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In Search of a Coherent Framework: Options for FDA Oversight of Genetic Tests

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I. INTRODUCTION

Over the past decade, genetic testing has become a mainstream part of medical care. Once used to diagnose rare, single-gene disorders, genetic tests are now harnessed to predict, diagnose or treat a wide range of diseases including complex conditions such as cancer[1] and Alzheimer disease.[2] Today there are more than 1,400 diseases for which genetic testing is available.[3] Thus, for many conditions, obtaining an accurate and reliable genetic test result is critical for good patient care.

However, the regulatory environment for genetic testing has not evolved as quickly as has the technology itself. Despite the efforts of numerous advisory committees since the 1990s to generate a coherent system of oversight,[4] the safety and effectiveness of most genetic tests today are not assured by the government. Although a diverse array of stakeholders believes more oversight is needed,[5] there has been a lack of consensus about what that oversight should be and who should provide it.

The Food and Drug Administration (FDA) plays a limited role in regulating genetic tests, but at times the agency has appeared poised to regulate more extensively. Its actions have spurred criticism by some who assert that FDA lacks the jurisdiction to regulate genetic tests and that the agency's involvement will stifle the availability of new tests, and praise by those who believe that FDA involvement will better protect public health.

In 2007, two bills were introduced in Congress that, if enacted, could lead to greater regulation of genetic tests by FDA.[6] Additionally, FDA has recently signaled

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[1] *See* National Guideline Clearinghouse, Colorectal Cancer Screening and Surveillance: Clinical Guidelines and Rationale-Update Based on New Evidence (verified June 24, 2003), *available at* http://www.guideline.gov/summary/pdf.aspx?doc_id=3686&stat=1&string= (last visited Nov. 6, 2007); U.S. Preventive Services Task Force, *Screening for Breast Cancer: Recommendations and Rationale*, 137 ANNALS OF INTERNAL MED. 344, 344-47 (2002); *see also* American Society of Clinical Oncology, Policy Statement Update: Genetic Testing for Cancer Susceptibility (adopted Mar. 1, 2003), *available at* http://jco.ascopubs.org/cgi/reprint/21/12/2397 (last visited Nov. 6, 2007).

[2] Richard Mayeux et al., *Utility of the Apolipoprotein E Genotype in the Diagnosis of Alzheimer's Disease*, 338 N. ENG. J. MED. 506, 506-11 (1998).

[3] University of Washington, Genetests Homepage, http://www.genetests.org (last visited July 24, 2007).

[4] For more detail on these advisory efforts, *see infra* Part II, section C: "FDA Regulation of Laboratory-Developed Tests."

[5] *See* Genetics and Public Policy Center, *Selected Annotated List of Comments to FDA's September 2006 Draft IVDMIA Guidance Document, available at* http://www.dnapolicy.org/resources/FDAIVDMIAcommentchart.pdf (last visited Oct. 1, 2007).

[6] For information on pending legislation, *see infra* Part V, "Executive and Legislative Efforts to Improve Oversight."

increased interest in regulating a subset of laboratory developed tests, again raising questions about the adequacy and coherence of the current system of oversight for genetic tests.

Part II of this paper presents a general overview of FDA's regulatory approach to in vitro diagnostic (IVD) devices and laboratory developed tests (LDTs), setting out a framework in which to situate the subsequent analysis of genetic testing oversight. Part III discusses FDA's approach to regulating genetic IVDs and genetic LDTs specifically. Part IV identifies concerns that have arisen as a result of the current regulation of genetic tests and Part V describes previous and current attempts that have been made to address them. Part VI presents options for how FDA could regulate genetic tests in the future. The article concludes that the current system of oversight does not provide adequate assurance of the safety and effectiveness of genetic tests, unfairly distinguishes between genetic tests based on how a clinical laboratory performs them and creates an unstable regulatory environment for clinical laboratories and device manufacturers that could deter development of new tests.

II. FDA REGULATION OF MEDICAL DEVICES

Because a subset of genetic tests are currently regulated by FDA as medical devices, and future regulation likely would be derived from FDA's medical device provisions, the following section offers a history of the agency's medical device authority.

A. *Statutory Authorization to Regulate Medical Devices*

The modern era of FDA medical device regulation began with the Medical Device Amendments of 1976 (MDA),[7] which amended the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA).[8] The Amendments for the first time gave FDA express authority to regulate the safety and effectiveness of medical devices and broadened the sanctions that could be imposed on manufacturers distributing devices in violation of the law. Under the MDA, FDA may require device manufacturers to submit premarket safety and effectiveness data to FDA.[9] Subsequent amendments have further broadened FDA's authority over medical devices[10] and have authorized user fee requirements for device manufacturers.[11]

The agency's regulatory requirements vary depending on a medical device's degree of risk. Class I devices pose the lowest level of risk and are subject only to "general controls,"[12] which include good manufacturing practices, record keeping and filing specified reports with the agency. Class II devices pose somewhat greater risk and are subject to additional "special controls," such as performance standards, postmarket surveillance, patient registries and device-specific guidances issued by

[7] The Medical Device Amendments of 1976. Pub. L. No. 94-295, 90 Stat. 539 (codified as amended at The Federal Food, Drug and Cosmetic Act of 1938, 21 U.S.C. § 301 et seq. (1994)).

[8] 21 U.S.C. § 301 *et seq*.

[9] *See id*.

[10] *See* The Safe Medical Devices Act of 1990, Pub. L. No, 101-629, 104 Stat. 4511 (codified as amended at 21 U.S.C. § 301 et seq.); The Medical Device Amendments of 1992, Pub. L. No. 102-300, 106 Stat. 238 (codified as amended at 21 U.S.C. § 301 *et seq*.).

[11] The Medical Device User Fee and Modernization Act of 2002 (MDUFMA), Pub. L. No. 107-250, 116 Stat. 1588 (codified as amended at 21 U.S.C. § 360i); Food and Drug Administration Amendments Act (FDAAA), Pub. L. 110-85 (2007).

[12] 21 U.S.C. § 360c(a)(1)(A).

FDA.[13] Class III products are considered to pose the greatest risk, and companies introducing new types of Class III devices must submit an application for premarket approval (PMA) to the agency.[14]

Devices in commercial distribution prior to 1976 were classified through the use of expert advisory panels, which made recommendations to FDA regarding appropriate classification of different types of devices. Devices entering the market after 1976 were presumptively Class III, requiring mandatory PMAs unless their manufacturers could demonstrate that the device was "substantially equivalent" to a device marketed prior to 1976 (termed "predicate" devices).[15] The process for demonstrating substantial equivalence requires submission of what is known as a "510(k) notification" to FDA in order to receive agency "clearance" of the application.[16] The 510(k) process is generally simpler and faster than a PMA application because the manufacturer has only to demonstrate equivalence to a predicate device. Forcing manufacturers to rely on a predicate device, however, limited their ability to use the 510(k) submission process. In 1997, Congress amended the law to permit devices lacking pre-amendment predicates to submit requests for "de novo" 510(k) classification."[17] The de novo 510(k) process is available only for low- or moderate-risk devices lacking a predicate; submission of a PMA is still required for higher risk devices.[18]

B. *FDA Oversight for In Vitro Diagnostic Devices*

The law defines medical devices to include any "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article, including any component, part or accessory" that is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease."[19] The definition clearly encompasses equipment, reagents and other components manufactured for use by clinical laboratories to analyze human specimens for health-related reasons. Through its implementing regulations, FDA made certain that any in vitro diagnostic could be regulated as a device. These regulations define "in vitro diagnostic" (IVD) products as:

> Those reagents, instruments and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease or its sequelae. Such products are intended for use in the collection, preparation and

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[13] Id. § 360c(a)(1)(B).

[14] Id. § 360c(a)(1)(C).

[15] Benjamin A. Goldberger, *The Evolution of Substantial Equivalence in FDA's Premarket Review of Medical Devices*, 56 FOOD & DRUG L.J. 317-8 (2001).

[16] *See* 21 U.S.C. § 360(j)-(k), 360c(f); Content and Format of a 510(k) Summary, 21 C.F.R. § 807.92 (1996); *see also* FDA, The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance, http://www.fda.gov/cdrh/ode/parad510.html (last visited Aug. 1, 2007).

[17] The FDA Modernization Act of 1997 (FDAMA), 105 Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended at 21 U.S.C. § 513(f)(2)).

[18] *See* Association of Medical Diagnostics Manufacturers, De Novo Classification for In Vitro Diagnostic (IVD) Devices: Questions & Answers, http://www.amdm.org/AMDM/051502-DeNovo.html (last visited Aug. 1, 2007). The de novo process cannot be used if FDA has already approved a PMA for a similar device. However, FDA has another mechanism for requesting reclassification of class III devices. *Id.*

[19] The Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 301(h)(2) (1994).

> examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act.[20]

Like other medical devices, IVD devices are classified based on their level of risk. In determining the risk of devices, FDA considers their intended use, as evidenced by the claims made in the product's labeling.[21]

1. *Types of IVD Products*

FDA regulates several different types of IVD products: general-purpose reagents; analyte specific reagents (ASRs); and test systems, also called test kits.

a. *General Purpose Reagents*

A general purpose reagent is "a chemical reagent that has general laboratory application, is used to collect, prepare and examine specimens from the human body for diagnostic purposes and is not labeled or otherwise intended for a specific diagnostic application."[22] General purpose reagents include cytological preservatives, decalcifying reagents, fixative and adhesives, tissue processing reagents, isotonic solutions and pH buffers.[23] General purpose reagents are Class I devices and are exempt from premarket notification 510(k) requirements, and their manufacturers need only conform with general controls such as maintaining certain records and, in some cases, following good manufacturing practices.[24]

b. *Analyte Specific Reagents*

Analyte specific reagents are "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."[25]

The ASR regulations, issued in 1997, were designed to accomplish several policy objectives, including ensuring the quality of materials used as components of in-house laboratory tests and providing appropriate labeling so that health-care users would understand how these tests were being validated.[26] Most ASRs are categorized as class I and are exempt from premarket notification requirements. Class I ASRs are subject to general controls only.

An ASR is considered Class II "when the analyte is used in blood banking tests that have been classified as class II devices," and are subject to special controls and guidance documents developed by FDA.[27] An ASR is considered Class III

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[20] In Vitro Diagnostic Products For Human Use, 21 C.F.R. § 809.3(a) (1996).

[21] *Id.* § 860.3(c)(2). A medical device is considered class III if it is "[life-]supporting or [life-]sustaining…or for a use which is of substantial importance in preventing impairment of human health, or [if the device] presents a potential unreasonable risk of illness or injury."

[22] *Id.* § 864.4010(a).

[23] *Id.*

[24] *Id.* § 864.4010(b).

[25] *Id.* § 864.4020.

[26] *See* Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 62 Fed. Reg. 62,243 (Nov. 21, 1997) (codified at 21 C.F.R. pts. 809 & 864).

[27] 21 C.F.R. 864.4020(b)(2).

if it is "intended as a component in a test intended for use in the diagnosis of a contagious condition that is highly likely to result in a fatal outcome and prompt, accurate diagnosis offers the opportunity to mitigate the public health impact of the condition."[28] Examples given in FDA regulations are ASRs that test for HIV/AIDS and tuberculosis.[29] An ASR is also regulated as a Class III device if "the analyte is intended as a component in a test intended for use in donor screening for conditions for which FDA has recommended or required testing in order to safeguard the blood supply or establish the safe use of blood and blood products."[30] Examples given are tests for hepatitis and tests for identifying blood groups.[31]

Manufacturers of Class II and Class III ASRs must demonstrate the analytical and performance characteristics of the ASR in the context of a specific cleared or approved test kit. Thus, as a practical matter, if a cleared or approved test kit does not exist, FDA will not approve a Class II or III ASR. In issuing the ASR regulations, FDA expected that "most Class II and III ASR's will not be marketed as independent components, separate from the test."[32] Class II or III ASRs must include in product labeling the statement that "[e]xcept as a component of the approved/cleared test (Name of approved/cleared test), analytical and performance characteristics of this ASR are not established."[33]

Regardless of classification, ASRs are regulated as "restricted devices," meaning FDA regulations place specific restrictions on their sale, distribution and use.[34] ASRs may be sold only to 1) IVD manufacturers, 2) clinical laboratories qualified to perform "high complexity" testing under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), or 3) non-clinical laboratories.[35] Advertising and promotional materials must contain specified information, such as information about the identity and purity of the ASR.[36] ASRs generally may not carry any statement regarding their analytical or clinical performance. Laboratories that develop tests using Class I ASRs must include in the test report the disclaimer that the test "was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by FDA."[37] Tests developed using ASRs may be ordered only by physicians or others authorized under state law to order laboratory tests.[38] There is no record of FDA action against a laboratory for providing ASR-based tests directly to consumers.

A decade after it issued the ASR rule, FDA began to have concerns about lack of manufacturer compliance with the ASR rule; indeed the rule had been dubbed by some as the "least understood and most abused" of FDA regulations.[39] FDA therefore issued draft guidance in September 2006 "in order to eliminate confu-

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[28] *Id.* § 864.4020(b)(3)(i).

[29] *Id.*

[30] *Id.* § 864.4020(b)(3)(ii).

[31] *Id.*

[32] 62 Fed. Reg. at 62,245.

[33] Labeling for In Vitro Diagnostic Products, 21 C.F.R. § 809.10(e)(1)(xi) (1997).

[34] *See* Restrictions on the Sale, Distribution and Use of Analyte Specific Reagents, 21 C.F.R. § 809.30 (1997).

[35] *Id.*

[36] *Id.*

[37] *Id.*

[38] *Id.* For a comparison of state laws on direct-to-consumer genetic testing, *see* Genetics and Public Policy Center, Survey of Direct-to-Consumer Testing Statutes and Regulations (June 2007), *available at* http://www.dnapolicy.org/resources/DTCStateLawChart.pdf (last visited Oct. 9, 2007).

[39] *See* Jeffrey K. Shapiro & Randy J. Prebula, *FDA's Regulation of Analyte-Specific Reagents*, MEDICAL DEVICE & DIAGNOSTIC INDUS., Feb. 2003, *available at* http://www.devicelink.com/mddi/archive/03/02/018.html (last visited Nov. 6, 2007).

sion regarding particular marketing practices among ASR manufacturers."[40] The agency sought "to advise ASR manufacturers that it views certain practices as being inconsistent with the marketing of an ASR."[41] Specifically, some manufacturers have believed that when they combine a Class I ASR…with other products, or with instructions for use in a specific test, the product remains exempt because of the presence of an ASR."[42] To the contrary, the agency explained that "when an ASR is marketed in certain ways," such as when multiple ASRs are "bundled together in a pre-configured or optimized manner so that they are intended to identify and quantify more than one chemical substance or ligand,"[43] then it is no longer an ASR but is a test system subject to additional requirements. Similarly, the inclusion of instructions for use with an ASR would cause it to be regulated as a test system.

FDA received more than 40 comments on the draft ASR guidance. Some stakeholders view the document as expanding, rather than clarifying, the scope of the ASR rule and contend that it will have a negative impact on laboratory practice by reducing the availability of ASRs.[44] FDA issued a final guidance in September 2007.[45]

c. *Test Systems*

IVD "test systems," also sometimes termed "test kits," are products that are manufactured for use by a laboratory to perform a specific laboratory test. Although the terms test system and test kit are not defined in FDA regulations, their hallmark is the inclusion of a specific clinical indication for use (i.e. product claims) and directions for use in product labeling. IVD test kits may include multiple reagents or may consist of a microarray or other testing platform.

FDA regulations establish broad categories for IVD test kits, such as clinical chemistry, clinical toxicology and immunology. Within each broad category are regulations that define particular types of devices and specify their classification levels. For example, a "breath-alcohol test system" is a "device intended to measure alcohol in the human breath. Measurements obtained by this device are used in the diagnosis of alcohol intoxication."[46] This device falls under the broad framework of "clinical chemistry and clinical toxicology test systems" and is designated Class I.[47] The broad category into which a genetic test will fall similarly depends on the specific characteristics of the test.

Overall, FDA regulations define several hundred different types of test systems. FDA can define new categories if it receives an application for a test system that

[40] Draft Guidance for Industry and Food and Drug Administration Staff; Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions; Availability, 71 Fed. Reg. 52,799 (Sept. 7, 2006).

[41] *Id.*

[42] *Id.*

[43] Food & Drug Admin., Draft Guidance for Industry and FDA Staff - Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions (Sept. 7, 2006), http://www.fda.gov/cdrh/oivd/guidance/1590.html (last visited Aug. 1, 2007).

[44] *See* Jeffrey N. Gibbs, *ASRs and IVDMIAs: FDA's new draft guidances*, IVD TECH., Mar. 2007, *available at* http://www.devicelink.com/ivdt/archive/07/03/012.html (last visited Nov. 6, 2007). In addition, the Washington Legal Foundation (WLF) challenged the draft guidance as a violation of the Administrative Procedure Act and the First Amendment. Washington Legal Foundation, WLF Criticizes FDA Efforts to Regulate Clinical Laboratories, ASRs, Mar. 9, 2007, *available at* http://www.wlf.org/upload/030907RS.pdf (last visited Nov. 6, 2007).

[45] Food and Drug Admin., Guidance for Industry and FDA Staff - Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions (Sept. 14, 2007), *available at* http://www.fda.gov/cdrh/oivd/guidance/1590.pdf (last visited Oct. 3, 2007).

[46] *See* Breath-Alcohol Test System, 21 C.F.R. § 862.3050 (1996).

[47] *Id.*

does not fit within previously defined categories. For example, as discussed below, FDA recently created a new regulation for gene-expression-profiling test systems for breast cancer prognosis in response to a de novo 510(k) clearance application.[48]

2. *General Requirements for IVD Products*

Like all medical-device manufacturers, manufacturers of IVD products are subject to FDA establishment registration and device listing regulations.[49] Under these regulations, manufacturers must provide the agency with information including the manufacturer's name and address, the name of an official contact person and a list of devices being manufactured.[50] Registration must be renewed annually, and device listing information must be updated within six months of any change to the list.

Additionally, like other device makers, IVD manufacturers must comply with the general statutory prohibitions against adulteration and misbranding of products.[51] Entities violating these prohibitions are subject to civil and criminal penalties.[52] Finally, IVD manufacturers are subject to FDA's medical device reporting (MDR) requirements, which mandate that manufacturers and others report to FDA information regarding device-associated deaths, serious injuries or malfunctions that could lead to death or serious injury if they were to recur.[53]

3. *Device Database*

FDA maintains a publicly-searchable database of IVDs that have been cleared or approved by the agency.[54] The database includes a description of the device, information about its regulatory classification, the predicate device upon which approval was based (if applicable) and other relevant information.[55] For test kits, performance characteristics of the test are also available, including data supporting the test's analytic validity, and, where required by FDA, its clinical validity.[56] No similar database exists for laboratory developed tests, thus much less information about these tests is available to the public.

C. *FDA Regulation of Laboratory Developed Tests: A Tale of Diminishing Deference*

The controversy concerning FDA regulation of genetic tests centers around the agency's authority to regulate the broader category of laboratory developed tests. No court has squarely addressed this issue.[57]

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[48] Medical Devices: Immunology and Microbiology Devices; Classification of Gene Expression Profiling Test System for Breast Cancer Prognosis, 72 Fed. Reg. 26,290 (May 9, 2007).

[49] Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices, 21 C.F.R. pt. 807 (1996).

[50] *Id.*

[51] The Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 331(b), 351 (1994).

[52] 21 U.S.C. § 333.

[53] 21 U.S.C. § 360i(a)

[54] Food and Drug Admin. Ctr. for Devices and Radiological Health, In Vitro Diagnostics database, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfivd/index.cfm (last visited Aug. 2, 2007).

[55] *Id.*

[56] *Id.*

[57] *But see* Clinical Reference Laboratory v. Sullivan. 791 F. Supp. 1499, 1509 (D. Kan. 1992), *aff'd in part and rev'd in part by* United States v. Undetermined No. of Unlabeled Cases, 21 F.3d 1026 (10th Cir. 1994), the FDA sought to prohibit a laboratory from offering HIV testing for insurance purposes using protocols and reagents that had not been submitted for FDA review. FDA asserted authority to

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LDTs differ from IVD test kits in that the laboratory assembles the test itself based on an in-house protocol, uses that test to analyze a patient specimen and issues a laboratory report with the test results. The laboratory does not, therefore, commercially distribute a test kit but does commercially distribute services derived from the development and performance of a test.

In assembling the test, the laboratory may use various general-purpose reagents, ASRs, or reagents the laboratory develops itself. If an ASR is used, the laboratory must comply with the restrictions specified for ASRs. If only general-purpose reagents are used, the laboratory is not subject to any FDA requirements.

Historically, FDA has not regulated LDTs directly, but has instead exercised enforcement discretion.[58] Although it has developed requirements for some reagents and equipment sold to laboratories for use in developing tests, laboratories have not been required to demonstrate the safety and effectiveness of the tests or reagents they develop in-house. Clinical laboratories, including those that use LDTs, are regulated under the Clinical Laboratory Improvement Amendments of 1988,[59] but such oversight focuses on the quality of the laboratory's overall operations and does not evaluate directly the safety and effectiveness of the individual tests performed. Moreover, CLIA has not been fully implemented with respect to genetic testing laboratories,[60] despite the fact that CLIA was enacted to strengthen federal oversight of clinical laboratories and to ensure the reliability of test results.[61]

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regulate as class III devices the specimen collection containers that were sent to and from the laboratory and traveled in interstate commerce. The laboratory countered that the collection containers were not devices, because the intended purpose of testing was not diagnosis but rather insurance risk assessment, and that FDA's real target was the testing procedures used by the laboratory, over which the agency lacked jurisdiction. The court held that specimen collection containers were medical devices within FDA's jurisdiction to regulate, but determined that the question of FDA's authority over the laboratory's protocols was not ripe for adjudication. The court concluded that CLIA "does not preempt FDA's authority to regulate" clinical laboratories and that "Congress intended to leave some regulatory overlap" between CLIA and the FDCA.

[58] *See, e.g.* Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 61 Fed. Reg. 10,484 (Mar. 14, 1996).

[59] The Clinical Laboratory Improvement Amendments of 1988 (CLIA), 100 Pub. L. No. 578, 102 Stat. 2903 (codified as amended at Certification of Laboratories, 42 U.S.C. § 263a (1994)).

[60] When CMS issued regulations implementing CLIA in 1992, it created "specialty areas" for laboratories performing high-complexity tests, which specified personnel, quality assurance and proficiency testing requirements for tests such as toxicology and immunology. *See* Medicare, Medicaid and CLIA Programs; Regulations Implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 57 Fed. Reg. 7,002 (codified at various parts in 42 C.F.R.) (Feb. 28, 1992). Genetic testing, which was in its infancy, was not included in these specialty areas. In response to recommendations from the SACGT, *see* Sec'y's Advisory Comm. on Genetic Testing, *Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT* 1, 1 (July 2000), *available at* http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf (last visited Oct. 26, 2007), CMS indicated that it would issue regulations for a genetic testing specialty, *see* Notice of Intent; Genetic Testing Under the Clinical Laboratory Improvement Amendments, 65 Fed. Reg. 25,928 (May 4, 2000). In April 2006 CMS put the issuance of a proposed regulation for a genetic testing specialty on the agency's "regulatory agenda." Dept. of Health & Human Serv. Regulatory Agenda, Pt. VIII, 71 Fed. Reg. 22,537 (Apr. 24, 2006). However, CMS inexplicably changed its mind and announced in September 2006 that it would not be issuing a specialty. Clinical Laboratory Improvement Advisory Comm., Meeting Summary (Sept. 20-21, 2006), http://www.cdc.gov/cliac/cliac0906.aspx (last visited Aug. 14, 2007).

[61] Numerous stakeholders have requested that the Centers for Medicare and Medicaid Services (CMS) issue regulations addressing genetic testing laboratories, and three organizations filed a Citizen Petition in 2006, but CMS has denied these requests. Letter from Sharon Terry et al. to Mark McClellan, June 6, 2006, *available at* http://www.geneticalliance.org/ws_display.asp?filter=policy.clia.letter (last visited Oct. 26, 2007); Letter from Reproductive Health Technologies Project et al.to Mark McClellan, July 13, 2006;Kathy Hudson, Sharon Terry & Peter Lurie, Petition for Rulemaking (Sept. 26, 2006), *available at* http://www.dnapolicy.org/resources/Petition_For_Rulemaking_September_2006.pdf (last visited Oct. 26, 2007); Letter from Dennis Smith to Kathy Hudson, Aug. 15, 2006, *available at* www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=83 (last visited Oct 26, 2007).

FDA has expressed concern at various times about the quality of LDTs. In explaining the motivation behind the ASR rule, FDA noted that

> [t]here has been a growing trend in recent years for more sophisticated clinical laboratories to develop and prepare their own tests that are intended to diagnose various medical conditions, using ingredients that they frequently purchase from biological or chemical suppliers.… These in-house developed tests…include a wide variety used in the diagnosis of infectious diseases, cancer, genetic and various other conditions. FDA currently regulates the safety and effectiveness of diagnostic tests that are traditionally manufactured and commercially marketed as finished products. However, in-house developed tests have not been actively regulated by the agency and the ingredients used in them generally are not produced under FDA assured manufacturing quality control. Other general controls also have not been applied routinely to these products.… The laboratories producing tests from ASR's and offering the tests as laboratory services are currently regulated by [CMS under CLIA].… However, these…regulations do not include the same product controls provided by FDA. As a result, neither patients nor practitioners have assurance that all ingredients in the laboratory developed tests are of high quality and capable of producing consistent results.… FDA is concerned that the present situation with respect to in-house developed tests, in which these ingredients are essentially unregulated and therefore of unpredictable quality, may create a risk to the public health.[62]

At the same time, FDA recognized "the clinical importance of in-house developed testing as a mechanism for providing novel, highly specialized tests in a relatively short time, sometimes for diseases that affect a relatively small proportion of the population."[63] FDA thus limited its focus to ASRs, while stating that "at a future date, the agency may reevaluate whether additional controls over the in-house tests developed by such laboratories may be needed to provide an appropriate level of consumer protection."[64] Thus, FDA was asserting jurisdiction in theory—if not exercising it in practice—over LDTs.

In issuing its final ASR regulations, FDA reiterated the position that it possessed jurisdiction that it was choosing not to exercise with respect to LDTs. In response to a comment critical of this stance,[65] FDA stated that although "clinical laboratories that develop such tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act," nevertheless "the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances and…significant regulatory changes in this area could have negative effects on the public health."[66] Thus, FDA concluded that the decision to regulate ASRs and not LDTs was a "reasonable regulatory step at this time."[67]

In September 2006, after a decade of near-complete enforcement discretion, FDA inserted its presence squarely into the laboratory with the release of a draft guidance

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[62] 61 Fed. Reg. 10,484.
[63] *Id.* at 10,484-10,485.
[64] *Id.* at 10,484.
[65] 62 Fed. Reg. 62,243, 62,249.
[66] *Id.*
[67] *Id.*

addressing in vitro diagnostic multivariate index assays (IVDMIAs).[68] The document, which took the clinical laboratory community by surprise, announced FDA's intent to regulate a subset of LDTs as medical devices because FDA perceived them to raise significant new safety and effectiveness concerns. As described in Part IIID below, IVDMIAs are characterized by the use of proprietary "algorithms" that generate patient- specific results based on multiple pieces of data, including the results of laboratory assays.[69] In explaining the decision to impose a greater degree of oversight on IVDMIAs than on ASRs, FDA stated that "manufacture of an IVDMIA involves steps that are not synonymous with the use of ASRs and that are not within the ordinary 'expertise and ability' of laboratories that FDA referred to when it issued the ASR rule. Therefore, IVDMIAs do not fall within the scope of laboratory developed tests over which FDA has generally exercised enforcement discretion."[70]

Shortly after the release of the draft guidance, the Washington Legal Foundation (WLF), a free-enterprise advocacy group, filed a Citizen Petition with FDA contesting the agency's jurisdiction.[71] The comment period for the draft guidance ended March 5, 2007, and FDA received nearly 70 comments to the docket.[72] FDA

[68] Food & Drug Admin. Ctr. for Devices and Radiological Health, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays* (Sept. 7, 2006), first version, *available at* 26 Biotechnology Law Report 151, No. 2 (Apr. 2007), http://www.liebertonline.com/doi/abs/10.1089/blr.2006.9979?cookieSet=1&journalCode=blr (last visited Oct. 26, 2007); *see also* Notice of FDA Draft Guidance, 71 Fed. Reg. 52,800 (Sept. 7, 2006).

[69] *See infra* Part III, section D.

[70] Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays, 71 Fed. Reg. 52,801 (Sept. 7, 2006).

[71] The petition called on the agency to cease its efforts to enforce medical device regulations against clinical laboratories providing in-house tests to diagnose and treat illnesses, asserting that FDA lacked the statutory authority to do so. WLF's challenge to FDA jurisdiction is derived from the language of the FDCA, which limits FDA's jurisdiction to "articles" that are "distributed in interstate commerce." *See* the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 et seq. (1994). Because LDTs are developed in-house and used to generate a test result, WLF and others who challenge FDA's jurisdiction argue that they do not meet the statutory requirement for regulation. WLF further argued that CMS, and not FDA, bears the authority to regulate clinical laboratories under CLIA. Washington Legal Foundation, Citizen Petition Regarding FDA Regulation of Laboratory Developed Tests 1-19 (Sept. 28, 2006), *available at* http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/06p0402/06p-0402-cp00001-01-vol1.pdf (last visited Oct. 26, 2007).

[72] Perhaps recognizing belatedly the controversy its draft guidance had generated, in February 2007 FDA held a public meeting to allow stakeholders to testify concerning the draft guidance, which was attended by more than 350 representatives of device manufacturers, clinical laboratories, academia, physician groups, and consumer and patient advocacy organizations. Food & Drug Admin. Office of In Vitro Diagnostic Evaluation and Safety, Public Meeting on In Vitro Diagnostic Multivariate Index Assays (IVDMIA) transcript (Feb. 8, 2007), *available at* http://www.fda.gov/cdrh/oivd/meetings/020807transcript.html (last visited Oct. 26, 2007).

About 30 representatives from the medical device industry, clinical laboratories, academia and consumer and patient organizations testified before FDA and expressed a wide range of viewpoints. Strong support for enhanced oversight of genetic tests by FDA was voiced by some patient advocacy organizations as well as by several manufacturers of IVD devices. *See, e.g.*, Testimony of Robert Erwin, President, Marti Nelson Cancer Foundation, Public Meeting on In Vitro Diagnostic Multivariate Index Assays (IVDMIA), *available at* http://www.fda.gov/cdrh/oivd/meetings/020807/Erwin.html (last visited Oct. 26, 2007). At the same time, supporters raised many practical questions about how the IVDMIA draft guidance would be implemented, what specific requirements IVDMIA manufacturers would be subject to, and how FDA requirements would interact with CLIA requirements. Some urged that FDA exercise caution to ensure that its oversight would not deter investment in new tests and thereby reduce the availability of potentially lifesaving tests. WLF and a few others challenged the agency's jurisdiction. *See* Testimony of Richard Samp, Chief Counsel, Washington Legal Foundation, Public Meeting on In Vitro Diagnostic Multivariate Index Assays (IVDMIA), *available at* http://www.fda.gov/cdrh/oivd/meetings/020807/Samp.html (last visited Oct. 26, 2007). In its revised draft guidance, FDA responded to some, but not all, the concerns raised by stakeholders. *See* Genetics and Public Policy Center eNews, *FDA revises draft guidance for IVDMIAs* (Aug. 2007), *available at* http://www.dnapolicy.org/news.enews.article.nocategory.php?action=detail&newsletter_id=25&article_id=107 (last visited Oct. 1, 2007). For an analysis of stakeholder comments in response to the first draft guidance, *see* Genetics and Public Policy Center, *Selected Annotated List of Comments to FDA's September 2006 Draft IVDMIA Guidance Document, available at* www.dnapolicy.org/resources/FDA/VDM/ACommentchart.pdf (last visited Oct. 26, 2007).

released a revised version of the IVDMIA draft guidance on July 26, 2007, and the comment period for the new version closed on October 17, 2007.[73] The agency has not indicated its time frame for releasing a final guidance.

As discussed below, the issuance of this document was spurred by the emergence of specific genetic tests, and its implementation is likely to have the greatest impact on a small subset of genetic LDTs.

III. APPLICATION OF FDA'S IVD REQUIREMENTS TO GENETIC TESTS

Perhaps because genetic tests were largely unavailable when the Medical Device Amendments of 1976 were enacted and implemented, there is no specific provision for genetic testing oversight in the FDCA or in FDA's regulations. Yet there is no dispute that the genetic tests are subject to, or exempt from, FDA regulation in the same manner as non-genetic laboratory tests. Depending on how they are marketed, genetic tests currently may 1) be regulated by FDA as IVD devices (i.e., test kits), 2) use FDA-regulated ASRs as a component but be otherwise unregulated, 3) fall within the new draft IVDMIA definition and potentially be subject to future regulation as a test system, or 4) be a non-ASR-based LDTs and not currently subject to any FDA regulation.

A. *Defining Genetic Tests*

The term "genetic test" has never been defined by FDA or by CMS under CLIA. It has, however, been defined in various ways in state laws,[74] by federal advisory committees recommending enhancements to genetic testing oversight, [75] as well as in pending

[73] Food and Drug Admin. Ctr. for Devices and Radiological Health, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays*, second version, 3-15 (July 2007), *available at* http://www.fda.gov/cdrh/oivd/guidance/1610.pdf. (last visited Oct. 26, 2007) FDA initially provided only 30 days to submit comments. However, in response to concerns raised by some stakeholders, FDA reopened the comment period. 72 Fed. Reg. 52885 (Sept. 17, 2007) (reopening docket and extending comment period to Oct. 17, 2007).

[74] *See, e.g.*, ARIZ. REV. STAT. ANN. § 20-448.02 (2007) (defining genetic testing as the "analysis of an individual's DNA, gene products or chromosomes that indicates a propensity for or susceptibility to illness, disease, impairment or other disorders, whether physical or mental, or that demonstrates genetic or chromosomal damage due to environmental factors, or carrier status for disease or disorder"); MASS. GEN. LAWS § 111.70G(5) (2007) (defining a genetic test as "a test of human DNA, RNA, mitochondrial DNA, chromosomes or proteins for the purpose of identifying genes, inherited or acquired genetic abnormalities or the presence or absence of inherited or acquired characteristics in genetic material"); *see generally* National Conference of State Legislatures, State Genetic Privacy Laws, *available at* http://www.ncsl.org/programs/health/genetics/prt.htm (last visited Aug. 13, 2007).

[75] Neil A. Holtzman, Michael S. Watson, eds., PROMOTING SAFE AND EFFECTIVE GENETIC TESTING IN THE UNITED STATES: FINAL REPORT OF THE TASK FORCE ON GENETIC TESTING 4-8 (1997), *available at* http://www.genome.gov/10002405 (last visited Oct. 26, 2007) (defining genetic testing as "[t]he analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers and establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn and carrier screening, as well as testing in high-risk families, are included. Tests for metabolites are covered only when they are undertaken with high probability that an excess or deficiency of the metabolite indicates the presence of heritable mutations in single genes"); Sec'y's Advisory Comm. on Genetic Testing, *Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT* 1, 1 (July 2000), *available at* http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf (last visited Oct. 26, 2007) ("A genetic test is an analysis performed on human DNA, RNA, genes and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes or karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations or phenotypes"); Notice of Intent; Genetic Testing Under the Clinical Laboratory Improvement Amendments, 65 Fed. Reg. 25,928 (May 4, 2000) ("Human genetic testing involves the analysis of chromosomes, dioxyribonucleic acids (DNA), ribonucleic acids (RNA) and genes and gene products (e.g. proteins and enzymes) to detect heritable or acquired disease-related disorders or conditions.").

federal legislation to prohibit genetic discrimination.[76] Some of these definitions include analysis of DNA, RNA, proteins or metabolites to detect heritable conditions, for the purpose of diagnosis, prevention or prediction of disease. Some include tests to detect acquired DNA mutations as well. Still others, including the pending federal legislation, do not specify whether the mutation is heritable or acquired.[77] For the purposes of this article, the term "genetic test" refers to a test on human DNA, RNA, proteins or metabolites to diagnose or predict a heritable human disease; to make treatment decisions, such as drug prescribing or dosing, based on individual's genetic makeup; or to predict disease recurrence based on the examination of combinations of multiple genes or gene expression products (e.g., RNA or proteins).

Some critics of enhanced oversight of genetic tests assert that genetic tests are not categorically different from any other laboratory tests and that establishing genetic-testing specific regulations would therefore be unwarranted "genetic exceptionalism."[78] They argue that genetic tests should be regulated in the same manner as other laboratory tests, which currently are unregulated if they are LDTs.

In contrast, this paper takes the position that many LDTs being offered by clinical laboratories today are in fact genetic tests; indeed, genetic tests likely comprise the fastest-growing category of LDTs.[79] Furthermore, many of these genetic tests, while of potentially significant clinical benefit, also have the potential to cause great harm if offered without adequate assurance of safety and effectiveness.[80] In addition, the information provided by at least some of these tests may be the sole basis for making a clinical decision with significant consequences. Yet the vast majority of these genetic LDTs are subject to no oversight to ensure that they are safe and effective.[81]

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[76] H.R. 493, 110th Cong. § 201(7)(A) (2007) (noting that "[t]he term 'genetic test' means the analysis of human DNA, RNA, chromosomes, proteins or metabolites, that detects genotypes, mutations or chromosomal changes").

[77] *Id. See also* VA. CODE ANN. § 38.2-508.4(A) (2007) ("'Genetic test' means a test for determining the presence or absence of genetic characteristics in an individual in order to diagnose a genetic characteristic.").

[78] Genetic exceptionalism is the concept that genetic information is qualitatively different from other forms of medical information and therefore requires special legal protections to prevent its misuse by employers, insurers and others. National Conference of State Legislatures, *supra* note 74, at http://www.ncsl.org/programs/health/genetics/prt.htm. Supporters of genetic exceptionalism argue that because the social meaning of treating people differently on the basis of their genetic make up is different from the social meaning of discrimination on the basis of health or illness, special legislation is warranted to prohibit genetic discrimination. *See, e.g.*, Deborah Hellman, *What Makes Genetic Discrimination Exceptional?* 19 AM. J. L. & MED. 77 (2003). Critics of genetic exceptionalism argue that genetic information is not so qualitatively different from other medical information that it warrants special legislation and that law makers should take a more comprehensive approach to health status discrimination. *See, e.g.*, Sonia M. Suter, *The Allure and Peril of Genetics Exceptionalism: Do We Need Special Genetics Legislation?* 79 WASH. U. L. Q. 669, 671 (2001). This paper does not take a position on the broader genetic exceptionalism debate, but also does not accept the premise that increased oversight for genetic tests would constitute genetic exceptionalism.

[79] *See* FROST & SULLIVAN RESEARCH SERV., U.S. GENETIC DIAGNOSTICS MARKETS F463–552 (Sept. 28, 2005); *See also* J. Alsever et al., *The Patient Knows Best,* Business 2.0, Nov. 9, 2006, *available at* http://money.cnn.com/magazines/business2/business2_archive/2006/10/01/8387104/index.htm (last visited Oct. 1, 2007) (stating that according to analysts the genetic-testing market will be worth $12.5 billion annually by 2009).

[80] Although there may be instances now or in the future in which concern arises over the safety and effectiveness of non-genetic LDTs, nothing in this paper would preclude consideration of additional oversight mechanisms for such tests as well. Indeed, while the focus here is on genetic tests, the principles presented in Part VI could be applied equally to non-genetic LDTs.

[81] As discussed *infra*, the Clinical Laboratory Improvement Amendments, 42 U.S.C. 263a, govern clinical laboratory quality through certification and associated requirements. 42 C.F.R. Part 493. CLIA does not require premarket review of the analytic validity of tests, and does not require proficiency testing for genetic tests, which is a means to gauge a laboratory's analytic validity. Additionally, at least as it has been interpreted by officials within the Centers for Medicare and Medicaid Services, CLIA does not address the clinical validity of tests. *See, e.g.,* Sec'y's Advisory Comm. on Genetics, Health and Society, Testimony of Judy Yost, Nov. 13, 2006, *available at* http://www4.od.nih.gov/oba/SACGHS/meetings/Nov2006/transcripts/Genetic_Tech-Hamilton-Yost.pdf (last visited Oct. 3, 2007).

B. *FDA Regulation of Genetic Test Systems/Kits*

Since 2003, FDA has cleared or approved eight molecular genetic test kits.[82] The first to be sanctioned—for Factor V Leiden, a genetic mutation causing thrombophilia (increased risk of blood clotting)—was cleared by FDA on December 17, 2003.[83] FDA issued regulations describing the test kit and similar devices as Factor V Leiden DNA Mutation Detection Systems, classifying them as class II and subject to a special controls guidance document.[84] Immediately following this decision, on December 18, 2003, FDA cleared a 510(k) notification by Roche for a test kit for Factor II, a related thrombophilia disorder.[85] FDA classified the kit under the same regulation as the Factor V kit, subject to the same special controls.[86] In December of the following year, FDA granted a petition for reclassification filed by Roche for its Roche Amplichip CYP450 Test, a microarray-based genotyping test for detection of the CYP2D6 genotype, making the Roche test and all substantially equivalent devices class II devices under the name "Drug Metabolizing Enzyme Genotyping System."[87] It was followed shortly thereafter by the approval of a 510(k) application submitted by Roche for Amplichip CYP450 Test in March 2005, for detection of the CYP2C19 genotype.[88] FDA classified the CYP2C19 portion of array under the same regulation as the CYP2D6 portion, subject to the same special controls.[89] In May 2005, FDA approved a petition for classification submitted for the Tag-IT Cystic Fibrosis Kit, which directly analyzes human DNA to identify twenty-three mutations that cause cystic fibrosis (CF).[90] In January 2006, FDA cleared a similar CF test kit manufactured by a different company that used the Tag-It device as a predicate.[91]

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[82] This count does not include infectious disease tests that detect viral DNA.

[83] *See* Medical Devices; Hematology and Pathology Devices; Classification of the Factor V Leiden DNA Mutation Detection Systems Devices, 69 Fed. Reg. 12,271 (Mar. 16, 2004) (codified at 21 C.F.R. § 864.7280). The device was intended for use "for the detection and genotyping of a single point mutation (G to A at position 1691) of the human Factor V gene" for use as an "aid to diagnosis in the evaluation of patients with suspected thrombophilia."

[84] Id.; *See also* Food & Drug Admin., Ctr. for Devices and Radiological Health, Guidance for Industry and Staff: Class II Special Controls Guidance Document: Factor v Leiden DNA Mutation Detection Systems (Mar. 16, 2004), *available at* http://www.fda.gov/cdrh/oivd/guidance/1236.html (last visited Oct. 26, 2007)

[85] Food & Drug Admin., 510(k) Summary (issued Dec. 18, 2003), *available at* http://www.fda.gov/cdrh/pdf3/k033612.pdf (last visited Oct. 26, 2007).

[86] *Id.*

[87] *See* Medical Devices; Clinical Chemistry and Clinical Toxicology Devices; Drug Metabolizing Enzyme Genotyping System, 70 Fed. Reg. 11,865-66 (Mar. 10, 2005) (to be codified at 21 C.F.R. pt. 862).

[88] Food and Drug Admin., Clearance Letter for Roche AmpliChip Cytochrome P450 Genotyping Test (Dec. 23, 2004), *available at* http://www.fda.gov/cdrh/pdf4/k042259.pdf (last visited Oct. 26, 2007).

[89] *Id.* Similar to the CYP2D6 test, the CYP2C19 test was intended to identify a patient's CYP2C19 genotype from genomic DNA extracted from a whole blood sample. The 510(k) cited the CYP2D6 test as a predicate device to which the Factor II kit demonstrated substantial equivalence.

[90] Food and Drug Admin., Clearance Letter for Tag-It Cystic Fibrosis Kit (May 9, 2005), *available at* http://www.fda.gov/cdrh/pdf4/k043011.pdf (last visited Oct. 26, 2007). The Tag-IT Cystic Fibrosis Kit, manufactured by Tm Bioscience Corporation of Toronto, Canada, is "intended as an aid in confirmatory diagnostic testing of individuals with suspected cystic fibrosis (CF), carrier identification and newborn screening" but is "not intended for stand-alone diagnostic purposes, prenatal diagnostic, pre-implantation or population screening." FDA classified the device as class II under the generic description "Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation detection system."

[91] Food and Drug Admin., 510(k) Substantial Equivalence Determination Decision Summary for the eSensor Cystic Fibrosis Carrier Detection System, *available at* http://www.fda.gov/cdrh/reviews/K051435.pdf (last visited Oct. 26, 2007).

In August 2005, FDA cleared a 510(k) notification submitted by Third Wave Technologies for its Invader UGT1A1 Molecular Assay, which detects variations in the UGT1A1 gene that produces the enzyme UDP-glucuronosyltransferase enzyme, affecting how certain drugs are broken down and cleared by the body.[92] FDA determined that the assay was substantially equivalent to the AmpliChip CYP450 Test for CYP2C19 and assigned it to the same regulatory category, subject to the same special controls.[93]

In July 2007, FDA approved its first PMA device for a molecular genetic test when it authorized the marketing of GeneSearch BLM Assay, which detects whether breast cancer has spread to nearby lymph nodes using two gene expression markers found in breast tissue.[94]

Most recently, in September 2007, FDA cleared a 510(k) notification submitted by Nanosphere Inc. for its Verigene Warfarin Metabolism Nucleic Acid Test, which detects variants associated with response to the blood-thinning drug warfarin.[95] According to FDA's press release, the test "is not intended to be a stand-alone tool to determine optimum drug dosage," but should be used "along with clinical evaluation and other tools," in order "to determine the best treatment for patients."[96] Also according to the press release, FDA cleared the device based on "results of a study conducted by the manufacturer of hundreds of DNA samples as well as on a broad range of published literature. In a three-site study, the test was accurate in all cases where the test yielded a result; 8 percent of the tests could not identify which genetic variants were present."[97]

With the exception of GeneSearch, which was approved pursuant to a PMA, FDA has cleared genetic test kits through its 510(k) notification process. In conjunction with clearance of the test, FDA has published a regulation defining the test

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[92] Food and Drug Admin., 510(k) Substantial Equivalence Determination Decision Summary for the Invader UGT1A1 Molecular Assay (Aug. 22, 2006), *available at* http://www.fda.gov/cdrh/reviews/K051824.pdf (last visited Oct. 26, 2007).

[93] *Id.*; FDA NEWS, *FDA Clears Genetic Test That Advances Personalized Medicine: Test Helps Determine Safety of Drug Therapy* (Aug. 22, 2005), http://www.fda.gov/bbs/topics/NEWS/2005/NEW01220.html (last visited Aug. 6, 2007). At the time of approval, Lawrence Lesko, director of FDA's Office of Clinical Pharmacology and Biopharmaceutics in the Center for Drug Evaluation and Research (CDER) stated, "[i]nformation on the UGT1A1 genotype can be an integral part of drug labels and will guide health professionals on how to dose medications such as irinotecan." *Id.* Irinotecan is a widely-used cancer therapeutic for colorectal cancer, and variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and potentially higher risks from the drug.

[94] *See* FDA NEWS, *FDA Approves First Molecular-Based Lab Test to Detect Metastatic Breast Cancer*, July 16, 2007, http://www.fda.gov/bbs/topics/NEWS/2007/NEW01667.html (last visited Aug. 17, 2007); In addition to molecular genetic test kits, FDA has also cleared an immunohistochemical test and related software, and a cytogenetic (FISH) test to detect Her2/Neu positive breast cancer. This test is used to identify women with breast cancer who are likely to benefit from Herceptin (Trastuzumab). Food & Drug Admin., Approval Letter for Insite™ Her-2/neu kit (Dec. 22, 2004) *available at* http://www.fda.gov/cdrh/pdf4/p040030e.pdf (last visited Oct. 26, 2007).

[95] According to the company's website, the test "is an *in vitro* diagnostic for the detection and genotyping of the *2 and *3 alleles of the *CYP2C9* gene and a singlepoint polymorphism (C to T at position 1173) of the VKORC1 gene, from EDTA-anticoagulated whole blood samples, as an aid in the identification of patients at risk for increased warfarin sensitivity." Nanosphere, Verigene® Warfarin Metabolism Nucleic Acid Test (IVD), Intended Use, *available at* http://www.nanosphere.us/VerigeneWarfarinMetabolismNucleicAcidTest_4472.aspx#IntendedUse (last visited Oct. 8, 2007).

[96] FDA, *FDA Clears Genetic Lab Test for Warfarin Sensitivity*, FDA NEWS, Sept. 17, 2007, *available at* http://www.fda.gov/bbs/topics/NEWS/2007/NEW01701.html (last visited Oct. 2, 2007). As of the writing of this article, FDA had not yet posted the 510(k) summary for this device.

[97] *Id.*

category and classifying all similar tests as Class II, and then issued a guidance document describing special controls to which devices within the class are subject.

Given the small number of test kits approved, it is difficult to make broad generalizations about what FDA has required of test kits and the overall burden that the approval process has placed on kit manufacturers. Nevertheless, some observations are possible.

First, while manufacturers have had to submit data to support the analytical validity of their tests, they have had to submit little or no independently-developed data to support tests' "clinical validity," which refers to whether there is a causal relationship between the presence of the mutation and the patient's current or future clinical condition. In the case of CF and Factor II and V Leiden, there is significant support in the literature for the clinical validity of the mutations detected by the tests, along with general clinical agreement that detecting these mutations is beneficial in diagnosis and treatment.[98]

In contrast, in the case of tests related to drug metabolism (CYP450 and UGT1A1), there is limited support for a clinical benefit from basing treatment-prescribing decisions on the results of genetic testing. Nevertheless, FDA permitted these tests to be marketed, albeit with very general claims of efficacy. In the case of Roche's AmpliChip test for CYP450 variants, FDA authorized a statement that "information about the [CYP2D6/2C19] genotypes may be used as an aid to clinicians in determining therapeutic strategy and treatment dose for therapeutics that are metabolized by the [CYP2D6/ 2C19] gene product."[99] No data from independent clinical studies were submitted to support the clinical sensitivity or specificity of the test. FDA also noted the presence of varying amounts of supportive data in these literature references to support phenotypic determinations for drugs that are metabolized by CYP2D6/2C19, and that clinicians should "use caution in predicting phenotype and adjusting treatment strategy for patients who express alleles that have not been investigated for activity in metabolizing a specific drug."[100]

The approved indication for UGT1A1 is "as an aid in the identification of patients with greater risk for decreased UDP-glucuronosyltransferase activity."[101] The 510(k) summary highlights the "variability in the knowledge of clinical util-

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[98] *See* University of Washington, GeneReviews: Cystic Fibrosis References, www.genetests.org (follow hyperlink to GeneReviews, enter "cystic fibrosis," follow hyperlink to References) (last visited Aug. 10, 2007); University of Washington, GeneReviews: Factor V Leiden Thrombophilia References, www.genetests.org (follow hyperlink to GeneReviews, enter "factor V leiden," follow hyperlink to References) (last visited Aug. 10, 2007).

[99] Roche Diagnostics, AmpliChip CYP450 Test (Sept. 15, 2006), *available at* http://www.amplichip.us/documents/CYP450_P.I._US-IVD_Sept_15_2006.pdf (last visited Oct. 26, 2007).

[100] Clearance Letter for Roche AmpliChip Cytochrome P450 Genotyping Test, *supra* note 88, at http://www.fda.gov/cdrh/pdf4/k042259.pdf. CYP450 testing currently is offered directly to consumers with claimed benefit for a wide range of prescription drugs, including selective serotonin reuptake inhibitors (SSRIs), a class of antidepressant medication. *See, e.g.,* Genelex, Drug Reaction Testing, *available at* http://www.healthanddna.com/drugreactiontest.html (last visited Oct. 9, 2007). However, in January 2007, the Agency for Health Care Research and Quality (AHRQ) published a report in which it concluded that there is "insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression." David B. Matchar et al, *Testing for Cytochrome P45- Polymorphisms in Adults With Non-Psychotic Drepression Treated With Selective Serotonic Reuptake Inhibitors (SSRIs)*. Evidence Report/Technology Assessment No. 146, AHRQ Pub. No. 07-E002 (Prepared by the Duke Evidence-based Practice Center for the Agency on Health Care Research and Quality) (Jan. 23, 2007), *available at* http://www.ahrq.gov/downloads/pub/evidence/pdf/cyp450/cyp450.pdf (last visited Oct. 9, 2007).

[101] 510(k) Substantial Equivalence Determination for the Invader UGT1A1 Molecular Assay, *supra* note 92.

ity with specific drugs that are metabolized by UGT1A1" and recommends that clinicians "use professional judgment in the interpretation of results from this type of test"; it also cautions that the test not be used "as the only test to determine specific drug dose."[102]

Thus, the amount of clinical validity data that has been required to support a 510(k) application for a genetic test has been highly test-dependent. Additionally, the indications for use that have been approved have been fairly general and not necessarily tied to a specific diagnostic or predictive use. It is also unclear whether laboratories using these devices include in test reports the cautionary language featured in the 510(k) summary, or whether clinicians are guided by FDA's recommendations in interpreting these tests. It should also be noted that whether the approved indication is general or specific, FDA does not regulate the use of tests for indications not contained in test labeling—so-called "off label" uses.

C. *FDA Regulation of Genetic ASRs*

When FDA issued its final ASR rule in 1997, the agency was aware that genetic LDTs were being provided for clinical use and were not regulated by the agency. Against this backdrop of unregulated genetic tests, the expert panel FDA convened to advise the agency on regulating ASRs expressed concern that Class I controls were insufficient to ensure the safety and effectiveness of the reagents used in genetic testing, and suggested that Class II or Class III regulation be required instead. In its proposed rule, FDA stated that "this recommendation by the panel may be too broad," and it questioned whether there was any meaningful distinction between tests that identify DNA and those that identify mRNA or protein products.[103] FDA solicited public comments regarding "the degree of regulatory control needed for [genetic] tests and reasonable bases for distinction, if any, among the ASR's used for human genetic testing."[104]

Ultimately, the ASR regulation did not assign any ASRs used in genetic LDTs to Class II or Class III. In the final rule, FDA explained the basis for this decision:

> FDA considered designating as Class III devices those ASR's that would be marketed independently for use in tests intended for use in overtly healthy people to identify a genetic predisposition to a dementing disease, or to fatal or potentially fatal medical disorders (e.g., cancers or Alzheimer's disease), in situations where penetrance is poorly defined or variable and latency is five years or longer. However, after reviewing the comments and currently available information, FDA has not yet identified criteria that would logically distinguish among genetic tests in order to determine which have the requisite impact to trigger more stringent controls. FDA has determined that the special issues related to genetic testing or predictive genetic testing do not warrant establishing a more stringent degree of regulatory control over ASR's used in these tests at this time.[105]

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[102] *Id.*
[103] 61 Fed. Reg. 10,484,10,486.
[104] *Id.*
[105] 62 Fed. Reg. 62,245-46.

FDA stated that it intended to "review agency policies relating to many aspects of regulation of genetic testing" after examining the then-pending recommendations of the National Institute of Health's (NIH's) Task Force on Genetic Testing.[106] It further stated that it might "propose additional regulation of genetic tests" after this review.[107] However, with the exception of the draft guidance on IVDMIAs, discussed below, no additional regulation has occurred.

Since 1997, there has been a significant rise in both the number of diseases for which genetic LDTs are available—from fewer than 500 in 1997 to more than 1,400 today.[108] Although some commercial ASRs used by laboratories to develop genetic tests have become available, and FDA has cleared a few genetic test kits, many laboratories that offer a significant percentage of genetic LDTs do not use commercial ASRs.[109]

D. *FDA Regulation of Genetic LDTs*

FDA's diminishing deference toward LDTs has been spurred by its concern about specific genetic tests. This section describes the evolution of FDA's approach to genetic LDTs over the past several years.

1. *2001: FDA Briefly Poised to Regulate All Genetic LDTs*

In 2001, FDA appeared poised to regulate genetic LDTs as medical devices. In briefings to the Secretary's Advisory Committee on Genetic Testing (SACGT), Dr. Steven Gutman, the Director of FDA's Office of In Vitro Diagnostic Products, suggested that genetic tests, including LDTs, could be regulated by FDA as Class II products subject to special controls, although some tests might be designated as Class III and others might need only Class I classification with general controls.[110] Dr. Gutman outlined FDA's development of a "premarket review template" that would require information on analytical validity, clinical validity, quality control and quality assurance, and clinical interpretation for all LDTs.[111] He indicated that the review template was being piloted in nine clinical laboratories that provided a range of testing services to evaluate the ease of preparation and submission of the template by those clinical laboratories.[112] Dr. Gutman also described the agency's plan to require all entities doing genetic testing to register with FDA and provide a list of the tests they were conducting to FDA.[113] During 2002 meetings of the SACGT, however, Dr. Gutman reported that FDA's authority to regulate laboratory developed genetic tests was under reconsideration. The situation remained unresolved as of the final meeting of the SACGT before its charter expired. Ultimately, FDA did not continue with the approach outlined by Dr. Gutman, although the agency never formally articulated the reasons for not doing so.[114]

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[106] *Id.* For a discussion of the Task Force's recommendations, *see infra* note 171.

[107] *Id.*

[108] Genetests Home page, *supra* note 3.

[109] *See* Genetics & Public Policy Ctr., unpublished data on file with GPPC, *infra* note 149.

[110] Sec'y's Advisory Comm. on Genetic Testing, SACGT Meeting Transcript, Statements of Dr. Steven Gutman (May 2, 2001), *available at* http://www4.od.nih.gov/oba/sacgt/sacgtmtg.htm (last visited Oct. 26, 2007).

[111] *Id.*

[112] Sec'y's Advisory Comm. on Genetic Testing, SACGT Meeting Transcript, Statements of Dr. Steven Gutman (Nov. 2001), *available at* http://www4.od.nih.gov/oba/sacgt/sacgtmtg.htm (last visited Oct. 26, 2007).

[113] Sec'y's Advisory Comm. on Genetic Testing, SACGT Meeting Transcript, Statements of Dr. Steven Gutman (Feb. 13, 2002), *available at* http://www4.od.nih.gov/oba/sacgt/sacgtmtg.htm (last visited Oct. 26, 2007).

[114] Sec'y's Advisory Comm. on Genetic Testing, SACGT Meeting Transcript (May 14, 2002), *available at* http://www4.od.nih.gov/oba/sacgt/sacgtmtg.htm (last visited Oct. 26, 2007).

2. *2004: FDA Prevents Marketing of OvaCheck*

In February 2004, FDA surprised the clinical laboratory community by effectively halting the release of a diagnostic test called OvaCheck.[115] OvaCheck, jointly developed by Correlogic Systems and researchers at FDA and the NIH, was designed to detect "subtle changes in patterns"[116] among proteins in the blood that would signal the presence of early-stage ovarian cancer. It had been slated to enter the market in March 2004.[117] However, in February 2004, FDA issued a letter inviting Correlogic's CEO to "discuss the nature and appropriate regulatory status of [the test] and the least burdensome ways that Correlogic Systems may fulfill any premarket review requirements that may apply."[118] OvaCheck was unique at the time in that it was a "multiplex test," with more than one protein used as a biomarker.[119] In singling out the technology, FDA was for the first time drawing a distinction around a "black-box" technology, whose algorithm remained proprietary and whose sensitivity and specificity had not been externally reviewed.[120] Indeed, in its letter, FDA acknowledged that while the agency had "in general not regulated laboratory-developed testing services," the "software intended for use in the OvaCheck…[was] subject to FDA regulation" under the FDCA.[121] The letter asserted that "[b]ecause these articles of software are 'intended for use in the diagnosis of disease,' they are 'devices' under the act, 21 U.S.C. 321(h)(2)," and that without a finding of substantial equivalence to class I or class II devices, they would require premarket approval.[122] OvaCheck has never been marketed.[123]

3. *2006: Letters to Companies Selling Genetic LDTs*

In 2006, FDA sent out several "untitled" letters to companies offering LDTs, signaling the agency's heightened regulatory concern about certain types of genetic

[115] *See* Lynn Wagner, *A Test Before Its Time? FDA Stalls Distribution Process of Proteomic Test*, 96 J NAT'L CANCER INST. 500, 500 (2004), *available at* jncicancerspectrum.oxfordjournals.org/cgi/reprint/jnci;96/7/501.pdf (last visited Oct. 26, 2007).

[116] Correlogic Systems, Inc., OvaCheck FAQs, http://www.correlogic.com/research-areas/ovarian-cancer-faqs.php (last visited Aug. 1, 2007).

[117] Michele G. Sullivan, *FDA Raises Regulatory Issues: Validity Testing Indefinitely Delays OvaCheck Release*, OB/GYN NEWS, Apr. 1, 2004, *available at* http://findarticles.com/p/articles/mi_m0CYD/is_7_39/ai_n5996295 (last visited Oct. 26, 2007).

[118] *See* Wagner, *supra* note 115, at 500.

[119] Prior technologies had been deemed more transparent because they tested for single-gene defects—making detection like an on-off switch—such that, in theory, the genetic test was less vulnerable to diagnostic error.

[120] Wagner, *supra* note 115, at 501.

[121] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Peter J. Levine, President, Correlogic Systems, Inc. (July 12, 2004), http://www.fda.gov/cdrh/oivd/letters/071204-correlogic.html (last visited July 31, 2007).

[122] *Id.*; *see also* Premarket Approval of Medical Devices, 21 C.F.R. pt. 814 (1996).

[123] According to Correlogic's Web site, the company remains "in discussions with FDA concerning the scope of the regulatory submission the agency will require." Correlogic Systems, Inc., OvaCheck FAQs, http://www.correlogic.com/research-areas/ovarian-cancer-faqs.php (last visited Aug. 3, 2007). In contrast, in 2005, FDA sent a letter to Agendia, the manufacturer of MammaPrint, stating its concern that the test "may not be in conformance with" the the FDCA, "including the requirements related to marketing clearance or approval." Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Dr. Bernard Sixt, Chief Executive Officer, Agendia B.V. (Apr. 6, 2005), *available at* http://www.fda.gov/cdrh/oivd/letters/040605-agendia.html (last visited Oct. 8, 2007). As discussed *infra*, this product was cleared by FDA in 2007.

LDTs.[124] A July 2006 report by the Government Accountability Office (GAO) describing fraudulent practices by companies selling "nutrigenetic" tests over the Internet[125] and the Senate hearing that followed,[126] likely spurred FDA to send some of these letters.[127]

In January 2006, FDA also sent an untitled letter to LabCorp concerning its PreGen-Plus colon cancer screening test. This letter, and the company's subsequent actions, demonstrate the contortions FDA has attempted in order to regulate a genetic LDT of concern and the evasive maneuvers undertaken by industry to avoid FDA regulation.

In its letter, FDA stated that PreGen-Plus, a "stool-based DNA testing service," was subject to FDA regulation.[128] FDA identified as its regulatory concern the "refined microtiter plates" used to isolate DNA, which the agency considered medical devices requiring the submission of a 510(k).[129] While the company apparently had previously asserted that the DNA capture devices were general-purpose laboratory equipment, the FDA letter disputed this assertion. Additionally, while LabCorp had argued that the devices should not be subject to premarket review because they were ordered only by LabCorp, were not commercially available and could not be used to independently render any diagnosis of disease, FDA countered that there was "no statutory or regulatory requirement that a device be purchased by more than one entity or be used 'independently' to diagnose disease in order to be subject to the 510(k) premarket clearance requirement."[130] FDA stated that the device could not be commercially distributed without an appropriate premarket determination from FDA, and that—in the absence of such regulatory compliance—it was adulterated and misbranded.[131]

The component at issue in the agency's letter, called Effipure, had been sold to LabCorp by Exact Sciences Corporation.[132] Following receipt of FDA's letter, LabCorp began developing an in-house DNA purification procedure that would avoid the need for Effipure.[133] LabCorp appears to have made this decision in order to change Pre-Gen Plus into a test wholly developed within the laboratory and not using any externally purchased components, thereby removing it from FDA's purview. It is unclear whether FDA will continue to seek regulate LabCorp's provi-

[124] *See* Table, Appendix 1.

[125] U.S. GOV'T ACCOUNTABILITY OFFICE, Testimony Before the Senate Special Committee on Aging, Statement of Gregory Kutz, Managing Director, Forensic Audits and Special Investigations, NUTRIGENETIC TESTING: TESTS PURCHASED FROM FOUR WEB SITES MISLEAD CONSUMERS 2-27 (July 27, 2006), *available at* http://www.gao.gov/new.items/d06977t.pdf (last visited Oct. 26, 2007).

[126] *At Home DNA Tests: Marketing Scam or Medical Breakthrough: Hearing Before the S. Spec. Comm. on Aging*, 109th Cong. 109-707 (2006).

[127] *See, e.g.*, Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Drew Fromkin, President, Clinical Data, Inc. (Aug. 2, 2006) (on file with FDA); Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Peter Vitulli, President, Sciona, Inc. (Aug. 20 2006) (on file with FDA); Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Howard C. Coleman, Chairman, Genelex Corp. (Aug. 20, 2006) (on file with FDA).

[128] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Brad T. Smith, Executive Vice President, Lab. Corp. of America (Jan. 12, 2006) (on file with FDA).

[129] *Id.*

[130] *Id.*

[131] *Id.*

[132] *See* SEC. & EXCH. COMM'N, FORM 10-Q QUARTERLY REPORT FOR EXACT SCIENCES CORPORATION 6 (June 30, 2006).

[133] *See* The Regence Group, Medical Policy: Laboratory Section—Analysis of Human DNA in Stool Samples, http://www.regence.com/trgmedpol/lab/lab37.html (last visited Aug. 7, 2007).

sion of the test; however, such action would be inconsistent with the enforcement discretion FDA has afforded most other LDTs.[134]

[Ed. Note: As this article was going to press, FDA sent a Warning Letter to Exact Sciences, which licenses Pre-Gen Plus to LabCorp, stating that the assay is a medical device requiring premarket approval or clearance. Exact Sciences Gets Warning Letter From FDA (Reuters), Oct. 16, 2007. The implications of this letter for LabCorp's continued distribution of the test are unclear.]

Letters sent by FDA to two other companies are particularly relevant to the agency's evolving approach to LDT genetic tests. On January 23, 2006, FDA sent a letter to Genomic Health concerning the company's Onco*type* Dx test.[135] The test examines the expression of 21 genes to predict the likelihood of breast cancer recurrence in women with newly diagnosed, early-stage invasive breast cancer. FDA's letter provided the statutory definition of a device, and stated that the agency had "no record that such a test has been the subject of premarket review by FDA."[136] The letter requested a meeting "to discuss the nature and appropriate regulatory status" of the technology "and the least burdensome ways that Genomic Health may fulfill any premarket review requirements that may apply."[137] The company continues to market the test and takes the position that it "should not be subject to regulation under established FDA policies," while acknowledging that FDA regulation may be required in the future.[138]

On January 27, 2006, a very similar letter was sent to InterGenetics regarding the OncoVue test, which evaluates "single nucleotide polymorphisms" (SNPs) together with personal history to estimate a woman's breast cancer risk.[139] At the time the company received the letter, a nationwide launch of the test was imminent. Nevertheless, following receipt of the letter, the company submitted an Investigational Device Exemption (IDE), which permits the company to offer the test on an investigational basis subject to certain restrictions. The company is now offering the test at 50 locations.[140] Based on the data received from patients administered the test under the IDE, the company plans to submit the test for premarket review.[141]

The company's president and CEO stated that he had informed FDA of the company's plan to develop the test four years earlier and had been told that FDA would not regulate the test.[142] He therefore viewed the FDA's action as imposing new rules on his test. FDA's issuance of the IVDMIA draft guidance six months after its letter to InterGenetics and Genomic Health can be interpreted as an attempt to articulate more formally a rationale for its regulatory approach to tests that use multiple biomarkers, including genes or gene-expression products, to predict a patient's future risk of disease.

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[134] *See* SEC. & EXCH. COMM'N, FORM 10-Q QUARTERLY REPORT FOR EXACT SCIENCES CORPORATION 17 (Sept. 30, 2006).

[135] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Randy Scott, Chairman, Genomic Health, Inc. (Jan. 23, 2006) (on file with FDA).

[136] *Id.*

[137] *Id.*

[138] *See* SEC. & EXCH. COMM'N, FORM 10-Q QUARTERLY REPORT FOR GENOMIC HEALTH, INC. 22 (Aug. 9, 2007).

[139] *See* InterGenetics, Inc., Comments to the Draft Guidance for Industry, Clinical Laboratories, and FDA Staff, In Vitro Multivariate Index Assays Draft Guidance (Sept. 7, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/06d0347/06D-0347-EC3-Attach-1.pdf (last visited Oct. 26, 2007).

[140] Intergenetics, Inc. What is OncoVue?, http://www.intergenetics.com/intergenetics/oncovue.html (last visited Aug. 6, 2007).

[141] *Id.*

[142] *Id.*

4. *2006: FDA Issues IVDMIA Draft Guidance*

FDA's letters to Genomic Health and InterGenetics foreshadowed the release in September 2006 of the FDA IVDMIA draft guidance. While the draft guidance was not limited to genetic tests, it was issued in response to concern about genetic LDTs, and the many future IVDMIAs that will likely use genetic markers. FDA's implementation of the guidance therefore may have the most significant impact, at least initially, on certain types of genetic tests.

In its September 2006 version of the draft, FDA defined IVDMIAs as "test systems that employ data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment or prevention of disease."[143] The first draft guidance identified three characteristic features of IVDMIAs: 1) they use clinical data, including data derived from in vitro assays, to empirically identify variables and derive weights or coefficients employed in an algorithm, 2) they employ an algorithm to integrate these variables and calculate a patient-specific result that cannot be independently derived or confirmed without access to a laboratory's proprietary information, and 3) results cannot be interpreted by a health care provider without information from the test developer regarding its clinical performance and effectiveness.

In response to critical comments, FDA's second draft guidance on IVDMIAs defines them instead as tests that 1) combine "the values of multiple variables using an interpretation function to yield a patient-specific result" used for diagnosis, prevention, treatment or mitigation of disease, and 2) whose results are "non-transparent and cannot be independently derived or verified by the end user."[144]

The first draft guidance announced FDA's intent to adopt a risk-based approach in regulating IVDMIAs and to require premarket approval or 510(k) notification depending on the "level of control necessary to assure the safety and effectiveness of the device."[145] Critics challenged the notion that FDA was acting in a risk-based manner, because all IVDMIAs are subject to greater scrutiny than other types of LDTs. FDA did not respond to this criticism, but merely reiterated its intent to be risk-based in its implementation of the guidance.[146]

The first draft guidance also stated that IVDMIAs would be subject to FDA's Quality System Regulation (QSR)[147]—which addresses the manner in which medical devices must be manufactured—as well as its Medical Device Reporting regula-

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[143] *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays*, *supra* note 68, at 1-2

[144] *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays*, *supra* note 73, at 4.

[145] *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays*, *supra* note 68, at 4.

[146] *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays*, *supra* note 73, The revised draft also did not articulate the legal basis of the agency's jurisdiction, other than citing to the device definition in the FDCA, and did not respond to the criticism that the agency should have proceeded via notice and comment rulemaking. Additionally, while the guidance provides some more detail about how to submit 510(k)s and PMAs, individual laboratories will still need to meet with FDA personnel to determine what specific data FDA will require regarding their test. Finally, the guidance did not respond to concerns about increased costs or deterred innovation other than stating that its approach is the "least burdensome" way to address the agency's concerns about safety and effectiveness. *Id.* at 3-15

[147] *See* FDA Quality System Regulation, 21 C.F.R. pt. 820 (1996).

tion,[148] which requires that certain adverse events be reported to FDA. Some commenters raised concerns about potential conflicts between FDA's QSRs and CLIA's requirements for laboratories. The revised draft therefore stated that FDA would exercise enforcement discretion with respect to its QSRs pending the issuance of a separate guidance document clarifying its requirements.

FDA approved its first IVDMIA in February 2007. The MammaPrint test, which is not currently marketed in the United States, uses gene expression products (mRNA) to determine the likelihood of breast cancer returning within five to 10 years after a woman's initial cancer.[149] Shortly after it cleared the MammaPrint device,[150] FDA issued a class II special controls guidance document for gene expression profiling test systems for breast cancer prognosis.[151]

In contrast to the test kits for CYP450 and UGT1A1, the 510(k) submission for MammaPrint included clinical data submitted by the company; the data were derived from a trial in 302 non-U.S. patients. The test was cleared with a very narrow intended use; it is intended "for use by physicians as a prognostic marker only, along with other clinicopathological factors," in "breast cancer patients who are less than 61 years old, with Stage I or Stage II disease, with tumor size ≤ 5.0 cm and who are lymph node negative."[152] Further, under "special conditions for use," FDA states that "MammaPrint is not intended for diagnosis, or to predict or detect response to therapy or to help select the optimal therapy for patients."[153] Additionally, because none of the studies used to support MammaPrint approval involved U.S. patients, the MammaPrint patient report states that the test's "performance characteristics and clinical utility in the United States population have not been established," and that "the metastasis free survival data is from an independent external patient group in Europe."[154]

IV. CONCERNS ARISING FROM THE STATUS QUO

Several concerns arise from FDA's current approach to genetic tests. These concerns stem from the lack of independent oversight for most genetic tests to ensure their safety and effectiveness, unfair regulatory burdens for the small group of tests that FDA does regulate as genetic tests and an unstable regulatory climate that may deter investment in and development of new, clinically valid genetic tests.

A. *Lack of Independent Oversight for Most Tests*

Today, the vast majority of laboratories conduct genetic testing using LDTs that do not use commercially-distributed ASRs. According to a survey of 190 genetic-testing laboratory directors conducted by the Genetics and Public Policy Center in

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[148] 21 C.F.R. Parts 803, 806.

[149] FDA., 510(k) Substantial Equivalence Determination Decision Summary for MammaPrint (June 4, 2007), *available at* http://www.fda.gov/cdrh/reviews/K062694.pdf (last visited Oct. 26, 2007).

[150] Following clearance, FDA issued a new rule classifying gene expression profiling systems for breast cancer prognosis. 72 Fed. Reg. 26,290.

[151] Food & Drug Admin.., *Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis* (May 9, 2007), *available at* http://www.fda.gov/cdrh/oivd/guidance/1627.pdf (last visited Oct. 26, 2007).

[152] 510(k) Substantial Equivalence Determination Decision Summary for MammaPrint, *supra* note 149.

[153] *Id.*

[154] *Id.*

2006,[155] 89 percent of laboratories offer at least some LDTs without ASRs, including 29 percent that exclusively use ASR-free LDTs and another 19 percent who use them for the majority of their tests.[156] Just 5 percent said that they employ FDA-approved ASRs in all of the tests they perform,[157] Additionally, only 45 percent of laboratory directors agreed with the statement that "FDA's regulation of ASRs has had a positive impact on the quality of genetic testing."[158]

For most genetic tests there is no independent external review of analytic or clinical validity before tests are offered to the public. As a result, there is no external assessment of whether the laboratory can reliably identify the presence or absence of a mutation or whether the presence of the mutation actually is correlated with disease or risk of disease in an individual. [159]

In addition to the absence of premarket review, there is also little postmarket oversight. While CLIA requires laboratories to be certified and inspected every two years,[160] it does not assess the clinical validity of the tests offered by clinical laboratories; each laboratory director makes a decision about whether to offer a test. CMS officials in the CLIA program have repeatedly asserted that CLIA does not permit oversight of clinical validity.[161] Even if the statute could be so construed, CMS's failure to implement regulations to ensure the analytical validity of genetic tests makes it unlikely, as a practical matter, that the agency would ever seek to regulate their clinical validity absent new legislation requiring it to do so.

Furthermore, while under CLIA laboratories are required to maintain records of known testing errors,[162] they are not required to report testing errors to CMS when they occur. Thus it is difficult for CLIA to provide real-time intervention if a problem is noted. Nor are laboratories required to gather evidence to assess clinical validity after the test is marketed, or to modify tests or claims based on new evidence.

Lack of FDA oversight also leaves health-care providers at an informational disadvantage in making treatment decisions for their patients. FDA's premarket review framework includes an investigational data-gathering phase during which data (including data from the scientific literature) are formally gathered and analyzed before a test is offered to the public.[163] In contrast, LDTs are subject to no similar mechanism to ensure that such data are generated.

FDA regulation of a product also gives the government authority to review the claims made in a product's labeling, and to require the disclosure of information the government deems necessary to provide adequate information to the end user.[164]

[155] Genetics & Public Policy Ctr., Survey of Laboratory Directors of Genetic Testing Laboratories (Dec. 2005-Mar. 2006) (unpublished data on file with GPPC).

[156] *Id.*

[157] *Id.*

[158] *Id.*

[159] According to the Center's survey, four in ten agreed that FDA should be more involved in reviewing the clinical validity of genetic tests and 46 percent believing that CLIA should be more involved. Just 16 percent agreed that "FDA should regulate all genetic tests as medical devices." *Id.*

[160] Ctrs. for Medicare & Medicaid Serv., Clinical Laboratory Improvement Amendments (CLIA): How to Obtain a CLIA Certificate, *available at* http://www.cms.hhs.gov/CLIA/downloads/HowObtainCLIACertificate.pdf (last visited Nov. 6, 2007).

[161] *See, e.g.,* Sec'y's Advisory Comm. on Genetics, Health and Society, Testimony of Judy Yost, Nov. 13, 2006, *available at* http://www4.od.nih.gov/oba/SACGHS/meetings/Nov2006/transcripts/Genetic_Tech-Hamilton-Yost.pdf (last visited Oct. 3, 2007).

[162] *See* The Clinical Laboratory Improvements Amendments of 1988, 42 U.S.C. § 263a (1994).

[163] 21 U.S.C. § 360(a)(1)(c); *see also* Premarket Notification Procedures, 21 C.F.R. 807.81 (1996).

[164] *See* Medical Device Reporting, 21 C.F.R. pt. 803 (1996).

Additionally, FDA posts all clearances on its Web site so that summaries of the data supporting test claims are publicly available.[165] In contrast, CLIA does not allow for sharing of the data on which test performance rests.

B. *The Current System Is Arbitrary and Inequitable*

The current system also is arbitrary in its disparate requirements for test manufacturers and clinical laboratories. Manufacturers that go through the added effort to manufacture a test kit are forced to compete with laboratories that do not have a similar regulatory burden, and are not similarly constrained in the product claims they may make.

The PreGen-Plus example described above provides but one example of the arbitrariness of the current system. Whether the "refined microliter plates" were "general purpose laboratory equipment," as LabCorp asserted, or a "medical device," as FDA claimed, seems a rather trivial distinction on its face. It is more likely—albeit admittedly supposition—that the agency's true concern in pursuing regulation of Pre-Gen Plus lay with whether the test was supported by adequate clinical evidence for use in colon cancer screening, i.e., whether it was safe and effective.[166] FDA would also likely have heightened concern about the test given that it is promoted and sold directly to consumers through a third-party vendor.[167] Yet, FDA's ability to answer essential questions about the safety and effectiveness of the test currently hinges on whether the test uses commercially-distributed components or components developed by the laboratory. It seems illogical to permit FDA in the former instance to require premarket review of the test but in the latter to prevent FDA from doing so. In addition to creating disincentives to the development of tests with demonstrated safety and effectiveness, such artificial regulatory distinctions do not serve the public's health, particularly when the public is unaware that such arcane distinctions determine whether or not there has been independent review of the tests they rely on to make critical health decisions.

FDA's approach to IVDMIAs also demonstrates the arbitrariness of the current system. While some IVDMIAs no doubt raise serious safety and effectiveness concerns, the draft guidance subjects all IVDMIAs to heightened scrutiny,

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[165] Food & Drug Admin., Product Approvals, http://www.fda.gov/opacom/7approvl.html (last visited August 7, 2007).

[166] According to LabCorp's information sheet on Pre-Gen Plus, the test is for use in "detection of clinically-significant colorectal neoplasia in asymptomatic, average-risk patients 50 years old and older; adjunctive test for those patients who receive an FOBT, flexible sigmoidoscopy or colonoscopy; enhance current methods for early detection of colorectal cancer." LabCorp, PreGen-Plus™ Colorectal Cancer Detection, *available at* http://www.labcorp.com/datasets/labcorp/html/chapter/mono/mo002100.htm (last visited Oct. 8, 2007). Under limitations, the information sheet states that the test "is not intended to replace a colonoscopy in those patients who are willing to undergo the procedure. Additionally, while it may be used adjunctively or in noncompliant patients, it is not intended as a primary screening tool for individuals at increased risk for developing disease." Id. Scientific evidence suggest that PreGen-Plus is more sensitive than screening using a fecal occult blood test (FOBT), but that neither of these tests is as accurate as colonoscopy. *See* Thomas F. Imperiale et al., *Fecal DNA Versus Fecal Occult Blood for Colorectal Cancer Screening in an Average-Risk Population*, 351 NEW ENG. J. MED. 2704, 2704-14 (2004). Currently, the American Cancer Society guidelines for colorectal cancer screening do not include PreGen-Plus as a recommended screening method. American Cancer Society, Guidelines for the Early Detection of Cancer, http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp (last visited Aug. 14, 2007). *See also* Brian Reid, *Wanted: A Test With Less Recoil*, WASH. POST (Mar. 8, 2004.).

[167] *See* DNAdirect, Colon Cancer Screening (PreGen-Plus), *available at* http://www.dnadirect.com/patients/tests/colon_cancer/index.jsp (last visited Oct. 8, 2007).

regardless of intended use, because of the technology used to perform the test (an alogorithm). In contrast, FDA currently regulates no single-gene tests, regardless of their intended use. This dichotomy foreseeably may lead to instances of both overregulation of IVDMIAs with fairly benign intended uses (whether to eat more green vegetables) and underregulation of single-gene tests that are used to make significant life decisions (whether to undergo a prophylactic mastectomy).

C. *Market Instability*

Finally, the current regulatory environment creates an unstable business climate that may deter the development of new, clinically valid genetic tests. FDA's "enforcement discretion" approach leaves open the possibility that the agency may suddenly change its stance from non-regulation to regulation at some unspecified point in the future, as it did when it issued the IVDMIA draft guidance. As several people commented in response to FDA's IVDMIA draft guidance, device manufacturers need to raise significant capital to bring a new test to market.[168] An assessment of the regulatory risk is a key aspect of a venture capitalist's decision to fund a new company or project. Uncertainty about whether or how FDA will in the future regulate a product that it does not regulate today is a significant deterrent to investors, and also may deter companies from devoting resources to certain projects. Additionally, manufacturers with devices already on the market may discontinue production in the face of sudden rule changes, particularly when the new rules lack clarity.

Thus, to foster a business climate conducive to the development of new genetic tests that will improve public health, those providing testing need clear guidance from FDA about what is required, along with the assurance of clear rules that do not change over time or without notice. Ironically, in 1997 FDA justified its ASR rule by an appeal to the need for market stability: "FDA also is concerned that continuing uncertainties about the regulatory status of commercially marketed ASR's may create an unpredictable business climate for manufacturers and suppliers."[169] Notwithstanding the ASR rule, FDA's current piecemeal approach is creating exactly the unpredictable business climate it feared a decade ago. As the experience of InterGenetics demonstrates, the concerns of the regulated industry are more than hypothetical.

V. EXECUTIVE AND LEGISLATIVE EFFORTS TO IMPROVE OVERSIGHT

The issue of genetic testing oversight is not new. It has been the subject of federal advisory committee review since 1995, when the NIH and the Department of Energy jointly established a Task Force on Genetic Testing.[170] Though that Task Force's 1997 report was expansive—containing 56 recommendations that focused particularly on which genetic tests should be offered to patients and their families, who should offer genetic tests, and what type of informed consent and genetic counseling should be required[171]—its recommendations were largely ignored. The

[168] Public Meeting on In Vitro Diagnostic Multivariate Index Assays (IVDMIA) transcript, *supra* note 72.

[169] 62 Fed. Reg. 62,244.

[170] *See* HOLTZMAN & WATSON, EDS., *supra* note 75.

[171] *Id.* In particular, the Task Force recommended that: 1) the genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of a disease. The

findings of its successor, the Secretary's Advisory Committee on Genetic Testing (SACGT), however, garnered a wider audience. The SACGT determined that the current oversight of genetic tests was insufficient to ensure their safety, accuracy and clinical validity.[172] In a January 19, 2001, letter to the SACGT's Chair, outgoing Department of Health and Human Services (HHS) Secretary Donna Shalala agreed, stating that the Department would implement the SACGT's recommendations, including FDA oversight of genetic tests.[173] But the message delivered to the SACGT a month later by the new Presidential Administration's representative from HHS was somewhat more equivocal.[174]

With the change of administration, the SACGT was replaced by the Secretary's Advisory Committee on Genetics Health and Society (SACGHS),[175] which initially indicated it would not take up the issue of genetic testing oversight. In March 2007, however, representatives from HHS Secretary Michael Leavitt's office charged the Committee with developing a "comprehensive map of the steps needed for evidence development and oversight of genetic and genomic tests to improve overall health quality."[176] The Committee was also asked to examine what evidence of human harms exists regarding genetic tests; whether those harms were attributed to problems with analytical validity, clinical validity or clinical utility; and what new models could be developed to demonstrate effectiveness of genetic tests, either by the private sector or through public-private partnership.[177]

Also during the same time period, two bills were introduced in Congress to strengthen government oversight. The Laboratory Test Improvement Act, introduced by Sen. Edward Kennedy (D-Mass.) and Sen. Gordon Smith (R-Ore.), would put into place a comprehensive system of oversight for all LDTs, including genetic tests.[178] Specifically, the bill grants explicit authority to FDA to regulate LDTs as medical devices, specifying that most LDTs will be classified as class II

observations must be independently replicated and subject to peer review; 2) analytical sensitivity and specificity of a genetic test must be determined before it is made available in clinical practice; 3) data to establish the clinical validity of genetic tests must be collected under investigative protocols and the study sample must must be drawn from a group of subjects representative of the population for whom the test is intended. Formal validation for each intended use of a genetic test is needed.

[172] SEC'Y'S ADVISORY COMM. ON GENETIC TESTING, DEVELOPMENT OF A CLASSIFICATION METHODOLOGY FOR GENETIC TESTS: CONCLUSIONS AND RECOMMENDATIONS 2-7 (Sept. 2001), *available at* http://www4.od.nih.gov/oba/sacgt/reports/Addendum_final.pdf (last visited Oct. 26, 2007). In brief, SACGT concluded that 1) additional oversight was warranted for all genetic tests; 2) new and innovative oversight mechanisms that would not delay development of new tests were required; 3) FDA should review and approve all new genetic tests for clinical use, whether testing was performed with test kits or laboratory developed method and 4) CLIA regulations should be augmented to provide more specific provisions for ensuring the quality of laboratories conducting genetic tests.

[173] Letter from Donna Shalala, Secretary of Health and Human Services, to Edward McCabe, Chair, Sec'y's Advisory Comm. on Genetic Testing (Jan. 19, 2001), *available at* http://www4.od.nih.gov/oba/sacgt/McCabe.pdf (last visited Oct. 26, 2007).

[174] Sec'y's Advisory Comm. on Genetic Testing, Testimony of Dr. William Raub, (Feb. 15, 2001), *available at* http://www4.od.nih.gov/oba/sacgt/sacgtmtg.htm (last visited Aug. 7, 2007).

[175] Notices: Establishment of Secretary's Advisory Committee on Genetics, Health and Society, 67 Fed. Reg. 65,126-27 (Oct. 23, 2002).

[176] Sec'y's Advisory Comm. on Genetics, Health and Society, Testimony of Sheila Walcoff (Mar. 26, 2007), *available at* http://www4.od.nih.gov/oba/SACGHS/meetings/Mar2007/transcripts/Walcoff-UpdateSecretaryOffice.pdf (last visited Oct. 26, 2007). Specifically, SACGHS was asked to "describe the existing pathways that examine the analytical validity, clinical validity and clinical utility of genetic tests" and identify what organizations are responsible for overseeing each of these, as well as the "potential pathways for communicating clear information to guide test and treatment selection by the healthcare provider."

[177] *Id.*

[178] *See* S. 736, 110th Cong. §§ 1-9 (2007).

medical devices, although FDA can impose a more stringent class III classification or less stringent class I classification under certain conditions.[179] It also requires all laboratories using LDTs to register with FDA as medical device manufacturers, and to submit to FDA a list of tests offered by the laboratory, the intended uses of the tests, information on the tests' analytical validity and information on the tests' clinical validity if they are intended for clinical use.[180]

The Genomics and Personalized Medicine Act of 2007, introduced by Sen. Barack Obama (D—Ill.) and Sen. Richard Burr (R—N.C.), would direct the HHS secretary to improve the safety and effectiveness of genetic tests.[181] Under this bill, the Secretary would be required to commission a study from the Institute of Medicine that would make recommendations regarding the development of a "decision matrix" for use in determining which tests to regulate and how they should be regulated.[182] Pending implementation of the matrix, FDA would be prohibited from requiring premarket review of any LDT.[183]

The prospect for passage of either of these bills is uncertain. Initially it was thought that the Kennedy-Smith bill would be included in the legislative package of reauthorization measures affecting pharmaceuticals and medical device user fees and marketing.[184] Several groups, including the Mayo Clinic and Genomic Health, sent a letter to Sen. Kennedy requesting "more time to provide feedback and discuss pathways that will not have unintended consequences on laboratory services."[185] Neither bill was introduced as part of the user fee package. However, Sen. Obama did introduce an amendment to S. 1082 that would have required the HHS Secretary to contract with the Institute of Medicine to conduct a study assessing the overall safety and quality of genetic tests and to prepare recommendations for improving federal oversight of the tests.[186] This study would have been the fourth government-sponsored study on genetic testing oversight.[187] As enacted, however, the amendment required an IOM study only if the SACGHS failed to complete its report by July 2008.[188]

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[179] *Id.* § 5.

[180] *Id.* If the submission is determined to be insufficient, FDA could require the laboratory test to undergo formal agency review. Laboratories that fail to undergo review of a test satisfactorily would be required to stop offering the test, and laboratories offering tests directly to the public without a health care provider intermediary (DTC tests) would be required to submit their tests for agency review within 180 days of the bill's enactment.

[181] S. 976, 110th Cong. §§ 1-7 (2007).

[182] *Id.* § 7(b)(3). The Secretary would then be required to implement the decision matrix within eighteen months of the bill's passage and to assign responsibility for reviewing tests to FDA or to the CMS, or neither, depending on how the test is evaluated under the matrix. In addition, the bill would require CMS to develop specialty areas for at least some genetic tests, and to develop criteria for establishing both the analytical and clinical validity of tests determined to be within the agency's purview.

[183] *Id.* § 4.

[184] S. 1082, 110th Cong. (2007).

[185] Letter from various organizations to Senator Edward M. Kennedy (Mar. 16, 2007), *available at* http://www.aab.org/Kennedy%20labs.pdf (last visited Oct. 26, 2007).

[186] National Institutes of Health Office of Policy Tracking and Analysis, Bill Tracking: Senate Bills, 110th Congress, http://olpa.od.nih.gov/tracking/110/senate_bills/session1/s-1082.asp (last visited Aug. 7, 2007).

[187] All previous studies have made recommendations for enhancements to CLIA and FDA regulation, but their recommendations have not been implemented.

[188] Pub. L. 110-85 (2007). Section 1103 provides: "a) REPORT.— If the Secretary's Advisory Committee on Genetics, Health and Society does not complete and submit the Regulatory Oversight of Genetic/Genomic Testing Report & Action Recommendations to the Secretary of Health and Human Services (referred to in this section as the "Secretary") by July of 2008, the Secretary shall enter into a contract with the Institute of Medicine to conduct a study to assess the overall safety and quality of

VI. OPTIONS FOR MOVING FORWARD

In spite of numerous previous attempts, and notwithstanding the rapid growth in genetic testing, there has been virtually no progress on designing a coherent and equitable regulatory framework for genetic tests. At the same time, there is increasing recognition that the status quo is unacceptable, both as a public health and as a business matter. And, as the comments submitted in response to FDA's IVDMIA draft guidance demonstrate, many stakeholders do not oppose—and some expressly support—some FDA engagement in genetic testing oversight, although there is considerable concern about the precise nature of that engagement. This section identifies the principles that should underlie any system of oversight and presents options for FDA oversight of genetic tests.

A. *Principles at Stake*

A prerequisite to developing options for genetic testing oversight is agreement on the objectives sought to be achieved. In the case of genetic tests, options for improving oversight should be designed around the following principles:

- Test accuracy: Oversight should ensure that genetic tests provide accurate, analytically valid information for diagnosis, treatment or prevention of disease.
- Parity of regulation: Genetic tests should be subject to similar regulatory requirements whether they are developed by a clinical laboratory or sold as a test kit. Additionally, genetic LDTs and non-genetic LDTs should be subject to comparable levels of oversight.
- Risk-based requirements: Oversight for genetic tests (as with all laboratory tests) should be commensurate with the level of risk posed by the test. Risk assessment should take into account the likelihood and consequences of a false positive or a false negative result, the clinical importance of the information and existing alternatives to testing for diagnosis, treatment or prevention of the disease or condition at issue.
- Clinical relevance: Oversight should ensure that only tests with demonstrated clinical validity are clinically available.
- Disclosure of information: Oversight should ensure that doctors and patients have adequate information about genetic tests so that they can make informed decisions about whether and when to test.
- Ongoing data collection and timely modification based on new data: Oversight should ensure that new scientific information about genotype-phenotype correlations are incorporated into test reports. Oversight should also allow manufacturers a mechanism efficiently to modify tests in order to improve their safety and effectiveness.
- Error reporting: Oversight should ensure that testing errors are identified and corrected in a timely manner.

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genetic tests and prepare a report that includes recommendations to improve Federal oversight and regulation of genetic tests. Such study shall take into consideration relevant reports by the Secretary's Advisory Committee on Genetics, Health and Society and other groups and shall be completed not later than 1 year after the date on which the Secretary entered into such contract. b) RULE OF CONSTRUCTION.—Nothing in this section shall be construed as requiring Federal efforts with respect to regulatory oversight of genetic tests to cease or be limited or delayed pending completion of the report by the Secretary's Advisory Committee on Genetics, Health and Society or the Institute of Medicine.

- Incentives for innovation: Oversight should include incentives for the development of new genetic tests so as to ensure patient access to new tests, particularly those for rare diseases and those that can improve current treatment decision-making for life-threatening diseases.

B. *Tools in the FDA's Regulatory "Toolbox"*

Premarket review is the regulatory function for which FDA is perhaps most well-known, and it is also the one most frequently cited for creating unreasonable burdens and delays. For some medical products, premarket review serves a vital purpose: It prevents unsafe and ineffective products from entering the market and ensures that products determined to be safe and effective are accompanied by appropriate information and warnings. For other products, such as those with a long history of safe use or with a low risk of adverse events, premarket review is unnecessary. Thus, FDA requires premarket review for implantable heart valves, for example, but not for adhesive bandages.

Even products for which premarket review is not required, however, are subject to other FDA requirements addressing product manufacture, use and record keeping. These regulatory tools tend to be less burdensome and time consuming than premarket review, but they also play a vital part in ensuring both the accountability of manufacturers and a product's safe, effective use in the marketplace over time. For example, manufacturers must register with the agency and list the products manufactured. This provides FDA with contact information in case of a problem with the product, and also provides data on the type of products on the market and number of manufacturers for them. Second, products regulated by FDA are subject to prohibitions on "adulteration" and "misbranding."[189] This allows FDA a means to sanction, through civil or criminal penalties, companies that are distributing products injurious to health or making false or misleading claims or that otherwise violate the statute. Third, companies manufacturing FDA-regulated products must report any known adverse events associated with their products. FDA can then issue alerts to manufacturers and end users of products found to have a safety problem and work with the manufacturer to correct them. FDA can also order the recall of medical devices it deems injurious to health. Thus, FDA oversight of products provides numerous tools by which the agency can ensure that products it regulates are safe and can alert the public to product dangers.

For some genetic tests—those with a long history of clinical use and for which the gene-disease link is well established—it would hardly make sense to require a laboratory to demonstrate clinical validity. But for newer tests, particularly those identifying diseases caused by the interactions between multiples genes and between genes and the environment, physicians and patients need to know what data support the use of the test and for what purposes.

Additionally, even for tests with established clinical validity, there is a need to ensure that they are performed accurately, that data collection is ongoing and is applied to update tests, that information provided to clinicians and patients about test interpretation is clear and understandable and that there is a mechanism to identify and correct errors when they are made.

How can these goals be achieved? There are many possible approaches to this question. Each regulatory approach has its own attendant benefits and limita-

[189] The Federal Food, Drug and Cosmetic Act of 1938, 21 U.S.C. § 301(a) (1994).

tions. With respect to other technologies, however, the FDA has demonstrated significant flexibility in tailoring its regulatory tools to create tiered requirements for varying degrees of risk.[190] FDA itself contemplated a flexible regulatory approach toward genetic testing when it issued its ASR rule, commenting that, in the future, "[a]dditional controls [for genetic tests] might include a broad array of approaches, ranging from full premarket review by FDA to use of third parties to evaluate analytical or clinical performance of the tests."[191]

Clearly, a one-size-fits-all approach will not achieve a proper balance between protecting the public from the harms of tests lacking proper validation while promoting development of and access to new and innovative tests. Instead, a tiered approach that matches the level of risk to the degree of oversight is necessary. Regulations should also place an equal burden on tests posing similar risks, regardless of the manner in which testing is performed.

C. *Options*

The following options reflect the range of possible approaches to FDA regulation of genetic tests. They are not intended to be mutually exclusive.

Option 1: Registration and listing by all laboratories offering genetic LDTs:

- FDA would require all laboratories offering laboratory developed genetic tests to register with the agency and to provide the name of the laboratory, its address and the laboratory director's name and contact information.
- Laboratories would be required to list in the database the types of genetic tests they perform, the indications for which each test is performed and the number of tests performed per year or, if the test is newly offered, the prevalence of the tested disease or condition in the population.
- Registration and listing information would be maintained by FDA in a publicly-accessible database.

Option 2: FDA establishes a genetic test database:

- The registry would contain information from registration and listing (Option 1)
- In addition, clinical laboratories would be required to submit to the registry summary information on analytic and clinical validity at the time a new test was offered.
- Tests currently on the market could remain on the market for a specified period of time while preparing their submissions.
- FDA would develop submission guidelines and a template for electronic submission.
- Certain categories of LDTs would not be required to submit information, e.g., LDTs that make only minor modifications to FDA-approved test kits, or LDTs below a certain testing volume.

Option 3: FDA inspection and CLIA/FDA collaboration:

- FDA would have authority to inspect clinical laboratory records demonstrating the clinical validity of LDTs. Such files must be maintained under CLIA, but CLIA inspectors do not always evaluate the clinical validity of the tests during inspection. FDA, in conjunction with CMS, would develop a guidance

[190] Human Cells, Tissues, and Cellular and Tissue-Based Products, 21 C.F.R. § 1271.3 (1996).
[191] 62 Fed. Reg. 62,244.

document outlining the type of data required to support clinical validity. Such inspections would be preceded by notice. If FDA determined there was insufficient evidence of clinical validity, FDA would notify CMS of its concern. If CMS declined to undertake enforcement action, FDA could undertake enforcement action under the FDCA.

Option 4: Requirement for premarket notification:

- The FDA would require laboratories to notify the agency ninety days before offering a new LDT. Notification would include a summary of analytical and clinical validity data. FDA may ask for more extensive data submission if the submission is determined to be insufficient. If FDA did not respond, the laboratory could market the test, and FDA could not later require more data absent evidence of public health risk.
- FDA would develop criteria for tests likely to be eligible for premarket notification.
- Certain LDTs, such as LDTs that make only minor modifications to FDA-approved test kits, or LDTs below a certain testing volume, would be exempt from the data submission element of notification.

Option 5: Class II special controls:

- FDA would classify all genetic LDTs as class II devices subject to special controls.
- FDA would develop Class II special control documents for LDTs addressing what information the laboratory must provide in the test report, including intended use, analytical and clinical validity and test limitations.
- LDTs could remain on the market pending the issuance of special control documents.
- Certain LDTs, such as LDTs that make only minor modifications to FDA-approved test kits, or LDTs below a certain testing volume, would be exempt from special controls requirements.

Option 6: Premarket review for high-risk genetic LDTs:

- FDA would require 510(k) submission for new genetic LDTs for serious conditions, where results could influence selection or dosing of therapy, or where the methodology used is not supported by adequate data.
- FDA could not require a laboratory to submit a PMA unless it determined that the type of data needed to establish safety and effectiveness could not be provided within 510(k) framework.
- High-risk LDTs for low-volume tests (tests performed fewer than a certain number of times per year or for diseases occurring below a certain frequency in the population) would be exempt from premarket review, but would be required to be labeled to indicate FDA had not reviewed them.

Option 7: Adverse event reporting for all laboratories offering LDTs:

- All laboratories offering genetic LDTs would be required to report to FDA any adverse events associated with the test of which they are aware, and corrective actions that were taken. An adverse event means a substantive error in test result reporting as well as any negative consequence (death, delay in treatment, wrong treatment provided) from that error. Each laboratory would establish an

adverse event hotline and designate personnel responsible for handling adverse event reports.

Option 8: FDA market incentives for rare-disease tests:

- FDA would grant Humanitarian Device Exemptions[192] for genetic LDTs for rare diseases, and permit them to be approved without clinical validity data, provided that such data were developed postmarket. FDA would waive the requirement for documentation that devices costing more than $250 do not exceed the costs of research, development, fabrication and distribution[193] since the cost of developing LDTs will likely be much higher.

VII. CONCLUSION

For more than a decade federal advisory committees have been raising concerns about the adequacy of genetic testing oversight, and have identified FDA as a key player in ensuring the safety and effectiveness of these tests. Yet FDA's involvement in genetic testing oversight has been intermittent and has proceeded in the absence of the articulation of coherent guiding principles. During this same period, genetic testing has gone from an esoteric enterprise for predominantly rare diseases to a mainstream part of medical care. Thus, advances in clinical genetic testing have far outpaced the regulatory framework needed to assure its safety and effectiveness. In addition to posing risk to the public, the status quo creates arbitrary regulatory distinctions that disadvantage test manufacturers while privileging clinical laboratories, and creates an unstable business climate for both test manufacturers and clinical laboratories that may deter investment in new and innovative tests. The success of genetic testing therefore depends on the development of a coherent framework for oversight that both provides adequate assurance of the safety and effectiveness of genetic tests and establishes an equitable and stable regulatory playing field.

[192] A Humanitarian Device Exemption (HDE) is "an application that is similar to a premarket approval (PMA) application, but exempt from the effectiveness requirements of sections 514 and 515 of the [FDCA]." Food & Drug Admin., Guidance for Industry and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers (July 18, 2006), *available at* http://www.fda.gov/cdrh/ode/guidance/1381.html; *see* The Federal Food, Drug and Cosmetic Act of 1938, 21 U.S.C. § 510(m)(2) (1994).

[193] 21 U.S.C. § 510(m)(3) provides that devices granted an HDE may not be sold "for an amount that exceeds the costs of research and development, fabrication and distribution of the device." 21 C.F.R. §814.104(5) provides that companies seeking an HDE and charging more than $250 must submit to FDA "a report by an independent certified public accountant" or "an attestation by a responsible individual of the organization" that verifies that "the amount charged does not exceed the costs of the device's research, development, fabrication and distribution."

Table: FDA letters sent by OIVD between January and December 2006 to clinical labs or companies offering genetic testing

Company Name	Products and Claims	FDA concern	Provisions of statute allegedly violated	Action Requested by FDA
Baylor College of Medicine, Medical Genetics Laboratories[1]	Chromosomal Microarray Analysis A microarray and analytical software intended for the diagnosis of prenatal, pediatric and adult genetic disorders that provides information that could help the physician make decisions about management of pregnancy or help guide medical decisions for the baby after delivery	No record of premarket review by FDA	Section 201(h) – device definition	Meeting
Clinical Data[2]	FAMILION Genetic test for cardiac channelopathies Also, nutrigenomic tests being sold directly to consumers through Genaissance	No record of premarket review by FDA	Section 201(h) – device definition	Meeting
Combimatrix[3]	Microarray based Constitutional Genetic Array Test (CGAT) Intended for diagnosis of mental retardation anomalies and identification of common genetic disorders	FDA aware that company planning to market the test as laboratory service. No record of premarket review by FDA	Section 201(h) – device definition	Meeting
CyGene[4]	Thrombosis DNA Analysis Osteoporosis DNA Analysis Glaucoma and Macular Degradation DNA Analysis Intended to assess risk factors that help determine the probability that an asymptomatic (healthy) individual with or without family history of a certain disease might develop that disease	No record of premarket review by FDA	Device definition	Meeting
Genelex[5]	Several genetic tests, including pharmacogenetic tests and tests which are intended to evaluate heart and bone health, detoxification and antioxidant capacity, insulin sensitivity and tissue repair	No record of premarket review by FDA	Section 201(h)	Meeting

[1] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Arthur Beaudet, Chairman, Dept. of Molecular & Human Genetics, Baylor College of Med. (Apr. 24, 2006) (on file with FDA).

[2] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Drew Fromkin, President, Clinical Data, Inc. (Aug. 2, 2006) (on file with FDA).

[3] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Amit Kumar, Chairman, CombiMatrix Corp. (July 19, 2006) (on file with FDA).

[4] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Martin Munzer, President, CyGene Laboratories, Inc. (Oct. 10, 2006) (on file with FDA).

[5] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Howard C. Coleman, Chairman, Genelex Corp. (Aug. 20, 2006) (on file with FDA).

Company Name	Products and Claims	FDA concern	Provisions of statute allegedly violated	Action Requested by FDA
Genomic Health[6]	Oncotype Dx Intended for use in predicting the likelihood of breast cancer recurrence in women with newly diagnosed, early stage breast cancer, in predicting distant disease recurrence, and in assessing a patient's benefit from certain types of chemotherapy	No record of premarket review by FDA	Section 201(h) defines medical device as "any instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article, including any component, part or accessory, which is intended for use in the diagnosis of disease or other conditions"	Meeting
Genox[7]	Various tests intended for use by physicians practicing anti-aging and preventive medicine in evaluating oxidative stress associated with diseases including Down syndrome, atherosclerosis, diabetes and macular degeneration	No record of premarket review by FDA	Section 201(h) – device definition	Meeting
Intergenetics, Inc.[8]	OncoVue Intended for use in determining a woman's lifetime risk of breast cancer	No record of premarket review by FDA	Section 201(h) – definition of medical device	Meeting
Laboratory Corporation of America[9]	PreGen-Plus Laboratory developed stool-based DNA testing service	Laboratory claims DNA-capture devices are general purpose lab equipment. FDA disagrees, says they are not generally useful in other lab methods. Laboratory also argues that test system not subject to 510(k) because not commercially available or used independently to diagnose disease. FDA says premarket determination required.	Adulterated and misbranded because no premarket approval or clearance in effect	Response requested in 30 days regarding how company will comply with FDA requirements

[6] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Randy Scott, Chairman, Genomic Health, Inc. (Jan. 23, 2006) (on file with FDA).

[7] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Rama Rathnam, President, Genox Corp. (July 19, 2006) (on file with FDA).

[8] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Craig D. Shimasaki, President, InterGenetics, Inc. (Jan. 27, 2006) (on file with FDA).

[9] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Bradford T. Smith, Executive Vice President, Lab. Corp. of America (Jan. 12, 2006) (on file with FDA).

Company Name	Products and Claims	FDA concern	Provisions of statute allegedly violated	Action Requested by FDA
Market America[10]	Gene SNP DNA Screening Panel and Revised Report Examines specific SNP variations in the customer's chromosomes and then offers nutritional formulas and recommends lifestyle changes based on the DNA analysis	No record of premarket review by FDA	Section 201(h)	Meeting
Salugen[11]	GenoTrim Intended to identify a patient's 'specific genetic pathways that may contribute to unique tendencies to gain and retain weight.	No record of premarket review by FDA	Section 201(h) – device definition	Meeting
Sciona[12]	Cellf Comprehensive Test Intended to analyze 19 genes that related to how the body manages bone health, heart health, antioxidant and detoxification, insulin resistance and inflammation.	No record of premarket review by FDA	Section 201(h)	Meeting
Seryx[13]	Signature Genetics Intended to help physicians deliver individualized care, including predicting the effectiveness of medications, the potential for adverse drug reactions and potential unsafe drug reactions.	No record of premarket review by FDA	Section 201(h) – definition of medical device	Meeting
Signature Genomics[14]	SignatureChip Designed to detect unbalanced chromosome rearrangements associated with known microdeletion syndromes and malformation/mental retardation.	No record of premarket review by FDA	Section 201(h) – definition of medical device	Meeting

[10] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Edward Medina, Market America, Inc. (Sept. 20, 2006) (on file with FDA).

[11] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Brian Meshkin, President, Salugen, Inc. (Aug. 4, 2006) (on file with FDA).

[12] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Peter Vitulli, President, Sciona, Inc. (Aug. 20, 2006) (on file with FDA).

[13] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Patrick Rambaud, President, Seryx LLC (Feb. 23, 2006) (on file with FDA).

[14] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Lisa G. Shaffer, Director, Signature Genomic Laboratories (Mar. 6, 2006) (on file with FDA).

Company Name	Products and Claims	FDA concern	Provisions of statute allegedly violated	Action Requested by FDA
Sure Gene[15]	AssureGene Intended to help family members determine the risk of having a child with schizophrenia and related disorders, as well as identify children at increased risk of developing schizophrenia later in life	No record of premarket review by FDA	Section 201(h)	Meeting

[15] Letter from Steven I. Gutman, Director, FDA. Office for In Vitro Diagnostic Devices Evaluation and Safety, to Timothy L. Ramsey, CEO, Sure Gene, LLC (Aug. 17, 2006) (on file with FDA).