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Joseph Ferrara
 Boston Healthcare Associates, Inc.,
 75 Federal Street, Boston,
 MA 02110, USA
 Tel.: +1 617 482 4004
 Fax: +1 617 482 4005
jvferrara@bostonhealthcare.com

Personalized medicine: challenges in assessing and capturing value in the commercial environment

'...the development of drugs that are highly targeted to patients most likely to benefit holds enormous promise for global healthcare.'

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The proposed value of personalized medicine is currently well understood. With an increased study of the molecular basis of disease, the development of drugs that are highly targeted to patients most likely to benefit holds enormous promise for global healthcare. For patients and physicians, personalized medicine offers apparently clear clinical advantages: a biomarker directly indicates the most appropriate therapeutic intervention. In turn, this leads to more predictable outcomes, enhanced efficacy through the identification of drug responders, and a potential reduction in adverse drug reactions. Of course, many questions remain: Will these medicines, rendered highly effective through companion diagnostics, improve patient compliance? Will they increase patient and physician demand? Drug companies also have questions: Will linking drugs to diagnostics shorten pharmaceutical development and approval timelines? Will the diagnostic/drug combination boost the value of both of these technologies, or only of the diagnostic, at the expense of the drug?

Differing perspectives on value

While there has been much discussion of the promise of linked diagnostic/therapeutic (Dx/Rx) combinations, there has been little examination of the key question surrounding the commercial opportunity for personalized medicine: How will stakeholders assess and capture value in a Dx/Rx market environment?

Stakeholders, such as biopharmaceutical companies, diagnostics innovators and payers, are all technology adoption influencers; however,

they will likely have differing, and perhaps conflicting, perceptions of value in a personalized medicine paradigm. In this respect, value must include the linked components of clinical, health economic and, of course, commercial value. How these stakeholders are assessing and attempting to capture value offers some insight into how the commercial environment for personalized medicine will take shape.

So how are these players assessing and capturing value in the emerging Dx/Rx market environment? It has not been easy. Perhaps this is because there have been so few examples of Dx/Rx combinations in practice to serve as guideposts for future assessment. Drug developers, diagnostics players and payers all stand to gain from the commercial success of personalized medicine models. However, many of these stakeholders are struggling to find the parameters and tools with which to assess the value of the paradigm, and to capture that value without threatening their current business models.

Biomarker impact on drug development: biopharma's moving target

The most widely cited example of a Dx/Rx success story is the Herceptin[®]/trastuzumab (Herceptin[®]) combination from Dako and Genentech/Roche for the treatment of certain breast cancer patients. In this combination, the benefits of trastuzumab were demonstrated to be greatest in the Her2-positive subset of breast cancer patients in the drug's clinical trials. For

patients and physicians, the advantages were clear: improving median survival and overall response rates to chemotherapy. For the drug's developers, fast-track approval was granted by the FDA based on the test/drug combination data; proving, in this case at least, that studying a subset of responders based on a companion diagnostic can shorten drug development and approval timelines.

For drug companies the conceptual trade-off is this: potentially lower attrition rates and shorter approval timelines in exchange for a targeted therapy that is highly effective in a subset of patients with the disease. In commercial terms, this means trading in the blockbuster model of therapies offered to the widest possible patient pool with lower median efficacy, for a Dx/Rx combination that is highly effective in a smaller patient population. Thus, there may be a smaller market, but the drug will go to market faster.

However, after trastuzumab, subsequent examples of Dx/Rx combinations have made the commercial picture murkier, not clearer. Similar to the trastuzumab model, most of the developments in the area have been in oncology. On the surface, oncology is an excellent therapeutic area for Dx/Rx investment. It is a complex, multifactorial disease that is life-threatening, with expensive therapeutic options that often have brutal side effects. Thus, oncology presents a strong clinical and economic opportunity for highly targeted therapies.

However, there have been mixed results in oncology in the drive to launch successful Dx/Rx pairings. The cases of cetuximab (Erbix[®]) and gefitinib (Iressa[®]) have demonstrated that it can be difficult to predict which drugs will benefit from companion biomarkers. The drugs, both approved in the USA for refractory advanced cancers and both epidermal growth factor receptor (EGFR) inhibitors, have had different approaches to companion EGFR testing, yielding unexpected commercial outcomes.

While cetuximab was FDA approved as third-line therapy for patients who test positive for EGFR expression, recent studies suggest that a portion of EGFR-negative patients may benefit from the drug. In the case of gefitinib, outcomes were not linked to EGFR protein expression in its clinical trials; however, a follow-on confirmatory study demonstrated the drug to be efficacious in a limited subset of patients in the clinical trial – a group that could have conceivably been identified with a test.

Since 1995, there have been over 150 Investigational New Drug/New Drug Application submissions to the FDA that included pharmacogenomic data, and some of these drugs could launch with companion tests. However, based on the apparent unpredictability of biomarker impact, it is unlikely that all of these drugs will launch with companion tests. Thus, while pharmacogenomics has been conceptually attractive to biopharmaceutical companies as a way to raise the productivity of research and development, in practice, the results have been mixed to date.

Diagnostics companies: searching for new value

For diagnostics companies, personalized medicine presents both near- and longer term opportunities. With annual revenue growth of over 20%, molecular diagnostics is widely considered to be the fastest growing segment in the *in vitro* diagnostics marketplace. Within molecular diagnostics, growth in diagnostics products linked to therapies is predicted to grow even faster.

In the near term, diagnostics players are focused on two activities in developing diagnostics that are linked to therapies. The first is an extension of the HercepTest model, where a drug company partners with a diagnostics company to develop a companion test in parallel with drug development. In this approach, the diagnostic company takes some risk, of course, that the drug may not be approved, but this risk is small compared with drug development risk. In some cases, drug companies may choose not to partner exclusively with a diagnostics company, but rather open the opportunity up to any diagnostic company willing to invest in test development and regulatory approval. This has been the approach taken by Novartis in c-Kit test development to support imatinib (Gleevec[®]).

The other near-term opportunity for diagnostics companies is the development of tests that can be linked to drugs already approved and on the market. This model offers ready potential for diagnostics players, since approved drugs present an opportunity for tests that can help to distinguish responders from non-responders. Emerging companies, such as Genomic Health, Inc. and Exagen Diagnostics, Inc., have developed tests that identify patients who are most likely to benefit from certain drugs based on prognostic information about disease recurrence. These tests address an immediate need that diagnostic companies can pursue directly without a pharmaceutical partner, and without linking their test's success to a drug approval.

However, perhaps most attractive to diagnostics players is the role that personalized medicine could play in raising the overall profile and value of the diagnostics industry. For diagnostics companies (and clinical laboratories for that matter), the longer term opportunity is to capture increased value for the diagnostics portion of the Dx/Rx combination. Currently, *in vitro* diagnostics represents only a fraction of healthcare spending compared with drugs. In order for diagnostics players to capture more value, one of two things would have to happen. First, payers would have to parse the value between the diagnostic and therapeutic combinations differently than current practice. This would require examining and valuing the health economics of patient stratification in a more robust way, which offers unique challenges to the payer. The other potential avenue for capturing more value for diagnostics in the paradigm entails diagnostics players taking on more of the financial risk of drug development. While such a model is unlikely to be attractive to a big pharma partner, emerging specialty pharmaceutical companies may present the opportunity to share some of this risk and potential future commercial reward.

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Payer perspective: evidence-based medicine requires evidence
 How payers approach policy and payment is a critical component in the realization and sustainability of the personalized medicine marketplace. The linking of a specific therapeutic to a certain diagnostic result is, of course, very attractive to payers. Improved efficacy of therapies improves outcomes, has the potential to reduce therapy expense by eliminating inappropriate prescriptions, and may indeed improve patient compliance. Again, the trastuzumab example is instructive: many payers in the USA, although not all, will pay for trastuzumab only after the companion test has been ordered. Thus, the Dx/Rx link is written into coverage policy. However, the gefitinib and cetuximab examples have proven difficult in terms of policy development: the unpredictable relationship between test and drug renders the evidence-based approach to coverage a challenge.

Another limitation in payers' ability to gather adequate evidence to support explicit coverage policies for linked diagnostics and therapeutics is one of infrastructure. Information technology systems currently available to payers have severe limitations in their ability to track diagnostic tests and link the results to coverage and payment for certain therapeutic interventions. Without more sophisticated information systems, it will be difficult for payers to enforce even explicit policies in this arena. This is further complicated for many private payers in the USA because diagnostics are paid as part of the medical benefit category, while most drugs are covered under the pharmacy benefit category. In effect, the value of the two technologies is assessed by two different decision makers commanding two separate budgets, making a unified technology impact analysis more difficult.

In fact, it could be argued that the very concept of personalized medicine and extensive stratification of patients that it entails runs counter to the idea of broadly applicable coverage policies. As this commercial environment evolves, it will be increasingly difficult for payers to deploy policy approaches that address an increasingly stratified patient pool.

Implications for assessing value

With so few commercial examples, it is a continuing challenge to assess the value of the Dx/Rx model. For this reason, stakeholders have approached personalized medicine with widely varying degrees of enthusiasm. Certainly, several biopharmaceutical players have embraced the paradigm, aggressively developing Dx/Rx programs. At the same time, many companies, even those that already have both biopharmaceutical and diagnostics businesses and would be likely candidates to shape this marketplace, appear to be taking a 'both/and' approach – continuing to seek blockbuster drugs, while searching for optimal Dx/Rx candidate programs.

What should command the most attention in the near term is the activity of the diagnostics players and their efforts to link tests to currently marketed drugs, and the payers who will do the hard work to assess their value.

Affiliation

- *Joseph Ferrara*
Executive Vice President, Boston Healthcare Associates, Inc.,
75 Federal Street, Boston, MA 02110, USA
Tel.: +1 617 482 4004
Fax: +1 617 482 4005
jvferrara@bostonhealthcare.com