Molecular Diagnostics: Are We There Yet?

In the second decade of the 21st century, we have viewed with awe the seemingly limitless potential of molecular medicine—first unlocking the genetic and epigenetic aberrations that lead to cancer and ultimately developing specific therapies that lack the toxicity and inherent limitations of our current approaches. On the path to this El Dorado is the clear need for the development of assays that can direct therapy. Assays are needed to identify a particular tumor type, confirm efficacy, detect early relapse, and warn of treatment toxicity or impending treatment failure. In serum, we have prostate-specific antigen (PSA), CA125, α-fetoprotein, and human chorionic gonadotropin as biomarkers to confirm effective therapy and detect relapse. In tumors, diagnostics identifying a tumor subset and directing therapy include estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) in breast cancer, EGFR receptor (EGFR) and ALK in lung cancer, BRAF in melanoma, and RAS in colon cancer. In RNA extracted from early-stage breast cancer, a particular gene signature identifies a subset of patients who may not require chemotherapy. In genomic DNA, UGT1A1 testing identifies patients unusually sensitive to irinotecan and dihydropyrimidine dehydrogenase (DPD) testing identifies patients sensitive to 5-fluorouracil (5-FU). In most cases, the slog from a laboratory-developed test to a clinically validated, even U.S. Food and Drug Administration (FDA)-approved test, is a long one. The difficulty of carrying out the many levels of validation needed to develop such tests is the subject of the CCR Focus section in this issue of Clinical Cancer Research. J. Milburn Jessup and Stephen Hewitt as the Guest Editors have assembled a team of experts to examine various aspects and challenges in the development of biomarkers, or molecular diagnostics. With Poste and colleagues, the Guest Editors provide an overview of this complex topic, outlining the transition of an assay from research use to clinical use. Hewitt and colleagues discuss the need to control preanalytic variables, whereas Williams and colleagues discuss the challenges of analytic validation and point to a new National Cancer Institute (NCI) program aimed at supporting investigators in assay development. Schilsky and colleagues discuss the transition to clinical trial, where assays will be used to determine enrollment or treatment arms. Finally, different roles of the government are highlighted, first as Meshinchi and colleagues discuss an expanded role of the FDA in regulating such assays as medical devices, whereas Andre and colleagues describe an approach in France to ensure state-of-the-art testing of tumors in all patients. This CCR Focus series is meant to stimulate translational and basic scientists to think ahead as biomarkers are identified and explored, to think about analytic and clinical validation, and to seek help in moving forward.

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Published online March 15, 2012.
doi: 10.1158/1078-0432.CCR-11-2207
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*Clin Cancer Res* 2012;18:1514.

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