Genetic Testing Issues for CLIAC Input

How to Approach the Issues

- Input needed for current MMWR report if possible:
  - Preanalytic processes
  - Performance characteristics applicable to laboratory-developed tests
  - Control procedures
  - Test report
- Strategies/approaches to addressing other issues?
  - Additional assessment?
  - Additional discussion and follow-up publication?
  - Other options?

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?

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?

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?

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?

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?

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?