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New Genetic Testing Devices

Paving the Way for Personalized Medicine

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In February 2007 the FDA approved the first molecular genetic profiling test for marketing. However, approval for the "MammaPrint Test," which measures the activity of genes located in breast cancer tumor tissue and helps doctors predict recurrence in patients, occurred while the FDA's final guidance related to genetic profiling tests was still pending. The FDA classified the MammaPrint Test as an "in vitro diagnostic multivariate index assay" (IVDMIA) device.

The regulatory requirements associated with an IVDMIA depend on whether it is a class I, II, or III device. (A device intended as an indicator of a patient's risk of cancer recurrence would be a class I device requiring pre-market notification, while the same device intended to predict which patients should receive chemotherapy would be a class III device that requires pre-market approval.) On May 9, 2007, the FDA published its final rule stating that the MammaPrint test can be classified as a class II device so long as there is sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness of the device. The final rule's effective date was June 8, 2007.

Meanwhile, stakeholders have argued that the IVDMIA definition is unclear and that providers will have difficulty determining which test services qualify as IVDMIAs. Much debate has arisen over the OncotypeDX diagnostic assay, for instance, which measures the likelihood of breast cancer recurrence and patient response to certain types of treatment. The Secretary's Advisory Committee on Genetics, Health, and Society suggested in a draft report, "Realizing the Promise of Pharmacogenomics," that OncotypeDX would fall into the IVDMIA category as defined in the FDA's draft IVDMIA guidance; however, others have stated that this classification is not so evident.

The following three key considerations determine how a genetic test will be classified and regulated:

1. Whether a laboratory uses its own reagents and protocols to develop a "home-brew" or in-house laboratory-developed test
2. Whether the test is performed using a "kit" that is manufactured and sold to clinics or laboratories that perform the test
3. Whether the test is part of a "test system" that uses data and an algorithm to generate a result used to diagnose a disease or condition, or mitigate, treat, or prevent a disease.

Only the primary ingredients of laboratory-developed genetic tests, known as analyte specific reagents (ASRs), are regulated by the FDA. The FDA considers ASRs to be in vitro diagnostic devices, but the ASR regulations themselves do not actually extend to the tests that are made from them unless those tests are sold to clinics or laboratories as kits. While, the FDA regulates genetic tests performed using commercially available ASRs, the FDA does not regulate "home-brew tests" because it believes that laboratories certified to perform "high complexity" tests under the Clinical Laboratory Improvement Act of 1988 (CLIA) have demonstrated the expertise and ability to use ASRs in test procedures and analyses.

The FDA, however, makes an exception from reliance on CLIA certification for laboratory-developed genetic tests used to prescribe treatment, such as IVDMIA devices. In September 2006, the FDA issued draft guidance defining an IVDMIA as a device within the meaning of the Federal Food, Drug, and Cosmetic Act. The FDA believes that the manufacturing of IVDMIAs involves steps that are not within the ordinary "expertise and ability" of laboratories and therefore requires that ASRs used in conjunction with treatment obtain FDA approval. The FDA indicated that characteristics of IVDMIAs, include, but are not limited to the following:

- Use of clinical data and in some cases demographic data to empirically identify variables
- Use of clinical data to derive weights or coefficients employed in an algorithm
- Employment of an algorithm to integrate variables and calculate a patient specific result
- Production of results that cannot be interpreted by another healthcare practitioner without information regarding the test's clinical performance and effectiveness.

In September 2006, the FDA also published draft guidance on commercially distributed ASRs, which explained that the following practices are inconsistent with ASR marketing:

- Combining or promoting for use a single ASR with another product such as other ASRs or general purpose reagents
- Promoting an ASR with specific analytical or clinical performance claims, instructions for use in a particular test, or instructions for validation of a specific test using the ASR.

These marketing restrictions suggest that genetic tests involving ASRs, accompanied by instructions or claims related to personalized treatment performance, would require pre-market approval by the FDA.

Within the next few months, the FDA is expected to publish a final version of its guidance related to IVDMIAs.

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