

# Companion Diagnostics

Strategies to Optimize  
Performance in the Era  
of Precision Medicine



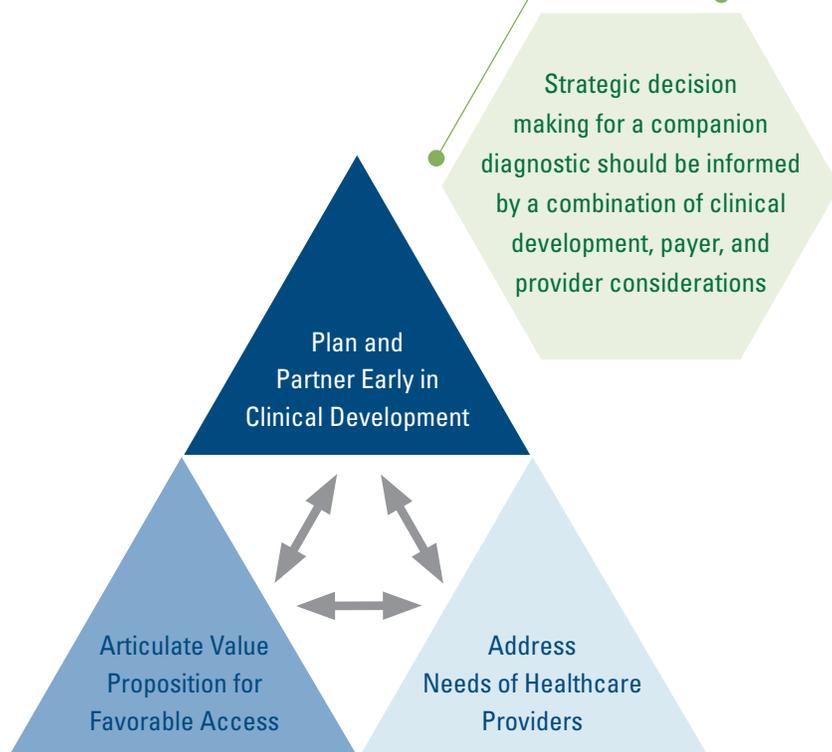
**Informed drug development in an era of “precision medicine” requires a clear understanding of the risks and benefits that accompany the pursuit of companion diagnostics, a difficult objective given the complexity and rapid evolution of the field. While business cases for companion approaches typically focus on pricing and volume considerations, there is also a need for careful analysis of the strategy associated with managing clinical development, securing access and reimbursement, and generating product demand among target physicians. Without a full accounting of and appreciation for these factors, it is challenging, if not impossible, to direct an efficient, forward-looking drug-diagnostic program capable of maximizing commercial potential.**

## The Companion Diagnostics Business Model

Drug developers have been talking about personalized medicine for well over a decade, but only in recent years have there been advances that suggest companion diagnostic approaches may soon attain broad applicability beyond oncology. Achieving the success and transformational potential that experts feel is possible in the coming era of “precision medicine” entails a delicate balancing act, as there are risks that have the potential to offset the benefits of a companion diagnostics-enabled business model.

Given the scientific and commercial complexities introduced in the presence of a companion diagnostic, pursuit of CDx-enabled therapeutics is not a trivial endeavor, particularly for firms that lack in-house diagnostic expertise and experience. With regulatory agencies and payers introducing stricter requirements for approval and coverage, respectively, diagnostic technologies will likely play an increasingly significant role in demonstrating the clinical and economic value of new therapies, raising the stakes for success while at the same time creating unique execution challenges. It is clear that the field will inevitably be propelled forward by the multitude of medical and technical

**FIGURE 1**



Strategic decision making for a companion diagnostic should be informed by a combination of clinical development, payer, and provider considerations

advances emerging from over a decade of research focused on the personalization of therapy. As a result, companion diagnostics are now poised to move beyond reasonably well-studied application areas such as oncology, with the potential to impact clinical decision making in a broad range of therapeutic areas.

While proponents have long advocated the benefits of precision medicine for patients, innovators have recognized that diagnostics limiting the addressable patient pool are a double-edged sword. Drug companies have typically pursued companion diagnostics as a requirement to achieve the clinical profile necessary for regulatory approval or to improve product positioning in an otherwise impenetrable competitive landscape. In both instances, innovators often focus the business case on the establishment of premium pricing to offset the lost prescription volume and

additional costs associated with the targeted companion diagnostic approach. However, commercial success in this environment is inherently complicated by the presence of the gating companion diagnostic, which entails addressing a unique set of success factors across clinical development, access and reimbursement, and demand creation (Figure 1).

## Charting A Course For Clinical Success

The management of a clinical development program for a drug-diagnostic combination is markedly different from that of a traditional therapy. A companion diagnostic introduces unique strategic questions that should ideally be addressed in the initial stages of development. If an innovator is able to commit early to the screening of a specific marker, a companion diagnostic approach can be leveraged to accelerate approval. Xalkori (targeting ALK+ in non-small cell lung cancer) and Zelboraf (targeting V600E in melanoma) are examples of drugs that translated the development challenges of the space into opportunities through early action (Figure 2). In contrast, ChemGenex’s development of omacetaxine (targeting the T351I mutation in chronic myelogenous leukemia) was stalled due to the company’s decision not to pursue an approved companion test prior to registration.

The selection of a partner for test development is another crucial step that is best taken early. A delay in committing to a diagnostic partner risks relegating the companion diagnostic to “exploratory” status in the eyes of the regulator or payer. This, in turn, can lead to the requirement for additional validation studies and delayed commercialization. Recently, new partnership models based on improvements in biomarker identification and

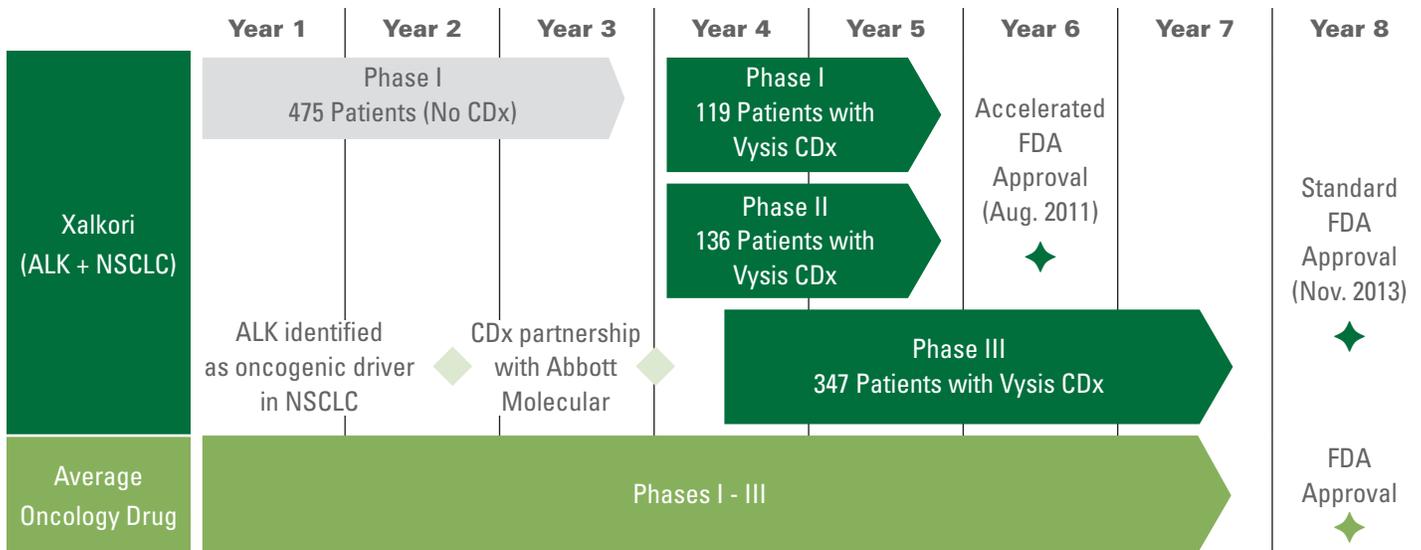
utilization have emerged to facilitate accelerated co-development pathways. For example, Foundation Medicine and AstraZeneca are currently engaged in a long-term partnership that aims to identify suitable biomarkers for a range of emerging oncology therapies through the application of sequencing techniques. Such a model diverges from the traditional one drug / one test scheme, enabling information on test utility and therapeutic value to be integrated into development at an earlier stage.

Similarly, Agios Pharmaceuticals has committed to partnering early in order to pair oncology therapies in Phase I with a companion test. These innovative approaches have the potential to accelerate approval by allowing for evaluation of both drug and diagnostic in comprehensive Phase II and III clinical trials.

In addition to accelerating decisions, the pursuit of a companion diagnostic increases the complexity of clinical development and requires modifying traditional trade-offs between risk and value. Measures must be taken by drug developers and their partners to ensure the timing and objectives of the programs are synchronized. Agreement on the metrics of success, both clinical and commercial, must also be achieved. However, these goals are often difficult to reach, as the two parties can approach the most basic issues with distinct perspectives and incentives. If not properly managed, this misalignment has the potential to undermine product development by closing

**FIGURE 2**

Xalkori was the first lung cancer therapy to be approved simultaneously with a companion diagnostic test, reducing the time to U.S. market entry by approximately two years relative to the average oncology drug



- Xalkori (crizotinib) is an anaplastic lymphoma kinase (ALK) inhibitor originally developed by Pfizer to treat cancers driven by the c-Met oncogene
- After ALK was identified as an oncogenic driver in select lung cancers, Pfizer shifted development towards NSCLC and entered into a diagnostic partnership with Abbott Molecular to support subsequent Phase I - III trials
- Xalkori and the companion Vysis ALK FISH Probe Kit received simultaneous FDA approvals in August 2011

down important channels of communication between partners. Furthermore, risk-reward calculations in this space must account for a variety of technical challenges, forecasting uncertainties, and access factors that do not exist in the more traditional realm of drug development. These elements introduce additional layers of complexity to the business case that executives on both sides of the development partnership must navigate to stay on a course destined for success.

## Ensuring Broad And Favorable Access

Assuming clinical development is successfully navigated, an additional set of challenges must then be addressed to achieve coverage for the drug-diagnostic combination. Specifically, it is critical for the developer to generate the requisite evidence to establish favorable access and reimbursement for the diagnostic on a widespread basis. It is important to note that, even with a targeted treatment approach, convincing payers to cover a screening test in the broader, “intend-to-treat” population may not be straightforward, particularly if the test carries a high price and the screen exhibits a low yield of treatment-eligible patients. Although there are no specific examples to date, the total cost of screening for eligible patients is considered as part of cost-effectiveness analysis. In a future environment where therapeutics are targeting increasingly less common sub-populations, it will be critical to ensure screening costs do not ultimately weaken the pharmacoeconomic rationale for targeted treatment.

Beyond price and yield considerations, the ability to secure favorable reimbursement will also be dictated by the level of unmet clinical need in the disease area, the degree to which test output impacts health outcomes, and the availability of comparable tests. Even if reimbursement is secured, challenges can exist due to patient cost-share burden associated with the diagnostic, as patients may be reluctant to pay for a test that has a low probability of resulting in biomarker-positive status and confirmed therapy candidacy.

The majority of companion diagnostics developed to date have been introduced in oncology, where the morbidity/mortality rate and high therapeutic costs have provided payers with strong incentive to reimburse companion tests. However, as healthcare budgets tighten, there is reason to believe that payers will increasingly utilize access restrictions for emerging companion approaches in other disease areas unless compelling evidence of clinical utility and cost-effectiveness is provided. It is also important to note that patient cost-sensitivity to co-pay burdens is likely to be much higher outside of the oncology space.

Shifting payer attitudes and a greater focus on value-based decision-making will ultimately create challenges for the developers of drug-diagnostic combinations. Increasingly stringent coverage policies, health technology assessments, and other payer analyses will likely compel drug-diagnostic developers to invest more heavily to establish clear links between test usage and improved outcomes during clinical trials to ensure widespread reimbursement upon market entry. Of course, it is possible to proceed with a less robust evidence base, but this is a risky proposition, as any payer-imposed, post-marketing validation studies will delay product adoption and revenue generation.

## Clearing The Hurdles For Maximum Physician Adoption

Reaching the market with reasonable access establishes a sound foundation for commercial success, but even then, innovators will face additional hurdles to product adoption. It is not realistic to expect that targeted treatments will be, as a matter of course, readily accepted and adopted by physicians practicing in the community. Indeed, not all physician groups are familiar with the implementation of companion diagnostics in clinical practice. While oncologists may be comfortable with targeted approaches

due to previous experience, other specialists and primary care physicians may not be compelled to treat (or not treat) on the basis of biomarker status. To drive uptake among these prescribers, it may be necessary to organize educational outreach and/or awareness programs to explicitly link the targeted approach and mechanistic rationale to clear improvements in disease management and patient outcomes.

Technical factors can also play a role in determining uptake. In certain situations, the requirement for an extra diagnostic step in patient workup may be perceived by physicians as an inefficient use of time and resources with limited impact on treatment decisions and patient outcomes. To maximize uptake, a companion diagnostic should provide a simple, unambiguous output with a direct link to a specific treatment decision. The ideal test would utilize an easily accessible sample input (i.e., saliva or blood, as opposed to tissue biopsy) and provide an easy-to-interpret readout (i.e., a qualitative binary output, as opposed to a quantitative multi-factorial readout) with a short turnaround time (Figure 3).

**FIGURE 3**

The commercial viability of a companion approach will depend on the developer's ability to address the key factors that drive test coverage and adoption among payers and physicians, respectively

Metric	Importance to Payers	Importance to Physicians	Key Insights
Ability to Impact Treatment Decisions	+++	+++	Thoroughly validated connection to intervention is critical for physicians and payers
Ease of Test Interpretation	++	+++	Simple output streamlines workflow and is more easily translated into clinical action
Ability to Reduce Treatment Costs	+++	+	Cost reduction via identification of responsive patients is compelling to payers
Sample Accessibility	+	++	Easily accessible sample minimizes the inconvenience for physicians and their staff
Time Required for Test Result	+	++	Rapid result accelerates decision making and therapeutic intervention

Key:	 Low Importance	   High Importance
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Physicians may be reluctant to integrate testing into their management paradigm if the diagnostic performs poorly on any one of these metrics. Such was the case with Xalkori upon its introduction to the non-small cell lung cancer market in the U.S. in 2011. Physicians' frustration with the lengthy turnaround time of the companion ALK-gene diagnostic led to low rates of screening, which in turn slowed initial use of the targeted therapy. In commercializing a drug-diagnostic combination, it is critical that such technical considerations are included in business planning discussions and that sufficient action is taken to address potential physician adoption hurdles.

## Priority Items On The Strategic Agenda For Innovators

Unique clinical development, pricing and access, and physician demand creation dynamics must be taken into consideration when setting strategic direction for a paired therapeutic/diagnostic. The ability to leverage a companion diagnostic's advantages and steer clear of its potential pitfalls will ultimately require a thorough understanding of these factors from both the perspective of the therapeutic innovator as well as the diagnostic partner. For pharmaceutical and biotechnology companies looking to enter the space from the therapeutic innovation side of the equation, it is critical to consider the following steps:

- Develop a forward-looking perspective and forge diagnostic partnerships early in the clinical development process
- Design a program that delivers the clinical and economic evidence required for establishing value in the eyes of payers

- Ensure physician and patient usage dynamics are taken into consideration when developing the test to optimize adoption
- Align diagnostic partner priorities with overall clinical development and commercialization priorities and key success factors

As the pharmacogenomics field matures, there is reason to believe that more success stories are around the corner for companion approaches. Deeper comprehension of biological mechanisms, along with novel analytical tools for biomarker detection, promise to further expand the footprint of drug-diagnostic combinations. In addition, the FDA has awarded several of the initial "Breakthrough Therapy Designations" to drugs linked with companion diagnostics (e.g., ibrutinib) and will soon issue guidance to clarify the requirements for expedited diagnostic approval. These developments provide a strong indication of the agency's desire and commitment to support the acceleration of targeted therapies. Executing on the critical action elements outlined above will better position developers to capitalize on these future trends and thereby derive greater value in an increasingly challenging marketplace.

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