The Promise and Personalized Medicine: Regulatory Controls and Tort Influences in the Context of Personalized Risks and Benefits

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THE PROMISE OF PERSONALIZED MEDICINE:
REGULATORY CONTROLS AND TORT
INFLUENCES IN THE CONTEXT OF
PERSONALIZED RISKS AND BENEFITS

Randy J. Prebula*

INTRODUCTION

In choosing which drug to give a patient, healthcare providers frequently must balance their understanding of the patient's symptoms and knowledge of the possible conditions that these symptoms suggest, with the acceptance that each possible drug candidate has known and hidden risks and benefits. Given the vast differences in patients' height, weight, sex, and age, coupled with the ways in which different drugs can be metabolized, enter the bloodstream, and work within the body, "physicians frequently must try different medications at different dosages until they find the one that seems to work best in a particular patient."¹ This current medical standard of trial and error exposes patients to drugs that may or may not help treat their condition,² and may even cause them unexpected harm.³

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1. Lars Noah, The Coming Pharmacogenomics Revolution: Tailoring Drugs To Fit Patients' Genetic Profiles, 43 JURIMETRICS J. 1, 5 (2002) (alluding to the trial and error process by which physicians frequently must adjust drug doses based on "the nature of their symptoms, progression of the underlying disease, presence of any concurrent disease conditions or concomitant use of other medications, and tolerance of potential side effects"); ERIC J. CASSELL, DOCTORING: THE NATURE OF PRIMARY CARE MEDICINE 70 (Oxford University Press 1997) (explaining how variation in characteristics and responses between patients creates inherent uncertainty in the clinical management of individuals).

2. Noah, supra note 1, at 6, citing John C. Ballin, Editorial, Who Makes the Therapeutic Decisions?, 242 JAMA 2875, 2875 (1979) ("As every physician recognizes, a drug may be the agent of choice for the majority of patients, but it is not necessarily the best therapy for all patients. Individual pharmacologic responses and idiosyncrasies
In response to these potential problems, and as a result of research into the human genome, researchers began to develop and propose the introduction of diagnostic tests aimed at detecting individual patient variation in genetic make-up and expression, and to correlate these genetic characteristics to specific drug therapies.\(^4\) While there is still considerable debate as to the effectiveness of such tests,\(^5\) the underlying premise is that they can detect an individual patient’s relevant genetic make-up and/or expression to help predict his or her ability (or likelihood) of metabolizing drugs.\(^6\) These types of tests also may help identify specific traits of diseases that may indicate which patient will or will not benefit from a drug.\(^7\) Under either of these approaches, these new pharmacogenomic (literally, “drug/genome”) tests are likely to provide significant opportunities to achieve the “true promise of personalized medicine – the provision of individually safe and effective treatment[...].”\(^8\)

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7. Crews, supra note 6, at 363 n.4.

By seeking to develop and offer such tests, medical device manufacturers, clinical laboratories, and drug manufacturers, however, are shifting from population-based risk/benefit analyses as to the utility of drug treatments to identified patient subgroups and even individual patient risk/benefit analyses.9 The significance of a pharmacogenomic test result, as well as its applicability to the patient's individualized treatment, differs from the traditional mechanism by which doctors balance a diagnostic result or a clinical benefit across the studied patient population.10 This change in focus with regard to both risks and benefits for personalized medicine tests will impact the direct, administrative controls and indirect common law (tort) influences by which such products are developed by manufacturers and laboratories, regulated by U.S. federal agencies, marketed to doctors and consumers, used by individual patients, and reviewed judicially in the context of patient injury.

In addressing the shift in focus from populations to individuals, this Note will: (1) provide a brief overview of the scope of personalized medicine; and (2) consider the interplay between diagnostic device manufacturers, clinical laboratories, and doctors in their caretaker relationship with patients. Then, it will further assess how each, in turn, impacts (a) the regulatory/administrative controls, and (b) tort influences impacting how pharmaceutical drugs are manufactured and distributed, with the goal of understanding how personalized medicine regulation can aid in bringing individualized medical benefits to fruition.

I. PHARMACOGENOMICS – A ROSE BY ANY OTHER NAME

Just as in law, an effective discussion of scientific and medical methods requires an understanding of the relevant terms of art. Within the context of genetics and the use of genetic information to identify individual patient characteristics, these terms and phrases, while maddeningly similar, carry important distinctions. As a brief primer, we start with genes—the specific

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10. Javitt Statement, supra note 9, at 111.
sequences of DNA present on pairs of chromosomes within our cells. Each of the approximately 20,000 to 25,000 genes in a man has a normal, or common, sequence of DNA bases strung like spiky beads on a twisted chain of sugars. This genetic sequence is referred to as each individual’s genotype. "Genetic" assays, like tests for Sickle Cell Anemia, Huntington’s Disease, and Tay-Sachs Disease, have existed for many years and are designed to identify which people have (or “carry”) a specific form of a gene in their cells. By understanding whether they are carriers of a gene, people can make more informed decisions as to potential medical risks if they elect to conceive children.

Over time, genes may develop specific mutations that impact the gene’s effectiveness in signaling for, or controlling the production of proteins, enzymes, hormones, and other substances that are necessary to keep the body healthy. Some of these mutated genes can, over a period of many generations and under the influence of a myriad of population and environmental factors, become common within families, ethnic groups, and geographical regions. Common gene variants are referred to as “polymorphisms.” The combination of genes, together with their possible


12. Hollon, supra note 11, at 1; Stein, supra note 11, at 915-16.


18. Id.

19. Id.
polymorphisms within a species, is referred to as the species' genome. Examples of several “genomic” tests that detect polymorphisms include tests:

(1) measuring the number of gene copies present in a cell (such as the DNA topoisomerase II(A), or the TOP2A gene in breast cancer cells);21 (2) detecting the presence of specific mutations in families of related genes (such as the Cytochrome P450 drug metabolizing enzyme producing genes and pseudo-genes);22 and (3) assessing the degree to which specific gene mutations are copied (transcribed) into RNA or used (translated) to make proteins, such as the Allomap Cardiac Allograft Gene Expression Profiling test system.23

Within the broad family of genomic tests, methods that identify polymorphisms can be used for a number of specific reasons. First, by identifying the presence of genetic variations in metabolic pathways, they can indicate how effectively drugs are likely to be metabolized, thereby providing information on what quantity or dose of a drug a person should be given.24 Second, by identifying individuals by genetic makeup, these tests can hint at which patients are likely to respond to a given family of drugs because members of a drug family are likely to be metabolized by similar


This information helps determine who should or should not be treated. These methods are typically referred to as pharmacogenomic tests.

Carrying a specific gene (as detected by genetic tests) or having a specific polymorphism (as detected by any of the genomic tests) may not alone, however, predict disease. For example, in the same way that a person who has the genes (i.e., genotype) for both blue and brown eyes will have brown eyes because the “brown eye” gene is dominant, patients carrying different genes and different polymorphisms for drug metabolism enzymes can express different drug metabolism rates. Which genes are “turned on,” how effective they are in being copied and translated, and whether there are other controlling genes present in the body that counteract the gene of interest all control our “phenotype,” or more accurately, how each individual person in a population exists and is observed in relation to the rest of the world.

Within the scope of in vitro diagnostic, or “IVD” tests, the Food and Drug Administration (FDA, or the agency) and device users (clinical laboratories and physicians) typically assess each assay’s relative risks and benefits. Risks include the potential for false positive or false negative results, as well as the impact that an inaccurate result may have on the diagnosis of the patient’s disease or condition based on the incidence or frequency of the test result in the general population. Benefits against which these risks are weighed include gaining accurate diagnostic information about a patient’s

25. Id.

26. See Noah, supra note 1, at 7-10.


30. Id.
health that can aid in their treatment. In this way, risks and benefits of any test are viewed as they relate to an individual always in the context of the known risks for a general population.

Pharmacogenomic testing, however, shifts the risks and benefits analysis. While the risk of individual false positive and false negative results still relate to the diagnosis of an individual patient, the result is not analyzed in the context of what doctors know about populations or incidence rates, but rather relates only and exclusively to whether this patient should or should not be treated. In short, the risks and benefits are specific to the patient alone.

II. REGULATORY CONTROL PROCESSES

A. In Vitro Diagnostic Medical Device Manufacturers

1. FDA Premarket Approval or Clearance

FDA regulates diagnostic tests, including the specific, FDA cleared or approved examples of genetic, genomic, pharmacogenomic, and phenotypic tests listed above, as well as any product that measures individual characteristics of human specimens (IVDs). Some of the most common characteristics of specimens that are currently tested include the presence or absence of chemical substances, naturally occurring biological markers, infectious disease agents, immunological responses to foreign substances, and genetic components. Doctors, clinical laboratories, and, in limited

31. Id.


33. THE PROMISE OF PHARMACOGENONICS, supra note 32.

34. See supra notes 21, 22, 23.

35. See 21 C.F.R. § 809.3 (2009).

cases, individuals in their own homes can use IVDs to assess hair, saliva, blood, plasma, serum, urine, or other body fluids, to provide diagnostic, prognostic, or therapeutic information about the current and/or future medical state of the individual from whom the specimen was obtained.  

FDA's definition of IVDs includes the chemical components of the test (alone or combined with other components), the instruments and equipment used to dispense, shake, incubate, and/or measure the results of the IVD (with or without the associated chemicals), and systems that combine chemicals and instruments into a single functional unit. Irrespective of where and by whom such tests are used, IVDs are regulated primarily as medical devices by the Center for Devices and Radiological Health (CDRH), pursuant to 21 U.S.C. § 321(h) of the Food, Drug, and Cosmetic (FDC) Act.

37. Id.

38. 21 C.F.R. § 809.3 (2009). "In vitro diagnostic products are 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." Id.

39. Id.

40. See Inter-Center Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health, http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121175.htm (last visited Feb. 22, 2010); see also Overview of IVD Regulation, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm#2 (last visited Feb. 22, 2010). This regulation notes that some IVDs are regulated as medical devices pursuant to the FDC Act by the Center for Biologics Evaluation and Research (CBER). Specifically, IVDs used in the diagnosis of human retrovirus infection are regulated as class III devices for which CBER will require a PMA approval application before they may be marketed in the United States. Additionally, IVDs used in blood donor screening and/or blood banking applications are regulated as biological products subject to section 351 of the Public Health Service Act (PHS Act). These IVDs require licensure by CBER, rather than PMA approval, before they may be marketed in the United States. Overview of IVD Regulation, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm#2 (last visited Feb. 22, 2010).
FDA has classified most types of medical devices into one of three classes—class I, II, or III. This classification is based on the combined risks and benefits the devices present to patients and the general population (both from the proper use of the device itself and the possible, but reasonably recognized potential failures or misuses of the device). For example, implantable devices that carry inherent, direct risks to patients as a result of their use (such as spinal implants and ceramic hip products) are class III devices, while sutures, clips, and staples (which, although implantable, carry fewer risks to patients) are class I or II devices. Similarly, diagnostic tests for fatal and highly contagious diseases, such as HIV or tuberculosis, are class III devices because of the risk to health that could occur if a test result were incorrect. Other tests that diagnose less serious or non-contagious diseases (such as liver enzyme imbalances and Lyme disease) are class II devices.

41. JONATHAN S. KAHAH, MEDICAL DEVICE DEVELOPMENT: REGULATION AND LAW 3-5 (Barnett International 2009).

42. Device Classification, FDA http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm (last visited Feb. 22, 2010) (offering examples and explanations for device classification levels); see also Kahan, supra note 41, at 5.


44. See Device Classification, supra note 42; see also Letter from Hira L. Nakhasi, Director, Division of Emerging and Transfusion Transmitted Diseases, to Marta Chase, Bayer Corporation (Sept. 11, 2004), available at http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091275.pdf and Letter from Sally A. Hojvat, Director, Division of Microbiology Devices, to Dan Bracco, Vice President of Clinical and Regulatory Affairs, Oxford Immunotec, Inc. (July 30, 2008), available at http://www.accessdata.fda.gov/cdrh_docs/pdf7/P070006a.pdf (demonstrating examples of PMA approved HIV and Tuberculosis tests).

45. See Device Classification, supra note 42; see also 21 C.F.R. § 862.1050 (1997) (demonstrating that liver enzyme assays are class II devices) and Letter from Sally A. Hojvat, Director, Division of Microbiology Devices, to Fran White, Regulatory
FDA also uses the device classification as a mechanism to define the level of controls necessary to reasonably assure product safety and effectiveness.\(^4\) General controls, which apply to all devices, include requirements for device listing, premarket notification review, labeling, and compliance with FDA’s quality systems regulation (QSR).\(^4\) Class I devices are subject only to general controls, unless they have been specifically exempted from these requirements based on an FDA determination that the device type presents little or no risk to patients.\(^4\) Special controls include written performance standards, FDA-recognized voluntary international consensus standards for specific kinds of products or product characteristics (such as sterilization methods, electrical safety requirements, and biocompatibility), postmarket surveillance requirements for adverse device events or patient injuries, and FDA written guidance documents.\(^4\) Class II devices are subject to both general and special controls, and most require FDA premarket clearance (or “510(k) Notice” clearance, as further discussed below).\(^\) However, they do not typically require extensive clinical evaluation to demonstrate that the product can be made consistently and work properly to meet its intended purpose in a safe and effective manner.\(^\) In addition to general and special controls, FDA further requires manufacturers to demonstrate the safety and efficacy of devices intended for life-sustaining or life-supporting purposes.

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47. Id.


49. Kahan, supra note 41, at 4, 20 (describing the three kinds of “controls and citing the ability of company’s to claim conformity to FDA recognized voluntary consensus standards).

50. Id.; see also Device Classification supra note 42.

high risk implants, and new, moderate-risk or high-risk devices that have not been found substantially equivalent to legally marketed devices. These class III devices require a Premarket Approval (PMA) application and successful completion of a preapproval inspection of the manufacturer’s facility and equipment to demonstrate compliance with QSR requirements. Thus, class III devices are the most stringently regulated.

Before a new device can be marketed, the manufacturer must obtain from FDA either 510(k) premarket clearance or PMA approval. However, if there is a low level of known risks with the device, it may be exempt from such requirements or be a candidate for an alternate submission. A 510(k) notice includes: (1) a brief description of the new device, photographs and engineering drawings; (2) draft promotional materials and labeling; (3) identification of legally marketed products (“predicate devices”) to which the new device is “substantially equivalent;” (4) narrative and tabular comparisons of the new device’s and the predicate devices’ intended use, indications, technological characteristics, and principles of operation; (5) software documentation (if the device uses software); (6) sterility information (if sterile); (7) biocompatibility information; (8) statements or declarations of conformance to applicable standards and guidance documents; and, (9) summaries of any performance testing. In some cases, laboratory and clinical testing may be required to support the 510(k) notice.

FDA reviews this documentation and issues an order either agreeing that the new device is substantially equivalent to the predicate devices or stating


54. Device Classification, supra note 42. See also Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360(k), 360e(a)-(b) (2009).

55. Device Classification, supra note 42.

56. Id.; see also Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360(k), 360e(a)-(b) (2009) and Kahan, supra note 41, at 75 (providing a complete list of the elements required for a 510(k) submission).

57. Device Classification, supra note 42. See also Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360(k), 360e(a)-(b) (2009) and Kahan, supra note 41, at 75 (indicating in the provided checklist that 510(k) submissions may include “bench, animal, and clinical data”).
the reasons why the device is not substantially equivalent. Substantial equivalence means that the new device is intended for virtually the same uses as the predicate devices and that it either has the same principles of operation and technological characteristics as the predicates, or, if the new device and the predicates do have differences, that such differences do not raise any new questions of safety and effectiveness. Importantly, a substantial equivalence determination by FDA does not indicate FDA’s acceptance that the new device has been conclusively shown to be safe and effective, but rather, it is a determination that the device is relatively similar to another product so as to be sufficiently controlled and capable of being safely sold for use. If FDA concludes that a device is not substantially equivalent, the device is classified as a class III device that requires a PMA (unless FDA agrees concurrently or soon thereafter to reclassify it into class I or II due to the device’s lack of risks compared to its relevant benefits and uses).

In a PMA application, FDA requires manufacturers to provide a complete description of the device and its components, together with all of the information typically required in a 510(k) notice and a detailed description of the methods, facilities and controls used to manufacture the device, training materials, and references to any standards relevant to the device’s safety and effectiveness. FDA also requires the results of any and all clinical trials, animal studies, and bench tests; published and unpublished literature concerning the prior use of the product; and any other information known to the manufacturer concerning the device’s safety or effectiveness. While a 510(k) notice must demonstrate that the device is substantially

58. Kahan, supra note 41, at 102-03.

59. Device Classification, supra note 42; see also Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360(k), 360e(a)-(b) (2009) and Kahan, supra note 41, at 56-57.


61. Id. at § 360c(a)(1)(C).


equivalent to a predicate device, a PMA must demonstrate by valid scientific evidence that the device is safe and effective.  

3. Potential Impact of Shifting Risk/Benefit Paradigm

FDA’s medical device regulations, as described above, are based intrinsically on the risks and benefits a product has in relation to both the patient and the general population. A shift in risk/benefit from a general, population-based approach to a narrower patient subgroup or individual analysis in the pursuit of personalized medicine, therefore, is unlikely to lead to any significant changes in regulatory structure. Put simply, the current administrative framework, as it relates to the makers of test systems, appears to be broad enough and flexible enough to encompass changing risk profiles.

This shift, however, could influence where a specific test may be placed within the administrative framework. For example, a genomic test that detects polymorphisms in Cytochrome P450 genes has already been regulated as a class II medical device when it is used to advise doctors of the likelihood that an individual patient may or may not be a fast metabolizer of certain classes of drugs. The risks and benefits of the test are restricted by the claims made in the product’s labeling, which describe the test as:

intended for use in testing DNA [extracted from clinical samples] to identify the presence or absence of human genotypic markers encoding a drug metabolizing enzyme. The device is used as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information.

The claim is also limited by the clinical data in the labeling that explains to users the purposes and limitations of the test. If, hypothetically, a company were to label the same test for use in directing whether a specific patient should be treated with drug x, rather than drug y (based on her weight, age, condition being treated, and genomic traits), it would appear to have a different risk benefit profile. Specifically, if the test were correct, the


66. See Gutman Letter to James F. Kelly, supra note 22.

67. See id. (emphasis added).

68. See id.
doctor might choose to replace one possible, approved medical treatment (with its own risks and benefits) with another drug (with different risks and benefits) based solely on the diagnostic test result, rather than relying on the test result "as an aid" in directing therapy or in helping the doctor reach a conclusion as to the most appropriate treatment regimen. This potential would appear to alter the risks to which patients may be exposed. By changing the application of the test from a more general purpose to a specific function that may increase patient risk because the results are personalized, the FDA could choose to regulate the test at a higher level as a class III assay to provide the agency an opportunity to assess the safety and effectiveness of this new use in a PMA submission. Rather than shifting or amending the regulatory framework, a change in underlying risks and benefits could move a given product to a different location within the preexisting schemes, thus requiring a heightened level of control and FDA oversight.

B. Clinical Laboratories

1. FDA Premarket Enforcement Discretion

In 1976, Congress enacted the Medical Device Amendments to the FDC Act to provide the regulatory framework by which medical devices, including IVDs (as outlined above) can be marketed by medical device manufacturers. Nothing in the amendments, however, referred specifically to clinical laboratories or the methods that laboratories could use to modify existing products or develop in-house assays to analyze patient specimens as a service on the order of a licensed healthcare provider. Thus, in essence, FDA's medical device regulations address the entities that make and sell medical devices, but not the clinical laboratories and doctors who may choose to modify or use the devices as they see fit within then existing state regulatory frameworks for the practice of medicine.

In 1988, however, Congress enacted the Clinical Laboratory Improvement Amendments (CLIA), with the Centers for Medicare & Medicaid Services


70. Kahan, supra note 41, at 3.

71. DAVID FEIGAL, REGULATION OF GENETIC BASED THERAPY 3, 9 (Canary Press), available at http://www.canaryfoundation.org/publications/Feigel.pdf (indicating that FDA oversight of diagnostic tests arises under the 1976 Medical Device Amendments, but that regulation of home brew diagnostic tests under FDA authority is "ambiguous").

(CMS) designated with the responsibility for implementing and enforcing the CLIA regulations. The 1988 CLIA regulations require clinical laboratories that modify marketed products or develop and conduct diagnostic tests within the clinical laboratory to comply with specific assay validation, quality assurance, quality control, and personnel proficiency testing requirements that are highly likely to insure that the in-house laboratory developed tests (also known as LDTs) are scientifically valid and reproducible. Since LDTs, including genomic/personalized medicine test methods developed and offered by a clinical laboratory, are developed in accordance with CLIA regulations and performed by qualified individuals who undergo routine proficiency testing, the tests have been generally accepted as scientifically valid and reliable tools throughout the healthcare system.

Although the development and use of LDTs (genomic or otherwise) by a clinical laboratory are thus regulated pursuant to 42 C.F.R. Part 493, in August 1992, FDA issued a draft Compliance Policy Guideline proposing to apply general medical device regulation to these laboratory methods. The laboratory community objected (and continues to object), arguing that their facilities are adequately regulated under CLIA, that the agency lacks legal authority to regulate laboratory testing services, and that FDA regulation would be duplicative of the well-defined and frequently reviewed CLIA regulations.

73. Id. at 3; see also Randy Prebula, & Jeffrey Shapiro, FDA’s Regulation of Analyte-Specific Reagents, Medical Device and Diagnostics Industry, MED. DEVICE & DIAGNOSTIC INDUS., Feb. 2003, at 1.

74. See generally 42 C.F.R. Part 493 (2009) (describing, within the subparts, the requirements by which clinical laboratories are expected to operate in the provision of laboratory testing services).


76. See generally 42 C.F.R. Part 493, supra note 74.

77. See generally Prebula & Shapiro, supra note 73.
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requirements.\textsuperscript{78} FDA withdrew its proposal, although the agency has insisted since that time that it maintains authority to regulate LDTs should it choose to do so.\textsuperscript{79} Thus, from FDA's perspective, all LDTs are regulatable diagnostic tests, although FDA chooses to exercise enforcement discretion to allow most of these tests to be marketed solely on the basis of the clinical laboratories' compliance with CLIA requirements.\textsuperscript{80} As FDA made clear, the agency recognized that "the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health."\textsuperscript{81} FDA reasoned that "laboratories will be responsible for both the quality and interpretation of results generated from those tests."\textsuperscript{82} Therefore, clinical laboratories can develop and offer diagnostic tests to healthcare providers "outside the penumbra of FDA oversight, to some degree."\textsuperscript{83}

Subsequent to the development of these FDA policies, however, the agency observed that medical device manufacturers and clinical laboratories could work in conjunction to attempt to circumvent premarket review of new IVDs.\textsuperscript{84} For example, as explained in the two FDA warning letters described below, medical device manufacturers could develop and seek to license their diagnostic test systems or technology to clinical laboratories, and then claim that such tests were developed within the laboratories.\textsuperscript{85}

\begin{enumerate}
\item See generally \textit{Recommendations of the SACGT, supra note 75}; see also Establishment of the Secretary's Advisory Committee on Genetics, Health and Society, 67 Fed. Reg. at 65, 126 (Oct. 23, 2002).
\item Analyte Specific Reagent Regulation, 62 Fed. Reg. 62, 243 (Nov. 21, 1997) (to be codified at 21 C.F.R. pt. 809 and 864); Prebula & Shapiro, supra note 73, at 1.
\item Analyte Specific Reagent Regulation, 62 Fed. Reg. 62, 249 (Nov. 21, 1997).
\item \textit{Id.}
\item Analyte Specific Reagent Regulation, 61 Fed. Reg. at 10, 484; Analyte Specific Reagent Regulation, 62 Fed. Reg. at 62,249.
\item Letter from Steven I. Gutman, Director, Office of In Vitro Diagnostic Device Evaluation and Safety Center for Devices and Radiological Health, to Jeffrey R. Luber,
In two recent examples of FDA enforcement actions against manufacturers taking the approach described above with their assays and CLIA laboratories, FDA determined that certain test systems being used by the Laboratory Corporation of America (LabCorps) did not qualify as LDTs. First, in FDA’s October 11, 2007 warning letter to EXACT Sciences Corporation, the agency established a boundary beyond which FDA viewed the degree of cooperation between a medical device manufacturer and a clinical laboratory when developing and/or validating an LDT as violative of the standards in regards to LDTs. FDA’s letter also provides an underlying framework which can be used to evaluate the risks of FDA regulatory oversight when a manufacturer and a CLIA-certified laboratory choose to market a diagnostic test. In pertinent part, the agency’s warning letter advises:

Based on the information collected [during a CMS inspection of LabCorp’s facilities], FDA has determined that the [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.

86. See Gutman letter to Luber, supra note 85 and Gutman letter to King, supra note 85.

87. See Gutman letter to Luber, supra note 85.

88. Id.
In the second, more recent example, FDA issued a September 29, 2008, warning letter to LabCorp, stating that an ovarian cancer diagnostic test offered by the clinical laboratory as an LDT is not in fact an LDT. Specifically, FDA stated:

Based on the information collected, FDA has determined that the OvaSure™ is a test that was designed, developed, and validated by investigators at Yale University and not LabCorp. Instructions for use and performance characteristics appear to have been developed by Yale investigators. In addition, the materials being used to produce this test including [redacted by FDA] and [redacted by FDA] are manufactured by [redacted by FDA] based on specifications by the workers at Yale. This device is not within the scope of laboratory developed tests over which the agency has traditionally exercised enforcement discretion.

Because both products described in these warning letters were not developed or manufactured within the clinical laboratory for use as a service, FDA viewed both tests as medical devices that were subject to agency regulation.

In addition to these enforcement actions against manufacturers, FDA also issued draft guidance indicating that the agency intends to enforce premarket requirements over some tests developed wholly within clinical laboratories (i.e. LDTs) when such tests combine multiple variables, are complex in design, and when the process by which the test produces a clinical result is neither transparent to, nor readily understood by, the healthcare provider who orders the test. As described in the draft guidance document, in vitro diagnostic multivariate index assays (IVDMIs) are a category of clinical laboratory developed assays that would be subject to FDA oversight. Specifically, FDA defined IVDMIs subject to FDA regulation as assays that:

89. See Gutman letter to King, supra note 85.

90. Id.


93. Id.
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 provide a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.\(^{94}\)

Rather than focusing on the reagents and materials used to develop the assays, the relationship between the supplier of materials and the developing clinical laboratory, or the instruments and analyzer systems used to perform the assay, FDA’s IVDMIA guidance focuses on how the LDT is used to generate a result and whether the result is readily understandable by the ordering physician in his position as a learned intermediary.\(^{95}\) Once an LDT is found to meet the criteria of an IVDMIA, FDA has indicated the agency’s intention to require 510(k) clearance or PMA approval for the assay, depending on the risks of the test when used for a specific diagnostic purpose.\(^{96}\)

Overall, the various activities for which FDA has issued letters asserting jurisdiction over LDTs, IVDs, or assay components have ranged from distribution of kit systems claiming to be LDTs to the development of complex and potentially risky devices by CLIA-certified laboratories, such as the Pre-Gen test and the OvaSure test described above.\(^{97}\) In retrospect, it seems clear that FDA has thrown out a wide enforcement net in an attempt to identify and focus on the activities of and relationships between both IVD manufacturers and clinical laboratories that pose the greatest risk of potential harm to public health. This is evident because the majority of products or services that FDA’s enforcement activity targeted are diagnostic tests that, in the agency’s view, are most likely to present a high risk to the patient, such as LDTs for interpretation of cancer-related outcomes.\(^{98}\) Whether this same

\(^{94}\) Id.

\(^{95}\) Id.

\(^{96}\) Id.

\(^{97}\) Gutman Letter to Luber, supra note 85; Gutman Letter to King, supra note 85.

level of scrutiny and concern will be applied to genomic LDTs remains to be seen.

2. Clinical Laboratory Improvement Amendments Requirements

Apart from possible regulation by FDA, CLIA regulates the laboratories themselves. Under the CLIA statute, a “laboratory” is defined as any facility for the:

- biological, microbiological, serological, chemical, immune-hematological, hematological, 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. These examinations also include procedures to determine, measure, or otherwise describe the presence or absence of various substances or organisms in the body.

Under CLIA, clinical laboratories may modify existing “FDA-cleared or approved test[s],” or develop their own tests, provided that the laboratory facility adhere to a number of specific requirements.

3. Potential Impact of Shifting Risk/Benefit Paradigm

Within the context of genomic tests, the greatest risk to clinical laboratories appears to lie not in the process of developing or validating such tests, but rather in the complexity of the test result and the medical impact (i.e., the risks and benefits) of the LDT method. By seeking to make such tests applicable to individual patients, the clinical laboratory may need to include multiple variables and interpretive algorithms that are


100. Id.

101. 42 C.F.R. § 493.1253 (b)(2) (2009). This regulation provides:

Each laboratory that modifies an FDA-cleared or approved test system, or introduced a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable: (i) Accuracy; (ii) Precision; (iii) Analytical sensitivity; (iv) Analytical specificity; (v) Reportable range of test results for the test system; (vi) Reference intervals (normal values); and (vii) Any other performance characteristic required for test performance.

Id.
nontransparent to users or mathematically complex to yield a desired, single, patient-specific result. Whether such a complex test continues to be viewed as a laboratory service to healthcare providers (for which FDA will exercise enforcement discretion), or as an IVDMA clinical laboratory product that is subject to full FDA regulation through either the 510(k) or PMA processes may depend on the agency’s and the clinical laboratories’ understanding of the product’s risks and benefits to the user, the patient, and the general population.

C. Doctors and Patients as Diagnostic Test Users

1. Current State of Regulation/Oversight

In addition to requirements for clinical laboratory licensure, many state laws specify that clinical laboratories may only perform tests pursuant to an order from a licensed physician or other individual authorized under state law to request tests. Furthermore, they may only report test results to the requesting physician or other individual authorized by law to receive the results. CLIA regulations require that tests be ordered by, and results sent to, an “authorized person,” but they defer to state law to determine who qualifies as an “authorized person.” Therefore, if a laboratory is licensed by a state that limits who may order a test and who may receive test results, the laboratory would need to comply with these requirements. For example, Florida law provides that “a clinical laboratory may examine human specimens at the request only of a licensed practitioner or other person authorized by law to use the findings of clinical laboratory examinations.”

A “licensed practitioner” is defined as a physician, dentist, or nurse practitioner licensed under Florida law. Under this approach, the doctor ordering a test and the laboratory performing it do so primarily under their state license authority, under which they would thus appear to be subject to state tort risks for the products or services they offer.


103. Id.

104. Id. at 63.

105. Id.

2. Potential Impact of Shifting Risk/Benefit Paradigm

The shift in risk/benefit analysis is unlikely to have any impact on the process by which states directly regulate healthcare providers in their licensing practices. How an individual doctor is trained to provide medical services to patients and licensed by a state appears to be relatively immune to the process by which individual patient risks and benefits are calculated, although the process does appear to have a direct impact on the standard of care the physician or healthcare provider offers to patients.107

III. STATE TORT INFLUENCES

Just as in the area of regulatory controls (discussed above), more indirect, non-administrative, tort-based influences appear to be uniquely attuned to whether the potentially-liable entity: (1) manufactures products; 108 (2) provides services; 109 and/or (3) sees patients within the context of a licensed healthcare provider relationship.110

A. In Vitro Diagnostic Medical Device Manufacturers

1. Current Mechanisms for Assigning Liability

Individual entities that manufacture and market products are traditionally subject to a hybrid of strict liability and negligence in tort.111 Specifically, according to the standard set forth in the Restatement (Third) of Torts, manufacturers of products may be held strictly liable for their product if and

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107. See infra Section III(a).

108. See Noah, supra note 1, at 24.

109. Id.

110. Noah, supra note 1, at 24 (noting numerous additional sources providing examples of the “more exacting standards,” including Bazel v. Mabee, 576 N.W.2d 385, 387 (Iowa Ct. App. 1998) (holding that a jury could find a physician negligent for using Betadine despite knowledge of the patient’s allergy); Lynch v. Bay Ridge Obstetrical & Gynecological Assocs., 532 N.E.2d 1239, 1240 (N.Y. 1988) (allowing a claim against a physician for negligently failing to diagnose plaintiff’s pregnancy and then prescribing a drug whose use was contraindicated early in pregnancy); Edward A. Marshall, Medical Malpractice in the New Eugenics: Relying on Innovative Tort Doctrine to Provide Relief When Gene Therapy Fails, 35 GA. L. REV. 1277, 1299-327 (2001) (arguing that malpractice doctrines are likely to adapt to accommodate advances in gene therapy)).

111. See Noah, supra note 1, at 24.
when it is “defective in design when the foreseeable risks of harm posed by the product could have been reduced or avoided by the adoption of a reasonable alternative design by the seller or other distributor . . . and the omission of the alternative design renders the product not reasonably safe.”  

Alternatively, in states that have adopted the Restatement (Second) of Torts, a manufacturer “who sells any product in a defective condition unreasonably dangerous to the user or consumer . . . is subject to liability for physical harm thereby caused to the ultimate user” simply on the basis of placing the product commercially in the marketplace, provided that the product reaches the user “without substantial change in the condition in which it is sold.”

The Restatement (Third) further provides that a product will be considered defective due to inadequate warnings or instructions when the “foreseeable risks of harm posed by the product could have been reduced or avoided by the provision of reasonable instructions or warnings by the seller or other distributor . . . and the omission of the instructions or warnings renders the product not reasonably safe.” Thus, product purchasers may seek damages based on the safety of the product, not on the reasonableness of the conduct of the manufacturer.

The general standard applicable to products is modified, however, in relation to prescription drugs and medical devices, where the plaintiff must establish that “the foreseeable risks of harm posed by the . . . medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable healthcare providers, knowing of such foreseeable risks, would not prescribe the . . . medical device for any class of patients.” As to prescription medical devices regulated by FDA, one can hypothesize that plaintiffs seeking to establish a defective product would need to demonstrate that the foreseeable risks of use so dramatically outweigh any potential benefits that doctors would fail to prescribe the test to any class of patients, let alone to any individual patient.

112. RESTATEMENT (THIRD) OF TORTS § 2(b) (2008).

113. RESTATEMENT (SECOND) OF TORTS § 402(a) (1965).


115. Id. at § 2(c) (2008); RESTATEMENT (SECOND) OF TORTS § 402(a) (1965).


117. RESTATEMENT (THIRD) OF TORTS § 6(c) (2008).
Within the context of pharmacogenomic tests, however, the manufacturer may be strictly liable to the individual who receives an incorrect test result through a failure to warn claim. Specifically, a:

prescription drug or medical device is not reasonably safe due to inadequate instructions or warnings [and a manufacturer may thus be liable] if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to: (1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warning; or (2) the patient when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings.

The manufacturer has several available defenses, as described below, to a failure to warn claim. First, the manufacturer can argue that it should have no duty to warn a laboratory of the risk of an erroneous test result beyond the adequate prescribing information within the product labeling. In essence, FDA approval of the device labeling as a comprehensive and accurate statement of the clinical utility and limitations of the test should mean that the clinical laboratory will likely already know that such errors can lead to adverse test results, because, as noted in The Restatement (Third) of Torts:

[i]n general, a product seller is not subject to liability for failing to warn or instruct regarding risks and risk-avoidance measures that should be obvious to, or generally known by, foreseeable product users. When a risk is obvious or generally known, the prospective addressee of a warning will or should already know of its existence.

Even though a manufacturer may not be required to provide clinical laboratories with a warning, it should nonetheless consider providing an

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118. *Id.* at § 6(d) (2008).


120. *RESTATEMENT (THIRD) OF TORTS* § 2, cmt. (j) (2008); Nat. Gas Odorizing, Inc. v. Downs, 685 N.E.2d 155, 164 (Ind. App. 1997) (defining the sophisticated user doctrine as one which exempts manufacturers from the duty of providing product users with a warning when the user’s knowledge of potential hazards posed by the product is equal or superior to the manufacturer’s knowledge).

adequate warning in order to reduce its risk of liability. An adequate warning can serve as an affirmative defense to liability. Plaintiffs, however, often argue that a particular warning was inadequate because it should have been worded differently. Thus, a pharmacogenomic test manufacturer should scrutinize carefully the language of any proposed warning.

In relation to a medical device manufacturer, one also should consider that the test is being sold to a trained professional who is using that product, prescribing the product, or ordering that the test be provided to a patient wholly within the physician’s or the clinical laboratory’s provision of a medical service. As such, the manufacturer could assert that the product is used only under the direction of a learned intermediary and that the test is only used by a sophisticated user. The learned intermediary doctrine similarly appears to apply when a product’s warnings and instructions are provided to a physician who stands between the manufacturer of the test and the patient. In the sophisticated user defense, if the clinical laboratory using the test knew or reasonably could have been expected to know about the product’s injury-causing risks, the manufacturer or distributor has no duty to warn the product’s end user.

122. See Lowe v. Metabolife Int’l, Inc., 206 F. Supp. 2d 1195, 1201 n. 4 (S.D. Ala. 2002) (stating that under Alabama law, proof of a warning issued by the manufacturer is an affirmative defense since the user who was made aware of the dangers inherent in using the product assumed the risk of injury from these dangers by using the product anyway).

123. See Restatement (Third) of Torts § 2, cmt. (i) (stating that, when assessing the adequacy of warnings, courts should consider a number of factors, including the “content and comprehensibility, intensity of expression, and the characteristics of expected user groups”); see also Strong v. E.I. Du Pont de Nemours Co., 667 F.2d 682, 686-87 (C.A. Neb. 1981) (stating that there is “no duty to warn if the user knows or should know of the potential danger, especially when the user is a professional who should be aware of the characteristics of the product”).

124. Id.


126. Id.

2. Potential Impact of Shifting Risk/Benefit Paradigm – How learned is the intermediary or sophisticated is the user?

In relation to medical device manufacturers, one must consider that the test is being sold to a trained professional (the doctor) who is using the product, prescribing the product, or ordering that the test be provided to a patient wholly within his or the clinical laboratory’s provision of a medical service. As such, the person best suited to protect the patient from a defective product, best able to assess the risks and benefits of any medical course of action and who bears liability for unreasonable uses of the test is the physician. Similarly, under the sophisticated user defense, whereby the risks associated with a complex product lie with the knowledgeable and highly trained users of the product, rather than the device manufacturer, a manufacturer may be shielded from products liability due to defective labeling or warnings. In either event, the manufacturer’s labeling and the sale of the device to a sophisticated user should “shield manufacturers from liability for disclosed risks . . . because the mere presence of the warning tends to shift liability to physicians.”

In shifting the risk/benefit analysis from populations to individuals, the learned intermediary doctrine would appear to weaken the device manufacturer’s defenses only to the extent that the learned intermediary is incapable of standing between the manufacturer and the patient. This impact could develop if the test method is overly complex or because the risks and benefits of the test method cannot be adequately communicated in the device labeling. Pharmacogenomic tests often are highly complex and, as a result, it is unclear just how learned any learned intermediary can be. Absent the interposition of the doctor, liability could revert to the manufacturer.

Similarly, sophisticated users, such as clinical laboratories who develop tests for their own use (as described above), may well understand how to perform complex tests, but they may not have a thorough understanding of the limitations or controls under which the results must be reported to be meaningful. If this defense also is unavailable to manufacturers, it raises the potential that the complexity of the test methods could limit their available defenses. As noted below, however, any shift in risk/benefit balancing that


129. Restatement (Second) of Torts § 388(k).


leads to a higher regulatory burden (i.e., PMA as opposed to a 510(k) notice) simultaneously decreases possible state tort implications by opening the possibility for federal preemption.\textsuperscript{132}

3. Limitations Imposed by FDC Act Preemption (Reigel v. Medtronic (2008))

In 1996, the United States Supreme Court ruled in Medtronic v. Lohr\textsuperscript{133} that clearance of a pacemaker through the 510(k) process did not lead to federal preemption of possible state tort actions.\textsuperscript{134} Because the pacemaker wires in Lohr had not been found to be safe and effective (as would be the case for a device approved through the PMA process), the plaintiff was able to recover in tort for an injury caused by a defective pacemaker wire (whether negligently designed, defectively manufactured, or defective due to inadequate warnings) when the wire failed and the patient underwent emergency surgery.\textsuperscript{135} In Lohr, the Court, however, left open the question as to whether the same analysis would apply to products approved through the PMA process.\textsuperscript{136}

In February 2008, the Court addressed this issue directly in Reigel v. Medtronic,\textsuperscript{137} where it held that "[t]he [1990 Medical Device Amendments of the FDC Act]'s pre-emption clause bars common-law claims challenging the safety or effectiveness of a medical device marketed in a form that received premarket approval from FDA."\textsuperscript{138} In Reigel, "Charles Riegel and his wife, petitioner Donna Riegel, brought suit against respondent Medtronic after a Medtronic catheter ruptured in Charles Riegel's coronary artery during heart surgery."\textsuperscript{139} Within this context, and as described above, any

\textsuperscript{132}See infra, subsection 3 & note 137 (describing Federal preemption under Riegel v. Medtronic, 552 U.S. 999 (2008)).

\textsuperscript{133}Medtronic v. Lohr, 518 U.S. 470, 470 (1996).

\textsuperscript{134}Id. at 497-501.

\textsuperscript{135}Id. at 481.

\textsuperscript{136}Id. at 493, 503.


\textsuperscript{138}Id. at 1001.

\textsuperscript{139}Id.
shift in the classification of a medical device, such as a pharmacogenomic test, into class III due to a balancing of individual patient risks would simultaneously place a product into a category where the manufacturer would be free under the *Riegel* analysis from common-law claims challenging the safety or effectiveness of the test method.

**B. Clinical Laboratories**

1. **Current Bases for Liability**

   In relation to products liability as a cause of action, “sellers of products face strict liability in tort, while providers of services generally do not.” Because clinical laboratories have historically been viewed by FDA and CMS as service providers, any basis for liability on the part of the laboratory would likely need to be established, for example, by negligence in the reasonable provision of medical services. This could be demonstrated by evidence that the laboratory mishandled or misidentified specimens in a way that could lead to inaccurate test results being reported to doctors and patients. Alternatively, hypothetical claims of negligent infliction of emotional distress, or even of an intentional tort (such as intentional infliction of emotional distress by extreme and outrageous conduct that intentionally or recklessly causes a patient victim severe mental stress) may arise under specific facts or situations. As a general matter, however, the clinical laboratory would not be subject to the same basis in strict liability simply by offering to conduct a requested, medically ordered test.

2. **Potential Impact of Shifting Risk/Benefit Paradigm**

   The shift in risk/benefit analyses for pharmacogenomic tests, however, creates a conundrum for the laboratories by blurring lines between services and products. FDA views IVDMIAs (the subset of clinical laboratory-developed tests where the results are complex and not readily transparent or intelligible to doctors) as products, not services, and seeks to regulate them as such. From a tort law perspective, this shift also appears to create the possibility that laboratory development of test services could be viewed as the creation and sale of a product, where strict products liability applies. If such a test is viewed as a product, not a service, and marketed by the clinical laboratory without FDA approval, the clinical laboratory would appear to have increased the likelihood of potential state tort oversight, without

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simultaneously benefitting from any federal preemption that would apply if the test were FDA approved through the PMA process.

C. Malpractice and Liability – the Physician-Patient Relationship in Personalized Medicine

1. Current Bases for Liability – Medical Malpractice/Negligence

As a licensed healthcare provider, doctors generally are not subject to tort liability as a product manufacturer. Rather, tort law uses the less exacting standards of medical malpractice to resolve personal injury claims arising from surgical and other medical procedures. Courts have held physicians liable for the negligent selection of prescription drugs, including cases involving inadequate testing for the selection of the best available drug for a particular patient. In addition, pharmacists may face tort liability for mistakes in compounding drugs, but they generally escape strict liability because courts regard them as providers of a service rather than sellers of a product.142

As such, if a doctor chooses to order a new pharmacogenomic test, or to use the results of such tests in the management of a patient’s care, that choice would usually be reviewed in the context of the professional standard of care by which any medical treatment, diagnostic method, or therapeutic intervention is assessed. If the doctor tests a patient adequately, within the reasonable professional standard of care using tests shown by the manufacturer, the clinical laboratory, or by peer-reviewed publication to be reasonably reliable in providing meaningful clinical results, the doctor’s exposure to potential malpractice-based liability would appear to be minimal. Failure to test a patient with readily available and easily understood, reliable test methods, however, may not meet the requisite standard of professional care.

2. Potential Impact of Shifting Risk/Benefit Paradigm

In shifting the risk/benefit analysis, changing the specificity and clinical utility of any test method from broad patient populations to individual

142. Noah, supra note 1, at 24 (noting numerous additional sources providing examples of the “more exacting standards,” including Bazel v. Mabee, 576 N.W.2d 385, 387 (Iowa Ct. App. 1998) (holding that a jury could find a physician negligent for using Betadine despite knowledge of the patient’s allergy); Lynch v. Bay Ridge Obstetrical & Gynecological Assocs., 532 N.E.2d 1239, 1240 (N.Y. 1988) (allowing a claim against a physician for negligently failing to diagnose plaintiff’s pregnancy and then prescribing a drug whose use was contraindicated early in pregnancy)); Marshall, supra note 110, at 1299-327 (arguing that malpractice doctrines are likely to adapt to accommodate advances in gene therapy).
patients, increasing the complexity of the test method, and reducing the ability of the healthcare provider to understand and apply the test results to a single patient's condition, issues are raised as to what is the reasonable standard of care. How can a doctor be aware of the risks of his actions if the process by which a result is obtained or the true clinical import of a result is not readily apparent? Can the true clinical nature of an individual patient result devoid of population based risk/benefit balancing be meaningful to his or her healthcare provider? In brief, a doctor may not be capable of meeting the requirements of providing professional care if the standard cannot be readily determined or if it shifts on the sands of undefined, amorphous risk/benefit calculations.

CONCLUSION

There are multiple administrative controls and tort influences in place that impact the approval, marketing, and use of diagnostic tests. These complex and overlapping control mechanisms, despite their common basis in user/patient risks and benefits, disparately impact manufacturers, clinical laboratory service providers, doctors, and patients. The interplay between the available control mechanisms is heightened, and may lead to unanticipated shifts in regulatory oversight and manufacturer liability, when viewed through the lens of novel, pharmacogenomic test methods. Due to a shift in the mechanism by which general risk benefit analyses move toward the individual patient's personalized medical treatment, manufacturers of diagnostic tests may find that FDA exercises greater regulatory scrutiny over their tests as class III devices, rather than through less rigorous pathways. Clinical laboratories may find the shift to personalized medicine-based risk profiles will create yet another avenue by which FDA oversight will be applied to their laboratory services, while both clinical laboratories and ordering physicians are likely to see a blurring of the lines between services and products, thus impacting the tort influences to which they are exposed and the sources of liability to which they may be held.