The Role of CLIA in the Oversight of Genetic Testing

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Background

- **CLIA enacted – 1988**
- **NIH/DOE Task Force Report - 1997**
- **CLIAC recommends changes to CLIA – 1998**
- **SACGT recommends increased oversight – 1999**
- **CDC Notice of Intent - May 2000**
- **Notice of Proposed Rule Making - 2002 ?**

What topics should be addressed by a CLIA Genetics Specialty?

- **Definition – What is included and excluded?**

- **General requirements**
  - Documentation of clinical validity
  - Person authorized to order a genetic test
  - Informed consent
  - Confidentiality
  - Genetic counseling

- **Requirements for specific testing phases**
  - Pre-analytic phase
  - Analytic phase
  - Post-analytic phase

Goals of Oversight

- **Achieve Balanced Rules: Access = Burden / Protection**
- **Achieve Timely Rules: Need Broad Public Input**
- **Achieve Long-lasting Rules**
- **Achieve Effective Implementation of Oversight**

Notice of Intent

Issues receiving the most comments:

1. Definition and categories for genetic testing
2. Documenting clinical validity
3. Who should be authorized to order a genetic test
4. Documentation of informed consent
5. Laboratory providing consultation/ counseling
6. Pre- and post- analytical phase requirements
7. Personnel qualifications/ responsibilities

Genetic Testing: Specialty & Subspecialties

CLIAC Recommends

- Three separate subspecialties
  - molecular genetics
  - cytogenetics
  - biochemical genetics
- Testing for acquired/somatic mutations should be included in each genetic testing subspecialty

Definition: Biochemical Genetic Testing

The analysis of human proteins and certain metabolites, which is predominantly used to detect inborn errors of metabolism, heritable genotypes, or gene products of genetic variations or mutations for clinical purposes.

Such purposes would 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.]

Definition: Cytogenetic Testing

An analysis performed on human chromosomes to detect heritable or acquired disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes.

Definition: Molecular Genetic Testing

An analysis performed on human DNA or RNA to detect heritable or acquired disease-related genotypes, mutations, or phenotypes or karyotypes for clinical purposes.

Steps to Establish "Clinical Validity"

Six steps recommended:

1. **Reason for introduction of a new test**
2. **Review available scientific studies (internal and external work)**
3. **Select methodology**
4. **Establish analytical validity**
5. **Use the test in an appropriate test population**
6. **The Laboratory Director must be able to interpret the test result and its implications for a given individual or family. The limitations of the test must be defined and reported**

NOTE: Director can delegate responsibility, but retains ultimate responsibility for ensuring clinical validity

Person Authorized to Order a Genetic Test

CLIAC recommendations:

- **Current CLIA defers to state laws; there should not be a federal requirement superseding state regulations.**
- **Self-referral is acceptable, providing the laboratory medical director(s) is (are) willing to accept ordering and informed consent requirements and the state law allows such ordering**
- **Interstate referrals are dependent upon individual state requirements (NY, CA, FL, etc)**

Informed Consent

CLIAC recommendations:

- **Premise: Informed consent is required for all tests**
- **The individual ordering testing must be able to obtain the appropriate level of informed consent**
- **The level of informed consent is dependent on predictive or diagnostic use of test**
- **Determination of level of IC may be derived from established professional standards (guidelines)**
- **The requisition should include an area for attestation from the person ordering the test that the appropriate consent was obtained**

Genetic Counseling

CLIAC recommendations:

1. **Genetic counseling (GC) needs to be available as appropriate**

2. **The laboratory should facilitate access to genetic services, when appropriate**

3. **The laboratory should not be required to have a documented relationship with genetic counseling resources because the laboratory cannot direct patient care**

4. **The laboratory should be required to recommend genetic counseling for family members, when indicated**

Clinical Consultant Qualifications

CLIAC recommendations:

Be an M.D., D.O., and have two years experience in genetic testing; or hold a Ph.D. in a relevant discipline, be Board certified, and have two years experience in genetic testing; ~~or hold an MS in Genetic Counseling, be Board certified, and have two years experience in genetic testing (prospective).~~

Test Requisition and Clinical Information

Information required on requisitions:

- ***Patient name***
- **Date of birth**
- ***Time and date of collection***
- **Gender**
- **Race/ethnicity (if applicable)**
- ***Unique identifier on specimen container***
- ***Specimen type (blood, amniotic fluid, etc.)***
- **Reason for the test; Relevant clinical and laboratory information**
- **Pedigree (where applicable, required for linkage analysis)**
- ***Referring health professional or authorized person***
- ***Check-off box to indicate if appropriate level of informed consent has been obtained (when required by law or regulation)***
- ***Check-off box to indicate if patient has declined having his/her samples used anonymously for QA/QC purposes***

Re-use of Tested Specimens

- **Use the informed consent process to establish prior approval for subsequent use of sample(s) for "genetic" testing QA/QC**
  - **if not approved, discard sample**
  - **if approved, use anonymously for QA/QC**
  - **if subsequently desired for research testing under IRB, then new consent needed**
  - **Panel and reflex testing needs to be clearly identified when originally ordered**

Result Reporting

The test report should include:

- *Name of the individual*
- *Date of birth*
- *Specimen collection time/date*
- *Time/date of receipt in the laboratory*
- *Specimen accession number or case number*
- Race/ethnicity (where applicable)
- *Indication for testing*
- Test performed, including mutation(s) tested (may be listed individually, or referenced to an easily obtainable reference)
- *Test result*
  - *Predictive values (PV): When applicable. Test limitations should always be reported*

(Cont.)

Result Reporting

The test report should include (Cont.)

- A statement interpreting the test result that includes (as indicated), clinical implications, follow-up test recommendations, and/or genetic counseling indications
- *Documentation if a preliminary report has been issued*
- *Notation of any deviations from the laboratory's standard practice (when applicable)*
- Signature of the Laboratory Director *and other authorized individual*
- A means to contact the Laboratory Director, or appropriate designee
- *Date of report*

Retention of Specimens

- **Specimens retention needs to be defined**
- **Need to determine how long a specimen should be retained when an individual refuses to allow a sample to be used for QA/QC**
- **Two options were outlined:**
  1. **Set a time limit (specifics to be defined)**
  2. **Set a policy making the Laboratory Director responsible for choosing a timeframe (to be defined in consensus document(s) developed by one or more professional and/or private groups**
- **This requirement also applies to both heritable and acquired genetic disorders**

Retention of Records

- It was agreed that the retention time will have to be a compromise between optimum retention and clinical practicality. The time frame recommended as a compromise was a minimum of 10 years
- Both positive and negative results need to be retained
- This requirement applies to testing for both heritable and acquired genetic disorders

Issues Requiring Further Discussion

- **Intended use: May not be able to regulate but guidance is needed on which tests are subject to requirements**
- **Mechanism for distinguishing genetic tests**
- **Criteria for clinical validity**
- **Level of informed consent: Intended use level?**
- **Practicality of "opt-out"**
- **Sample retention: Timeframe and format**

Future Needs

- Private/public collaboration on guidance for genetic tests and testing
- Awareness of global lessons learned
- Innovative methods for delivery of educational materials
- “State-of-the-Art” production of materials containing known genetic mutations