

PANEL 3**Co-Development of Diagnostics and Therapeutics***Daniel Hayes, MD, University of Michigan**Steven Gutman, MD, MBA, Food and Drug Administration**Richard Frank, MD, PhD, GE Healthcare**Nancy Roach, C3: Colorectal Cancer Coalition**Richard Simon, DSc, National Cancer Institute**Ray Woosley, MD, PhD, Critical Path Institute***Personalized cancer therapy requires co-development**

For decades, cancer therapies worked by non-selectively inhibiting rapidly dividing cells. The effectiveness of treatments was thus determined by how much toxicity could be tolerated and how well toxicity could be managed. Today, advances in molecular biology, genetics and imaging have enabled the identification of more specific disease targets and the development of therapies which act directly on those targets. Several examples of targeted cancer therapies include the following:

- Endocrine therapies (such as tamoxifen and the aromatase inhibitors);
- Anti-HER2 therapies for breast cancer (such as trastuzumab and lapatinib);
- Imatinib, the first drug to directly turn off the signal of a protein known to cause a cancer; and
- Anti-EGFR therapies for patients whose tumors overexpress the EGFR protein due to a specific gene mutation (such as cetuximab, gefitinib and erlotinib).

Determining whether individual cancer patients are likely to respond to targeted therapies – and thus more effective, efficient use of those therapies – is a key step in fulfilling the promise of personalized medicine. Unfortunately, the development of diagnostic tests to identify patients who will benefit from targeted therapies has typically lagged behind the development of the therapies themselves. A diagnostic test may be developed after a corresponding treatment has received regulatory approval (often aided by archived specimens collected during trials of the therapy); prior to the development of a corresponding treatment (in which case the diagnostic test could be used to measure efficacy of future therapies); or at the same time as the targeted therapy (co-development).

Ideally, therapies and their targets would be developed and approved in parallel, so that both are marketed at the same time. However, few co-development efforts have been successful to date, and the promise of personalized cancer therapy remains largely unfulfilled. This paper will serve as background to the Panel 3 discussion at the Brookings Conference on Clinical Cancer Research by (1) describing the current problems and barriers to development of diagnostics, and (2) identifying promising models for regulatory review of diagnostics in general and for co-development in particular.

Three barriers to effective co-development

Currently, there are three main impediments to the efficient development of diagnostics for tumor markers, which we will define as molecular or process-oriented assays beyond classic hematoxylin and eosin pathology or standard imaging, that indicate future behavior of a cancer – either independently of therapy (designated prognostic factors) or specifically related to the likelihood that a therapeutic strategy will work (designated predictive factors). Summarily, problems exist in the (1) translational research and product pipelines in diagnostics for tumor markers, (2) processes for regulatory evaluation and approval globally, and (3) inadequate reimbursement for innovative, highly effective diagnostics for tumor markers.

Problems in Translational Research and Pipelines

Translation of basic-science discoveries in the field of cancer genomics into products and therapies has been slow in recent years, which has concerned all parties invested in this research area. In order to address this problem, the National Institutes of Health launched the Roadmap Initiative, and the U.S. Food and Drug Administration (FDA) created the Critical Path Initiative (CPI). The CPI delineated the “pipeline problem” for both therapeutics and diagnostics in 2004, noting that the rate of development has declined for new drugs and diagnostics over the preceding several years despite an explosion in scientific discovery.¹ According to Phillips, et al., who conducted interviews with stakeholders from the diagnostics industry and regulatory agencies, addressing translational-research challenges in the area of biomarkers and diagnostics is essential. Specific scientific challenges include identification markers of abnormal cellular signaling pathways, identification of pre-treatment biomarkers that predict patient response to specific therapies, and development of *in vitro* assays and imaging diagnostics with sufficient sensitivity and specificity to be clinically useful. These barriers combine with the issues below to discourage venture capitalists and other investors from funding diagnostics companies’ research, further contributing to an empty pipeline.²

Current Regulatory Challenges

The FDA faces the challenge of simultaneously addressing scientific rigor, practicality, and efficiency in the process of regulating co-developed technologies to use in risk assessment, screening for early detection, diagnosis, staging and prognosis for choice of therapeutic approach, and monitoring of treatment effect for individualization of regimen. Clear understanding of what data are required by FDA to demonstrate the benefits of using a particular biomarker test is essential to warrant pharmaceutical and device companies’ investment in their clinical trials.

Currently, diagnostic and therapeutic products applications are reviewed in two distinct Centers at FDA, each with their own criteria for approval. Different regulatory statutes and standards at the Centers make co-development of tumor markers and drugs particularly challenging. Historically, predictive tests (tests that predict whether a patient will respond to a specific drug) and drugs have been developed separately. For example, the test that evaluates HER2 status in women was developed prior to the research that demonstrated that trastuzumab increased survival in women with HER2+ tumors. It is comparatively difficult to design a clinical-trials program that shows the safety and efficacy of a drug and demonstrates the functionality and clinical utility of a companion diagnostic. This difficulty leads to significant increases in both research costs and time to market. Adding to the complexity are tests that evaluate multiple markers simultaneously, associated labeling changes, and determination of the appropriateness of prospective clinical trials addressing the use of the marker versus *prospectively planned analyses* or retrospective studies of archived tumor samples. Given that diagnostics and therapeutics are equally essential for personalized cancer medicine, addressing these joint issues in their regulatory evaluation is critical.

The imperative is to use “qualified” biomarkers in research and “approved” diagnostics in clinical practice to promote the appropriate use of cancer therapies, resulting in improved patient outcomes, more efficient delivery of health care, and wider access to novel therapeutics and diagnostics.

Inadequate Reimbursement

Reimbursement for diagnostic products by private payers and Medicare does not provide adequate support for sustaining the development and use of new diagnostics that meet criteria for clinical utility. Payment for lab tests is largely based on the tests’ incremental costs, rather than a broader determination of their value. The policies for fee determination and adjustment were enacted in the mid-1980s, and are outdated in light of the newfound importance of molecular diagnostics in targeted cancer treatments. Typically, reimbursement is set by a fee cap, known as the National Limitation Amount (NLA).³ The NLA is calculated in two steps. First, the median fee paid for a specific

test by Medicare's regional carriers is determined. Some of these payment rates, though occasionally adjusted for inflation, are based on lab charges from 1983.⁴ Then the median fee is reduced by a specified percentage; over the years, this percentage has decreased from 115 percent of the median fee for lab fees to only 74 percent.⁵

Fees for new tests are set according to mechanisms known as "gap-filling" or "cross-walking." While the cross-walking procedure applies to tests that resemble pre-existing technology, gap-filling is used to determine reimbursement for innovative tests. The gap-filling procedure gives regional Medicare carriers wide latitude in setting their own payments for a new test. CMS collects this information and uses it to establish an NLA for the test. This process can result in fees that are set below the cost of the test and which cannot be easily changed.⁶

The consequences of poor reimbursement include less investment in new diagnostic tests and the failure of some diagnostics companies. The recent bankruptcy of Immunicon – developer of the first quantitative assay for circulating tumor cells – and the subsequent acquisition of its assets by Johnson & Johnson have been interpreted by some observers in the cancer community as yet another sign that the current reimbursement environment cannot sustain the development and commercialization of diagnostics unless the costs of diagnostics can be subsidized by a corresponding treatment.

But large pharmaceutical companies have also been reluctant to engage in drug-diagnostic co-development. These firms may perceive that diagnostic development slows the drug development process while adding little value to research portfolios. Given current reimbursement policies described above, diagnostics are less profitable than treatments. Thus, diagnostics that result in targeted use of a comparatively well-reimbursed treatment can reduce not only revenue but also profit margins. Drug developers are also sensitive to the risk that an otherwise marketable treatment could be denied FDA approval if its corresponding assay is not approved.

In order to modernize reimbursement and thus the economic incentives for contemporary diagnostic technology, the clinical and economic value of these tests must be demonstrated and communicated to payers and patients in meaningful terms. Such evaluations must consider the cost offsets that come from reduced untargeted utilization of therapies based on the sensitivity and specificity of the test. New models of reimbursement for stand-alone diagnostics may need to differ from reimbursement for diagnostic-therapeutic combinations.

Three recommendations

Perhaps the most direct way to remove the barriers above is to develop a clear path for the co-development, co-review, and co-approval of therapeutic/diagnostic combinations. We recommend three specific lines of activity to accomplish that objective:

- 1) A clear pathway for development of diagnostics for tumor markers should be developed in consultation with the community external to the FDA, and the procedures and timeline for doing so should be clearly outlined in an FDA Guidance. Members of the community that should be engaged in this effort include relevant Device Advisory Panels – in particular, the Immunology and Hematology Panel responsible for providing input on tumor markers – professional societies, and the FDA-convened Oncologic Drugs Advisory Committee (ODAC), made up of extramural experts who assess data on cancer treatments and make non-binding recommendations on whether or not treatments being considered should be approved.

External professional societies possess expertise in diagnostic development. For example, the American Society of Clinical Oncology has had a standing Tumor Markers Guidelines Committee for the last decade, and the National Cancer Center Network has a strong record of developing clinical guidelines that have included use of tumor markers. Likewise, the American Association

for Cancer Research has recently partnered with the FDA and the National Cancer Institute (NCI) to review the field of tumor marker development. These organizations could provide experience and expertise to develop a clear pathway for marker approval, and to generate a committee similar to ODAC to address Tumor Markers (see the third recommendation). However, it is also important to ensure that unique diagnostic and device issues are considered as well by including participation by relevant members of the Center for Devices and Radiological Health and in some, cases, Center for Biologics Evaluation and Research panels.

- 2) Tumor-marker clearance and approval should be based on demonstrated clinical benefit. However, when a marker is being co-developed with a therapy, this pathway should be approached in the most practical manner possible to avoid delay in patient access to a drug known to work.
- 3) An ODAC-like advisory committee should be developed for tumor marker clearance and approval in order to improve consistency and coordination with other oncology programs in the agency. Membership in this system should include an appropriate mixture of expertise including clinicians, trialists, laboratorians, statisticians and representatives of consumer and advocacy groups. The proper mix of expertise is critical to ensure good science and sound public policy.

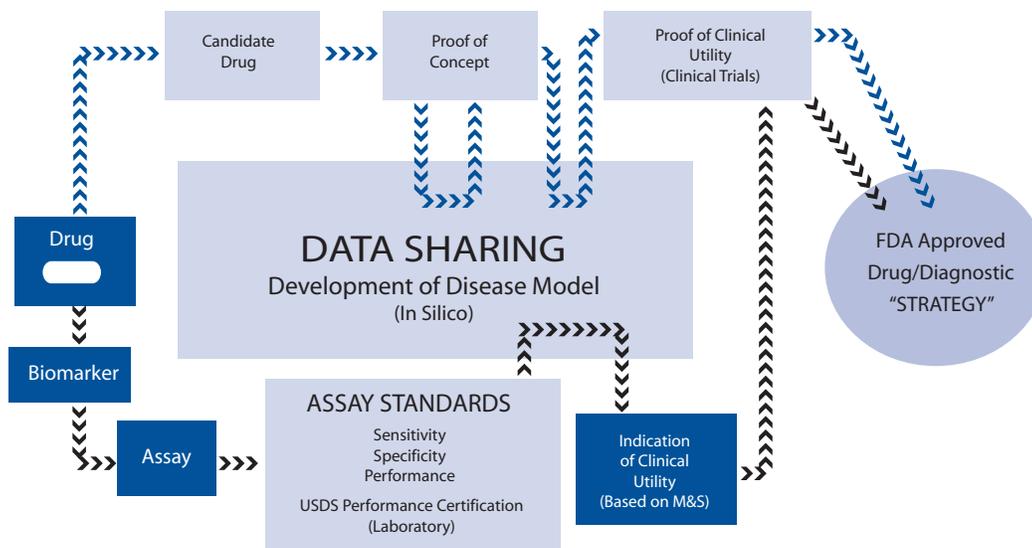
Regulatory review of co-developed combinations

In April 2005, the FDA issued a concept paper, "Drug-diagnostic co-development," which outlined preliminary Agency thoughts on how to prospectively co-develop a drug or biological therapy and diagnostic test in a scientifically robust and efficient way.⁷ Among the important issues discussed in that paper are:

- *Review procedure issues:* processes and procedures for submitting and reviewing a co-developed drug-test product
- *Analytical test validation:* the in vitro ability to accurately and reliably measure the analyte of interest, including analytical sensitivity and specificity, with focus on the laboratory component of drug/test development
- *Clinical test validation:* the ability of a test to detect or predict the associated disorder in patients, including clinical sensitivity and specificity, and/or other performance attributes of testing biological samples
- *Clinical test utility:* elements that should be considered when evaluating the patient risks and benefits in diagnosing or predicting efficacy or risk for an event (drug response, presence of a health condition)⁸

Figure 1, also presented in the concept paper, depicts a possible pathway for the development and regulation of a therapy and a corresponding assay. In this model, the regulatory process is coordinated so that the diagnostic and the therapy would, if approved, enter the market at the same time. Co-development remains on the Center for Drug Evaluation and Research (CDER) Guidance Agenda for 2008, and we recommend that it be prioritized and completed.

The clearance and approval of all diagnostic tests, whether or not co-developed, should be based on demonstrated clinical benefit. However, efforts to refine the regulatory process for diagnostics should also ensure that regulation of biomarkers does not become so burdensome as to discourage co-development and to render tumor-marker evaluation impractical. This can potentially be accomplished by defining different models for study designs addressing the clinical utility of biomarkers for *existing drugs* versus biomarkers that are paired with *new drugs*. Different guidelines for conducting prospective studies versus retrospective analyses of archived samples should also be introduced.

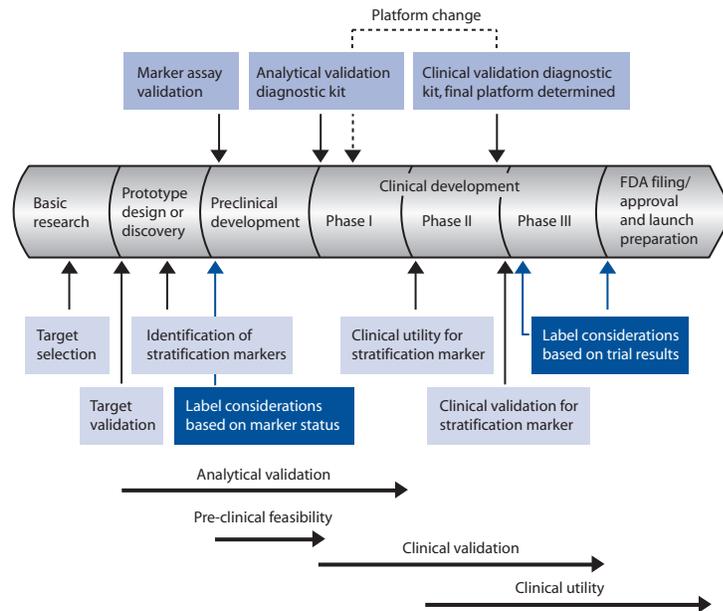
Figure 1. Drug-device co-development process: key steps during development⁹

Finally, an advisory committee similar to the ODAC should be created at the FDA to address co-development of targeted therapies and companion diagnostics. The purpose of this committee would be to improve consistency and coordination across oncology programs at the Agency, allowing for more efficient approval of effective therapies.

A potential scientific approach to co-development

The principal scientific challenge in co-development is the absence of a proven effective therapy to demonstrate the utility of the diagnostic test, and the absence of a proven effective test to demonstrate the effectiveness of the treatment. Because our panel has not evaluated all the possible methods for co-development, we do not provide a consensus recommendation here. However, we describe below one such proposal which we hope will stimulate further discussion of alternatives and solutions.

The Critical Path Institute (C-Path) has proposed a co-development process that employs retrospective data and pre-competitive data-sharing to validate biomarkers by testing their ability to predict patient-level variability in disease outcomes (Figure 2).¹⁰ After a disease target is identified, diagnostic development and treatment development should begin at the same time. To ensure that assays will perform consistently in clinical laboratories across the nation, the creation of an independent laboratory – similar to an Underwriters Laboratory or the U.S. Pharmacopeia – is needed to certify the performance of assays. Once the reliability of an assay's performance is established (certified), the assay's clinical value must be determined. Although it is generally assumed that a clinical trial will determine the assay's clinical value, it is not possible to assess this value if the assay does not correspond to a drug with proven efficacy. In this situation, the disease model can be used to conduct simulations of the possible outcomes of clinical trials with a hypothetical drug (e.g., an EGFR antibody) to test the potential reliability of the diagnostic test. This model would also incorporate the test's performance characteristics into the simulation.

Figure 2. A pathway for co-development using a quantitative disease model¹¹

If the model predicts that the diagnostic test has a reasonable likelihood of accurately identifying a population responsive to the hypothetical drug, the test could then be deemed “qualified” for use in the development of a new drug with the same general characteristics of the hypothetical drug. If a clinical trial finds that the population identified by the diagnostic test has the desired clinical outcome when treated with the drug predicted to be effective, the data would be submitted as a “strategy” for approval by the FDA. Instead of a drug approval or a diagnostic approval, the strategy approved would assume that the drug would only be recommended for use when the diagnostic test predicts a beneficial response—the realization of truly personalized medicine. In this model, Phase III data could be utilized to seek FDA approval of both a therapy and its companion diagnostic test. Analogous efficiencies in regulatory processes should be considered for biomarkers, including imaging, which also quantify treatment effect and enable further individualization of the regimen in accordance with individual patients’ responses to treatment.

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