Genetic Testing, CLIAC Report

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Discussion Format

- Background for CLIAC Involvement
  - NIH Report
  - SACGT
  - CDC/CMS/FDA Related Oversight Roles
- Procedures Followed by CLIAC
- Key Recommendations
- Some Key Remaining Issues
- Time line summary

NIH Task Force

- Created by the NIH Working Group on Ethical, Legal, and Social Implications of Human Genome Research.
- Charge: Review genetic testing in the United States, and make recommendations to ensure the development of safe and effective tests.

NIH Task Force: Recommendations

- There should be a framework for ensuring that new tests are safe and effective prior to their use for genetic testing.
- A new Secretary's Advisory Committee on Genetic Testing should be established to advise upon: new test introduction, testing process, competency of providers to use tests, and test availability for rare diseases.
- CLIA oversight for genetic tests should be expanded

Secretary's Advisory Committee on Genetic Testing (SACGT)

- Advise the Secretary on all aspects of the development and use of genetic tests. Including:
  - safe and effective incorporation of genetic technologies into health care
  - assessing the effectiveness of existing and future measures for oversight of genetic tests
  - identifying research needs related to the Committee's purview

SACGT Recommendations: Oversight of Genetic Tests

- The FDA should regulate laboratory developed genetic tests (“home brews”), using an innovative, flexible approach
- CLIA should be augmented to incorporate specific provisions for genetic testing laboratories
- Private-public collaborations are needed to ensure continued analysis of post market data

CLIA Responsibilities for Genetic Tests for Patient Care

- CDC: Researches issues, develops policy, initiates draft regulations
- FDA: Categorizes tests: High or moderate complexity; waived
- CMS: Investigates issues, drafts and/or finalizes regulations, enforces CLIA
- CLIAC: Provides advice to the Secretary of HHS on issues pertaining to CLIA

(PC)

Major Background Issue

- 866 genetic diseases are listed in GeneTests
- 511 are offered in clinical (CLIA) labs
- 355 diseases are offered exclusively in research labs (**41%**)

(Compiled by Dr. Ledbetter from GeneTests website, 10/01)

Functional Definition: Patient Care Test

- CLIA applies to all patient care tests:

Definition of a Patient Care Test:

A patient care test is a test whose results are provided to a patient, a patient's family, or health care provider.

(JHMI)

(This is independent of whether the laboratory is or is not under IRB oversight.)

Oversight Responsibilities (SACGT)

Who is responsible

Activity	IRB	CLIA	FDA
Research (development)	X		
Research, (limited patient Reports)	X	X	
Wide use patient reports, fully validated test, +/-continued research	+/-	X	X

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Initial CLIAC Recommendation:

1. Genetic testing should become a new testing category, separate from other high complexity testing categories.
2. It should cover both heritable and acquired mutation testing
3. It should include three subspecialties
   - molecular genetics
   - cytogenetics
   - biochemical genetics

Strategy Employed by The Genetic Working Group

1. Establish a definition of a genetic test
2. Identify specific issues/concerns that apply to genetic testing
3. Review the CLIA 88 regulations for high complexity testing; define where they needed to be clarified or modified for genetic tests
4. Define possible policies/strategies to address the identified needs

Definition: Molecular Genetic Testing

- An analysis performed on human DNA *and* RNA to detect heritable or acquired disease-related genotypes, mutations, *or* phenotypes 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

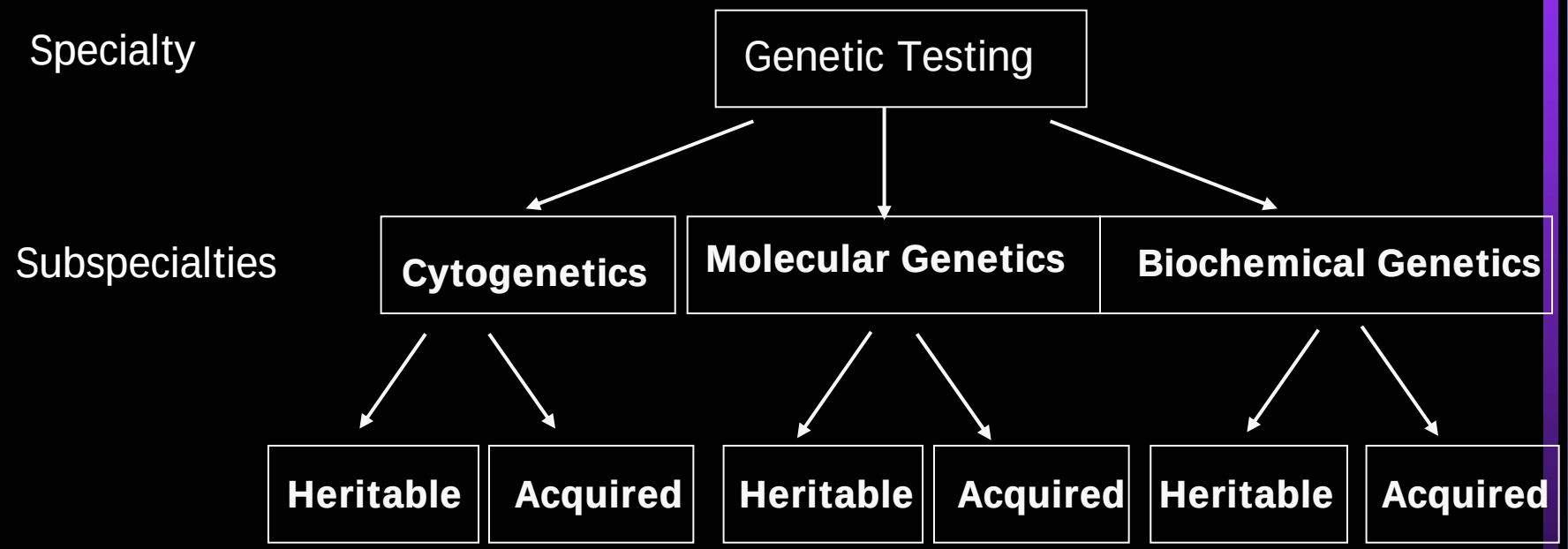
Definition: Cytogenetic Testing

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

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.]*

Proposed Genetic Testing Specialty and Subspecialties



Some Major CLIAC Recommendations

- General requirements: All phases of a test
  - Who can order a genetic test
  - Informed Consent
- Requirements for Specific Testing Phases

Recommendations for Test Components

- **Pre-analytical:** Includes test ordering, requisitions, specimen handling, transportation, required clinical information, informed consent, etc.
- **Analytical:** Personnel requirements, test performance, test validation, quality control, proficiency monitoring, etc.
- **Post-analytical:** Result reporting, test interpretation, confidentiality, etc.

Pre-analytical Issues

Person Authorized to Order a Genetic Test

- Current CLIA defers to state laws; there should not be a federal requirement superseding state regulations. Interstate referrals are dependent upon individual state requirements (NY, CA, FL, etc)
- Self-referral is acceptable, provided the laboratory is qualified under state law to accept ordering and meets the informed consent requirements

Pre-analytical Issues
Test Requisition and Clinical Information

- Date of birth
- Time and date of collection
- * Gender , Race/ethnicity (if applicable)
- Unique identifier on specimen container
- Specimen type (blood, amniotic fluid, etc)
- Relevant clinical or laboratory information
- * Pedigree (where applicable, required for linkage analysis
- * Check-off box to indicate if appropriate level of informed consent has been obtained
- * Opt-out check-off box

Pre-analytical Issues

Informed Consent

- Premise: Informed consent is required for all tests
- The individual ordering testing must obtain the appropriate level of informed consent
- The level of informed consent depends on factors such as whether a test is used for predictive or diagnostic testing
- The level is disease dependent; may be derived from established professional standards and or guidelines.
- The laboratory should assist in determining appropriate level of informed consent.
- The requisition should Include an area for attestation signifying that appropriate consent was obtained.

Definitions: Validity

Analytical Validity: Primarily concerned with ability to accurately measure the presence or absence of a given analyte or allele.

Clinical Validity: Ability to separate clinical disease or future disease from no disease or no risk of disease through measuring that analyte or allele; clinical sensitivity, specificity, and predictive values, relating the change to presence or absence of disease.

[Clinical Utility: Clinical validity plus full knowledge of test , including gene penetrance, etc.; its significance in populations to be tested.]

Analytical Phase

Clinical Validation of a Genetic Test

Add to the CLIA regulations

- A confirmatory test must have a defined predictive value which can be communicated to the care giver.
- Predictive value should be defined in terms of ethnic populations where applicable.
- Limits of the information available must be specified.

Analytical Phase:
Proficiency Testing

- When commercial proficiency testing is available, laboratories must enroll and participate in programs commensurate with tests performed.
- When PT does not exist, the regulations should specify or reference required alternatives. Examples include:
  - Split samples sent to another laboratory
  - Blindly test samples
  - Test samples in duplicate by separate technologists,

Analytical Issues

Personnel Requirements:

- Current CLIA requirements are adequate for:
  - Laboratory Director
  - General Supervisor
  - Testing Personnel
- Technical Supervisor:
  - Require relevant doctorate (MD, DO, PhD), appropriate certification, subspecialty training and experience
- Clinical Consultant:
  - Relevant doctorate (MD, DO, PhD), with 2 years appropriate experience in genetic diseases

Post-analytic phase
Special reporting requirements

- The laboratory director / clinical consultant / technical supervisor must ensure that reports of test results include pertinent information required for clinical interpretation that is meaningful to a non-geneticist healthcare provider.
- When individual interpretation of the test result is required, the signature of the director or designee must appear on the report.

Post-analytical phase

Result Reporting

Special Requirements are marked with (*) and color

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 (methodology, if applicable), including mutation(s) tested (may be listed individually, or referenced to an easily obtainable reference)

(Cont.)

Post-analytical

Result Reporting (cont.)

* **An interpretation of the test result that may include clinical implications, follow-up test recommendations, and/or genetic counseling indications, as indicated**

Documentation if a preliminary report has been issued

Notation of any deviations from the laboratory's standard practices (when applicable)

* **Signature of the Laboratory Director and/or other authorized individual**

* **A means to contact the Laboratory Director, or appropriate designee**

Date of report

Additional Issues and Next Steps

Re-use of Tested Specimens

- **Use the informed consent process to establish prior approval for subsequent use of sample(s) for genetic testing in QA/QC (include the "opt-out" option)**
  - **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**

Additional Oversight Issues

- Currently, CLIA and CMS oversight has not fully addressed clinical validation of laboratory developed tests. Practical survey guidelines need to be considered.
- Oversight responsibilities of IRB's need to be clarified, as does definitions of application of CLIA to research laboratories that return results to patients or their health care providers.
- IRB's need education/guidance as do research laboratories to assist them with CLIA.

SACGT Working Groups:
Key Issues Involving Laboratories

1) Informed Consent: Who decides what level of consent is appropriate for a given test? What is the laboratory's role in assuring patient consent?

2) Rare Diseases: Definition of a rare disease. Limited test sites, mainly research labs , with laboratory developed, (home brew) tests that are of limited industrial interest. There are no proficiency tests, there are patent issues

3) Data Work Group: Who is to provide the data and how? Privacy? Cost? Definitions of a test, etc.

SACGT Additional Concerns Supportive of CLIAC's Reports

- Waived tests were of major concern as they apply to genetic testing in part because of the documentation by CMS and others, that quality cannot be assured, as used in the field, and because of pre- and post analytical considerations..
- SACGT wrote a letter to Secretary Thompson advising attention to the issue of waived tests as they pertain to genetic testing.

Key Events in Formulating a Genetic Testing Policy

- NIH/DOE Task Force Report - 1997
- CLIAC establishes Genetics Working Group 1 – 1997
- CLIAC recommends changes to CLIA to address genetic testing – 1998 (provided to SACGT in 1999)
- CDC develops Notice of Intent to seek public comment on CLIAC recommendations – 2000
- Genetic Work Group 2 considered responses to NOI, makes final recommendations to CLIAC - 2001
- CLIAC finalizes recommendations, - 2001
- Final regulation development initiated -

Additional Activities:
CDC Div of Laboratory Services

- Genetic Working Group meetings
  - Clinical professional societies, laboratorians, regulatory agencies
- Proficiency testing initiatives:
  - Methods development; meeting to explore options
- Educational CD: Genetic testing
- HIV rapid test oversight initiative

Bridging the Genetics Grand Canyon

- Lord's prayer – 66 words
- Ten Commandments - 179 words
- Gettysburg address - 286 words
- Declaration of Independence – 1300 words
- Regulation on cabbage sale – 26,911 words