

Personalised Medicine – the Future of Blockbuster Pharma?

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October 2013



Personalised Medicine

- Personalised medicine is revolutionising the pharma and biotech industries.
- Over the next few years, the established business models will change out of all recognition to enable companies, healthcare systems and patients to benefit from those changes.
- Personalised medicine does not sound the death knell for the existing industry, but rather offers a plethora of new opportunities provided that structures, decision-making practices and processes evolve with the changing environment.

Arguably, personalised medicine has been around in some form for many centuries. Hippocrates (460 – 370 BC) individualised treatment of disease with the concept of “balanced humours”. A surplus or deficit of one or more of the four humours (black bile, yellow bile, phlegm and blood) would lead to disease which could be treated by restoring the balance in the affected individual. Galen (131 – 200 AD) associated the four humours and their balance with one of four temperaments - melancholic (thoughtful), choleric (ambitious), phlegmatic (relaxed) and sanguine (sociable). This view of medicine and the individual, with some variations, persisted for over two millennia until the 18th and 19th centuries.

The modern concept of ‘personalised medicine’ - the prescription of specific therapeutics best suited to specific populations based on pharmacogenetic / pharmacogenomic information or other biomarkers - has been in existence since the 1960s, though it was not until 1999 that the term was first published.^{1,2} Progress since then has been rapid but not without difficulties.

Personalised Medicine – Driving the Next Generation of Blockbusters?

Our hugely increased understanding of genetics, the underlying causation of diseases, and how those diseases respond to treatments has been underpinned by phenomenal progress in supportive technologies such as computational biology and genotyping. It is this marriage of technological progress and scientific advancement that is now enabling us to start to understand the true potential of personalised medicine. However, accompanying those advances is deeper insight to the complexity surrounding personalised treatments.

For example, historically, lung cancers were differentiated histologically as small cell (SCLC) and non-small cell (NSCLC), each being treated somewhat ineffectively with different chemotherapeutics. With the knowledge that there are different causations for these cancers, a much more targeted approach to treatment is possible. Pfizer’s crizotinib (Xalkori) has been shown to be effective (in terms of response rate, duration of response and progression free survival) in a small sub-population identified with an ALK positive NSCLC biomarker test. The sub-population is predominantly younger non-smokers with a chromosomal rearrangement that generates an EML4 / ALK fusion gene resulting in NSCLC.³ This mutation represents around 3-5% of the NSCLC patient population or approximately 40,000 new cases per



"The concept of personalised medicine is steadily evolving from a theoretical concept into an integral part of modern medicine."

EMA Roadmap to 2015

annum worldwide.⁴ So far, so good – improved outcomes for patients, no prescribing redundancy, and potential savings for the healthcare system.

However, affordability now rears its ugly head – England's National Institute for Health and Care Excellence (NICE) recently rejected crizotinib on cost-benefit grounds, whilst its companion over the border, the Scottish Medicines Consortium, approved its use.⁵ Though a challenge for the drug, it is far from the end of the road. Leaving aside any negotiations around pricing or payment by results for NSCLC, trials are on-going in a variety of other indications that may yet see crizotinib becoming an even more successful drug both financially and clinically. And if it does, it will not be alone.

The crizotinib experience highlights many of the key issues and opportunities surrounding personalised medicine. These include the need for precise biomarkers to identify a tightly defined, susceptible patient population and the importance of demonstrating a watertight cost-benefit case. Importantly, it also presents a further strong challenge to the notion that personalised medicine signals the end of blockbuster drugs. Herceptin, Avastin, Soliris and others are all personalised medicines that have reached these heady heights.

The blockbuster is not dead, it just looks different.

Sequential Decisions Underpin Success in Personalised Medicine

The pathway to success for personalised medicines is rather more convoluted and complex than the conventional route. In the older model there are already a number of (difficult) key development and launch decisions - the decision to enter the clinic, the decision to start phase III trials, the decision on market entry sequence and so forth. For personalised medicines all the same decisions apply, plus an overlay of judgements on, for example, diagnostic and biomarker technologies and more extensive payer / provider review and discussion.

In addition, personalised medicine is becoming a highly competitive arena in which to operate, with many new entrants, players with differential bargaining power and the ever-present potential for further technological advance. In these respects it has the hallmarks of 'disruptive innovation' for the industry. In the mid-1990s Clayton M. Christensen coined the term 'disruptive technology' to describe



a new technology that unexpectedly displaces an established one.⁶ Christensen later modified this to 'disruptive innovation' to recognise that the disruption results not from the technologies *per se*, but rather it is the business model the technology enables that creates the disruption.

For example, personal computer technology displaced the role of mainframes and offered opportunities that could never have been realised using the existing technology. Similarly, PCs are in turn being replaced by mobile smart phones and tablets. In the pharma and biotech sector, we have already seen the chemical revolution, followed by the pharmacological revolution, the information revolution, the biotech revolution and now the genetics revolution, all in the space of a lifetime. Each of these has engendered disruptive innovations giving rise to new companies, new approaches and radical redesign of existing businesses. There seems little doubt that the personalised medicine revolution will have similar sector wide impact.

So, what new or different decisions need to be made to ensure that companies survive and flourish in the personalised medicine revolution?

Identification of Appropriate Biomarkers and Companion Diagnostics

Biomarkers of one form or another have long been used in pre-clinical and clinical trials to indicate efficacy, pharmacokinetic activity and so forth. Personalised medicines, however, require predictive biomarkers that will help identify susceptible patient populations. For many diseases, true evaluation of the disease state may require invasive, risky and expensive techniques such as biopsies. The identification and characterisation of appropriate biomarkers, which can be used as proxies, is therefore vital.

This is exemplified in oncology, where drugs are clinically effective in around 20% of cases, but the average success rate for all therapeutic classes is around 50%. The drugs either just do not work outside specific target patient populations or have intolerable side effects. Development of effective companion diagnostics and biomarkers thus offers the potential not only for significant clinical benefit, but also major financial advantages including vast improvement in R&D productivity.

Many of the more aggressive breast cancers that do not respond well to either hormonal treatment or chemotherapeutics have an amplification



"For the first time in my career, pricing is becoming a really interesting piece of the dynamic. If you believe you have a sustainable business model that can turn out more product than anybody else, why wouldn't you do this?"

Andrew Witty, CEO, GSK

of the HER2/neu gene. This has proved to be an excellent prognostic marker for Herceptin treatment. Merck Serono's Erbitux competes with Avastin in the advanced colorectal cancer market. A sub-population of patients, representing around 60% of all cases, does not have a mutation in the KRAS gene. In this group, treatment with Erbitux has been shown to prolong patient lives compared to treatment with Avastin. Erbitux, unlike Avastin, is sold with a companion diagnostic, a genetic test for KRAS mutations that is performed before starting treatment. This diagnostic ensures that only those patients likely to benefit are treated and that they are treated with the most effective drug - a competitive edge for Merck Serono.

In contrast, the neuroscience space has proved more challenging. Identification and development of an effective treatment for Alzheimer's disease has doubtless suffered because of the lack of appropriate robust markers – amyloid plaque deposition, Tau protein detection, BACE1 expression and other approaches have so far proved to be of limited value in prediction and treatment of this terrible disease.

Timing for / Selection of Diagnostics Partners

As outlined above, working with the right biomarkers and diagnostics partners is critical for the development and adoption of new therapies in the personalised medicine arena. But identifying the right partner, with the right companion diagnostic and engaging them at the right time is challenging.

Historically, diagnostics has been a very different business from pharma and biotech, with much faster development times and shorter lifecycles requiring very different technological, scientific and commercial expertise - and providing significantly smaller margins. Companies operating in the personalised medicine space (arguably all pharma and biotech companies eventually) will need to build, buy or partner diagnostic capability. Novartis' decision to acquire the diagnostic company Genoptix is just one example of big pharma's moves in this area.

The right combination of therapy / diagnostic / biomarker and regulatory authority understanding of that combination is critical to successful commercialisation. In one example, PricewaterhouseCoopers has highlighted how this can go wrong.⁷

Of the 28 million people who currently take Plavix (clopidogrel) to



"A new age of medicines will work very well in a select few...pharmaceutical firms have shown new willingness to develop drugs for very rare diseases partly because they have found they can charge a small fortune for the ones that work."

*Matthew Herper. Forbes
September 2011*

prevent heart attacks, strokes, blood clots, and stent occlusions, an estimated 20 per cent respond poorly. In 2011, the FDA added a boxed warning to Plavix highlighting that the drug can be less effective in people who cannot metabolise the drug to convert it to its active form. ThromboVision developed a device called the 'T-Guide' to measure platelet aggregation, thus enabling identification of those patients who could benefit from this treatment. However, according to ThromboVision, FDA rejected T-Guide's 510(k) (notification of intent to market a medical device) based on its misunderstanding of the statistical analysis of the clinical data and the rigid application of guidance documents that were ill-suited to this type of technology.

The CEO of ThromboVision said, "*in hindsight, we would seek regulatory approval in Europe, achieve early revenue, then secondarily focus on obtaining FDA clearance and US market entry. The US should rethink this whole paternalistic, zero-risk attitude because that regulatory environment makes it safe to do incremental change but very difficult to do dramatic, revolutionary change*". However, the increasing focus in Europe on regulatory process and establishing clinical evidence for medical devices, moving closer to the US approach, means that the 'hindsight strategy' proposed by ThromboVision may not be possible in the future.

Optimising the Route to Commercialisation

Choosing the most expeditious route to successful commercialisation has been a long-standing challenge for pharma and biotech – which should be the first market(s), which should be the first indication(s) (assuming a choice), what would be the optimal sequence of submissions, how do we best ensure reimbursement, what is the impact of these decisions on clinical trial structure etc. These multi-factorial decisions have become even more complex with the advent of personalised medicine; additional factors serve to complicate the already difficult commercial decision-making process.

A key decision is how to compellingly present and negotiate the cost-benefit equation. Former President of Pfizer Global R&D, John La Mattina, points out that Alexion's Solaris, for atypical haemolytic uremic syndrome, costs \$440,000 per patient per annum, a figure that has attracted considerable adverse comment – but the treatment saves significantly more than that in care costs.⁸ Notwithstanding this simple and compelling arithmetic, it is an argument unlikely to convince agencies such as NICE, or those who look at overall healthcare costs.



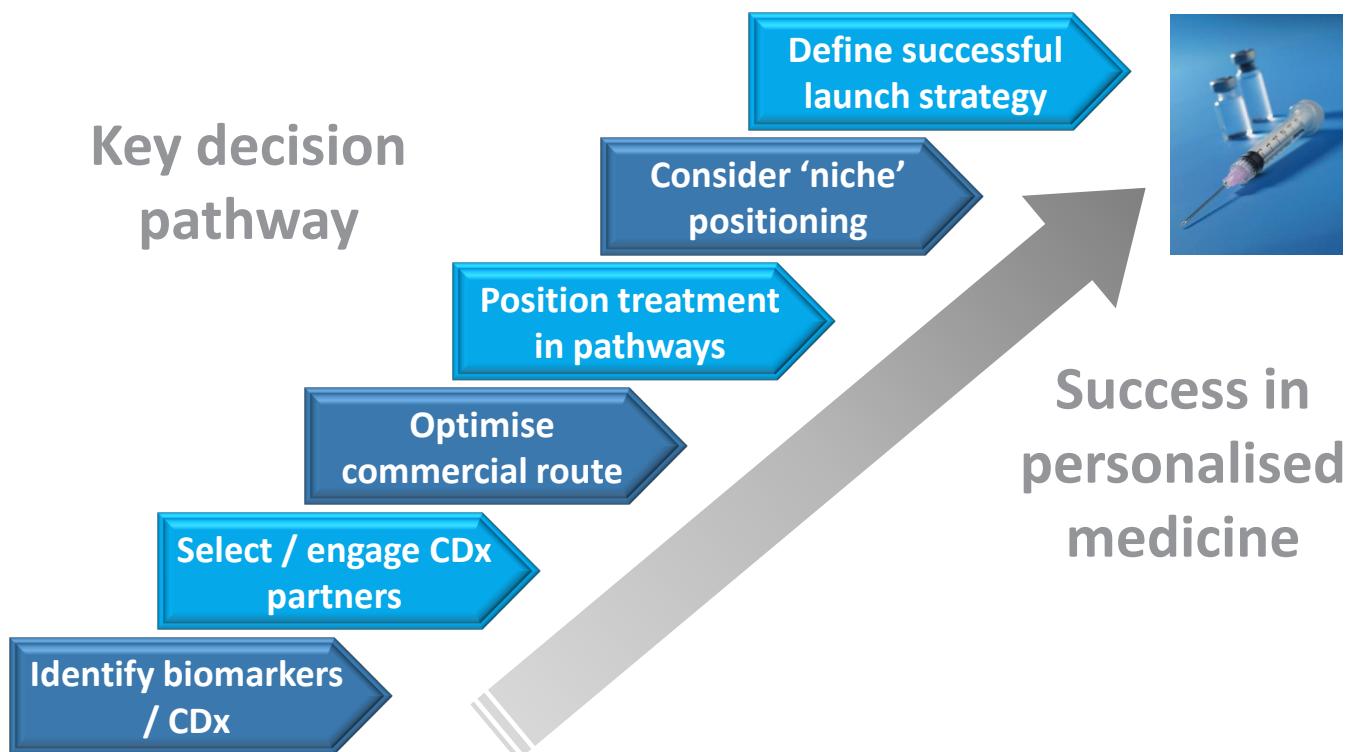


Figure 1: The key decision pathway for success in personalised medicine.



O'Sullivan *et. al.* recently highlighted this with the cost of Vertex's Cystic Fibrosis treatment ivacaftor (Kalydeco).⁹ The price for this is around \$300k per annum – but it has to be taken for many years, potentially costing many millions of dollars for a successful outcome. O'Sullivan suggests that wherever the cost is borne – whether by the individual, by insurers or by the state – the underlying problem of an "*unsustainable pricing structure*" for these sorts of medicines remains. Whatever the rights and wrongs of the cost-benefit argument, receptiveness to personalised medicines may vary by individual health authority and, most certainly, the willingness and ability to pay will vary by payer organisation or patient. This emphasises the importance of deciding the order of market entry since initial launch countries may be used for reference pricing.

The dramatic rise in Managed Entry Agreements across Europe in recent years suggests that payers have recognised the benefit that the personalised approach offers in managing healthcare costs.¹⁰ Structured access approaches such as risk-sharing and pay-for-performance enable patient access whilst ensuring that payers only have to cover the costs of successful outcomes. Italy is a strong leader in this field with a considerable number of agreements since 2006, largely focused on oncology therapies. The introduction of Patient Access Schemes as part of the healthcare reforms in England & Wales in 2009 has seen the risk-sharing approach become an increasingly common measure to enable patient access for expensive medicines. A relatively new measure, it is set to increase in importance for companies seeking to obtain reimbursement for innovative therapies and has certainly shaped thinking around new value-based pricing approaches.

A challenge in this area is that the majority of these agreements are private commercial arrangements, and thus at present it is hard to know how each payer might structure a scheme and what level of commonality there is between them across countries.

Initial / On-Going Positioning in Treatment Pathways

Many diseases have established and specialised treatment pathways that may be disrupted by personalised medicines.

One early example of disturbance of the traditional medical consultation / diagnosis / treatment paradigm is the introduction of Myriad Genetics' BRACAnalysis, which detects the BRCA1 or BRCA2 gene mutation,



responsible for the majority of hereditary breast and ovarian cancers. Initially, national and private healthcare insurance companies refused to pay or reimburse the \$3,000 cost of diagnostic testing. They were forced to reverse this decision as so many private individuals paid out of their own pockets for the tests and others demanded the same quality of treatment.



Ensuring that services are established to support the new treatment pathways, and supporting healthcare providers, may therefore prove to be one of the keys to success. Patients increasingly demand much greater involvement in managing their own treatment, and demand direct engagement with suppliers. This changes the traditional interface role of clinical staff and the mechanisms by which appropriate treatments are identified. For example, companies work directly with AIDS activists in advancing patient understanding of anti-retroviral drugs and how these may work differently in different populations. Inevitably, the internet provides endless opportunity for the propagation of information, facts and fantasy, bypassing the more established sources of knowledge.

A further example is the treatment of Alzheimer's Disease (AD). Before the advent of symptomatic treatment, the disease was considered irreversible; patients and their carers were simply referred to social care services for support. The introduction of the acetylcholinesterase inhibitor donepezil in the mid-1990s gave neurologists and psychiatrists a new intervention that improved the quality of life for some AD sufferers, but which disrupted established service provision requirements as patients required much more contact time with healthcare staff, in repeated visits to outpatient clinics, to assess their cognitive function and capabilities.

Additional disruption was caused by an increase in patient / carer demands for treatment and assessment as the potential benefits emerged. The specific, personalised treatments for certain sub-populations of AD currently in the pipeline will no doubt provide further disruption. These treatments offer the hope of halting or even reversing the course of the disease, but are dependent upon identification and development of appropriate diagnostics to identify the sub-population of patients who may benefit.

The care pathway then becomes far more complex. An initial assessment provides an indication that the patient has AD, the first challenge being to differentiate AD from other forms of dementia. This will probably lead to a detailed diagnostic analysis and a wait of



several days or weeks before a further assessment is made to indicate the most appropriate treatment or intervention(s); but at the moment the relevant prognostic and diagnostic biomarkers remain a matter of on-going debate. The diagnostic may indicate several choices, which have to be made with the informed consent of the patient and/or carer. The acetylcholinesterase inhibitor experience suggests that healthcare services will often not be set up for the required changes.

Instead, it will be up to the companies launching the new interventions, with the support of clinicians who have gained experience during the clinical development programme, to support local healthcare payers and providers to make the systemic adjustments that will be necessary. For example, the most common current GP referral for dementia is to a psychiatrist and the initial assessments are interview-based (e.g. the mini mental state evaluation), whereas the most likely future route would see initial referral to a specific diagnostic service, which does not currently exist. One stark choice for companies launching the new interventions will be the extent to which they will need to support the development of the underpinning service provision.

Considerations with “Niche” Interventions

“We won’t have to do those dinosaur trials [massive phase III studies]; it will change the whole attitude to drug development.”

Dr Alexander Eggermont. CEO, Institut Gustav-Roussy

A number of successful personalised medicines started life as orphan drugs, for example Genentech’s Rituximab (Rituxan, currently the world’s second most profitable drug), Novartis’ ranibizumab (Lucentis) and Celgene’s lenalidomide (Revlimid). Whilst the difficulties in identifying patients for clinical trials and perceptions of a specialised niche product may be seen as competitively disadvantageous, the shorter trial times, speedier review, tax credits and the potential for premium pricing may more than offset these initial disadvantages. A recent analysis by the Pharmaceutical Research and Manufacturers of America (PhRMA) highlights 452 drugs for rare diseases now in development.¹¹ Whilst this is tremendously encouraging for patients poorly served by existing treatments, PhRMA themselves point out that despite the difficulties of development, *“rare diseases provide opportunities to study human physiology and biomedical science from unique perspectives, leading to insight into more common disorders”*. It is likely that a number of these treatments will join the growing armamentarium of commercially and clinically successful personalised medicines in due course.

In addition, a recent Boston Consulting Group analysis has reaffirmed how orphan or similar designation can be advantageous through the first-to-market benefit – even with products with a slightly lesser



therapeutic advantage than the second or third to market.¹² This emphasises the importance of rapid development and fast track designation – crizotinib again provides a benchmark with a 6-year development time from lead compound identification to FDA approval.¹³ Changes in the regulatory environment continue to aid the development of personalised medicines. The FDA's recently enacted 'Breakthrough Therapy' designation enables medicines in development that show compelling clinical efficacy, even in small numbers of patients, to be fast tracked toward approval. This is a further step on the road to reduced development time and cost that will ultimately benefit patients, payers, producers and society.

Launch Strategy

As with all new products in any field, launch strategy encompasses a multitude of interconnected decisions. A singular complication in the world of personalised medicines is the need to pair diagnostics or biomarkers with their associated targeted therapeutics. Which should be launched first or should they be brought to market simultaneously? Recent thinking suggests that biomarker research should start at least 2-4 years prior to clinical trials to identify a panel of biomarker candidates that can be established, validated and qualified prior to human testing.¹⁴ To ensure their precision and accuracy, biomarkers need to be validated in a variety of patient populations and this has been the subject of guidance from US and European regulatory authorities. Additionally, sales teams will need additional expertise and training in understanding disease pathways, biomarkers, patient segments and sub-population attributes etc.

Realising the clinical and commercial benefits of personalised medicines requires not only a clear definition and understanding of the decisions to be made, but also introduction of new approaches to ensure identification and engagement of all key players in the decision-making processes.



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In Summary - Personalised Medicine is a Global Game Changer

The old business model was dependent on a somewhat 'shotgun' approach, developing broadly effective medicines for large populations of patients with unmet needs. The advent of personalised medicine has given rise to a specificity that is revolutionising the industry. With this revolution has come a new understanding of cost-effectiveness, predicated on precision treatments for smaller populations. The implications of this innovation are still being played out – and will be for some time – but will certainly have global impact, will change the structure of the pharma and biotech industry and will transform the economics of healthcare in general.

Personalised medicine is no longer a niche sector for a few specialised companies. Our understanding of the underlying science, our ability to manage big data and the development of new technologies has combined to make personalised medicine the new mainstream. Successfully exploiting the opportunities personalised medicine presents will demand new decision-making skills and processes, development of new expertise and formation of new and unconventional collaborations.

Are we prepared for the hard decisions that will underpin such change?



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