC studies, CMS data, government reports
  - Information from professional groups
  - Industry reports
  - Voluntary laboratory directories: GeneTests

Ongoing Activities

- Participation in SACGHS taskforce workgroups
- Genetic Testing Reference Materials (Get-RM) Coordination Program
- Improving availability of quality genetic testing
- ISO Genetics Project Group
- CLIA surveyor training
  - Northeast region, March 2007
  - Western region, May 2007
  - Annual meeting, October 2007

Purposes of MMWR Report

- Clarify applicability of current CLIA requirements to GT
- Discuss strategies to enhance the oversight for GT under the current CLIA framework
- Summarize CLIAC recommendations for areas needing additional quality measures
- Discuss essential good laboratory practices for ensuring quality performance
  - Appropriate test requests
  - Prompt test initiation
  - Quality test performance
  - Timely identification and prevention of potential errors
  - Appropriate result interpretation
  - Improved patient safety
- Provide guidance to the public

MMWR Report Outline

- Background and needs
- Methods and information gathering
- Issues to be addressed:
  - Method validation when introducing new GTs to patient testing
  - Preanalytic processes
  - Analytic processes
  - Postanalytic processes
  - Facility and quality management
  - Personnel
  - Definition of GTs
- Recommended good laboratory practices
  - Regulatory requirements
  - Professional guidelines, voluntary standards
  - CLIAC recommendations for good laboratory practices

Method Validation – CLIA Requirements

493.1253 Standard: Establishment and verification of performance specifications

- Verify for each unmodified FDA-cleared or approved test system:
  - Accuracy
  - Precision
  - Reportable range of test results for the test system
  - Manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population.
- Establish for each modified FDA-cleared/approved test system, lab-developed test, or test system with no performance specifications provided, as applicable:
  - Accuracy
  - Precision
  - Analytical sensitivity
  - Analytical specificity to include interfering substances
  - Reportable range of test results for the test system
  - Reference intervals (normal values)
  - Any other performance characteristic required for test performance

Method Validation – Issues Needing Input

- For laboratory-developed GTs:
  - How to determine which performance characteristics are applicable to specific tests?
  - Who should decide?
- Clarifications on certain performance characteristics for specific GTs:
  - Reference intervals (also under test report requirements under 493.1291(d))?
  - Reportable range?
  - Analytical sensitivity?
- Genotype-phenotype correlation
  - Should laboratories establish or document this information and make it available to clients?

Preanalytic Processes

- CLIA -
  - General requirements
    - Test request
    - Specimen submission, handling, referral
  - Flexible for labs and professional guidelines – Solicit any additional information relevant and necessary for a specific test to ensure accurate and timely testing and reporting of results, including interpretation, if applicable
- Voluntary professional and accreditation guidelines – more specific for GT (e.g., ACMG S&Gs, CAP Mol Path Checklist, CLSI MM1-A)
  - Informed consent
  - Race/ethnicity info
  - Pedigree and family history
- CLIAC recommendations (see handout)

Preanalytic Issues Needing Input

- Laboratory's role in providing information to users/clients to aid in test selection and request
  - Issues reflected from public comments & ongoing discussions
    - Labs need and need to solicit appropriate information
    - Information labs provide facilitates informed decision making
    - For in-house developed tests, information is only available from the labs
  - Quality management system approach
- What information to provide to improve appropriateness of test selection and requisitions?
  - Intended use?
    - Target gene(s), sequence(s), mutation(s)
    - Purpose of testing
    - Targeted patient population
  - Performance specifications?
  - Limitations?

Analytic Processes – Control Issues Needing Input

- Blank control(s) in molecular amplification procedures
  - Essential for monitoring carryover/cross-contamination
  - Addressed in ACMG, CLSI guidelines
  - Sometimes used as neg. control for mol. ID testing; however, not for human genetic testing
  - Not reflected from current control requirements under 493.1256
  - Survey Procedures and Interpretive Guidelines
    - Facility requirements for molecular amplification procedures, 493.1101(a)(3):
      - Should have a mechanism to detect cross-contamination of patient specimens
      - May include a “blank” control in each run of patient testing
- Recommended good laboratory practice for MMWR?

Analytic Processes – Control Issues Needing Input (Cont.)

- Frequency of control procedures
  - CLIA: At least once each day of patient testing under 493.1256
  - Laboratories may perform molecular or other GTs more than one time each day
- Recommended good laboratory practice for MMWR?
  - Are there GTs that are run without blank controls or other needed controls?
  - How to determine if laboratories have adequate alternative mechanisms for detecting immediate error in absence of controls?
  - Information sources?
  - Additional guidance?

Analytic Processes – PT and Alternative Approaches to PT

- §493.1236(c) requires labs to at least twice annually verify the accuracy of any test or procedure not on the regulated analyte list
- 2001 CLIAC recommendations
  - A two-tier system, including formal PT and interlaboratory comparison programs, should be developed
  - PT programs should be developed for GT subspecialties and diseases evaluated, and should reflect commonly performed tests
  - It is necessary to decide how to use methodology-based PT in addition to test-specific challenges
  - Requirements should not be less stringent for low-volume tests and rare disease testing
- Issues needing input:
  - More specific guidance to performance evaluation for GTs?
  - Recommended good laboratory practices?

Postanalytic Processes- Test Report Issues Needing Input

- Result interpretation
  - 493.1291 (c)(6) requires inclusion of the test result and, if applicable, the units of measurement or interpretation, or both.
  - Issues:
    - How to determine if result interpretation is applicable to specific genetic tests?
    - Who should make such a decision?
- Recommended good laboratory practices?

Personnel – CLIA Requirements

- CLIA requirements
  - Most GTs are high complexity testing, therefore subject to personnel requirements for high complexity testing
  - Clinical cytogenetics: Specific qualification requirements for technical supervisor (TS)
  - 493.1235 Personnel competency assessment policies: Laboratories must establish and follow written policies and procedures to assess employee and, if applicable, consultant competency
  - Responsibilities of laboratory director (LD) and TS
- Survey Procedures and Interpretive Guidelines
  - Refer to LD responsibilities for establishing policies and TS responsibilities to monitor specific testing personnel competency
  - Probes (examples):
    - How does the laboratory evaluate the competency of its employees?
    - If a laboratory utilizes a consultant, how does the laboratory determine if the consultant is competent? Does the laboratory have a policy/procedure to determine consultant competency?

Personnel Issues Needing Input

- How can the general personnel competency requirements be used to enhance oversight for laboratories performing GTs?
- What specific guidance can be provided to laboratories, especially for those performing molecular and biochemical GTs?
  - Establishing policies and procedures to monitor each individual's competency and identify remedial training or continuing education needs?
  - Assess and monitor specific testing personnel competency?
    - Technical supervisor competency?
    - Clinical consultant competency?

GT Definition - Challenges and Issues

- Challenges
  - No commonly agreed upon definition at present
  - GTs may be performed in several current specialties and subspecialties (e.g., FVL)
  - Integration of molecular methods to current specialties and subspecialties (e.g., DNA-based HLA typing)
- Issues
  - Is there a need to revisit the CLIAC recommended definition of GTs in light of ongoing efforts in the U.S. and internationally?
  - What are the areas of testing that the recommended good laboratory practices should apply to?

Publication Plan

- Current MMWR R&R report in preparation
  - Submission date: Nov. 21, 2007
  - Projected publication time: 16 weeks later
- Issues needing additional discussion
  - Additional assessment?
  - Follow-up publication?
  - Other options?

Thank you!

Please see issues/questions for discussion