

## It's All About the Test: The Complexity of Companion Diagnostic Co-development in Personalized Medicine

*In the middle of difficulty lies opportunity.*

—Albert Einstein

*We are continually faced with great opportunities which are brilliantly disguised as unsolvable problems.*

—Margaret Mead

These words distill the essence of the topic we present in this *CCR Focus* section. The idea of "personalized medicine" as a paradigm in oncology has captured the imagination of physicians and patients alike. A Google search finds 940,000 hits on the term, and another 109,000 for the term "precision medicine." In this paradigm, a cancer is analyzed by one or more tests that will direct the patient and the physician toward a more effective therapy, and hopefully one that is also less toxic than the "unselected therapies" painstakingly developed before we understood the heterogeneity of the molecular basis of human tumors. And so there has been an increasing focus to find and validate molecular targets for cancer therapy, and then to make drugs for those targets. Notable successes have been achieved in particular cancer types—such as trastuzumab in HER2-positive breast cancer, imatinib for BCR-ABL in chronic myelogenous leukemia, c-KIT in gastrointestinal stromal tumors, vemurafenib for B-RAF mutations in melanoma, erlotinib and gefitinib for the EGF receptor (EGFR) mutation in non-small cell lung cancer (NSCLC), and crizotinib for the ALK mutation in NSCLC. With the development of drugs against these targets has come the recognition that not all tests are equally accurate, although incredibly important decisions are being based on these tests. Although quality, safety, and efficacy standards must be met before a drug can be prescribed to patients, the value of a laboratory test does not have to be proven. Investigators may argue that another layer of oversight in the development of cancer therapies is not desirable, and will limit innovation. However, the wide array of commercially available molecular tests doctors can order and patients and payers can purchase, often lacking the scientific rigor we want, undermines this argument. We are at the threshold of using next-generation sequencing platforms to assess cancers in patients outside of the clinical trial setting. If these tests become widely employed and doctors use the results to support their use of approved agents off-label in "creative ways," we risk having a "lost generation" of information that should be available to future investigators. This *CCR Focus* section addresses these issues and highlights the approaches regulatory bodies in both the United States and Europe have taken in companion diagnostic development. These are complex issues in drug development—the receiver–operating characteristic curve of a test is surely less exciting than the waterfall plot of best responses. Eric Rubin and I, as Guest Editors, have brought together experts to challenge our thinking on this subject. Parkinson and colleagues highlight the importance of proving clinical utility before a test becomes commercially available. Senderowicz and Pfaff examine the differences in regulatory approaches in the United States and Europe that have led to different outcomes for drug approvals. Mansfield discusses the evolution of FDA thinking on this topic, including the mandate that a targeted drug should be co-developed with a test. Pignatti and colleagues discuss the evolution of thinking at the European Medicines Agency. Finally, Byron, Crabb, and their NICE coauthors lay out the Health Technology Assessments that are performed to determine whether tests and drugs will provide sufficient clinical benefit to be routinely used, coming full circle back to clinical utility. These are thoughtful articles meant to inform those working on new cancer therapeutics, and meant to prompt earlier attention to the importance of co-developing both diagnostic test and drug.

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**See all articles in this CCR Focus section, "The Precision Medicine Conundrum: Approaches to Companion Diagnostic Co-development."**

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