Better Testing

How pharma can get a flying start in a value-based drug pricing era

Diaceutics

Contents

Foreword

A shift to value-based pricing for drugs in the US market has been much anticipated by payers and the pharma industry alike. However, better testing has not featured adequately in the debate to date.

This Ebook reveals a body of evidence and debate from Diaceutics, published over recent years, that has built steadily towards a deeper understanding of how better testing will play a central role in helping both pharma and payers achieve the optimal economic model. Whilst better testing has been positioned as a reflex of targeted therapy prescribing, in reality it stands ready to unlock the financial promise of precision medicine. The opportunity to reshape patient treatment pathways around better testing will help address the disruption which often comes with sudden price adjustments in therapy pricing.

Diaceutics has actively invested in big data and novel stakeholder discussions to understand the value of better testing in unlocking the financial promise of precision medicine. It has anticipated the era of great drug price controls in response to rising therapy prices and argues that economic models should embrace better testing as a way to equalize the sharing of value, minimize disruption to the pharma business model and simultaneously enable significantly greater numbers of patients to benefit from the best therapy.

Peter Keeling, CEO, Diaceutics, June 2017

Diaceutics is a global group of experts from the laboratory, diagnostic and pharmaceutical industries. Our goal is to help pharmaceutical companies to integrate diagnostic testing into their treatment pathways. We are empowered through a real-time flow of testing data from our worldwide laboratory network which we use to help our pharma clients understand and leverage the diagnostic landscape.

Chapter 1:

An overview of the role precision or personalized medicine, and specifically the diagnostic, can play in adding value to a therapy, and why pricing models need to be reviewed to reflect the value that complementary and companion diagnostics can have on the overall targeted therapy value.

Diagnostics ignored in targeted therapy pricing, access and value

Peter Keeling provides insight on the role personalized medicine can play, specifically the diagnostic, in adding value to a therapy and why pricing models need to be reviewed to reflect the value that complementary and companion diagnostics can have on the overall targeted therapy value.

There is a rising storm of debate around 'excessive' therapy prices on one side and, on the other, the exploration of 'new models' to articulate the positive impact which the pharma industry's 10 per cent of the health cost pie has on the other 90 per cent of healthcare spend.

At one end of the spectrum, payers are seeking and getting steep discounts from launch onwards for new therapies[1]. (*This combative approach is surely equivalent of Tesla launching their new people's car with 30 per cent off from day one!*) Payers' empowerment comes from the arrival in the US of cost-effectiveness groups like the non-profit Institute for Clinical and Economic Review (ICER), whose methods closely resemble those of the National Institute for Clinical Care and Excellence (NICE), the successful gatekeeper to therapy pricing in the UK[2]. Whether we agree with the methods deployed by ICER in terms of their inclusiveness or not, they are getting the ear of Medicare and presidential hopefuls[3] and will serve to intensify the pricing debate.

Does personalized medicine help or hinder the debate?

Of course, not all of the therapies under pricing scrutiny are personalized with the use of biomarkers. It does seem as if the pharma industry has, by implication, leveraged its existing Health Economic Assessment (HEA) models to consistently cross the $100,000 per patient barrier in return for dramatically improved outcomes in smaller patient segments targeted with the use of biomarkers. It is a pity then that the diagnostics at the heart of this segmentation are so ignored.

Our observation here is a simple one. Current HEA models which focus on therapy pricing generally ignore the value of the diagnostic in two ways:

1. Diagnostic value is seldom expressed in its own right despite its huge impact on improving therapy value. As recently reported in GenomeWeb from the American Society of Clinical Oncology's annual meeting, "researchers presented data from a cost-effectiveness analysis of Opdivo and Keytruda when administered with PD-L1

testing and without. In studies of patients who had non-squamous cell tumors with PD-L1 expression in 1 per cent or more of cells, the cost per QALY gained decreased from $176,000 to $105,000. For Keytruda, when patients had PD-L1 expression in 50 percent of more cells, the cost per QALY gained dipped from $163,000 to $138,000"[4].

2. The financial and clinical promise of personalized medicine is NOT optimally delivered in the premium pricing of late stage therapies (despite their clinical impact on outcomes), but rather in integrating diagnostics and therapy ever earlier into the treatment pathway. Diaceutics has already published on the opportunity to harness personalized medicine to strike a more balanced value for all stakeholders[5]. Indeed to give this balanced value model a chance to breathe, we, along with a group of physician, pharma, laboratory and diagnostic stakeholders, have established a unique not-for-profit initiative - pmconnective.org - to get specific with the value equation at a disease level. This pre-competitive initiative has already started to identify the barriers to a balanced value approach with the goal of developing a collaborative (versus combative) model.

We are conflating access with value

We will be the first to decry the lack of reimbursement infrastructure which dogs new companion and complementary diagnostic launches across the leading healthcare markets. We continue to encourage our clients to invest time to navigate this neglected field[6].

However, we must not confuse the access barriers to optimal testing (a pain to manage though they are) with the need to articulate the profound impact which diagnostics can have on the value of targeted therapy. We laud the three year journey which EPEMED and the Office of Health Economics (OHE) have been on to argue for a new evaluation framework dedicated to diagnostics. EPEMED and OHE have proposed "a broader framework for considering the value contribution of complementary diagnostics and provides policy recommendations to support the implementation of this comprehensive framework for assessing their potential value contribution."[7]

Frankly, the inclusion and articulation of diagnostic value needs to be elevated alongside the articulation of the targeted therapy and it is no more acceptable to talk about personalized medicine value only for therapies, than it is to describe the value of a new car without its tyres.

As we all search for new models which collaborate to unlock value rather than battle to protect historic turf, we encourage access and reimbursement experts everywhere to better understand the heroic power of diagnostics to reshape the debate.

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Pharma finance and the Trump effect

In the month that Donald Trump becomes the 45th President of the United States, Philip White, CFO, Diaceutics, assesses the possible impact of the new administration on the world of pharma, diagnostics and precision medicine as rising drug prices come under fire.

Few investors cheered Donald Trump's election as President of the United States as much as those who held large positions in pharma stock. His opponent, Hillary Clinton, had wanted to tackle pharma and drug pricing, so a Trump win prompted a wave of relief across the sector. Markets and analysts were buoyed and there was a 10 per cent jump in the NASDAQ Biotech index. Skip forward to January 2017 and the JP Morgan Healthcare Conference in San Francisco[1], where top pharma executives were presenting their plans for 2017 and beyond. But the mood of positivity was suddenly cut short when Mr Trump described the pharma industry as "getting away with murder".

In the opening remarks of his first press conference since the US election, Mr Trump chose to single out pharmaceutical companies for criticism over their product pricing.

"Pharma has a lot of lobbies, a lot of lobbyists and a lot of power. And there's very little bidding on drugs. We're the largest buyer of drugs in the world, and yet we don't bid properly. And we're going to start bidding and we're going to save billions of dollars over a period of time." Donald Trump, 11 January 2017[2].

His comments sent the shares of drug makers tumbling. The NASDAQ Biotech index lost 3.7 per cent in early trading while J&J shares fell 1 per cent and Pfizer's by 2.2 per cent.

Has there been a volte-face on drug pricing from Mr Trump?

During the campaign trail, Mr Trump had been quiet on pharma and drug pricing, so it came as a surprise when he appeared to flip into to a prolonged attack on drug pricing. It was the Clinton campaign that caused unease in pharma boardrooms with Hillary proposing that the White House could influence drug prices in the private market by empowering regulators to penalise companies for unjustified price increases. She also suggested allowing authorities to use cheaper alternative treatments, which could create competition and drive a better bargain for the government. She made a significant example of Martin Shkreli - the 'bad boy' of pharma - and joined the public in a backlash against his price increase of a life-saving cancer and Aids drug from $13.50 per pill to $750[3].

During the election campaign the pharma stock price fell adversely as Clinton seemed to be ahead but following Mr Trump's win stocks rebounded positively in a 'not-Hillary' bounce. They dipped back following his news conference comments and they have remain subdued [to 20.01.2017].

Confidence is growing around the precision medicine market

Diaceutics attended the JP Morgan Healthcare Conference and saw that the trend lines reported by pharma executives were broadly positive on the future of precision medicine:

- The sector is on the cusp of delivering potentially game-changing immunotherapy drugs and their combination therapies;
- There is clear movement towards precision medicine;
- Evidence of greater collaboration in drug development and cross-sector convergence against a backdrop of increased M&A activity following a successful 2016 deal map;
- Increased understanding around the importance of diagnostics and testing strategy.

But the volume of drug pricing discontent is getting louder

While there is a growing positivity for precision medicine and its potential for healthcare, there is growing concern about its price. Several factors have placed drug prices at the front of the public's mind. These include the recent pricing cases, like that of Shkreli, and the fact that medical costs are increasing for individuals covered by the Affordable Care Act (ACA, or Obamacare). Also, drug prices have outpaced the rate of inflation (in 2016 drug prices increased by 6 per cent compared to all prices increasing at 2 per cent). These all add to existing public discontent. It would seem therefore that Mr Trump's remarks are broadly in line with the sentiment of most Americans, whereas executives at the conference immediately responded by stating that drug pricing is more complicated and follows investment levels in R&D.

What can the pharma and healthcare industries expect from the new administration?

We must expect that as President, Mr Trump will begin a process to review prices. How extensive this will be we will have to wait to find out. Bargaining, however, or allowing companies to tender against each other in a competitive process that will drive down the price, would be more complicated than it sounds. It would be difficult for the Trump administration to say no to a drug regardless of price if there were no alternatives. If a regulatory authority could choose one cancer drug over another, it would amount to picking winners and losers in the market. There's no saying where this would go but it would be an undesirable situation in terms of the future growth and development of the industry.

In response, the pharma industry is likely to pre-empt the Trump administration and fast-track an industry-led regulatory body. We will also see a move towards evidence-based economic impact models, because proving the value of precision medicine drugs will become more important as the attempt to control pricing is stepped up.

More broadly, Mr Trump's other proposed policy initiatives, namely cutting taxes, deregulation of the banks and planned infrastructural investment, are intended to grow the economy. Certainly, cutting the taxes allowing US drug makers to release billions of trapped dollars overseas is a positive move. Amgen, Gilead, Merck, Pfizer, BMS and Eli Lilly currently have a total $100bn in trapped cash overseas. The deregulation of the banking sector will also allow greater funding in the biotech sector and this in turn increasingly feeds

the pharma pipeline. Mr Trump is aware of the strength of corporate America. As 2016 closed, Bloomberg reported US market capitalisation was 38 per cent of the world's total, a ten-year high[4].

Conclusion

The election of Donald Trump ushers in a new era for the US pharma and healthcare industries as they look on and await the details behind the proposed policies. The repeal of the ACA, drug pricing reviews and a renewal of US-based manufacturing are some of the goals Mr Trump is hoping to achieve. In the meantime, pharma will remain positive and take a 'wait and see' approach. Those of us concerned with the success of precision medicine and diagnostics have to hope that improved patient outcomes is high on the list of the new administration's goals, and that it doesn't all come down to costs.

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Drug pricing models

In the wake of numerous articles on the high cost of new drugs, several organizations have developed drug pricing models. With a number of these scorecards arriving at the same time to raise the profile of cost versus value, could they pose a major threat to pharma? Jeff Waldron, of the PM Connective, examines three recent models and attempts to find out.

The drug pricing models published recently come from organizations that have their own entirely self-specific reasons for doing so, and transparency and accuracy are not the only key attributes—as with everything, "where you stand depends on where you sit!"

So, providers want to explain why they prescribe such expensive medications, hence the educational aspect of the Memorial Sloan Kettering model. Pharma companies, on the other hand, are loathe to discuss pricing due to the negative press they've been receiving.

Pharmacy Benefit Managers (PBMs), are caught in a classic 'double edged sword' situation. They want to control Rx costs for plan sponsors, but, at the same time, set drug sales revenue as a goal. Express Scripts, the largest US PBM, tell us they are deploying a unique pay-for-performance drug pricing model based on a combination of the Memorial Sloan Kettering and ICER models. This plan will price the same drug differently for different diseases and applications.

In the US, private payers have by far the largest market share of medical and pharmacy plan members and they protect their corporate pricing acidulously. Their pricing structures vary widely and are determined by clinical, business-related and geographical factors, as well as plan sponsor category and plan type. Prices fluctuate over time as well. The major government payer, CMS (Medicare and Medicaid) has somewhat more transparent pricing, but it also varies.

Thus, drug pricing models offer educational value, defence of high costs and, in some cases, specific comparative pricing to guide policy and buying decisions. How is a provider, payer or patient supposed to judge cost against value?

DrugAbacus from Memorial Sloan Kettering

This model helps us to ask what is the 'right price' for a new drug. It takes 54 new cancer drugs approved since 2001 and lets you compare the company's price to one based on value - the 'Abacus Price.' How does DrugAbacus find the value of a drug? It doesn't. You do. It stores everything about these drugs that might be relevant to their value (based on the data sent to the FDA to get the first approval). It uses the idea that a drug's value can be broken up into its parts, leaving you to decide which parts should matter and with what weighting. The results are then compared to the drug's actual price.

The DrugAbacus tool is quite informative as an educational model. It depicts the key attributes to be evaluated in determining a drug price. You can select a particular disease, and it shows quite handily all of the drugs used to treat that disease and their relative pricing. You can even alter the embedded variables used to calculate the drug price, such as dollars per life-year or cost of development. By way of example, Iressa (AZ) returns an actual price of $2,069 and a DrugAbacus price of $454. One major limitation of the model is that it only prices the drug at initial launch in 2014 adjusted US dollars. Nonetheless, the model is an interesting and useful tool for general understanding of the determinants of drug pricing.

Value Framework from the Institute of Clinical and Economic Review (ICER)

The Value Framework is intended to address 'problems' such as poor reliability and consistency of value determinations by payers, finding a transparent way to analyse and judge value and the tension between long- and short-term perspectives. Its goal is to find a common language and descriptive model of the components of value for all stakeholders. With a grant of $5.2m, ICER expects to provide benchmark prices for up to 20 drugs over two years, beginning with the new category of potent cholesterol-lowering drugs developed by Sanofi and Regeneron.

The framework considers the following aspects that lead to an assessment of care value:

- ***Comparative Clinical Effectiveness***: the comparative net health benefit and the level of certainty in the evidence on net health benefit. ICER uses its Evidence-Based Medicine (EBM) matrix to describe the judgement of the scientific staff.
- ***Incremental Cost per Outcomes Achieved***: the cost per aggregated health measure (QALY).
- ***Other Benefits or Disadvantages***: information about the intervention to caregivers, the delivery system or other patients not captured in the available 'clinical' evidence.
- ***Contextual Considerations***: can include ethical, legal or other issues (but not cost) that influence the relative priority of illnesses and interventions.
- ***Potential Budget Impact***: estimations of net changes in total health care payer costs over an initial two year timeframe and alternative measurements of the net budget impact of all known eligible patients switching to or beginning a new care option.
- ***Provisional Health System Value***: an early judgement based on the care value, potential budget impact and affordability of a new drug.
- ***Managing Affordability***: an action step, ideally supported by enhanced early dialogue among stakeholders to firstly determine the extent to which real-world constraints in uptake will limit the actual budget impact of the new service, and secondly to decide if this expected budget impact is manageable in the current health care landscape.

Overall, the ICER model is a rigorous, research-based analysis customized to the particular therapy and disease and the components are more academically derived than DrugAbacus. The ICER approach may not be as user-friendly, but that's because it's not a tool—it's a scientific, quantified, organized and well thought out research methodology that is consistently applied.

The American Society of Cancer Oncology (ASCO) has recently released a **Scorecard**, or conceptual framework, for assessing the value of new cancer therapies based on treatment benefits, toxicities and costs. Developed by the ASCO ***Value in Cancer Care Task Force***, the framework will ultimately serve as a user-friendly, standardized tool that physicians can use with their patients to discuss the relative value of new cancer therapies compared with established treatments. It is currently a discussion draft with ASCO inviting input on the proposed framework.

ASCO's framework seems to add complexity beyond the ICER model. It uses many of the same considerations and variables, but it relies on extensive explanations and justification along with a visually complex structure.

My overall assessment of these models is that they are the first steps in the transition to a much more transparent health care system that allows all stakeholders to make effective decisions that yield improved health outcomes and better economic value. Advanced new personalized therapies, combined with state-of-the-art diagnostics, are poised to offer dramatic improvements in treating many major diseases, but the value tools are not in my view sufficiently explicit about the value of integrating one or more diagnostics alongside these therapies. Since the pricing of recent personalized medicine therapies (targeted by specific biomarkers) is triggering much of the development of these tools, it will be important that the diagnostic and therapy values are equally clear. In the long run, this will help both payer and pharma negotiate the right price for the right drug at the right time.

Further information

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- Institute of Clinical and Economic Review (ICER) Drug Research - http://www.icer-review.org/icer-ljaf-drug-assessment-announcement
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- Real Endpoints subscription-based RxScorecard - http://www.realendpoints.com
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The return on investment of better CDx planning based on early PD-L1 observations in NSCLC

Sanna Jousi of Diaceutics assesses the financial benefits of integrating the planning, analytical and action steps for successful development and commercialization of testing into targeted therapies.

The anti PD-1 therapy market promises to be the largest single oncology market, with peak sales projections of $33 billion. Five major pharma companies have active asset programs in the space, each leveraging testing in second and first line cancer treatments differently. Merck and BMS have already launched Keytruda and Opdivo. A number of indications and therapy strategies will be specifically interdependent on the efficiency of the PD-L1 testing market so this merits a better understanding of the financial relationship between diagnostic market efficiency and lost therapy revenues.

Current PD-L1 testing options use IHC, the same platform which enabled the HER2 Herceptin franchise but which also took five to seven years to optimize. Retrospective analysis has identified up to $3 billion in lost revenue opportunity for Herceptin due to IHC testing issues.

To help determine the similar readiness of PD-L1 IHC testing to support therapy launches, Diaceutics has tracked key diagnostic drivers in real time and modelled their impact on estimated lost anti PD-1 therapy revenue for one indication only—second line NSCLC—in its first year of launch and over the following four years.

We have used the Diaceutics Financial Planner to reverse-model the current relationship between PD-L1 testing and therapy revenues generated to date. The metrics were used on target population patient penetration, dosing and laboratory adoption observed to date in second line NSCLC (US).

Using this platform we assessed the sensitivity of several drivers. Second line NSCLC drivers modelled:

- Dosing advantage in high expressers
- More accurate test answers
- Greater conversion to therapy from test positives
- Greater test adoption by physicians
- All drivers optimized together

Disclaimer: This is an illustrative model only and is not intended to reflect existing or future therapy forecasts in the anti PD-1 space

The Base Case (Scenario 1) looked at revenues predicted within the model from 2015 to 2019 in second line NSCLC. The projected cumulative base case value for a therapy label dependent upon testing is $1.3 billion in the US market (Figure 1).

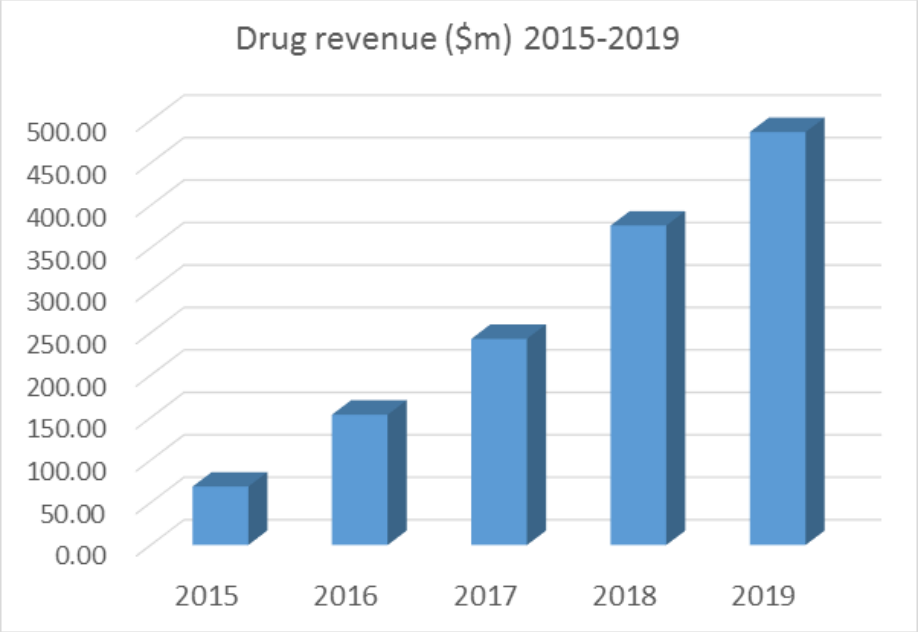

Figure 1. Drug revenue ($m) 2015-2019

Looking at the relative dollar impact of each optimized driver (cumulative five year revenues) revealed that whilst optimized dosing in high expressing PD-L1 patients (>50 per cent) is the biggest single contributor, improving test accuracy and driving greater demand for testing confer significant revenue gains (Figure 2).

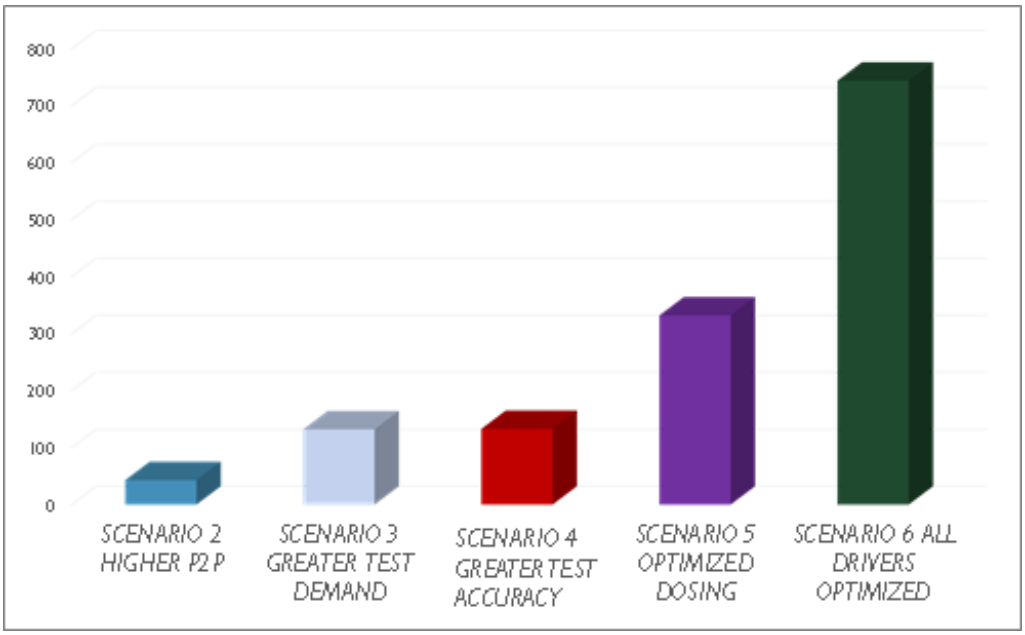

Figure 2. Relative dollar impact of each optimized driver.

Using the model to determine the relative percentage impact of each optimized driver (cumulative five year revenues) showed that having all drivers optimized would confer an additional eight per cent of revenue over the single drivers alone.

Another way to consider this is as year on year lost treatment revenue. The model suggests that therapies have already lost around $40 million in treatment opportunity due to suboptimal testing. This accumulates over five years to $744 million in lost therapy opportunity in second line NSCLC alone, otherwise achieved if all drivers had been optimized (Figure 3).

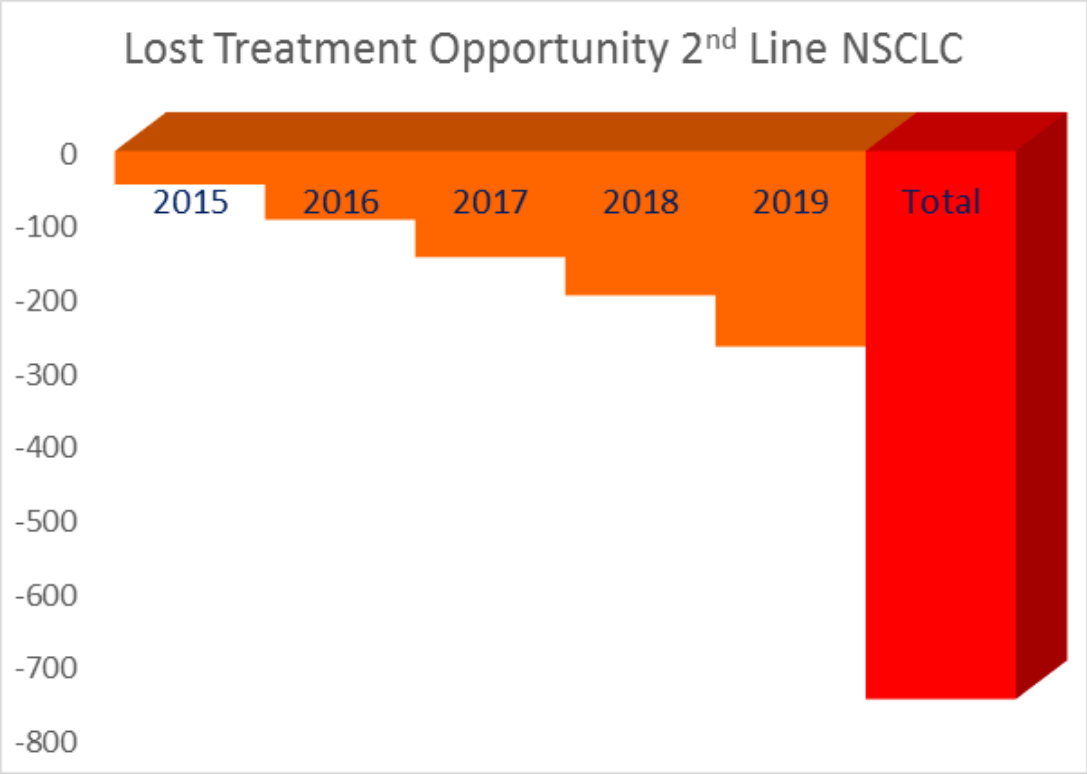

Figure 3. Lost treatment opportunity in second line NSCLC ($m).

Finally, when looking at the ROI of diagnostic driver investments expressed in anti PD-1 therapy dollars we saw that investment in greater test accuracy delivers the single greatest dollar for dollar return, but having all drivers optimized provides $24 for every $1 invested in diagnostics for this indication.

Conclusion

A suboptimal PD-L1 diagnostic marketplace is already resulting in lost treatment opportunities. As the dependence upon PD-L1 testing grows over the years and across indications, this is highly likely to magnify.

The Diaceutics model suggests that up to $744 million in lost treatment revenue is at stake in this one indication alone.

Based on this indication, an investment in optimizing the PD-L1 diagnostic marketplace is likely to confer more than $20 additional therapy revenue for every $1 spent on diagnostic investment. Improved quality of testing will deliver the greatest dollar for dollar return and linking higher dosing to high PD-L1 expressing patients should see the single highest dollar amount return.

Pharma asset and management teams are always concerned about the ‘opaque impact’ of investing in diagnostic optimization. By employing real time tracking of the PD-L1 market and reporting this in ‘lost treatment dollars’ it is our intention to highlight the significant financial benefit of earlier and better planning in diagnostic market optimization.

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Chapter 2:

As therapy pricing comes under pressure, better testing can assist in value restoration for the pharma industry

Why PM1.0 will not create radical health care change prompting the need for PM2.0

Peter Keeling of Diaceutics explores the concept of PM2.0 in this article for the *pharmaphorum* website.

The five forces behind 2.0 anything...

The nomenclature '2.0' has become synonymous with second generation trajectories. We have all experienced the benefit of the Web2.0 movement, a term coined in 1999 by Darcy DiNucci and subsequently popularized at conferences from 2004 onwards. On the surface Web 2.0 suggested a new version of the internet, however, it was not intended to refer to an update to any single technical specification, but rather to cumulative changes in the way web pages are made and used with particular reference to social media.[1]

A closer analysis of the 2.0 concept suggests that five dynamics align to create the conditions which trigger a step past a '1.0' trajectory, including:

1. A better understanding of the limitations and potential of current technology by those closest to it.
2. An adequate flow of investment towards continuous experimentation.
3. A (formal or informal) systems integration of previously disparate stakeholders around that new trajectory.
4. Greater transparency of the significant (versus moderate) returns available.
5. Advent of individual or corporate leadership accelerating the change.

Let's consider these five forces at work in a familiar example. On my first birthday in 1961[2] the then US president, John F Kennedy, announced before a special joint session of Congress the dramatic and ambitious goal of sending an American safely to the moon before the end of the decade.

All five 2.0 forces can be seen at work in achieving this clear technological leap. Firstly, President Kennedy did not set this new vision without NASA informing him of the limitations and possibilities of 1950s rocket propulsion systems as witnessed in the Gemini and Mercury programs. Secondly and thirdly, NASA acted as funder and systems integrator for this goal, managing the most complex of supply chains from life support systems to lunar landing modules and, in doing so, triggered one of the most rapid periods of continuous experimentation in history. In terms of incentive, the political returns to winning the cold war against the USSR were deemed enormous, particularly after the shock that a Soviet, not an American, was the first man in space in 1957. Lastly, despite the many social and racial problems of the era and potential application of federal dollars, JFK's leadership in setting the new space trajectory set the world alight, resulting in Armstrong and Aldrin landing on

the moon on July 20, 1969. By setting the moon landing goal, JFK ensured the world stepped past 'space exploration 1.0'.

Let's face it, the PM 1.0 definition has had an inauspicious start...

How do these concepts help us assess where we are with personalized medicine? First of all we need to contextualize personalized medicine or PM1.0. Let's face it, PM1.0's definition has really had an inauspicious start. Simultaneously slighted by investors and industry leaders as relating to a niche (read minor fringe activity), only for those experimenting in oncology, or confused as an ersatz buzz phrase for everything from sports monitoring devices to regenerative ageing surgery[3], in the first part of the last decade personalized medicine was often overhyped and constantly reshaped in favour of someone else's preferred definition. I have personally witnessed the targeted therapy and companion diagnostic space being subjected to constant (and frankly confusing) renaming, with terms like theranostics, pharmacogenetics, personalized healthcare, precision medicine and stratified medicine. More telling perhaps has been the label (communicated up to the 'C suite' and from there to investors) from many close to the pharmaceutical science that 'the science is not there yet. A phrase used to correctly suggest that we still have a long way to go to understand one (and only one) dimension of personalized medicine, namely the genetic and molecular underpinnings of personalizing treatment.

Our own in-depth analysis of PM1.0 suggests that despite recent industrial thawing towards a personalized medicine-enabled business model, itself triggered by accelerated approvals of biomarker aided therapies[4], personalized medicine is really still a series of disconnected building sites and stakeholders. Moreover, PM1.0 is often too narrowly confined from within the pharmaceutical industry, to investments in responder testing for targeted therapy. Nor have the incentives for PM1.0 been clear. Given the financial uncertainties implied by subsetting small patient cohorts for therapies subject to $1 billion development fees, the response by many in the pharma industry is to default to a personalized medicine approach versus a 'one size fits all' therapy launch only when the regulatory pathway dictates such an approach. Whilst leading companies have supported some degree of central strategic planning and training, our observation is that in the majority of cases where a therapy will be commercialized with a test, it is the FDA or EMEA that are arbitrating the choice of personalized medicine on a particular asset versus a CEO-led strategic missive.

If we look instead at payers, likely the only other major industrial player with the wherewithal to organize an acceleration of personalized medicine, the picture is equally reactive. Yes, there are payer-led initiatives. United Healthcare[5,] for example, currently supports up to $.5 billion on genetic testing for their patients [2013]. Aetna has had a central personalized medicine person in place assessing the space for as long as Diaceutics has existed. However, by the nature of their industrial architecture payers are highly data-driven[6] and too often this has been lacking in PM1.0 and has consequently not triggered a payer-led drive towards accelerating personalized medicine.

In my view, whilst pharma and payers will increasingly be willing participants in PM1.0 this incrementalism will not translate into the radical health care change implied (and feasible) by

an era of personalized medicine. However, our research also suggests that the forces for PM2.0 and a more radical acceleration of personalized medicine are aligning in anticipation of individual or corporate leadership. We outline in broad terms our case for PM2.0 below.

The case for PM2.0

To assess the case for PM2.0 with a structured lens we applied the five forces (cited above) aligning for a 2.0 trajectory to personalized medicine and further discuss below.

1. Understanding the limitations and potential of PM1.0 technology
With some 70 targeted therapies and companion diagnostics (biomarkers) on the market[7] and the now almost daily translation of genetic research into bedside innovation, the last ten years have seen a period of rapid learning about the power (and limitations) of the early application of technologies underpinning personalized medicine. In translational medicine labs across the globe new insights are being harvested, giving us a smarter future perspective of where the 'technology can go' even if it is not there yet.

2. Investment in personalized medicine experimentation
As recent investment analyses illustrate[8] personalized medicine is benefiting from an ever higher profile among professional investors as well as industry leaders. This in turn is triggering higher levels of clinical and industrial experimentation incorporating everything from supercomputers[9] to next generation sequencing[10]. Nor is such experimentation limited to technology. Involvement in, for example, social media and smart phone applications in patients' personalized health care empowerment is a significant force for change and is symbolic of the disparate stakeholders aligning around the personalized medicine concept.

3. Systems integration in personalized medicine
Perhaps a little more opaque, but nonetheless recent publications have started to argue that personalized medicine lends itself to a systems integration approach, as Ginsberg *et al* argued in a recent *JAMA* paper, " ... to minimize health care cost increases, genomic approaches must replace existing inefficient technologies and reduce the use of downstream resource"[11]. Our own research into the transformative capabilities of personalized medicine, suggests a significant clinical dividend is available, but only when personalized medicine is introduced as part of a total system in a disease. Specifically, to replicate a PM2.0 world we have modelled the combined impact of a systems integration in melanoma derived from better early diagnostics, prognostic testing and responder testing alongside new first line targeted therapies aimed at reducing second line surgery and the burden of five-year surveillance, both of which conspire to drive up the cost of melanoma[12]. Figure 1 illustrates marginal and transformative clinical impact of a systems integration model applied in one disease area (melanoma). We have replicated these models in infectious and metabolic disease and see similar profound impact.

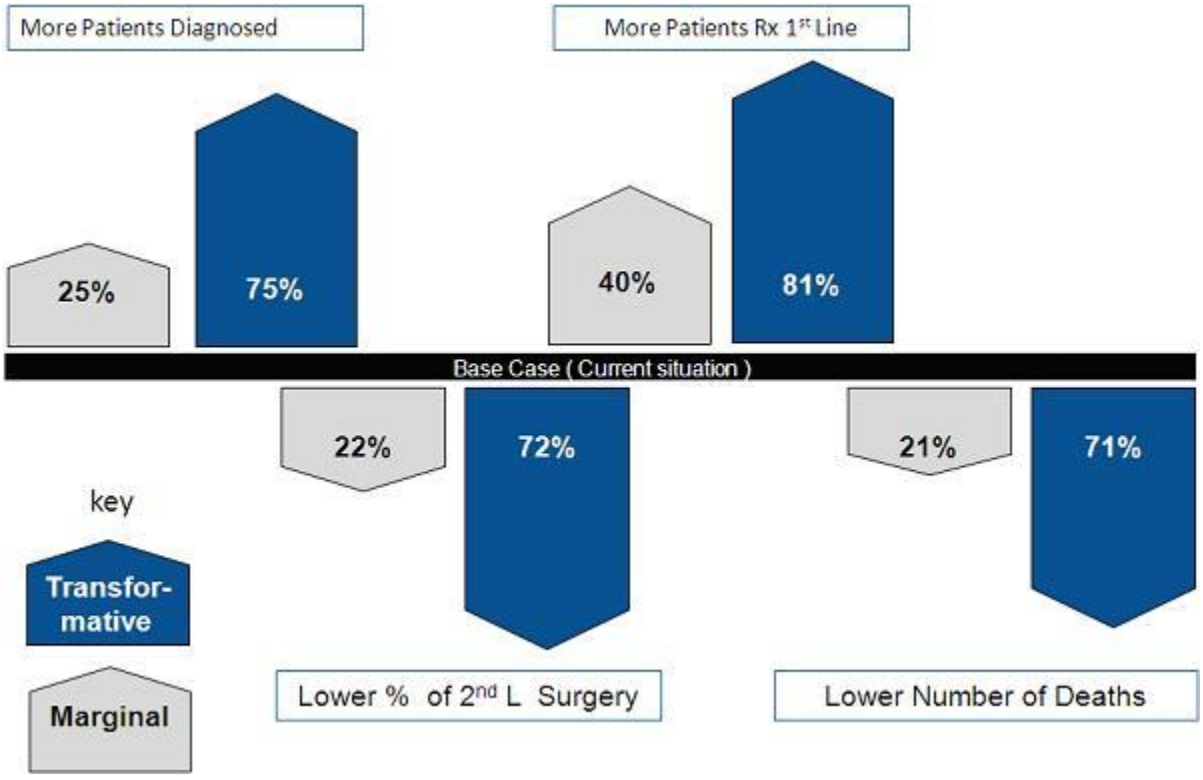

Figure 1: Melanoma PM2.0 clinical impact analysis.

4. Greater transparency of the significant (versus moderate) returns available from PM2.0

Within pharma there are already the whispers (to be fair Roche has been promoting the investor benefits of personalized medicine for some years now) that personalized medicine might make economic good sense. In a reversal of the widely held perspective that treating small patient groups meant financial suicide for large pharma, the triple benefits of accelerated regulatory approval, smaller clinical trials and significant clinical impact for patient subgroups have already delivered early revenue and time to peak sales opportunities versus the 'one size fits all' model. Using our intervention-based business models we have tried to elucidate better the potential future impact on pharma and payer profits of a shift to a PM2.0 paradigm. What these models point to is that a systems integration approach in personalized medicine could also provide significantly more revenue for pharma and significant cost reduction for payers than their current business models. Figure 2 describes the increases and decreases in costs in our Melanoma 2.0 model. We note that both industrial groups (pharma and payers) obtain a significant economic dividend from a PM2.0 aligned program.

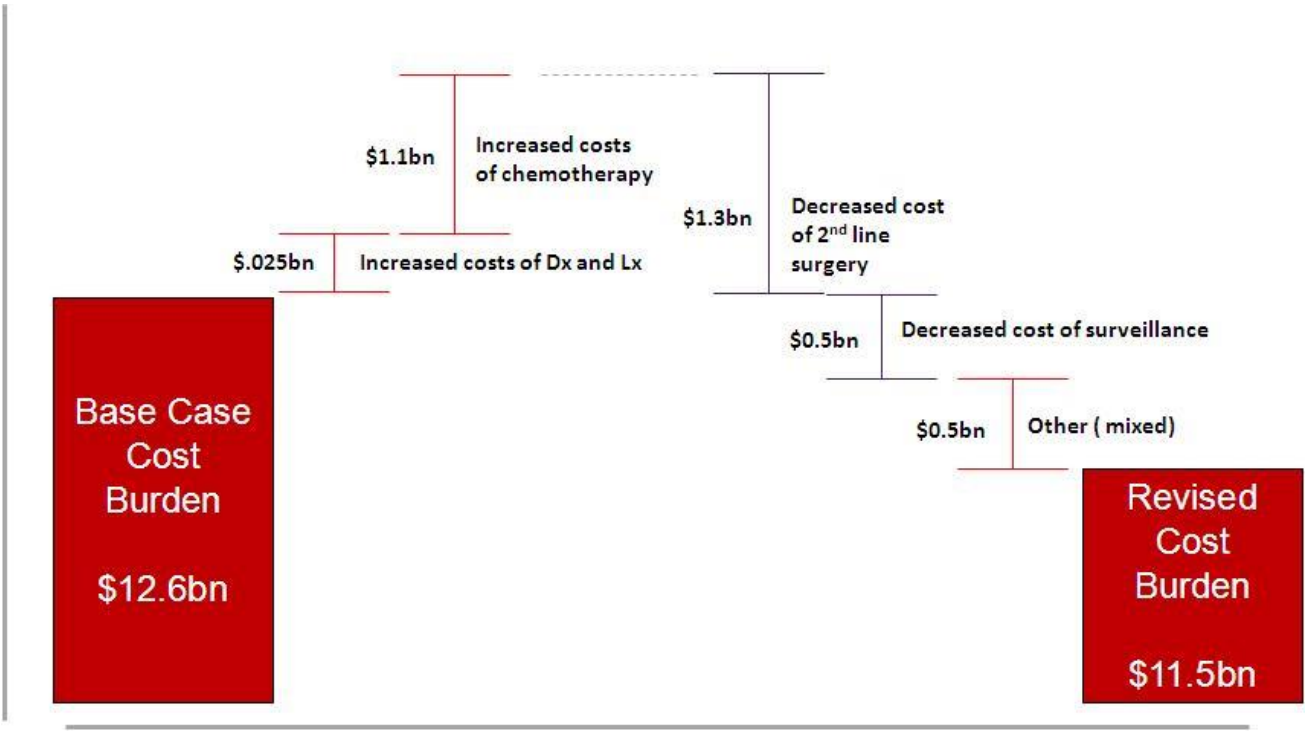

Figure 2: Melanoma PM2.0 economic impact analysis: Melanoma transformational model shown only.

5. Advent of individual or corporate leadership accelerating PM2.0 change

One of the major gaps, in my view, mitigating against a PM2.0 drive to date has been lack of 'C suite' leadership from pharma and payers. I acknowledge that many CEOs and R&D heads now list personalized medicine as a pillar of growth for their business but that is not the same as organizing a business model shift towards personalized medicine. Nor do I subscribe to the academic view from the likes of Christenson that personalized medicine will ultimately disrupt (threaten) the pharma and payer business models in the same way that the PC changed forever the mainstream computer business in the 1980s.[13] One of the strengths of the pharma model has been to manage and spread risk in a long cycle business. Take GSK as an example. Andrew Witty has met the challenge of declining R&D productivity not only with new internal innovation process but by promising shareholders that China (and developing countries) is an area for significant growth. Given that only 3 per cent of GSK's revenues in 2012 emanated from China there are decades of opportunity to offset the risks of long cycle therapeutic discovery. GSK's model is well configured to survive without a compulsion to lead personalized medicine into a new trajectory. At the other end of the spectrum, Severin Schwan's embrace of personalized medicine as integral to Roche's future is either prescient or an outlier to his peers in the industry. The arrival on the disease management scene of a new entrant called Calico, backed by Google and led by a personalized medicine veteran in Art Levinson, has the potential to increase the competitive pressure on large industry incumbents but will not competitively impact in the short term without the bold purchase of, say, Astra Zeneca or one of the other recently troubled Pharmacos. The bottom line, however, is that at the minute personalized medicine does not seem to have its Bill Gates or JFK.

Discussion and summary

I have tried in this brief piece to apply a slightly different lens to the directions for personalized medicine. It is neither the only lens nor the optimum one, but it does highlight several truths.

When well organized, personalized medicine can deliver the called-for health care step change and provide the industrial rewards commensurate with (or greater than) other successful investment in health care reforms. However, despite our perspective that the five forces for a PM2.0 trajectory are aligning, they are not yet in alignment. We are left wondering if the goal, for example, to consign diabetes to the clinical and economic equivalent of the common cold within the next decade is impossible, or simply the absence of a singular vision or perhaps visionary.

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Chapter 3:

Medium term, better testing helps with the development of new value-based models

A new disease level precision medicine model; starting with melanoma

In just a few months, the PM Connective expects to complete a new model for melanoma that will offer clinical and financial benefits in precision healthcare. Early indicators suggest the model will provide substantial improvements in health outcomes and lower overall healthcare costs by shifting the entire management of melanoma from the expense of treating late stage disease to earlier interventions when, significantly, this aggressive condition is curable. But just how robust is the model? Peter Keeling and Jeff Waldron of Diaceutics and The PM Connective believe that to understand the strength of this innovative tool it is important to look at the nature of the disease, and how the model was developed.

Managing melanoma better

The PM Connective chose to design its model first in melanoma. The importance of a valuation model in melanoma is that the condition can be cured if found and treated in the early stages when it affects only the skin. Unfortunately, this is currently not the case for a number of patients.

Melanoma is one of the least common forms of skin cancer, but it is one of the most aggressive, because of its potential to spread to other parts of the body. Almost one million Americans live with this condition, and rates are rising, especially among children and teenagers. But while the disease accounts for around 1 per cent of skin cancers diagnosed in the USA, it causes most of the skin cancer deaths.

Data on patient distribution by disease stage indicates that more than 235,000 Americans have Stage 0-I of the disease (when the tumors are still on the skin), and 30,000 are living with more advanced melanoma where the tumors have metastasized to other parts of the body (Stages III and IV). Yet while around $2,600 million a year is spent treating the two early stages, when a cure is still possible, a significant $6,800 million is spent treating Stages III-IV. Clearly, if more people were diagnosed and treated with first line therapies sooner it could have a huge impact on their clinical outcomes.

Historical cost data suggest that more effective deployment of diagnostics and therapies could reduce deaths from metastatic melanoma in the USA by between 21 per cent and 71 per cent. This premise is substantiated by early indications from the PM Connective's model for melanoma, which suggests that early interventions could indeed save patients' lives.

"There needed to be an organisation that could look at the value of precision medicine and demonstrate how it could transform people's lives now, with existing or near market technologies and education at the micro level," says Peter Keeling, CEO of Diaceutics, which founded and sponsors the Connective. A small task force, led by Keeling, was

therefore set up to find the terms of reference for this organisation, and at the end of six months Diaceutics established the not-for-profit PM Connective with the goal of seeing what changes could be identified to help articulate and extract the full value of precision medicine within melanoma. The vision to better integrate currently available or near market technologies into each healthcare stakeholder's process, gave inspiration to the name PM Connective itself.

Grass roots knowledge bank

The PM Connective is now a collaborative network of around 160 key representatives from all healthcare stakeholders, or 'silos'. This level of experience, expertise and integration means the Connective is essentially a grass roots knowledge bank for the complexities of dealing with this disease, its technologies, treatments and costs.

Moreover, by creating a collaborative network the Connective has ensured each silo has an understanding of the perspective and issues faced by each of the other silos, and that together they could build a model that provides value and benefits to each individual silo. Importantly, targeting the model at the disease-specific level further ensures it is focused and its recommendations can be readily implemented.

To date, the Connective has held two workshops to convene all healthcare silos for an integrated conversation instead of one-on-one discussions. These workshops, which looked at the disease holistically, were held in April and December 2016, at Rutgers Cancer Institute of New Jersey, an early supporter of the Connective under the guidance of Dr. Howard Kaufman, the Institute's Associate Clinical Director and Chief Surgical Officer. Prior to each workshop a detailed survey was sent to each collaborator to garner their ideas, and to broaden their reach if some of them couldn't make it on the day.

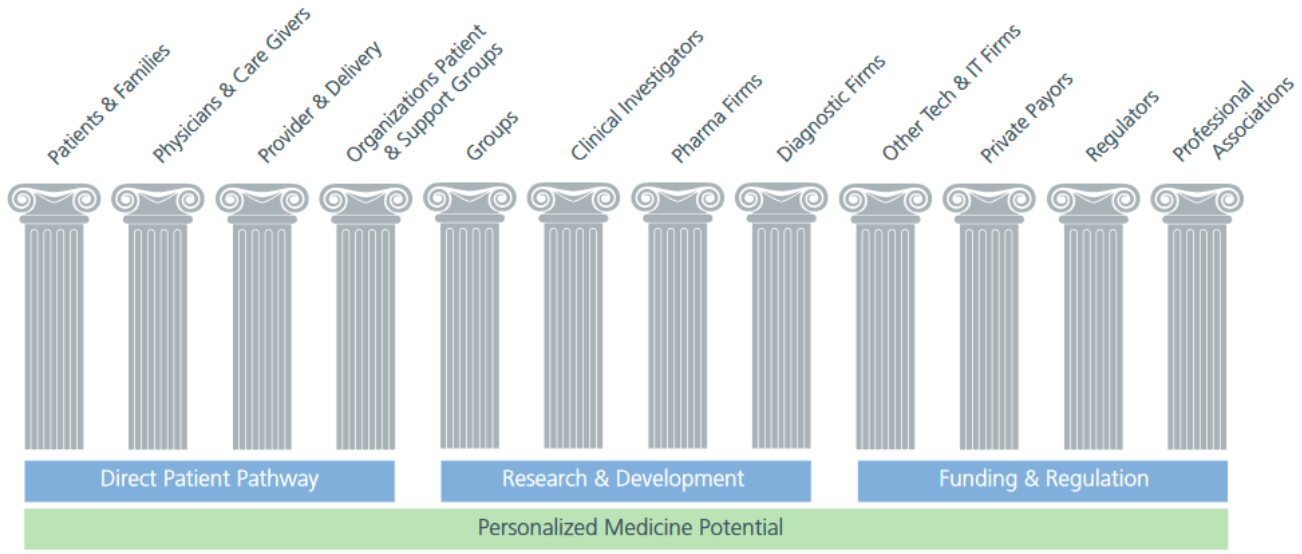


Figure 1. Vision of integrating all healthcare 'silos'

The first workshop focused on establishing the hurdles to implementation of precision medicine – which the collaborators whittled down to six critical high-level issues. Information from the two surveys, and the first workshop, was then distilled and synthesised in preparation for the second workshop, where the collaborative network developed a broad range of potential precision medicine solutions. These are currently being fully defined, examined and processed through the valuation model to quantify and prioritise interventions for implementation. The solutions have been sorted by topical areas and each has been prioritised (A, B or C) and given an estimated timing (near term, medium term, or long term).

In summary, these solutions are:

Clinical practice and operational

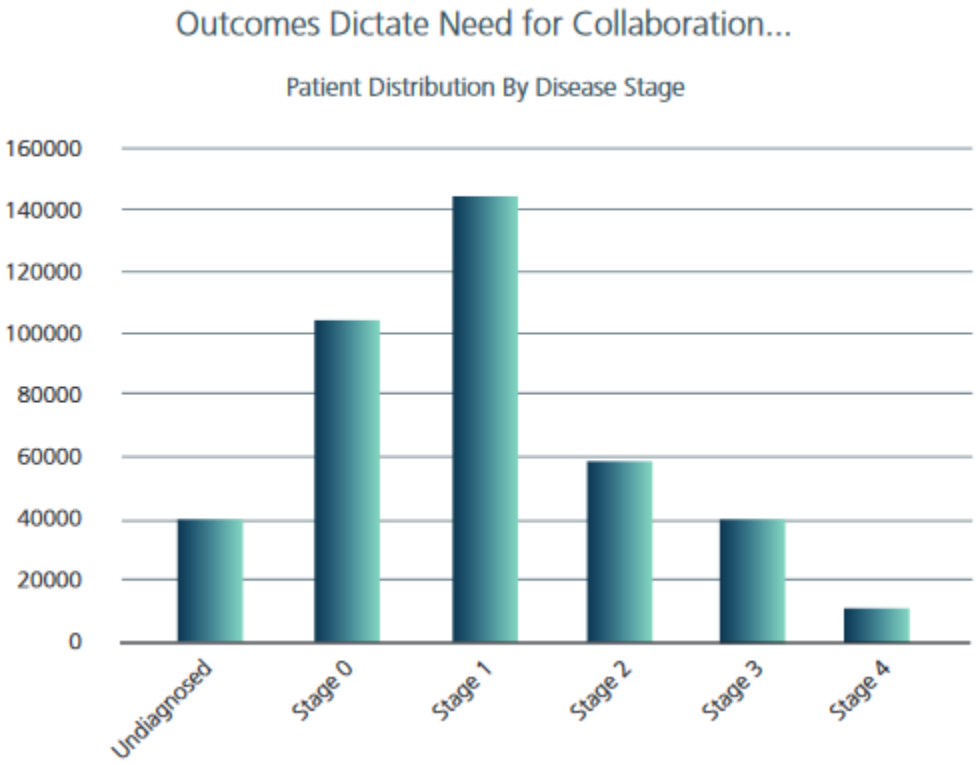
Improved clinical collaboration (priority A – near term)
Melanoma is usually diagnosed and treated at a local level, usually a community hospital, and if the disease progresses the patient is often transferred to a regional facility such as a specialist cancer centre. Generally, these transfers do not include full transmittal of early diagnostic and/or therapeutic results, such as tumor samples, resulting in either delayed response by the specialised facility or the need to take new tumor samples and biopsies. The reason for this, in part, is because the local hospital does not receive additional reimbursement for providing data or samples to the specialty facility. At a more general level, a precision medicine approach requires full collaboration between providers, possibly with reimbursement tools to encourage the process.

Melanoma risk characterization (priority A – medium term)
Initially, patients often present with Stage I or II melanoma. Some will respond positively to early treatments and may exhibit no-evidence-of-disease, while others may progress to the metastatic phase. If there were substantiated diagnostic assays to better predict risk characterisation, treatments given in the early stages of melanoma could be segmented to provide more aggressive targeted therapy and/ or earlier adjuvant therapy to patients most likely to benefit. This involves a combination of prognosis and predictive elements. Prognosis is the risk characterization part, which provides information on who is more or less likely to relapse. Predictive assays can tell you if a patient is likely to respond to a specific therapy or not. Integration of both aspects is difficult, but offers the most potential for improved outcomes.

New options for melanoma adjuvant therapy (priority A – medium term)
More adjuvant therapy options are needed. For example, early identification and treatment of breast cancer patients using the HER 2 biomarker and Herceptin improved outcomes, but it wasn't until Herceptin was used as an adjuvant therapy in qualified patients that vast improvements in breast cancer outcomes were seen.

Immunotherapy's emergence as 1st-line treatment displaces traditional targeted therapy (priority A – near term)
Sequence and timing of both targeted therapy and immunotherapy needs to be better defined. Providers are increasingly using immunotherapy as a 1st-line treatment for melanoma but if a patient doesn't respond this poses difficult decisions about when to switch

to more traditional targeted therapy. Complications occur involving both 'pseudo-response' to immunotherapy that doesn't last, and where targeted therapy may be less effective in later stages than earlier ones. The key challenge is to find a way to better stratify/identify patients who are most likely to respond to immunotherapy so they are treated with that first, whereas those less likely to respond are provided with targeted therapy or other treatments first.



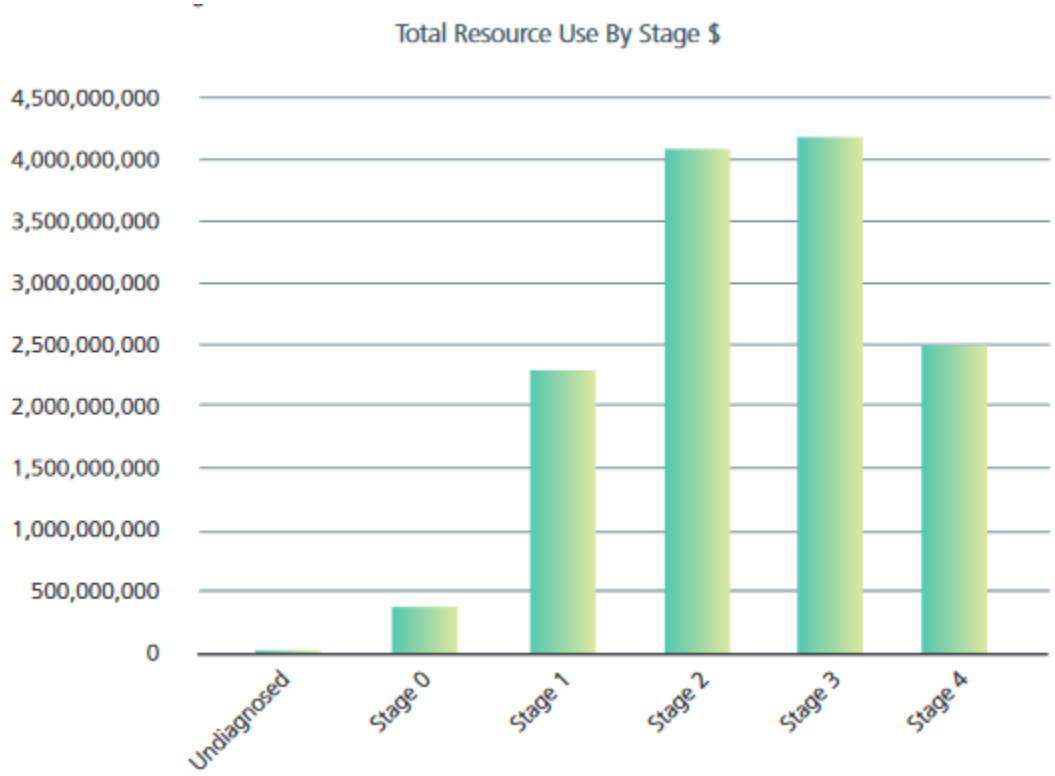
Consideration of clinical trials as standard-of-care for select patients (priority A – near term)
Rapid development of novel therapies, including combination therapies, has led to clinical trials becoming de facto standard-of-care for patients, particularly with metastatic disease. At the Rutgers Cancer Institute roughly 60 per cent of metastatic melanoma patients are part of clinical trial therapies. This is easier at centres of excellence with associated medical schools like Rutgers, but needs to be promulgated more widely.

Improvements needed in transition from pre-clinical to clinical trial process (priority B – longer-term)
Greater collaboration and integration of the pre-clinical research stage with the clinical trial process has the potential to ensure the most attractive research topics and targets get funded and orchestrated through both processes.

Diagnostics

BRAF testing for melanoma is a critical determination but often occurs later in the patient pathway (priority A – near term)
BRAF gene mutation is the most common oncogenic driver mutation of metastatic melanoma. Treatment with BRAF and MEK inhibitors can result in a high tumor response

rate and improve the survival of patients with BRAF V600 mutation. An analysis presented at the 2015 European Cancer Congress showed the estimated two-year overall survival rate with dabrafenib/trametinib was 51 per cent. Treatment guidelines and standard-of-care need to be re-examined to determine the optimal timing of NRAF testing.

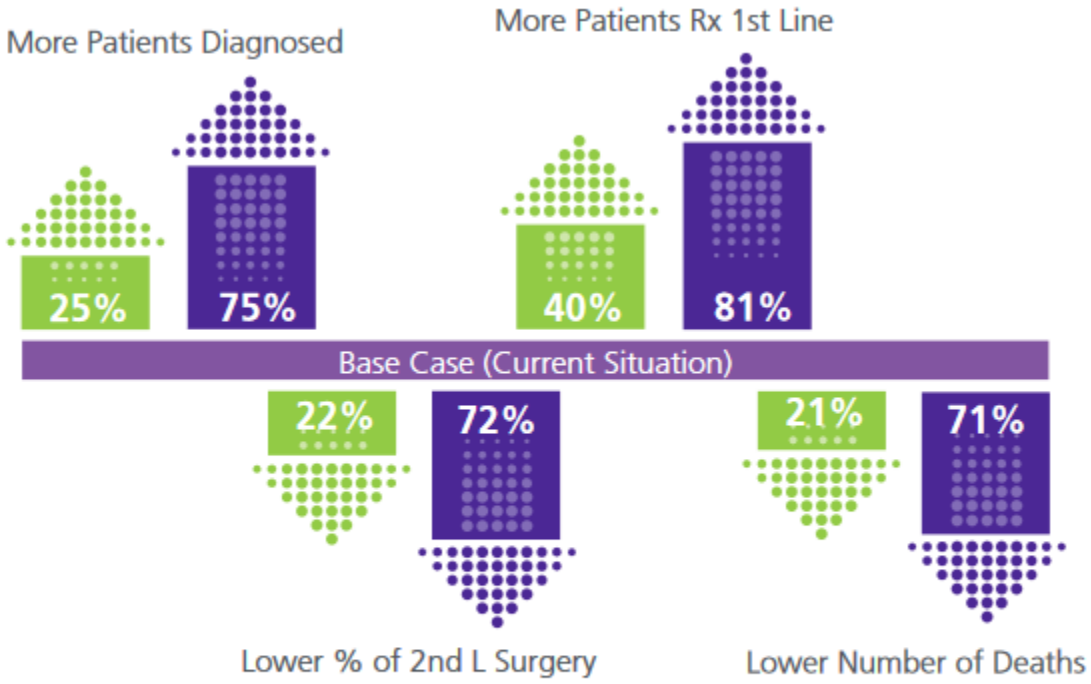


Next generation sequencing (NGS) will become an essential diagnostic tool but is yet to be proven (priority A – medium term)
NGS is likely to become essential for diagnostics in melanoma, particularly for risk characterisation. An industry-wide focus on the clinical utility of NGS will hopefully drive validation and acceptance.

Liquid biopsies can be effective tools but lack validation and costs can be high (priority B – medium term)
Liquid biopsies can be effective in risk characterisation, determining tumor burden and therapeutic drug monitoring to better measure patient response. However, lack of validation of performance and cost considerations currently limit their usefulness. An industry-wide focus would help.

Innovation in diagnostics is held back by lack of incentives (priority B – longer term)
Reimbursement difficulties and lack of patent protection means the diagnostics industry has a challenging path to innovation. Payers will need to examine reimbursement of FDA-approved and laboratory developed tests (LDTs) diagnostics to encourage innovation of critical assays that help determine the use of extremely costly new therapies. One approach would be to create some form of incentive system for diagnostics firms similar to that used

by the US Department of Defense for its vendors. It specifies “advanced market commitments” (incentives) for the development of new products or services.



Graphs depict the results of our study of melanoma, but we found consistency across cancer, metabolic, and sepsis diseases.

Diagnostic tests have differing effectiveness with little standardisation (priority B – longer term)
Lack of standardisation for diagnostics implies varying degrees of effectiveness by a given laboratory. Most assays are not FDA-approved and can often be (LDTs), resulting in confusion in the marketplace and lack of value for approved and validated testing. The worlds of FDA versus CLIA testing certification remain a challenge for providers.

Pharmaceuticals

Adverse clinical and cost consequences of ‘step-edit’ or ‘fail first’ policies (priority B – longer term)
Policies dictate patients must first demonstrate lack of results on existing treatment options before being approved for new and often costlier therapies. Most new therapies get approved in metastatic patients for later lines of therapy. It is the fastest way to get to market and begin generating revenue to fund the follow-on studies to move the drug to earlier stages and earlier lines of therapy. Thus, more data is needed to support better first-line treatment such as anti-PD-1 immunotherapies.

Benefits of combination therapy versus monotherapy are difficult to measure (priority B – longer term)
Many metastatic melanoma patients respond well to treatment using combination therapies, but options are difficult to determine and guidelines are lacking on standard-of-care. In addition to developing new drugs, there is a need for improved evaluation of the benefits and sequence of combination drugs, both as primary and adjuvant therapies.

Reimbursement

Lack of reimbursement for new diagnostic technology is often an obstacle to clinical interventions (priority A – near term)
Tumor-based NGS testing, liquid biopsies, and panels of tests for multiple biomarkers all face intense scrutiny from payers regarding efficacy and cost effectiveness. As more therapies become available, diagnostics that prove effective in determining which patients are most likely to benefit from them will gain more reimbursement. Concerted cross-silo industry effort is required to accelerate this process.

Undetermined impact of new healthcare payment models alters reimbursement (priority B – longer term)
In the USA, innovations such as Accountable Care Organizations (ACOs) versus historical fee-for-service payment mechanisms pose a significant challenge to the healthcare system. Capping reimbursement to providers would dramatically change reimbursement decisions and guidelines. Thus, payers may not be the only decision-making stakeholder in the reimbursement process.

Lack of transparency for the quality and cost of healthcare options and decisions (priority B – longer term)
Patients are being asked to assume much greater roles in selecting and paying for diagnostics and therapies for their medical conditions, but the industry is unable to offer the proper tools to allow them to make informed decisions. The solution will eventually be tools that indicate the pros and cons of therapeutic options along with measures of quality and cost of care by prospective providers.

Regulatory

Mismatch of regulatory approval processes with pace of diagnostic and therapeutic innovation (priority B – longer term)
Regulators are struggling to keep pace with the rapid development of, and clinical trials for, a vast array of new diagnostic and therapeutic options, including companion and/or complementary testing.

Guidelines and education

Clinical guidelines are inconsistent, often out of touch with the latest tests and therapies and not backed by hard evidence (priority B – medium term)

Cancer centres of excellence, like Rutgers, are leading the charge in clinical practice, but guidelines and education will be critical in reaching all provider organisations and instilling consistency driven by verifiable and replicable health outcomes.

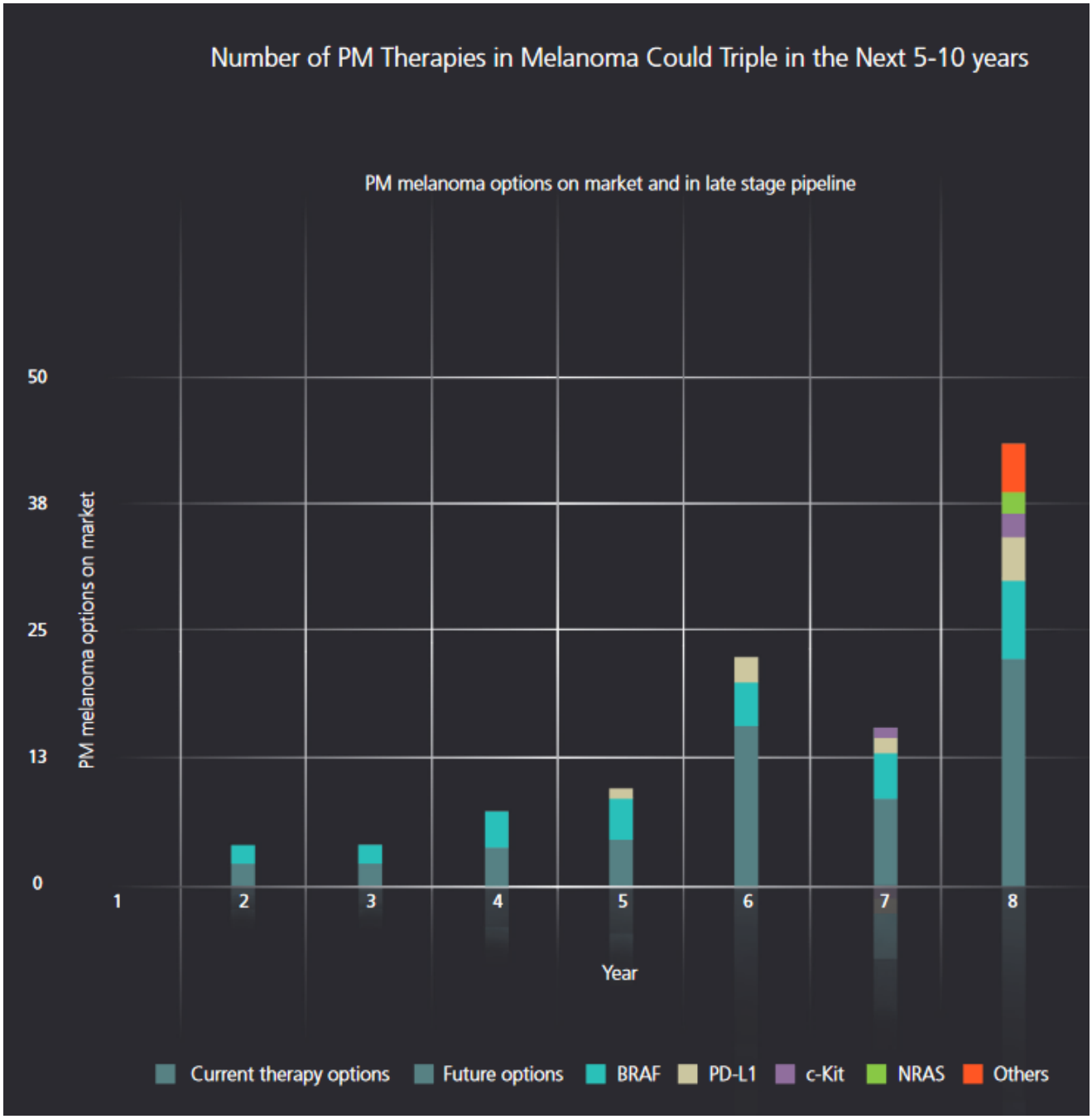


Figure 2. Therapies in the late stage pipeline are linked to BRAF status, but also to PD-L1 expression, NRAS, c-Kit and other biomarkers

Continuing education and public communications on melanoma causes (priority A – near term)
Melanoma is increasing in younger people but some therapies are unsuitable for younger age groups. For example, young women with metastatic melanoma may not be good candidates for immunotherapy if it could also damage reproductive organs. Similar to breast cancer awareness, much greater public education and awareness will help drive prevention, as well as earlier diagnosis and treatment.

Identifying the benefits
At the third workshop, due to take place before the end of 2017, collaborators will be challenged with valuing each of these potential changes and identifying not only the benefit across all silos, but also the benefits within each silo. The workshops and collaboration have confirmed that most barriers can be identified and, for many of the key ones, solutions are nearer at hand than previously anticipated. It is the incentive to change which is missing.

Broadly, it is assumed these changes will involve accelerated disease interventions for both diagnostics and therapies; enhanced clinical investigation; faster regulatory payer input, review and approval, including reimbursement; improved education of providers and patients along with better access by patients; and reduced duplication between healthcare silos. By articulating the financial and clinical value which the change will unlock it is intended to enable a better dialogue between the silos and the articulation of different incentives and collaborative agreements.

With many of the components of radical disease level impact already available, and with the number of precision medicine therapies in melanoma likely to triple in the next five to ten years, patients deserve access to innovative treatments that can significantly improve their health outcome. This melanoma model, and the ensuing valuation framework, should provide each healthcare silo with a sound economic argument for utilising precision medicine. As Jeff Waldron, Executive Director of the PM Connective says, on this basis “it would be hard for an individual silo to say no”.

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Realizing the value of precision medicine: Today

Peter Keeling and Jeff Waldron of Diaceutics and The PM Connective discuss their mission to answer the complex question of how to advance precision medicine.

For eight years, a group of 200 healthcare experts from six different stakeholder groups set aside their competitive agendas to search for an answer to the complex question: how can we advance precision medicine? These biannual meetings, sponsored by Diaceutics, were designed to bring together multiple stakeholders in a spirit of mutual investigation and collaboration.

What became increasingly apparent to a core section of this group was that a possible solution may lie outside the current focus on how precision medicine could transform people's lives in the future through anticipated pipeline technologies and innovations, and lobbying for access to these high-cost therapies. They reasoned that if the existing precision medicine toolbox could be re-managed, it could be possible to unlock the value of this technology now, rather than five or ten years down the line, producing better outcomes for patients and an economic win-win for all stakeholders. Two years on and this expanded group, known as the PM Connective, is tantalisingly close to proving it. By mid- to end-2017, the Connective expects to have a personalised valuation model that will demonstrate how, by moving the management of a condition higher up the treatment pathway – from the expense of late-stage disease to early stage treatment – it is possible to better share the value of precision medicine across stakeholders. And by 2020 it hopes to publish its final paper explaining the learnings, how the framework can be deployed, and the value it can bring across not just melanoma but other diseases where the precision medicine promise remains fragmented.

Diagnostics are healthcare's orphans At the heart of this ambitious project is the understanding that diagnostics are currently 'orphans' in precision medicine, underutilised and requiring deep pockets to drive adoption. To date, this poorly understood business model dynamic is one of the drags of the precision medicine landscape. Analysis by the Connective reveals that payers are slow to adopt diagnostics. Indeed, without a major pharmaceutical sponsor it could be four or five years before just 25 per cent of US doctors are using the test in the way it was originally designed. "Diagnostics are the poor relation," states Peter Keeling, CEO of Diaceutics, which founded and sponsors the PM Connective. "Patient journeys don't start with new drugs, they start with diagnostics, but the dilemmas associated with diagnostic issues, such as a patient having to deal with a lifelong disease or terminal illness diagnosis, or the need for patient counselling, means physicians are often hesitant to adopt a new diagnostic without clear guidance on its utility."

The same reticence is true of US payers who, besides the pharmaceutical industry, form the other major industrial player with the resources to accelerate the uptake of precision medicine. While there have been payer-led initiatives, such as United Healthcare's $5 billion investment in genetic testing for its patients, or Aetna's appointment of a centralised precision medicine specialist, the sector has been slow to take up the technology without data-driven evidence.

Metastatic melanoma model

The PM Connective aims to make that evidence tangible to payers by initially focusing its valuation model at the disease specific level. It chose to start building the model around metastatic melanoma – a cancer with unmet patient needs, but highly curable if treated early. The disease also has the right combination of both new drugs and new diagnostics near or on the market that are underutilised, and a pressing need for higher levels of education on the clinical and economic value of precision medicine in melanoma across both the patient and primary and secondary care settings.

As one of our key collaborators, Dr. Howard Kaufman from the Rutgers Cancer Institute, explained “melanoma has turned out to be an interesting disease as it exemplifies many of the key issues facing oncology today. It has challenging disease scenarios, is clearly a paradigm for both precision medicine and immunotherapy, and is confronting the growing need for a combination of prognostic and predictive elements to better stratify patients for primary and adjuvant therapies.” Thus, our collaboration group is examining prognostic tools that address the risk characterisation of who is more or less likely to relapse, as well as predictive assays that may help tell if a patient is likely to respond to a specific therapy or not. Integration of both technologies and expertise is extremely difficult, but offers the most potential for improved outcomes.

While work is currently underway on valuing specific interventions developed by the Connective, results from modelling historical costs are encouraging.

The Health Economics data suggests that in contrast to current practices, patient management at stages 0-1 of the disease delivers the greatest patient and economic impact. For example, investment in development and diffusion of improved diagnostics could identify 46 per cent of patients at stage zero of the disease (versus base of 23 per cent), reducing second line surgery by 72 per cent for stage III and above, and lowering the overall cost of melanoma treatment by more than $1 billion per year.

There are also promising indicators on an economic level, with suggestions, for example, that while per patient management for stages 0-1 of the disease could increase by 10 per cent, surveillance costs could reduce by up to 20 per cent through access to improved patient self-monitoring technology.

These figures are merely representative of the types of savings that could be possible, but early evaluation of the Connective’s melanoma model suggests substantial improvements in health outcomes and lower overall costs are likely.

Building a different bridge

“As an industry we’ve lost our way in the value discussions about precision medicine,” says Keeling. “We’ve become confused by mixed signals and mixed agendas. When you get the sequence correct – new diagnostics, new treatments, new levels of education – managed and integrated, it’s possible to unlock a more balanced value that can be shared among stakeholders. It’s like trying to build a bridge with ten Lego bricks but finding it doesn’t quite

meet in the middle. We think again and use the Lego in a different way, and we have a working bridge."

Indeed, this 'different bridge' would redistribute the value of precision medicine to the various stakeholders, or 'silos', of healthcare. For example, a simple shift of 3 per cent of pharma's revenue could be redistributed to diagnostic and laboratory companies to incentivise more timely testing.

Jeff Waldron, Executive Director of the PM Connective, acknowledges: "Evaluation of the model is complicated because in order to reduce healthcare costs someone is going to get less revenue. So we have to quantify how the precision medicine interventions we've identified will benefit each stakeholder, for example, by better positioning of diagnostics on the treatment pathway, ensuring greater uptake of early drug therapies, and reducing payer costs and patient co-pays, as earlier stage treatments lower spend on more costly end-of-life treatments. If we prove our first-line medicine approach in melanoma greatly reduces healthcare costs and improves patient outcomes it's hard for stakeholders not to buy into this."

Importantly, the true value of this initiative is that while melanoma was an obvious disease to prove the Connective's hypothesis, the process is not disease specific. "I think the underlying value of the Connective isn't what we're doing in melanoma, it's to road test a process that can be redeployed in other disease areas," says Keeling. The Connective is already looking at early onset asthma as its next disease target.

Disconnected stakeholders

Until now, stakeholders in personalised medicine have been disconnected, working in their own silos, so no one organisation or stakeholder has governance over the entire precision medicine toolbox. This results in underutilised therapies and diagnostics, and patchy education on how to drive value from these tools. By taking on the mantle of a single organisation that integrates the views of each of the 12 healthcare stakeholders – drawn from the direct patient pathway, R&D, and funding and regulation – the PM Connective has effectively ensured the disease model should meet each of the stakeholders' individual needs and expectations.

Operating as a not-for-profit organisation, the PM Connective has brought together up to 160 key representatives from within these healthcare silos to establish the hurdles that encumber each stakeholder in implementing precision medicine, and to pinpoint the solutions. They include Drs. Howard Kaufman, Shridar Ganesan and Janice Mehnert (Rutgers Cancer Institute of New Jersey), Suzie Chen (Rutgers Pharmacy School), Javier Leaniz (Novartis), Erika Hedden (Merck), Ralph Riley (Janssen Diagnostics), Paul Langley (University of Minnesota and Maimon Research), Gil L'Italien (Alexion and Yale Medical School), Eloise Aita (Diaceutics), Gregg Mayer (BioCore Strategies), Mark Trusheim (MIT Sloan School), and Jerry Conway (Foundation Medicine).

Their proposed solutions are currently being defined, examined and processed through the valuation model to quantify and prioritise interventions for implementation, so the

Connective's health economists and advisor groups can integrate these components into an economic value message.

"We've travelled a long journey and there is a tantalising glimpse that suggests our original hypothesis of utilising a better architecture of existing diagnostics treatments and education can really unlock the financial and value promise of precision medicine," says Keeling. "If we achieve this, and we believe we can, there will be multiple winners along the way towards transformative patient care."

Realising the benefits

For these benefits to fully play out, however, the PM Connective needs to attract more collaborators, in particular among patient advocates – who can help educate patients about the value of early melanoma diagnosis and treatment – and the pharmaceutical industry. To date, the Connective's proof of concept stage has been funded by Diaceutics, and 'in kind' by Rutgers Cancer Institute, which donated workshop facilities. However, outside financial sponsorship is required to move to the next stage.

Waldron says: "Everyone I talk to is genuinely enthusiastic and interested in the PM Connective. Until now, some experts have viewed it as an idealistic goal or mission, which of course it is, but the collaborative model for melanoma is now starting to show real promise, and there are benefits to being in the collective network, not least connecting with peers in all silos of the healthcare system to improve organisational linkages and understanding of other perspectives."

Many CEOs and R&D heads now list precision medicine as a pillar of growth for their business. The deliverables for the pharmaceutical firms that engage with the Connective include:

- Motivation to find ways to advance therapeutic assets
- Help with finding diagnostic partners
- Reimbursement considerations through the Connective's collaboration with payers
- Possible access to patient aggregated data and educational opportunities through its network of Patient Support Groups
- PM Connective, cancer centres of excellence, and clinician/investigator collaborators may offer outside expertise to validate and confirm findings and possibly aid clinical trial participation.

"I think we've suffered from a series of headlines about the hundred dollar genome or new technology that will revolutionise, for example, Alzheimer's disease," says Keeling. "Those of us close to it are witness to the fact that those technologies, though brilliant, often sit in the margins for years. What makes the work we're doing important is that we are trying to make it accountable now."

With practical and financial support from the industry and other stakeholders, a new precision medicine model and valuation framework that will not just lower healthcare costs but provide better clinical outcomes for patients is indeed tantalisingly close to being

realised. “Going forward, the big challenge is to stay focused and keep our one simple agenda,” says Keeling. “That’s what makes us unique”.

Interested parties and potential supporters can contact Jeff Waldron at JR.Waldron@PMConnective.org

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Towards a balanced value business model for personalized medicine: An outlook

Novel targeted drugs, mainly in oncology, have commanded substantial price premiums in the recent past. Consequently, the attention of pharmaceutical companies has shifted away from the traditional low-price and high-volume blockbuster business model to drugs that command high, and sometimes extremely high, prices in limited markets defined by targeted patient populations. This model may have already passed its zenith, as the impact of more and more high-priced drugs coming to market substantially increases their combined burden on payers and public health finances. This article by Christof Koelsch, Joanna Przewrocka and Peter Keeling, Diaceutics, introduces a new 'balanced value' business model for personalized medicine, leveraging the emerging opportunities to reduce drug development cost and time for targeted therapies. This model allows pharmaceutical companies to charge prices for targeted therapy below the likely future thresholds for payers' willingness to pay, at the same time preserving attractive margins for the drug developers.

Background: a new balanced value personalized medicine model

The traditional 'one size fits all' (OSFA) blockbuster model prevalent throughout the 1980s and 1990s was built on the principle of selling large volumes of relatively low priced drugs. It was developed with the need to spend vast amounts of money not only on clinical development, but also on the massive sales push required to achieve competitive market shares. Compare this to the personalized medicine (PM) model illustrated by the launches of several targeted drugs over the last 15 years, mainly in oncology and often in the form of a biologic. This model appears to have signified a paradigm shift towards the exact opposite of the old blockbuster model and towards the model applied to orphan drugs: pharmaceutical (Rx) companies' revenues and profits were now dependent primarily on achieving premium prices (i.e., drug prices in the several thousand dollar per unit or per treatment cycle range; even more expensive drugs, priced at several tens of thousands per unit or per treatment cycle, are sometimes referred to as super premium-priced drugs), as these targeted drugs were often indicated for smaller, much more precisely defined patient populations.

Recent developments, however, indicate both a substantial medium-term threat to this newfound model and a potential solution towards yet another model quite probably more likely to be sustainable in the longer run. Novel biologics in oncology could be priced at anything up to a hundred thousand US$ per treatment cycle, (e.g., US$88,000 per year of treatment with Avastin®, US$93,000 for a course of treatment with Provenge® [1], or approximately US$17,000 for a month treatment with Erbitux® [2]), and still gain reimbursement in key markets, at least in part owing to their strong scientific and clinical rationale. Other recent launches, however, even in oncology, have faced much stiffer opposition from payers on both sides of the Atlantic, compare the recent noncoverage decisions by the UK National Health Service for the breast cancer drug Halaven® (eribulin), priced at almost GB£4000 per month [101], or for Nexavar® (sorafenib) in hepatocellular carcinoma (liver cancer), priced at GB£27,000 per treatment cycle [102], or, in the US, the limited Medicare coverage of non-Hodgkin's lymphoma drugs Bexxar® and Zevalin®. As

more and more high priced targeted medicines are launched in a broadening range of indications, payers and governments are becoming more concerned about the substantial burden such a shift towards multiple high priced drugs will impose on healthcare systems. One predictable response to such an assault on public funds will be even tighter scrutiny of access and reimbursement decisions. The focus on value for money considerations on one hand will be weighed against the coordinated, cost-effective management of new drug reimbursement approvals in the context of overall healthcare budget management on the other. In short: having a novel targeted therapy in the starting block is unlikely to be for much longer a de facto license to apply premium pricing to ensure return on investment (ROI). It is our view that PM's ability to guarantee highly profit - able business for Rx industry by balancing the declining volumes of the new drug generation by far higher unit prices may have already passed its zenith.

However, there may be a new PM business model on the horizon, announced by the approval and launch of two novel cancer drugs within the same month in August 2011: Roche's Zelboraf® and Pfizer's Xalkori®.

Both drugs still use the orphan drug model of low volume at premium price; however, their particular value to their respective owners, Pfizer and Roche, as well as to the industry as a whole may be found elsewhere. Xalkori and Zeboraf are probably the first drugs launched that appear to demonstrate that another, as yet unfulfilled promise of PM can indeed be achieved, that of reducing development time and cost through smart targeting.

In this article, we will explore how the example set by these two drugs could provide a stronger incentive to Rx companies to adopt a new, more sustainable business model to make PM a valuable investment for all stakeholders involved, a model which we call 'balanced value' PM. Why balanced value PM? Because we believe the time has come for a 'new deal' in Rx development and commercialization to ensure a balanced approach to creating value for all the main stakeholders involved: Pharmaceutical companies, who bear the cost and risk of novel drug discovery and development; diagnostic companies, whose testing products and services will increasingly play the role of crucial access gatekeepers, as PM moves to center stage in more therapy areas; payers, who inevitably have to manage expenses and ensure they and their insured members receive convincing clinical value in return for the financial investments they make; physicians, who increasingly move away from the focused role of clinical decision maker towards directly or indirectly managing often tight treatment budgets; and, above all, the patient, who expects optimal, individualized treatment at affordable prices.

Evolution of the Rx business model in the era of PM

Drivers of drug revenue

The complex financial relationship between PM drugs and their ROI has already been described in detail in scientific and business literature. In an article by Roth et al. in 2010, the authors demonstrate that multiple microeconomic drivers need to be optimized to ensure adequate ROI for any targeted therapy [3]. Vernon et al. in their 2006 Economic and Developmental Considerations for Pharmacogenomic Technology, summarize:

> "The product development and marketing decisions of pharmaceutical companies are myriad and complex. The innovation of PG (Pharmacogenomics) has added another level of complexity to this process, considering the dimensions of tests that could be developed, the drugs for which they could apply, and the reactions of competitors, payers, patients, physicians, regulators and other involved parties" [4] .

In order to fully understand the promise of the new balanced value PM model we propose, let us take a few steps back and briefly recap some of the main drivers of financial value for any Rx, OSFA or PM asset.

On the cost side, critical elements of the equation are the cost of development, which is primarily driven by the complexity of clinical development (trial duration, cohort size and so on) and the cost of commercialization. These commercialization costs include not only advertising, sales force investment and other marketing and sales costs to achieve the required share of voice in competitive Rx markets, but also the supporting investment in generating relevant publications, providing input to healthcare policy, and so on, for any particular asset. While we focus our considerations in this article on these two factors, it should be noted that there are also important indirect factors in this equation, for example, the cost of capital and, if applied to a portfolio of assets rather than a single asset, the allocated cost of development failure – successfully launched drugs have to recoup the R&D costs of those that never made it to market. We have deliberately excluded the cost of manufacturing the physical drug from our comparison. We believe that the pursuit of a targeted PM strategy versus a nontargeted OSFA strategy for one particular drug will not usually have any noteworthy impact on drug manufacturing costs, if the particular drug formulation and presentation remain unchanged, and if for this comparison we disregard the impact of different size scale effects in manufacturing.

On the revenue side, the price per unit of drug sold is quite obviously a critical value driver, as well as the number of units sold in a given year, the time it takes to achieve its peak sales, its competitive market share and the number of years a drug is on the market. More specifically, the number of years during which a drug is on the market and benefits from patent exclusivity that protects it from generic competition and thereby allows it to uphold an attractive unit price. This last factor is indeed a direct result of the number of years required to develop the drug, as patent protection will be sought early in the development cycle but is limited to 20 years overall, at least in Europe and the US, hence, by and large, the faster the drug reaches the market, the longer it will enjoy exclusivity and high prices.

Critical levers to drive drug ROI compared: yesterday's OSFA versus today's PM

In the traditional blockbuster model, development time appeared to be very much a given, and reduction of development cost could really be influenced through increasing levels of use of contract research organizations and operational efficiency measures only. Prices were negotiable in principle, though they needed to remain within a rather narrow corridor appropriate for a mass market product. Investment in drug commercialization, while technically at the discretion of the asset's owner, was effectively a non-negotiable item, as it increasingly became the most, if not the only effective means of pushing up the decisive factor, the number of Rx units sold per year. Substantial investment in drug marketing and

sales was no longer a choice; the prisoner's dilemma faced in a highly competitive mass market had turned sales and marketing spending into a non-negotiable item, with the effect that the cost of commercialization spiraled upwards with every major launch in the most contested therapy areas.

The traditional OSFA blockbuster model and the current PM model both agree that the period of actual exclusivity in the marketplace is usually limited to 5–11 years, as the manufacturer typically applies for a patent at some point during the clinical trials, with full development taking anywhere from 9 to 15 years [5,103]. This complexity of development shared by both models also means the cost of development will be high – recent estimates suggest average costs of around US$1.3 billion per drug [104], if you include allocated cost of failure in a given portfolio.

But there are also fundamental differences between the traditional OSFA blockbuster model and the current PM model. While the traditional OSFA business model is built on high volumes of drug units sold at relatively low price (e.g., statins), a typical current PM drug will be sold at high to very high unit price, but in limited volumes only (e.g., Glivec®, which is indicated for the treatment of acute myeloid leukemia with a target market of some 30,000 patients in the USA). Hence, in the current PM model, the one factor that becomes the decisive lever to pull has shifted from driving prescription volume to driving up the unit price of the drug. Consequently, Rx companies have reallocated their resource and time investment from sales forces to market access teams, and the standard-setting institutions in the payer world. The National Institute for Clinical Excellence (NICE) and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) in Europe and the leading Health Maintenance Organizations (HMOs) in the USA, and the public benchmarks they set have become the arbiter of value for novel drugs.

Premium pricing appears well justified at first glance for many of these targeted therapies as they conceptually guarantee improved outcomes, because they are given to patients only who have a very high probability of being responders, that is, those who will indeed benefit based on genetic, proteomic or other factors from taking these drugs. Regardless of the fact that the therapeutic benefit of many of these novel therapies may still be rather limited despite their targeting, this brave new world of targeted therapies is threatened, ironically, by the very success of this model. Globally, payers are increasingly conscious of the total budget impact of high-priced targeted therapies. If there are a few expensive drugs, for a few patients in selected indications only, they can manage; if there is a premium priced treatment option (or even common combinations thereof) in pretty much every oncology indication, it starts to hurt and restrictions will inevitably follow. And oncology is only the start. How will payers cope if – or rather when – similarly expensive targeted drugs become available for diabetes or Alzheimer's disease?

With the prospect of a wave of novel targeted drugs entering markets in the next decade, we wonder if the end is already in sight for this much desired new treatment paradigm, as we will not be able to afford it much longer. Or can we find a smart way out of this conundrum?

How can a shift towards a balanced value PM model help secure ROI for Rx companies?

As many as 15 years ago, when the first 'genomics bubble' of the late 1990s and early 2000s was building, industry experts and analysts experimented with the idea that the real value of the then novel PM paradigm for Rx industry would be found in its ability to significantly reduce the time and cost required to develop a new PM drug and achieve regulatory approval. A report published in 2001 by consulting firm The Boston Consulting Group claimed:

> "The staggering investment needed to develop a drug – US$880 million and 15 years is the pregenomics average - could be reduced by as much as US$300 million and 2 years by applying genomics technologies" [105].

This claim was regularly renewed by industry experts, for example, Aspinall *et al*. in their 2007 Harvard Business Review article, suggesting that:

> "Focusing clinical trials on targeted subpopulations would slash their size, duration and cost" [6].

Trusheim *et al*. in 2011, stressed the importance of a supportive regulatory framework for PM drugs and claimed that, conversely:

> "Future regulatory guidance requiring a demonstration of safety in biomarker - negative as well as biomarker-positive subpopulations would further reduce potential savings in cost and time and might increase cost and duration of trials in comparison to all-comers approach" [7].

Roth *et al*. summarized:

> "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 shift the sales and adoption curve of such therapies enabling faster ROI " [3].

While this concept is highly convincing in theory, evidence for this working in real world development and commercialization of drug/test combinations has until very recently been sorely lacking, and the absence of any 'accelerated launch' success stories did most certainly con - tribute to the growing disappointment across the industry and investor community that eventually led to the burst of the first 'PM bubble' during the first half of the 2000s. As recently as 2009, Novartis's then CEO Dan Vasella struggled with the opportunity of PM:

> "(Vasella) accepts that linking individual genetics with specific therapies is the big challenge for his industry today, but he is still looking for a suitable business model " [106] .

It appears that some of the evidence that Vasella was looking for has now arrived: enter Xalkori and Zelboraf, both approved in August 2011. Zelboraf (vemurafenib) is a novel kinase inhibitor, indicated for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation [107]. Zelboraf is manufactured by Genentech, a subsidiary of Roche, and its companion diagnostic – cobas 4800 BRAF V600 Mutation Test – is manufactured and marketed by Roche Diagnostics [108]. In other words: both drug and test were developed by Roche, using their two healthcare arms in therapeutics and diagnostics. It is the first and currently only personalized drug for the population of patients with BRAF V600E mutation-positive metastatic melanoma [109].

The drug was approved for the US market on 17 August 2011. The US FDA gave Zelboraf the green light based on the safety and effectiveness study results established in a single international Phase III trial of 675 patients. The trial was designed to measure overall survival, the amount of time a patient lives after the treatment. For patients who were treated with Zelboraf the median overall survival has not been reached, while the median survival for those who received dacarbazine was 8 months [108]. Because of the convincing early findings with this drug, the FDA did not require Roche to replicate them in a following trial [110].

When the drug obtained FDA approval in 2011, industry observers were impressed not only by the drug's ability to deliver the promised clinical results, but at least equally by the speed with which Roche had managed to carry the drug through the clinical development phases. Altogether, Zelboraf reached the market within just over 4.5 years [111], including the time spent on regulatory review, a mere 3.5 months, from submission to approval [110].

Xalkori (crizotinib) is another kinase inhibitor, indicated for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC), which is caused by a defect in the ALK gene [112]. It is the first and only therapy targeting this subpopulation of patients, and was the first new drug to enter the US market for lung cancer in more than 6 years [113]. Xalkori was developed by Pfizer, and approved on 26 August 2011, together with its companion diagnostics – Abbott Molecular's Vysis ALK Break Apart FISH Probe Kit – which identifies the presence of the ALK fusion gene in NSCLC patients [114].

Xalkori's approval was based on results established in two multicenter, single-arm studies enrolling a total of 255 patients with late stage ALK-positive NSCLC. The percentage of patients whose tumors responded to treatment has been measured, and the results revealed that amongst the Xalkori-treated patients there were three complete responses (1%). Treated patients had 50 and 61% objective response rate in each study, respectively [113].

There was no data available demonstrating improvement in patient reported outcomes or survival with Xalkori at that time; however, data from the Phase II trial showed that the drug had an effect on an end point that is reasonably likely to translate to a clinical benefit to patients. Only after the FDA approval a Phase III clinical trial was conducted, as part of

Pfizer's post-marketing commitments, to evaluate Xalkori in confirmatory, randomized, open-label trials. On 19 June 2012, Pfizer announced that this trial met its primary end point, demonstrating that Xalkori significantly improved progression-free survival when compared with pemetrexed or docetaxel [115].

Pfizer managed to push Xalkori through the clinical development within 7 years from the lead discovery, and 5 years after the start of PhaseI trials, having shown a very high response rate already in the initial trials. The FDA's accelerated review efforts contributed to this success story too, by reaching a decision for approval in a single review cycle, less than 5 months after Pfizer's submission [110].

What lessons can be learned from Xalkori and Zelboraf?

So what can the industry learn from these two launches? How can emulating their respective development and commercialization strategies help establish a novel approach to generating healthy profit margins through PM drugs, even in the face of increasing price consciousness by payers?

Let's assume a future scenario in which external pressures put a more restrictive cap on reimbursable prices for targeted therapies, maybe a range somewhere in between current high-price targeted therapies and the low-priced mass market drugs of recent years. Let us further assume that these targeted therapies will, by the nature of their targeting, be indicated for tightly defined subpopulations only, so not be commanding high volumes of prescriptions. How could such a therapy possibly attract the strategic focus and investment from a major Rx company?

We believe that three levers can be pulled to turn these therapies into successful, highly profitable assets, and we furthermore believe that evidence for successfully implementing such strategies already exists.

Critical lever 1: development time

The first lever to pull is to use targeting to reduce development time, thus expanding the length of patent protection for the drug on the market and reducing development cost at the same time.

What was the secret to Pfizer's successful reduction in development time for Xalkori? Pfizer's Xalkori is a new therapy in an already crowded NSCLC market with efficacy only for a small (5–7%) percentage of patients who are ALK-positive as detected by an FDA-approved test. Aligning with the FDA's latest guidance on targeted therapies and companion diagnostics, the company worked closely with the FDA and with its partner, Abbott Molecular, during the clinical studies, to ensure the simultaneous review and approval of Xalkori along with a diagnostic test to identify presence of the ALK fusion gene. The simultaneous approval of Xalkori in parallel with Abbott Molecular's ALK FISH test marks the first time a Pfizer oncology drug or indeed any lung cancer medication was developed and approved in parallel with a diagnostic test.

From a diagnostic point of view, we understand that critical success factors in the approach Pfizer took were: first, a properly integrated drug/test development approach from an early stage onwards. Roth *et al*. found in their study published in 2010 that:

> "…additional net present value could be realized, even when diagnostic development was initiated late in the development process … but that the greatest gains were realized the earlier the planning for companion diagnostics was incorporated into the development lifecycle" [3].

This may not always be possible, as the pursuit of a targeted approach for a drug does of course require a good indication of where to target, that is, the discovery of one or more biomarkers that provide the opportunity for such targeting. Not every asset will benefit from such a discovery early in its development cycle. But once such candidate biomarkers are identified, full alignment of therapy and diagnostic development with a view to commercializing a test, or tests, alongside the drug are essential to maximize the opportunity. Such an integrated drug/test development approach pursued by Pfizer did not depend on, but will have benefited considerably from the early yet well-considered selection of a lead diagnostic partner. That lead diagnostic partner was not only able to provide biomarker services to support the drug's clinical development but could also seamlessly move on to the development of a commercially viable test kit to be reviewed and approved by the FDA alongside the drug asset it supports. Second, Pfizer's early partnership with Abbott did not only ensure the availability of a viable commercial option for ALK testing across the key markets for Xalkori from the first day of drug's use in routine clinical practice, it also helped streamline the development process by obviating the need for a complex technology transfer from a diagnostic discovery boutique to a larger commercial diagnostic partner.

Reduction in development time directly influences two important drivers of a drug's lifetime value: the cost of development, which we will discuss more broadly in the next section, and the time during which the drug can formally or effectively enjoy market exclusivity protected from 'me too' competitors. DiMasi and Faden illustrated in 2011 that over recent decades, the period of exclusivity for drugs dropped from an average of approximately 10 years in the 1970s to somewhere under 3 years in the early 2000s [8]. In the same study, the authors showed that while during the 1980s only approximately 40% of novel drugs were closely followed by a direct competitor, the time of the first-in-class approval had already reached Phase II. That number increased to 75% in the early 2000s; in other words: by 2003, three-quarters of novel drugs would be able to expect a direct, me-too competitor being launched within a very few years after their own approval, fighting the first-to-market incumbent for market share. Consequently, reducing time to market while maintaining the quality of clinical development has been a major goal for every Rx company in recent years. In a 2005 publication, authors from the London School of Economics estimated the combined direct and indirect value of 1 year's reduction in development time to be anywhere between US$250 million and US$500 million, a number determined by calculating scenarios for a nontargeted blockbuster drug following the traditional OSFA model (Prozac [fluoxetine], manufactured and sold by Eli Lilly) [116]. If we apply only the lower end figure of the London School of Economics estimate to the time gained versus the therapeutic area average as defined by Xalkori and Zelboraf, we can safely assume that the reduction in development

time alone for these two assets and the resulting extension of their market exclusivity should gain their respective owners several hundred million US$ in revenue. Furthermore, since the net present value of early revenues is substantially greater than revenues 6–8 years post launch, the impact of added revenues emanating from 1–2 years of early launch can have profound impact on a Rx company's investment model.

Applying this concept to other novel targeted assets will of course require a series of adjustments, taking into account the specific situation of each asset – disease area, development stage, clinical and competitive context and so on, for the drug, but also the development stage and level of validation of the biomarker, diagnostic environment in the disease area and various other factors on the diagnostic side. However, we believe that there exists a real opportunity, just recently validated, to create substantial value for an individual asset as well as on a portfolio basis, by reducing time to market through the pursuit of a targeting strategy.

However, the Rx industry alone will be unable to successfully implement such strategies, as regulators will have to accept that novel targeted therapies may not be appropriately reviewed and approved applying exactly the same criteria and requirements that make the development of nontargeted therapies such a long and winding, and often futile effort. One very important, though certainly not the only question in this context is whether regulators will more consistently move away from the arguably often difficult to rationalize requirement for clinical data in biomarker-negative patient groups where an indication for a novel drug is sought in a biomarker-positive group only. Drug developers will need a reliable and consistent revised regulatory approach that appropriately incentivizes the development of targeted drugs rather than disincentivizing it by requiring the same broad clinical development but offering a much more tightly defined indication in return.

Critical lever 2: development cost

The second lever is development cost, which is a function of a number of different variables.

On an individual asset level, therapeutic area and geographical differences in the clinical program will contribute to higher or lower development costs, as will the number of patients that need to be enrolled to obtain statistically significant and clinically meaningful trial results, the duration of the clinical trials and the complexity of procedures required to obtained critical data. A typical clinical development program in most disease areas will require a few hundred patients in Phase II and more likely several hundred to several thousand in Phase III, with a regulatory submission being made upon completion of PhaseIII. In oncology, it has become more common lately to seek regulatory approval based on Phase II data alone, if such data are sufficiently powerful to demonstrate the clinical benefit of the drug. Patient stratification, in principle, is a means to achieving such statistically powerful results in a relatively small patient population, by focusing the trial entirely on a subset of patients expressing a particular biomarker predictive of their response to the treatment under evaluation. However, such stratification will also mean an indication for the drug in this particular responder population only, once approved, with the consequent need for a companion diagnostic to identify these patients. In the past, many Rx companies have therefore shunned this approach, trading in the opportunity to shorten and derisk their

clinical trial programs for a nontargeted indication for use in the broader disease population, if and when they managed to complete their clinical studies successfully. By contrast, Pfizer, in their clinical program for Xalkori, used a stratified approach from the outset and were able to gain approval with a Phase II trial of 250 patients only. Assuming a rather conservative average cost per patient enrolled for a Phase II or III trial of US$30,000 [117,118], Pfizer's ability to obtain marketing approval based on a stratified trial of 250 patients expressing a particular biomarker alone, as did Pfizer with Xalkori, compared with a typical Phase III size of around 900–1000 patients enrolled at least offers an opportunity to save US$20 million in a single Phase III trial alone. Also, this does not yet take into calculation that Pfizer even managed to obtain approval without any prior Phase III study, nor does it consider that Pfizer's risk of not reaching their primary end points at all would have likely been much higher in an all-comers' design.

On a portfolio level, development cost is indeed above all a function of failure and success. Failure of therapies to demonstrate clinical efficacy in all-comer trials is one of the primary cost burdens on drug company portfolios. The working assumption is that 4 out of 5 therapies will fail in Phase II trials [9], and one out of two will fail in Phase III trials [10], with the cost of failure being allocated to the total portfolio and the need for those assets that succeed to market to recoup the expenditure on failed assets. The ability to identify the responder subsets for both Xalkori and Zelboraf via the respective biomarkers to predict response early in the clinical development process removed significant development risk and meant that the cost of development of these two therapies were not added on to the cost of failure burden of their respective owner's portfolio of assets in development. Again, the state of science may not always make this early start possible, but where such information exists at an early stage, leveraging this knowledge into designing a streamlined development approach can make a substantial difference in development costs.

We accept that the total benefit of this impact becomes evident only when significant numbers of the portfolio under development are targeted therapies. This, however, is not too esoteric a scenario: according to recent research from various sources, Rx pipelines are slated to have a substantial part of all drugs in development by 2018 targeted or otherwise positioned by biomarkers in some way. Research by the Tufts Centre for the Study of Drug Development suggests that 30% of all drugs in late clinical development, 50% of all drugs in early clinical development and as much as 60% of all drugs in preclinical development rely on biomarker data [119]. Going beyond a quantification of those therapies that are already publicly known as being targeted, Diaceutics in their 2011 report 'Pharma Readiness For Personalized Medicine' estimated that up to 46% of assets currently in Phase III development could potentially benefit from a targeted or PM approach [120].

Roche's CEO Severin Schwan suggested a similar trajectory for his company, saying that:

> "In 10 years we would see half of our portfolio to be targeted therapies. And if anything, I would assume in 20 years this percentage is going to increase" [121].

An admittedly simplified 'back of the envelope' calculation comparing a hypothetical Rx portfolio made up of nothing but OSFA assets with one that combines 70% of OSFA and 30% of targeted assets (see Figure 1) indicates that the overall success rate of the mixed

portfolio could be almost double that of the pure OSFA portfolio, if targeting drugs could reduce the failure rate for drugs by 50% in each stage of the development half that of nontargeted drugs.

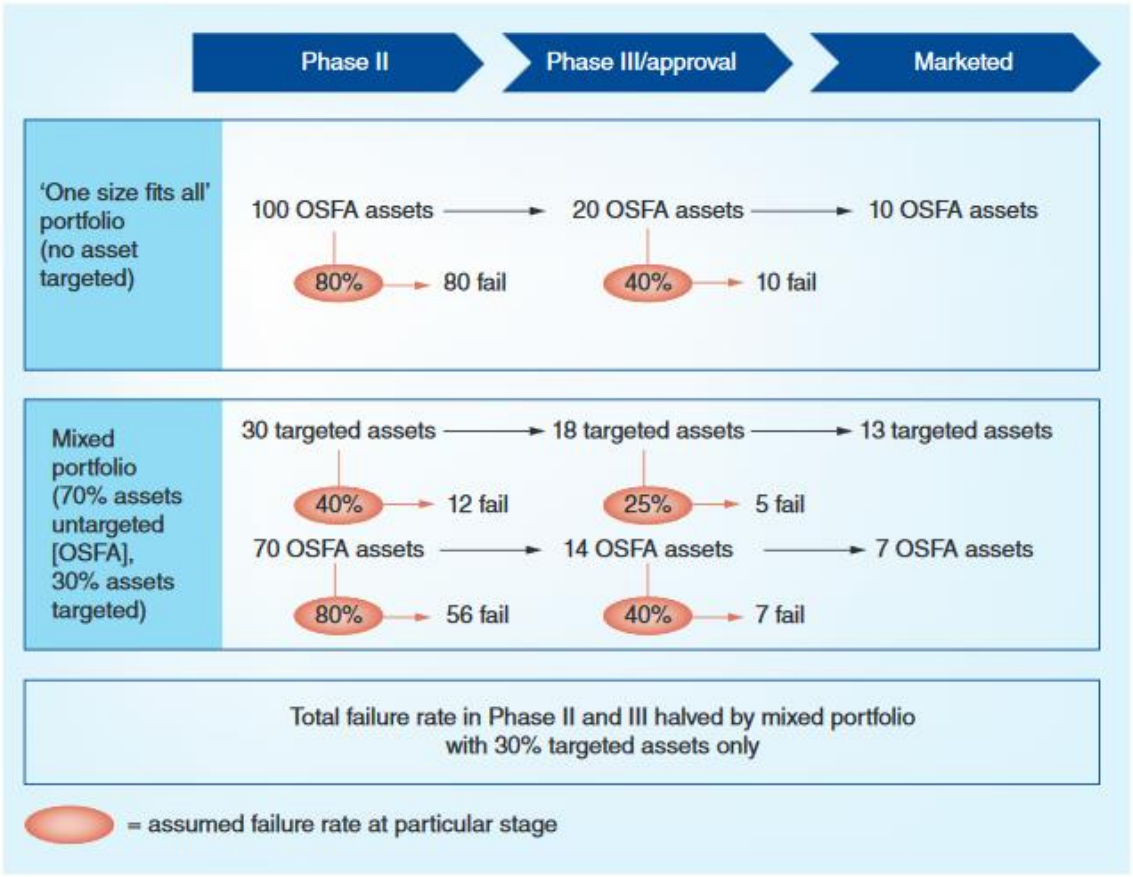

Figure 1. Success rate for a hypothetical 'one size fits all' only portfolio compared with a hypothetical mixed portfolio of one size fits all and personalized medicine assets. OSFA: One size fits all.

This may be an ambitious assumption, however, it illustrates well the conceptual attractiveness of targeting, to derisk and reduce the cost of development not only at an individual drug but at a portfolio level, as, consequently, the allocated cost of other assets' development failures that burdens the fully loaded cost of developing one successful drug could be cut substantially, and possibly be halved in the longer run, assuming other cost drivers in development do not significantly change.

Critical lever 3: drug price

The third lever is drug price. For most goods traded in a free market, the upper limit of pricing such goods is effectively defined by a trade-off between target customers' demand for the goods and their willingness and ability to pay. In the highly regulated markets for prescription medicines, these two factors are often disconnected from each other, as ability and willingness to pay no longer reside with the customers as such, the patients, but with their intermediaries, the payers. Individual payers and public healthcare systems in many

countries have established a variety of sophisticated mechanisms to determine their ability and willingness to pay for particular drugs. They carefully manage access to novel drugs in local markets, drug pricing and reimbursement, either as separate steps or as part of an integrated decision process. Drug price, or rather the acceptable upper limit of a particular drug's price to the payers, is determined by increasingly complex and time-consuming cost–benefit reviews, using ever so slightly different criteria in each market.

While such approaches looking at an individual drugs' cost–benefit ratio, traditionally often measured as cost per quality adjusted life-year or derivatives thereof, are now well established, payers are becoming increasingly aware of and consider the impact of new drug introductions on their overall budget. In recent years, even very expensive drugs could gain reimbursement if only the difference in the clinical benefit they provided (however that was measured) in the eyes of the particular payer matched the price premium charged. However, the impact of such high-priced drugs on total annual healthcare expenses within a closed system, public or private, is moving further into focus, the more premium priced drugs are launched. In other words: payers' primary focus in setting upper price limits for novel therapies has shifted from determining their willingness to pay for the particular individual novel drug, to gauging their ability to afford these novel drugs in the context of the total portfolio of therapeutic interventions they have to cover. Payers have already flagged their reluctance to pay the full price for recent PM launches in oncology. Since up to 40% of experimental drugs in today's pipelines are developed to treat various cancers, substantial pushback from payers against continued premium pricing of such therapies appears almost inevitable. This is particularly true as many current and future therapies will be used in various two- or multi-drug combinations with other similarly high-priced, targeted therapies.

With these dependencies in mind, premium pricing has become a double-edged sword for the Rx industry, where often difficult to predict reimbursement decisions create a considerable new area of business risk: while a premium price tag appears to be the only way for a drug's owner to recoup the hefty investment in the extended clinical development path for that asset – as well as a few others that failed on their way to the market – increasing cost consciousness among payers has significantly narrowed the pricing corridor between the maximum acceptable price for payers and the minimum acceptable price for Rx companies. These cost containment pressures have become a threat to Rx industry and to public healthcare systems alike: should the current drug development and commercialization paradigm continue to hold, patients' access to innovative medicines will become increasingly restricted while many R&D-based Rx companies will find it more and more difficult to remain a profitable business.

However, in the balanced value PM model we propose, a new and different bargain could be struck between manufacturers, payers, regulators and, ultimately, patients: in return for a commitment from Rx companies to offering better targeted and hence ultimately more (cost-effective therapies at more moderate prices, public healthcare systems could offer Rx companies a more efficient development route and faster market access for their targeted therapies. This may sound like a great concept, but how would it work?

Implicit in the patient stratification of PM lies the need to synchronize the availability of testing with the clinical demand for the new drug. The inefficiencies of the diagnostic market

are such that test adoption often runs at a slower pace than that for the heavily marketed treatment. The causes for this disparity are numerous, but the primary culprit is the historic lack of adequate reimbursement for diagnostic tests. Because the diagnostic industry's margins and ROI are so thin, they do not have the cash reserves to market tests in the same way that drugs are marketed, which results in a misalignment between the usual speed of adoption of a drug and that of a test, even if the two are otherwise closely connected. Integrating the price and cost–benefit value of testing and treatment into a single value proposition in access and reimbursement negotiations, in return for parallel reimbursement of the test and treatment, will enable the treatment to have a faster adoption curve in the market, no longer slowed by its diagnostic companion. In this way the pricing negotiation between manufacturers and payers can enable earlier access to therapy since such therapy will be targeted (via the test) to the patient cohort where the greatest economic value for the payer lies.

If we add to such earlier market access enabled by an integrated drug/test cost–benefit assessment the impact of pursuing a PM approach on development time, cost and risk, as considered in the previous sections of this article, the ROI calculation for a particular drug asset could change dramatically. Once a particular asset in development promises to reach the market quickly, requiring a limited number of small to medium size clinical trials, undergoing a favorable cost–benefit assessment in tandem with its companion diagnostic and hence enabling earlier and more quickly increasing revenue streams for its owner, the flexibility for Rx companies to charge a more palatable and competitive price suddenly becomes a much more realistic prospect.

A hypothetical example: comparing the models

How many of the premium and super premium price drugs that were declined broad reimbursement coverage in recent months and years could have managed to pass smoothly through access negotiations had they followed such a balanced value PM model is difficult to determine in hindsight, given the various other influences on such assessments.

But let us nevertheless consider an example of how this might work in the real world. Taking the example of the UK, where NICE is observing a rule of thumb limit of approximately GB£30,000 (approximately US$48,000, using current exchange rates) per quality adjusted lifeyear gained over comparable therapy options as the upper limit for a favorable review [122], a cancer drug priced at GB£60,000 (approximately US$96,000, using current exchange rates) a year would meet with immediate skepticism and concern, and would have to demonstrate a truly stunning incremental clinical benefit not to hit a wall when it comes to a reimbursement decision. The same drug, with the same clinical benefit but priced at a much more modest 6,000 (US$9,600), or an even lower GB£600 (US$960) a year would probably have sailed through the reimbursement negotiations almost under the radar, enabling early sales and broad uptake without delay. Under the present development paradigm, such early sales would probably not outweigh the huge investment in getting this drug approved for use. Consequently, the drug's owner could not expect to make a profit with this asset in line with industry margins, if any at all, and would often be very reluctant to offer anything beyond the usual standard rebates already built in to Rx companies' forecasts and pricing targets. If the drug's owner had the opportunity, though, of halving time and cost

of development, the savings generated by this streamlined development, in combination with earlier sales and faster uptake and a substantially reduced risk of not obtaining broad reimbursement at all in a particular market, might make such a substantial downward adjustment in drug prices a much more reasonable, if not downright attractive, lever to pull.

Now, let's apply these principles and numbers to the three business models we outlined above and compare the balanced value PM approach to a competitive OSFA and the current PM approach, in terms of the achievable ROI.

For this hypothetical and admittedly highly simplified comparison, we will assume that:

- The OSFA will be priced at US$600 per year (equal to somewhat less than US$2 per day), indicated for and used by 10 million patients globally, with 8 years of patent exclusivity, developed at a cost of US$1 billion (fully loaded) and commercialized globally at an additional cost of US$1.5 billion.
- The PM drug following the current low volume, high-cost PM model is priced at US$25,000 per year (equal to approximately US$80 per day), indicated for 500,000 patients globally, developed at the same cost of US$1 billion and enjoying the same period of market exclusivity of 8 years, while commercialization costs may be more moderate, at US$750 million only.
- Finally, the PM drug following the new, balanced value PM model, will be priced at a relatively modest US$5,000 per year (equal to approximately US$16 per day), indicated for and used by 500k patients globally, with 11 years of patent exclusivity, developed at a cost of US$500m (fully loaded; to reach this level of development cost reduction, the asset may have to be part of a portfolio dominated by similar balanced value PM assets, achieving a similarly increased success rate and thereby reducing the allocated cost of failure for other assets in the portfolio) and commercialized at an additional cost of US$750 million.

Applying our 'back of the envelope' ROI calculation as per the equations shown in Figure 2, it becomes apparent that the OSFA and the balanced value PM model end up very close to each other, with the simplified ROI indicator for the OSFA drug being US$19.2 for every US$1 invested, against a surprisingly even somewhat higher ROI indicator of US$22 for every US$1 invested in the balanced value PM asset.

This simplified comparison will of course not work out so nicely for every asset in the Rx industry's pipeline, and for many assets, there may in fact be no choice. After all, the definition of the target population for a PM drug is first and foremost a function of the underlying biology – you cannot simply choose your responders. The biomarkers that help you target your therapy also need to be available and validated prior to entering the final stages of clinical development, in order to allow for a streamlined clinical trial program that mirrors the targeted nature of the drug. Where this is not the case, the cost of development may in fact be higher rather than lower than that for a comparable nontargeted asset, as the collection and assessment of diagnostic markers will incur additional costs while the desired savings from streamlining the clinical trial program are unlikely to fully materialize.

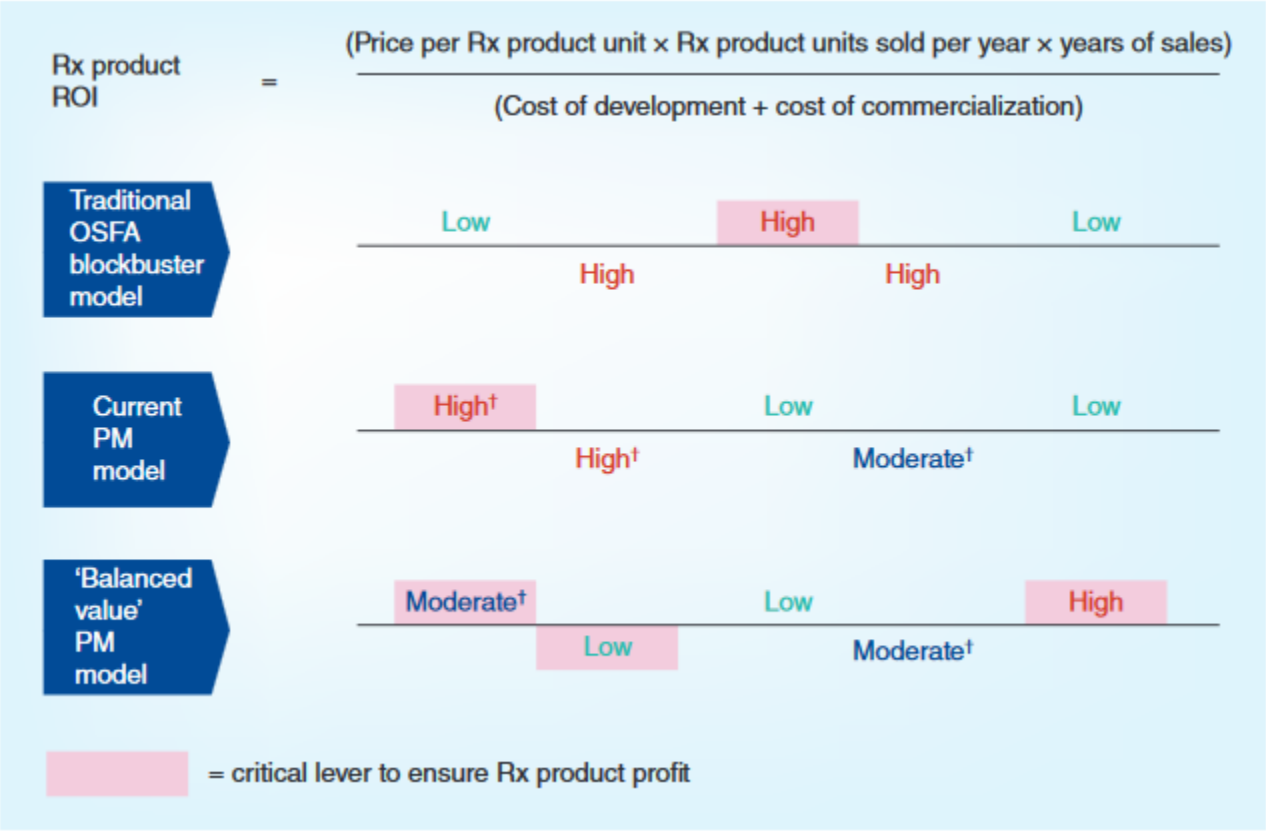

Figure 2. How can shifting to a balanced value PM business model help maintain profitability for pharmaceutical companies? † Included price of Dx/cost of Dx development and commercialization. Dx: Diagnostic; OSFA: One size fits all; PM: Personalized medicine; ROI: Return on investment; Rx: Pharmaceutical.

Furthermore, for any specific example, the achievable price point may be lower, while years of exclusivity may be shorter and costs of development and commercialization higher. Also, the proper calculation of drug ROI and the comparative assessment of ROI for targeted and nontargeted scenarios requires a much more sophisticated consideration of additional drivers and influences than what is possible and appropriate in a conceptual article such as this one, as shown by Roth *et al*. [3].

What this example suggests, nevertheless, is that in order to maintain a healthy business for its owners, not all targeted therapies must inevitably cost a fortune. Super-premium pricing is no longer an inevitable prerequisite of PM.

But why would any Rx company price their drug at a modest US$5000 per year if other PM drugs, maybe even in the same or a very similar indication and with comparable clinical benefits, cost ten-times the price? Well, because such a more moderate price point may, in the future, be the only way to generate any revenues at all. Would you prefer to obtain reimbursement and generate a ROI of 22:1 in a sizeable public healthcare market, or rather be refused reimbursement and generate marginal sales in a very limited private market only? This is of particular concern in a future PM environment where more than just one targeted drug option may be available even for smaller patient subpopulations. The answer

to this question is probably: it depends. It depends on the particular profile of the drug in question, the unmet need and the relative clinical benefit, the particular reimbursement situation in the market, and the number of patients willing to pay for the drug in question. But quite certainly the decision between premium price and moderate price is no longer an obvious one.

We strongly believe that within the foreseeable future, at least in some therapeutic areas, we will indeed see a shift towards a balanced value PM model, balanced in securing the well-deserved ROI for the Rx companies carrying the substantial risk of developing and commercializing such novel targeted therapies while at the same time providing a better deal for patients and payers. PM is not doomed to be yet another nail in the coffin of affordable healthcare.

Implications of the new balanced value PM model for the Rx industry

What does this mean for Rx companies? How can and must the industry prepare for this balanced value PM model?

Mastery of cost–effectiveness research has become a very important capability for Rx companies in recent years, and the demonstration of a favorable relative cost–benefit ratio achievable by a novel targeted drug in a specific patient population can be expected to remain critical to securing a market success for that particular therapy. What, in our view, is changing in the context of a move towards the new balanced value PM model, is the need for a new set of determinants and boundaries that are defined by the need to demonstrate balanced value.

Value based pricing will increasingly require Rx companies to make a very robust case for their asking price, centered on the clinical benefit provided in a particular patient subpopulation but at the same time demonstrating broader value in the context of a tougher competition for healthcare resources across all disease areas and therapeutic interventions. Identifying the optimal price for a novel drug will be just as important and perhaps just as difficult as today, only the parameters will be different in the new balanced value PM model, requiring, above all, a deep understanding of the combined targeted therapy value proposition of the combination of drug and test.

This ability to robustly gauge the value of a drug/test combination, in our view, will quite probably be one of the most distinguishing yet underestimated success factors in the race for Rx leadership over the coming decade. While slowly but increasingly being built up across the industry, such mastery in PM value assessment needs to be applied in the drug development cycle earlier than is currently the norm. Drug developers need to become more conscious of the value they create in offering an integrated disease management solution, to use a term somewhat compromised by dissatisfying earlier attempts. It will be to Rx companies' benefit to look, and analyze, and calculate beyond their historically limited 'drug only' access and reimbursement strategy.

We accept that, beyond the need for a different approach to Health Economics and Pricing, implicit in this new balanced value PM model is a broader reengineering of key aspects of

the Rx development and commercialization model. This will inevitably be context-specific to each individual company's competitive advantages, portfolio, cost of capital and a series of other factors – one reason why we introduce this new model purely as a theoretical construct in this article. Nonetheless, Xalkori and Zelboraf illustrate that some of this reengineering is already underway and being led by exemplary projects where the emphasis has clearly been on early planning, joined up thinking and deeper external ties. However, it is our contention that the applicability of a balanced value PM model can only be determined early on in the lifecycle of a project, suggesting that one of the first questions an asset team need to ask themselves is, 'do we have an opportunity here to fully leverage the power of PM, or are there still compelling reasons for us to rather follow either the OSFA model or the orphan drug pricing model?' From a portfolio point of view, Rx R&D managers should be encouraging this type of analysis and apply it as early as Phase I, while repeating it at each decision point.

Future perspective

Over the past years much has been said about the distortions of the drug industry's revenue and profit model. Through the business model adjustments suggested in this discussion paper, the new balanced value PM model may not only be an attractive approach to maintaining attractive profit margins that, in our view, the Rx industry should be entitled to in a competitive market, but at the same time help to build a more rational and more socially acceptable paradigm for drug access and pricing.

We can envisage a new equilibrium to have started to emerge by 2020 in at least the more advanced of the world's prescription drug markets, in which the new balanced value PM model we describe addresses the financial needs and expectations of Rx, diagnostic companies and payers alike, as well as offering more effective and efficient therapy choices to patients and physicians. In order to achieve this new equilibrium, support from regulators and the political stakeholders will be required, in offering drug and test developers a sufficiently flexible and speedy approval process, taking into account the specific targeted proposition at the core of PM and more consistently integrating review approaches and processes for drugs and tests. Payers will need to reconsider the relative value of the diagnostic test in the overall targeted therapy package, and will need to offer an appropriate reward for the developers of such tests enabling a more effective and efficient use of novel therapies. Pharmaceutical companies will need to adjust their discovery and development strategies and set-up as well as their thinking about the commercialization of novel targeted therapies, beyond their drug assets alone.

Diagnostic manufacturers will also be impacted by the shift to a balanced value PM model. Since one of the most important factors influencing their ROI in a particular diagnostic is the market uptake of that diagnostic, a faster reimbursement or accelerated adoption of their test as a result of this new model could benefit them significantly. On the other hand, diagnostic companies may be negatively impacted by the desire on the payer side to apply the same 'broad access in return for more moderate pricing only' approach to novel molecular diagnostics, the one area in diagnostic companies' portfolios that currently allows them to charge premium prices of several hundred to several thousand dollars per test, too.

Whether the advantages of a balanced value PM model would outweigh the disadvantages for diagnostic companies or not will depend on the extent to which the inherent value of the diagnostic as an essential component of any targeted therapy will translate into a higher share for the owners of the diagnostic components of the total revenues gained from the total targeted therapy 'package'. Earlier and more strategically shaped partnerships between Rx and diagnostic companies will be critical, in which the diagnostic partners act and are being treated at eye level, and defining and quantifying balanced value for diagnostics remains an important subject for further discussion.

While all this will also fundamentally depend on the scientific foundation for novel targeted therapies being continuously further validated and expanded, we are confident that many targeted therapy assets already in advanced development could benefit from and become trailblazers of the model we describe. PM promises a more rational approach to the way patients are treated with drugs. Let us work together to make sure the way this works as a business is put on an equally rational basis, providing a balanced value proposition to all stakeholders alike.

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