CLINICAL LEADER

Will Special Interests Derail The Future Of Personalized Medicine?

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Treatment of cancer using chemotherapy (chemo) drugs began soon after WWII, when a compound called nitrogen mustard was studied and found to work against cancer in the lymph nodes. In the years that followed, many chemo drugs have been developed that work by non-selectively inhibiting rapidly dividing cells. In other words, chemo drugs kill cancer cells, but they also kill healthy cells in patients. The effectiveness of chemo treatments has therefore traditionally been determined by how well the toxicity of chemo drugs can be tolerated and/or managed in a patient.

Today, however, scientific advances in molecular biology, genetics and imaging have begun to change the way cancer is being treated. Research scientists are having success both in identifying specific cancer biomarkers, and in developing therapies which act directly on those targets. As a result, the era of the one size fits all chemo drug is fading - doctors now have the option to prescribe cancer therapies that are ultimately more effective on the disease and gentler on the patient. Examples of this new breed of targeted cancer therapies include the following:

- Endocrine therapies (such as tamoxifen and the aromatase inhibitors) ;
- Anti-HER2 therapies for breast cancer (such as trastuzumab and lapatinib) ;
- Imatinib, the first drug to directly turn off the signal of a protein known to cause a cancer; and
- Anti-EGFR therapies for patients whose tumors overexpress the EGFR protein due to a specific gene mutation (such as cetuximab, gefitinib and erlotinib).

Drugs such as these are ushering in the age of personalized or precision medicine, where patients receive treatments that are targeted to their unique biochemistry. Another important piece of the personalized medicine puzzle, however, is the development of the diagnostic techniques that effectively identify the patients that will benefit from targeted therapies. Unfortunately, the development of these diagnostic tests (typically known as in-vitro diagnostics or IVDs) has often lagged behind the development of the therapies themselves.

Companion Diagnostics and the Age of Precision Medicine

The increasing need for personalized medicine, and resulting demand for companion diagnostics, has led to the integration of the previously separate activities of drug and diagnostic development. The age of precision medicine, with treatments targeted to specific patients based on a companion test identifying the need for such a treatment, is upon us. The first companion diagnostic test was approved in 1998 to support Herceptin® (trastuzumab) in the treatment of metastatic breast cancer. Since that time, the number of companion diagnostics on the market has grown rapidly. A 2014 report by the Personalized Medicine Coalition documents the steady development of the personalized medicine field. According to the report, there were 13 prominent examples of personalized drugs, treatments and diagnostics on the market in 2006. By 2011, there were 72, and in 2014, there were 113.[1] Additionally, the non-profit Regulatory Affairs Professionals Society (RAPS) reported in 2015 that 28% of new drugs and biologics were approved alongside a diagnostic.[2] The FDA's website now lists several dozen approved companion diagnostics. The growth in companion diagnostics is not just a US phenomenon; drugs with required testing that have been approved by the European Medicines Agency (EMA) have followed a similar trajectory.

While oncology remains the largest segment of drugs with companion diagnostics that are on the market, and will likely remain so for the foreseeable future, other therapeutic areas are beginning to emerge, including cystic fibrosis, human immunodeficiency virus (HIV), and severe growth failure.

Barriers to Codevelopment

While the practice of precision medicine is clearly on the rise, only a handful of drug diagnostic combinations have had the drug and diagnostic test approved simultaneously, presenting manufacturers and sponsors wishing for joint market authorization with a unique set of challenges. A few of these issues are presented below:

Regulatory Challenges – Biomarker-driven clinical trials introduce significant regulatory challenges when the goal is simultaneous approval for both biomarker assay and drug, as both the test and the drug must meet regulatory standards for marketing approval and clinical use. The main challenge is that, within the FDA, review of IVDs and drugs resides in different divisions of the agency – the Center for Devices and Radiological Health (CDHR) and Center for Drug Evaluation and Research (CDER), respectively. Both of these agencies apply separate review processes and have different approval standards. Investigators and sponsors often find it challenging to design clinical trials that are acceptable to both divisions and provide conclusive evidence of the safety and effectiveness of both the test and the drug. Fortunately, the FDA has recently published a draft guidance document designed to assist companies planning to develop a drug paired with a companion diagnostic test.

Identification and Recruitment of Patients for Clinical Trials – Factors like the prevalence of the marker, tissue availability, testing costs and patient access to information and clinical trial sites can make the identification and recruitment of patients with the targeted marker profile inefficient. With only 10% of cancer survivors reporting awareness of the possibility of enrollment in a trial, for example, and only 3% actually enrolling,[3] conducting traditional safety and efficacy trials in a subpopulation identified by a molecular target can be costly and time consuming.

Misaligned Incentives Between Partners – Oftentimes, there are different sponsors for both the therapeutic drug and the companion diagnostic (IVD). This situation creates the potential for misaligned incentives that can inhibit the kind of cooperation between partners necessary to bring a drug with a companion diagnostic test to market. Unlike the drug developer that can count on a lifetime of revenue from chronic treatment of a patient, the diagnostic developer only gets paid per test. The potential profits from the partnership are clearly much higher for the drug developer, and this imbalance is amplified by the fact that few diagnostic companies have a sales force to educate health care providers on ordering the appropriate diagnostic test. The drug developer thus wants the most accurate test available to the greatest number of physicians at the lowest cost in the shortest period of time, with all attention focused on selling the greatest volume of pharmaceuticals. Diagnostic developers, on the other hand, may not have an interest in developing a companion diagnostic test, especially if the test is for a limited patient population. For the partnership to move forward, there must be negotiation that involves drug developers taking on some of the costs required to bring the companion diagnostic to market.

Reduced Profits for Drugs Already on the Market - Diagnostics that result in targeted use of a comparatively well-reimbursed treatment can reduce not only revenue but also profit margins. Drug companies therefore do not have the necessary incentive to work on the development of a companion diagnostic for successful drugs that are already out in the market.

Inadequate Reimbursement for Diagnostic Services – Insurance companies are obviously interested in maximizing effectiveness of treatments so as to minimize pay outs, and their reimbursement structures reflect this. Insurance policies are therefore not willing to pay for all types of diagnostic tests. Insurance providers are much more interested, for example, in diagnostic tests that provide information on the potential efficacy of a given treatment, or that provide information on multiple potential treatment options in a therapeutic area. As multiple therapeutic agents are approved for similar clinical conditions, insurance companies want to identify the best product for a particular patient and avoid paying for multiple similar tests. This is an area where the interests of insurance companies and drug developers diverge, as no drug developer wants a companion diagnostic that could potentially point to the use of a competitor's product. Companion diagnostic companies that seek to partner with drug companies to help defray the costs of developing a companion diagnostic thus often face the difficult position of being caught in the middle between drug developers and insurance companies - forced to choose between getting financial support from a drug developer to create a companion diagnostic that may receive inadequate reimbursement from insurance companies, or being on their own to create a diagnostic test that provides information on multiple potential treatment options. The consequences of poor reimbursement for diagnostic services include less investment in new diagnostic tests and the failure of some diagnostics companies.

Conclusion

Companion diagnostics are a critical element to the advancement of precision medicine. Recognizing the need to address the challenges to this novel area from a regulatory perspective the FDA has released a draft guidance on the codevelopment of therapeutic products and screening tests. This document sets the expectation that companion diagnostics and corresponding therapeutic products should be approved or cleared by the FDA at the same time, representing new opportunities for developers to work together to more clearly define a process and coordinate a timeline for development. The regulatory landscape will continue to evolve, but an even larger challenge for co-development may be more commercial than regulatory, as there are fundamental differences between developing tests and drugs, including vastly differing markets and technical resources. In the end, solutions will likely require both regulatory change, as well as, new commercial models, such as incentives for codevelopment.

References

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