Crosswalk of the 2001 CLIAC Recommendations regarding Genetic testing and the Current CLIA Requirements

(Note: The CLIAC recommendations refer to the final set of recommendations, which were revised based on public comments on the May 2000 Notice of Intent and approved by the full Committee at the February 2001 CLIAC meeting.)

Issues	CLIAC Recommendations	Current CLIA	Notes/Clarifications
Definition of Genetic Tests	**Molecular genetic test:** An analysis performed on human DNA and RNA to detect heritable or acquired disease-related genotypes, mutations, 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. **Cytogenetic test:** 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. **Biochemical genetic test:** 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.]	No definition for genetic tests.	The current CLIA regulations recognize a specialty of clinical cytogenetics, but do not define genetic tests over all.

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Individuals Authorized to Order Genetic Tests	• There should not be a federal requirement superseding state regulations. Interstate referrals should depend upon state requirements. • If state law allows individuals to self-order tests, laboratory directors should decide which tests to offer and whether additional assistance and considerations are needed. • Ordering of predictive tests should not be restricted to genetic professionals.	Under **§493.2 Definitions** - An authorized person means an individual authorized under State law to order tests or receive results, or both.	The May 2000 Notice of Intent (NOI) solicited public comments, as suggested by CLIAC, on the issue whether there should be a federal requirement superseding state regulations for individuals authorized to order genetic tests. Based on the public input, CLIAC recommended that the current CLIA definition for authorized person is appropriate and no change is needed.
Confidentiality of Genetic Test Information and Test Results	• Currently CLIA provides general requirements for ensuring confidentiality of patient information. • The importance of confidential handling of genetic testing information should be emphasized. • Electronic records are suitable for confidential storage with proper oversight.	**§493.1231 Standard: Confidentiality of patient information**. The laboratory must ensure confidentiality of patient information throughout all phases of the total testing process that are under the laboratory's control.	The requirements under 493.1231 apply to all laboratory testing under CLIA, including genetic testing.
Test Request	CLIAC recommended the following information be solicited on test requisitions: • <u>Patient name</u> • <u>Date of birth</u> • <u>Time and date of collection</u> • <u>Gender</u> • Race/ethnicity (if applicable) • <u>Unique identifier</u> on specimen container • <u>Specimen type</u> • Reason for requesting the test • Relevant clinical or laboratory information • Pedigree (where applicable) • <u>Name of referring physician, health professional or other authorized individual</u> • Check-off box to indicate if appropriate	**§493.1241 Standard: Test request** (c) The laboratory must ensure the test requisition solicits the following information: (1) The name and address or other suitable identifiers of the authorized person requesting the test and, if appropriate, the individual responsible for using the test results, or the name and address of the laboratory submitting the specimen, including, as applicable, a contact person to enable the reporting of imminently life threatening laboratory results or panic or alert values. (2) The patient's name or unique patient identifier. (3) The sex and age or date of birth of the patient. (4) The test(s) to be performed. (5) The source of the specimen, when appropriate. (6) The date and, if appropriate, time of specimen collection.	The CLIAC-recommended elements that have been included in the CLIA regulations are underlined.

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	level of informed consent has been obtained • Check-off box to indicate if the patient has declined having residual samples used anonymously for QA/QC purposes. **Additional recommendations:** • At the laboratory director's discretion, a specimen may be stabilized until the clinical information for accurate testing is available. • Rely on professional societies and accrediting agencies to develop guidelines to improve collection of information needed by laboratories.	(7) For Pap smears, the patient's last menstrual period, and indication of whether the patient had a previous abnormal report, treatment, or biopsy. (8) Any additional information relevant and necessary for a specific test to ensure accurate and timely testing and reporting of results, including interpretation, if applicable.	
Validation of New Genetic Tests	<u>Analytic validation:</u> • Laboratories must verify or establish reproducibility for each method within and between runs, and between technologists. • Methodology must be appropriate for conditions being evaluated. • Quality control parameters must be applicable. • Reagents must be validated. <u>Clinical validation</u>: • The following six steps should be considered in establishing clinical validity: 1) The laboratory director has a reason for considering the introduction of a new test; 2) Ensure a review is conducted of available scientific studies. 3) Select methodology; 4) Establish analytical validity; 5) Use the test in an appropriate test population;	**§493.1253 Standard: Establishment and verification of performance specifications** (b)(1) Verification of performance specifications. Each laboratory that introduces an unmodified, FDA-cleared or approved test system must do the following before reporting patient test results: (i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics: (A) Accuracy. (B) Precision. (C) Reportable range of test results for the test system. (ii) Verify that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population. (2) Establishment of performance specifications. Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text	The CLIA regulations emphasize the analytical performance of laboratory tests.

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	6) The test results and their implications can be interpreted for a given individual or family. The limitations of the test must be defined and reported. • Clinical validation requirements should reflect the following: 1) Predictive values should be required when applicable. Test limitations should always be reported but predictive values could vary as knowledge increases. 2) Number of positive probands that need to be tested should be appropriate based on disease, and subject to professional guidelines rather than regulations. This may be the responsibility of the laboratory director and the technical supervisor.	book procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable: (i) Accuracy. (ii) Precision. (iii) Analytical sensitivity. (iv) Analytical specificity to include interfering substances. (v) Reportable range of test results for the test system. (vi) Reference intervals (normal values). (vii) Any other performance characteristic required for test performance. (3) Determination of calibration and control procedures. The laboratory must determine the test system's calibration procedures and control procedures based upon the performance specifications verified or established under paragraph (b)(1) or (b)(2) of this section.	
Specimen Identification and Integrity	The following information should be required to ensure identification of the subject being tested: date of birth, gender, ethnicity, patient or family number, specimen source, time of collection, and name of person obtaining the sample.	**§493.1232 Standard: Specimen identification and integrity**. The laboratory must establish and follow written policies and procedures that ensure positive identification and optimum integrity of a patient's specimen from the time of collection or receipt of the specimen through completion of testing and reporting of results.	CLIA requires laboratories to ensure positive identification and optimum integrity of patient specimens through the entire testing process. Most of the CLIAC-recommended information (as underlined) has been required for laboratory records.
Quality Control (QC)	• Quality control requirements should be appropriate for each subspecialty. Establish general requirements as appropriate, and have specific requirements for each subspecialty. • More specific requirements for in-house assays are not needed under CLIA. Rely	**§493.1256 Standard: Control procedures** - This section contains general requirements for control procedures, including control requirements for molecular amplification procedures under (d)(3)(v). **§493.1276 Standard: Clinical cytogenetics**	The general CLIA requirements for control procedures are applicable to genetic testing; the control requirements for molecular amplification procedures are applicable to molecular genetic testing and molecular microbiology

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	on professional and/or private organizations to establish specific standards.	- This section includes specific quality systems requirements for clinical cytogenetic testing.	testing.
Contamination Control	• The laboratory must be designed to minimize contamination. • Amplification procedures which are not in wholly closed systems must have separation between preparative and post-amplification steps. • Work processes must minimize risk of mixing samples, and risk of contamination of equipment, reagents, and/or supplies.	**§493.1101 Standard: Facilities** (a) The laboratory must be constructed, arranged, and maintained to ensure the following: (1) The space, ventilation, and utilities necessary for conducting all phases of the testing process. (2) Contamination of patient specimens, equipment, instruments, reagents, materials, and supplies is minimized. (3) Molecular amplification procedures that are not contained in closed systems have a uni-directional workflow. This must include separate areas for specimen preparation, amplification and product detection, and, as applicable, reagent preparation.	The CLIAC recommendations have been covered under the CLIA requirements for facilities.
Proficiency Testing (PT)	• A two-tier system, including formal proficiency testing and inter-laboratory comparison programs, should be developed for genetic testing. • Proficiency testing programs should be developed for subspecialties of genetic testing and diseases evaluated, and should reflect commonly performed genetic tests. • It is necessary to decide how to use methodology-based proficiency testing in addition to test-specific challenges. • Requirements should not be less stringent for low-volume tests and rare disease testing.	**§493.1236 Standard: Evaluation of proficiency testing performance** (c) At least twice annually, the laboratory must verify the accuracy of the following: (1) Any test or procedure it performs that is not included in Subpart I of this part. (2) Any test or procedure listed in Subpart I of this part for which compatible proficiency testing samples are not offered by a CMS-approved proficiency testing program.	The CLIA requirements under 493.1236(c) applies to regulated analytes for which CMS-approved PT programs are not available and unregulated analytes, including genetic tests.
Test Report	The following information should be required on test report: • Name of the individual; • *Date of birth*; • *Specimen collection time/date*;	**§493.1291 Standard: Test report** (c) The test report must indicate the following: (1) For positive patient identification, either the patient's name and identification number, or a unique patient identifier and identification number.	Some of the CLIAC recommendations (underlined) have been included in the general CLIA requirements for test report. The CLIAC recommendations that have been addressed in other sections of

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	• 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; • *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. **Additional recommendations:** • Reports must be signed by the person with highest qualification, who may be the technical supervisor or laboratory director. • For inherited disease testing, at least one person signing the report must have board certification in medical genetics. • Reports should not be sent out until appropriate clinical information critical for interpreting test results is received by the laboratory.	(2) The name and address of the laboratory location where the test was performed. (3) The test report date. (4) The test performed. (5) Specimen source, when appropriate. (6) The test result and, if applicable, the units of measurement or interpretation, or both. (7) Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability. (d) Pertinent ``reference intervals'' or ``normal'' values, as determined by the laboratory performing the tests, must be available to the authorized person who ordered the tests and, if applicable, the individual responsible for using the test results. **§493.1276 Standard: Clinical cytogenetics** (d) The laboratory report must include a summary and interpretation of the observations, number of cells counted and analyzed, and use the International System for Human Cytogenetic Nomenclature.	CLIA are shown in italic. For example, the patient's date of birth and specimen collection time/date are required under 493.1241 Test request; result interpretation is required for cytogenetic test report under 493.1276.

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Retention of Records and Specimens	Record Retention • 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. • Copies of patient reports of genetic testing shall be retrievable for a minimum of 10 years, or longer if required by State law. Electronic reports are acceptable. • Both positive and negative results need to be retained. • This requirement applies to testing for both heritable and acquired genetic disorders. • Requirements should depend on the type of testing performed (for example, records of newborn screening testing might need to be retained for more than 10 years.) • Requirements should be comparable to those of pathology reports, which must be retained for at least 10 years under CLIA. Specimen retention • The laboratory must have a policy defining specimen retention. • Specimen retention needs to be defined but duration and format require additional thought and discussion. • Need to decide 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	**§493.1105 Standard: Retention requirements** (a) The laboratory must retain its records and, as applicable, slides, blocks, and tissues as follows: (1) Test requisitions and authorizations. Retain records of test requisitions and test authorizations, including the patient's chart or medical record if used as the test requisition or authorization, for at least 2 years. (2) Test procedures. Retain a copy of each test procedure for at least 2 years after a procedure has been discontinued. Each test procedure must include the dates of initial use and discontinuance. (3) Analytic systems records. Retain quality control and patient test records (including instrument printouts, if applicable) and records documenting all analytic systems activities specified in Sec. Sec. 493.1252 through 493.1289 for at least 2 years. In addition, retain the following: (i) Records of test system performance specifications that the laboratory establishes or verifies under Sec. 493.1253 for the period of time the laboratory uses the test system but no less than 2 years. (ii) Immunohematology records, blood and blood product records, and transfusion records as specified in 21 CFR 606.160(b)(3)(ii), (b)(3)(iv), (b)(3)(v) and (d). (4) Proficiency testing records. Retain all proficiency testing records for at least 2 years. (5) Quality system assessment records. Retain all laboratory quality systems assessment records for at least 2 years. (6) Test reports. Retain or be able to retrieve a copy of the original report (including final, preliminary, and corrected reports) at least 2	The current CLIA requirements for record retention are applicable to genetic tests - test requisitions, test procedures, analytic systems records, PT records, quality system assessment records, and test reports of genetic tests must currently be retained for a minimum of 2 years. CLIA does not have specific requirements for retaining specimens for genetic testing. Laboratories must meet the requirements under §493.1232 Standard: Specimen identification and integrity, to ensure positive identification and optimum integrity of a patient's specimen from the time of collection or receipt of the specimen through completion of testing and reporting of results.

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	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. 3) This requirement also applies to both heritable and acquired genetic disorders.	years after the date of reporting. In addition, retain the following: (i) Immunohematology reports as specified in 21 CFR 606.160(d). (ii) Pathology test reports for at least 10 years after the date of reporting. (7) Slide, block, and tissue retention— (i) Slides. (A) Retain cytology slide preparations for at least 5 years from the date of examination (see Sec. 493.1274(f) for proficiency testing exception). (B) Retain histopathology slides for at least 10 years from the date of examination. (ii) Blocks. Retain pathology specimen blocks for at least 2 years from the date of examination. (iii) Tissue. Preserve remnants of tissue for pathology examination until a diagnosis is made on the specimen.	
Laboratory Director Qualifications	The current CLIA requirements for the qualifications of directors of laboratories performing high complexity testing are adequate for genetic testing.	**Condensed from §493.1443 Standard; Laboratory director qualifications** - • Be an M.D. or D.O. certified in clinical and/or anatomic pathology; • Be an M.D., D.O., or D.P.M., and have 1 year of laboratory training during residency and two years of supervisory experience in high complexity testing; • Hold a doctoral degree in a chemical, physical, biological, or clinical laboratory science, and be certified and continue to be certified by a board approved by HHS; or • Be grandfathered.	The laboratory director qualification requirements under 493.1443 apply to laboratories performing high complexity testing.
Laboratory Director Responsibilities	CLIAC recommended the following regarding the laboratory director's role in documenting the clinical validity of genetic tests his or her laboratory performs: • The definition of clinical validity and analytical validity need to be clarified.	Under **§493.1445(e)(3)(i)** and **(ii)**, responsibilities of laboratory directors for high complexity testing include - • Ensuring test methodologies selected have the capability of providing the quality of results required for patient care.	The CLIA regulations emphasize the analytical performance of laboratory tests, while requiring the selection of test methodology appropriate for the clinical use of the test results.

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	• Examples need to be used in defining the responsibilities of laboratory directors. • Laboratory directors may delegate the responsibility for ensuring clinical validity of any test their laboratories offer, but remain responsible for the testing quality overall. • Laboratories should verify performance specifications as documented in literature references or by test developers, and demonstrate test results are comparable for the same patient populations.	• Ensuring verification procedures used are adequate to determine the accuracy, precision, and other pertinent performance characteristics of the method. Under **§493.1451**, responsibilities of technical supervisors for high complexity testing include - (b)(1): The technical supervisor is responsible for selection of the test methodology that is appropriate for the clinical use of the test results.	
Technical Supervisor Qualifications	• Be an M.D. or D.O. with certification in clinical and/or anatomic pathology; and have two years of sub-specialty training in genetics and two years supervisory experience in high complexity genetic testing, or four years of supervisory experience in high complexity genetic testing in the relevant subspecialty; • Be an M.D., D.O. or Ph.D. and be certified in the appropriate medical genetics specialty and have two years experience directing or supervising high complexity genetic testing in the relevant subspecialty; • Hold a doctoral degree in a chemical, physical, biological, or clinical laboratory science, and have four years of training or supervisory experience in high complexity genetic testing in the relevant subspecialty; or • Be grandfathered for limited time.	**§493.1449** Standard; Technical supervisor qualifications (p) If the laboratory performs tests in the specialty of clinical cytogenetics, the individual functioning as the technical supervisor must- (1)(i) Be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine licensed to practice medicine, osteopathy, or podiatry in the State in which the laboratory is located; and (ii) Have 4 years of training or experience, or both, in genetics, 2of which have been in clinical cytogenetics; or (2)(i) Hold an earned doctoral degree in a biological science, including biochemistry, or clinical laboratory science from an accredited institution; and (ii) Have 4 years of training or experience, or both, in genetics, 2 of which have been in clinical cytogenetics.	Under CLIA, qualification requirements for technical supervisors are specified for the following current specialties or subspecialties of high complexity testing: Bacteriology, mycobacteriology, mycology, parasitology, virology, diagnostic immunology, chemistry, hematology, cytology, histopathology, oral pathology, radiobioassay, histocompatibility, clinical cytogenetics, and immunohematology. For the pathology subspecialties (cytology, histopathology, and oral pathology) and the specialty of immunohematology, technical supervisors must be M.D.'s with appropriate board certification, training, or experience. For histocompatibility and clinical cytogenetics, technical supervisors are required to have a doctoral degree and appropriate training or experience.
Clinical	• Be an M.D., D.O., and have two years	**§493.1455 Standard; Clinical consultant**	The qualification requirements for

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Consultant Qualifications	experience in genetic testing; or • Hold a Ph.D. in a relevant discipline, be Board certified, and have two years experience in genetic testing.	**qualifications.** The clinical consultant must be qualified to consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment and management of patient care. The clinical consultant must-- (a) Be qualified as a laboratory director under Sec. 493.1443(b)(1), (2), or (3)(i) or, for the subspecialty of oral pathology, Sec. 493.1443(b)(6); or (b) Be a doctor of medicine, doctor of osteopathy, doctor of podiatric medicine licensed to practice medicine, osteopathy, or podiatry in the State in which the laboratory is located.	clinical consultants for moderate complexity testing are essentially same as those for high complexity testing.
Clinical Consultant Responsibilities	When deemed necessary, the laboratory shall assist those ordering tests by suggesting follow-up tests and, when appropriate, expedite the function of obtaining relevant clinical information.	**§493.1457 Standard; Clinical consultant responsibilities**. The clinical consultant provides consultation regarding the appropriateness of the testing ordered and interpretation of test results. The clinical consultant must - (a) Be available to provide consultation to the laboratory's clients; (b) Be available to assist the laboratory's clients in ensuring that appropriate tests are ordered to meet the clinical expectations; (c) Ensure that reports of test results include pertinent information required for specific patient interpretation; and (d) Ensure that consultation is available and communicated to the laboratory's clients on matters related to the quality of the test results reported and their interpretation concerning specific patient conditions.	The clinical consultant responsibility requirements under 493.1457 apply to all laboratories performing high complexity testing.
General Supervisor Qualifications	• Be qualified as a laboratory director or technical supervisor; • Be an M.D. or D.O. or hold a doctorate or master degree in a chemical, physical, biological or clinical laboratory science,	**Condensed from §493.1461 Standard: General supervisor qualifications** - • Be qualified as a laboratory director or technical supervisor; • Be an M.D., D.O., D.P.M.;	The qualification requirements for general supervisors under 493.1443 apply to all laboratories performing high complexity testing.

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	and have two years experience in high complexity genetic testing; • Hold a baccalaureate degree in a chemical, physical, biological or clinical laboratory science; and have three years experience in high complexity genetic testing; or • Be grandfathered.	• Have a doctorate, master, or baccalaureate degree in a chemical, physical, biological or clinical laboratory science, and have one year training or experience in high complexity testing; • Have an associate degree or equivalent in a chemical, physical, biological or clinical laboratory science, and have two years training or experience in high complexity testing; or • Be grandfathered.	
Documentation of Informed Consent	• Informed consent should be required for all laboratory tests. • The individual ordering a test must be able to obtain the appropriate level of informed consent. • The level of informed consent can be dependent upon the purpose of testing, for example, whether a test is performed for predictive or diagnostic purpose; and should be determined based on established professional standards and guidelines. • The laboratory should be available to individuals ordering genetic tests to assist in determining the appropriate level of informed consent. • Test requisition should include a means for attestation from the person ordering the test, such as a checkbox and/or signature, that appropriate consent to testing and to potential use of residual specimens has been obtained.	The CLIA regulations do not require laboratories to document informed consent for the tests they perform. Requirements relating to providing information for patient preparation and test request include: - 493.1103(a): Have written policies and procedures for preparation of patients. - 493.1103(c): Oral explanation of instructions to patients for specimen collection, including patient preparation, may supplement written instructions. - 493.1457(b): The clinical consultant must be available to assist the laboratory's clients in ensuring that appropriate tests are ordered to meet the clinical expectations.	Some states require laboratories to document informed consent for the genetic tests they perform.
Use of Tested Specimens for Quality Control and Quality Assurance Purposes	• The informed consent process should be used to establish prior approval for subsequent use of sample(s) for quality control and quality assurance in genetic testing: - if not approved, discard sample; - if approved, use samples	No requirements are provided under CLIA regarding re-use of tested specimens.	Some states have specific requirements regarding the use of tested specimens for QC, quality assurance, and other purposes.

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	anonymously. • Specimen re-use should be included in the general CLIA requirements and not be restricted to genetic tests.		
Genetic Counseling	• Genetic counseling needs to be available as appropriate, but is not necessary for every test. • The laboratory should facilitate access to genetic counseling when appropriate, but requirement needs to be simple and minimal. • The laboratory should not be required to provide genetic counseling. • The laboratory should be required to recommend genetic counseling to health care providers for family members when indicated.	There is no requirement for genetic counseling under CLIA.	The CLIA regulations require laboratories performing nonwaived testing to have qualified clinical consultants available to provide clinical consultation to their clients.