Predictive Biomarkers in Advance of a Companion Drug: Ahead of Their Time?

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Abstract
Because of a surge in molecular testing capabilities concurrent with the rising numbers of targeted therapies in clinical development, the commercial use of predictive biomarkers before clinical validation is available is a topic of growing relevance to medical oncologists. Increasingly, patients will present questions about, requests for, and results from commercial biomarker tests for their oncologists to address. The sheer numbers of tests reaching the market, along with forecasted American Medical Association reforms in current procedural terminology coding and increasing FDA oversight of in vitro companion diagnostic device development, are likely to draw intense scrutiny to the regulation of commercial molecular testing in the near future, which will also require clinicians to remain abreast of the level of clinical validation of the biomarker tests available in practice. In addition to the direct risks of novel biomarker testing, including financial cost and ethical issues, the indirect risks encompass those associated with any clinical decision based on the biomarker test results. A great need exists for comprehensive and dynamic practice guidelines for all types of biomarker testing according to tumor type. (JNCCN 2012;10:303–309)

Among the records that accompany new patients to a medical oncologist's office, it is increasingly common to find a report from a commercial molecular diagnostic laboratory characterizing a wide array of genetic features of that patient's tumor. Desperate to hear the oncologist's interpretation of their tumor's unique features, patients may ask about the significance of a PI3KCA mutation, epidermal growth factor receptor (EGFR) gene amplification, or a specific gene signature with respect to the treatment decisions ahead. These conversations are becoming more common and are likely to increase with an unprecedented wave of new cancer biomarker tests approaching the market.

Although using the unique features of tumors and hosts to guide treatment decisions is a long-sought goal of personalized medicine in oncology, many new biomarker tests lack sufficient evidence for clinical validity and/or utility. This is particularly true for assays intended to predict the toxicity or efficacy of drugs that remain in clinical development with unproven clinical benefit. The discordant commercial maturation of therapeutics and their companion biomarkers arises largely from disparate development and regulatory environments and,
ultimately, leads to the question at hand: how and when should novel predictive biomarker tests be integrated into clinical practice in relation to their cognate targeted therapeutics?

As an index of the timeliness of this question, in July 2011 the FDA released a new draft guidance on the development of in vitro (IVD) companion diagnostic devices, defined as devices that “provide information that is essential for the safe and effective use of a corresponding therapeutic product.”

Assays to identify predictive biomarkers associated with treatment response or toxicity are a subset of IVD companion diagnostic devices with particular relevance to the development of targeted therapeutics in oncology. The new FDA guidance intends to establish a role for FDA clearance or approval of IVD companion diagnostic devices when included in FDA labeling of a therapeutic product, based on the risk of harm when devices without adequate analytic and/or clinical validation are used to guide treatment decisions. Analytic validation shows the technical performance of an assay, including its precision, reproducibility, and accuracy, in relationship to a gold standard; clinical validation refers to a test result’s significant association with a specific clinical end point, such as response to a particular drug or class of drugs, recurrence risk, survival, or toxicity.

Following on the themes of this FDA draft guidance, this article discusses the complex issues presented by the increasing commercial availability of many predictive biomarker tests in oncology while the drugs whose benefit they predict remain in the investigational realm.

**The Promise of Predictive Biomarkers**

Emerging technologies facilitating the comprehensive molecular analysis of tumors confer great potential to identify therapeutically relevant characteristics of a patient or a patient’s cancer that may anticipate toxicity, efficacy, or both. The identified molecular events, collectively referred to as biomarkers, may include critical driver mutations, evidence for addiction to a signaling pathway, or features suggesting sensitivity or resistance to a specific class of therapy, such as DNA damaging agents, on the part of tumor or host. Predictive biomarkers are vitally intertwined with the treatment strategies whose benefit or risk they anticipate, leading to an evolving paradigm of codevelopment. The ultimate goal is to use biomarker assays to identify patient subpopulations who will experience greater benefit and/or less toxicity from the drug being developed. Recent proofs of principle include the demonstration of efficacy of vemurafenib in BRAF V600E mutant melanoma, crizotinib in ALK-rearranged non–small cell lung carcinoma (NSCLC), and EGFR inhibitors in patients with NSCLC whose tumors harbor EGFR mutations.

At a growing number of academic centers and commercial reference laboratories across the country, patients with advanced cancers undergo comprehensive tumor molecular analyses in search of therapeutically relevant biomarkers. Early-adopting centers may use the identified mutations to guide assignment to clinical trials of novel targeted therapeutics. At the 2011 ASCO Annual Meeting, investigators from the MD Anderson Cancer Center (MDACC) reported their analysis of up to 11 cancer-associated mutations in tissue from 1144 potential candidates for phase I trials. In 60% of tumors, no mutation was found, whereas a single mutation was identified in a third of cancers. A matched investigational therapy was available for 175 patients (15.3% of the overall study population). Compared with patients who received unmatched therapy, patients treated with matched therapy had significantly better response rates (27% vs. 5%; \( P < .0001 \)) and improved median overall survival (13.4 vs. 9.0 months; \( P = .017 \)). Although this design cannot fully distinguish prognostic from predictive strength of the matched mutations, and is limited by the lack of randomization, the example of the MDACC initiative hints at the promise of matched therapy while highlighting the enormous resources required to make it available to all patients.

**What Lies Ahead on the Market**

Building on the examples described earlier, a broad range of technologies is increasingly accessible and affordable for tumor and host molecular testing in patients with cancer outside of the confines of a clinical trial. These technologies focus on either genetic (DNA-based) changes or phenotypic (such as RNA- or protein-based) molecular markers. Most DNA-based tests are currently designed to detect point mutations through polymerase chain reaction amplification and direct sequencing, or through more
sensitive and efficient methodologies, such as mass spectrometry, fluorescent probes, and multiplex assays. Although these assays are straightforward and amenable to analytic validation, they currently focus on 1 to more than 100 known mutations. For copy number changes, deletions, or translocations, fluorescence in situ hybridization is frequently used for specific known events, and array comparative genomic hybridization (aCGH) used for broader assessment.

For phenotypic molecular markers, immunohistochemistry continues to be a standard approach with which to interrogate aberrations in single protein expression, whereas complex signature-based assessments, typically using either RNA arrays or reverse-phase protein arrays, may be better suited for robust assessment of pathway activity or drug sensitivity. Next-generation sequencing options, including exome or whole-genome sequencing, although providing additional challenges with respect to analytic validation and incorporation into molecular diagnostic laboratories, are likely to become increasingly available as data analysis capabilities are streamlined and have the potential to simultaneously assess both genetic and phenotypic molecular markers.

A recent report from the Tufts Evidence-Based Practice Center under contract to the Agency for Healthcare Research and Quality identified more than 100 genetically based tests for cancer-related conditions that are currently commercially available and often marketed via direct-to-consumer methods. The number of available tests on the market is expected to grow significantly in the next decade with the evolution of both new biomarkers and technologies.

Commercialization Before Clinical Validation

Most predictive biomarker assays are considered laboratory-developed tests and currently are regulated according to the quality standards established by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which require analytic validation of a test’s performance. For a molecular biomarker to be used to guide care of a patient, it must be performed in a CLIA-certified laboratory. However, although performance of the assay in a CLIA-certified laboratory helps ensure analytic validation, the assay is not required to have shown clinical validity for association with a specific clinical decision. Simply put, performance of an assay in a CLIA-certified laboratory helps ensure that assays are accurate, precise, and reproducible, but provides no assurance that the result has any clinical significance. Given the increased analytic complexity associated with emerging molecular biomarkers, particularly for the subset of biomarkers based on a gene signature or multiplex mutational assays, analytic validation is a necessary first step in biomarker development, and is necessary before proceeding with testing for clinical validation.

The FDA requires clinical validation and proof of safety before commercialization of new drugs and genetic tests sold as kits for widespread use in hospitals, laboratories, or physicians’ offices. Although laboratory-developed tests that are not packaged into kits and are performed at a single or small number of reference laboratories are within the purview of the FDA, they have not been subject to significant regulation because of discretionary enforcement on the part of the agency. The recent FDA draft guidance on the development of IVD companion diagnostic devices suggests that the requirement for FDA approval may be expanded in the future to include those predictive biomarker tests intended for use as companions to targeted therapeutics, independent of kit status and use setting, although the downstream effects of this draft guidance remain to be seen.1 In addition, the FDA has recently reconsidered its discretionary enforcement policy and is likely to start providing more oversight for laboratory-developed tests, at least those considered high-risk, and producers of the assays may need to provide evidence for both analytic and clinical validation.

Currently, many if not most of the commercially available predictive biomarker tests in oncology remain to be validated by sufficient clinical evidence to justify their use as companion diagnostics. This is largely because of the differences in developmental paths and current regulation of drugs and in vitro diagnostics, the historically low frequency of biospecimen collection and assessment in early- and late-stage trials, and a waning concern on the part of drug manufacturers that companion diagnostics may unnecessarily limit market size. In addition, for predictive biomarkers whose efficacy is linked to that of a specific therapeutic or class of therapeutics, their clinical validation cannot be achieved in advance of
that of the therapeutics in question. As a result, only a small subset of commercially available biomarker tests are recommended for clinical use by the practice guidelines of the NCCN or other organizations, and an even smaller fraction of these are recommended for use as companion diagnostics.

The Allure of Adopting Novel Predictive Cancer Biomarkers Into Practice

Strong arguments can certainly be made in favor of performing novel predictive biomarker testing in oncology patients before the approval of the associated targeted therapeutics, especially when the therapeutics are available in the investigational setting. For example, in motivated and fit patients with life-threatening cancers for whom standard treatments have failed, commercially available biomarker testing may inform and refine the search for a clinical trial, thereby sparing the time, expense, and lost opportunity of determining eligibility for multiple trials of targeted therapeutics without advance knowledge of biomarker testing results. Oncologists may also be inclined to recommend commercial biomarker testing in patients with a dismal prognosis in the hope of identifying a target that would confer eligibility for a clinical trial even before the failure of standard therapy, under the premise that an unknown benefit exceeds the expected benefit from standard therapy. Additionally, commercial testing enables a small percentage of patients to receive treatment through compassionate use programs for drugs such as crizotinib or vemurafenib, which are in the later stages of drug development but not yet labeled by the FDA for commercial use. Understandably, patients with incurable cancer and their providers want to use all available resources to maximize quality and quantity of life while minimizing treatment side effects, and aggressive early adoption of predictive biomarkers is a natural manifestation of this dynamic.

Hazards and Risk of Harm From Predictive Biomarkers Without Clinical Validation

The indirect risk associated with any clinical decision stemming from the inappropriate use or premature adoption of any biomarker test result must be recognized as a risk of the biomarker. A fundamental premise of the new FDA draft guidance on IVD companion diagnostic devices is the potential for “severe therapeutic consequences” when these devices have inadequate analytic and/or clinical validity. Whether the decision is to give or withhold a particular standard chemotherapy agent or to recommend a clinical trial of a targeted therapeutic, a distinct risk of harm is present when using predictive biomarker test results in clinical practice. This risk is particularly germane when mature validation studies lack evidence of efficacy and safety of both the marker and the agent. In patients found to have a specific genetic aberration on comprehensive testing, a decision to forego a standard treatment option in favor of participation in a clinical trial of an associated targeted therapy can result in significant toxicity and the lost opportunity to receive alternate treatments if the targeted therapy proves inefficacious. Finally, predictive markers for drug sensitivity, such as RNA-expression patterns, may reflect host sensitivity rather than tumor sensitivity, and using these markers to guide therapy may be associated with increased toxicity rather than increased efficacy.

An important consideration for the clinician when presented with comprehensive biomarker testing results is that a specific target genetic aberration may play different roles depending on the tissue of origin, potentially because of differences in cell signaling across tumor types. This principle may explain the apparent differential efficacy of vemurafenib as a single agent in melanomas and colorectal cancers harboring BRAF V600E mutations. Also instructive is the recent finding that KRAS G13D mutations may not be associated with nonresponse to EGFR-targeted antibodies in advanced colorectal cancers, unlike other codon 12 and 13 mutations. These examples show that a biomarker with clinical validity in one tumor type may not apply to others, and that seemingly subtle variations in a biomarker test result may greatly alter the test’s meaning. Because of this high degree of complexity, clinical decision-making using biomarker assays cannot be extrapolated from one setting to another in advance of the data.

Although increasingly affordable, testing costs can range from hundreds to thousands of U.S. dollars, and the financial cost of commercial biomarker testing is another potential downside. Payor reimbursement is variable. Currently, “stacking” current procedural terminology (CPT) molecular test codes
Biomarkers in Advance of a Companion Drug

(wherby a separate code is submitted for each of the individual molecular pathology services required to perform a given assay, such as nucleic acid extraction, polymerase chain reaction, and sequencing) is used for most biomarker tests. The stacking codes model obscures rigorous study of adoption and reimbursement patterns for individual tests. In 2012, a reform of this process by the American Medical Association (AMA) is expected to require that most individual tests are billed under a unique CPT code, thereby enabling identification and tracking of the test being performed. The AMA reform may influence payer reimbursement practices, and may draw increasing scrutiny to commercial molecular diagnostic testing by payors and policymakers. In other cases, patients may pay for the cost of testing themselves, leading to a spectrum of ethical concerns pertaining to access to testing, particularly with the prevalence of direct-to-consumer test marketing.

Following on these questions surrounding cost and access to testing, myriad other ethical, legal, and social implications (ELSI) arise when examining the role of genetically based tests in oncology, and in medicine in general. These complex issues, although beyond the scope of this article, are an important area of study and have led to the development of the ELSI Research Institute within the National Human Genome Research Institute (http://www.genome.gov/ELSI/), and support from the NCI for projects and centers studying the translation of genomic-based testing into policy and clinical practice, such as the Center for Translational and Policy Research on Personalized Medicine (TRANS Perez) at the University of California, San Francisco (http://clinicalpharmacy.ucsf.edu/Transpers/center/).

The Interface Between Predictive Biomarker Testing and Clinical Research

Collectively, the issues of inadequate clinical validation, risk, and the codependent relationship with investigational therapeutics strongly support the intensification of biomarker research. These issues, along with the surge in development of targeted therapies and molecular testing capabilities, have drawn high-level attention to the essential requirement for biomarker integration into drug development, leading to models for drug testing in both biomarker-positive and biomarker-negative cohorts; support for enrichment and adaptive trial designs; and the recognition that significant additional resources are required to perform companion molecular testing and to generate prospective, clinically annotated biorepositories. The FDA has also developed new biomarker qualification guidance and new draft guidance on the development of IVD companion diagnostic devices, which address the complex issues of the drug and diagnostic relationship.

When performed outside of the research setting, commercial biomarker “pre-testing” offers the advantage of accelerated accrual to clinical trials of targeted therapeutics, particularly in the case of rare targets, and may improve the options and outcomes for some patients. However, beyond the paramount counterpoint, which is the risk of harm discussed earlier, commercial biomarker testing outside of the research setting also fails to capture a wealth of data, from prevalence to associations with diagnosis, prognosis, and treatment response, which collectively are essential for biomarker clinical validation. Whether commercial biomarker testing results in a greater, lesser, or the same number of patients who subsequently undergo similar testing in the research setting is unknown. Biomarker pre-testing also creates a new type of selection bias in clinical trials of targeted therapies through enriching the screened populations for the target in question, resulting in study populations also enriched for access to this testing and invalidating comparison to historical controls.

With adequate resources, an optimal model may be to perform tumor molecular analyses in all consenting patients with advanced malignancies treated at cancer centers with access to investigational therapeutics programs, directed according to the type of cancer but independent of a specific clinical trial, in addition to the companion diagnostic device testing that will increasingly be a part of individual investigational therapeutic trials. This testing should be conducted under the auspices of biospecimen research with attendant informed consent, banking of clinically annotated specimens when feasible, and longitudinal registries.

The importance of following patients over time and linking clinical outcomes with molecular biomarkers and therapeutic interventions cannot be overstated. Given the fragmentation of organ-based cancer classification occurring as molecularly defined subgroups are recognized, little likelihood exists that
prospective trials will be feasible for all matches between predictive molecular diagnostics and specific therapeutic. As a result, clinicians are likely to be dependent on retrospective analysis of biomarker–treatment pairs and, for this retrospective analysis to be believable, multiple independent repositories.

Variations on this model are in practice at selected centers, including MDACC as described earlier, and promise to move the field forward while achieving the immediate advantages of biomarker testing, including the expeditious matching of patients to targeted therapy trials based on tumor profiling, and the identification of patients who may be candidates for a compassionate use program.

Conclusions

Because of a surge in molecular testing capabilities concurrent with the rising numbers of targeted therapies in clinical development, the commercial use of predictive biomarkers before clinical validation is available is a topic of growing relevance to medical oncologists. Increasingly, patients will present questions about, requests for, and results from commercial biomarker tests for their oncologists to address. The sheer numbers of tests reaching the market, along with forecasted AMA reforms in current procedural terminology coding and increasing FDA oversight of IVD companion diagnostic device development, are likely to draw intense scrutiny to the regulation of commercial molecular testing in the near future, which will also require clinicians to remain abreast of the level of clinical validation of the biomarker tests available in practice. In addition to the direct risks of novel biomarker testing, including financial cost and ethical issues, the indirect risks encompass those associated with any clinical decision based on the biomarker test results. A great need exists for comprehensive and dynamic practice guidelines for all types of biomarker testing according to tumor type.

The most important conclusion arising from these points is the imperative for wide-reaching and systematic predictive biomarker integration in the clinical research arena to harness the immense potential, and limit the risk, of molecularly targeted therapies in oncology.

References


