Introduction
Since the first draft of the human genome was published in 2001, DNA sequencing technology has advanced at a remarkable pace. Launched in 1990, the Human Genome Project sought to sequence all three billion base pairs of the haploid human genome, an endeavor that took more than a decade and cost nearly three billion dollars. The subsequent development of so-called “next generation” sequencing (NGS) methods has raised the possibility that real-time, affordable genome sequencing will soon be widely available. Currently, NGS methods can be used to sequence up to 60 billion base pairs per day. Whole-genome sequencing costs an estimated $5,000-10,000, with that number predicted to fall to $1000 in the near future.

In the past few years, the availability of high-throughput NGS methods has led to a proliferation of potential and actual clinical applications for NGS. NGS therefore has the potential to usher in the long-awaited era of personalized medicine. On the other hand, the sheer amount of data generated by NGS threatens to overwhelm both physicians and patients. In addition, because NGS largely has been performed by clinical laboratories, the methodology has not been subject to direct governmental oversight, although the laboratories themselves are subject to oversight by the Center for Medicare and Medicaid Services (CMS) and by state governments. Clinical laboratories have begun to use NGS to develop numerous predictive genetic tests, including, for example, the fields of neurological disorders, oncology, and prenatal testing.

As a result of NGS’s growing use in clinical diagnosis, the Food and Drug Administration (FDA) has taken a more active interest in NGS, with some FDA employees publicly stating that the Agency has authority to regulate NGS based diagnostic tests. The intended target(s) and scope of such asserted authority is not yet clear, particularly since an NGS platform can be used for both basic research and clinical diagnostic use, and FDA indisputably lacks authority over the former. Some have raised concern that FDA regulation would stifle the progress of sequencing technology. Others support FDA regulation of NGS, arguing that regulations are needed to ensure the accuracy of diagnostic tests performed using the technology.

This article reviews the development of NGS and provides an overview of NGS methods. It describes the regulatory framework for the clinical laboratories that perform NGS under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and state law. It describes FDA’s current oversight approach for diagnostic products and tests, and the potential theories under which FDA might seek to regulate NGS. It also discusses the potential implications for NGS on the practice of medicine.
Development of NGS
Gene sequencing, the process of determining the order of nucleotides (the “letters”) in a sequence of DNA, was first developed in the 1970s. The dominant method, which was developed by Fred Sanger and is known as the di-deoxy method, starts with single-stranded template DNA and involves synthesizing the complementary strand by using the enzyme DNA polymerase and a mixture of all four nucleotides corresponding to the bases A, C, G, and T and a lower concentration of chemically modified terminator nucleotides with a radioactive tag attached. As the DNA strand is elongated, the DNA polymerase enzyme incorporates either a regular nucleotide, which allows DNA synthesis to continue, or one of the modified nucleotides, which terminates DNA synthesis at that position. Because there are millions of DNA molecules, and incorporating a terminating base is relatively rare, this results in DNA fragments of varying lengths. The fragments can be separated by using gel electrophoresis, and the order then can be determined by visualizing the fluorescent tag.

Since its creation, Sanger sequencing has been improved to allow automation and increased throughput. For example, modern methods typically involve the use of four different base-specific fluorescent dyes rather than radioactive labeled nucleotides, and capillary electrophoresis rather than gel electrophoresis. In addition, sequencing reactions generally take place in 96-well plates, which each contain a single template DNA molecule. Sanger sequencing, as improved through these mechanisms, historically has been considered to be the “gold standard” for sequencing and is widely used in both research and diagnostic settings.

Nevertheless, certain limitations of automated Sanger sequencing led to the need to develop new and improved sequencing technologies, particularly for sequencing large amounts of DNA, such as whole genomes. Since 2005, researchers have focused on developing new, high-throughput sequencing methods, which are referred to as next generation sequencing (NGS). There are various NGS methods, which rely on a combination of template preparation, sequencing and imaging, and genome alignment and assembly methods, in order to allow for rapid sequencing of large volumes of DNA at a significantly lower cost than traditional methods.

One feature that unifies all NGS methods is that they do not sequence the entire genome from end-to-end. Instead, they employ “massively parallel” sequencing — meaning running thousands of sequencing reactions simultaneously — of clonally amplified or single DNA molecules that are spatially separated. The substantial amounts of sequencing data generated by NGS methods must then be put into a coherent order to allow for interpretation, using either “alignment” to a known reference standard or “de novo” assembly. Each of these methods has its own challenges and limitations. A large variety of software programs for alignment or de novo assembly have been developed and made available to researchers.

In the past few years, the availability of high-throughput NGS methods has led to a proliferation of potential clinical applications for NGS, including the identification of common genetic variants that affect the development of neurological diseases or cancer, diagnosis of inherited disorders in infants, and prenatal screening. Although individual genomic tests developed by using NGS methods generally do not qualitatively differ from genomic tests developed using other technologies, such as microarrays, the amount of data that can be generated by NGS methods is much greater. Indeed, whole genome sequencing typically detects about 3-4 million sequence differences when compared to a reference sequence. Of those, typically 30,000-50,000 variants occur in the protein-coding portions of genes; these are the variants most likely to cause or contribute to health issues.

Some have raised concerns that the sheer volume of data generated by NGS threatens to overwhelm physi-
cians and patients.29 For example, one geneticist who participated in ClinSeq, a pilot clinical study of NGS, stated that the study subjects generally said upfront that they wanted all the available data returned to them.30 When it came time to return the results, however, the geneticist found that subjects often were “confused and overwhelmed” when the researchers returned results from a single variant that showed an unexpected risk for cancer susceptibility.31 What most surprised another geneticist was the reaction of some of the subjects’ treating physicians. That geneticist stated that, in many cases, physicians were “dismissive or angry” when the geneticists found a mutation that predisposes to cancer in a subject with no personal or family medical history.32

In addition to the volume of data, there are also difficulties in interpreting NGS results, particularly because most variants are uncharacterized and some are novel.33 Out of the 30,000–50,000 variants in the protein-coding regions of an individual’s genome, typically only three to eight provide “actionable” information for the patient.34 Moreover, no matter how advanced NGS technology and genetic testing become, there will always be some mutations that are of unknown significance because “the normal mutation rate will continue to generate a nearly infinite spectrum of genomic variation.”35

Even when NGS is used to identify a genetic disease known to be caused by a specific mutation, ensuring accurate results can be challenging. This is not only because many commonly used databases used to identify pathogenic sequences contain errors, but also due to variable quality of the primary medical research used to populate the databases.36

The vast quantities of data that can be generated with NGS, coupled with the challenges in interpreting such data, have led some to argue that NGS meth-ods need to be subject to appropriate regulation. The current regulatory framework, however, involves a patchwork of partially overlapping federal and state requirements that have not yet been fully developed.

Regulation of Clinical Laboratories

Federal Oversight of Clinical Laboratories

Clinical laboratories are regulated pursuant to the Clinical Laboratory Improvement Amendments of 1988 (CLIA),37 which is administered by the Centers for Medicare and Medicaid Services (CMS). CLIA defines a “clinical laboratory” as a facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.38

CLIA provides that “[n]o person may solicit or accept materials derived from the human body for laboratory examination or other procedure unless there is in effect for the laboratory a certificate issued by the Secretary under this section applicable to the category of examinations or procedures which includes such examination or procedure.”39

In enacting CLIA, Congress directed the Secretary of the Department of Health and Human Services (HHS) to establish standards to ensure the quality of all phases of laboratory testing, including pre-analytic (sample acquisition, handling, and storage), analytic (selection and performance of ordered tests), and post-analytic (interpretation and reporting of test results),40 and implementing regulations to address each of these aspects of testing.41 In the bill’s legislative history, Congress noted that errors in any of the phases of laboratory testing “can significantly undermine the overall accuracy and reliability of clinical laboratory testing.”42 Under CLIA, clinical laboratories are regulated according to the complexity of the tests or procedures they perform. Laboratory tests are categorized as waived or as low, moderate, or high complexity depending on factors such as the level of training or experience needed to perform the test.43 Clinical laboratories performing moderate or high complexity tests are subject to more stringent regulation than laboratories performing lower complexity or waived tests.

Laboratory examinations and procedures are categorized as “waived” under CLIA if they have been approved by FDA for home use, or the Secretary of HHS has determined that they are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result.44 Specific criteria for test waiver are set forth in CLIA regulations.45 Neither CMS nor FDA has classified any NGS platform as waived.

Personnel involved with all stages of testing at a clinical laboratory, including those involved only in interpretation of results, must meet certain education and training requirements specified in the regulations.47

State Regulation of Clinical Laboratories

States are responsible for administering the CLIA program for laboratories within their jurisdiction. States that have a laboratory licensure program equivalent to the federal CLIA program can apply for approval from the federal government, and laboratories meeting the
state licensure requirements are then deemed to be in compliance with CLIA. States with requirements that are stricter than the federal program may apply for exemption. Two states, Washington and New York, have obtained such CLIA exemptions.

State laws also may restrict from whom a laboratory may accept a test request and to whom test results may be provided. Some states explicitly authorize laboratories to accept samples from and deliver test results for specific tests (such as cholesterol or pregnancy tests) directly to patients without authorization from a healthcare provider. Other states, such as New York, categorically prohibit direct-to-consumer testing.

FDA Regulation of Medical Devices

Unlike CMS, which regulates clinical laboratories, FDA regulation is specific to particular “articles,” such as drugs and medical devices. Any future regulation of NGS by FDA would likely would be predicated on the agency’s jurisdiction to regulate medical devices.

Accordingly, the following section offers a history of the agency’s medical device authority.

Statutory Authority to Regulate Medical Devices

The current framework for FDA’s regulation of medical devices began with the Medical Device Amendments of 1976 (MDA), which amended the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA). 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. Subsequent amendments have further broadened FDA’s authority over medical devices and have authorized user fee requirements for device manufacturers.

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, 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 guidelines issued by FDA. Class III devices 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.

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).

The process for demonstrating substantial equivalence requires submission of what is referred to as a “510(k)” (based upon the section of the FDCA giving rise to the requirement) to FDA in order to receive agency “clearance” of the application. The 510(k) process is generally simpler and faster than a PMA application because the manufacturer has only to demonstrate substantial equivalence to a predicate device. Requiring manufacturers to rely on a predicate device, however, limited their ability to use the 510(k) submission process. In 1997, Congress amended the FDCA to permit devices lacking predicates to submit requests for “de novo” 510(k) classification. The de novo process is available only for low- or moderate-risk devices lacking a predicate; submission of a PMA is still required for higher risk devices.

FDA Regulation of In Vitro Diagnostic Products

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.” The definition clearly encompasses equipment, reagents and other components manufactured for use 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 products” (IVDs) 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 examination of specimens taken from the human body.

FDA Regulation of IVD “Test Systems”

Under the FDCA, FDA regulates not only individual components used by laboratories in developing tests, but also combinations of components grouped together, i.e., “test systems” or “test kits.” Although the
term test kit is not defined in FDA regulations, its 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. 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 does not fit within previously defined categories. For example, in 2007, FDA created a new regulation for gene-expression-profiling test systems for breast cancer prognosis in response to a de novo submission.64

RESEARCH USE ONLY (RUO) AND INVESTIGATION USE ONLY (IUO) IVDS

FDA allows the distribution of an unapproved or uncleared IVD for the purpose of generating the data required for the 510(k) or PMA submission. Under the FDCA and FDA regulations, a medical device generally may be distributed for investigation of safety and effectiveness only pursuant to the investigational device exemption (IDE) regulations.65 FDA has established special rules for IVDs. Under these rules, a manufacturer is permitted to distribute an IVD as an “RUO” or “IUO” product without complying with most of the IDE regulations in certain, limited circumstances.66

An RUO IVD cannot be used for human clinical diagnosis or prognosis, regardless of whether confirmatory tests or procedures are used. Under FDA regulations, RUO status is limited to the initial research phase of product development that is necessary to identify test kit methods, components, and analytes to be measured.67

An IUO IVD may be used for human clinical diagnosis or prognosis, but only in the context of a clinical study designed to determine the safety and effectiveness of the device for its intended clinical use. The study should be performed under a protocol sufficient to assess the IVD’s safety and effectiveness, and the manufacturer should document its efforts to collect data to support the appropriate PMA or 510(k) submission.68 The study protocol should also be approved by an institutional review board (IRB) and be executed in compliance with applicable informed consent requirements.69

To qualify for RUO or IUO status, the manufacturer must satisfy additional criteria. First, in the case of an IUO, the IVD must be used in testing that is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used as “a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.”70

Second, the labeling of an RUO or IUO IVD must bear one of two statements, depending on the use of the device. An RUO device must be labeled “For Research Use Only. Not for use in diagnostic procedures.”71 An IUO IVD must be labeled “For Investigational Use Only. The performance characteristics of this product have not been established.”72 According to FDA regulations, an IUO product is one that is used for product testing before full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful).

FDA’s Position Regarding the Legal Consequences of Selling RUO IVDS to a Clinical Laboratory

FDA regulations do not impose any obligation on manufacturers of RUO IVDs to monitor or prevent clinical use of an RUO-labeled IVD.73 In a 2011 draft guidance, however, FDA took the position that the agency may infer the manufacturer’s intended clinical diagnostic use of a product for the purposes of determining whether it is a “device” subject to regulation under the FDCA based upon “the circumstances surrounding the distribution of the product and the manufacturer’s knowledge that its product is offered and used for a purpose for which it is neither labeled nor advertised.”74 FDA relied for its interpretation on the agency’s regulation defining “intended use.”75

The draft guidance thus states that FDA “may consider a manufacturer’s knowledge of the purposes for which its customers offer and use its IVD product, and the manufacturer’s provision of technical support for those activities, to be evidence that the IVD product is intended to be used for such purposes.”76 It also states that, if a manufacturer of an RUO IVD becomes aware that one of its customers is using the product for clinical diagnosis, the manufacturer should “halt” sales to the customer or “comply with FDA requirements for IVD products, including premarket review requirements, if applicable.” The draft guidance was widely criticized as an overreach of FDA’s statutory authority. The final guid-
With a few notable exceptions, FDA has generally exercised “enforcement discretion” with respect to LDTs, meaning that in practice, LDTs have not been required to comply with the requirements applicable to IVDs. FDA maintains that it could regulate clinical laboratories that develop such tests as device “manufacturers,” but also asserts that it is exercising “enforcement discretion” by choosing not to.

FDA Regulation of Laboratory Developed Tests

Historical Policy of Enforcement Discretion

Although, as mentioned, clinical laboratories historically have been regulated by CMS pursuant to CLIA, FDA has from time to time sought to regulate as medical devices certain test systems (or their components) developed and offered by clinical laboratories, including genetic tests. Indeed, FDA’s Office of In Vitro Diagnostics and Radiological Health (OIR) — formerly known as the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) — has long taken the position that laboratory developed tests (LDTs) are medical “devices” subject to FDA regulation and that clinical laboratories performing LDTs are device manufacturers. FDA has described LDTs as “a class of in vitro diagnostics that are manufactured, including being developed and validated, and offered, within a single laboratory.”

LDTs differ from IVD test systems 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 system but does commercially distribute services derived from the development and performance of a test. Although FDA has not issued any regulations defining the term “laboratory developed test,” the agency has issued Warning and Untitled Letters alleging that a test marketed as an LDT is an IVD subject to regulation as a medical device when a laboratory licensed methods or software from another organization for use in a test.

There are unresolved jurisdictional questions regarding FDA’s authority to regulate LDTs as medical devices, as well as potential legal challenges should FDA articulate new regulatory requirements through the issuance of guidance documents rather than through notice-and-comment rulemaking. If FDA were to exercise such authority, LDTs likely would be subject to the same regulatory requirements that currently apply to in vitro diagnostic requirements, compliance with good manufacturing practices (GMPs) and — depending on their classification — premarket review, and the failure to comply with these requirements would be unlawful.

With a few notable exceptions, FDA has generally exercised “enforcement discretion” with respect to LDTs, meaning that in practice, LDTs have not been required to comply with the requirements applicable to IVDs. FDA maintains that it could regulate clinical laboratories that develop such tests as device “manufacturers,” but also asserts that it is exercising “enforcement discretion” by choosing not to. FDA has justified this choice by asserting that:

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.

At the same time, however, FDA acknowledged concerns about the “marketing of test services based on tests that have not been reviewed independently for safety and effectiveness.” Thus, FDA has asserted that it could “at a future date,...reevaluate whether additional controls over...in-house tests are warranted to provide an appropriate level of consumer protection.” Such additional controls “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.”

FDA has made exceptions to its exercise of enforcement discretion and imposed requirements over some types of LDTs. These exceptions are described and analyzed below. Generally, FDA has made exceptions on an ad hoc basis, in response to a perceived risk to the public. FDA’s proposed approach to “in vitro diagnostic multivariate index assays” (IVDMIAs), although ultimately abandoned by the agency, is illustrative. These assays interpreted multiple gene expression signals in combination, using a proprietary algorithm, to develop an individualized treatment recommendation. FDA issued a draft
guidance document stating that such tests would no longer be subject to enforcement discretion. FDA asserted that IVDMIAs “do not fall within the scope of the LDTs over which FDA has generally exercised enforcement discretion” because they include “complex, unique interpretation functions,” consisting of algorithms generally performed by software, that combine multiple sources of data to generate a classification or score correlating to a person’s prognosis or risk for developing a disease. The draft guidance noted that such tests:

are developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratories, and clinicians who order these tests. Additionally, IVDMIAs frequently have a high risk intended use. FDA is concerned that patients are relying upon IVDMIAs with high risk intended uses to make critical healthcare decisions when FDA has not ensured that the IVDMA has been clinically validated and the healthcare practitioners are unable to clinically validate the test themselves. Therefore, there is a need for FDA to regulate these devices to ensure that the IVDMA is safe and effective for its intended use.

As another example, FDA has asserted that LDTs marketed directly to consumers fall outside the scope of its enforcement discretion. In 2000, for example, FDA sought to exert control over drugs-of-abuse tests marketed directly to consumers by asserting authority over the specimen collection containers. Specifically, FDA used those provisions to require that all testing using the containers “be performed...using screening tests that have been approved, cleared, or otherwise recognized by FDA as accurate and reliable for testing.”

More recently, FDA has issued a number of Warning and Untitled Letters to DTC genetic testing companies in part because they distributed test sample collection kits directly to consumers. Most recently, FDA issued a Warning Letter to 23andme, which used NGS methods to provide its DTC genetic testing services, raising significant concerns about the accuracy of the predictive tests being offered by the company. FDA closed the enforcement action after the company agreed to stop selling its health-related testing services.

Recent Developments
At various times, FDA has appeared poised to regulate LDTs as a class, rather than on an ad hoc, episodic basis, but thus far the agency has not proposed a coherent regulatory framework. In July 2010, FDA held a two-day public meeting on LDT oversight and indicated that FDA was reconsidering its policy of enforcement over LDTs and that requirements for LDTs would likely be phased in over time. The rationale for this increased oversight was that “diagnostic tests are playing an increasingly important role in clinical decision making and disease management,” and “LDTs that have not been properly validated for their intended use put patients at risk,” including risk of missed diagnosis, wrong diagnosis, and failure to receive appropriate treatment.

More recently, agency officials have stated that FDA intends to exercise enforcement discretion with respect to “standard” LDTs — other than those offered directly-to-consumer (DTC) — pending the issuance of guidance documents outlining the Agency’s approach to LDT regulation. FDA has not issued any guidance or draft guidance documents addressing LDTs since 2010. Although CDRH’s 2012 guidance agenda listed three planned draft guidances on LDTs, the CDRH 2103 guidance agenda does not include any planned LDT guidances or draft guidances.

This shift may be related to a provision enacted as part of the Medical Device User Fee Amendments of 2012, which states that FDA must notify the House Energy and Commerce Committee and the Senate HELP Committee at least 60 days prior to issuing guidance on FDA regulation of LDTs and must include the anticipated details of the draft or final guidance.

Federal and State Oversight of NGS

CLIA and State Regulation
Because NGS methods generally have been developed in-house and performed by clinical laboratories as LDTs, they primarily have been subject to oversight under CLIA and state laws governing laboratories. CLIA regulations define the evaluation of analytical reliability to include performance characteristics such as accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference range or intervals, and other performance metrics. Some have raised a concern that these performance characteristics do not readily translate to NGS methods due to the complexity of the technology and the bioinformatics requirements for the analysis of large amounts of genomic data obtained through high-throughput sequencing.

In addition, CLIA and related state laws are limited to regulation of clinical laboratories. Therefore, those aspects of NGS testing that were performed by entities other than a clinical laboratory (e.g., the interpretive component), would fall outside the scope of CLIA,
although they could be regulated by the states as part of the practice of medicine.

As a result of the limitations of CLIA and state regulation of NGS, the U.S. Centers for Disease Control and Prevention (CDC) convened a national workgroup, known as the Next-Generation Sequencing: Standardization of Clinical Testing workgroup, which generated guidelines and recommendations for NGS. The workgroup stated that NGS requires three levels of validation: (1) platform validation; (2) test validation; and (3) informatics validation. Platform validation involves establishing that the system can correctly identify each type of variant that the test is designed to detect. Once platform performance has been established, assays need to be validated for their ability to identify variants in the specific regions of the genome under investigation. Finally, the extensive informatics, or analysis, process must be validated to ensure and document that appropriate software is used to generate accurate sequence data, including with respect to variants.

Even when the guidelines are followed, however, the workgroup still recommended confirmatory testing of all clinically actionable variants detected by NGS by Sanger sequencing or analytically validated genotyping assays because NGS “is a relatively new technology, clinical laboratory experience is limited, and the error profiles of existing platforms are variable.” Although this is clearly a conservative approach, it also risks losing some of the time and cost savings generated by the advent of NGS methods and, accordingly, making the tests less available to patients who may be interested in and may benefit from them.

**FDA Regulation**

In June 2011, FDA held a one-day public meeting on analytical validity of NGS methods. Although FDA limited the scope of those NGS systems that were used clinically, the Federal Register notice announcing the meeting was notable in that it appeared to presume — without any analysis — that FDA has statutory jurisdiction to regulate NGS systems. The meeting therefore jumped ahead to the issue of the “open scientific questions” relating to establishing analytical validity for NGS. This view was supported by the FDA employee responsible for coordinating the public meeting, who publicly stated one week before the meeting that OIR would regulate NGS tests as medical devices.

These statements did not appear to acknowledge the procedural and jurisdictional issues FDA may face by trying to regulate LDTs, over which the Agency has, as described above, historically exercised enforcement discretion. Moreover, regardless of whether an NGS system is developed by a clinical laboratory or another entity, as noted by Elizabeth Mansfield, Director for Personalized Medicine within OIR, NGS differs from devices FDA traditionally has regulated in that “the people who make the platform aren’t actually going to know what everybody’s going to use it for and everybody will be using it in slightly different ways.” What Mansfield left unsaid is that, under the FDCA, whether an article is subject to regulation as a medical device depends on its manufacturer “intending” that article to be used for a “device” purpose enumerated in the statute, such as diagnosis, treatment, or other medical use. In construing a manufacturer’s intended use, for the purpose of determining FDA jurisdiction, courts historically have adopted a claims-based view under which the intended use is determined based on the claims made for the product in connection with sale, and not based on the purchaser’s actual use of the product.

Therefore, if a clinical laboratory or other developer of an NGS system makes express or implied clinical diagnostic claims for the system, it could cause the system to become a medical “device” subject to FDA regulation. If, however, the developer of an NGS system simply claims that the system can detect and report the sequence of genomic DNA (i.e., generate a series of letters) and it is third-party health care providers or interpretive services who independently take the raw data and analyze it for a clinical diagnostic use, then FDA’s jurisdictional hook is less clear.

As demonstrated by FDA officials’ public statements, FDA likely would try to find a basis upon which to regulate such NGS systems, particularly if the health care provider or interpretive service was using the system for what the Agency views to be a high-risk area, such as prenatal genetic testing. It is, however, unclear upon what basis FDA could assert jurisdiction over the NGS systems under those circumstances.

FDA could seek to regulate as a medical device the software, including algorithms, used by the NGS developer to generate its sequencing results or by the interpretive service or health care provider in generating the test results. FDA has, in guidance, stated its intent to regulate as devices stand-alone software intended for clinical use, as well as software that constitutes an accessory to a medical device. The level of data that FDA expects in a premarket submission depends upon the Agency’s “level of concern,” which varies from minor (i.e., latent design flaws are unlikely to cause any injury to the patient or operator) to major (i.e., latent flaw or failure could directly result in death or serious injury to the patient or operator directly or indirectly through incorrect or delayed information
or through the action of a healthcare provider). To the extent that FDA sought to regulate the NGS developers’ software, it would suffer from the same flaw as an attempt to regulate the underlying NGS system, namely the non-clinical diagnostic intended use. In addition, any attempt by FDA to regulate the activities of a state-licensed interpretive service or other health care provider could be viewed as an unauthorized interference into the practice of medicine, which FDA statutorily is prohibited from doing.

FDA also has exercised jurisdiction over certain databases used to capture, store, and retrieve information from medical devices and could potentially use these regulations to exert authority over the databases used by NGS developers and interpretive services. For example, FDA proposed a rule on February 8, 2008, in which it signaled its interest in regulating stand-alone software that transfers, displays, reformats, or stores data from a medical device — so-called medical device data systems (MDDS). FDA proposed to classify MDDS products as Class I and to require all MDDS manufacturers to comply with the design controls (notably, software design validation and verification) in the QSR. According to the Agency, compliance with the QSR would significantly reduce the risk of incorrect treatment or patient diagnosis.

FDA issued the final rule in 2011. This regulation is similarly unavailing. In particular, the MDDS regulation does not appear to encompass the transfer of data from non-device instruments, such as NGS systems that are not promoted for clinical diagnostic use.

Finally, FDA has issued a regulation classifying as Class I laboratory information systems (LIS), which are electronic devices intended to store, retrieve, and process laboratory data. Because the LIS classification regulation encompasses only those storage, retrieval, and processing “devices,” it excludes electronic storage, retrieval, and processing media that are not intended for a “device” use, such as the databases used by an NGS developer to determine a DNA sequence. Therefore, despite FDA officials’ statements to the contrary, FDA’s jurisdiction over NGS systems, in the absence of clinical diagnostic claims, is unclear.

**Implications for the Practice of Medicine**

NGS methods involve standard laboratory testing procedures as well as a new interpretive element, using complex computer algorithms, that is necessary for other laboratory tests. The interpretation function is independent of the “wet” laboratory portion of the testing and could be conducted by a clinical laboratory or by a third-party entity or company. When the interpretation is conducted by a clinical laboratory it is subject to regulation under CLIA and the personnel who perform the interpretation must, like all other testing personnel, meet the criteria specified in the CLIA regulations. CLIA regulations do not, however, include specific personnel requirements for the interpretation of NGS data.

On the other hand, if a clinical laboratory were to outsource the interpretive component of NGS testing, a new market could potentially begin to open up for third-party interpretive services providers, such as individuals with training and expertise in bioinformatics and genetics.

As mentioned, such interpretive services would not be subject to regulation under the FDCA, and if they were not performed by clinical laboratories, also would not be subject to regulation under CLIA. The practice therefore likely would be constrained only by applicable genetic privacy laws, as well as laws governing the practice of medicine.

Absent the development of third-party interpretive service providers, it is unlikely that health care providers would have sufficient expertise to be able to sufficiently perform the complex calculations on the voluminous raw data generated by NGS platforms necessary for accurate and reproducible results interpretation. This process, which includes identifying variants of interest and determining which of the 3-4 million variants in the average genome are medically actionable, relies heavily on complex computations (as well as accessing and analyzing databases evaluating sequences) for which many health care providers may have little experience or training. More fundamentally, “the entire field of NGS analysis is in constant flux, and there is little agreement on what is considered to be the ‘best practice.’” Given this backdrop, it is likely that state laws will need to continue to ensure that physicians and patients are provided accurate interpretation of NGS-based sequencing data.

Finally, it is worth noting that a number of non-regulatory entities have begun to consider these challenges raised by NGS. For example, the National Institutes of Health recently invested more than $25 million for three groups to develop a Clinical Genome Resource (ClinGen), which will work closely with the National Center for Biotechnology Information to deliver authoritative information about variant interpretation through its ClinVar database. Professional societies like the American College of Medical Genetics and Genomics have begun setting standards for sequencing and reporting of clinical genomic findings. The College of American Pathologists (CAP), which accredits the majority of clinical laboratories in the United States, added 18 NGS-specific requirements to its molecular pathology checklist in 2012 that address
both the wet bench and bioinformatics components of NGS, and CAP’s NGS working group plans to update the checklist to address additional issues, including proficiency testing.

Conclusion

Over the last decade, NGS technology has advanced rapidly to the point where whole-genome sequencing is on the brink of widespread public availability. With its bioinformatics-based interpretive component, NGS adds new complexities to the already fragmented and uncertain regulatory landscape for genetic testing. NGS requires new types of training and expertise, more accurate, comprehensive, and freely available variant databases, as well as open-sourced algorithms to facilitate more efficient and consistent filtering of the vast amount of data generated through NGS. Clear standards for interpretation and reporting of NGS-based results — including so-called “incidental findings” — and privacy protection for sequence data will also be key to adequately protecting patients. These are not areas that fit easily within existing regulatory paradigms.

At this early stage, regulators can play an important supporting role, including convening stakeholders with an eye towards identifying key issues requiring resolution, developing consensus-based standards, and providing technical support as needed. NGS, while still in its infancy, can be expected to continue its rapid pace of integration into clinical care. Certainly, there are many scientific, legal, regulatory, and ethical issues to be worked out in the coming years. Perhaps most critical in the short term is ensuring that all entities providing NGS-based testing clearly understand and adopt new standards for this burgeoning field.

Acknowledgement

The views expressed in the article are exclusively those of the authors and do not necessarily reflect those of Sidley Austin LLP, Allen Boone Humphries Robinson, or their partners.

References


4. See infra notes 23 through 26.


9. Id.

10. Id.

11. Id.

12. Id.

13. Id.


16. This white paper uses the term “next generation sequencing” to refer to rapid DNA sequencing methods that determine the four bases of the human genome in a strand of DNA. Specifically, NGS involves the use of 2nd/3rd/4th-generation sequencing technologies to perform genome-wide sequencing of multiple genes or alleles spread across the genome for clinical (prognostic, diagnostic, therapeutic) purposes. This definition encompasses the sequencing of multiple genes or complete genomes.

17. See Metzker, supra note 15.

18. See Voelkerding et al., supra note 7.

19. Id., at 40.

20. See Metzker, supra note 15; see also Voelkerding et al., supra note 8; Shendure and Lieberman Aiden, supra note 3.

21. See Voelkerding et al., supra note 7.


27. See Biesecker, supra note 3.

28. Id.

29. See Biesecker et al., supra note 26.

30. Id.

31. Id.

32. Id.

33. Id.

34. See Biesecker, supra note 3.

35. Id.

36. Id.

37. See CLIA, supra note 6.

38. Id. § 263a(a).

39. Id. § 263a(b).

40. Id. § 263a(f).


45. 42 C.F.R. § 493.15(b) (1993). Waived tests are “simple laboratory examinations and procedures” that (1) are cleared by FDA for home use; (2) use “methodologies that are so simple and accurate as to render the likelihood or erroneous results negligible”; or (3) pose “no reasonable risk of harm to the patient if the test is performed incorrectly.” The specific CLIA-waived tests are: Dipstick or tablet reagent urinalysis (non-automated) for: bilirubin, glucose, hemoglobin, ketone, leukocytes, nitrite, pH, protein, specific gravity, and urobilinogen; Fecal occult blood; Ovulation tests – visual color comparison tests for human luteinizing hormone; Urine pregnancy tests – visual color comparison tests; Erythrocyte sedimentation rate – non-automated; Hemoglobin – copper sulfate – non-automated; Blood glucose by glucose monitoring devices cleared by the FDA specifically for home use; Spin microhematocrit; and Hemoglobin by single analyte instruments with self-contained or component features to perform specimen/reagent interaction, providing direct measurement and readout. 42 C.F.R. § 493.15(c) (1993). FDA has granted waived status to certain IVDs based on these criteria. See CLIA - Tests waived by FDA from January 2000 to present, available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfclia/testswaived.cfm?start_search=A> (last updated July 8, 2014).


47. Testimony of Thomas Hamilton, Director, Survey and Certification Group, CMS before the House Subcommittee on Criminal Justice, Drug Policy, and Human Resources of the Committee on Government Reform (June 27, 2006), available at <http://www.cms.hhs.gov/apps/media/press/testimony.asp?co unter=1892kintNumPerPage=10&checkDate=&checkKey=&rchType=1&numDays=3500&srchOpt=0&srchData=&keywor dType=All&chkNewsType=7&kintPage=&showAll=0&year=&age r=0&desc=false&lcboOrder=date>.


52. See generally 21 U.S.C. et seq.


56. Id. § 360c(a)(1)(B).

57. Id. § 360c(a)(1)(C).


63. 21 C.F.R. § 809.3(a) (2013).


66. Compliance with the requirements described here also establishes an exemption to the investigational new drug (IND) requirement applicable to devices that are considered drugs or biological products. See 21 C.F.R. §§ 312.2(b)(2)-(3), 601.21 (2013).


69. See 21 U.S.C. § 360j(g); 21 C.F.R. pts. 50, 56 (2013).

71. N.Y. Dist., FDA, to Paul Reiter, President, Millennium Biotechnology, Inc. (January 12, 2009) (stating that IVDs were not RUO, despite manufacturer’s assertion that they were for research use only, when there was “no evidence that they were labeled that way”), available at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm162698.htm> (last visited July 8, 2014).

72. Id. § 809.10(c)(2)(ii) (2013).

73. An analogous scheme exists for investigational use only (IUO) IVDs. These are IVDs that are “being shipped or delivered for product testing prior to full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful)...” Id. § 809.10(c)(2)(ii). IUO products, like RUO products, must not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure, and must be labeled with the statement, “For Investigational Use Only. The performance characteristics of this product have not been established.”


75. See 21 C.F.R. § 801.4 (2013). Section 801.4 implements 21 U.S.C. § 352(f), which provides that a device is “misbranded” if it lacks “adequate directions for use.” Section 801.4 states: “The words intended uses or words of similar import in 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article. This intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised... if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.”

76. See FDA RUO/IUO Draft Guidance at 10.


79. Federal Register 76 (June 17, 2010): 34,463, 34,463.

80. See Warning Letter from Steven I. Gutman, M.D., M.B.A., Dir., OIVD to David P. King, Pres. & CEO, Laboratory Corp. of America (Sept. 29, 2008), available at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048114.htm> (stating that test intended to be used as a tool to identify high-risk women who might have ovarian carcinoma, which had been “designed, developed, and validated by investigators at Yale University” and for which materials specifications and performance characteristics were developed by Yale investigator was “not within the scope of laboratory developed tests over which the agency has traditionally” declined active regulation); Letter from Steven I. Gutman, M.D., MBA, Dir., OIVD to Jeffrey R. Lubers, Pres., EXACT Sciences Corp. (Oct. 11, 2007), available at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076536.htm> (last visited July 8, 2014) (stating that colorectal screening test “designed, developed, validated, and marketed” by EXACT Sciences and offered by LabCorp facilities, and for which EXACT Sciences provided instructions for use, validation information, and performance claims was “not within the scope of laboratory developed tests over which the agency has traditionally” declined active regulation); Letter from Steven I. Gutman, M.D., MBA, Dir., OIVD to Peter J. Levine, Pres./CEO, Correlogic Systems, Inc. (July 12, 2004) (stating, with respect to an ovarian cancer detection assay, that FDA would regulate the software developed at Correlogic’s reference laboratory and licensed/transfered to the customer laboratories but would not, consistent with its policy of enforcement discretion, seek to regulate the activities of the clinical laboratories or of Correlogic’s reference laboratory).

81. See, e.g., Citizen Petition Submitted by Daniel Popeo, Chairman & General Counsel, and Richard Samp, Chief Counsel, Washington Legal Foundation (September 28, 2006) (FDA Docket No. 2006-P-0402) (challenging FDA’s jurisdiction over LDTs); Secretary’s Advisory Committee on Genetic Testing Meeting Transcript 51 (October 26, 1999) (statement of David Feigal, Director, CDRH) (recognizing that the in-house development of tests by clinical laboratories could be considered part of “the practice of clinical pathology medicine and... not something that FDA has jurisdiction over”).


85. Id.


87. Federal Register 61 (March 14, 1996): 10,484, 10,484.


89. Id., at 4-6.

92. See Untitled Letter from James Woods, Deputy Director, Patient Safety and Prod. Quality, Office of In Vitro Diagnosti-
cic Equipment Evaluation and Safety (OIVD), CDRH, to James Plante, Founder and CEO, Pathway Genomics Corp. (May 10,
2010); Untitled Letter from Alberto Gutierrez, OIVD, CDRH, to deCODE Genetics (June 10, 2010) [hereinafter deCODE
Genetics Letter]; Untitled Letter from Alberto Gutierrez, OIVD, CDRH, to 23andMe, Inc. (June 10, 2010) [hereinafter
23andMe Letter]; Untitled Letter from Alberto Gutierrez, OIVD, CDRH, to Navigenics (June 10, 2010).
93. See Warning Letter to 23andMe (November 22, 2012).
94. See Transcript, FDA Public Meeting on Oversight of LDTs 75 (July 19, 2010) (presentation of Elizabeth Mansfield, Direct-
or for Personalized Medicine, OIVD), available at <http://www.fda.gov/downloads/MedicalDevices/NewsEvents/Workshop-
sConferences/UCM226203.pdf> (last visited July 8, 2014).
96. See, e.g., Presentation of Alberto Gutierrez, “What about Pub-
llic Health?” AACC Webinar, October 5, 2011; see Ashford,
supra note 83.
97. See CDRH, Documents CDRH is Considering for Development
(FY2012), available at <http://www.fda.gov/MedicalDevices/
DeviceRegulationandGuidance/Overview/MedicalDeviceUser-
FeeAndModernizationActMDUFMA/ucm109196.htm#5> (last
visited July 8, 2014).
98. See CDRH Fiscal Year 2013 (FY 2013) Proposed Guidance
Development, available at <http://www.fda.gov/MedicalDe-
vices/DeviceRegulationandGuidance/Overview/MDUFAIII/
ucm321537.htm#list13> (last visited July 8, 2014). The agenda
does include, on the “B list,” a draft guidance for “Direct to
Consumer (DTC) Genetic Testing: IVDs.” (last visited April 29,
2014).
Note: As this issue was going to press, FDA notified Congress that
it intended to issue draft guidance outlining a risk-based
framework for LDTs.
100. A. S. Gargis, L. Kalman, and M. W. Berry et al., “Assuring the
Quality of Next-Generation Sequencing in Clinical Laboratory
102. See Gargis, supra note 100.
103. Id.
104. Id.
105. Id.
106. Id.
107. Id.
108. See Federal Register 76 (May 19, 2011): 28990; Transcript,
CDRH Public Meeting on Ultra High Throughput Sequencing
for Clinical Diagnostic Applications – Approaches to Assess
fda.gov/downloads/MedicalDevices/NewsEvents/Workshop-
sConferences/UCM266607.pdf> (last visited July 8, 2014).
109. See, e.g., Federal Register 76 (May 19, 2011): at 28,990 (stat-
ing that the purpose of the FDA public meetings is to “start
discussion on approaches that can provide the most useful
information in establishing safety and effectiveness of genomic
sequencing technologies when used clinically” (emphasis
added)).
110. See Transcript, CDRH Public Meeting on Ultra High Through-
put Sequencing, supra note 106, at 10.
111. See Heger, supra note 6.
112. See Transcript, CDRH Public Meeting on Ultra High Through-
put Sequencing, supra note 107, at 76.
114. See, e.g., Ass’n of Am. Physicians & Surgeons Inc. v. FDA, 226
stated that it may only regulate claimed uses..., not
all foreseeable or actual uses.”); see also Millet, Pit and Seed
Co., Inc. v. United States, 436 F.2d 1039 (6th Cir. 1970) (“[W]e
do not agree with the apparent theory of the government
that if any consumers use a product as a drug, such use, if
known by the seller, is determinative on this issue. Carried
to its logical extreme, this would mean that every merchant
who sells carrots to the public with knowledge that some of
his consumers believe that the ingestion of carrots prevents
eye diseases and hold the carrots out for use as a drug, as
that term is defined in the Act”). A few cases have recognized an
exception to the broad principle that manufacturer claims are
the basis for assessing a product’s intended use for purposes of
the FDCA. Courts have held that FDA is entitled to regulate a
product as a drug or medical device based on nearly exclusive
use of the product for its drug- or device-like properties. See
Action on Smoking & Health v. Harris, 655 F.2d 236 (D.C.
Cir. 1980); see also Clinical Reference Lab., Inc. v. Sullivan,
791 F. Supp. 1499, 1507 (D. Kan. 1992), aff’d in part, 21 F.3d
1026 (10th Cir. 1994) (“[T]he intended use may also be shown by
the product’s actual use”); United States v. 22 Rectangular or
116. See FDA, Guidance for the Content of Premarket Submis-
sions for Software Contained in Medical Devices (May 11, 2005),
available at <http://www.fda.gov/downloads/MedicalDe-
vices/DeviceRegulationandGuidance/GuidanceDocuments/
ucm089593.pdf> (last visited July 8, 2014).
117. Id., at 5.
119. 21 U.S.C. § 396 (Nov 21, 1997) (“Nothing in this chapter shall
be construed to limit or interfere with the authority of a health
care practitioner to prescribe or administer any legally mar-
keted device to a patient for any condition or disease within a
legitimate health care practitioner-patient relationship.”)
120. Federal Register 73 (February 8, 2008): at 7,500.
123. Federal Register 76 (Feb. 15, 2011): 8649 (codified at 21 C.F.R.
§ 880.6310 (2011)).
Practice Guidelines: ACMG Clinical Laboratory Standards for
Next-Generation Sequencing,” Genetics in Medicine 15, no. 9
127. For example, as of July 2013, fourteen states licensed genetic
counselors, and another four states passed bills that eventually
will require licensure. See National Society of Genetic Coun-
selors, States Issuing Licenses for Genetic Counselors (last
ld/fid=19> (last visited July 8, 2014). The states that currently
require licenses include California, Delaware, Illinois, Indi-
ania, Massachusetts, Nebraska, New Mexico, Ohio, Oklahoma,
Pennsylvania, South Dakota, Tennessee, Utah, and Washing-
ton. Id. The states that have passed bills to eventually require
licensure include Hawaii, New Hampshire, New Jersey, and
North Dakota. Id.
128. A. Nekrutenko and J. Taylor, “Next-Generation Sequencing
Data Interpretation: Enhancing Reproducibility and Access-
129. Id.