

PERSONALIZED MEDICINE REGULATION
PATHWAYS FOR
OVERSIGHT
OF DIAGNOSTICS

PERSONALIZED MEDICINE REGULATION: PATHWAYS FOR OVERSIGHT OF DIAGNOSTICS

EXECUTIVE SUMMARY

WHILE THE POTENTIAL BENEFITS OF PERSONALIZED HEALTH CARE ARE STRAIGHTFORWARD—knowing what works, knowing why it works, knowing whom it works for, and applying that knowledge to address patient needs—the intervening variables that determine the pace of personalized medicine’s development and adoption are far more complex. Among those variables are the laws and regulations that govern personalized medicine products and services used in clinical practice.

THE PERSONALIZED MEDICINE COALITION COMMISSIONED THIS PAPER TO PROVIDE an overview of the different and evolving regulatory environments pertaining to personalized medicine products and services so that all stakeholders can share a common understanding of the current system. It outlines the various laws and regulations that govern personalized medicine diagnostics, which are currently marketed as products and professional services used in clinical practice. It also describes legislative proposals intended to change the way personalized medicine products and services are regulated.

After defining the status of personalized medicine today, the paper discusses the different organizations which play a role in regulating personalized medicine and laboratory developed tests (LDTs) in particular. It also defines key policy questions, and describes the basic regulatory framework for LDTs that could potentially be subject to regulation by the U.S. Food and Drug Administration (“FDA”), should FDA’s jurisdiction be upheld, including the ongoing regulation of LDTs by the Centers for Medicare and Medicaid Services (“CMS”) under the Clinical Laboratory Improvement Amendments (“CLIA”).

While the FDA has long regulated in vitro diagnostic products (“IVDs”) as medical devices—and has taken the position that it has the authority to regulate LTDs—the agency has exercised what it describes as “enforcement discretion” and has not actively regulated them. The agency has stated its intention to apply risk-based oversight of LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (“FDC Act”); yet some stakeholders have questioned whether the FDA has jurisdiction and whether it is an appropriate regulatory authority to do so. A variety of FDA enforcement actions, rules, citizen petitions, and guidance documents outlined in the paper shed light on FDA’s evolving policies pertaining to LDTs.

The paper also includes a description of different proposals regarding how best to regulate LDTs, including:

- the appropriate regulatory organization to oversee LDTs;
- the avoidance of duplicate and/or conflicting regulations or oversight;
- the creation of a regulatory framework based on risk to patients;
- the generation of additional standards to assess LDTs’ clinical validity;
- and whether any additional review or submission of data should be required before an LDT is performed in clinical practice.

I. INTRODUCTION

THE UNITED STATES HAS BEEN A GLOBAL LEADER IN THE KEY DISCOVERIES that serve as the foundation of personalized medicine and has preceded most other nations in the clinical application of a large number of the resultant discoveries. Two separate agencies in the Department of Health and Human Services (HHS) hold primary responsibility for overseeing personalized medicine services and products used in clinics, laboratories, and hospitals around the country. While health care professionals have wide discretion to diagnose and treat individual patients as they deem appropriate, pharmaceutical products, biological products, and medical devices used to provide personalized medicine in patient care must clear a number of regulatory hurdles set forth by the FDA before being placed into interstate commerce.¹

In addition, CMS, its approved accreditation agencies, or states, where applicable, must certify clinical laboratories as meeting and maintaining certain standards before those labs are able to perform tests and interpret and report the results to health care providers and, where permitted by law, to consumers.² As both the FDA's and CMS's regulatory schemes include certain exemptions to their requirements for medical products and laboratory tests used in clinical investigation or research,³ this paper outlines the regulations that apply under various circumstances to the development and offering of personalized medicine products and services used in U.S. clinical practice, focusing on diagnostics.

While this paper addresses regulatory requirements permitting use and performance of personalized medicine products and services in clinical practice, it does not address other policy issues relevant to personalized medicine, including: public investment in personalized medicine or the costs of research; coverage and reimbursement of personalized medicine tools (e.g. third party payment for medical goods and services); taxation of personalized medicine products and services; or medical malpractice and product liability issues potentially resulting from use or performance of personalized medicine products or services.

Some contend that the regulation of personalized medicine tests and services by multiple agencies, and the different standards that have been applied, has led to confusion and uncertainty in the market. The FDA has struggled with whether and how to regulate LDTs. LDTs traditionally have been, and currently are, required to meet CMS's clinical laboratory requirements; it is unclear, however, whether and when FDA requirements may also apply to certain types of LDTs performed in personalized medicine and what position the FDA and CMS will take on this issue in the future. After setting forth the regulatory frameworks governing personalized medicine products and services, this paper outlines positions and proposals set forth by different stakeholders regarding how best to regulate LDTs.

II. WHAT IS PERSONALIZED MEDICINE?

THE PHRASE “PERSONALIZED MEDICINE” CAN COVER A VAST ARRAY OF INNOVATIVE products and services that draw on advances in technology to shape medical treatments to the needs of individual patients. The President’s Council of Advisors on Science and Technology defined personalized medicine as “the tailoring of medical treatment to the specific characteristics of each patient.”⁴ This includes the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Discoveries from the mapping of the human genome have enhanced our ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or who have a particular response to a certain treatment method. Information about genes, proteins, and genetic dispositions both inspires the development of new treatments and improves our ability to decipher what treatments may be either particularly useful or unhelpful for certain individuals.

The clinical benefits of personalized medicine are still evolving, but there are five areas of present development which show great promise:⁵

- **Diagnosis/Prognosis**—to assess particular subtypes of a disease or the unique characteristics of a condition
- **Treatment prediction**—to analyze whether a patient, infectious agent, or tumor with particular characteristics will respond to a certain treatment
- **Dosing**—to determine appropriate amounts or strengths of treatment to administer to a particular individual
- **Safety**—to anticipate adverse treatment reactions in certain subpopulations
- **Monitoring**—to track and observe a patient’s response to a course of treatment, in part to evaluate any necessary modifications to the chosen treatment course

Targeted therapeutics and companion diagnostics are two important components of products and services that enable personalized medicine. Targeted therapeutics, usually drugs or biologics, are treatments designed to benefit a particular subpopulation, or whose use in another subpopulation might be especially disadvantageous or require different dosing. Companion diagnostics are accompanying laboratory tests and professional services identifying or measuring genes, proteins, or other substances associated with a targeted therapeutic or relevant to a subpopulation of patients that can yield important information on the proper course of treatment for a particular patient.

Note that in 2011, draft guidance on companion diagnostics was jointly released by FDA's Center for Drug Evaluation and Research, Center for Devices and Radiological Health, and Center for Biologics Evaluation and Research. The guidance defined a companion diagnostic device as an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.⁶ In contrast, personalized medicine products and services that provide prognostic information about a patient's disease, e.g., the likelihood of disease recurrence, although important in an individual's treatment management, are not essential for the safe and effective use of a therapeutic product and thus are not considered companion diagnostics.

An example of personalized medicine relates to some breast cancers that include over-expression of human epidermal growth factor receptor 2 (HER2), a cell surface protein. Targeted therapeutics like Herceptin (trastuzumab) and Tykerb (lapatinib) have been designed to help treat women whose breast cancers include over-expression of HER2. A diagnostic test (companion diagnostic) that indicates whether a woman's tumor cells are over-expressing HER2 can help establish whether a woman might benefit from treatment with one of these targeted therapeutics. As such, the companion diagnostic for detecting HER2 over-expression is essential for the effective use of the targeted therapeutic for treating HER2 over-expression breast cancers. In such a case, the treating physician may use a companion diagnostic together with a therapeutic to tailor treatment to a particular patient's needs.

As this example illustrates, companion diagnostic tests are a vital part of personalized medicine that can yield crucial information necessary for guiding therapeutic treatment decisions and unlocking the potential of targeted therapeutics to serve their desired populations. Other diagnostic tests used in personalized medicine include those that provide information on patient prognosis but may not be essential for determining the safe and effective use of a specific therapeutic agent and therefore are not companion diagnostics. For instance, another laboratory test for women with certain kinds of breast cancer analyzes how a particular patient's tumor genes are expressed, yielding information on the risk that her breast cancer will recur in the future. In combination with other information, this analysis of the patient's tumor gene expression serves as a prognostic marker.

These personalized medicine diagnostic tests can be either IVD products, regulated by the FDA under the device authorities, and/or LDT services, regulated by CMS under CLIA. As discussed in more detail below, companion diagnostics can be a subset of either IVDs or LDTs that bear particular significance in personalized medicine.

There are also other products that assist personalized medicine, including software or computerized algorithms designed to support health care professionals in determining the proper course of care for a specific patient. Additionally, products sold to consumers for use in their own homes could be considered a type of personalized medicine that can produce information about a person's genetic make-up or other characteristics that might be used to guide appropriate preventive treatments or lifestyle changes.

III. WHO MIGHT REGULATE LABORATORY DEVELOPED TESTS USED IN PERSONALIZED MEDICINE?

THERE ARE SEVERAL DIFFERENT ENTITIES THAT PLAY A ROLE IN THE REGULATION of laboratories and LDTs, including companion diagnostics, performed in personalized medicine.

A. FOOD AND DRUG ADMINISTRATION

The FDA regulates pharmaceutical products, biological products, and medical devices placed into interstate commerce. The FDA issues rules regarding which of the foregoing products may be legally sold in the U.S. FDA requirements generally include premarket review of devices to support safety and effectiveness, postmarket adverse event reporting, a process for product recalls, and quality system regulation for manufacturing and other processes. Funding for the FDA's activities comes both from annual appropriations as well as user fees collected from regulated industry. Some types of tests used in personalized medicine, such as IVDs, constitute medical devices, thereby falling within FDA's regulatory jurisdiction. Section IV of this paper describes the FDA's regulation of medical devices, and discusses whether and when the FDA might also have authority to regulate LDTs under the medical device authorities of the FDC Act.

B. CENTERS FOR MEDICARE AND MEDICAID SERVICES

CMS oversees regulations of all clinical laboratories that perform testing on human samples for diagnosis, prevention or treatment, or for the assessment of an individual's health. CMS, through its CLIA authority, certifies clinical laboratories as meeting certain standards, which vary depending on the types of tests being performed, and that certification allows the laboratories to perform testing on samples like human blood, urine, or tissue, including companion diagnostic testing and other testing relevant to personalized medicine. CLIA requirements generally include qualifications for laboratory personnel, quality systems for lab testing, oversight of test requests and reports, and proficiency testing. In 2012, approximately 225,000 clinical laboratories fell under CMS's jurisdiction.⁷ Almost all funding for CMS's activities in this area comes from fees CMS collects from the regulated laboratories. Section IV below discusses relevant CMS requirements for clinical laboratories that perform testing for use in personalized medicine.

C. FEDERAL TRADE COMMISSION

The Federal Trade Commission (FTC) has broad post-market authority to oversee the advertising of products and services in the United States. For example, the FTC prohibits advertising that is false, misleading, unfair, or deceptive, whether relating to IVD test kits or LDTs.

D. LABORATORY ACCREDITATION ORGANIZATIONS

In addition to obtaining CLIA certification directly from CMS, typically through state agencies that survey labs for compliance with CLIA requirements, clinical labs also can be CLIA certified through being accredited by one of the independent accreditation agencies approved by CMS for this purpose. These include the College of American Pathologists (CAP) and COLA, among others. Before approving an independent accreditation agency, CMS must determine that the accreditation agency's standards are equal to or more stringent than those set forth in the CLIA regulations, though the standards may differ from CLIA and may include additional requirements.⁸

E. STATE LABORATORY REGULATORY AGENCIES

The federal standards for clinical labs are set forth in the CLIA regulations, but several states also have their own requirements for clinical laboratories operating in their state or testing specimens that originate in the state. These state regulations can differ from, and may be more stringent than, the CLIA requirements. California, for example, requires that all laboratories conducting testing in that state, or on California specimens, obtain a California laboratory license. A handful of other states, including New York and Florida, also require that laboratories conducting tests on specimens originating in that state must be licensed by the state, regardless of where the laboratory is located (e.g., a California lab testing specimens from New York must obtain a New York laboratory license in addition to its California license). As discussed below, the CLIA statute also gives states the option to apply to CMS for exemption from CLIA if the state's own lab standards are at least as stringent as those under CLIA. Currently, New York and Washington State have obtained CLIA exemption.

IV. REGULATION OF LABORATORY DEVELOPED TESTS

ONE KEY QUESTION IN THE REGULATION OF LDTs, INCLUDING COMPANION DIAGNOSTIC LDTs used in personalized medicine, is whether some or all of these tests may require review and marketing approval/clearance by the FDA. Some observers question the relationship of possible FDA regulation to existing CLIA and state regulations and how those would be reconciled if FDA regulates some or all LDTs. While some products sold commercially to clinical laboratories (e.g., IVDs) are currently regulated by the FDA, there is not clear agreement regarding the appropriate nature and scope of the regulation of LDT services, which many argue do not clearly fall within the scope of FDA's jurisdiction to regulate. The FDA has indicated its evolving concerns regarding the rapid expansion of the number and type of LDTs being offered, including concerns about possible patient risks associated with the intended uses of certain LDTs.

A. FDA REGULATION

1. General Overview

The primary statute governing the FDA is the FDC Act.⁹ Different centers within the FDA regulate different types of medical products. In general, the Center for Devices and Radiological Health (CDRH) regulates medical devices; the Center for Drug Evaluation and Research (CDER) regulates drugs, including targeted therapeutics; and the Center for Biologics Evaluation and Research (CBER) regulates biological products, as well as some in vitro reagents for uses like blood typing and HIV screening. Products that contain more than one kind of medical product (a drug and a device or a device and a biologic) are classified as combination products. Combination products may be regulated by multiple FDA centers. CDRH includes an Office of In Vitro Diagnostics and Radiological Health (“OIR”) that regulates IVDs.¹⁰ The OIR includes a Director of Personalized Medicine.

Under the FDC Act, the FDA has authority to regulate medical devices. A medical device is defined as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is ... intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals.”¹¹ This definition includes in vitro reagents, which can be key components of some tests used in personalized medicine. FDA defines commercial distribution as “any distribution of a device intended for human use which is held or offered for sale.”¹²

FDA regulations further define IVDs as: “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 examination of specimens taken from the human body.”¹³ Many products used in personalized medicine may include instruments, reagents, and systems intended for use in the diagnosis of disease or other conditions in order to cure, mitigate, treat, or prevent those diseases or conditions. As discussed below, products and services incorporating these components have been subject to varying levels of FDA regulation over time.

The FDA regulates medical devices, including IVD products, both before they are sold in the market and after they are available to end users. FDA oversees products under its jurisdiction through regulations as well as through guidance documents that provide insight into FDA’s policies but which are not legally binding.¹⁴

Before a company can sell a new medical device in commerce, the manufacturer must obtain some form of regulatory approval from FDA, unless the device is exempt from these requirements. Generally, the FDA may “clear” medical devices for marketing via the 510(k) notification or may approve devices through the premarket approval (“PMA”) process. Medical devices that are substantially equivalent to a predicate, meaning another legally marketed class I or class II device that did not require PMA approval, typically may be cleared through the 510(k) process. Novel and/or high-risk devices that are not substantially equivalent to any legally marketed predicate device require PMA approval.¹⁵ A third regulatory pathway known as *de novo* reclassification was created for low to moderate risk devices that lack a predicate device.

2. Risk-based Classification

The specific regulations applicable to a medical device, including the different premarket review pathways discussed above, depend on the medical device’s classification in FDA’s risk-based system. The FDA has classified most types of medical devices into one of three classes (class I, II, or III) based on the level of controls that the FDA has deemed necessary to reasonably assure a device’s safety and effectiveness.

CLASS I DEVICES are subject to general controls, such as requirements for device labeling,¹⁶ device listing with the FDA,¹⁷ 510(k) premarket notification, and compliance with the FDA’s quality systems regulations (“QSR”).¹⁸ General controls apply to all devices. Most class I devices are exempt from 510(k) premarket review requirements, and in some cases, are also exempt from compliance with FDA’s quality systems regulations, other than minimal record keeping and reporting requirements.¹⁹

CLASS II DEVICES are subject to general and special controls, such as performance standards, postmarket surveillance, and FDA guidelines. Most class II devices require premarket review by the FDA through the 510(k) clearance process prior to commercialization.

CLASS III DEVICES are generally implantable devices; devices represented to be used for life-sustaining or life-supporting purposes; or, new devices that have not been found substantially

equivalent to legally marketed class I or II devices. Class III devices require approval of a PMA application and are the most stringently regulated.

In general, the premarket review process in some circumstances can take several months to years and may include significant costs to collect the information needed for the FDA to allow a device to be sold in the market. Additionally, those submitting requests to the FDA for permission to sell their devices must pay submission fees that in FY13 range from \$2,480 to \$248,000, depending upon the type of submission and whether the FDA classifies the sponsor as a small business.²⁰

Once the FDA grants permission for a device to be introduced into commerce, those selling the device have additional obligations to comply with FDA regulations in areas such as manufacturing, product labeling, adverse event reporting, and product recalls.²¹ Most of the burden of FDA regulations falls to those introducing medical devices into commerce, as well as those with some responsibility in the manufacturing, export, or import processes. Health professionals who use medical devices in a clinical setting may also have obligations to report to the FDA any adverse events that could be related to a medical device.²²

3. In Vitro Diagnostics (IVDs)

The FDA has long regulated commercially distributed IVD products, including in vitro diagnostic reagents and equipment for laboratory testing. IVDs can include well-established tests, such as determining whether a patient has high hormone levels or certain bacterial infections, as well as tests of a person's DNA and related DNA-products. IVDs often come in kits that contain the reagents, equipment, and calibrators needed to run the test and produce a result for clinical use. Kits are most often class II or class III medical devices, requiring that the FDA review information about the device before it can be introduced into commerce. These kits also include labeling regarding how to run the assay and, importantly, the specific uses for which FDA has granted clearance or approval.

In the FDA premarket review process, the entity wishing to sell an IVD test kit submits a packet of materials to the FDA. Applicants often need to provide the FDA with information about bench testing on the device. For IVDs, this information frequently includes evidence that the test is precise, accurate, and reliable. The FDA often also requires that those seeking to sell IVD test kits submit data from clinical studies of the device. This data would validate that the test performs as intended and labeled in clinical use.

4. Enforcement Discretion over Laboratory Developed Tests (LDTs)

Even when an agency like the FDA has authority to regulate a given product, it may choose not to actively exercise that authority. For instance, although the FDA has the authority to regulate certain kinds of medical devices, it may choose not to actively enforce those regulations under all circumstances. This principle is known as the exercise of enforcement discretion.²³ Historically, the

FDA has enforced its regulations with respect to IVD products developed by medical device manufacturers and sold to clinical laboratories for use in clinical practice. The FDA has maintained that it also has authority to regulate LDTs,²⁴ but this claim has been disputed. In practice, the FDA has exercised regulatory authority over LDTs to varying degrees under different circumstances.

a. FDA Action and Inaction

Since the early 1990s, there have been many examples of FDA's varying regulation of LDTs. For instance, in 2005, the FDA issued a letter to Agendia BV regarding the company's offering of the MammaPrint assay. The assay was offered by the Agendia laboratory as a gene expression profiling service that provided prognostic information to determine the risk of progressive disease and survival in breast cancer patients. The FDA viewed the MammaPrint testing service as potential commercial distribution of a medical device and in the 2005 letter to the company requested a meeting to discuss the proper regulation of the product. Agendia ultimately sought and successfully received clearance for the MammaPrint assay as an in vitro diagnostic multivariate index assay ("IVDMIA") through the de novo reclassification process, rather than by arguing that the LDT should be regulated only under CLIA and not by the FDA. The FDA has sent similar letters to other companies, not all of whom have agreed to pursue FDA clearance or approval for their products or services.

In another example, the FDA permitted an LDT to serve as a companion diagnostic for a targeted therapeutic, without the LDT being subject to FDA regulation as a medical device. Monogram Biosciences, Inc. provides the HIV diagnostic Trofile co-receptor tropism assay, a biomarker with an established and clinically accepted utility. The company provided the assay simultaneously with FDA's 2007 approval of Pfizer's HIV drug Selzentry (maraviroc). The Trofile test was used for patient selection in Selzentry's clinical development program, and detectable tropism is stated as a specific indication for the drug. As a result, in order to guide the use of Selzentry, the FDA approved the drug with labeling requiring that tropism testing be performed to identify patients infected with CCR5-tropic HIV-1. This was the first HIV drug approval to require the use of a diagnostic to identify patients who are most likely to respond to the drug, in this case a class of drugs known as CCR5 antagonists. The labeling requirement for the drug did not, however, specify the Trofile assay. Rather, the drug's labeling only required that diagnostic testing be performed to identify tropism.

Although the FDA has appeared to exercise enforcement discretion with respect to Monogram and the Trofile LDT (without requiring premarket review or applying other FDA regulations to the Tropism assay), FDA officials have since indicated that this practice of allowing an LDT to be a companion diagnostic, i.e., those tests that are essential for the use of a targeted therapeutic without FDA market clearance or approval is not a practice that should be repeated.²⁵

Moreover, OIR's Director of Personalized Medicine has stated that an LDT that falls within the scope of a companion diagnostic to a drug or biologic would need to undergo premarket review by FDA.²⁶

There are also several examples where the FDA has threatened to take enforcement action related to tests offered by CLIA-certified clinical laboratories. In cases where the FDA deems there is a high degree of cooperation between an IVD manufacturer and a CLIA-certified laboratory, the agency may sometimes view the manufacturer and the lab to be joint manufacturers of a regulated medical device, resulting in the need for the filing of a 510(k) notice or a PMA submission. For instance, in the FDA's October 11, 2007 warning letter to Exact Sciences Corporation regarding certain test services offered by LabCorp, the agency established a boundary beyond which FDA views the degree of cooperation between a manufacturer and the clinical laboratory when developing and/or validating an LDT to require FDA premarket review. The following is a relevant excerpt from that letter:

Based on the information collected [during a CMS inspection of LabCorp's facilities], FDA has determined that [EXACT Sciences'] PreGen-Plus assay [for colorectal screening] is a test that was designed, developed, validated, and marketed by EXACT Sciences rather than a test that was developed and validated by LabCorp. As such, this device is not within the scope of laboratory developed tests over which the agency has traditionally applied enforcement discretion. For example, information collected at LabCorp indicates EXACT has provided instructions for use, validation information, and performance claims to LabCorp for the PreGen-Plus assay. In addition, equipment and reagents that are required for the test are specified by EXACT (and, in some cases, provided by EXACT), including [equipment] for sample preparation.

Several groups have filed formal citizen petitions requesting that the FDA either more actively regulate LDTs or, alternatively, cease its efforts to regulate the tests and related services. In 2006, the Washington Legal Foundation petitioned the FDA to not regulate LDTs on the grounds that Congress assigned this responsibility elsewhere (to CMS).²⁷ Genentech filed another citizen petition in 2008, requesting that the FDA exercise its claimed legal authority to regulate LDTs.²⁸ The American Clinical Laboratory Association ("ACLA") filed a response to Genentech's petition arguing, among other points, that the FDA lacked jurisdiction over LDTs.²⁹ The FDA has not formally and substantively responded to any of these petitions.

b. FDA Policies

The FDA has also issued a rule and several guidance documents that address regulation of LDTs. In the 1990s, the FDA declined to exercise what it regarded as its jurisdiction over LDTs, but instead implemented a rule regulating the use, labeling, and distribution of analyte

specific reagents (“ASRs”), certain kinds of in vitro reagents often sold to clinical laboratories.³⁰ Analyte specific reagents measure a single substance, such as an antibody, receptor protein, or nucleic acid sequence. These reagents often serve as the building blocks for LDTs. The FDA’s regulations for ASRs exempt most of these reagents from the FDA premarket review process, although they do require compliance with QSRs and restrict sales of ASRs to those laboratories certified under CLIA to perform high complexity tests. The regulations also limit the information that may be included in the reagent’s labeling.³¹

Rather than focusing on the LDT itself, the ASR regulations established restrictions addressing how ASRs could be used to develop and perform in certain IVDs and LDTs. The final rule was the culmination of a lengthy process in which the FDA sought to determine how, if at all, it would regulate clinical laboratories that develop LDTs using ingredients purchased from third-party biological and chemical suppliers. Nonetheless, the report of results generated by tests using ASRs must include a disclaimer regarding the lack of FDA clearance or approval. The required disclaimer states: “This test was developed and its performance characteristics determined by (laboratory name). It has not been cleared or approved by the U.S. Food and Drug Administration.”³²

Subsequent to the FDA’s issuance of the ASR rule, the FDA expressed its view that the diagnostic industry’s implementation of the rule appeared to be an attempt to circumvent premarket review of new IVDs. Consequently, the FDA began issuing warning letters and other pronouncements concerning these practices, and in 2006–2007 ultimately issued a guidance document for ASRs to clarify the FDA’s position concerning this set of products.³³ Concurrently, the FDA also issued a draft guidance document for in vitro diagnostic multivariate index assays (IVDMIA).³⁴ In this draft guidance, the FDA identified a category of LDTs for which FDA would end enforcement discretion and require clinical laboratories developing such LDTs to seek premarket review.

After a February 2007 public meeting and numerous comments from industry and affected trade associations, the FDA issued a revised version of the IVDMIA draft guidance in July 2007.³⁵ This revised draft guidance defined IVDMIA more specifically and provided examples of the category of clinical laboratory developed assays that would be subject to FDA oversight. Specifically, FDA defined IVDMIA subject to FDA regulation as assays that: (1) combine the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a “classification,” “score,” “index,” etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease; and (2) provide a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.

Although the FDA indicated its intent to require premarket review of these clinical laboratory tests, including possibly requiring data from clinical testing, the FDA’s approach towards this category of LDTs was criticized by many stakeholders and has not been implemented. In announcing a subsequent public meeting held in 2010, the FDA indicated that it was considering a more comprehensive framework for regulating LDTs.³⁶ Like FDA regulation of IVDs, such a

framework would likely prescribe different regulations based on varying levels of risk associated with different laboratory developed tests.³⁷

In 2011, the FDA issued a draft guidance document pertaining to the process for approving targeted therapeutics and their accompanying companion diagnostics that provided additional context for understanding the FDA's current approach towards LDTs.³⁸ As discussed in the examples above, the FDA has not always required that a companion diagnostic accompanying a targeted therapeutic be subject to the FDA premarket review process.³⁹ However, according to this 2011 draft policy, where a companion diagnostic is essential for the safe and effective use of a targeted therapeutic, the FDA would regulate the companion diagnostic as a medical device and subject that test to the FDA premarket review process. This guidance document does not specifically reference LDTs and has not yet been finalized.

c. Notice to Congress before Issuing New Guidance on LDTs

Under the Food and Drug Administration Safety and Innovation Act (FDASIA) enacted on July 9, 2012, the FDA must give Congress 60 days' notice before issuing any new draft or final guidance on the regulation of LDTs under the FDC Act.⁴⁰ This notice must describe in detail the actions that the FDA intends to carry out with regards to regulating LDTs. Apart from this request for prior notice of any planned FDA guidance, Congress has not yet taken any more explicit steps to weigh in on the FDA's recent approach towards LDTs.

B. CMS REGULATION

1. General Overview

Separate from any FDA regulations, CMS oversees the regulation of tests performed in clinical laboratories under the Clinical Laboratory Improvement Amendments (CLIA) to the Public Health Service Act (PHSA) and the extensive regulations implementing CLIA.⁴¹ All clinical laboratories performing testing on human samples in the U.S. are subject to CLIA regulation, whether the tests they perform are developed by the performing lab or are sold to them by test kit manufacturers.⁴² Under CLIA, "laboratory" is defined broadly as any facility for the "examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."⁴³ The CLIA statute and regulations are intended to ensure that clinical laboratories consistently provide test results that are both valid and reliable (e.g., accurate). In requiring that test results be valid, the CLIA statute makes no distinction between analytical and clinical validity.⁴⁴

Clinical laboratories, as noted earlier, must receive CLIA certification in order to conduct testing, and certification is specific to each lab location. Laboratories receive certificates that allow them to perform certain types of tests, based on both the complexity of the test and the type of tests the lab performs (e.g. routine chemistry, bacteriology, cytogenetics). CLIA certification may

be granted through federal survey (usually HHS contracts with state laboratory agencies in each state to oversee CLIA certification within the state); through accreditation by private entities that have been approved by HHS for purposes of assuring CLIA compliance (e.g., COLA and the CAP⁴⁵); or, instead, a state may apply to HHS for exemption from CLIA, if the state can demonstrate that its own laboratory standards are equal to or more stringent than CLIA requirements (currently Washington state and New York have CLIA exemptions). Regulated laboratories pay CLIA certificate fees for each laboratory location; fees range from \$150 to \$7,490 biennially, based on the type of certificate and test volume.⁴⁶

2. Complexity-Based Categories

CMS requires CLIA-certified labs to adhere to various requirements based on the complexity level of the tests performed by the lab and the type of tests a clinical laboratory performs. Most clinical laboratory tests fall into one of three categories: (1) high complexity; (2) moderate complexity; or (3) waived, which requires the lowest level of regulation.⁴⁷ Labs performing higher complexity tests are subject to more stringent CLIA requirements. In general, the CLIA regulations include requirements related to laboratory personnel qualifications, quality control and assessment systems and procedures, patient test management (e.g., how test requests and test reports are handled), and proficiency testing requirements.⁴⁸

Personnel requirements address qualifications and responsibilities for particular laboratory positions, such as the lab director and technical consultant. Quality control requirements are designed to ensure that a test system is working properly and that the test results are accurate, while quality assurance rules require ongoing laboratory monitoring and performance improvement. Patient test management regulations address how labs handle test requests, accessioning, record keeping, referral, and results reporting. For proficiency testing, a lab must successfully test samples of a known type in order to prove its proficiency in performing a particular test and to receive a certificate for a given testing specialty.

Although CMS determines the requirements that apply to labs performing tests of a certain type or complexity, the CLIA regulations give the FDA responsibility for deciding which of the three categories for test complexity a test falls within, based on criteria set forth in the regulations. Typically, the complexity categorization is determined by the FDA as part of the clearance process for the test kit or device, but LDTs, which are not subject to this FDA clearance process, are considered to be “high complexity” tests. Due to their default categorization as high complexity tests, LDTs are subject to the most stringent CLIA regulations.

3. Requirements for LDTs

Under the CLIA regulations, clinical laboratories are permitted to either: (1) modify existing FDA-approved or cleared tests, or (2) develop their own tests (LDTs), provided that the

laboratory facility adheres to a number of specific requirements. These requirements dictate that: “[e]ach laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book [sic] procedures) or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:

- (i) Accuracy.
- (ii) Precision.
- (iii) Analytical sensitivity.
- (iv) Analytical specificity to include interfering substances.
- (v) Reportable range of test results for the test system.
- (vi) Reference intervals (normal values).
- (vii) Any other performance characteristic required for test performance.”⁴⁹

Once the performance specifications for the LDT are established, the laboratory must determine the type and frequency of calibration and the control procedures for the test system.⁵⁰ For all test systems, CLIA requires that calibration verification must be conducted at a minimum of every 6 months.⁵¹ Daily quality control and function checks must be performed prior to patient testing, to ensure an instrument is functioning correctly and is properly calibrated. Additionally, when function checks are critical to test performance, the laboratory must have mechanisms in place to monitor items such as nucleic acid amplification equipment and cell washers. These requirements vary for different types of test systems.⁵²

This system of CLIA regulations allows for a lab to develop a test, validate the test’s performance specifications in its lab, and then proceed to perform the test in clinical practice without needing to provide notification to or receive advance approval from an outside body, unless applicable state law provides otherwise (e.g., New York). Since LDTs default to being high complexity tests under CLIA, labs offering these tests must still comply with the most stringent CLIA requirements relating to quality control and quality assurance. Laboratories offering these tests are also subject to survey and inspection to verify that they are complying with the appropriate CMS requirements.

While CLIA regulations do not explicitly require a laboratory to verify an LDT’s clinical validity, the CLIA regulations do require laboratory directors to ensure that “the test methodologies selected have the capability of providing the quality of results required for patient care.”⁵³ In addition, CLIA requires that each high complexity laboratory have a clinical consultant who is available to provide consultation to the laboratory’s clients to ensure that appropriate tests are ordered to meet the clinical expectations, that reports of test results include pertinent information required for specific patient interpretation, and that consultation is available and

provided to the laboratory's clients on matters related to the quality of the test results reported and their interpretation.⁵⁴

Further, some laboratories choose to comply with more demanding accreditation standards and the specific requirements of accreditation agencies may differ from the CLIA requirements as long as they meet or exceed the standards set forth in CLIA regulations. For instance, the CAP, which accredits many laboratories as complying with CLIA requirements, requires documentation related to clinical validity in its Molecular Pathology Inspection Checklist.⁵⁵ Additionally, the state of Washington reviews some LDTs for clinical validity, and the state of New York also requires the submission of clinical validity data for non-FDA-cleared or -approved tests.⁵⁶

Tests falling within particular CLIA specialties must also adhere to additional proficiency testing requirements for that specialty. Some personalized medicine tests may fall within existing CLIA specialties and be subject to these requirements, and all personalized medicine tests are subject to general proficiency testing requirements. For example, although there is no CLIA specialty specific to genetic tests, there are specific proficiency testing standards for the cytogenetics sub-specialty. Alternative proficiency assessment must be performed twice a year for laboratory tests which do not fall within a CLIA-designated specialty. In 2008, an advisory committee to the Secretary of HHS endorsed CMS's decision not to create a CLIA specialty for genetic tests.⁵⁷

C. COMPARISON OF FDA AND CMS REGULATION OF DIAGNOSTIC TESTS

As outlined above, FDA's approach to regulating the manufacture and commercial distribution of diagnostic medical devices and CMS's approach to regulating diagnostic test services performed by laboratories differ in several key areas. There are different regulatory objectives and review processes for CLIA requirements regarding LDTs and for FDA requirements pertaining to the 510(k) and PMA pathways. Among these differences, for example, are the following:

- **REQUIREMENTS FOR EVIDENCE OF ANALYTICAL AND CLINICAL VALIDITY.**

FDA regulated personalized medicine IVD diagnostic tests require clinical evidence to support the intended use and indications for the test (i.e. the test's ability to identify or predict the disorder of interest) in addition to requiring review of analytical performance. CLIA regulations for LDT diagnostic test services require the demonstration of analytical performance and that the test methodologies selected have the capability of providing the quality of results required for patient care. However, this information is not required to be reviewed by an external body prior to the lab offering the test service unless required by state law. Some laboratories voluntarily choose to comply with more demanding accreditation standards that include assessments of whether clinical performance has been established. Satisfying these higher standards may be required to submit clinical validity data for non-FDA-cleared or approved tests in order to obtain licensure under certain state law requirements.

- **TIME TO MARKET.** The premarket review process for personalized medicine diagnostic tests can take several months to years and may include significant costs to collect the information needed for FDA clearance or approval. Furthermore, FDA can require approval or clearance of new premarket submissions if changes are made to diagnostic tests after FDA approval or clearance. Laboratories using FDA cleared or approved tests must still subject these tests to CLIA quality controls. CMS's CLIA regulations permit a laboratory to develop a test, validate the test's performance specifications in its lab, which can take many months, and then proceed to perform the test in clinical practice, without the need to provide notification to or receive approval from an outside body unless required under applicable state law. This pathway also applies to any modifications or new claims made to LDTs, although some accreditation agencies require labs to notify them with updates to their testing menu.
- **LABELING AND PROMOTION.** FDA regulations permit the promotion of IVD diagnostic tests according to their cleared or approved intended uses only. Under FDA regulations, IVD manufacturers may not advertise or promote a device for uncleared/unapproved indications or in a manner that is inconsistent with labeled claims. CMS regulations do not restrict the clinical claims for LDTs developed by CLIA laboratories. It is important to note, however, that the advertisement of clinical claims for LDTs is subject to oversight by the FTC and applicable state law. Further, FDA regulations require that laboratory results reported using LDTs developed from ASRs carry the following disclaimer: "This test was developed and its performance characteristics determined by (laboratory name). It has not been cleared or approved by the U.S. Food and Drug Administration."⁵⁸
- **QUALITY PROGRAMS & POSTMARKET CAPABILITIES.** The quality programs required for IVD and LDT diagnostic tests have different elements, many of which may or may not overlap. These differences include that FDA's Quality System Regulations ("QSR") require design controls for development and validation of diagnostic assays, purchasing requirements, and other manufacturing and process controls for commercially distributed product, but these items are not required under CLIA regulations for LDT services performed solely in the laboratory.⁵⁹ Rather, LDTs typically follow good laboratory practice standards and CLIA requirements for laboratory personnel, quality control, proficiency testing, and on-going monitoring and assessment to ensure that a test system is working properly, the test results are accurate, and the results are of the quality required for patient care. IVD diagnostic test manufacturers are subject to periodic FDA inspections to ensure compliance with QSRs while CLIA laboratories are subject to their own quality system policies and procedures and mandatory biennial inspections for compliance with CLIA regulations, including proficiency testing requirements.⁶⁰

In terms of postmarket authority, FDA regulations require the reporting of adverse events potentially associated with a product and also provide a process for product recalls. The CLIA regulations require labs to establish and follow policies and procedures to monitor, assess, and correct any problems identified in their analytic systems, to establish and follow corrective action policies and procedures, and to provide notice and implement corrections when errors in patient test results are detected.⁶¹

- **FINANCIAL CONSEQUENCES.** CLIA laboratories currently pay a user fee for initial laboratory certification and biennial re-certification based on the volume of clinical testing. The CLIA program funded almost entirely through laboratory user fees. IVD manufacturers are subject to varying levels of fees for IVD diagnostic premarket submissions and pay an annual establishment registration fee under an FDA program funded partially through industry user fees and partially through annual appropriations. As a result of the Patient Protection and Affordable Care Act,⁶² beginning on January 1, 2013, IVDs, along with other medical devices (with a few exemptions) will be subject to a 2.3% federal excise tax. If LDTs were to be fully regulated by FDA as IVDs, many of these additional fees and taxes, if not waived, would apply to laboratories performing LDTs, in addition to the CLIA user fees that laboratories already pay.

V. PAST AND RECENT PROPOSALS FOR REGULATION OF LDTs

Different sectors of the medical community have articulated a range of views on the appropriate regulation of clinical laboratory tests, specifically LDTs. This section discusses several different stakeholder positions on how best to regulate these tests. Some within the clinical laboratory community argue that the current regulatory system best allows for the kinds of rapid innovation found in personalized medicine and facilitates patient and physician access to valid tests that would not otherwise be available. Others, including developers of IVD test kits, have articulated concerns about what they regard as the currently bifurcated pathway and differing criteria, in light of the growing complexity and use of LDTs, and in light of the evolving needs in personalized medicine.

A number of legislative proposals have been put forward for regulation of LDTs, none of which have been enacted. A brief overview of these proposals provides some backdrop on the various efforts concerning the regulation of personalized medicine products and services and sets the stage for efforts moving forward. In sum:

- Senate Bill S.736, the “Laboratory Test Improvement Act of 2007” (co-sponsored by Senator Edward Kennedy (D-MA) and Senator Gordon Smith (R-OR)),⁶³ would have amended the FDC Act to regulate all LDTs as medical devices. The intent of this bill was to give the FDA clear authority for the oversight of LDTs. The regulatory framework used in this model was based on the FDA’s existing medical device classification scheme and would have required all clinical laboratories with LDTs to register with the FDA as device manufacturers. CLIA laboratories providing test results based on an LDT would then be required to submit documentation to the FDA on the intended use and analytic and clinical validity for each LDT. FDA would, in turn, review the LDT submissions and decide whether 510(k) clearance or PMA approval was needed based on the categorization of the LDT as a class II or class III medical device.
- Senate Bill S.976, the “Genomics and Personalized Medicine Act of 2007” (co-sponsored by Senator Barack Obama (D-IL) with Senators Richard Burr (R-NC) and Robert Menendez (D-NJ)),⁶⁴ outlined a mechanism to improve the government’s understanding and development of a framework to enhance the innovation of genomics research in disease diagnosis, drug safety, and the identification of novel treatments. This bill would have established a collaborative group, “the Genomics and Personalized Medicine Interagency Working Group,” to “facilitate collaboration, coordination, and integration of activities within the Department of Health and Human Services (DHHS) and other federal agencies.”

- The “Better Evaluation and Treatment Through Essential Regulatory Reform for Patient Care Act,” for which discussion drafts were circulated by Senator Orrin Hatch’s (R-UT) office, but not introduced in Congress, sought to achieve consensus amongst stakeholders, i.e., clinical laboratories, diagnostic companies, patient groups, investors, and companion therapeutic manufacturers. This proposal, should it be introduced and enacted, would create a new regulatory classification for all in vitro diagnostic tests (LDTs and IVD tests collectively called in vitro diagnostic products (“IVDP”)), separate and distinct from medical devices. In this proposed regulatory model, review of premarket submissions for IVDPs would be based on a risk scale associated with the risk to the patient as a result of inaccurate information provided from these products and services. High and moderate risk IVDPs would require FDA premarket review prior to commercial introduction and low risk IVDPs would be exempt from FDA premarket review. However, this proposal would establish a new “competent and reliable scientific evidence” standard for evaluating the evidence to support the accuracy and reliability of an IVDP. The proposal also seeks to avoid duplication of quality systems regulations between the FDA and CLIA and would maintain CLIA oversight of laboratory operations. Existing LDTs and IVD tests would be grandfathered under the new regulatory structure.
- H.R. 3207, the Modernizing Laboratory Test Standards for Patients Act of 2011, was introduced by Representative Michael Burgess (R-TX) in October 2011.⁶⁵ This legislation would create a review process through CMS for LDTs, while clarifying that LDTs are not medical devices as defined in the FDC Act and therefore are not subject to FDA jurisdiction. The CMS review process would include assessments of a test’s analytical validity and clinical validity for certain identified clinical uses. Laboratories could continue to use a test while CMS completed its clinical validity review process, and currently marketed tests would remain in clinical use unless there was a significant modification to the test or CMS believed there was insufficient evidence to support a test’s clinical validity. H.R. 3207 would also create a registry for all LDTs and direct-to-consumer DNA tests, listing their intended uses/purposes and information about analytical and clinical validity. This legislative proposal would also create obligations for adverse event reporting to CMS, as well as give CMS recall-like authority over clinical tests whose submissions do not demonstrate clinical validity and pose a risk of immediate harm to the public health. Financing for CMS’s additional regulatory activities could be derived entirely through new CMS user fees.

A. KEY ISSUES

One common feature of many positions on the regulation of LDTs is that the regulatory system should be risk-based. Risk is usually viewed in terms of the risk to a patient should a test function incorrectly or provide an inaccurate result when used in clinical practice (i.e., a false positive or false negative result and the attendant ramifications for incorrectly managing a patient's care, including in comparison to the current standard of care). Other issues addressed by proposals on LDT regulation include the current scope of the FDA's jurisdiction to regulate them. Many policy proposals seek to explicitly limit or expand the FDA's regulatory authority over LDTs. Other proposals seek to address the degree to which current the FDA and CMS regulations might overlap. In general, many argue that having similar regulations implemented simultaneously by multiple agencies is overly burdensome and an inefficient use of resources. In particular, there is concern in the lab community that FDA regulation of LDTs would subject laboratories to regulation by both FDA and CMS, while IVD manufacturers would be subject only to FDA regulation.

Another central feature of the various regulatory proposals for LDTs is the extent to which either the FDA or CMS oversee the analytical validity or clinical validity of these tests. Some stakeholders maintain that current CLIA standards either adequately evaluate tests developed and performed within clinical laboratories or can be enhanced to do so. Others argue that LDT services are not rigorously tested for clinical performance in the same manner as IVD products that go through the FDA premarket review process. Many of the proposals described below seek to strengthen requirements for demonstrating an LDT's clinical validity. These proposals differ as to whether reviews of clinical validity are best handled by CMS or the FDA. Partly because the FDA would likely need to seek new resources in order to conduct reviews of clinical validity, proposed changes to the existing regulatory landscape also contemplate the amount of resources that would be required to conduct these reviews and whether the FDA has these resources. Representative positions of several stakeholders are discussed in more detail below.

B. AMERICAN CLINICAL LABORATORY ASSOCIATION (ACLA)

ACLA has indicated in public statements that it supports appropriate additional regulatory oversight of LDTs by CMS through enhancement of the existing CLIA regulatory framework but does not support regulation of LDTs as medical devices by the FDA. ACLA endorsed H.R. 3207, the Modernizing Laboratory Test Standards for Patients Act of 2011, introduced by Representative Michael Burgess (R-TX) in October 2011.⁶⁷ According to the association, all ACLA members produce and perform LDTs and thus will be directly affected by change in the oversight of these tests.

The ACLA website states that "independent and hospital based clinical laboratories, physician pathology practices, and university medical centers all develop and validate tests in their own laboratories for physician directed patient care. Examples of low risk, well established LDTs range

from Pap smears, manual blood cell counts, erythrocyte sedimentation rates, microbiology cultures and susceptibility tests, among many others—to the new advanced diagnostics that derive from the mapping of the human genome and help fulfill the promise of personalized medicine. There are many more examples of LDTs in use that allow for rapid response to keep pace with our nation’s most costly and menacing chronic diseases and emerging public health threats.”

ACLA’s website also states the association’s position as follows: “Applying a strict paradigm based upon the regulation of ‘traditional’ medical devices and applied to all LDTs will have major consequences to clinical laboratories—whose businesses and facilities are set up for far different purposes and in far different ways than those of device manufacturers, even IVD manufacturers—and will place those laboratories in jeopardy of being unable to comply and, in many cases, unable to continue important work in the development of cutting-edge LDTs. This will have the unintended effects of slowing the availability of important tests and negatively affecting patient care.”

C. COLLEGE OF AMERICAN PATHOLOGISTS (CAP)

CAP has indicated in public statements that “LDTs are developed and validated by the laboratory that performs clinical testing—LDTs are not ‘test systems’ produced by independent manufacturers and sold as stand-alone products to testing facilities. Although there are currently several thousand LDTs used in clinical care, the vast majority of clinical laboratory tests performed today are not LDTs and rely on packaged test systems produced by independent manufacturers and sold to testing facilities. The large majority of LDTs are used ‘locally’ within a region and not marketed nationwide.” With this in mind, CAP supports a risk-based system with additional regulatory oversight for LDTs.⁶⁸ CAP has proposed strengthening CLIA standards for all categories of LDTs and stratifying oversight based on risk with a targeted FDA review of high risk LDTs. This proposal would create three categories of LDTs based on risk (low, moderate, high). Risk would be defined based on both the consequence of an incorrect test result or interpretation leading to serious morbidity or mortality as well as the level of understanding of the test or the transparency of the test’s methodology. Low and moderate risk LDTs would be subject to strengthened CLIA standards for analytical and clinical validity, while high risk LDTs would be subject to FDA review. All laboratories would continue to be subject to CLIA regulations in addition to FDA regulations.

D. ADVANCED MEDICAL TECHNOLOGY ASSOCIATION (ADVAMED)

The Advanced Medical Technology Association (AdvaMed) and its in vitro diagnostics division AdvaMedDx, have indicated in public statements support for “AdvaMed’s Risk Based Approach” proposal. According to the association, this proposal “aims to modernize the regulation of all diagnostics. The approach is grounded on the view that no matter where a test is made, it presents the same risk benefit profile for patients. Key principles include that FDA should oversee the safety

and effectiveness of all diagnostics, including those FDA currently considers to be lab developed tests (LDTs). At the same time, FDA should focus its resources on novel technologies with the highest risks and exempt lower risk tests from premarket submission.”

“The proposal is consistent with global risk management principles and sets forth a rational transparent tier triage process intended to support the overall review process for test developers and facilitate access to new safe and effective technologies. It specifically outlines a decision process for risk assessment of clinical lab tests, which includes clinical use of a test as well as novelty of analyte, novelty of technology, experience or training of person performing the test, and factors that reduce or mitigate risk.”

“Notably, the proposal supports a transitioned approach for which focus would be on higher risk tests which present the highest or unknown risk to patients. Examples of higher risk tests include tests supporting the safe and effective use of therapeutics (or companion diagnostics), tests for cancer diagnosis, tests that directly or very strongly influence management of serious disease, and tests for serious or fatal communicable diseases. This position also emphasizes that patient access to specialized test categories (i.e., rare diseases, rare usage) should not be disadvantaged. Underlying the approach is the view that in light of widespread and differing use of LDTs since the Medical Device Amendments of 1976 and cited gaps in LDT regulation (e.g., premarket clinical validation, quality system regulation, adverse event reporting system, process for recalls, etc.), FDA is best equipped with the infrastructure and expertise to assure the safety and effectiveness of diagnostic tests. AdvaMed believes such an approach supports innovation, the future of personalized medicine, and overall public health.”⁶⁹

E. ASSOCIATION FOR MOLECULAR PATHOLOGY (AMP)

AMP members develop, perform, and interpret LDTs in academic medical centers, community hospitals, and commercial reference laboratories. In January 2010, AMP released its position on oversight of LDTs.⁷⁰ The AMP position emphasizes the essential role of LDTs in medical practice and patient management and recommends that oversight for most tests should be within a CLIA enhanced environment with strengthened enforcement capability, proficiency testing, and increased transparency of laboratory information. The position notes that some tests may require greater scrutiny from regulators such as tests with nontransparent algorithms. In May 2012, AMP announced the formation of a working group to consider the numerous proposals introduced since FDA declared its intention to abandon its regulatory policy of enforcement discretion toward some LDTs and to publish a refined position and recommendations. The AMP Working Group plans to complete its work in early 2013.

VI. CONCLUSION

There appear to be significant differences of opinion among stakeholders on the optimal level for regulation of LDTs. This paper has described the various organizations that play a role in regulating LDTs, as well as some of the particular regulations that might apply to these tests. Although the FDA has indicated its intent to regulate LDTs, it remains to be seen what such a framework would entail, how it would interact with CLIA and applicable state law, when it would be issued, and whether it would survive a challenge from those disputing FDA's claim of authority to regulate LDTs. The different stakeholder positions discussed in this paper outline alternative systems for LDT regulation to either replace or enhance any FDA proposals, including proposals to strengthen CMS requirements under CLIA.

Given the contrasting FDA and CMS regulations in this area, stakeholders in the laboratory sector view proposals for oversight by FDA in addition to the existing CLIA regulatory framework as creating a disproportionate burden on laboratories that would slow innovation to the detriment of physicians and patients and strain both laboratory personnel and financial resources. Some other stakeholders view the current regulatory landscape as no longer sustainable in light of the growing availability and complexity of LDTs over the past 30 years and argue that a risk-based FDA approach can sustain and promote innovation. Whether the various stakeholders working with Congress, the interested government agencies, and other authoritative bodies can reach an understanding on the optimal path forward remains to be seen.

ENDNOTES

- ¹ 21 U.S.C. §§ 331, 393; 42 U.S.C. § 262.
- ² 42 U.S.C. § 263a; 42 C.F.R. § 493.2.
- ³ *See, e.g.* 21 U.S.C. § 360j(g); 42 C.F.R. § 493.3(b)(2).
- ⁴ President's Council of Advisors on Science and Technology. Priorities for Personalized Medicine. September 2008. (Available at: http://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf).
- ⁵ Radensky, P. Regulation of Biomarker Clinical Laboratory Tests Used in Personalized Medicine. *BioPharm Int'l*. 2008; 21 (12). (Available at: <http://www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=568932&pageID=1&sk=&date=>).
- ⁶ Food and Drug Administration. Draft Guidance for Industry and Food and Drug Administration Staff - In Vitro Companion Diagnostic Devices. July 14, 2011 (Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm>).
- ⁷ Centers for Medicare & Medicaid Services. Clinical Laboratory Improvement Amendments (CLIA). CMS Website. (Available at: <http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=clia/>).
- ⁸ Centers for Medicare & Medicaid Services. Accreditation Organizations/Exempt States. CMS Website. (Available at: http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Accreditation_Organizations_and_Exempt_States.html).
- ⁹ 21 U.S.C. § 301 *et seq.*
- ¹⁰ This FDA office was formerly known as the Office of In Vitro Diagnostics Device Evaluation and Safety ("OIVD").
- ¹¹ 21 U.S.C. § 321(h).
- ¹² 21 C.F.R. § 807.3(b).
- ¹³ 21 C.F.R. § 809.3(a).
- ¹⁴ FDA Website. Guidance Documents – About Guidance. (Available at: <http://www.fda.gov/MedicalDevices/Device-RegulationandGuidance/GuidanceDocuments/ucm108067.htm>).
- ¹⁵ 21 U.S.C. §§ 360(k), 360e(a)-(b).
- ¹⁶ 21 C.F.R. §§ 801, 809.10.
- ¹⁷ 21 C.F.R. § 807.20.
- ¹⁸ 21 C.F.R. § 820.
- ¹⁹ Reporting requirements can include adverse event reporting and notifications to the FDA when safety events occur that could be associated with a medical device. 21 C.F.R. Part 803.
- ²⁰ The size of the fee depends on whether the company is a small business and whether the application is a 510(k) premarket notification or a Premarket Approval Application (PMA). MDUFA III Fees. FDA Website. (Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MDUFAlIIII/ucm313673.htm>).
- ²¹ *See* 21 C.F.R. Part 806.
- ²² 21 U.S.C. § 360i(b); 21 C.F.R. § 803, 803.30-803.33.
- ²³ Secretary's Advisory Committee on Genetics, Health, and Society. U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services. April 2008, p. 32. (Available at: http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf).

- ²⁴ Medical Devices; Classification/Reclassification/Restricted Devices; Analyte Specific Reagents; Final Rule. 62 Fed. Reg. 62243, 62249 (Nov. 21 1997).
- ²⁵ Thomae, M. Companion Diagnostics: LDTs Need Approval Too. Myraqa Website. June 26, 2012. (Available at: http://myraqa.com/blog/companion_diagnostics_ldts_app).
- ²⁶ FDA on Personalized Medicine. IN PERSON. *IVD Technology*. November/December 2010, 22-27.
- ²⁷ Washington Legal Foundation. Citizen Petition Regarding FDA Regulation of Laboratory Developed Tests. Sept. 28, 2006. (Available at: <http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/06p0402/06p-0402-cp00001-01-vol1.pdf>). Many others have discussed the foundation and scope of FDA's jurisdiction to regulate LDTs. Hathaway, C. et al. The Changing Regulatory Landscape for *In Vitro* Diagnostic Medical Devices: Increased Scrutiny of Laboratory Developed Tests and the Safety of Personalized Medicine. *FDLI Update*. Sept./Oct. 2010, p. 21-24; Javitt, G. In Search of a Coherent Framework: Options for FDA Oversight of Genetic Tests. *Food & Drug Law J.* 62: 617-652 (2007); Kahan, J. and Tiedy-Stevenson, S. Parallel Universes Collide. *IVD Technology*. Mar. 1, 2007. (Available at: <http://www.ivdtechnology.com/article/parallel-universes-collide>); Kazon, P. Recent FDA Actions on LDTs and Genetic Testing: Where Have We Been and Where Are We Heading? *BNA Medical Devices Law & Industry Report*. Aug. 25, 2010; Weiss, R. The Long and Winding Regulatory Road for Laboratory-Developed Tests. *Am J Clin Pathol.* 2012; 138:20-26.
- ²⁸ Genentech. Citizen Petition; Regulation of *In Vitro* Diagnostic Tests. Dec. 5, 2008. (Available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0638-0001>).
- ²⁹ American Clinical Laboratory Association. Comments to Genentech Citizen Petition. Feb. 18, 2009. (Available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0638-0006>).
- ³⁰ 21 C.F.R. §§ 809.10(e), 809.30, 864.4020.
- ³¹ Food and Drug Administration. Guidance for Industry and FDA Staff - Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions. Sept. 14, 2007. (Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078423.htm>).
- ³² 21 C.F.R. § 809.30(e).
- ³³ Food and Drug Administration. Guidance for Industry and FDA Staff - Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions. Sept. 14, 2007. (Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078423.htm>).
- ³⁴ Food and Drug Administration. Draft Guidance for Industry, Clinical Laboratories, and FDA Staff - *In Vitro* Diagnostic Multivariate Index Assays. Sept. 7, 2006. (Available at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0347-gdl0001.pdf>).
- ³⁵ Food and Drug Administration. Draft Guidance for Industry, Clinical Laboratories, and FDA Staff - *In Vitro* Diagnostic Multivariate Index Assays. July 26, 2007. (Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm>).
- ³⁶ Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments. 75 Fed. Reg. 34463 (June 17, 2010). <http://www.gpo.gov/fdsys/pkg/FR-2010-06-17/html/2010-14654.htm>; Food and Drug Administration. FDA/CDRH Public Meeting: Oversight of Laboratory Developed Tests (LDTs), Date July 19-20, 2010. FDA Website. (Available at: <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm>); Genome Web. FDA Shelves IVD MIA Final Guidelines in Order to Focus on Overall LDT Regulation. June 23, 2010. (Available at: <http://www.genomeweb.com/dxpgx/fda-shelves-ivdmia-final-guidelines-order-focus-overall-ldt-regulation>).
- ³⁷ Oversight of Laboratory Developed Tests, 75 Fed. Reg. at 34464.
- ³⁸ Food and Drug Administration. Draft Guidance for Industry and Food and Drug Administration Staff - *In Vitro* Companion Diagnostic Devices. July 14, 2011 (Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm>).

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- ⁴⁰ Food and Drug Administration Safety and Innovation Act of 2012, Pub. L. 112-144, § 1143.
- ⁴¹ 42 U.S.C. § 263a.
- ⁴² Research labs that do not report patient-specific results are exempt from CLIA. 42 C.F.R. § 493.3(b)(2).
- ⁴³ 42 U.S.C. § 263a(a); 42 C.F.R. § 493.2.
- ⁴⁴ See 42 U.S.C. § 263a(f)(1).
- ⁴⁵ College of American Pathologists Website. (Available at: http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=accreditation).
- ⁴⁶ CLIA Certificate Fee Schedule. Centers for Medicare & Medicaid Services Website. (Available at: http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_Certificate_Fee_Schedule.html).
- ⁴⁷ 42 C.F.R. § 493.5. There is another category of tests termed Provider Performed Microscopy, but these are tests performed on-site by health care providers for their own patients and involve relatively simple microscopic exams.
- ⁴⁸ 42 U.S.C. § 263a(f)(3).
- ⁴⁹ 42 C.F.R. § 493.1253(b)(2). CLIA State Operations Manual Appendix C, Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services (Rev. 1, May 21, 2004) provides additional detail on definitions of accuracy, precision, analytical sensitivity, analytical specificity, reporting ranges, and reference intervals. (Available at: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_c_lab.pdf).
- ⁵⁰ 42 C.F.R. § 493.1253(b)(3).
- ⁵¹ 42 C.F.R. § 493.1255.
- ⁵² 42 C.F.R. § 493.1254.
- ⁵³ 42 C.F.R. §§ 493.1407(e)(3)(i), 493.1445(e)(3)(i).
- ⁵⁴ 42 C.F.R. § 493.1457.
- ⁵⁵ ACLA Comments to Genentech Citizen Petition, at 6. (Available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0638-0006>).
- ⁵⁶ Secretary's Advisory Committee on Genetics, Health, and Society. Genetic Testing Report, p. 35-37.
- ⁵⁷ Secretary's Advisory Committee on Genetics, Health, and Society. Genetic Testing Report. Earlier in the 2000's, CMS did consider creating a genetics proficiency testing specialty. Clinical Laboratory Improvement Advisory Comm., Meeting Summary (Sept. 20-21, 2006). (Available at: <http://www.cdc.gov/cliac/cliac0906.aspx>); Dept. of Health & Human Serv. Regulatory Agenda, Pt. VIII, 71 Fed. Reg. 22,537 (Apr. 24, 2006); Notice of Intent; Genetic Testing Under the Clinical Laboratory Improvement Amendments, 65 Fed. Reg. 25,928 (May 4, 2000).
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MISSION

The Personalized Medicine Coalition (PMC), representing innovators, scientists, patients, providers and payers, promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health system. The Coalition's mission is to educate policymakers and the public about the power and potential of individualized health care and raise the profile of personalized medicine so that both patients and the health system will benefit from improved clinical care and increased overall value.



PERSONALIZED
MEDICINE COALITION

1710 Rhode Island Ave., NW
Suite 700
Washington, DC 20036

P: 202.589.1770

pmc@personalizedmedicinecoalition.org