



Drug–diagnostic co-development: how to harness the value

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Some years ago, we developed a value assessment process that was predicated on certain assumptions about how valuation might be influenced by drug development and marketing factors. Here, we discuss how our assumptions have held up particularly in light of regulatory and reimbursement changes. In addition, we assess how the relationship models derived from the value-assessment process have been substantiated by reviewing some recent cases of testing and stratification.

Introduction

Our modelling [1] identified four key points where a companion diagnostic (CDx) might impact on the development and marketing of an associated targeted therapeutic (Fig. 1). This value modelling suggested an overall net present value (NPV) uplift of US\$1.8 billion on a drug lifecycle, which at base-line (i.e. without a cognate test), was approximately US\$0.9 billion NPV. Although, this value uplift has been corroborated by independent modelling [2], and indeed the core business relationships derived from our modelling [3] substantiated by real-life deal making, we have become aware that several assumptions used to derive the model might now be erroneous. Here, we look at several situations where events have overtaken our original hypotheses. We particularly consider four issues:

- (i) Requirement for biomarker-negative patients to receive targeted therapy.
- (ii) Impact of tested but not treated patients: Abacavir 96% test and treat versus Iressa 10% test and treat.
- (iii) Adoption rates and pricing: role of pharma, regulators and payers in the CDx pricing process.
- (iv) Lifecycle management and line extension: AstraZeneca/Prometheus Laboratories (budesonide).

In addition, we look at the relationship scenarios that we derived from the value modelling and we present cases where the scenarios have been enacted.

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Impact of inclusion of biomarker-negative patients into co-development strategies

A key modelling assumption, which now requires revision in light of intervening regulatory developments, concerns the proposed reduction in study size of clinical proof of principle/pivotal trials. This reduction in part served to underpin subsequent assumptions concerning an accelerated co-development pathway and resulting uplift in risk-adjusted net present value (rNPV) of the therapeutic. This original assumption was based on the analysis of primary and secondary research [4,5], which predicted that the US Food and Drug Administration (FDA) and other competent authorities would routinely accept randomised control data submissions on biomarker-positive patient cohorts only.

At present, little consensus exists formally among regulators on drug–diagnostic co-development strategies. We believe this is because traditional all-comer approaches are relied upon to set cut-off limits for the sensitivity and specificity of the CDx, in addition to studying safety and effectiveness of the therapeutic. The FDA's Oncologic Drugs Advisory Committee (ODAC) has proposed prospective patient stratification based on biomarker response, followed by a clinical study on biomarker-positive and -negative cohorts to assess clinical response in both sets of patients. This is driven in part by observations in landmark studies, such as Iressa Pan-Asia Study [6], where biomarker-negative patients fared less well than the standard of care when given targeted therapies (TRx). It remains to be seen whether targeted therapies would in reality be given to those who are predicted through testing to be unresponsive.

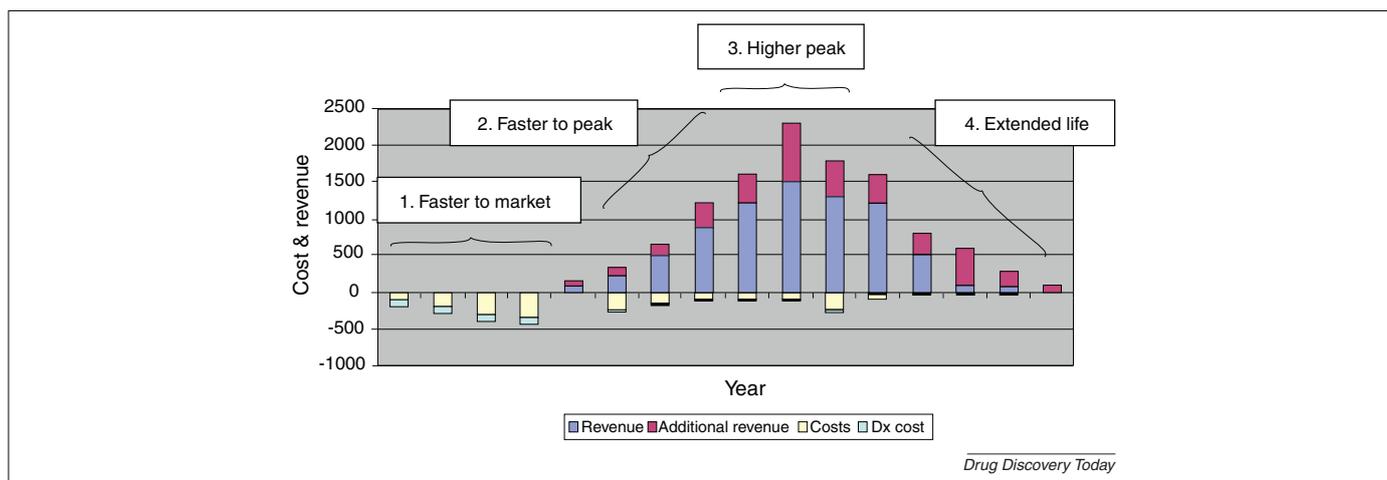


FIGURE 1

Impact of companion diagnostics on drug lifecycle income. Adapted, with permission, from [1].

McClellan *et al.* [7] recently proposed several principles for trial design of 'targeted approval trials'. In cases where evidence exists that biomarker-positive patients will respond to treatment the candidate stratified medicine should be prospectively evaluated in the biomarker-positive subpopulation identified by the CDx. This assumes that sufficient biomarker-positive patients can be recruited to the trial to provide sufficient powering to enable robust statistical analysis.

Impact of test but not treat on drug–diagnostic pricing relationship: Abacavir- and Iressa-associated testing

In our various valuation scenarios, but particularly the integrated co-development model (Fig. 3a), our assumption had been that pharma would bear the costs of developing the CDx from biomarker validation through clinical testing of prototype diagnostic to test registration and co-launch. The outlay in paying for test development, approximately US\$20 million or 40-fold less than drug development, would be recouped by test pricing based on value-based reimbursement that assessed the companion diagnostic test-targeted therapeutic (CDx–TRx) bundle. However, it is now obvious that in many cases of efficacy prediction for targeted therapies, only 5–10% of the tested population might actually receive the cognate treatment, with approximately 90% of the population tested but not treated. Thus the TRx partner might only see reimbursement for therapies in 10% of cases. In such a scenario, it might still be feasible for the pharma partner to support a test price burden of approximately US\$200 if the bundle is reimbursed at a fee greater than US\$2000; however, recouping of the CDx investment could take some time. Thus two trends that we did not foresee are: (i) the sharing of test development costs by a diagnostics partner, and (ii) by extension, the diagnostic partner sharing the therapeutic development risks in return for royalty payments based on TRx sales.

For safety testing associated with rare adverse events, the pharma partner would soon see benefit because 90% (-plus) of patients who were tested would be treated with the cognate therapy. Thus for the GSK HIV therapy, Abacavir, the human leukocyte antigen (HLA) allele associated with severe inflammatory response

is seen in approximately 5% of the target population and thus 95% of those tested receive medicine, and so it is simple to absorb testing cost in drug price. Finally, the activating *KRAS* mutation has a prevalence of approximately 40% and so approximately 60% of those tested would benefit from drugs, such as cetuximab and panatumumab. Reimbursement of the *KRAS* is discussed below.

The role of pharma in detailing CDx tests with physicians

Our modelling largely ignored the role of pharma companies in promoting the use of CDx(s) because many of the cases evident at the time suggested that pharma representatives would not promote testing. Thus, the 3-year, US\$5 million investment relationship between Aventis (<http://www.sanofi.co.uk/l/gb/en/index.jsp>) for its drug, enoxaparin (Lovenox[®]), and the PharmaNetics CDx termed the Enox, dissolved acrimoniously with a lawsuit alleging that Aventis failed to fulfil its obligation to promote the test and was falsely advising physicians that the test was not necessary (PharmaNetics v. Aventis; <http://www.law.com/jsp/cc/PubArticleCC.jsp?id=900005400412>). However, Merck-Serono (<http://www.merckserono.com/en/index.html>), who has the European license for the Centocor/Johnson and Johnson (<http://www.jnj.com/connect/>) drug cetuximab (Erbix[®]), took a more supportive approach to promoting and gaining reimbursement for the *KRAS* predictive CDx test from DxS/Qiagen (<http://www.qiagen.com/default.aspx>). Through co-promotion, the number of eligible metastatic colorectal cancer patients being *KRAS* tested, to determine if they could benefit from Erbitux, or other epidermal growth factor receptor (EGFR)-targeted therapies increased from 2.5% in 2008 to 42% in 2009 and 69% in 2010 [8]. Unfortunately, only approximately 50% of those testing wild type for *KRAS* currently receive the cognate therapy [9]. In the UK, Merck-Serono also paid for the *KRAS* test to be conducted in a limited number of reference laboratories, but used the evidence gained to persuade National Institute for Health and Clinical Excellence (NICE) that the *KRAS* test should be positively assessed for full reimbursement by the National Health Service (NHS) [10]. It remains to be seen

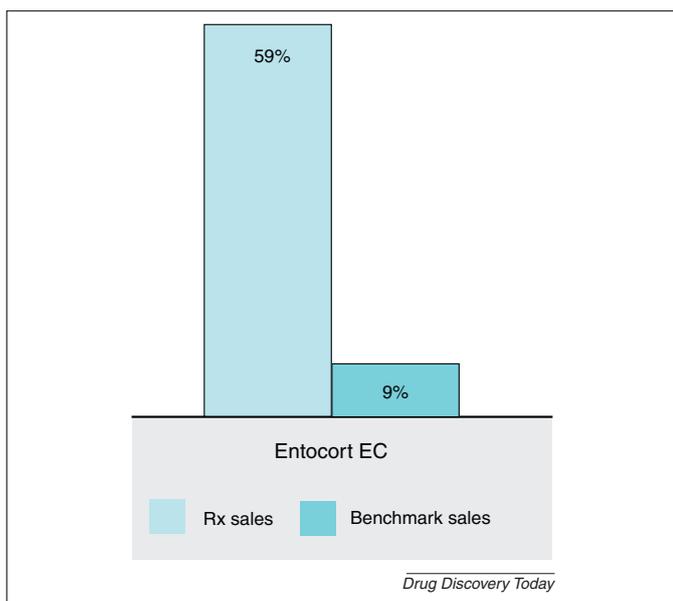


FIGURE 2 Late lifecycle benefits of companion testing. *Abbreviations:* Rx. Adapted, with permission, from [11].

whether this pragmatic approach to CDx pricing and reimbursement will be widely adopted, but pharma companies undoubtedly offer a sales force that exceeds most in the diagnostics industry and thus represents a promotional resource for CDx partners.

Impact of drug–diagnostic relationships on lifecycle management: Prometheus Laboratories: Entocort[®] EC and Serology 7 testing

An example of the ability to extend or rescue pharmaceutical product sales exists in the field of inflammatory bowel disease (IBD), a condition that is principally made up of Crohn’s disease and ulcerative colitis. Entocort EC, an oral, modified-release formulation of budesonide, was developed by AstraZeneca (<http://www.astrazeneca.co.uk/>) and launched in 2001 for the treatment

of Crohn’s disease. Owing to poor sales performance of Entocort EC by AstraZeneca, Prometheus was able to license the US commercialisation rights to the steroid from AstraZeneca in 2005. Prometheus developed a serological-based diagnostic test, Serology 7, to distinguish between sub-types of IBD. The positioning of both drug and diagnostic by Prometheus has had a dramatic effect on sales performance: this has grown by 59% annually since Prometheus took over the rights, compared with 10% in territories where the drug is subject to conventional pharmaceutical detailing (Fig. 2) [11]. Furthermore, Prometheus has been able to increase the ex-wholesale drug price by 120%.

Importantly, the Serology 7 test provides the physician with a diagnosis of Crohn’s disease. Subsequently, the disease can be managed using a variety of treatment modalities. It does not provide a steer on the use of Entocort EC *per se*. However, bundling the drug and diagnostic together has been effective in increasing the prescribing rates for the drug. Although it is acknowledged that Entocort EC is a proprietary formulation, this drug–diagnostic relationship has significance for generic drugs whereby a diagnostic can provide the basis of a treatment decision within a class of drug effect and can still selectively drive pharmaceutical sales.

Relationship scenarios

By extending our value modelling to look at how the added value created by a CDx might be apportioned between pharma and diagnostics partners, we derived four relationship models [1] that assessed the relative needs of each partner (partner influence) and the cash flow (direct or indirect) to the diagnostic test provider (Fig. 3a). In the intervening years, we have seen several CDx relationships develop, including various vendors of a CDx for trastuzumab (Herceptin[®]) from Roche (<http://www.roche.com/index.htm>)/Genentech (<http://www.gene.com/gene/index.jsp?hl=en&q=Genentech&meta=>) [9], the utility of KRAS tests from DxS/Qiagen (<http://www.qiagen.com/announcements/dxs.aspx>), and various other targeted therapies and associated tests (e.g. BRAF mutations, activating mutations of the AKT pathway, amplification of *ErbB2* and *MET*, the *EML-ALK4* translocation). Infectious

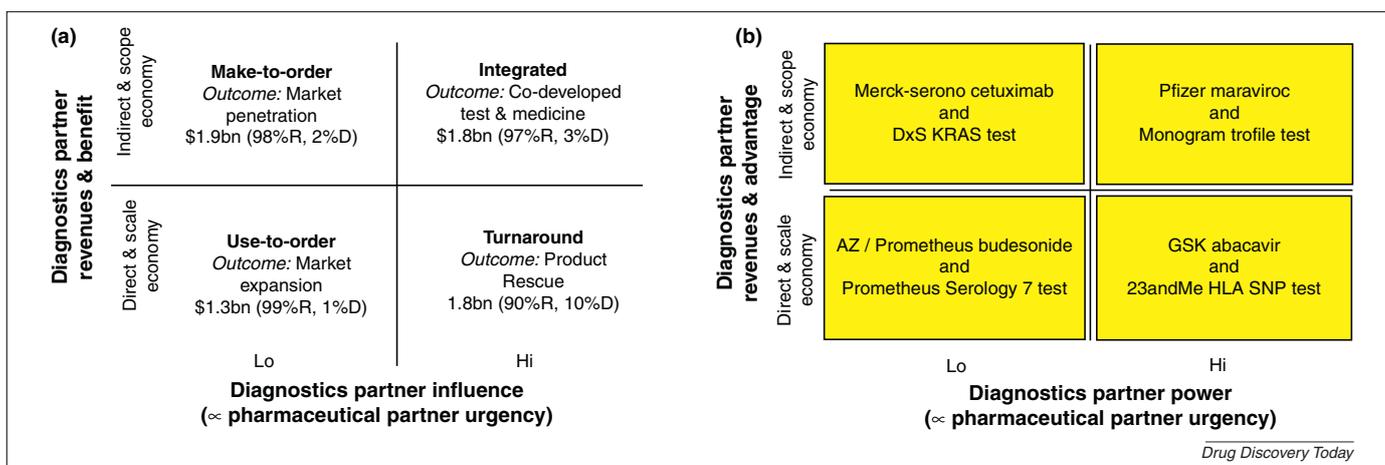


FIGURE 3 Rx–Dx relationships imagined (a) and real (b). *Abbreviations:* D; HLA: human leukocyte antigen; SNP: single nucleotide polymorphisms; R = pharma company share of NPV, D = diagnostic company share of NPV. Adapted, with permission, from [1].

diseases and cancer have continued to be at the vanguard of stratified medicine, although predictive safety testing has also been responsible for drug rescue in several therapeutic areas. It is thus possible to identify case studies that mirror the relationships that we have identified (Fig. 3b). We have discussed the KRAS/cetuximab, the Serology 7/budesonide and the HLA/Abacavir cases and next we briefly describe the Monogram/Pfizer (<http://www.pfizer.co.uk/default.aspx>) relationship, which reflects our integrated (co-development) relationship scenario.

Pfizer undertook a screening program that showed that chemokine antagonists, such as maraviroc, could also inhibit HIV binding and entry (infection) of target cells, but only if the virus had the C-C chemokine receptor type 5 (CCR5) tropism. To identify patients with this virus sub-type, Pfizer commissioned Monogram to develop a rapid, phenotypic assay for viral tropism, subsequently known as the Trofile test. Pfizer paid for the development of this test, which was conducted only in the Monogram

laboratories in San Francisco, and was used in clinical trials during development of maraviroc. Pfizer investment also ensured that the test was approved (CE-marked) ahead of the approval and launch of maraviroc.

Few other cases of true co-development of CDx tests exist and most relations are formed around the retrospective need for stratification for efficacy or safety.

Concluding comments

We have looked at several assumptions around our CDx value-assessment modelling, and indeed some have been proven correct whereas others have been overtaken by events and thus require re-consideration. We also reviewed our relationship scenarios and we can reliably associate real-life case studies with each of the four scenarios. Thus, our future scoping over the past 5 years has been valuable but it has been 'events, dear boy, events' [12] that has made prediction so challenging.

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