Pharma Readiness for Diagnostic Integration 2017

Opinion pieces on the precision medicine and diagnostic marketplace in 2017 and beyond

Diaceutics

Contents

Introduction

This Ebook is a collection of opinion pieces specially written for Diaceutics' *Pharma Readiness for Diagnostic Integration 2017*. Created by Peter Keeling, CEO of Diaceutics and Jeff Waldron, Executive Director of PMConnective.org, they comment on the current and future state of the precision medicine marketplace at a time when the industrial, clinical and research activity is driving us with acceleration towards a long-promised transformation of healthcare delivery.

We hope it will be a useful tool for initiating discussions, creating awareness within your team about the impact and potential of the diagnostic landscape in the near future, and offer predictions about the world of diagnostics.

A range of expert insights on the topic of diagnostics and precision medicine can be found at http://www.diaceutics.com/resources/expert-insights/ and more Ebooks can be found at http://www.diaceutics.com/resources/ebooks/

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.

Precision medicine: Looking for disruption in the wrong place?

The pace of precision or personalized medicine (PM) right now is dizzying. The technology forecasters (Diaceutics included) warned everyone of the coming tsunami of pipeline precision therapy assets likely to be dependent upon an actionable biomarker. We also recognised that the affordability of genetic and molecular clinical disease profiling and the advance of health-tracking wearables such as phones and watches, will all eventually collide in cancers and diseases beyond oncology to deliver more precise intervention and better outcomes. Somehow this all seemed like light years away. Yet 2016 has been a landmark year for PM, with a big rise in PM market-related events being recorded in the first half of the year alone.

We will be the first to admit that we still need to join the dots between technologies to optimize the PM market. The regular misalignment of companion diagnostic adoption versus potential targeted therapy demand is a case in point and something we have spent ten years trying to change. To this we can add that sub-optimal education levels across stakeholders (laboratories/physicians/patients) seldom support the perfect supply and demand curves expected in mature healthcare markets and, of course, the uncertainties of the still unfolding science of PM in areas like immuno-oncology create gaps in our understanding of how to integrate PM into the patient pathway.

Clearly no single event will push PM over the edge towards its long promised transformation of healthcare delivery, but the sheer momentum of industrial, clinical and research activity being pointed away from imprecise towards precise medicine is without doubt accelerating the timeframe for us all.

Clayton Christenson in The Innovator's Dilemma called it right. The Harvard Business School professor points out that disruption will not come from the PM delivery chain - healthcare markets across the world are rapidly embracing and enjoying the benefits of PM - but from the inability of the suppliers (the innovators) to reinvent their business models fast enough to keep up, let alone lead the PM trajectory.

We should all (ourselves included), therefore, be aware that we risk being passed by as the pace of PM quickens.

Segmentation via testing is the new black

Diaceutics is often asked by clients for the ‘so what’ impact of precision medicine (PM) on their targeted therapy launches. This has mainly been answered by communicating the importance of getting the basic diagnostic market infrastructure right in order to support seamless therapy prescribing. We also explain how reimbursement gaps, sample management delays and poor stakeholder education can repeatedly beleaguer companion diagnostic launches and indirectly hold back therapy prescribing. Each novel biomarker has its own rocky road to easy clinical access so we don’t expect these issues to go away any time soon.

Simply put, the ‘so what’ impact for many target asset launches is that unless you focus early and diligently on building an efficient diagnostic market architecture, therapy access with the ensuing clinical and financial impact will be reduced. Our own estimate of the first PD-L1 launches in 2015/2016 suggests the impact of insufficient investment in PD-L1 testing infrastructure has cost pharma $770m in lost revenue on one indication alone in its first 18 months.

However, there is now an argument for moving our ‘so what’ impact horizons past the infrastructure 101s to the much more important understanding that PM is really about segmented patient management. This is not an issue when you have single or even dual targeted therapy launches into an indication. Herceptin, Epzicom and Tysabri were all launched under virtually monopolistic market conditions. Testing infrastructure issues were about increasing access to those therapies. Iressa/Tarceva, Zelboraf/Tafinlar were dual therapy launches that raised regulatory label issues over which test to choose and when, but

even here the breakthrough therapies found their place. It is only when we have four to five therapies launching into an individual indication in a compressed timeframe, as with Anti-PD1 therapies targeting NSCLC, that the competitive rubber hits the road. Consider for a second the NSCLC physician's choices in 2012 -chemotherapy and first generation TKIs. Four years later the targeted therapy choices now include Xalkori, Opdivo, Keytruda, Tagrisso, Xalkori, Iressa, Gilotrif, Alecansa and Portrazza. In four more years we could see numerous therapy combination recommendations, as well as a revival of older chemotherapy drugs newly targeted with PD-L1. In fact, we count 18 therapy choices for the same patient population by this stage -brilliant news for patients.

The 'so what' impact for pharma competitors seeking to carve out and sustain market share by relying solely on outcomes, dosing convenience and price will not cut it. The winners here will be the marketers who recognise that understanding physician testing behaviour, and then shaping the biomarker educational and use landscape, will win the upcoming segmentation war. Only then will testing move from a rescue remedy for drugs to become a marketing tonic.

The diagnostic industry: Locked in yesterday's business model

Make no mistake, the pharmaceutical industry right now could not manage to support the commercial roll-out of its targeted (precision) medicines (PM) without the scientific and technical support of the diagnostic industry. As the FDA migrates to a dual approval of medicines with their companion or complementary diagnostics, the interdependence between these different industries is solidified. Simply put, the diagnostic industry is now firmly part of the supply chain in the development of a PM future.

In 2016, 87 diagnostic companies were active in some way in the PM testing marketplace. Admittedly some of these are small technical houses sitting alongside veterans like Ventana, Qiagen and Thermo-Life Sciences, but it shows the diagnostic supply chain is thriving. However, there is a critical dilemma in the business partnering model between the pharma and diagnostic industries, namely which one is really responsible for developing the commercial testing marketplace? Diaceutics observes that pharma commercial teams continue to 'learn on the job' as they work out how to develop diagnostic markets which will enable their drugs. This happens because the diagnostic development partner has limited the team's responsibility to installing the test in a few primer labs across key markets. It is the equivalent of Pirelli delivering its tyres to Porsche and saying, "Thanks guys, now can you drag us into the marketplace alongside you?"

We all know the problems—partnering frameworks are couched in a way that make it tricky for a diagnostic company to take ownership of or be accountable for developing the marketplace for its test. In reality, there are no revenue-sharing milestone payments from pharma to diagnostic companies to guarantee a test will hit ALL the labs near their prescribers. And diagnostic companies have no incentive to promote a test that might generate less than $1m in profit. As far back as 2008 Diaceutics worked with pharma and diagnostic executives to research integrated commercial business terms for a win-win

situation in PM. Sadly, (with one or two exceptions where we have shaped the commercial agreement) we still do not see any significant evolution in this critical dynamic. One positive consequence, however, is the increasing involvement of laboratories in owning what we call the laboratory-physician interface, or LPI. Since market development is as much about education and service delivery, it seems that laboratories and not diagnostic companies are emerging as the better partner for pharma when tackling the increasing complexities of the PM market.

PD-L1: A chance to get things right?

The extraordinarily dynamic PD-L1 testing and anti-PD-1 therapy space allows, for the first time, a real-time analysis of a truly competitive personalized medicine market, giving us the chance to analyse in detail the PD-L1 testing market's trajectory and ultimately improve our understanding of novel biomarker adoption in our increasingly dynamic and competitive landscape. Despite the uncertainties hanging over the first generation of PD-L1 tests, our data point to the fact that the space will require ever more PD-L1 testing and that by 2018 PD-L1 will become a hyperconnected oncology biomarker led by NSCLC.

In short, the data suggest a rapid integration of PD-L1 testing despite its uncertain molecular interpretation. One year after launch, PD-L1 already appears to be more integrated into oncology clinical trials than other biomarkers were 18 months post-launch. Use in over 70 US labs shows PD-L1 testing has a fast track pattern of uptake in parallel with treatment recommendations. This is all very encouraging, but there are issues including:

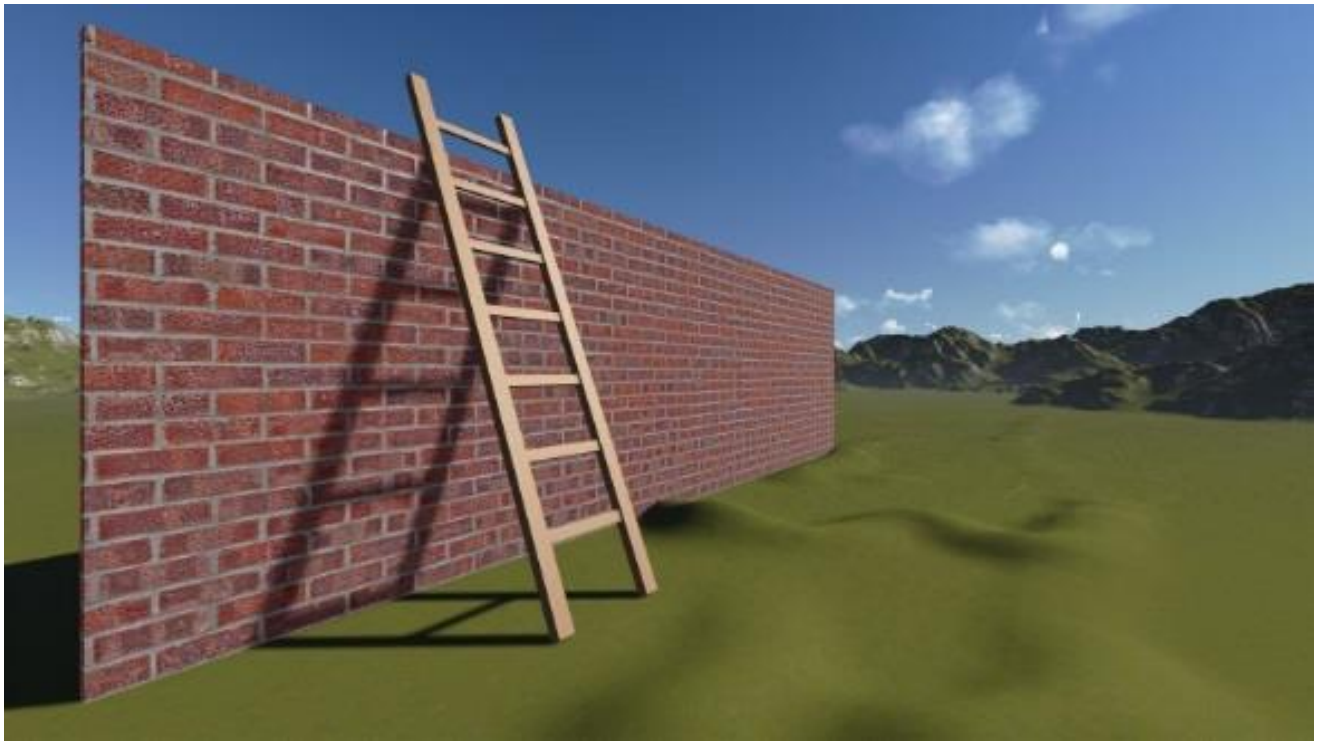
- Of the 70-plus US labs that have adopted PD-L1 testing, the majority have opted to make an LDT available. Kits are important in priming the market but, as with other biomarkers, labs decide on the best test going forward, so their impact in the space should be not be ignored. This appears at odds with FDA attempts to de-limit LDT use, although with a changing US administration this may be binned.
- Test availability can impact prescribing choices and the way labs offer a test could be a disruptive factor for pharma. Our research shows if only one PD-L1 test is offered by a lab it appears to limit prescriber choices.
- PD-L1 biology of expression determines that late disease is likely to reveal higher levels of PD-L1 expression whereas pre-treatment can also interfere with PD-L1

levels, so a patient's position in the diagnostic journey may be key to segmentation. This is not well articulated in clinical guidance.

Clinical trials for immuno-oncology therapies in NSCLC reveal that PD-L1 will need to be integrated alongside more established biomarkers like ALK and EGFRm as part of future patient segmentation strategies. Testing guidelines are constantly lagging behind biomarker launches and this is likely to be increasingly so in the PD-L1 space. This inevitably limits direct-to-patient communication and prevents patients' easy understanding of the space. PD-L1 is unlikely, therefore, to be patient led, as HER2 is today.

Our real-time observation of PD-L1 reveals many issues of novel biomarker integration into treatment pathways and drug launch programs. Precision medicine continues to progress yet we still suffer from the lack of pre-launch market development of critical biomarkers, even though most of the PD-L1 issues have been seen before. Optimizing the potential of a still underdeveloped PD-L1 testing market could help to realise the $32bn per annum in expected drug revenues, but learning from it could shape hundreds of billions of dollars in future dependent therapy revenues.

The microeconomics of precision medicine are in poor shape



The promise of precision medicine (PM) was always both clinical and financial. Unarguably, our delivery on the clinical promise is well underway—new approved targeted therapies prove that molecular targeting of patient subsets delivers significantly better outcomes and our pipeline analyses illustrate the best is yet to come. In contrast, our delivery on the financial promise has barely begun and, in almost every dimension, the microeconomics of PM are in poor shape.

Let's revisit the promised financial hypothesis of PM here. We expected the utilization of behavioural, genetic and molecular targeting to eliminate wasted healthcare cost, deliver greater incentives to all stakeholders and create transparency around value. Given that (in 2016) we are 18 years on from Herceptin's first use, the current reality is somewhat different. We see:

1. Sparse evidence of PM-enabled reduced healthcare cost emanating from real world health economists; it may exist…it's just not adequately reported[1];
2. Huge incentive imbalances across the supply chain stakeholders, with pharmaceutical companies migrating PM to a high-priced model while innovative front line laboratories are existentially squeezed by the indirect consequences of blunt reimbursement or national healthcare policies[2];
3. Little in the way of joined-up discussion at the disease level about where the value of PM actually lies and even less ownership of the debate[3];

4. Delivering on the financial promise starts with an illustration of what is broken, and in this regard at least there are some bright lights:
    The OHE/EPEMED-sponsored work to point out the undervaluation of diagnostics in PM[4];
    A growing understanding of how pricing models should reflect the value of diagnostics[5];
5. The ripple effect across the industry C suites from Opdivo's failed 1st line NSCLC study and its profound impact on the BMS share price[6];
6. The embryonic work of groups like the PM Connective that explore financial opportunities at disease level as part of a PM architecture.

We are confident that, in the long term, a market economy will deliver a clear and obvious financial landscape for PM which makes great economic sense all round. In the short term, however, a step change is needed when it comes to dialogue, specifically between chief financial officers, economists, payers, policymakers and patient advocacy groups, all of whom need to re-arm with a better understanding of the financial drivers resident within the economic underbelly of PM. Without this, the short-to mid-term clinical promise of PM will be limited to the low hanging fruit and that would be a missed opportunity.

References

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Undelivered precision: Lack of integration is the remaining obstacle

Precision medicine (PM) has offered this tantalizing promise for the last 20 years—earlier identification and intervention in the patient pathway using advanced diagnostic tools and precision therapies could have a transformative impact on disease. Oncology has been the logical starting point due to the adverse health outcomes and high costs, and many cancers, if caught early, can be treated effectively, cured or managed as chronic conditions now with targeted therapy.

Diagnostics and precision therapies have developed to a point where their pace of arrival on the market will continuously eclipse existing standards of care. Factor in the emergence of immunotherapies and innovative diagnostic tools like next generation sequencing and we already have the clinical options to succeed in PM. We can continue to fund and push for even better tests and treatment, but why not efficiently utilize the tools we already have available to deliver the promise of PM?

Currently, each player in the industry operates largely independently but only an integrated approach from all sides (clinical, scientific, technical, managerial, education, reimbursement and regulatory) can implement and ultimately deliver the financial as well as clinical potential of PM.

The numerous stakeholders (sitting separately in what we term ‘siloes’) in the US healthcare system are rational players maximizing their own value. Unsurprisingly, integration is unappealing for these stakeholders and the true obstacle to PM. It’s only the adoption of a

value framework that can change behaviours and drive more collaboration which will unlock the financial promise of PM. In driving the development of a new valuation framework in one disease area - melanoma - via our support of the PM Connective (www.pmconnective.org), we hope to clearly demonstrate not only cumulative value for PM across silos but, more importantly, the quantitative and qualitative benefits (for each silo) of collaborating to reach PM solutions. The scientifically measured and replicable results will provide a 'GPS system' to guide integration and collaboration both across and within the healthcare silos.
The PM promise can be realised but it will require a new method of delivery to achieve its biggest impact.

All therapies live in an unlit diagnostic ecosystem

Our work over the past decade has convinced us in Diaceutics that whilst the term precision medicine (PM) is a useful scientific and clinical hypothesis promising to carry us into more targeted patient care, it is in fact also a label which obscures a larger interdependence between testing and therapy. Diaceutics has thus shifted its view away from perceiving PM as a construct only for targeted therapies and companion diagnostics (where the science allows us), to the realisation that EVERY therapy actually exists in its very own, often unlit, diagnostic ecosystem.

Illuminating this diagnostic ecosystem has just as much a role in guiding the right patient to the right drug at the right time as the handful of companion diagnostics we have used as our narrow flagbearer in PM. In fact, across the 23 companies analysed in our 2017 Pharma Readiness for Dx Report we believe that $200bn of therapy assets already have a direct or indirect dependency on their own diagnostic ecosystem.

But what if these diagnostic ecosystems could made more visible…would that profoundly impact patient access to therapies and, in turn, the return on investment for pharma brand teams competing for available patient share? Those of us who see the untapped diagnostic opportunities across the treatment pathway have, therefore, a key task in front of us -namely to quantify, analyse and communicate (with evidence) to pharma asset and financial leaders how $1 invested smartly in the diagnostic ecosystem will return $40-$60 back in new therapy revenue and, crucially, get more of the right patients on the right drug.

Within this report we have yet again returned to the dialogue that by incorporating non-companion (or complementary) tests in our analysis (as well as the brand new ‘C’ for

Conduit Dx™) and framing the relationship between therapy ROI and the efficiency of the diagnostic and its ecosystem, we hope to awaken a whole new way of looking at PM. This is the view that precision is not narrowly confined to a few drugs, but rather lights up the opportunity for all drugs to achieve their full clinical potential faster.

We dare to imagine that every therapy commercial team has a bright, three dimensional map of the diagnostic ecosystem into which their therapy is launched, and this enables them to ask the question, “What if there were a test which could do…?”