Driving personalized medicine: capturing maximum net present value and optimal return on investment

In order for personalized medicine to meet its potential future promise, a closer focus on the work being carried out today and the foundation it will provide for that future is imperative. While big picture perspectives of this still nascent shift in the drug-development process are important, it is more important that today's work on the first wave of targeted therapies is used to build specific benchmarking and financial models against which further such therapies may be more effectively developed. Today's drug-development teams need a robust tool to identify the exact drivers that will ensure the successful launch and rapid adoption of targeted therapies, and financial metrics to determine the appropriate resource levels to power those drivers. This special report will describe one such benchmarking and financial model that is specifically designed for the personalized medicine field and will explain how the use of this or similar models can help to capture the maximum net present value of targeted therapies and help to realize optimal return on investment.

Mollie Roth[1†],
Peter Keeling[2]
& Dr Dave Smart[3]

†Author for correspondence:
¹Corporate Counsel
VP-Business Development
Diaceutics
Tel.: +1 202 280 5887
mollie.roth@diaceutics.com
²Chief Executive Officer
Diaceutics
peter.keeling@diaceutics.com
³Senior Advisor
Diaceutics
dave.smart@diaceutics.com

The pharmaceutical industry has spent decades and invested significant resources researching and understanding the optimal drivers to ensure the adoption of 'one-size-fits-all' (OSFA) drugs so that the maximum net present value (NPV) is captured. Extensive business intelligence has also been invested in designing financial metrics to understand the resources those drivers require to ensure therapy adoption and an optimal return on investment (ROI). These two functions – the drivers and financial metrics that are necessary to drive the adoption of therapies – have been built into robust benchmarking models against which drug-development teams can measure the work being carried out on new therapies to ensure their successful launch and adoption.

However, by contrast, to date there has been very little work carried out on building a similar benchmarking model specific to the field of personalized medicine (PM). Without such a model, and without business intelligence on relevant analogs and robust financial metrics that provide the foundation for such a model, pharmaceutical development teams naturally tend to depend on methods they have used historically. Working on the assumption that a targeted therapy is merely the combination of a stand-alone test and a OSFA drug, these teams deploy the same drivers used for OSFA drugs and allocate resources to targeted therapies in sums that are significantly larger than what the intended market for such a therapy would seemingly require. Unfortunately, these teams are all too often surprised to discover that in spite of their best efforts and ample resources, the drug still fails to meet its therapeutic goals.

This is because, as obvious a statement as it may seem, a targeted therapy is simply not the same as a OSFA drug. Contrary to what may seem logical, a targeted therapy cannot simply be resourced as though it were a OSFA drug and hoped to succeed. In-depth research and analysis of the PM space to date, as well as the numerous cases where analogies may be drawn from outside what are traditionally considered 'personalized medicine cases', clearly indicates that targeted therapies require different resources and inputs, and have different drivers that are necessary to successfully achieve the therapy's goals.

Compounding the difficulty in this space is the fact that companion diagnostics do not often behave in the market in the same way that traditional stand-alone diagnostics have done historically. Put simply, targeted therapies – those drugs whose use is guided by and intended to be used with a companion diagnostic test – are fundamentally different products and do not behave in the market in the same way as either a OSFA drug or a stand-alone diagnostic test. New research and new benchmarking models are needed that are specifically tailored to this new drug-development paradigm.

This special report describes a study undertaken to demonstrate the effect of a companion diagnostic on a specific disease area – rheumatoid arthritis (RA) – where only OSFA drugs had previously been available. The study further considered how companion diagnostics could be used to reshape the existing OSFA therapy market. This study was the genesis of a benchmarking and financial model that was specifically designed for the PM field. This paper will describe that model and explain how the use of this or similar models can help to capture the maximum NPV of targeted therapies and help to realize the optimal ROI.

Lack of robust benchmarking analysis to date

While much has been discussed of late regarding the various investment metrics and possible returns to be realized from PM (e.g., see [1–6]), very little discussion has been directed at exactly how to ensure the success of these targeted therapies. While one can find numerous articles and editorials on the success of PM, as exemplified by Herceptin® (Genentech, CA, USA) and Tarceva® (Genentech, CA USA and OSI Pharmaceuticals, NY, USA), these articles contain almost no discussion of why and how these targeted therapies were apparently successful, while other therapies, such as Epzicom™ (GlaxoSmithKline, London, UK) and Tykerb® (GlaxoSmithKline), were not.

In fact, stakeholders seem curiously hesitant to construct or deploy a robust lens designed to illuminate exactly what drives a successful targeted therapy, or to measure the outcome of such planning using any sort of concrete financial discipline. Little work has been carried out to determine what exactly drives a successful targeted therapy, to rank those drivers based on their relative strengths and to translate those metrics into a development program that provides the same type of standardized, proactive approach to planning a targeted therapy that already exists for OSFA drugs. More specifically, we believe that the absence of robust financial benchmarking models based on generally accepted

accounting procedures (GAAP) and specifically applied to the targeted therapy space is serving to hinder the analysis and diffusion of PM within and across multiple product teams, and is preventing relevant investment analysis by senior management and institutional investors alike.

It is imperative that the industry implements the same sort of disciplined benchmarking and financial analysis that currently enables the development of OSFA therapies, in conjunction with the creation of GAAP that are specifically geared towards targeted therapies. By implementing this same discipline, team leaders, management and corporate-level executives will be able to provide coherent answers as to what the exact drivers are that must be hit in development and launch in order to optimize the NPV of targeted therapies and to ensure the greatest ROI (Box 1).

Optimizing the NPV on personalized medicine: a pharmaceutical model

Acknowledging that the drug-development process is costly, time consuming and highly complex [7,8], drug-development teams currently adopt a standardized, orderly and proactive approach to the development process of OSFA drugs. This allows for the best possible use of the team's time and resources, reduction of as much risk as possible of the asset being abandoned and the possibility of optimizing NPV and maximizing ROI for the drug.

In order to achieve this proactive approach to drug development, the industry deploys a robust set of benchmarks, GAAP, financial metrics based on prior drug launches and analogs to evaluate what has worked and, equally importantly, what has not worked. This allows development teams to evaluate their activities and benchmark them against the 'prior art' in the space in order to optimize the NPV of a new asset by ensuring that all of the drivers necessary for the success of the launched therapy are properly hit and resourced. Given the length and cost of the drug-development process, it is imperative that careful consideration of all of the significant factors that have a substantial impact

---

Box 1. Definitions of NPV and ROI.

- Net present value (NPV) is a standard method for considering the present value of a specific investment's future net cash flow, discounting the initial investment. NPV uses the concept of the time value of money to consider the value of investing in longer-term projects that will divert cash flows from being deployed elsewhere. If the NPV is positive, the investment should be made, while if the NPV is negative, the full value of the investment would be better realized elsewhere.
- Return on investment (ROI) is a measure of the ratio of money gained or lost on a project, relative to the amount of money invested.

on the development and future success of the therapy are undertaken in order to appropriately allocate resources.

As a consequence of the lack of similar benchmarking work carried out to date in the PM field, exploration of targeted therapies is almost institutionally confined to those instances where during development, drugs are found to only work in responder groups. By contrast, a robust benchmarking model would allow for the broader exploration of how a companion diagnostic strategy might be leveraged in other instances, such as helping to develop a market or improve drug adherence in drug classes where poor adherence is a persistent and significant clinical concern. This myopic view of the potential of targeted therapies highlights the fact that drug-development teams are, perhaps unknowingly, entrenched in a culture of avoidance of targeted therapy development, maybe because they do not have the proper tools to benchmark and assess their activities.

There is also an underlying misconception that the same drivers that ensure the success of a OSFA therapy will also work for a targeted therapy, and there is a tendency to allocate resources in a similar manner on the assumption that 'more is better'. Lacking indepth research and business intelligence on relevant analogs, these teams naturally depend on methods they previously carried out, often relying on a superficial analysis of what works and what fails in the diagnostic space based on minimal due diligence and experiences with OSFA drugs. In other words, unlike OSFA development teams, who rely on a rich vein of research and an analysis of what has worked in the past, teams tasked with developing targeted therapies must often start from scratch and reinvent the development process with every targeted asset.

However, in order to capitalize on the potential NPV and realize the maximum ROI of targeted therapies, the development teams must come to understand what drives such therapies to be successful in the market. It is clear from the only marginal success of many targeted therapies (see also [9]) that it takes more than simply a viable market and a reasonable amount of science. In fact, Diaceutics (Belfast, Northern Ireland, UK) estimates that the Herceptin franchise, which is typically viewed as the poster child for PM, has lost an estimated US$3 billion in additional cumulative revenue as a result of the poorly executed companion diagnostic strategy since the first launch of the drug. What is required is a standardized development model

that is specific to the targeted therapy space, which highlights what activities are most likely to result in a successful launch and provides an understanding of the proper resources required to drive those activities.

Initial study: effect of a companion diagnostic in the rheumatoid arthritis space

In 2005, Roche Molecular Diagnostics (Basel, Switzerland), through their SynergysDx initiative, engaged Diaceutics in assessing the impact of a novel prognostic on a profiled targeted therapy's ROI, and more particularly, to demonstrate the effect of a companion diagnostic on a specific disease area in which only OSFA therapies had been available to date. More specifically, Diaceutics was asked to apply an early iteration of its 'Case-Based Reasoning (CBR) Financial Benchmarking Model', which utilizes an evidence-based methodology to predict future events based on the past trends of similar cases with similar characteristics. Diaceutics was also asked to model what the value would be, in terms of NPV and ROI, of pairing a diagnostic test with a novel disease-modifying drug, which otherwise only worked in 35% of all patients.

The original work was focused in the therapeutic area of RA. Owing to prescription complexity and market competition, any new RA drug faced tremendous challenges that could potentially be overcome by a targeted approach. At the time, DMARDs were evolving into a highly competitive drug class, with a forecast that by 2012 there would be 30 varieties on the market, equating to approximately US$10 billion, or between 50–80% of the overall RA treatment market. However, new DMARDs were expected to have the same or fewer responder profiles as those on, or near to, the market at the time, and their efficacy was limited by the late identification of 25% or more patients. Therefore, a primary goal for any future treatment innovation was to be able to enhance the impact of DMARDs by identifying the patients who are most likely to suffer greatest and to enable them to be treated early and aggressively.

Together with Roche, we modeled a novel candidate therapy (NCT) as a disease-modifying injectable biologic drug, targeted at RA patients of 35 years of age or older who would be most likely to suffer severe and work-restricting disease and for whom early and aggressive therapy would slow progression to severe disease. In conjunction with this NCT, we also modeled a novel candidate prognostic (NCP), designed to

facilitate the early identification of patients who possess the combination of cytokines associated with progression to severe disease [10]. The initial work on the model was validated and presented by Roche at the IBC Personalized Medicine Conference held in Boston (MA, USA) on 15 September 2005.

■ Initial model & research method

The Diaceutics financial benchmarking model utilizes CBR, a research tool originated by the US Navy that first appeared in commercial applications in the early 1990s. Since then, it has been used in a wide number of applications in both the academic and commercial fields. CBR is of particular use to decision-makers when a wide body of previous situations or cases exist that can be called on to determine the values for decision variables and decision tree frameworks, by comparing the hypothetical case with the known value or behavior of something similar. CBR collects previous examples that are similar to the current problem, or from which reasonable analogies may be drawn, to enable the creation of reasonable answers to solve present problems, rather than simply relying on heuristic or speculative resolutions. As Angus Hastie, Director of Marketing and Business Development for Roche Molecular Diagnostics stated, "[c]ase-based reasoning takes the guess-work out of the fiscal assessment … by finding real-world cases, pooling them, and examining the trends" [101].

The first iteration of the Diaceutics CBR Financial Benchmarking Model relied on 53 cases compiled from a combination of published studies, IMS data, research from selected industry journals and commissioned research. Although at the time there were only a few examples of therapeutics being sold directly in conjunction with diagnostics, there were many more existing cases where therapeutics had worked in harmony or disharmony with diagnostics in the market. Thus, reasonable analogies could be drawn from these cases and applied to determine how a companion diagnostic might be used to differentiate a new entrant into the RA space. The 53 cases spanned ten therapeutic areas reaching back over 14 years.

Utilizing this proprietary library of analogs, next Diaceutics identified all of the therapies whose market position had been affected or influenced, either directly or indirectly, by the use of a diagnostic. Initial analysis of these analogs determined that seven variables (or drivers) were most likely to impact a pharmaceutical revenue stream for a blockbuster or speciality drug. These seven drivers directly or indirectly impacted the therapy revenue and profit stream and were, in turn, directly or indirectly impacted by key commercialization decisions. Direct drivers refer to those variables that can be directly influenced by the availability of a diagnostic. 'Indirect' refers to those variables that have no diagnostic element, but whose value may be influenced by the availability of a diagnostic. The seven drivers were:

- Therapy price

- Responder profile to therapy

- Earlier therapy use

- Faster therapy adoption

- Competitive advantage through differentiation conferred by the diagnostic

- Patient adherence

- Speed of erosion of the market owing to generic competition

Further assumptions built into the model included a responder rate to the NCT out of the entire DMARD candidate RA patient pool of 50%, and a trial and error rate of 18%, which represented those patients who would empirically be identified for the NCT without the use of the NCP but who would respond to therapy. It was assumed that 80% of all patients from the entire patient RA pool would be tested with the NCP and that 56% of those would have a positive test result. Of that positive prognostic test result group of 56%, we modeled three different percentages of candidates who would thereafter proceed to long-term therapy at rates of 36, 42 and 56%, respectively. These rates of physician propensity to prescribe (P2P) – defined as the rate of prescriptions written by a physician in response to a positive test result – are based on the low, medium and high rates of P2P noted for the use of *HER2* testing and Herceptin since its initial launch in 1998 [102].

The following specific assumptions were used to model the potential drivers for a targeted DMARD. ROI, including overall revenues and development costs, was only accessed for the US market, assuming a 12-year life-cycle from launch. Earnings before net income and tax were calculated on a 15% trading margin based on research that estimates this average across the industry [7,8]. Development costs for

the therapy were estimated at US$360 million with NPV and ROI calculations based on an 11% cost of capital (Box 2). Finally, no additional costs attributable to marketing for the diagnostic were included in the model, nor were any costs of development associated with the novel candidate test (Box 3).

■ Initial study findings

Overall, the analysis revealed that a companion diagnostic, used to its optimum potential to shape the therapeutic market and to increase research and development (R&D) productivity, creates an additional NPV reservoir in PM. In this particular field of disease-modifying drugs, of which there were five at the time, we calculated the NPV for the existing therapies to be US$195 million. Combined analysis of the seven drivers set at the mean of all cases in the database, and at a P2P rate of 36%, suggested that a NCT used in conjunction with a NCP would deliver a positive NPV of US$34 million, representing a total value of US$229 million compared with the base case [11]. In other words, the PM-specific CBR Financial Benchmarking Model, built on assumptions and cases that are specifically relevant to the PM field, indicated that the cost of developing and implementing a companion diagnostic in the field of RA could potentially increase the ROI for such therapies by as much as US$34 million, even at late-stage planning.

In our estimation, this reflected the most conservative scenario undertaken with the least amount of proactive, standardized planning. By adjusting the drivers to allow for more relevant comparative cases and, most crucially, by initiating planning much earlier in the development life-cycle, the reservoir of NPV could be optimized to US$174 million or a US$369 million improvement over the base case. While the total additional NPV reservoir represented, perhaps, an astonishing range (US$34–174 million), our analysis suggested that it reflected a very true range of market possibilities presented by the NCT/NCP profile. Our sensitivity analysis suggested that

estimates of the market impact of all drivers would need to be overestimated by 33% before our NPV would become negative.

Most notable were our findings that a significant additional NPV could be realized, even when companion diagnostic development was initiated late in the development process, as seen in FIGURE 1, but that the greatest gains were realized the earlier the planning for companion diagnostics was incorporated into the development life-cycle. Furthermore, we also note that while these drivers can have a positive effect on the overall success of the targeted therapy, any missteps in implementing a driver can have an equally negative effect on the asset's overall NPV.

Based on the outcome of the Roche study, we continued to research and develop the Diaceutics CBR Benchmarking and Financial Model in order to provide drug-development teams with a standardized, robust tool for demonstrating exactly which drivers are most effective in ensuring a successful targeted therapy. This would allow teams to tap into the pool of additional NPV, which the initial model demonstrated to exist in PM, in order to maximize the ROI of the targeted therapy and, more importantly, to provide evidence to support their activities and resource allocation.

Over the last 4 years, our continued research has resulted in an expansion in the number of analogs from 53 to over 200 instances in which a test and drug have interacted negatively or positively in the marketplace. Using these analogs to specifically benchmark targeted therapies, we built out the initial model further to create a fully interactive, evidence-based benchmarking and financial model, designed to allow teams to assess and benchmark the work being carried out on the development of a targeted therapy. From the seven drivers identified in the initial study, our analysis has revealed a further three drivers that have a significant impact on the potential success of a targeted therapy.

To validate the model, we ran it against all the available information on the development process and sales curve of Herceptin as well as against three other targeted therapies currently

Box 2. NPV and ROI calculations.

The financial metrics employed were based on traditional financial metrics used throughout the pharmaceutical industry in the one-size-fits-all drug development model. Thus, we considered NPV as the present value (at year 0) of the product, including accumulated earnings and initial investments, discounted for the time value of money (over 12 years). The ROI utilized the internal rate of return as the average return on the investment over a 12-year period with accumulated revenue being equal to the total revenue earned over the same time period.

NPV: Net present value; ROI: Return on investment.

Box 3. Consequential costs.

Research indicated that taken together these two costs were relatively inconsequential, representing approximately US$50 million in additional cost over the development lifecycle, which would have reduced the NPV by US$15 million or less. Furthermore, a base case was established demonstrating that without a companion diagnostic strategy, the novel candidate therapy would have a negative NPV of -US$260 million and would obviously not have preceded any further in development.

being marketed for diabetes, infectious diseases and oncology. To demonstrate this model, as seen in FIGURE 2, we started with the base curve for the adoption of a OSFA drug as defined by the work completed by DiMasi *et al.* in 1994, which looked at the typical sales curve of drugs launched between 1963 and 1992 as a function of time to adoption (illustrated by the green line in FIGURE 2). Based on the validation process
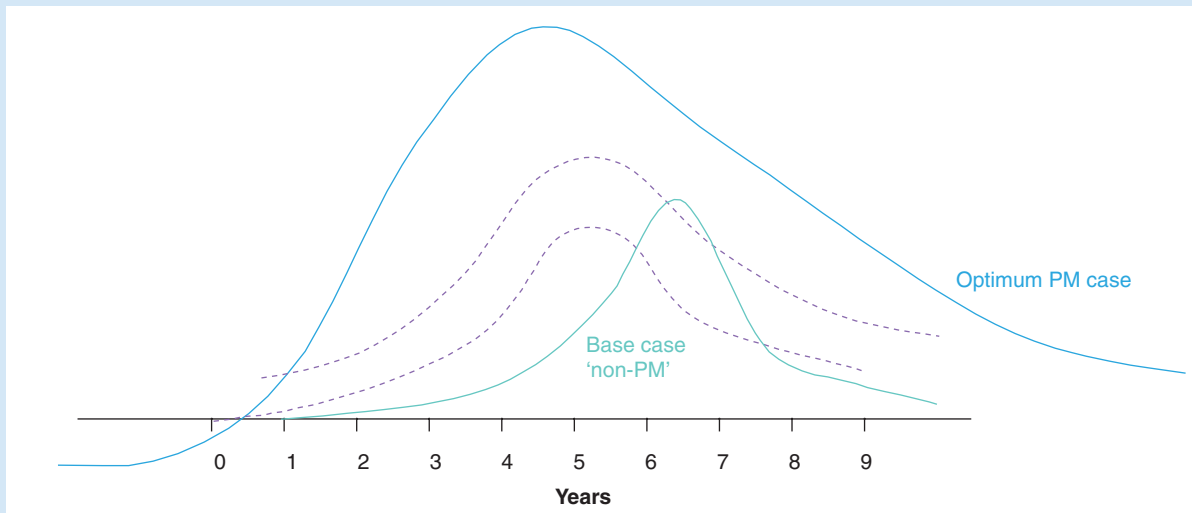
described above, we hypothesized that, realistically, any one targeted development project is only likely to be able to take advantage of, and sufficiently optimize, three–four of the ten drivers, as illustrated by the violet 'Optimum PM Case' line in FIGURE 2.

As illustrated in FIGURE 2, the Diaceutics CBR Financial Benchmarking Model clearly demonstrates that undertaking certain PM-specific
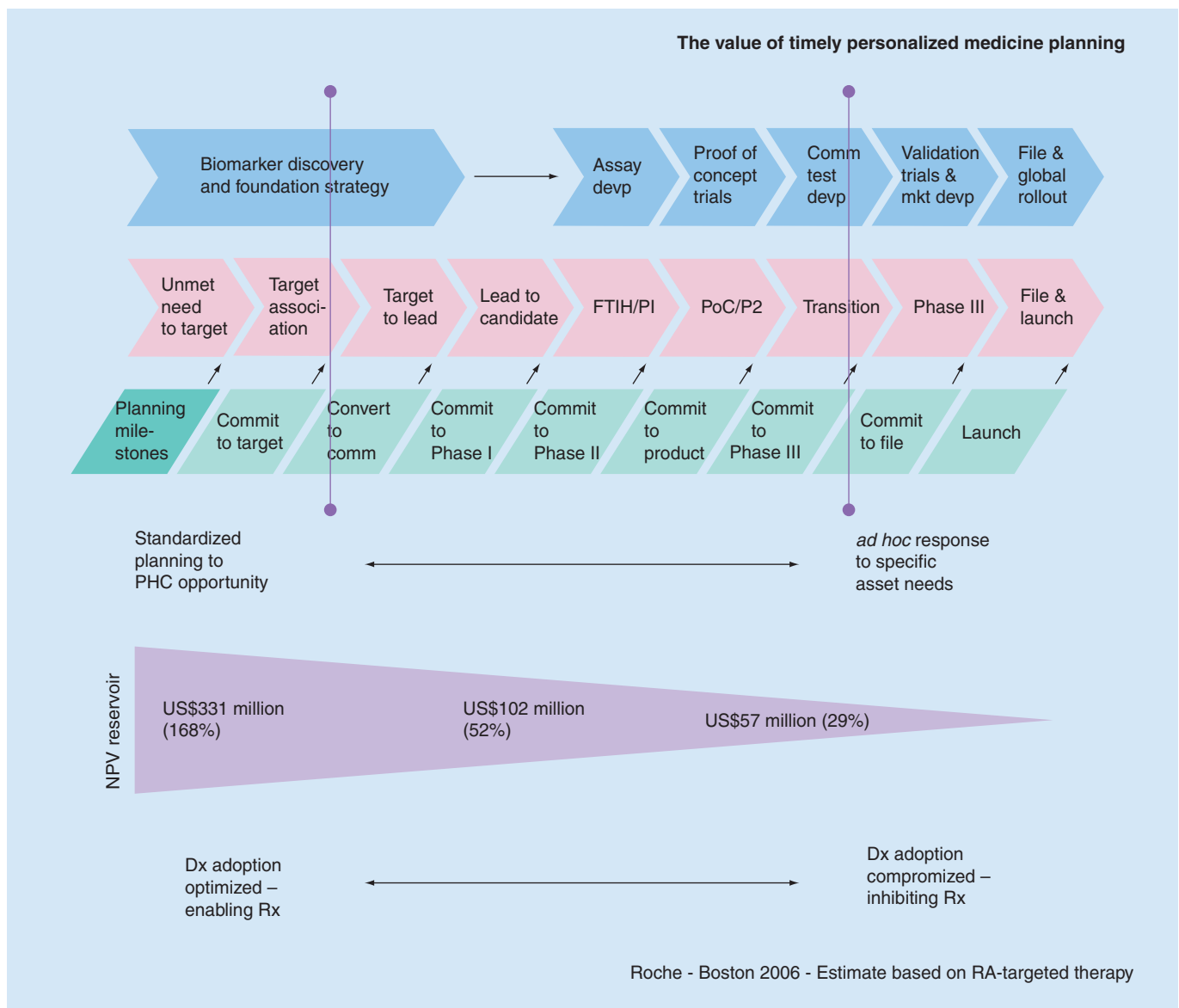
Figure 1. The value of timely planning. Diaceutics Case-Based Reasoning Financial Benchmarking Model.
NPV: Net present value; PHC: Personalized healthcare.

Ten financial drivers in personalized healthcare

Figure 2. Ten financial drivers in personalized medicine. The green line represents the adoption timeline for a nontargeted therapy. Purple lines represent the intermediate positive effects of undertaking fewer or different drivers. The blue line represents the optimum targeted therapy adoption timeline with all relevant drivers deployed.
OSFA: One-size-fits-all; PM: Personalized medicine; R&D: Research and development.

activities or drivers and allocating the appropriate resources to those drivers increases the NPV of targeted therapies by shifting the adoption and sales curve of such therapies to earlier in time. This allows teams to capture a market share earlier in the adoption curve, thereby increasing the overall ROI. However, the Roche study and model also demonstrated the critical point that undertaking development of a biomarker into a companion diagnostic in an incomplete or hesitant manner can have an equally negative impact on NPV. This provides even further justification for the importance of GAAP specifically tailored to this space.

Ten drivers of targeted therapies

A brief review of the ten drivers that the Diaceutics CBR Financial Benchmarking Model indicates as having the most significant impact on the potential success of a targeted therapy are listed below.

◼ Optimize research & development investment

One of the great hopes for the implementation of PM is the possibility that it will reduce the time and cost of drug development. However, at present, implementing a PM strategy is likely to increase the cost of R&D. Project-specific

investments in biomarkers, pharmacogenetics and diagnostics must be accounted for in the project and are likely to be additional to the costs for OSFA therapies. While this may be offset by smaller clinical trials at Phase III, failure to consider potential targeting strategies sufficiently early in the planning process can undercut these potential cost savings.

Unfortunately, the current US regulatory environment, with regard to companion diagnostic approvals and the necessity to obtain clinical trial data in 'all-comers' rather than simply in the biomarker-positive population, significantly undercuts the possibility of this as a future savings strategy. However, this may still be possible outside the USA where regulatory schemes are presently more flexible.

■ Value Rx pricing

Pricing premiums for significantly improved clinical efficacy and improved safety are likely supportable in PM. Research corroborates the widely held belief that the ROI from a targeted therapy will never generate more revenue than what could have been created under a traditional OSFA model [12]. However, that same research finds that those returns will not be as low as is widely believed based on premium pricing structures [12]. In addition, the opportunity to introduce evidence-based, value-based pricing models may allow for higher payer-supported pricing points in the future.

■ Earlier Rx market revenue

Although the regulatory landscape is still evolving, it is hoped that PM will eventually lead to the allowance of smaller and more elegantly designed clinical trials, as well as expedited regulatory reviews. In tandem, these two opportunities will allow for earlier therapy launches that, in turn, will further shift the sales and adoption curve of such therapies, enabling faster ROI. This early-to-market opportunity is already practiced in orphan drug areas and was utilized in the case of Herceptin.

■ Faster Rx adoption

Research demonstrates that historically, the average time for drugs to reach peak sales is 4.5 years [7,8]. This adoption curve is lengthened when looking at diagnostics, which historically have a slower market-diffusion and adoption rate than drugs. So, how to get doctors to adopt new drugs used in conjunction with tests more quickly? Research on analogs demonstrates that by providing physicians with clear, concise and specific evidence demonstrating the value proposition of a targeted therapy, more physicians will become 'early adopters'.

Diagnostic tests can actually help to provide that evidence by assisting in the prognosis and monitoring of patients and by eliminating skepticism on behalf of prescribers that are typically slower to adopt new technologies. Furthermore, in certain instances, the use of diagnostics means that there will be less potential for adverse events, easing physicians' concern. With this, there will be a wider base of early adopters, which will speed up the adoption of the therapy and increase its usage in the rest of the physician population.

As with the prior driver, anything that moves a therapy to market faster will result in a faster ROI. Thus, a proper and focused commercialization effort, where diagnostics illustrate and enable understanding of an unmet need, is imperative to properly prepare the market to be receptive to a new targeted therapy. When properly deployed, this driver can achieve faster-to-peak sales curves than the normal.

For example, Merck (NJ, USA) effectively used a companion diagnostic strategy to increase awareness of bone=density measurement prior to, and during, the launch years of Fosamax®. This directly helped Fosamax achieve and retain market leadership.

■ Better Rx differentiation

The pharmaceutical industry has long redefined markets as drugs mature, face competition or go off-patent using the standard 'Four Horsemen' of differentiation – efficacy, safety, convenience and cost–effectiveness. This product differentiation can result in the ability to capture a greater market share, charge higher prices, deflect competitive initiatives, command greater buyer loyalty and stimulate earlier trial and referrals of products [13].

Forget the idea that segmentation results in smaller markets. A drug being given to 1000 patients that is only effective in 500 patients is not a treatment for a patient population of 1000. It is a drug that is only appropriate for 500 patients. Targeted therapies may actually allow a company to reach beyond those 500 patients. According to IMS Health (CT, USA), prescribers are more likely to use a drug that comes with a test, at a rate of 70–90% higher than other more traditional drugs, because the test provides greater evidence of likely positive patient outcome.

For example, consider the case of Takeda's Actos® (Osaka, Japan), a peroxisome proliferator-activated receptor (PPAR) agonist for the

management of diabetes. In 2005, it was used to treat approximately 1.5 million diabetics in the USA. According to EvaluatePharma® (London, UK), it had 50% of the market share, putting the 'hypothetical' total patient pool at 3 million diabetics. However, epidemiology studies, demonstrated that there were almost 9 million US patients with insulin-resistant diabetes at that time, a significant percentage of which could hypothetically have benefited from Actos. Why weren't these patients switched to Actos? The answer, perhaps, goes back to physicians' reluctance to switch their patients' therapies, even if they are not achieving optimal results. But the additional confidence gained and the higher degree of evidence made possible through the use of a diagnostic test may be just what the doctor ordered. Thus, by actually segmenting the market and by treating that segment more efficiently, companies have the potential to access at least similar patient numbers to what was seen in the Blockbuster Model.

It is already well understood that the simple step of differentiating your product in the crowded clinical marketplace – whether through better dosing, reduced adverse effects or greater efficacy – can greatly increase returns for a comparably small input. Personalization represents the possible 'Fifth Horseman' and is an effective and powerful tool for segmenting and defining clinically meaningful patient populations for whom the drug works. Personalization can enable therapies to be regarded as niche and as such, they are significantly differentiated from remaining competition. In niche drug markets, therapies can enjoy the monopolistic benefits typical of a 'first-to-market drug', although they are only appropriate for a discrete patient subset.

■ Higher propensity to prescribe

Research on PM-specific analogs demonstrates that one of the most important drivers in ensuring the success of a targeted therapy is ensuring that a high rate of prescriptions are written by a physician in response to a positive test result, or P2P.

Unfortunately, drug-development teams often instinctively believe that their commercialization efforts only need to go as far as ensuring that the physician is aware of the test on the assumption that a positive test result will automatically lead to a drug prescription. However, research clearly indicates that this is not the case and that ensuring a high rate of P2P requires very specific commercialization efforts that are not normally undertaken as part of the OSFA protocol.

For example, one study looking at barriers to the adoption of Herceptin found that a full 7 years after the launch of the drug and test, 20% of physicians failed to understand how to correctly interpret the test results they were receiving [14]. This lack of understanding, which was not being addressed by the manufacturer, led to a significantly lower number of prescriptions being written. Sales data from IMS Advanced Oncology Analyzer™ indicated that even after 8 years of marketing in the USA, Herceptin's P2P for its advanced breast cancer indication was only 70%, and only 40% in early-stage breast cancer, in 2007 [102].

■ Improved Rx compliance

It is widely accepted that the lack of patient compliance with medical recommendations, especially for drug therapy regimens, represents a complex challenge. Studies have demonstrated than noncompliance causes 125,000 deaths annually in the USA [15] and leads to 10% of hospital admissions, costing the healthcare system approximately US$15.2 billion annually [16].

However, diagnostics incorporated into patient management can be an effective patient motivator for compliance to drug regimens. A model for this can easily be seen in the use of routine low-density lipoprotein and high-density lipoprotein cholesterol testing to help patients better adhere to therapy [17]. Interestingly, the cost of supporting a diagnostic monitoring strategy can be significant and may not be financially attractive in all therapy areas. By contrast, the ability to improve adherence levels by only 1–2% may be worth adopting a more comprehensive diagnostic strategy where adherence levels hover between 50 and 60%.

■ Extended Rx life-cycle

Utilizing diagnostics to identify unmet demand can lead to new patentable indications and may have a role in extending the drug life-cycle. While this is, as yet, largely unexplored in the PM setting, analysis of surrogates for how proprietary biomarkers can provide greater market share to generic therapies implies the potential of designing better strategies earlier. This approach underpins the business model of Prometheus Laboratories (CA, USA) in the Crohn's disease area.

■ Dx adoption

Driving Dx adoption is critical to enabling access to a targeted therapy with very close label links between the drug and test. Driving test

adoption is time critical and costly and can often lead to revenue-destroying effects for an interdependent drug. Our model shows that without a significant commercial sponsor, most tests can take more than 10 years to reach any significant use. This can be improved with the benefit of smart strategies and significant commercial muscle but it also comes at a cost. Consider, for example, the US$50–100 million plus investment of Genomic Health (CA, USA) in support of the marketing of Oncotype Dx®, its highly novel breast cancer screening tool [103].

While the Oncotype Dx test does not have the benefit of having a specific newly launched drug alongside it, the costs of driving diagnostics into the market to reduce their historic adoption lag are clearly demonstrated by the amount and extent of work undertaken by Genomic Health to make Oncotype Dx so successful in such a short period of time. Similar investments and efforts can be seen in the work carried out to drive the ThinPrep® test from Cytyc Corporation (MA, USA) and the Digene® (MD, USA) HPV test.

■ One-size-fits-all tax/bonus

The pharmaceutical industry currently faces millions of US dollars in direct annual litigation expenses and immeasurable negative effects, both affecting its reputation and bottom line, from the negative perception of the industry arising from those lawsuits. Utilizing diagnostics to filter out patients who are likely to experience adverse events is an effective way of avoiding the significant revenue and reputation destruction that may occur when minor clinical trial adverse event observations translate into significant whole population impacts and the resulting litigation. This 'OSFA tax' is factored into the costs of development and the decision matrix of whether or not to pursue certain assets through development. Thus, a drug-development strategy that reduces this 'tax' risk should be regarded as providing a bonus owing to the probability of avoiding the OSFA litigation downside (and concomitantly, OSFA therapies should be taxed with the probability of incurring these litigations).

Conclusion

The key point to be taken from this research is that assuming that the economics of a OSFA therapy are applicable to a targeted therapy is a dangerous premise that has not proven itself in actual development. While it seems instinctively correct that placing the same resources behind a targeted therapy should result in a success equal to that experienced with a OSFA drug, that is simply not the case. Targeted therapies do not act in the same way as OSFA drugs in the marketplace and development teams need a better understanding of what and how much real investment it takes to actually drive a targeted therapy to success before PM can move forward.

This need is particularly urgent given the current estimates that anywhere between 25–50% of future drug launches could be PMs targeted by genetic or molecular tests, imaging or computer-based algorithms [18]. An understanding of the real worth of investing in PM, and how to ensure those opportunities are maximized, seems noticeably absent. Rather than focusing on providing the 'proof in the pudding' of this new development model, instead, the majority of publications and discussions to date seem to focus on the attitudes of payers or consumers to paying for such targeted therapies or the potential improved opportunities that these new drugs represent for the diagnostic industry. These discussions put the 'cart before the horse' in failing to provide insight into how exactly targeted therapies can successfully be developed.

As further development work is carried out on targeted therapies, these drivers need to be captured, measured and further incorporated into benchmarking models that utilize a set of PM-specific GAAP metrics, to allow them to be used in a disciplined and standardized way and to be proactively managed and deployed by individual teams. Furthermore, these drivers need to be fully incorporated into internal and external investment meetings so that the financial metrics behind them are more transparent and fully understood. Only by deploying the same type of resources used to date in the OSFA area in order to research and construct a robust benchmarking model that is specifically appropriate to the PM field will the pharmaceutical industry ensure that these new targeted therapies meet their expected potential.

Future perspective

At present, stakeholders in the PM space mainly view this ongoing shift in the drug-development paradigm through a narrow lens, predominantly as an aid to enhance R&D productivity within the currently challenged OSFA drug-development model. In our view, PM certainly has far greater potential than this limited application as an R&D enhancement tool. Not only do we see its ability to significantly reshape the current market dynamics for the pharmaceutical industry, but we also anticipate that it will prove to be a cornerstone in the new foundation of how

healthcare is delivered, providing the vehicle by which a more integrated, joined up overall value chain of healthcare may be structured. We have already seen a limited number of companies endeavoring to put into place an internal structure, not only to ensure that PM is infused throughout their organizations, but also to consider how this greater potential of PM might be leveraged to change the market dynamics for therapies from development to delivery.

However, in a landscape that is rapidly changing as a result of both internal and external pressures currently being brought to bear on the healthcare industry as a whole, stakeholder perspectives about their business models, the assumptions that drive their current business, their usual practices, standard operating procedures and roles must also change. It is not possible to successfully develop, launch and drive adoption of a targeted therapy when your perspective is that it is not much different to a OSFA drug paired with a stand-alone diagnostic. While it may seem sophomoric, it needs repeating: a targeted therapy and companion diagnostic are not simply a stand-alone therapy and a stand-alone diagnostic marketed together. When developed and launched in combination, it may be said that the two are greater than the sum of their parts, requiring new insights and business intelligence to allow them to achieve optimal goals.

Much has been written about the need for payers and regulatory agencies to change their usual perspectives and to take a more flexible and open-minded approach to PMs. While this is true, it is also true that change must begin at home. In this case, that home is with the two primary stakeholders in PM, the pharmaceutical

and diagnostic industries. While both have made great strides in shifting their foci and adjusting their understandings and expectations of how PM can and should work, too many of the individuals toiling down in the engine rooms of the industry – in clinical R&D, as heads of asset teams and those tasked with the commercialization strategy – are receiving insufficient support. A strong vision and direct guidance is needed on how to accomplish the Herculean task of shifting the very developmental foundation on which this industry rests.

The future, and not so distant future, possibilities of how PM may be integrated into the healthcare chain are intriguing – from initial steps of broadening the concept of companion diagnostics used to guide therapy beyond today's mostly molecular focus to including the use of positron emission tomography scans and functional MRI in a future where we all carry our genome on a credit card-sized device in our wallets. However, as the vanguard of the movement toward those future possibilities, it is imperative that we keep our focus properly trained on today and the near-term possibilities in order to put into place a strong foundation for how to successfully build out the future of PM.

Bibliography

1 Epstein RS, Frueh FW, Geren D *et al.*: Payer perspectives on pharmacogenomics testing and drug development. *Pharmacogenomics* 10(1), 149–151 (2009).

2 Keckly P: *The ROI For Targeted Therapies: A Strategic Perspective.* Deloitte Center for Health Solutions, Washington DC, USA (2009).

3 Davis JC, Furstenthal L, Desai AA *et al.*: The microeconomics of personalized medicine: today's challenge and tomorrow's promise. *Nat. Rev. Drug Discov.* 8(4), 279–286 (2009).

4 Phillips KA, Liang SY, Van Bebber S; Canpers Research Group: Challenges to the translation of genomic information into clinical practice and health policy: utilization, preferences and economic value. *Curr. Opin. Mol. Ther.* 10(3), 260–266 (2008).

5 Vernon JA, Johnson SJ, Hughen WK, Trujillo A: Economic and developmental considerations for pharmacogenomic technology. *Pharmacogenomics* 24(4), 335–343 (2006).

6 Stallings SC, Witt WP, Crown WH *et al.*: An economic framework for evaluating personalized medicine. *Sloan Industry Studies Working Papers* WP-2004–2003 (2004).

7 DiMasi JA, Seibring MA, Lasagna L: New drug development in the United States from 1963 to 1992. *Clin. Pharmacol. Ther.* 55, 609–622 (1994).

8 Kaitin KI, DiMasi JA: Measuring the pace of new drug development in the user fee era. *Drug Inf. J.* 34, 673–680 (2000).

9 The pink sheet, targeted therapies could make Rx companies more credible. 68(26), 22 (2006).

10 The intended use statement for the NCP was: "The NCP is indicated as an aid in the assessment of patients for whom NCT treatment is being considered".

11 We note that all ROI/NPV analyses are highly sensitive to the cost of capital and discount rate assumptions; for example, a 4% increase in the cost of capital removes US$129 million from all of our drivers' NPV.

12 Vernon JA, Johnson SJ, Hughen WK, Trujillo A: Economic and developmental considerations for pharmacogenomic technology. *Pharmacogenomics* 24(4), 335–343 (2006).

13 Keeling P, Roth M: Getting Personalized. *Pharmaceutical Executive* October (2008).

14 Woelderink A, Ibarreta D, Hopkins MM, Rodriguez-Cerezo E: The current clinical practice of pharmacogenetic testing in Europe: *TPMT* and *HER2* as case studies. *Pharmacogenomics J.* 6, 3–7 (2005).

15 Smith D: Compliance packaging: a patient education tool. *Am. Pharm.* NS29(2) 42–45, 49–53 (1989).

16 Schering Report IX: The forgetful patient: the high cost of improper patient compliance. (1997).

17 Benner JS, Pollack MF, Smith TW, Bullano MF, Willey VJ, Williams SA: Association between short-term effectiveness of statins and long-term adherence to lipid-lowering therapy. *Am. J. Health Syst. Pharm.* 62, 1468–1475 (2005).

18 Pickering L: Companion diagnostics: enabling personalized medicine in cancer. *Spectrum Reports, Biomarkers and Diagnostic,* 27 October (2006).

■ Websites

101 Dutton G: Molecular diagnostics as clinical tools: new applications help research advance to full bedside utility, genetic engineering and biotechnology news
www.genengnews.com/articles/chitem.aspx?aid=852&chid=1

102 IMS Advanced Oncology Analyzer, MAT Q3 (2007)
http://imsoncology.com/Media/ims oncology eu.pdf

103 Diffusion and use of genomic innovations in health and medicine: workshop summary, translation of genomic technology at the clinical level, a primary care provider view of translating genomic innovation, conversation with Dr Steven Shak of genomic health
www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=nap12148&part=a200150e2ddd00031.