

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## FDA Regulation of Laboratory-Developed Tests



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### H&O How are laboratory-developed tests (LDTs) being used in oncology?

**VM** In oncology, many LDTs are being used to identify patients who might benefit from targeted therapy. The past decade has seen a large increase in the number of targeted therapies approved by the US Food and Drug Administration (FDA), and many more are currently under investigation. Many of the targeted therapies require a companion diagnostic, meaning an assay that identifies a certain biomarker that can predict whether a patient is more or less likely to benefit from the treatment. With chemotherapy, there is usually a spectrum of response seen among treated patients and thus, in general, companion diagnostics had not been central to drug development. With targeted therapies, the likelihood of benefit is more binary. The manufacturers of these assays should therefore be held to the highest standards because accurate results are essential to allow the patient and doctor to make the most informed treatment decision.

Increasingly, these assays are tissue-based analyses of an alteration in the DNA derived from the tumor. One example is the assay testing for epidermal growth factor receptor (*EGFR*), which is used in conjunction with targeted therapies such as afatinib (Gilotrif, Boehringer Ingelheim) and erlotinib (Tarceva, Genentech/Astellas). The approval of the cobas EGFR Mutation Test v2 (Roche Molecular Systems) for identification of patients with non-small cell lung cancer who may benefit from erlotinib is one such example. For melanoma patients, the cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems) detects mutations in the *BRAF* gene to predict sensitivity to vemurafenib (Zelboraf, Genentech). This simple test looks for a single mutation.

The greater challenge, and opportunity, arises with tests intended for use with therapies that target multiple genes or combinations of genes and identify genomic alterations that are harder to detect with simpler sequencing approaches. There is a continuum of tests. The simpler ones are already on the market. The more complex ones, which may potentially serve to define eligibility for multiple FDA-approved agents, are under evaluation now. An example is a test being developed by Foundation Medicine as a potential companion diagnostic for rucaparib (Clovis Oncology), an investigational poly ADP-ribose polymerase (PARP) inhibitor, that simultaneously evaluates alterations in more than one gene. As the number of targeted therapies increases, assays that identify a single biomarker will become more obsolete.

### H&O What is the FDA approach to the regulation of LDTs?

**VM** Previously, there had been no direct FDA evaluation of a particular assay's merits. In July 2014, the FDA announced its intention to issue a draft oversight framework for LDTs. I believe that the details will be available this year. The FDA has clearly stated that their intention is not to bring the laboratory industry to a halt, but to gradually phase in oversight to provide greater quality and confidence in the results obtained from LDTs.

### H&O What has led to the idea of increased FDA oversight for these tests?

**VM** The key is for the test to be robust in its sensitivity and specificity, and to have been rigorously, analytically validated. Tests that meet these criteria become important

because they distinguish populations that have a certain biomarker and are likely to respond to treatment from populations who do not have that biomarker. Tests that are associated with any meaningful number of false negatives or false positives—causing patients to be deprived of a beneficial treatment or erroneously assigned to a treatment—can be more detrimental than beneficial. The idea of potential FDA oversight of these tests has been raised because the stakes are so much higher now.

In the future, there is the possibility that companies could seek approval of their testing assays or their testing platform independent of the targeted therapy to which it is linked. As an oncologist, it would be reassuring to know that a particular assay has been approved by the FDA, which implies that it has been held to a higher scrutiny.

### H&O How are these tests currently validated?

**VM** The validation process is variable. For pharmaceutical agents, the process is clear and transparent. Data from clinical trials are scrutinized by the regulatory authorities before they issue an approval. With laboratory-developed tests, the key components are the analytic validation and the clinical validation. At Foundation Medicine, analytic validation for our broad-based genomic profiling test required approximately 18 months of work, deep academic collaboration across multiple institutions, and many millions of dollars. We have worked with 3 academic centers to compare our results with those from orthogonal platforms with the same analytes, to define the concordance and adjudicate discordances. The results have been published in a peer-reviewed journal. This approach tends, unfortunately, to be the exception rather than the rule. Oftentimes, the regulatory authorities are unable to obtain insight into the validity of different assays, which has raised the concern that the FDA should more closely scrutinize the laboratories developing these tests. Ideally, there would be a well-established, high standard for analytic and clinical validation.

Some organizations have begun to develop their own guidelines. For example, evidence-based guidelines providing recommendations for testing of the *EGFR* mutation and anaplastic lymphoma kinase (*ALK*) rearrangement in lung cancer have been provided by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. There needs to be a high standard so that the physician and patient can rely on the results from these tests.

### H&O What are the Clinical Laboratory Improvement Amendments?

**VM** The Clinical Laboratory Improvement Amendments (CLIA) were enacted in 1988 by the Centers for Medicare & Medicaid Services (CMS), which has oversight of the CLIA process. These amendments require that clinical laboratories are certified by their state and the CMS before they can accept human samples for diagnostic testing. These regulations attempt to provide some clarity for the different metrics in assay development, assay reproducibility, concordance across laboratories, and concordance within a laboratory. CLIA certification is the first hurdle to the development of LDTs. The CLIA process is a necessary, but perhaps no longer sufficient, process for laboratory certification. In this era of an ever-increasing number of precision medicines, accompanying “precision diagnostics” will be required.

### H&O Are there any other types of LDTs in development?

**VM** There is an interest in identifying DNA changes by assessing circulating tumor DNA. Cells shed by tumors are lysed and then release their DNA content. In some cases, that DNA content can be quantitated and analyzed for the presence of certain mutations. This type of strategy may be helpful in situations in which it is difficult to obtain a biopsy to more comprehensively analyze a tumor.

### Disclosure

*Dr Miller is an employee and stockholder of Foundation Medicine, Inc.*

### Suggested Readings

Clinical Laboratory Improvement Amendments (CLIA). Centers for Disease Control and Prevention. <https://www.cdc.gov/clia/>. Updated March 16, 2015. Accessed March 30, 2016.

Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol*. 2013;31(11):1023-1031.

Laboratory developed tests. US Food and Drug Administration. <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm>. Updated November 17, 2015. Accessed March 30, 2016.

Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol*. 2013;8(7):823-859.

Liu FW, Tewari KS. New targeted agents in gynecologic cancers: synthetic lethality, homologous recombination deficiency, and PARP inhibitors. *Curr Treat Options Oncol*. 2016;17(3):12.