The Perfect Gatekeeper

Demand for companion diagnostics is on the rise as precision medicines expand therapeutic options. Successfully developing both companion diagnostics and precision medicines requires high-quality information to guide decisions at every step.
What is (and what is not) a companion diagnostic?

COMPANION DIAGNOSTICS ARE DEFINED BY THEIR USE

In 2014, The U.S. Food and Drug Administration (FDA) issued a Guidance Document to outline the oversight and approval of in vitro companion diagnostic devices. The document defines a companion diagnostic as a device that “provides information that is essential for the safe and effective use of a corresponding therapeutic product”. It also lists specific uses, such as the identification of patients likely to benefit or suffer adverse effects from a therapeutic product and the assessment of patient response to a treatment, so therapy can be adjusted to increase safety and effectiveness (1). The European Commission defines a more narrow use for companion diagnostics: “a device specifically intended for and essential to the selection of patients with a previously diagnosed condition or predisposition as suitable or unsuitable for a specific therapy with a medicinal product or a range of medicinal products” (2). While the majority (15/23) of approved or cleared companion diagnostics listed on the FDA website are molecular assays to detect DNA (3), neither definition restricts the nature of the tool itself (Figure 1). As personalized medicine expands into medical areas other than oncology, it is likely that non-molecular tests will become more prevalent as companion diagnostics (4).

Figure 1. Twenty-three companion diagnostic devices have been cleared or approved by the U.S. FDA. All but one are relevant to cancer medications and are designed to detect specific DNA or protein markers. PCR = polymerase chain reaction; FISH = fluorescent DNA in situ hybridization; CISH = chromogenic in situ hybridization; IHC = immunohistochemistry. Data from U.S. FDA website (3).
TO PROVIDE ESSENTIAL INFORMATION

A critical aspect of both definitions is an explicit connection of the companion diagnostic to a therapeutic product. The FDA requires that the device provide information that is “essential” for use of a medication. This means “the use of a diagnostic device is required in the labeling of the therapeutic product” (1). This “essential” requirement emphasizes the pivotal role of such tests in the treatment course of a patient. A companion diagnostic indicates whether a patient is candidate for a particular therapy, giving the physician a specific course of action: “yes, the patient should receive this treatment”, or “no, the patient should not”. The companion diagnostic is a “gatekeeper” for treatment decisions (5) and this role links the development of a companion diagnostic to the indication, safety and efficacy profile of its coupled therapeutic product. Conversely, the performance of that product is impacted by the clinical utility of the companion diagnostic. This interdependence calls for a flexible development strategy that is carefully planned and informed at every stage.

HAND-IN-HAND DEVELOPMENT

Despite the interdependence of a drug and its companion diagnostic, priorities of the development partners are often misaligned. For example, the drug developer gets paid per prescription, whereas the diagnostic developer gets paid per test or a development service fee. With a companion diagnostic that qualifies patients for life-long drug treatment, the disparity in earnings can be dramatic. Reimbursement policies for test and drug may also differ; often the drug is covered by insurance but not the test. Finally, despite high development investment, difficult approval process, and strict post-market surveillance, diagnostics do not enjoy the same intellectual property protection as drugs (6).

One way to increase overlap in interests of all stakeholders is to couple the development and approval of drug and companion diagnostic as early as lead discovery. Under this model, development of each component is informed and supported by the development of the other, co-creating value for all involved (6). For example, patient selection with a robust companion diagnostic can reduce size, length and cost of clinical trials and the development of the companion diagnostic can support lead discovery and target identification for the drug. The FDA suggests a co-development model (1) and recent approvals, like crizotinib (Pfizer’s Xalkori) and its companion diagnostic, attest to the value of this strategy.

INFORMATION TO DRIVE SUCCESS

Each step of the drug-diagnostic co-development model entails risks, and decisions made at any one step can impact outcomes at any later stages. The companion diagnostic will not be used in a vacuum, but rather in an ecosystem of guidelines and treatment protocols for a given indication area. It is important to know that ecosystem: What is the current standard of care and how can it be improved? How will a new medication and its companion diagnostic influence treatment plan? Which therapeutic products are currently under development for the indication area? What kinds of specimens are routinely collected?

Developing a companion diagnostic outside the boundaries of this ecosystem will decrease its acceptability and market access. Up-to-date and comprehensive information about the indication area and competitive landscape must support every decision along the way; not only to establish optimal parameters for the assay, but also to evaluate objectives and either redirect or abort a project in time.

The following is a brief exploration of the stages of the co-development model, highlighting important tasks at each stage (Figure 2) and the type of information that supports successfully accomplishing these.
Some definitions

A **biomarker** is a measureable indicator of a particular disease or other physiological state.

The **clinical sensitivity** and **specificity** of a companion diagnostic describe the ability of the validated assay to detect “responsive” and “non-responsive” (or “at risk” and “not at risk”) patients.

**Positive predictive value** and **negative predictive value** are the respective probabilities that a positive and negative result from a companion diagnostic reflects the real status of a patient.

In a clinical trial, the therapeutic product under scrutiny is tested against an alternative therapy or **comparator**.

**BIOMARKER SELECTION AND FEASIBILITY**

A successful diagnostic development program builds on a solid biomarker hypothesis. This hypothesis describes the value of one or more biomarkers in predicting the response of a patient to the coupled drug. Ideally established during early research and preclinical stages of the drug development, this hypothesis must be relevant to the drug mechanism of action and can thus also inform lead discovery. The quality of the hypothesis emerges from a thorough understanding of biological systems, disease etiology and drug mechanism of action (7), which, conversely, relies on a systematic review of the disease and its treatment to reveal novel therapeutic strategies and to guide in-house research toward refining the biomarker hypothesis. A performance evaluation of available therapies, reported adverse effects and case studies of treatment problems, such as resistance development, present unique opportunities to improve patient care through better targeted therapies.

Having identified a relevant biomarker, an assay to detect that marker is developed. Assay design must meet the users’ expectation of handling and perception of reliability. The test should integrate easily into existing diagnostic and therapy workflows. To this end, test development should take into account timing, location and process for diagnosis. For example, is testing done in a clinical lab or at point of care? What kind of training can be expected to perform the test? How quickly are results needed? The test must also work with clinical specimens that are either already collected for diagnostic purposes or require minimal effort and take patient safety into account. Thus, a systematic review of established diagnostic strategies and sample processing with corresponding outcomes should guide the test architecture.

**Pharmaceutical Development Process**

**Lead Discovery**
- Develop biomarker hypothesis
- Conduct market assessment
- Design assay to test hypothesis
- Demonstrate feasibility

**Preclinical**
- Develop protocols
- Construct prototype
- Assess interpretation rules
- Create necessary controls

**Clinical Trials**
- Establish analytical characteristics
- Determine cutoff
- Verify assay
- Develop manufacturing specifications

**Approval and Launch**
- Confirm cutoff
- Demonstrate clinical impact
- Determine diagnostic metrics like clinical sensitivity & specificity
- Demonstrate drug efficacy & safety

**Post-Market Studies**
- Marketing & education
- Confirm drug efficacy & safety
- Establish clinical utility
- Monitor assay acceptance
- Post-market surveillance
- Achieve reimbursement

**Companion Diagnostic Development Process**

*Figure 2.* Interconnected development processes in the drug–diagnostic co-development model. Alignment of process steps and information sharing at every stage are hallmarks of the co-development model. Listed in between the two workflows are some of the relevant tasks for the development of the companion diagnostic (graphic adapted from Akhmetov et al. 2015).
PROTOTYPE AND ANALYTICAL VALIDATION
A prototype of the assay is tested in early-stage clinical trials. The prototype should include a protocol covering the complete workflow, from obtaining and preparing samples to interpreting and reporting results. Sensitivity and specificity of biomarker detection, reactivity patterns in patient samples (e.g., with other biomarkers) and control materials should be established. Interpretation rules and course of action for each obtained result must fit practical testing requirements and have an obvious impact on therapy decisions. Knowledge of established diagnostic strategies and therapy guidelines ensures suitability of the developed prototype, and an examination of clinical trial documentation of approved and failed drugs and diagnostic devices can help identify potential pitfalls in the practical implementation of the prototype.

Determining a valid cutoff for the biomarker is critical. Ultimately, the cutoff plays an important role in the acceptance of a companion diagnostic, because physicians and patients will consider the likelihood of a positive result in their decision to perform a test. More immediately, the cutoff assigns patients to testing groups in clinical trials. A cutoff that is too narrow may exclude patients who would benefit from the therapy and generate small treatment groups, which can increase trial length and costs. Conversely, a cutoff that is too broad can make the drug appear less effective than it would be in a more select group of patient. The optimal cutoff is a function of the performance of the companion diagnostic and the magnitude of patient response to the coupled drug. Early-stage clinical trials examine those parameters, but known frequencies of other biomarkers relevant to the indication and the clinical utility of other companion diagnostics can play a role in determining a meaningful cutoff.

CLINICAL VALIDATION
The clinical impact of the companion diagnostic—that it provides essential information for the use of the coupled drug—is demonstrated in late-stage clinical trials. Choice of trial design is based on biomarker frequency and data supporting the relationship between companion diagnostic result and treatment outcome. Also informative, however, are outcomes of clinical trials for similar assays and drugs in the indication area to balance practical considerations, such as trial length and cost, with obtaining important diagnostic metrics, such as clinical specificity and sensitivity and positive and negative predictive value.

In an untargeted clinical trial design, study subjects are randomly assigned to treatment with the coupled or comparator drug regardless of companion diagnostic result. Such designs enable calculation of diagnostic metrics but the treatment effect predicted by the biomarker is diluted by the inclusion of patients who test negative. An alternative design stratifies the patient population based on the companion diagnostic before randomly assigning subjects to the coupled or comparator drug, eliminating the dilution effect. If frequency of the biomarker is low, however, the arm of the clinical trial with patients who test positive will have a small sample size and may require a long time to achieve statistical significance. The highly effective precision drugs vemurafenib (Roche/Genetech’s Zelboraf) and the aforementioned crizotinib were approved based on enrichment trials where only patients who test positive for the biomarker are included in the trial and randomly assigned to treatment. For drug–diagnostic pairs with a strong relationship between biomarker status and patient response, superiority of the coupled drug over the comparator can be demonstrated with a relatively small sample. However, the design does not enable calculation of important diagnostic metrics. These must then be established in post-market trials.
POST-MARKET ASSESSMENTS

A long, information-intensive period in the development of a companion diagnostic begins once it is approved for market entry. Life cycle management of a companion diagnostic requires meticulous monitoring of product performance and competitive landscape. Detailed information about the advantages of the companion diagnostic and coupled drug over the competition enables optimizing the positioning of the test. Records of unforeseen use problems drive corrective action and highlight areas for product improvement. Also, regulatory compliance requires tracking adverse events and regular reporting on the safety, effectiveness and reliability of drug and companion diagnostic. Data for such reports is collected in post-market clinical trials, complemented with spontaneous reporting and primary literature screening and triage.

Price optimization and reimbursement achievement require demonstrating clinical benefits from the drug guided by its companion diagnostic. Results from post-market clinical trials and patient registries can make a strong case for reimbursement of drug and test, however, other aspects also attest to the value of a drug–diagnostic pair. Using information about the complete indication ecosystem—literature and regulatory documentation on the performance of all medications and therapy lines—demonstrated that the benefits should also include measures of improved quality of life, of healthcare savings from reduced interventions, of optimized resource and medication use from avoided ineffective treatments and of saved time (6).

LOOKING INTO THE FUTURE

Approved companion diagnostics today are coupled to a specific drug and typically test only for the biomarker that is relevant to that drug. This limitation makes sense from the perspective of drug developers, who are interested in having a test that prompts the decision to use their particular therapy. Payers, however, are increasingly interested in tests that provide information about multiple potential treatment options, about changes in disease progression that should trigger adjustments in treatment, or about prognosis of disease recurrence given a particular treatment (8). These uses deviate from the “one-drug, one-test” model that dominates the companion diagnostics market. On one hand, that type of information will require testing for several relevant biomarkers. On the other hand, the information will no longer be coupled to a single therapy.

In the future, companion diagnostic developers will find themselves caught between the interests of pharmaceutical companies and payers. They will need to revamp the concept of a companion diagnostic and the business model under which they operate. What this will look like is not clear, but venturing into multiplexed assays will require even more information. Multiple biomarkers will need to be assessed for links to a disease and to one another. Pharmacovigilance strategies will need to encompass the performance of a developed diagnostic device in multiple indications and associated with multiple therapeutic products. The successful companion diagnostic developer will be a savvy information manager, able to collect, filter and interpret the right information, as well as identify new opportunities that maximize the impact of developed products.
REFERENCES