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SYMPOSIUM

Personalized Medicine in Diabetes: Regulatory Considerations

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Abstract

Personalized medicine has become a topic of great interest because of its potential to improve patient care and optimize therapeutic strategy. The U.S. Food and Drug Administration (FDA) is interested in promoting personalized medicine, whenever appropriate, to protect and promote the public health. The ability to better diagnose, screen, and manage patients with diabetes in order to individualize care should lead to better health outcomes and a large benefit to public health. This article describes FDA regulatory considerations for devices intended for use as personalized medicine tools for the diagnosis and treatment of patients with diabetes.

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Introduction

In 2004, the Food and Drug Administration (FDA) published a report entitled, "Challenge and Opportunity on the Critical Path to New Medical Products."[1] This report outlined the concept behind the Critical Path Initiative, an endeavor to stimulate and facilitate a national effort to modernize the scientific process through which research discoveries are translated into innovative new medical products. (For additional information on the FDA's Critical Path Initiative, see http://www.fda.gov/oc/initiatives/criticalpath/.) Personalized medicine, or the use of patient-specific information to individualize therapy and disease management, is a major theme in the report and is touted as a mechanism to achieve better clinical outcomes for patients. The realization of personalized medicine may help clinicians to give the correct dose of the correct therapy for a given patient, identify patient populations in which a particular drug is most effective, or avoid dangerous side effects of therapies in certain populations. This concept has great potential, but significant challenges still exist, such as an incomplete understanding of the mechanism of disease or mode of action of certain drug therapies.

Arguably, health care providers in the field of diabetes management have been practicing personalized medicine for many years. Blood glucose monitoring is used by diabetes patients, and their health care providers help manage their disease by supplying information regarding nutritional and treatment decisions. In fact, one major Critical Path project, the Artifical Pancreas Initiative, is aimed at helping diabetes patients achieve glycemic control. An "artificial pancreas" is a system that includes, ideally, a method of assessing blood glucose concentration in real time, an insulin pump, and an automated algorithm that would control insulin delivery based on the blood glucose values. In addition to the potential medical benefits that an artificial pancreas will provide, it will improve the lives of diabetes patients and their families and provide much needed relief to our health care system.

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Abbreviations: (CDRH) Center for Devices and Radiological Health, (FDA) Food and Drug Administration, (IDE) investigational device exemption, (IVD) *in vitro* diagnostic device, (IVDMIA) *in vitro* diagnostic multivariate index assay, (R&D) research and development

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In addition to the extraordinary effort to develop the artificial pancreas, researchers are also focusing on developing new and better biomarkers for diabetes prevention and management. Scientists aim to discover the genetic or physiological underpinnings of disease or risk of disease and hope to turn these discoveries into better diagnostic and therapeutic products. For example, it may be that, if one could determine with great sensitivity and specificity a population of people who are at higher risk of developing type 2 diabetes based on a genotype, health care providers could begin diabetes intervention well before the damaging symptoms of disease manifestation. However, although many new univariate genetic and biochemical markers related to diabetes have been identified, none have been demonstrated to be diagnostically useful as stand-alone prognostic or diagnostic tests. This may be because diabetes is such a complex, multigenic disease; thus complex, multivariate biomarkers may be required to add clinically actionable information.

Multivariate biomarkers are becoming increasingly common as scientists try to discover new diagnostics for common complex diseases such as cancer, cardiovascular disease, and diabetes. The FDA has defined this type of composite biomarker as a category of tests called *in vitro* diagnostic multivariate index assays (IVDMIAs), which involve the use of multiple signals obtained from multiplex or serial laboratory tests, often supplemented with multiple clinical or demographic inputs. (The FDA's draft guidance on IVDMIAs may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm.) These multiple signals are combined to generate a single, patient-specific test result (e.g., a "score," "index," diagnosis, or risk). The clinical significance of this result cannot be verified by health care practitioners relying on current medical knowledge or generally accepted information from the clinical community. For example, a microarray-based test that integrates the mRNA expression levels of multiple genes into a pattern intended to determine which patients will respond to a particular drug would be an IVDMIA. This type of test has great potential to improve patient care and optimize therapy, but they are also quite difficult to design and validate correctly.

Food and Drug Administration Regulation of Diagnostic Tests

Diagnostic tests such as these that may facilitate the advancement personalized medicine are considered medical devices (see definition of "device," Food, Drug, and Cosmetic Act, 21 U.S.C. 321(h)) in the United States. The U.S. Congress enacted the Medical Device Amendments of 1976, expanding government's oversight role of medical devices sold in the United States. The FDA was authorized to establish the regulations and procedures to carry out this oversight of medical devices before and after the devices were introduced in the marketplace. During the years that have elapsed, the FDA has developed evolving, risk-based regulations and policies that are designed to promote and protect the public health by regulating medical devices. The FDA regulations also set as an equally important goal the establishment of an environment that encourages the discovery of new medical products for the benefit of the citizens of the United States. *In vitro* diagnostic tests (IVDs) (for full definition, see 21 CFR §201.119) are considered to be medical devices for purposes of regulatory oversight and are defined as reagents, instruments, and systems intended for use in the diagnosis of disease or in the determination of the state of health in order to cure, mitigate, treat, or prevent disease. Thus by statute, *in vitro* diagnostic tests that are to be commercialized for the diagnosis and management of patients are subject to FDA regulation.

Within the FDA, the Center for Devices and Radiological Health (CDRH) reviews devices prior to marketing to assure that they demonstrate a reasonable assurance of safety and effectiveness for their intended use. Each regulated device is assigned one of three classes related to the level of FDA oversight prior to marketing. Like all other medical devices, IVDs are classified for CDRH regulatory purposes based on the sponsor's intended use of the device. The claimed intended use of the device should specify, where appropriate, the analyte the device is intended to measure, the clinical purpose of measuring the analyte, and the populations to which the device is targeted. Class I devices are considered low risk, and many of these types of devices are exempt from premarket review by the FDA. Class II devices (and class I devices that are not exempt from premarket notification) are considered to carry more risk and are reviewed by the FDA and allowed to be marketed if found to be similar (in terms of safety and effectiveness) to another legally marketed device that is intended for the same type of use. Class III devices are considered the highest risk devices, and these devices usually require a premarket application (approval of such applications involves a more in-depth review and documentation of the safety and effectiveness of the device; for additional information on medical device regulation, see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm).

The risk of an IVD is primarily related to the quality of the information derived from the test's results. That is, the risks to the patient as a result of false positive or false negative results are often tied to the clinical decisions that would be made based on the incorrect results. For example, if a device were being used to determine that a patient will benefit from a drug that has significant toxicity, it could be a high-risk device. The patient may be given a drug that is not effective for them and experience unnecessary side effects with no clinical benefit following an incorrect test result. The converse is also true; a patient who could potentially benefit from the therapy could be suboptimally treated based on incorrect diagnostic test results, resulting in adverse clinical events. To make sure the benefits and limitations of a test are known, vigorous analytical and clinical validation of IVDs is necessary.

Validation of a New Diagnostic Test

Methods for analytical validation for most tests/technologies are well established and include investigations of performance parameters, including reproducibility/robustness, accuracy, linearity, limits of detection/quantification, and endogenous/exogenous interferences. A good understanding of a test's analytical performance is crucial to enable interpretation by the clinician once the test is clinically validated. For example, if the variability of a test is too large, it may not be appropriate for uses where the clinically meaningful target range is narrow. Thus analytical parameters should be thoroughly understood prior to initiating clinical validation studies for new biomarker tests.

Analytical validation for genetic or genomic biomarkers may present some particular challenges. For example, samples of rare alleles may be difficult to find when validating a genetic test. In addition, for genomic or proteomic tests, or tests measuring large genetic deletions or translocations, it may be difficult to find an analytical reference standard by which to establish accuracy of the new marker. Finally, for new types of technologies, standards and quality control materials are rare or nonexistent, so evaluation of performance over time or across platforms can be challenging.

Once a test has been analytically validated, robust clinical evaluation is crucial to establishing the sensitivity, specificity, and/or predictive value of the new marker. In general, development of a new clinical diagnostic test requires two stages: research and development (R&D) and independent clinical validation. In the R&D phase, the test developer works to optimize the clinical test parameters such as clinical cutoffs, number and identity of features, coefficients, test platform(s), and algorithms/classifiers. All test parameters, including these features, should be locked down before the independent validation phase begins. For example, if one is developing a new IVDMIA intended to measure RNA expression to predict response to a particular drug, the R&D phase may include several small studies designed to choose the genes and optimize the interpretation algorithm. Once the test developer has confidence that the genes and algorithm are final, independent clinical validation is necessary.

Clinical validation should be performed on specimens that are distinct from the specimens that were used in the R&D phase. Importantly, the study should be designed so that the intended use population of the test is assessed in the trial. Retrospective specimens, such as specimens collected during a prospective study of diabetes patients, may be acceptable, provided the study design supports the intended use of the test, specimens were appropriately collected and stored, and sampling bias can be avoided (e.g., if DNA is available for only 30% of specimens in a trial, it may not be appropriate for validation of a genotyping test in that population). In cases where acceptable retrospective specimens are not available, prospective studies may be needed to clinically validate a new biomarker test. Note that, if, once the clinical validation study is complete, the data do not demonstrate that the new test is clinically useful, the test developer would need to return to the R&D phase, re-optimize the test inputs and parameters, and perform a new independent clinical validation on the revamped test.

Clinical validation of a new test is generally the most challenging phase of device development. Clinical studies, whether prospective or retrospective, must be carefully planned with prespecified statistical analysis plans, clinically relevant inclusion and exclusion criteria, and carefully thought-out study protocols. The FDA recommends that, when designing clinical validation plans, test developers engage the services of qualified statisticians and trialists, as well as medical experts who routinely care for the intended use population and understand the potential medical utility of the new test. Resources committed up front often result in diagnostic development programs with a higher likelihood of success.

The FDA encourages manufacturers who are developing a new IVD test to communicate with the Agency as early

as possible. This can be done via the pre-investigational device exemption (IDE) process. The goals of the pre-IDE process for medical devices (a mechanism by which the FDA can provide test-specific protocol review and regulatory guidance) accomplishes two things: (1) allows the FDA the opportunity to become familiar with the new test before seeing the formal premarket submission and (2) provides manufacturers feedback on regulatory path and the type of data appropriate to support the test indication. (Additional information on the FDA's pre-IDE process can be found at *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126600.htm*.) This may be especially important for devices in emerging fields such as personalized medicine, where both review policy and regulatory science are continually evolving.

Summary

There are still significant challenges to those who wish to use personalized medicine in the prevention, diagnosis, and treatment of diabetes. Scientists, clinicians, and regulators must try to reach a delicate balance in the discovery and validation of new diagnostic biomarkers. How can one best apply new and innovative biomarker tests while assuring that patients are protected from inadequately studied diagnostic tools? What level of clinical evidence for new tests would assure FDA approval, adoption by clinicians, and payer reimbursement? These types of questions are not easily answered, and progress sometimes seems slow.

However, there is good reason to be optimistic that diabetes patients will soon benefit from new diagnostic and therapeutic tools generated by the translation of research discoveries into clinically meaningful tests. Personalized medicine is being promoted at high levels of the federal government, including the National Institutes of Health, the FDA, and even Congress. This increased awareness is sure to lead to funding opportunities, programmatic support, and potentially improved clinical acceptance. Real advances are being made every day to advance personalized medicine for all patients, including those living with diabetes, and the potential payoff is substantial.

References:

1. U.S. Department of Health and Human Services. Challenge and opportunity on the critical path to new medical products. Washington DC: U.S. Department of Health and Human Services; 2004.