Genetics & Public Policy CENTER

Regulatory Brief

Regulatory Environment for Genetic Testing

Human genetic testing involves the laboratory analysis of chromosomes, deoxyribonucleic acids (DNA), ribonucleic acids (RNA), and genes and gene products (e.g., proteins). Like other diagnostic laboratory tests, genetic tests are subject to some federal regulatory oversight when they are performed for the purpose of detecting diseases or conditions, or predisposition to such diseases or conditions. Currently, genetic tests are subject to regulation through three statutory and regulatory mechanisms:

- The Clinical Laboratory Improvement Amendments of 1988:[1]
- the Federal Food, Drug, and Cosmetic Act:[2] ; and
- applicable regulations for the protection of human subjects, during the investigational phases of test development.[3]

Four agencies within the Department of Health and Human Services (DHHS) have roles in various aspects of the oversight of genetic test development and use: the Centers for Medicare and Medicaid Services (CMS); the Food and Drug Administration (FDA); the Centers for Disease Control and Prevention (CDC); and the Office for Human Research Protections (OHRP). Other agencies within DHHS support research activities and demonstration projects that generate knowledge and experience concerning genetic testing. In addition, from 1998 to September 2002 the Secretary's Advisory Committee on Genetic Testing served as an advisory body to the Secretary of DHHS concerning the medical, scientific, ethical, legal, and social issues raised by genetic tests. This committee made several recommendations to the Secretary of DHHS, including that all new genetic tests should be subject to FDA oversight.[4] This recommendation has not been acted on by the current DHHS Secretary. In October 2002 the Secretary announced the establishment of a new committee, the Secretary's Advisory Committee on Genetics, Health, and Society, to discuss and make recommendations concerning the use of genetic technologies.[5]

The Clinical Laboratory Improvement Amendments of 1988 (CLIA)

All laboratory tests performed for the purpose of providing information about the health of an individual must be conducted in laboratories registered with the CLIA program, which is administered by CMS. Unless subject to a specific exemption, the laboratories must be certified.[6] Certificates are valid for no more than two years.[7] The type of certificate required will depend on the type of tests being conducted by the laboratory. Laboratories accredited by entities approved by an accreditation body approved by CMS may obtain a certificate based on that accreditation.[8] Certification may require inspection by CMS inspectors or inspectors from accredited organizations.[9] Regulations issued by CMS to implement CLIA set forth the conditions that laboratories must meet in order to be certified.[10] These regulations address issues including personnel qualifications, quality control procedures, and proficiency testing programs. In total CLIA covers approximately 175,000 laboratory entities.[11]

Under CLIA, laboratory tests are categorized according to their level of complexity, and are designated as waived, moderate, or high complexity.[12] The regulatory requirements increase as the level of test complexity increases. CLIA also has specific requirements for certification of laboratories in specialty areas such as cytology and microbiology.[13] Currently, CLIA does not have a separate specialty category for

genetic tests. CLIA does not require evaluation of the clinical validity or clinical utility of a particular test, or address whether and to what extent informed consent or genetic counseling must be provided.

CMS, in partnership with CDC, also develops standards for laboratory certification. In addition, CDC conducts studies and convenes conferences to help determine when changes in regulatory requirements are needed. In May 2000, CDC issued a Notice of Intent regarding genetic testing under CLIA.[14] The notice announced that HHS would be preparing a notice of proposed rulemaking (NPRM) based on recommendations of the Clinical Laboratory Improvement Advisory Committee (CLIAC). The CLIAC recommended that a new genetic testing specialty be created to address "unique testing issues in the pre-analytic, analytic, and post-analytic phases of testing that could affect the accuracy and reliability of test results, and related issues such as informed consent, confidentiality, counseling, and the clinical appropriateness of a genetic test." The notice solicited comments on the recommendations of the CLIAC. CDC is currently working on developing the NPRM.

The Food and Drug Administration

FDA regulates diagnostic test kits used by laboratories to perform genetic testing as in vitro diagnostic devices (IVDs) under the Medical Device Amendments of 1976,[15] which amended the Federal Food, Drug, and Cosmetic Act. Like other medical devices, IVDs are subject to premarket approval or clearance requirements. During premarket review, FDA assesses the device's accuracy, as well as its clinical sensitivity and specificity. FDA has published specific regulations applicable to in vitro diagnostic devices.[16] FDA also performs the test categorization to determine level of complexity for commercially marketed IVDs.[17]

Most genetic testing performed by clinical laboratories does not involve the use of test kits, however. Instead, genetic tests are developed in house by laboratories and marketed as clinical laboratory services. These tests are referred to as in-house tests or "home brew" assays. FDA has in the past asserted regulatory jurisdiction over home brew assays but, with one exception, has elected not to exercise that authority as a matter of enforcement discretion. In 1997 FDA issued a regulation classifying "analyte specific reagents" (ASRs) as medical devices.[18] ASRs are reagents used by clinical laboratories in developing home brew assays, and can be considered the "active ingredients" of such tests.[19] Most ASRs, including those used in genetic tests, are not subject to premarket approval requirements, but must comply with "general controls" such as labeling and good manufacturing practices (GMP) requirements.[20] In addition, laboratories must be certified to perform high complexity testing in order to purchase ASRs.[21]

Protection of Human Subjects

Entities engaging in clinical research to develop genetic tests may be subject to federal regulations for the protection of research subjects. Among other provisions, these regulations require that experimental protocols involving human subjects be reviewed by an Institutional Review Board. Both OHRP and FDA administer regulations governing the protection of human subjects. OHRP regulations apply to all institutions conducting DHHS-funded research,[22] while FDA regulations apply to research conducted for the purpose of developing a product for commercial use.[23] However, FDA regulations do not apply to laboratories developing home brew assays.

The States

State health agencies, particularly state public health laboratories, have an oversight role in genetic testing, including the licensure of personnel and facilities that perform genetic tests. State public health laboratories and state-operated licensure programs that have been "deemed" equivalent to the federal CLIA program are

responsible for quality assurance activities. States may impose requirements more stringent than the requirements of CLIA, but must at a minimum meet the federal requirements. States also administer newborn screening programs and provide other genetic services through maternal and child health programs.[23]

The Private Sector

Some professional organizations also provide oversight in voluntary partnership with CMS and CDC. These groups, including the College of American Pathologists (CAP) and NCCLS, also develop laboratory and clinical guidelines and standards. A number of organizations are involved in helping to assure the quality of laboratory practices and in developing clinical practice guidelines to ensure the appropriate use of genetic tests.

Other organizations, such as the American Academy of Pediatrics, the American College of Obstetrics and Gynecology, the American Society of Human Genetics, and the National Society of Genetic Counselors, are also involved in the development of guidelines and recommendations regarding the appropriate use of genetic tests. Finally, patient advocacy groups, as well as individuals and families with genetic conditions, play an important role in setting standards and in developing guidelines through advocacy and monitoring of health care practices.

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[1] P.L. 100-578, 102 Stat. 2903 (1988), codified at 42 U.S.C. § 263a et seq.
[2] Chapter 675, 52 Stat. 1040 (1938) (as amended), codified at 21 U.S.C. § 301 et seq.
[3] 45 C.F.R. Part 46; 21 C.F.R. Part 50, and 21 C.F.R. Part 56.
[4] Secretary's Advisory Committee on Genetic Testing, Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT (July 2000).
[5] 67 Fed. Reg. 65126 (Oct. 23, 2002).
[6] The statute defines a "clinical laboratory" as a "facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings." 42 U.S.C. § 263a(a).
[7] 42 U.S.C. § 263a(c)(2).
[8] Id. § 263a(e).
[9] See List of Approved Accrediting Organizations Under the Clinical Laboratory Improvement Amendments (CLIA) .
[10] 42 C.F.R. Part 493.
[11] For information about the CLIA program, see the CLIA Program website .
[12] Id. §§ 493.5, 493.17.
[13] Id. §§ 493.901 et seq.
[14] 65 Fed. Reg. 25928 (May 4, 2000).
[15] P.L. 94-295, 90 Stat. 539 (1976).
[16] 21 C.F.R. Part 809.
[17] 64 Fed. Reg. 73561 (Dec. 30, 1999).
[18] 62 Fed. Reg. 622 (Nov. 21, 1997) (codified at 21 C.F.R. §§ 809.10(e), 809.30, 864.4010(a), and 864.4020).
[19] FDA regulations define ASRs as: "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens." 21 C.F.R. § 864.4020(a).

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[20] See 21 C.F.R. § 864.4020(b) (classification of ASRs).
[21] Id. § 809.30.
[22] Human subject protection regulations administered by OHRP are codified at 45 C.F.R. Part 46.
[23] Human subject protection regulations administered by FDA are codified at 21 C.F.R. Parts 50,56.
[24] For information on these programs, see the National Newborn Screening & Genetics Resource Center .

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