

Making Personalized Cancer Medicine a Reality: Challenges and Opportunities in the Development of Biomarkers and Companion Diagnostics

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Abstract

The origins of this article stem from discussions at the American Association for Cancer Research Clinical and Translational Cancer Research Think Tank meeting held in San Francisco in early 2010. This article synthesizes the opinions and issues considered at that meeting, and discusses many of the important events that have since occurred in the field of personalized cancer medicine. Although investigators continue to make progress in better linking individual patient biology with risk determination, diagnosis, prognosis, and treatment selection, the pace of this progress continues to be limited by many of the issues identified in the meeting. *Clin Cancer Res*; 18(3); 619–24. ©2012 AACR.

Introduction

More than a decade of clinical experience with biologically targeted cancer therapeutics has both revealed their great potential and exposed the inadequacies of historical pathology-based classification systems as a basis for treatment selection. Studies have repeatedly shown the biologic heterogeneity of patients who have been categorized within classically defined disease entities. It is now generally acknowledged that improved biologic profiling of individual patients is needed in order to better link patients with biologically relevant targeted therapies. This approach has been variously labeled as personalized medicine, stratified medicine, precision medicine, and other variably satisfactory terms that try to express the principle that to achieve maximum effectiveness, targeted therapeutics require biologically characterized patients. Despite this general recognition, the pace of progress in linking targeted therapies with appropriately characterized patients (personalized medicine) has been frustratingly slow. Part of the difficulty relates to the complexity of the biology involved and the incomplete definition of the pathogenesis of different malignancies. However, a significant difficulty is also posed by the complexity of the process involved in translating new biologic and technologic developments into routine clinical medicine. This complexity includes the large numbers of stakeholders who are involved in this process, as well as technologic, clinical, regulatory, reimbursement,

and educational challenges. If progress is to be made in this area, these hurdles need to be recognized and overcome. Participants in the American Association for Cancer Research (AACR) Clinical and Translational Cancer Research Think Tank meeting held in San Francisco in early 2010 (1) identified the AACR as an organization that is ideally structured to play a catalytic role in this transition to more biologically driven cancer drug development and treatment. In this article we summarize the issues raised during the workshop, comment on recent progress in this area, and identify strategies to address potential hurdles.

Progress Toward Achieving Personalized Cancer Medicine: Recent Successes in Linking Therapeutic and Companion Diagnostic Development

The value of linked therapeutic and diagnostics development is shown by the example of 2 targeted therapies for solid tumors that were recently approved by the U.S. Food and Drug Administration (FDA) simultaneously with a companion diagnostic to identify enriched subpopulations of patients who are more likely to respond to the drug (Table 1). In August 2011, the drug crizotinib (Xalkori; Pfizer) was approved for the treatment of patients with late-stage non-small cell lung cancer (NSCLC) whose tumors have an *ALK* gene rearrangement (2). A companion diagnostic (Abbott Laboratories) that identifies the different translocations was simultaneously reviewed and approved by the FDA. The *ALK* rearrangement is found in 3% to 7% of NSCLC patients, and therefore conventional development of this drug in unselected NSCLC patients would likely have been unsuccessful. In the same month, the drug vemurafenib (Plexxikon/Daiichi Sankyo/Genentech) and its companion diagnostic, the Cobas 4800 *BRAF* V600 mutation test [developed through Roche Diagnostics (3)], were approved for use in melanoma. This mutation is found in

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Table 1. Recent contemporaneously approved targeted anticancer drugs and their companion diagnostics

| Drug | Target/ malignancy | Diagnostic | Therapeutic developer | Diagnostic developer | Approval date |
|---------------------------|-----------------------|--|----------------------------|---------------------------------|---------------|
| Zelboraf (vemurafenib) | <i>BRAF</i> | Cobas 4800 <i>BRAF</i> V600 mutation test | Daiichi Sankyo Roche AG | Roche Molecular Diagnostics | August 2011 |
| Xalkori (crizotinib) | <i>ALK</i> | EML-4 <i>ALK</i> mutation | Pfizer, Inc. | Abbott Molecular Diagnostics | August 2011 |

NOTE: These drugs were recently approved after parallel review by the FDA's Center for Drug Evaluation and Research and Center for Devices and Radiological Health.

~60% of melanomas and less commonly in other solid tumors. Melanomas that lack the mutation are not inhibited by the drug; therefore, identifying the population of patients who would more likely benefit from the treatment accelerated development of the drug facilitated a successful regulatory review and led to an improved therapeutic profile. These examples illustrate the benefits of parallel diagnostics and therapeutics development and regulatory review. However, they also show how much remains to be accomplished with respect to continued biomarker and companion diagnostic development. First, the contemporaneous approvals represent rare events in combined marker and drug approval. Second, the value of the patient selection is limited in that not all patients respond even within these marker-selected enriched patient groups, and the responses achieved vary significantly in extent and duration.

These recent successes also highlight the very real challenges involved in the attempt to achieve therapeutic individualization, particularly with respect to clinical trial design and execution (4). Efficient administration of an agent such as crizotinib, which targets a small fraction of patients with NSCLC, naturally implies the screening of a large number of patients (e.g., 20–25) for every patient who might be eligible for a trial. This number increases significantly when one includes the effects of exclusion criteria and informed consent in reducing the number of patients entering clinical trials. The cost of development of diagnostic tests; the infrastructure required to access, distribute, and process clinical trial tissue samples; and the regulatory requirements associated with the use of such tests (e.g., performance of the tests under stringent regulatory requirements in certified laboratories) are substantial. The burden on clinical investigators (e.g., obtaining appropriate tissues and informed consent for testing) and local institutional review boards is increased by additional underappreciated and frequently unreimbursed costs.

Challenges to the Development of Personalized Medicine

Remarkable technologic advances have enabled major progress in the genomic characterization of patient tissue

samples. Improved methods for genomic sequencing and gene expression and proteomic technologies conducted at both tissue and single-cell levels of resolution are providing important new information. These results reveal an important biologic heterogeneity not only among patients with similar clinical diagnoses but also within the individual patient's malignant cell populations (5). Considerable work is being devoted to achieving a biologic definition of individual patient risk and predicting therapeutic effectiveness. Much of the research conducted to date has been done by academic biomedical investigators. Although it is necessary to define the relationship between biology and therapeutics, this level of investigation is not in itself sufficient to change clinical practice. For clinical practice to change, investigators in clinical laboratories must use rigorous methods to develop commercially available tests that can meet the requirements of regulatory review. In addition to passing regulatory requirements, such tests increasingly must be shown by their developers to have clinical utility, that is, they must add to the quality of patient care and/or introduce health care efficiencies. Developers of this level of clinical test face major practical hurdles, as discussed below.

Regulatory Considerations

The FDA, as evidenced by its decade-old Critical Path Initiative, has long been supportive of efforts to use newer biologic characterizations of different cancers to improve drug efficacy in patients. In addition, the Voluntary Exploratory Data Submissions program, first introduced in 2004, has enabled companies to discuss genetic and other biologic information related to their therapeutic agents outside of the formal regulatory submission process (6). Yet, even though the first approval of a therapeutic linked with a diagnostic test [trastuzumab (Herceptin; Genentech) with the HercepTest for breast carcinoma] was granted in 1998, there remains considerable uncertainty with respect to the regulatory status and paths for review of clinical tests linked with the use of therapeutics.

The approval of laboratory tests falls under FDA medical device regulation and is carried out by the FDA's Center for Devices and Radiological Health. Some 30% of the clinical trials regulated by the FDA are subject to Investigational

Device Exemption regulations, under 21 Code of Federal Regulations (CFR) 812. The other 70% of FDA-regulated clinical trials involve drugs and biologics, and are regulated by Investigational New Drug regulations (21 CFR 312) by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. Although the observation of Good Clinical Practice, a regulatory definition, pertains to both device- and drug-associated clinical trials, the development of diagnostic tests for such trials involves unique considerations. Tests have to be developed and carried out in laboratories that have been certified according to the Clinical Laboratory Improvement Act of 1988 (CLIA) through an accreditation process managed by the Center for Medicare Services. Many of the specialty laboratory tests that have been developed in recent years have been classified as laboratory-developed tests (LDT). LDTs are developed in specific CLIA-accredited laboratories, such as university hospital laboratories. Even if a test meets the CLIA requirements of analytical validity, in that it has been shown to be both accurate and reproducible within the laboratory, it may not be submitted for FDA approval. Uncertainty in the diagnostics industry increased recently after the FDA made a series of public statements, held a number of meetings, and issued warning letters to diagnostic test developers stating that it intends to more closely regulate higher-risk clinical tests, such as LDTs associated with clinical therapeutic decisions. This situation was clarified recently with the FDA's issuance of a series of draft guidances (Table 2), including an important draft guidance for comment on *in vitro* companion diagnostic devices (7). Although at this writing it still a draft guidance for comment, important points are made

in the document, including the definition of an *in vitro* companion diagnostic device as one that identifies patients who are most likely to benefit or be at risk from a therapeutic product, or one that monitors response to treatment for the purpose of adjusting treatment. The guidance also addresses the various issues involved in developing a diagnostic with an investigational agent as opposed to an already approved therapeutic. It also notes the desirability of codeveloping therapeutics and parallel diagnostics, emphasizes the value of early consultation with regulators, and commits regulators to the performance of timely parallel reviews. Of importance, it states that an Investigational Device Exemption (IDE) review will be expected for any clinical trial in which treatment decisions, including patient selection and treatment assignment, are based on a biomarker. In this situation, a diagnostic device (clinical test) will be considered a significant risk device, and the trial will have to be conducted under full IDE regulations. Other recent guidances relevant to the development of personalized therapeutics address risk classification for device approval and clearance, and the related streamlining of the so-called *de novo* process for diagnostic test approval. All of these guidances represent the FDA's commitment to expediting new drug approval. Of particular importance for the field of personalized medicine is the Agency's recent declaration of intent to produce guidances on enrichment strategies in clinical drug development (8). As a specific example of how such a diagnostics-driven, expedited pathway to drug approval might work, the FDA also recently committed to producing a draft guidance on the use of pathologic complete response as a surrogate endpoint for accelerated approval in primary high-risk breast cancer.

Table 2. Examples of recent FDA draft guidances related to the development of diagnostic tests necessary for personalized medicine

| Draft guidance for industry and FDA staff | Date of issue | Comments |
|--|---------------|---|
| Commercially Distributed <i>In Vitro</i> Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions | June 2011 | Discusses issues concerning diagnostics for research or investigational use, and the boundaries related to use in clinical practice. The goal is to prevent the use of laboratory tests with unproven performance characteristics and manufacturing controls. |
| <i>In Vitro</i> Companion Diagnostic Devices | July 2011 | Defines <i>in vitro</i> companion diagnostic devices. Discusses the importance of the process used to grant premarket approval for or clear (for a 510K) a diagnostic product for use in therapeutic product labeling. Provides guidance for regulatory pathways and the FDA's expectations regarding enforcement policy. |
| Design Considerations for Pivotal Clinical Investigations for Medical Devices | August 2011 | Describes principles that should be followed in the design of clinical studies related to the development of diagnostic tests. |
| Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Review | August 2011 | Gives insight into the factors that the FDA considers when making benefit-risk determinations for diagnostic devices. |

Reimbursement Considerations

Although the evolving regulatory landscape poses challenges to the development of personalized medicine, the notion that the development of clinical tests that directly affect clinical treatment decisions involving regulated therapeutics should itself be regulated seems to be only common sense. As a corollary, if the development of such clinical tests requires the generation of levels of clinical evidence similar to those required for the development of therapeutics, then reimbursements for these tests should in some manner reflect the costs and skills required, as well as the clinical value realized. Payers have a significant potential to benefit from personalized medicine approaches that can both improve patient care and reduce the use of ineffective therapies. However, current diagnostic reimbursement policies do not support the development of such high-value tests. Medicare, the largest and most influential payer, has historically reimbursed for clinical tests based on the time and the cost of materials associated with performing the test. Medicare reimbursement does not generally recognize the clinical value of the test, or the increased complexity and higher levels of evidence required to generate personalized medicine tests. Therefore, the anticipated low levels of clinical-test reimbursement represent a major impediment to the development of highly predictive clinical diagnostic tests, as well as the development of successful business models for diagnostics companies.

Pharmacy benefit managers, such as CVS Caremark and Medco, have identified the potential of personalized medicine approaches to improve patient outcome and reduce health care costs. For example, Medco has supported pharmacogenomics studies related to optimal warfarin dosing (9). Furthermore, as more emphasis is placed on comparative effectiveness in health care, the potential for biomarker-guided improved use of resources is emerging. The Health Care Reform law of 2010 established the Patient-Centered Outcomes Research Institute to conduct studies on the comparative risks and benefits of approved drugs and devices, including diagnostic tests.

Future Directions

The practical challenges of developing parallel and linked therapeutics and diagnostics are daunting. The 2 processes are highly complex and fundamentally different. Historically, they have been managed by very different types of organizations whose agendas have not always been aligned. Similarly, simultaneous drug and diagnostic development followed by a coordinated regulatory review requires considerable alignment and coordination between and among developers and regulators.

Implications for the development of therapeutics

In the longer term, the development of linked diagnostics and therapeutics may offer all of the potential benefits of personalized medicine discussed above. However, the reality is that in the shorter term, the use of extensive new

biologic tests in clinical trials of drugs adds to the complexity and cost of the drug-development process. As a result, resource-constrained industry and academic development teams are often faced with decisions regarding the number and kind of samples to be obtained, and the benefits of linking sample analysis with clinical trial analysis of regulatory endpoints versus the obvious additional costs. Decisions to incorporate biomarker strategies into registration-directed clinical trials must depend on the estimated likelihood of success of the therapeutic in an unselected population, the levels of evidence required for a potential diagnostic test to aid in patient selection, the state of development of the test itself, and clinical trial design methodologic issues regarding the incorporation of such markers in a trial with regulatory intent. However, notwithstanding the difficulties and increased costs, it is increasingly clear that with the rapid pace of biologic characterization of clinical organ-based cancers, the failure to incorporate a diagnostic test selection strategy into registration clinical trials carries its own risks. Similarly, even when biomarker-driven therapeutic individualization is not immediately possible (for instance, as occurred in the early days of development of EGFR inhibitors), an unwillingness to obtain adequate biospecimens for future biomarker development as part of proof-of-concept trials should be considered unacceptable.

Once it is determined that potential benefit exists in managing the risk of the trial outcome with the parallel incorporation of a potential selection test, a number of considerations arise. These include the necessity for (i) a sample-collection strategy that includes obtaining all necessary patient permissions for sample analysis during the trial consenting process; (ii) a strategy for ensuring high compliance in sample access, which may include mandatory sample accession for trial eligibility; (iii) ensuring that diagnostic test methodology development and test conduct will be accomplished by a competent, minimally Good Laboratory Practices (GLP)- and preferably CLIA-certified test developer; (iv) high levels of ongoing coordination by the diagnostics and therapeutics development teams; and (v) a codevelopment strategy that includes early and continuing regular consultations with regulatory authorities.

Implications for the Diagnostics Industry

The concept of personalized medicine has presented the diagnostics industry with both unprecedented opportunities and significant challenges. Opportunities are created because of the important role played by diagnostic technologies in ensuring the efficient use of targeted therapeutics. Challenges exist because the diagnostics industry historically has been focused on technology, producing highly accurate assays to measure particular biologic molecules but leaving interpretation of their clinical meaning and their value for clinical decision making to others. Furthermore, producing highly predictive clinical tests that often involve multiparametric algorithms is more technically complex than producing accurate measurements of individual

analytes (10). The challenges include meeting the important goal of generating sufficiently high levels of clinical evidence to warrant their use in making appropriate therapeutic decisions. This is an industry that has not generally had to develop the skills associated with generating high levels of clinical evidence, and in any case historically has not been rewarded for such activity.

Given the much greater expense, time, and highly annotated clinical sample sets required to develop these more-determinative tests relative to conventional diagnostics, it is a challenge to understand how their development will be supported. Current business models for the diagnostics industry do not support significant research and development activities. Indeed, the current generation of startup molecular diagnostics companies faces the daunting business challenges of ever-increasing regulatory requirements before commercialization without subsequent compensatory reimbursement reward. Individual examples of National Cancer Institute (NCI)-funded clinical trials that could serve as the basis for companion diagnostics in cancer treatment are available. Few early-stage drug development clinical trials have involved support for biomarker work, with the I-SPY 2 study funded by the Biomarkers Consortium of the NIH Foundation being a particularly notable exception. I-SPY 2 is a clinical trial that was designed to more efficiently test promising targeted drugs in women with high-risk breast cancer. It uses an adaptive clinical trial design in which experience from the first patients entered into the trial influences treatment assignments for subsequent patients (4). Patients with locally advanced breast cancer who are candidates for neoadjuvant therapy are partitioned into 8 subtypes based on hormone receptor status (positive or negative), HER2 status (positive or negative), and MammaPrint signature (positive or negative). The primary endpoint is pathologic complete response at the time of surgery, 5 months after initiation of chemotherapy. Other exploratory biologic and imaging studies (e.g., volumetric MRI) are being conducted in parallel but are not being used for patient assignment or endpoint determination. Currently, we have few similar examples of formal clinical studies to investigate the role of companion diagnostics in major treatment decisions. The ongoing TAILORx study involving the Oncotype DX clinical test in adjuvant breast cancer treatment is one example. Oncotype DX and MammaPrint are commercially available gene expression-based clinical tests that have been shown to accurately identify patients who are both at greatest risk of relapse following treatment for primary breast cancer and are most likely to benefit from adjuvant chemotherapy. This is a relatively unique clinical trial. NCI-sponsored phase III trials in various diseases have obtained biospecimens in many trials testing new agents or combinations; however, there has been little prospective support of biomarker development for such trials, and only haphazard and inadequately supported retrospective exploitation of these irreplaceable biologic resources.

It seems, therefore, that for this field to move forward, some additional new sources of financial driving force

will need to emerge. It may be that in some situations, enlightened drug developers will find a competitive advantage in sponsoring predictive clinical test development in parallel with their drugs. Roche, Abbott, and Novartis are examples of pharmaceutical companies with large associated commercial diagnostic units, albeit with varying degrees of coordination with their therapeutics development divisions. In other cases, the financial support may come from disease-focused foundations. For example, the Multiple Myeloma Research Foundation (MMRF) is now attempting to accelerate personalized medicine diagnostics development just as it successfully catalyzed drug development in myeloma. It is also possible that new participants will emerge in the clinical diagnostics industry, and that these deeper-pocket companies will see companion diagnostics and next-generation personalized medicine tests as a growth area worthy of investment. For example, Novartis recently acquired Genoptix, a specialty hematology clinical diagnostics company, and the nutrition company Nestle acquired Prometheus, another molecular diagnostics company. GE HealthCare recently acquired Clariant, a specialty clinical diagnostics company, and announced a \$100 million fund to develop innovative approaches for triple-negative breast cancer in collaboration with Kleiner Perkins Caulfield & Byers and other venture capital firms. These are all interesting developments, but it is unclear whether the exception will determine the rule, and just how the new era of personalized medicine, highly predictive diagnostics will be financed.

An Important Role for Patients and Advocacy Groups

Patients have much to gain from the more rational application of therapeutics through the concepts of personalized medicine, and certain disease-based advocacy groups are taking the lead in promoting personalized cancer medicine for their own disease area. As noted above, the MMRF has been a leader over the past decade in encouraging pharmaceutical and biotechnology companies to investigate the use of their agents in myeloma, even though it is a relatively uncommon malignancy. The MMRF's activities have contributed in part to the approval of several new active agents for this disease. More recently, the foundation initiated a personalized-medicine strategy for myeloma that includes sponsoring the complete genomic sequencing of myeloma cells from a number of patients (11). The Foundation also initiated a prospective collection of clinical samples that will be taken from patients serially through the course of their disease treatment. These tissue samples will then be biologically characterized by a range of genomic technologies. The goal of this initial activity is to better understand the relationship between the biology of individual patients' myeloma and their response to current therapy, as well as the effects of therapy on the evolution of an individual patient's myeloma.

Educational Challenges

The education of stakeholders, including patients and their advocacy groups, clinicians, biomedical researchers, the pharmaceutical and biotechnology industries, the diagnostics and device industries, regulators, and payers will be essential to drive the adoption of personalized cancer medicine concepts and technology (12). Although these groups have different drivers and motivations, they all will benefit from efficient access to timely, objective, authoritative, and contextually interpreted information. It is interesting to speculate about which organizations or entities will evolve to fill this information requirement. For example, the molecular characterization reports from some of the specialty diagnostic companies read essentially as academic documents, linking the individual patient's molecular findings with the current literature concerning the clinical implications of these findings. True companion diagnostics linked by drug label specifically with the use of particular drugs can be the basis of education by the pharmaceutical or biotechnology company. It also seems clear that this is a major potential role for professional societies such as the AACR, whose mission directly involves linking new scientific discoveries with clinical applications in cancer therapy.

The Need for a Policy Change Involving Personalized Medicine

Given the importance of personalized-medicine concepts for improving cancer treatment, and the complexity of

achieving this goal given the numerous regulatory and reimbursement hurdles, a policy change is in order. A wide range of institutions and organizations, including the Institute of Medicine and the Personalized Medicine Coalition, have suggested policy initiatives in the area of personalized medicine. These suggestions include calls for a more stable and predictable regulatory environment, and, as reviewed above, some progress has been made in this area. It has also been suggested that Medicare and other payers should recognize the improved quality and efficiency of care that is made possible by personalized medicine by increasing the reimbursements for newly developed diagnostic tests. Higher reimbursements for clinical tests would serve as a continuing stimulus for innovation and more-rapid transfer of newer technologies to clinical applications. Academic investigators should work together with pharmaceutical and diagnostic industry partners to identify additional valid targets in different cancers, create agents against these targets, and efficiently develop these targeted agents in parallel with highly predictive clinical tests to achieve improved and more cost-effective clinical treatments.

Disclosure of Potential Conflicts of Interest

D. Parkinson is employed by and has an ownership interest in Nodality, Inc.; B. Johnson is coinventor of a patent for EGFR testing utilized by Genzyme and serves as a consultant to Genentech, Pfizer, Chugai, and AstraZeneca. G. Sledge disclosed no potential conflicts of interest.

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