Evidence-Based Laboratory Medicine in Oncology Drug Development: From Biomarkers to Diagnostics

Vijay Modur, 1* Eric Hailman, 1* and J.C. Barrett 2

BACKGROUND: The promise of targeted therapies in molecularly defined subsets of cancer has led to a transformation of the process of drug development in oncology. To target cancer successfully and precisely requires high-quality translational data. Such data can be generated by the use of biomarkers that answer key questions in drug development.

CONTENT: Translational data for aiding in decision-making and driving cancer drug development can be generated by systematic assessments with biomarkers. Types of biomarkers that support decisions include: pharmacodynamic assessments for selecting the best compound or dosage; assessment of early tumor response with tissue biomarkers and imaging, mutation, and other assessment strategies for patient selection; and the use of markers of organ injury to detect toxicity and improve safety. Tactics used to generate biomarker data include fit-for-purpose assay validation and real-time biomarker assessments. Successfully translated and clinically informative biomarkers can mature into novel companion diagnostic tests that expand the practice of laboratory medicine.

SUMMARY: Systematic biomarker assessments are a key component of the clinical development of targeted therapies for cancer. The success of these biomarker assessments requires applying basic principles of laboratory medicine to generate the data required to make informed decisions. Successful biomarkers can transition into diagnostic tests that expand the laboratory medicine armamentarium.

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Drug development for oncology has been transformed in recent years with the success of molecularly targeted therapies. Targeting agents are designed to inhibit key pathways involved in cancer cell growth and survival without affecting healthy cell populations. This approach aids in maximizing efficacy and safety. Because of the heterogeneity in the mechanisms driving cancers, targeted therapies will often have efficacy only in cancer patients with a given molecular subtype in which the target is a driver of oncogenesis. Development of a new agent in this molecularly defined disease subset can yield a high response rate, but the approach creates the challenge of obtaining enough information from a small patient population that would allow decision-making for the agent’s continued development. The evidence-based application of biomarker studies to answer key translational questions at each clinical stage can aid in decision-making and accelerate drug development.

Crizotinib, a drug highly selective for its target (anaplastic lymphoma kinase), is transforming the treatment of lung cancer. It exemplifies the paradigm of targeted therapy and shows that efficacy can be obtained if a drug can achieve the right exposure in the right patient population (1). Because the drug’s parameters (specificity for its target, the dose achieved, and its safety) were balanced from the beginning to show high levels of efficacy, the development of crizotinib proceeded rapidly, and the drug gained rapid regulatory approval. In the vast majority of oncology drug-development programs, however, initial studies suggest drug efficacy, but subsequent investigations do not confirm it. Biomarkers can be important in these situations for identifying the right patient subsets, optimizing the dosage and treatment schedule, determining the molecular pathways in tumor cells affected by drug exposure, and monitoring for efficacy by using sensitive readouts to enable drug development. To achieve these goals requires an integrated strategy that addresses the key translational questions.

After a drug has shown efficacy in a selected patient population and has become available to patients for routine use, the development of diagnostic tests that aid physicians in managing patients in an evidence-based manner can help maximize the clinical
utility of the drug. At this point, the biomarker continuum shifts from drug development to diagnostics. Therefore, it is not surprising that biomarker efforts in drug development have matured into diagnostic tests over the years to gradually expand the practice of laboratory medicine (Table 1).

In this review, we discuss the impact of biomarker studies when they are applied systematically across drug development in oncology. The approach is based on formulating the key translational questions, identifying the best biomarkers to measure in clinical trials, and applying principles of evidence-based laboratory medicine to generate and interpret the data necessary for making informed decisions. When the principles of evidence-based laboratory medicine are applied, key biomarkers can be classified into 5 categories according to the questions they answer and the impact they have on drug development. In due course, clinically informative biomarkers will have a downstream impact on personalized medicine (Table 2).

Our Understanding of Biological Pathways Drives the Selection of Biomarkers for Clinical Studies

Current targeted therapies in oncology inhibit key nodes in biological pathways that have a diversity of effects. Some of the effects are specific to the tumor, but many also affect normal tissue. Understanding the target, its impact on the pathway, and the downstream biological effects are critical to planning biomarker assessments in trials. For instance, the phosphoinositide 3-kinase (PI3K)3 pathway has attracted major attention as an enabler of tumor progression. Many inhibitors of the PI3K pathway are currently in drug development (2). Classic experiments have shown that numerous receptor tyrosine kinases engage the PI3K pathway, leading to an enzymatic cascade of activating PI3Ks, RAC-α serine/threonine-protein kinase (AKT), PRAS40 (proline-rich AKT substrate of 40 kDa), mTOR (mammalian target of rapamycin), forkhead transcription factors, and numerous other proteins. The downstream biological effects of inhibiting different components of the pathway include changes in glucose metabolism, inhibition of the tumor-proliferation rate, induction of apoptosis, and inhibition of angiogenesis (2). In trials of PI3K inhibitors, knowledge of the pathway is crucial to planning biomarker assessments. Some markers that are immediately downstream of the pathway are suitable for pharmacodynamic (PD) assessments, whereas other markers that are appropriate for assessing the degree of cellular effect on the tumor may serve as important response markers. Finally, markers that indicate a constitutive activation of the pathway have potential for use as selection markers (Fig. 1).

PD Markers

PD markers determine whether a drug engages and inhibits a target—and the degree and timing of the inhibition. This information can be used to make drug-development decisions concerning the proof of mechanism, dose/schedule, selection of best compound, and formulation. In a simple case, if a drug shows a robust PD effect but has no clinical efficacy, the mechanism of action being tested in the selected tumor type is unlikely to be successful. That would necessitate a major review of the path forward. On the other hand, if a drug fails to inhibit its target, alternative approaches (a different compound or formulation) with an improved drug profile might be considered for testing the mechanism of action. In less extreme cases, PD information from a trial is useful for selecting the optimal dose and treatment schedule in phase I/II

### Table 1. Diagnostic tests that have developed from biomarkers used in clinical trials.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Matrix</th>
<th>Associated drug</th>
<th>Utility in drug development</th>
<th>Diagnostic utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTx/creatinine ratio</td>
<td>Urine</td>
<td>Alendronate</td>
<td>Used to assess PD response</td>
<td>Increased concentrations suggest increased bone resorption</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>Blood</td>
<td>Imatinib, nilotinib, dasatinib</td>
<td>Tumor marker</td>
<td>Response monitoring in CMLa</td>
</tr>
<tr>
<td>BRAF V600E mutation</td>
<td>Melanoma tissue</td>
<td>Vemurafenib</td>
<td>Predictive marker</td>
<td>Selection of patients for therapy</td>
</tr>
<tr>
<td>Everolimus TDM</td>
<td>Serum</td>
<td>Everolimus</td>
<td>PK</td>
<td>Dose adjustment</td>
</tr>
</tbody>
</table>

* CML, chronic myelogenous leukemia; TDM, therapeutic drug monitoring.

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3 Nonstandard abbreviations: PI3K, phosphoinositide 3-kinase; AKT, RAC-α serine/threonine protein kinase; PRAS40, proline-rich AKT substrate of 40 kDa; mTOR, mammalian target of rapamycin; PD, pharmacodynamic; PK, pharmacokinetic; RANKL, receptor activator of nuclear factor κB ligand; NTx, N-terminal telopeptide; FDA, US Food and Drug Administration; MMR, major molecular response; CA125, cancer antigen 125; CTCAE, Common Terminology Criteria for Adverse Events (criteria).
Table 2. Classes of biomarkers and their impact on drug development.

<table>
<thead>
<tr>
<th>Translational question</th>
<th>Type of biomarker</th>
<th>Impact on drug development</th>
<th>Impact on laboratory medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is it the right patient—does the cancer express the unique target?</td>
<td>Predictive marker</td>
<td>Selection of the right patient to accelerate development</td>
<td>Diagnostic test to identify patients who will benefit from therapy</td>
</tr>
<tr>
<td>Is the target being hit by the drug?</td>
<td>PD marker</td>
<td>Go or no go, improve formulation or dose, and schedule optimization</td>
<td>Diagnostic test to determine drug effect in individual patients</td>
</tr>
<tr>
<td>Does the drug lead to expected downstream effects?</td>
<td>Mechanism-of-action markers</td>
<td>Design rational combinations; facilitate identification of novel indications</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Do the expected downstream effects lead to clinical efficacy?</td>
<td>Response markers</td>
<td>Early evidence of antitumor effect—accelerate development</td>
<td>Novel tumor marker</td>
</tr>
<tr>
<td>Is there a need to monitor or mitigate toxicity?</td>
<td>Safety markers</td>
<td>Optimization of therapy</td>
<td>Diagnostic test to monitor or mitigate toxicity</td>
</tr>
</tbody>
</table>

trials for subsequent clinical development in phase III trials (Table 3).

To be useful, PD measurements should be available from most—or all—of the patients treated. This consideration has particular relevance during dose escalation in phase I trials, because the number of patients typically treated at each dosage level is small. Ideally, PD assessments should determine whether the target is inhibited in tumor cells; therefore, such investigations require the availability of tumor tissue obtained via biopsy, with the exception of trials for leukemia. Because the feasibility of obtaining high-quality tumor biopsy samples is low for the majority of patients in a first-in-humans trial, surrogate tissues become essential for PD assessments. The surrogate tissues most amenable to routine clinical analysis are blood and skin, although oral mucosa and hair follicles are also potentially useful (3). In practice, PD results obtained with surrogate tissue are combined with data from a limited number of paired (i.e., pre- and post-treatment) tumor biopsies, pharmacokinetic (PK) data, radiology data, and efficacy data to provide an overall view and weighting of the evidence regarding whether the drug exposure obtained at doses used during the trial will be sufficient to inhibit the target. An example of this strategy from a recent trial is described below.

MK2206 is a potent and highly specific inhibitor of AKT, an enzyme that regulates cell proliferation, growth, survival, and metabolism (4). In anticipation of the difficulties in obtaining tumor biopsies in clinical studies, the investigators measured the inhibition of the target in the phase I clinical trial by assessing PRAS40 phosphorylation in plucked hair follicles. The desired levels of target inhibition were consistently demonstrated in hair follicle samples at the maximally tolerated dosage (60 mg administered on alternate days). In addition, analysis of paired tumor biopsies subsequently obtained from a selected set of 9 patients in the trial revealed parallel decreases in AKT phosphorylation of up to 88%. Of the 33 patients in the trial, 6 patients experienced disease stabilization of ≥4 months, and 1 patient with pancreatic adenocarcinoma who experienced a partial response had a 60% decrease in the tumor marker CA19-9 (4). These data demonstrated that MK2206 administered at 60 mg on alternate days inhibits AKT, a finding consistent with the apparent antitumor activity.

The effect of denosumab, a monoclonal antibody that targets RANKL (receptor activator of nuclear factor κB ligand) and thereby inhibits osteoclast activity (5), can be tracked accurately with markers of bone resorption, such as N-terminal telopeptide (NTx), a cross-linked collagen-degradation product (6). Denosumab induced a dose-dependent decrease in the urinary NTx/creatinine ratio, indicating osteoclast inhibition (7). This PD activity therefore was tracked in clinical trials with the urinary NTx/creatinine ratio. The quantitative nature of the urinary NTx/creatinine ratio, PK levels, and the observed variation in the 2 parameters in patients allowed modeling of the PK–PD relationship. Simulation of the model with 2000 virtual patients predicted that a 120-mg dose every 4 weeks would lead to a 90% suppression in the urinary NTx/creatinine ratio in >95% of patients (8, 9). This dosing schedule was implemented in phase III trials of denosumab for treating or preventing prostate cancer metastasis (10), the results of which led to the drug’s recent clearance by the US Food and Drug Administration (FDA). Consistent with the prediction from the PK–PD modeling described above, the selected dose produced a median reduction in the urinary NTx/creatinine ratio of 84% in the denosumab arm of a phase III trial (11).

Response Markers

Tumor markers like major molecular response (MMR) in chronic myelogenous leukemia and cancer antigen
125 (CA125) in ovarian cancer can be used as early-response markers, and even as surrogate clinical end points (12). A threshold level of MMR for the transcript of the chimeric oncogene BCR-ABL (breakpoint cluster region–Abelson tyrosine kinase) at 12 months on therapy has been used as a surrogate marker for the accelerated registration of nilotinib for treating Philadelphia chromosome–positive chronic myelogenous leukemia (13). Not only did nilotinib demonstrate superiority for achieving an MMR, but the number disease-progression events also was reduced, indicating a superiority of nilotinib over imatinib (2 vs 14 events, respectively) at this early time point. This finding underscores the utility of MMR as a surrogate end point. Discovering novel tumor markers that can be used as indicators of drug efficacy can greatly accelerate drug development by replacing conventional measures of outcome, which have longer time courses.

A recent study that compared radiology with CA125 for assessing response in a large phase III clinical trial showed a high concordance between the 2 measures, suggesting that CA125 concentration can be a substitute (i.e., a surrogate marker) for measuring clinical benefit. Given the lower expense and simpler logistics of tumor marker assessments with CA125, more

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**Fig. 1. Potential biomarkers for clinical trials of inhibitors of the PI3K pathway.**

Activation of PI3K by receptor tyrosine kinases (RTKs) leads to downstream signaling via AKT and mTOR, which in turn leads to regulation of glucose metabolism and promotion of angiogenesis, cellular survival, and cell cycle activity. Inhibitors of PI3K, AKT, and mTOR (“blocked” horizontal lines) are currently being evaluated in oncology clinical trials. Our understanding of the mechanism of PI3K pathway activation has suggested biomarkers for clinical trials of these agents. Potential patient-selection markers include genetically induced alterations in upstream RTKs and in the PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) gene, which encodes PI3K. Candidate PD markers include the phosphorylation state of proximal signaling proteins, such as AKT, ribosomal protein S6 (S6), and PRA540, as well as the plasma C-peptide concentration, which reflects glucose metabolism. Biomarkers for early detection of tumor response include tissue-based measures of apoptosis and proliferation, and in some cases circulating tumor markers of disease burden, such as cancer antigen 19-9 (CA19-9), prostate-specific antigen (PSA), and circulating tumor cells (CTCs). PIP2, phosphatidylinositol (4,5)-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PTEN, phosphatase and tensin homolog; PDK1, pyruvate dehydrogenase lipoamide kinase 1; S6K1, ribosomal S6 kinase 1; FOXO, forkhead box protein; GSK3β, glycogen synthase kinase 3; HER2, human epidermal growth factor receptor 2; P, phosphorylation.

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*4 Human genes: BCR, breakpoint cluster region; ABL, Abelson tyrosine kinase; EML4, echinoderm microtubule associated protein like 4; ALK, anaplastic lymphoma receptor tyrosine kinase; EGFR, epidermal growth factor receptor; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; BRAF, v-raf murine sarcoma viral oncogene homolog B1; NRAS, neuroblastoma RAS viral (v-ras) oncogene homolog; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha.*
trials in the future may choose to assess response with CA125 instead of radiology (14).

**Predictive Markers**

The cornerstone of developing oncology drugs for targeted therapy is to identify the molecular subtype with predictive markers to facilitate the selection of patients into clinical trials (15). For diseases in which the underlying mutation is pathognomonic, such as basal cell carcinoma or gastrointestinal stromal tumor, screening for the genetic defect is not necessary. In such instances, patient recruitment does not pose serious logistical challenges. On the other hand, for conditions in which mutations occur in only a fraction of tumors that are otherwise indistinguishable at diagnosis, a plan that includes clinical parameters combined with reflex testing may be necessary in order to select patients. Carrying out such a plan requires robust assays that have been validated analytically for patient selection. Such assay validation needs to conform to the highest level of stringency in the “fit-for-purpose” validation plan (16). Once a validated assay has been established, the logistics of screening patients for selection in a trial becomes critical for success.

In the case of the EML4-ALK (echinoderm microtubule associated protein like 4–anaplastic lymphoma receptor tyrosine kinase) gene fusions in lung cancer targeted by crizotinib, a drug recently cleared by the FDA, screening of all non–small cell lung cancer patients to select those appropriate for therapy yields a selection frequency of approximately 4%–5%. If only light smokers or nonsmokers are tested, however, the frequency increases to 10%–20%; even greater enrichment can be achieved by excluding patients who have previously been tested for EGFR (epidermal growth factor receptor) and KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) mutations (17, 18). Such a strategy of combining clinical stratification with reflex testing can be an important lesson for clinical laboratories concerned with providing cost-effective testing for lung cancer mutations.

Some institutions are conducting molecular subtyping for the most prevalent mutations in many, if not all, tumor samples obtained from incoming patients. The results of such testing are used to select the most appropriate therapy, including participation in clinical trials. The Lung Cancer Mutation Consortium is a National Cancer Institute–sponsored initiative in which patients with advanced non–small cell lung cancer are recruited into a study that provides genotyping in select laboratories, followed by accrual into various trials for targeted cancer therapy. This type of collaborative program benefits individual patients while improving medicine over the long term, and it represents a prototype for the future of personalized medicine and drug development (19).

**Safety Markers**

In oncology, safety monitoring in clinical trials is performed according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria, which had mainly been developed for chemotherapy (20). Because of well-established CTCAE criteria, exploratory safety biomarkers are rare in oncology trials, but the safety of therapies is coming under increasing scrutiny as cancer is being converted from a subacute condition to a chronic disease with lengthening survival times, and as less toxic targeting agents are developed and combined with existing therapies. The role of cardiac troponin measurements in managing the cardiac complications caused by trastuzumab therapy is a clear example of this trend. Of the patients who receive trastuzumab with chemotherapy, 28% develop complications caused by trastuzumab therapy is a clear example of this trend. Of the patients who receive trastuzumab with chemotherapy, 28% develop cardiotoxicity (21). This cardiotoxicity can be detected with high-sensitivity troponin assays, and the long-term cardiac prognosis can be improved by concurrent administration of angiotensin receptor inhibitors and β-blockers (21). This example constitutes the beginning of a trend in which the long-term safety of therapies for cancer will be monitored to improve patient outcomes.

**Validation of Biomarker Assays**

Appropriate validation of analytical assays is the foundation of the systematic approach to biomarkers. Without assay validation, any positive impact of biomarker efforts is not possible. The analytical validation

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**Table 3. Biomarkers used at each phase of clinical development.**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Objectives of trial</th>
<th>Main biomarker focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Safety</td>
<td>Safety markers</td>
</tr>
<tr>
<td></td>
<td>Establish dose</td>
<td>Preliminary PD markers and PK/PD assessments</td>
</tr>
<tr>
<td>II</td>
<td>Proof of concept</td>
<td>Predictive markers</td>
</tr>
<tr>
<td></td>
<td>Patient selection</td>
<td>Advanced PK/PD assessments</td>
</tr>
<tr>
<td></td>
<td>Dose optimization</td>
<td>Potential mechanism-of-action markers</td>
</tr>
<tr>
<td>III</td>
<td>Efficacy to demonstrate patient benefit</td>
<td>Response markers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Predictive markers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mechanism-of-action markers</td>
</tr>
</tbody>
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Clinical Chemistry 59:1 (2013)
of assays includes the process of determining reproducibility, precision, linearity, and spike-in recovery (when applicable), and guidelines from such established institutions as the CLSI have discussed the topic extensively. An important concept for biomarker studies during the early phase of drug development is “fit-for-purpose” assay validation (16). In this approach, assay-validation parameters are allowed to have varying degrees of stringency, depending on the question being addressed. For PD measurements, population analysis of data permits the relaxation of parameters associated with analytical imprecision, because it tends to average out between comparison groups. On the other hand, the stringency for validation should be high for predictive markers, assays for which might be developed into a companion diagnostic test, and the FDA requirements for developing in vitro devices should be given careful consideration.

Real-Time Biomarker Assessments

One of the major components of success for the biomarker strategy is the ability to produce data in a timely manner so that it can positively affect decision-making. Time-sensitive biomarker measurements include predictive markers that allow efficient recruitment into trials and PD markers that can be used during dose escalation for dosing decisions. Time-sensitive assessments stress the chain of biomarker logistics substantially and affect decisions about where and when biomarker analyses are performed. A high level of preparation for the logistics of a trial before it starts—combined with support from the site, site monitors, trial leaders, and the laboratory—is necessary to generate time-sensitive data.

Selection of a Clinical Laboratory for Biomarker Studies

In many cases, assays for the molecular or biochemical biomarkers selected for measurement in oncology clinical trials are not routinely available, a consideration that makes early identification of an appropriate laboratory a key step in ensuring that biomarker data will be available in time to influence drug development. During assay development and validation, flexibility and close communication with clinical and research teams are often the key elements for success in making a biomarker assay available to meet the aggressive timelines of a clinical trial. Other important elements include: a rapid turnaround of biomarker data for real-time assessments, especially during the dose-escalation phase and during the selection of patients for enrollment in a clinical trial; detailed assay validation to ensure the consistency of assay results over time; and quality systems and information technology to ensure the reliable transmission of data for incorporation into the clinical database.

Biomarker assays for clinical trials may be performed by an internal laboratory, a commercial central laboratory, or local or regional laboratories, which are often academic laboratories affiliated with clinical sites. An internal laboratory, i.e., one that is part of the company or entity sponsoring the trial, offers the potential advantages of responsiveness and flexibility, familiarity with the drug program and the internal processes of the sponsor, and opportunities for close collaboration with internal research laboratories that might have developed and used the assay in preclinical studies. Alternatively, a commercial central laboratory will often be able to supply integrated testing, sample management, and data-management services; therefore, it may be able to supply efficient and reliable biomarker testing and data delivery as part of the trial package. Finally, biomarker testing can be done at local or regional academic laboratories in support of clinical trials, a relationship that can provide opportunities to develop novel diagnostic tests.

Development of Companion Diagnostics

The development of therapies targeted for selected patient populations may lead to a requirement to develop and market an in vitro companion diagnostic device, commonly known as a “companion diagnostic.” Although the regulatory guidance regarding the process of developing companion diagnostics is evolving (22), many of the guiding principles have been well established. Given these principles, what is required is a pragmatic approach that includes a strong scientific basis, an analytically validated assay for patient selection, and the systematic collection of extra samples for developing the diagnostic test. In most instances, the pragmatic approach is expected to lead to the following paths, depending on the development paradigm. The first, and ideal, scenario is to use the proposed final test method to select patients for recruitment into a pivotal clinical trial. This path can be followed in a few select instances, when time is sufficient, to identify the marker and then stringently validate an assay that can be mated to a mature diagnostic technology. The recent development of a BRAF (v-raf murine sarcoma viral oncogene homolog B1) gene mutation test in conjunction with vemurafenib therapy for melanoma is a recent example of this path (23). In the second path, the patient population is well described, and patients are selected for clinical trials with accurate assays that perform to the high standards established by industry guidelines. The assay, however, is not the intended final diagnostic test method or platform. In this instance, extra samples are collected systematically from almost
all patients for the purpose of a bridging study for demonstrating a high concordance between the assay used for patient selection and the final diagnostic test needed to satisfy the requirement of the companion diagnostic. This path has been chosen for the assessment of KRAS mutations in excluding patients from treatment with panitumumab for colorectal cancer (24).

Before the initiation of any new pivotal clinical trials, engaging early with regulatory authorities to address any major issues can ensure the timely identification and mitigation of potential problems that could occur on the path leading to successful development of a companion diagnostic. Some of these issues might include: testing the marker-negative population to obtain the negative predictive value of the test, determining the adequacy of the bridging studies if a bridging approach is to be used, and assessing whether the patient pool used for patient selection would be different from the patient population likely to use the diagnostic test. Owing to the rapid evolution of the field of oncology therapy, some issues may never be resolved by the time of the launch of the drug/companion diagnostic.

The Future

Biomarker and diagnostic advances in oncology drug development can create a positive feedback loop between bench and bedside that can lead to rapid advances in drug and diagnostic development. For instance, the analysis of data from long-term targeted therapy for chronic myelogenous leukemia has shown that the decrease in the BCR-ABL transcript is biphasic, with an early phase of rapid decline followed by a slow and sustained phase of decrease. Mathematical modeling suggests that the initial phase is associated with tumor debulking and that the subsequent slower response reflects the reduction of a slowly proliferating compartment resembling cancer stem cells (25). Parallel studies have established molecular mechanisms that underlie the persistence of early tumor progenitor cells, and they have proposed novel combination therapies to target both the tumor bulk and the early-progenitor compartment with a combination of a tyrosine kinase inhibitor and a hedgehog signaling pathway antagonist (26). Designing and carrying out new clinical trials to test such combinations may determine whether a cure for chronic myelogenous leukemia is possible with drug therapy alone. Nevertheless, creating such a positive feedback loop between biomarkers and basic research is inevitable and is expected to provide a source of opportunities for pharmaceuticals and diagnostics.

Knowledge of the oncogenic drivers and matching targeted therapies is changing the way patients are classified and treated. The rapid fragmentation of melanoma with therapies specifically targeting mutations in the molecular drivers BRAF, NRAS [neuroblastoma RAS viral (v-ras) oncogene homolog], and KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) is an example of the future of cancer therapy (27). Some clinical laboratories have already taken a leap forward by offering testing of melanoma samples for these genotypes. Such testing goes beyond currently available therapies and allows patients to seek out clinical trials with novel agents. The future success of these novel therapies may convert melanoma to a chronic long-term affliction that requires the monitoring of patients with novel tumor markers. Such developments may lead to profound alterations in patient management, emphasizing the importance of evidence-based laboratory medicine.

Some of the changes are already on the horizon. Recently Medco, a pharmacy benefit manager, has launched Advanced Oncology Solutions™, which links patient prescriptions to specific laboratory tests associated with targeted therapies, to ensure that patients are assessed with the best available laboratory evidence (28). As electronic health records roll out, it will become easier to link patients’ diagnoses and laboratory tests, thereby improving patient care and entraining the practice of evidence-based laboratory medicine into a patient’s journey through the healthcare system. At the same time, the relationship between drug development and laboratory medicine is becoming closer, which is likely to lead to advances with tremendous patient benefits. As the momentum for these changes continues to grow, the practice of laboratory medicine will become increasingly important for patient care.

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