Time to Embrace Companion Diagnostics to Accelerate Precision Medicine

An Amplity Health White Paper

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An Introduction to Companion Diagnostics

Precision Medicine and Companion Diagnostics

Conventional pharmacotherapy is characterized by a trial-and-error approach in which medications are tried sequentially.[1] The success rates from treatment with this approach are relatively low, and efficacy and safety outcomes can vary substantially between patients.[1] The cause for this variability lies in the variability of the disease itself as well as in differences in the physiological makeup of the patients. Moreover, the trial-and-error approach can lead to serious health consequences for patients as well as to adverse economic effects on the healthcare system and society overall.[1] The most important shortcoming of the trial-and-error approach to pharmacotherapy is that patients with progressive diseases like cancer and rheumatoid arthritis may not receive the appropriate treatment in time. During the period in which various treatments are tried and found ineffective, cancer patients can have a significant disease progression and those with rheumatoid arthritis may accumulate irreversible joint damage.

In contrast to conventional pharmacotherapy, precision medicine develops treatment plans that are based on a patient's unique biological makeup, environment, and lifestyle.[2] In precision medicine, biomarkers that can reveal a specific pathological process or the response to intervention are used to obtain key information that underlies treatment decisions.[2] As result, precision medicine is changing the treatment paradigms for many diseases from a 'one size fits all' to a 'targeted testing and treatment' approach.[2] To implement this approach, targeted treatments are paired with a companion diagnostic test that is designed to determine whether a given patient is a viable candidate for a specific treatment and/or whether a patient is responding to the treatment.[2] Companion diagnostics are therefore essential to the success of targeted precision medicine treatments. Moreover, companion diagnostics enable the timely treatment of progressive diseases because an effective treatment can be initiated as soon as the companion diagnostic test identifies the patient as an appropriate candidate for a specific targeted treatment.

What are the Applications of Companion Diagnostics?

Pharmacological treatment should be initiated in a timely fashion and be guided by an in-depth understanding of both the pathophysiology of the disease as well as the mechanism of action of the drug.[1] Companion diagnostics are designed to establish the connection between the disease pathophysiology of an individual patient and the mechanism of action of the medication that is being considered.[1]

The main application of companion diagnostics to date has been in oncology and rheumatology. In both cancer and progressive diseases like rheumatoid arthritis, early diagnosis and early intervention are critically important. In the case of cancer, an incorrect treatment decision may be followed by dissemination of the disease which can leave the patient with a very low or no chance of a cure, possibly resulting in death.[1] Similarly, in rheumatoid arthritis, delayed or incorrect treatment may result in irreversible joint destruction and/or disability.[1] In addition to outcome prediction, companion diagnostics can also be used to monitor treatment response and/or detect acquired resistance to cancer therapy. For instance, in cancer therapy, DNA or RNA from apoptotic or necrotic cancer cells is released into the bloodstream, and measurement of these nucleic acids may serve as a "liquid biopsy" and substitute for tumor tissue biopsies.[1]

The History of Companion Diagnostics

Trastuzumab (Herceptin, Roche/Genentech) was the first treatment developed in combination with a companion diagnostic. Trastuzumab's mechanism of action targets the HER2 oncogene, and during the drug development, it was recognized that only women whose tumors overexpressed the HER2 oncogene were benefitting from trastuzumab.[1] Determining whether a given patient would respond to treatment with trastuzumab required the development of a novel in vitro diagnostic test that could accurately and reproducibly detect and quantify HER2 in a specific patient. In 1998, this immunohistochemical assay for HER2 (HercepTest, Dako) was approved together with trastuzumab.[1,3]

The term "companion diagnostic" was first introduced in 2006.[3] At the time, biomarkers were proposed as a means to simplify the drug discovery process, make clinical trials more efficient and informative as well as to individualize therapy.[3] Since then, the term companion diagnostic has been adopted by regulatory authorities to describe a biomarker assay that is developed in parallel with a specific drug.[3]

The success of targeted treatments depends on the accurate identification of patients who exhibit the required biomarker expression. For instance, in the phase I single-arm, open-label trial of the ALKI inhibitor ceritinib, on which 2014 approval was based, a response rate of approximately 50% was achieved among the 163 participants with non-small-cell lung carcinoma (NSACLC). This response rate would not have been achievable without the companion diagnostic that enabled the preselection of patients who were likely to respond.

The use of a companion diagnostic for preselection also allows for trials with fewer patients that can be completed more quickly, and therefore enable a targeted therapy to come to market faster than a conventional therapy. Companion diagnostics are developed side by side with the targeted treatment and ideally launched simultaneously. In practice, however, the approval of the companion diagnostic occurs several days to several weeks after the approval of the targeted therapy because the biopharmaceutical and diagnostic companies that respectively own the therapy and the test have different strategies for execution that result in slightly different timing for the approvals.

The clinical validation of the companion diagnostic is usually performed in the late phases of clinical testing, during phases IIb and III trials. This timing means that the reliability of the companion diagnostic is established in parallel with the safety and efficacy of the targeted treatment.[3] During this clinical validation, the companion diagnostic must demonstrate its ability to reliably identify patients as likely responders or non-responders.[3] The final challenge for the drug/diagnostic combination is to demonstrate that the identified group of likely responders are those that benefited most from the drug.[3]

After the safety and efficacy requirements for the drug/diagnostic combination are fulfilled, regulatory approval will be granted for both, ensuring that the companion diagnostic becomes available at the same time as the drug and that the use of the drug can be guided by the companion diagnostic from the beginning.[3] Figure 1 summarizes the major steps in the development of a companion diagnostic assay, from biomarker discovery to regulatory approval.[3]

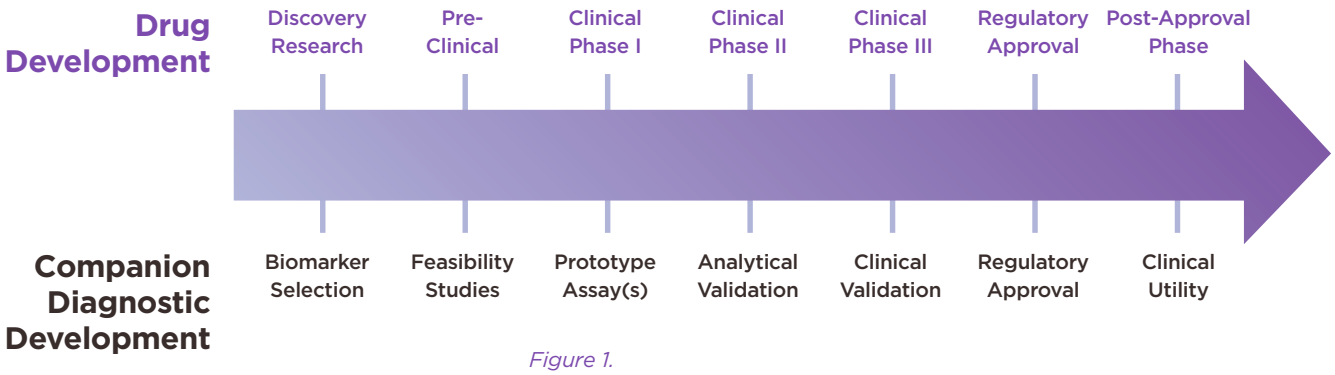

Figure 1.
Timeline of the parallel development of drug and diagnostic from biomarker discovery to regulatory approval (Jørgensen and Hersom, 2016).[3]

In the US, the development of drug/diagnostic combinations is governed by the 2014 guideline on in vitro companion diagnostic devices and the 2016 draft guidance on the principles for co-development of an in vitro companion diagnostic device with a therapeutic product.[4,5] It is the policy of the FDA to require the co-approval of the therapeutic products and companion diagnostics when the companion diagnostic is essential to the safe and effective use of the therapeutic product.[6]

Since the introduction of trastuzumab, an increasing number of drug/companion diagnostic combinations have been developed and gained regulatory approval.[3] Examples of drugs with companion diagnostics include the PD-1/PD-L1 inhibitors such as pembrolizumab (Keytruda, Merck) or ALK inhibitors such as crizotinib (Xalkori, Pfizer). For a timeline of FDA approvals of drugs with companion diagnostics see Figure 2.[3]

By the end of 2019, approximately 200 FDA-approved therapies with a biomarker cited in the label as essential or recommended for prescribing were on the market in the US.[2] About seven million patients annually are undergoing biomarker tests for targeted oncology therapy in the US and Europe.[2]

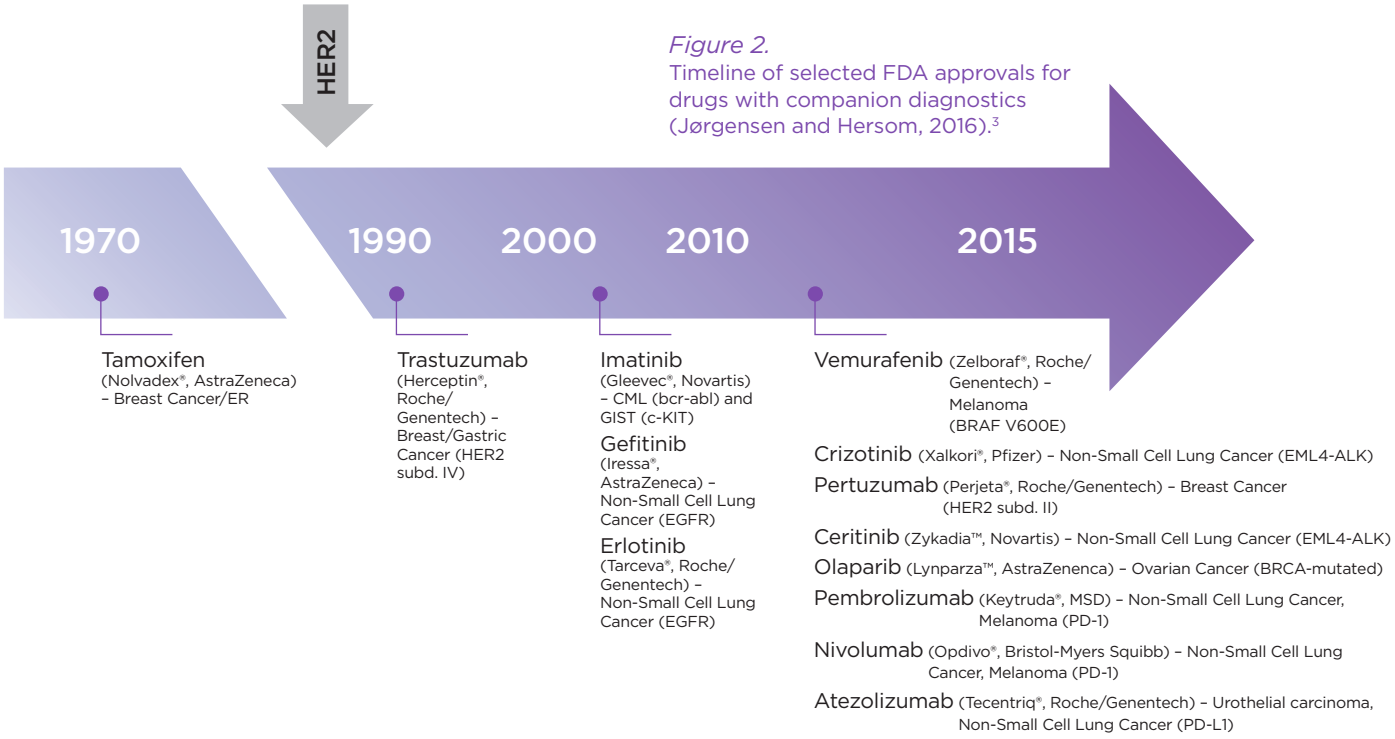

Figure 2.
Timeline of selected FDA approvals for drugs with companion diagnostics (Jørgensen and Hersom, 2016).[3]

The Commercialization of Companion Diagnostics:
CHALLENGES AND OPPORTUNITIES

Introduction

As discussed in the first part of this white paper, companion diagnostics are key elements of precision medicine.[1] Their purpose is to reliably identify patients who can benefit from targeted treatments to increase the overall effectiveness of pharmacotherapy and, in the case of progressive conditions, to deliver effective interventions before irreversible damage occurs.[1] To this end, companion diagnostics are developed in concert with the targeted therapeutics they are intended to support.[7] The FDA has developed guidelines for this co-development process under which the targeted therapeutic and the companion diagnostic receive simultaneous regulatory approval to ensure the companion diagnostic is available at the time the therapeutic is launched into the market.[6]

The Changing Landscape of Companion Diagnostics

Biomarker-based treatments that are paired with a companion diagnostic have been on the market for over 2 decades.[7] Today the number of biomarker-based treatments is growing and the treatments span multiple disease states.[2] In 2018 and 2019, approvals of treatments that were paired with a companion diagnostic represented 42% and 56% of the total number of FDA-approved treatments respectively, see Figure 3.[2] In addition to the already approved therapies with companion diagnostics, approximately 500 clinical trials related to precision medicine are currently underway.[2] Based on this number of trials, Keeling et al. estimate that approximately 50 new precision medicine treatments with associated companion diagnostics could be issued over the next 5 years.[2] In this highly competitive landscape, the performance of the companion diagnostic can be the key to commercial success.

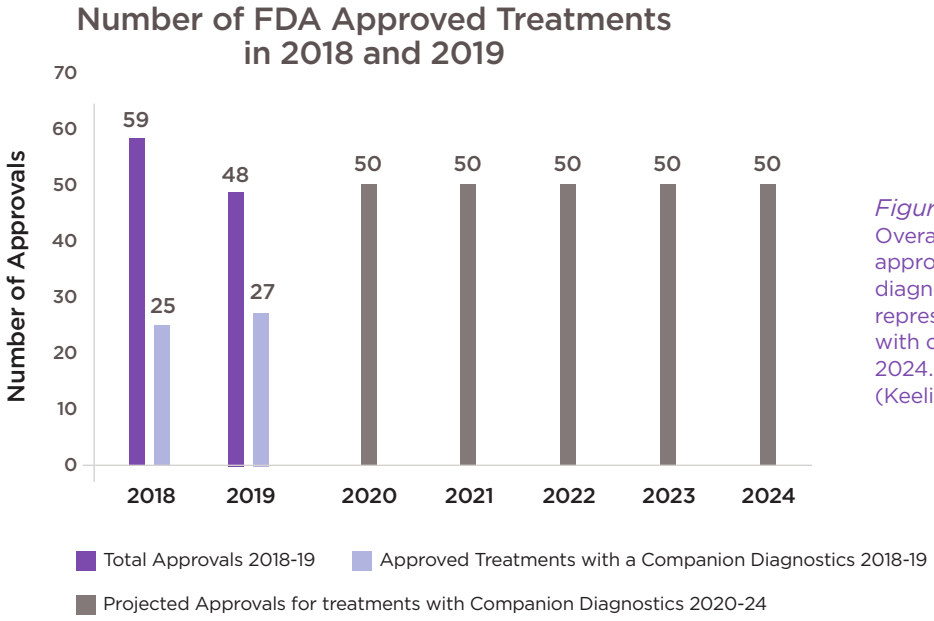

Figure 3.
Overall number of approved treatments and approved treatments with a companion diagnostic in 2018 and 2019. Grey bars represent projected approvals for treatments with companion diagnostics from 2020 to 2024. Data from Keeling et al., 2020. (Keeling et al., 2020)

Hurdles to the Use of Companion Diagnostics

Companion diagnostics frequently fail to fulfill their intended role since they are subject to challenges of commercialization, clinical implementation, and delayed uptake. We will explore each of these phenomena in turn.

Commercialization hurdles are mainly due to a lack of investment on the part of the biopharmaceutical companies launching a drug/diagnostic combination. The pre-launch budget for a companion diagnostic is usually between US$3 and $12 million, which represents about 6% of the budget allocated to the commercialization of the targeted therapeutic.[2] This unequal allocation of resources between targeted therapeutics and companion diagnostics fails to recognize testing with the companion diagnostic as an important driver of revenue. Each US dollar spent on testing drives between $30 and $60 in additional treatment that would otherwise be lost.[2]

Several common hurdles impede the adoption of companion diagnostics into clinical practice, see Figure 4.[2]

- Physicians do not request the companion test due to a lack of awareness.
- Samples for the required companion diagnostic test are not available or of low quality. Low-quality samples can compromise the test accuracy.
- Companion diagnostic testing may not be offered by existing labs. Ideally, the companion diagnostic tests should be available in labs that physicians prefer and trust.
- Unreliable and inconsistent test quality can result in misguided treatment decisions, negative impact on patient outcomes, and an undermining of physician confidence in companion diagnostic testing and/or the targeted therapeutic associated with it.
- Companion diagnostic test results may not be available in time to meet the decision-making window during which the targeted therapy can be initiated.
- Companion diagnostic tests may be insufficiently reimbursed, disincentivizing labs from adopting the test.

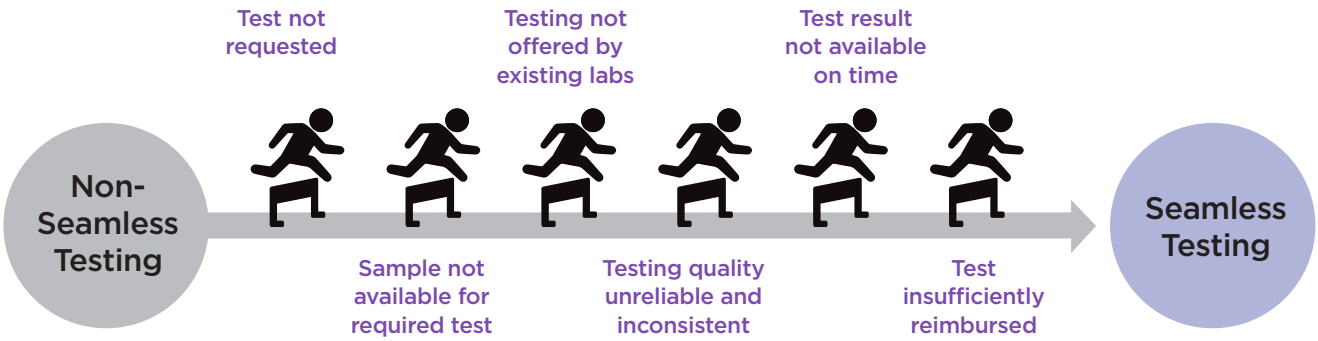

Figure 4.
Common hurdles to the adoption of a companion diagnostic test (Keeling et al., 2020)

An important consequence of the expansion of clinical trials and regulatory approvals described above is that the period of exclusivity for any new drug/diagnostic combination can be very short. While trastuzumab and its companion diagnostic enjoyed exclusivity for years, today's competitive launches may be only months or even days apart. As mentioned previously, about 50 approvals of therapeutics with companion diagnostics are expected for 2020-2024, see Figure 3. This means that on average, one new targeted therapy will be launched every week over the next 5 years. With many of these therapies addressing similar or closely related disease states, each of these newly launched targeted therapies will enjoy only a brief period of exclusivity in which to establish itself in the market.

However, the time lag between launch and the achievement of sufficient lab coverage is on average 3 years, and full clinical uptake of the companion test whereby the test is available to all eligible patients takes on average 4.5 years, see Figure 5. This period, during which a newly launched drug/diagnostic combination has not yet demonstrated its full clinical potential, is often the time when competitors come to market with a similar product.

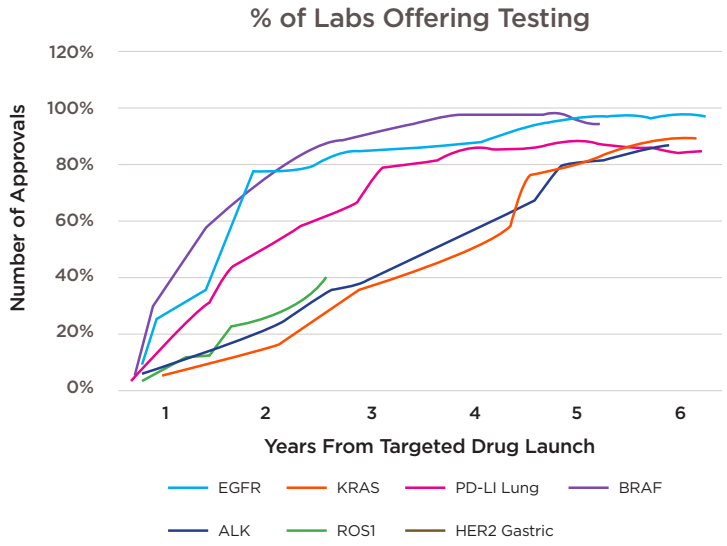

Figure 5A. Time to lab uptake of diagnostic tests following launch of treatment

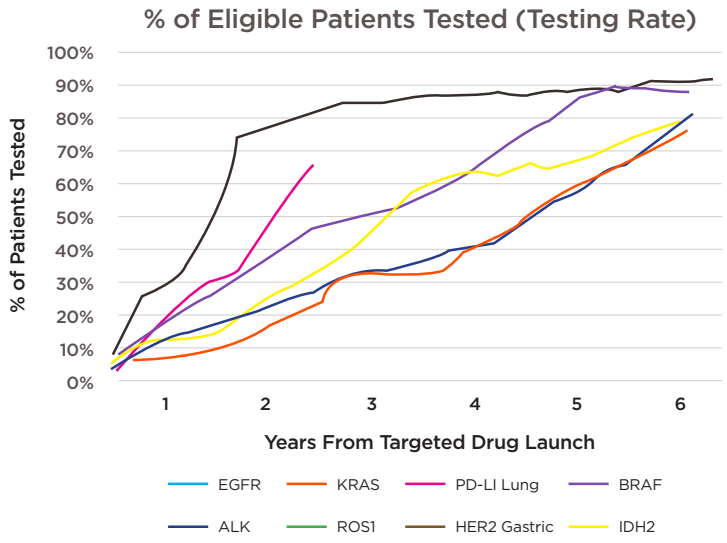

Figure 5B. Time it takes for diagnostic tests to reach eligible patients

Figure 5A and 5B.
The time lag from launch to complete uptake of a companion diagnostic by labs can be several years (5A), and it can take several years after the launch of a targeted treatment for the companion diagnostic to reach all eligible patients (5B). (Keeling et al., 2020)

Due to these hurdles, the development of a companion diagnostic test does not guarantee that the appropriate patient population is detected in clinical practice and as a result, patients do not have access to precision medicine treatments at a time in their patient journey when such treatments would be helpful.[2] It is estimated that due to the unavailability of companion diagnostic testing, nearly 78,000 patients annually miss out on targeted therapy, which corresponds to an annual revenue loss of US$8.3 billion per year for biopharmaceutical companies.[2]

Stakeholders and Commercialization Channels

For biopharmaceutical companies, commercializing a drug/diagnostic combination means that they will have to work with unfamiliar stakeholders.[8] Commercializing products with companion diagnostics may carry novel technological, regulatory, or educational requirements for which established solutions do not exist.[8]

Key stakeholders in the development and commercialization of therapies with companion diagnostics include patients, physicians, biopharmaceutical companies, diagnostic companies, clinical research organizations (CROs), labs, and payers. Testing can be a physician barrier to the use of the targeted therapeutic if the test is not well understood or complicated. However, if the testing barrier is removed, the efficacy of the therapeutic becomes the deciding factor for physician acceptance. The sales interests in the commercialization of therapies with companion diagnostics are split between biopharmaceutical companies that sell the therapeutic and test manufacturers that sell the test equipment. In this situation, the biopharmaceutical companies are dependent on the companion diagnostic test, but lack the knowledge required to promote it. Difficulties arise due to differences in language, terminology, and information flow between biopharmaceutical companies, diagnostic companies, and laboratories.

CROs play a critical role in the performance of clinical studies, but they are geared towards conventional clinical trials without a companion diagnostic. CRO services include guidance on operational aspects of the trial, site selection, and regulatory compliance. The criteria for site selection include sufficient patient numbers, capacity to perform the trial, clinicians with a record of high-impact publications and high professional visibility, and the ability to accept patient referrals. Gaps in CRO coverage of trials of therapeutics with companion diagnostics can occur because CROs prioritize their clients according to their own business needs, which means that some trials may be insufficiently supported.

Moreover, clinical studies are highly controlled environments that are not replicated in real-world clinical practice. While clinical studies follow a strictly defined protocol, real-world hospitals and labs have their own unique processes that differ from hospital to hospital, lab to lab, and country to country. Real-world patient variability will also be greater than that found in clinical studies. These differences between hospital settings and the operational issues faced by labs and hospitals are not addressed by CROs. Finally, CROs focus on conventional measures of quality and compliance but rarely engage in the clinical and scientific discussions that are necessary in the context of a trial of a therapeutic with a companion diagnostic.

Labs are tasked to perform the companion diagnostic test, but often lack the necessary equipment or incentive to invest in such equipment. Patient benefits as well as the benefit to the business must be understood by the laboratories to make appropriate investments.

Important considerations for investment and access to the companion diagnostic include:

- How many patients will be tested?
- How often will the patients be tested?
- What is the reimbursement landscape?

At present, education on testing is not a key driver to the business of any of the stakeholders involved in the commercialization of companion diagnostics. Consequently, neither biopharmaceutical companies nor test manufacturers have developed a process for the commercialization of companion diagnostics, and no party within the commercialization process makes the communication and alignment between stakeholders easy.

However, when companion diagnostic testing becomes easy and reliable it will emerge as a key brand differentiator that drives better patient outcomes and ultimately greater return on investment for biopharmaceutical companies and test manufacturers.[6]

Diagnostic Liaisons Help Overcome the Barriers to Commercialization of Companion Diagnostics

Diagnostic Liaisons add value by ensuring that all stakeholder groups are connected to one another and trained in the importance of the innovative treatment. They can also identify critical gaps and obstacles related to the introduction of companion diagnostics.

Diagnostic Liaisons support the development and introduction of companion diagnostics from the early stages of research to launch and beyond by:

- Supporting the implementation of clinical studies
- Mapping hospitals
- Training various teams within biopharmaceutical companies
- Representing Medical Affairs to various stakeholders
- Having broadly focused scientific conversations that cover all clinical trials within the therapeutic area
- Operationalizing the companion diagnostics or companion diagnostic process at launch with Reference Laboratories as well as with community hospitals
- Supporting pharmaceutical sales teams by addressing diagnostic questions around the therapy that are beyond the understanding of the field force
- Monitoring and supporting the quality of testing results in the marketplace

Diagnostic Liaisons can help speed up clinical trials and help ensure a more successful outcome by connecting all stakeholders and thereby ensuring faster and more accurate patient selection. In doing so, Diagnostic Liaisons not only address an important gap in the service of CROs but help lay the foundation for brand success.

By providing education on testing, Diagnostic Liaisons play a key role in the marketplace that is currently unfilled. Once stakeholders realize that the companion diagnostic can generate efficacy for the therapeutic, the companion diagnostic turns from a barrier into a key advantage.

The key advantage that a companion diagnostic gives to all stakeholders is that it matches the right patient with the right treatment at the right time by:

- Identifying patients who are likely to respond to the targeted therapy
- Ruling out patients who are unlikely to respond to the targeted therapy
- Making the key diagnostic information readily available
- Enabling the initiation of targeted therapy at a point in the patient journey at which the targeted therapy is likely to be effective, i.e. before disease progression or irreversible damage has occurred
- Avoiding unnecessary, time-consuming, and costly medication trials that fail to address the specific biologic makeup of the individual patient

Importantly, successful testing with a companion diagnostic can establish the reputation of a pharmaceutical company with benefits beyond the marketing of a single drug. Having a well-understood companion diagnostic that employs a clearly understood diagnostic process can be the key to maintaining a leadership position in the face of competitive launches or it can propel a therapy that is a latecomer to the marketplace into a leadership position.[6]

Conclusion

Precision medicine outperforms conventional pharmacotherapy by developing treatment plans that are based on a patient's unique makeup, environment, and lifestyle. Companion diagnostics can exponentially improve the success of precision medicine by testing for biomarkers that reveal the specific pathological process or response to intervention that can vitally inform treatment decisions. No longer a 'one size fits all' approach to treatment, this targeted testing and treatment model can save patients critical time on their patient journey and greatly improve outcomes.

Amplity Health has been highly effective in both the medical and commercial aspects of companion diagnostics. We have provided both medical field education and execution, as well as commercial implementation strategies on behalf of our pharma clients. We believe that Amplity can assist with your companion diagnostic plans and efforts. We look forward to the conversation.

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