SHORT COMMUNICATION

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Assessing the Value-Adding Impact of Diagnostic-Type Tests on Drug Development and Marketing

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Abstract

Objective and methods: We explore the cash value of the companion diagnostics opportunity from the perspective of the pharmaceutical partner. Cashflow-based modeling is used to demonstrate the potential financial benefits of key relationships between the pharmaceutical and diagnostics industries.

Results: In four scenarios, the uplift in the net present value (NPV) of a proprietary medicine can exceed $US1.8 billion. By simple extrapolation, the uplifted NPV calculations allow realistic and plausible estimates of the companion diagnostic opportunity to be in the region of $US40 billion to $US90 billion.

Conclusion: It is expected that such market valuation could drive a macroeconomic change that shifts healthcare practice from reactionary disease-treatment to proactive health maintenance.

One of the main drivers cited for many of the pharmaceutical and diagnostic company mergers of recent years has been synergy savings to accommodate the spiraling costs of drug development and to fill ailing pipelines with better quality therapies.[1] Such therapies include targeted medicines, particularly within the oncology therapeutic area, that are hoped to offer higher benefits with diminished safety risks. Targeted therapies are expected to be highly effective via a well defined mode-of-action against specific molecular entities. As targeted therapies only work well in a subset of the treated population – treatment responders identifiable by diagnostic-type tests – marketing executives in particular are correctly predicting the demise of the blockbuster model.[2,3] Synergy saving and blockbuster models illustrate the pervasiveness of cash value in much of the decision-making in the industry.

Similarly, the consolidation of the diagnostics sector, while partly motivated by diagnostic industry-specific drivers, such as greater automation, the increase in point-of-care capabilities, and the rise in molecular diagnostic technologies,[4] is also founded on recognizing the migration of the pharmaceutical sector towards targeted therapies and the need for diagnostic-type testing.[5] Indeed, the General Electric acquisition of Amersham Health and the acquisition of Ventana by Roche[6] were based on the rise in personalized medicines. Implicit in the development of the stronger integration of diagnostics with pharmaceuticals is the potential for the diagnostics sector to gain greater value propositions.

In addition to sector-specific value drivers and opportunities in targeted medicines, a growing influence is regulator attitudes in all three major healthcare territories. Within the last 5 years, regulatory agencies in the US, EU, and Japan have each released guidance on the applications of pharmacogenomic (PGx) and companion diagnostic (CDx)[1] tests to pharmaceutical development, registration, and marketing.[7-9] Thus, there is a multi-perspective drive towards the better integration of the products of the pharmaceutical and diagnostics industries.

The cash value of the CDx opportunity has not been explored in depth; in this paper we attempt to do this primarily from the pharmaceutical partner perspective, but will also illustrate the opportunity for the diagnostics industry. CDx value is particularly

1 The traditional diagnostic parameters of sensitivity, specificity, accuracy, etc., may be illustrated by comparison with a treatment diagnosis/outcome rather than a disease diagnosis/outcome. It is implicitly assumed that the CDx test performance meets these parameters.

Table I. Assumptions used to derive baseline pharmaceutical net present value (NPV)

Assumption	Discounted cashflow impact	References
Phase IIB/III as bulk of development costs	Consider NPV modeling over 15 year period (post-phase IIA) 2005–20	11,12[a]
Phase IIB/III duration of 20 and 29 months, respectively, registration decision within 10 months	Clinical costs in years 2005–9	11,12 [a,b]
Phase IIB/III study size of 200 and 1000 patients, at per patient costs of $US20 000 (US, UK), $US50 000 (Japan)	Annual costs of $US100 million–$US300 million	13[a]
Reaches market within 10 months of regulatory approval in any major region (US, EU, Japan)	First revenues in mid-2009	14 [a,b]
Marketing may account for 5–10% of sales income	Marketing costs of about $US100 million per year from 2009–16	13,15,16
Medicine has peak sales exceeding $US1 billion, equivalent to 10% market penetration.	Peak sales $US1 billion–$US1.5 billion	14
Medicine reaches peak sales of $US1 billion after 32 months on market	Peak sales period begins 2012	13,14
Medicine has 5 years at peak sales before attrition from generic and branded competition	Peak sales period lasts 2012–6	13,17
Use discount factor to capture some risk as increased costs of capital	15% discount rate	[a]

a Primary research.

b Data on file at PJB PharmaPredict (http://www.pjbpubs.com/pharmaprojects_plus/predict.htm) and EvaluatePharma® (http://www.evaluatepharma.com/).

illustrated using a model based on the co-development of medicines with partly validated biomarkers.[2]

Methodology

The core methodology used is a financial instrument called 'discounted cashflow' (DCF),[10] which looks at the time-value of money by applying a discount factor (df), say of 10%, to set off cashflows over a specified timeframe. The result of DCF analysis is a single cash figure known as 'net present value' (NPV).

The DCF parameters, also known as assumptions, used in the analyses reported in this paper, are all derived by a combination of primary and secondary research. The assumptions, and their sources, used to derive a baseline NPV (bNPV) for a single pharmaceutical entity are listed in table I. An added-value NPV (avNPV), gained through co-development of a CDx, was derived using assumptions based on sources referenced in table II. The ratio of avNPV to bNPV may give a guide to how any medicine might benefit from a companion test, and the difference between avNPV and bNPV (δNPV) is a valuable indicator (see table III).

Table II. Assumptions used to derive added-value pharmaceutical net present value for a proprietary medicine developed and marketed in conjunction with a companion diagnostic test

Assumption	Discounted cashflow impact	References
Cost savings from reducing phase IIB/III duration by 12 months	$US18 million	18[a]
Reduction in study sizes of 10% (≥120 patients)	$US2.4 million–$US6 million	13,18[b]
Savings from earlier failure (10% earlier, 3% savings)	$US15 million	11,12
Increased period of exclusivity (faster to peak, lifecycle management)	$US1 billion per annum of extended exclusivity	14-17
Higher peak sales from market penetration (10–15%)	Peak sales up by $US500 million–$US800 million to $US1.5 billion–$US2.3 billion	11,12,14
Use discount factor to capture reduced risk as decreased costs of capital	10% discount factor	[b]

a Data on file at PJB PharmaPredict (http://www.pjbpubs.com/pharmaprojects_plus/predict.htm) and EvaluatePharma® (http://www.evaluatepharma.com/).

b Primary research.

2 The US FDA has produced a set of definitions that precisely articulate the meaning of words such as biomarker, surrogate, etc. (see http://www.fda.org/definitions).

Table III. Cashflow terminologies

Term	Definition	Meaning
DCF	Discounted cashflow	Financial instrument to illustrate cash income and expenditure over a defined period of time
df	Discount factor	Figure used to illustrate the time-value of money, often by comparison with higher or lower risk investment
NPV	Net present value	Summation of cashflows over defined number of years, with cash value reduced in each year by df
bNPV	Baseline NPV	In this instance, the bNPV is that of a hypothetical medicine that has no companion diagnostic test
avNPV	Added-value NPV	The NPV for a hypothetical medicine up-lifted by a CDx, the latter co-developed with the medicine
δNPV	Differential NPV	Simply the difference between the up-lifted NPV (avNPV) and the bNPV

A third set of assumptions – shown in table IV – were used to apportion the added-value generated from the pharmaceutical partner to the diagnostic test provider, including scenarios whereby pharmaceutical product sales gave rise to royalty payments to the CDx provider.[19]

Industry metrics[21,22] – included in table V – allowed risk-adjusted expected NPV (eNPV) calculations and, finally, a total market value for CDx testing was derived, based on a simple extrapolation δNPV to additional therapies and therapeutic areas.

Results

Baseline Net Present Value (NPV) Calculation

The assumption used to generate the bNPV for the lifecycle of a proprietary medicine (Rx) is shown in table I. These assumptions are grounded in real data gathered either from primary research conducted by Integrated Medicines Ltd or from literature published by pharmaceutical commentators cited in table I. The bNPV, from the cashflow pattern depicted in figure 1a, is positive and amounts to $US892 million, based on a 15% discount factor. This seems to be a plausible outcome for a product that costs nearly a billion US dollars to develop but reaches peak sales in excess of $US1 billion after several years on the market.

Added-Value NPV Calculation

The assumptions used to develop the added-value NPV (avNPV) for a proprietary medicine developed and marketed in conjunction with a CDx are shown in table II. Each assumption is supported by analyses conducted by a number of pharmaceutical consultancy houses and, thus, are also grounded in real data. The potential up-lift provided by more efficient development, faster and higher peak sales, and extension of product lifecycle, takes the avNPV to $US2694 million (~$US2.7 billion) based on the cashflow pattern depicted in figure 1b and a 10% discount factor. The δNPV in this instance is approximately $US1800 million ($US1.8 billion), which is a plausible and realistic benefit for the overall impact of a CDx.

Additional Scenarios

Our analyses for the co-development of a CDx with a Rx highlights an impact at four points in a Rx lifecycle:[20,23]

1. development efficiency;
2. ramp up to peak sales;

Table IV. Assumptions used to derive apportionment of added-value pharmaceutical net present value generated from the pharmaceutical partner to the companion diagnostic test (CDx) provider

Assumption	Discounted cashflow impact	Source
Pharma partner co-markets CDx with medicine, diagnostics company does not spend on CDx marketing	Rx-CDx marketing costs up on Rx costs by $US20 million at peak	Primary research based on tables I and II
Pharma buys CDx tests direct from diagnostics company	CDx costs of $US40 million per annum	Primary research based on tables I and II
Pharma will fund CDx development	Approximately $US5 million per annum 2005–9	Primary research based on tables I and II
Pharma offers 3% drug royalty to diagnostics partner (alternate scenario of no royalty also modeled)	Peak of $US75 million to diagnostics partner	Primary research based on tables I and II, and Gilham[20]
Diagnostics company retains all rights to CDx content	No cost impact	Primary research based on tables I and II

Rx = proprietary medicine.

Table V. Revenue distribution from net present value (NPV) modeling. Relationships including royalty payments (R) are annotated

Model	Combination value	Base value	Added value	C	Rx	%Rx	Dx	%Dx
Integrated	2694	892	1802	2.02	2610	96.88	84	3.12
Make-to-order	2796	892	1904	2.13	2747	98.25	49	1.75
Use-to-order	2176	892	1284	1.44	2152	98.90	24	1.10
Turnaround	891	−914	1805	−1.97	800	89.79	91	10.21
Integrated (R)	2694	892	1802	2.02	2342	86.93	352	13.07
Turnaround (R)	891	−914	1805	−1.97	700	78.56	191	21.44

C = ratio of NPV for companion product versus NPV of Rx alone; **Dx** = diagnostic partner share; **Rx** = pharmaceutical partner share.

3. increased peak sales;
4. extended lifecycle.

The relative contribution in our modeling of each impact point to the $US1.8 billion δNPV is (1) −$US776 million, (2) +$US76 million, (3) +$US2198 million, and (4) +$US319 million, but we recognize that these sums will vary substantially based on company and therapy area-specific metrics. However, the calculations illustrate the likelihood that research will be more expensive because of CDx co-development, but that the sales income is sufficiently elevated to compensate for this cost.

We also recognized that the initial scenario that we developed for co-development of Rx and CDx is only one of several that might arise in reality, based on the pharmaceutical partner needs and how the diagnostics partner might sell its product. These additional scenarios, described in Little and Blair[23] in more detail, are shown in figure 2. Importantly, our initial scenario of *integrated* co-development is one of four, two of which, *integrated* and *turnaround*, suggest that the diagnostic partner has a high degree of relationship power. This diagnostic partner power is important when we considered how the financial benefit captured as a δNPV in each scenario might be apportioned.

Apportionment of Added Value to Companion Diagnostic Test Provider

When we considered how δNPV might be apportioned between partners in our initial *integrated co-development* scenario, we viewed an indirect income from enhanced diagnostic product sales as being the source of increased income for the diagnostic partner. However, it seems appropriate to consider that in scenarios of high diagnostic partner power, the diagnostic partner might reasonably negotiate access to Rx sales royalty in the range of 3% of net sales.[24] The full set of assumptions used in determining apportionment of δNPV is shown in table IV, and the actual impact of negotiating a sales royalty income on apportionment of δNPV is shown in table V.

Although the δNPV does not change, the percentage distribution of the δNPV to the diagnostic partner increases from 3.1% without royalty distribution to 13.1% with royalty income. A similar uplift is seen in the *turnaround* scenario where the diagnostic partner also has high power. In this case, the diagnostic partners share of the δNPV rises from 10.2% without royalty income to 21.4% with royalty income. Clearly, the latter apportionments are very attractive to the diagnostic partner, but acquiring Rx net sales royalty will be a difficult negotiation.[25] **3**

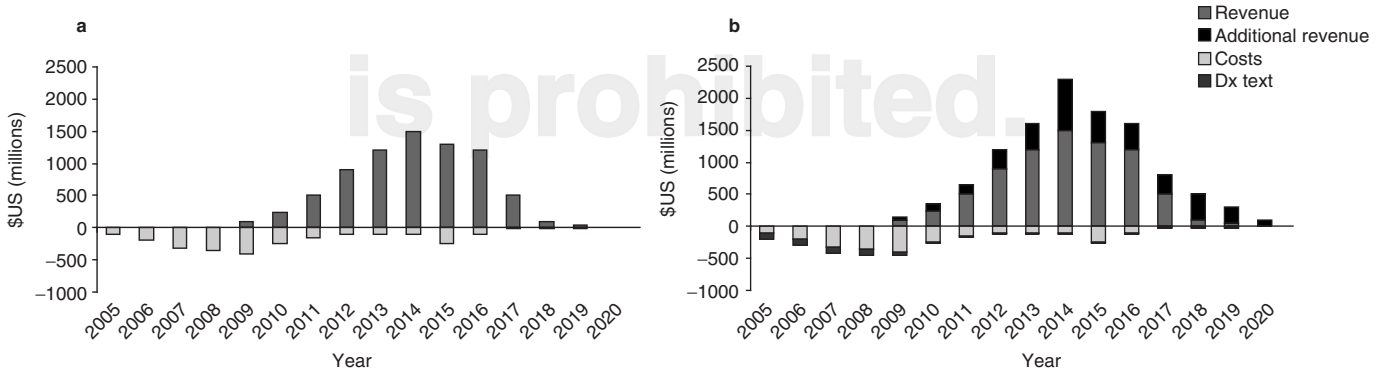

Fig. 1. Discounted cashflow (DCF) for development of a proprietary pharmaceutical product. (**a**) Baseline (net present value [NPV] = $US892; 15% DCF); and (**b**) added-value NPV for a companion diagnostic test (NPV = $US2694; 10% DCF). **Dx** = diagnostic partner share.

3 Information gathered from primary interviews with pharmaceutical company executives performed by Integrated Medicines Ltd.

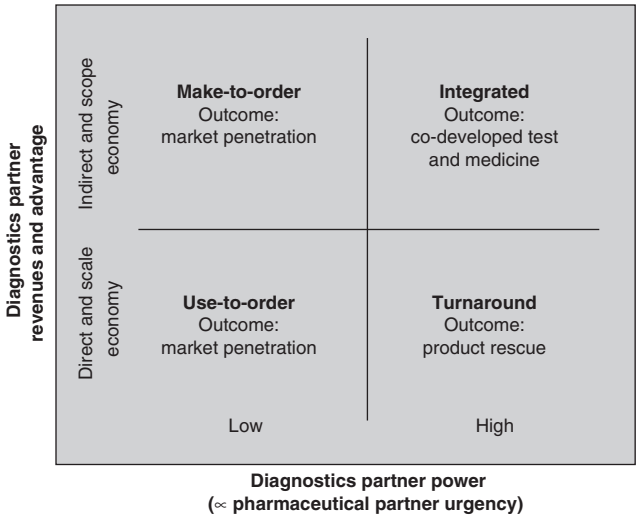

Fig. 2. Scenarios for the development of companion diagnostic tests (reproduced from Little and Blair,[23] with permission).

Risk-Based NPV

By looking at industry metrics, particularly those metrics related to taking a drug from phase IIB clinical trials through to registration and launch,[11,12] and then considering, on the basis of primary research, how a CDx could enhance the efficiency behind those metrics on a portfolio basis, we were able to derive a risk-adjusted expected NPV (eNPV) [table VI]. In this case, the δeNPV is $US862 million rather than $US1802 million.

Opportunity Valuation Based on Aggregate Added-Value NPV

From the uplifts in drug NPV observed for the basic calculation (δNPV) and drug eNPVs in the risk-adjusted calculations (δeNPV), we were able to derive an approximate value for the companion diagnostics opportunity in the range of $US43 billion–$US90 billion (figure 3). This is based on simple assumptions that within any 1 of the 10 major therapeutic areas (the areas of infectious disease, oncology, neurosciences, metabolic, respiratory, cardiovascular, inflammation, vaccines, genitourinary, and musculoskeletal) pursued by pharmaceutical and biotechnology companies, there will be, on average, 5 products that will have the potential uplift in NPV described in the integrated case above. The mid-range for the market valuation is $US67 (figure 3).

Real Examples

Many of the examples where diagnostics have been associated with medicines are described in Abrahams[26] and reflect either an attempt to predict safe dosages of medicines (warfarin, mercaptopurine, and irinotecan) or the effectiveness of medicines (antiretrovirals, imatinib, and trastuzumab). The latter cases occupy the therapy areas that are in the vanguard of personalized medicine (infectious disease and oncology). However, there are currently two examples – also, coincidentally, in infectious disease and oncology – that have appeared in the press recently that illustrate how 'integrated scenario' modeling might play out in the coming years.

- August 2007: Pfizer used a test from Monogram Biosciences to develop and register their novel anti-HIV therapy, marivaroc (Selzentry™),[4] and will now use this test (Trofile™ HIV tropism assay) in the market place to facilitate uptake and appropriate use.[27]
- September 2007: Merck and Celera Diagnostics reached agreement to collaborate on the content of companion diagnostics to facilitate the development and, presumably, marketing of the pharmaceutical partners' oncology medicines.[28]

A final example of how a companion test might be used is illustrated by a comment from the UK National Institute for Clinical Excellence[29] in which they say that the UK National

Table VI. Risk-adjusted added-value pharmaceutical net present value (NPV)

Trial phase				Cumulative risk	NPV ($US million)		Risk-adjusted
II	III	pre-registration	registration		base-case	CDx enhanced	eNPV ($US million)
Baseline attrition rates[a]							
0.52	0.76	0.89	0.94	0.331	892		295
CDx adjusted attrition rates[b]							
0.57	0.81	0.4	0.99	0.429		2694	1157

a Data on file at PJB PharmaPredict (http://www.pjbpubs.com/pharmaprojects_plus/predict.htm) and EvaluatePharma® (http://www.evaluatepharma.com/).

b Primary research with industry experts.

CDx = companion diagnostic test; **eNVP** = expected NPV.

4 The use of trade names is for product identification purposes only and does not imply endorsement.

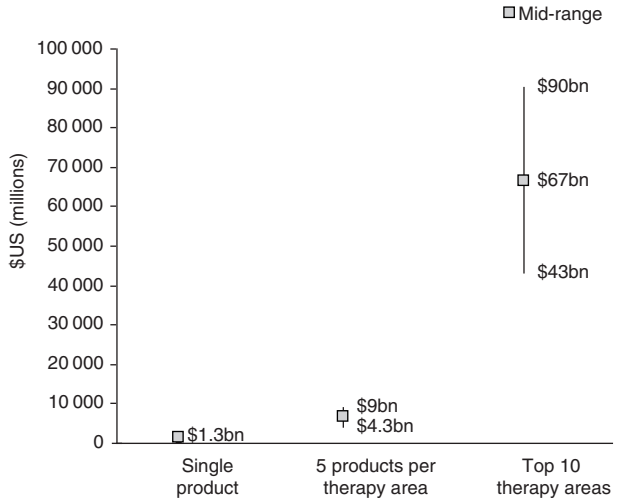

Fig. 3. Market opportunity for companion diagnostics based on extrapolation to top ten therapy areas (inflammation, oncology, CNS, respiratory, cardiovascular, infectives, metabolic, musculoskeletal, genitourinary, and vaccines) targeted by pharmaceutical companies.

Health Service will only reimburse Millennium Pharmaceuticals for bortezomib (Velcade®) when it proves to be effective based on a single, well-validated biomarker.[30] The value of a test predicting response to bortezomib is abundantly clear to all stakeholders.

Conclusions

The market opportunity highlighted by our NPV-based analysis of companion diagnostic relationships is a realistic and plausible estimate of $US43 billion–$US90 billion. As this market is based on NPV cashflows over a 15-year period – from 2008 to 2023 – it does not address the opportunity on a per annum basis. We are aware of this potential shortcoming but merely sought, in the first instance, to highlight the approximate size of the opportunity for pharmaceutical and diagnostic partners. This opportunity is based primarily on one form of relationship. There are three relationship scenarios in addition to the *integrated* scenario[23] that informs the market valuation. Each of these three additional scenarios also suggest a δNPV of about $US1.8 billion, and so the market opportunity could also be in the $US90 billion range (prior to risk adjustment). What changes specifically within each scenario is the distribution of the δNPV between the two partners, *not* the total uplift in pharmaceutical NPV that the relationship scenarios offer.

As our analyses really focus on the relationship of pharmaceutical companies with diagnostics companies, they do lack any marcroeconomic perspectives. However, it seems reasonable to expect that the potential patient benefits offered by more effective and safer therapies will lead to cost-savings throughout the entire healthcare system. This could be reflected in improvements to insurance policies, reimbursement strategies, and hospital care provision. In due course, the overall effect will be the adjustment of global healthcare systems, particularly in the West, from a reactive disease-management proposition to a proactive disease-prevention proposition as the test-and-treat partnership becomes more predictive of response and benefit.[13,31-34]

In this respect, the valuation exercises that we describe may well turn out to be key drivers in forging relationships in the pharmaceutical and diagnostics industries that then further drive macroeconomic and pragmatic adjustments to 21st century healthcare provision.[35-38] As these relationships evolve, it may be that they move from a fairly strict exclusive partnership towards more flexible, limited-duration exclusive partnership networks, such that medicine and test developers extract further value by aligning with generic medicines or tests. In any case, we believe our 'guide prices' will provide a firm footing for a commitment to Rx-CDx relationships.

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