CLEARVIEW
Healthcare Partners

Creating Value in Precision Medicine Through Proprietary Diagnostics

Great progress has been made in the field of precision medicine and targeted therapy development. However, the full value proposition of this approach has not yet been realized. A key challenge is that there has not been strong alignment between the therapy and diagnostic interests and business models.

We are now at the precipice of seeing a shift in the business case for prevision medicine. To be successful though we must answer several important questions. What are the key features of a propriety diagnostic tool that would enable isolation of a unique market opportunity? What is the business model that should be deployed to incentivize investment in this type of tool? In this paper, we will outline the answers to these questions and provide some examples of exciting technologies which may tap this potential.

THE BRIEF

Value of a Prioprietary Dx

Outlining the potential opportunity that could be unlocked by a proprietary diagnostic

Key Features of a Proprietary Dx

Describing the technological, regulatory, and commercial elements that will be required for success

Potential Business Models

Determining how to secure and allocate the value generated

Introduction

The pharma industry has historically had a mixed relationship with predictive biomarkers which inform therapy selection. On the one hand they see value in identifying patient sub-populations which are more likely to respond to therapy and leveraging this information to execute faster trials and secure regulatory approval sooner. On the other, however, there are concerns that they may be conceding the potential market opportunity associated with an "all-comers" indication.

Whether they like it or not most pharma companies have now learned to incorporate biomarkers into their early clinical development planning so that at least they will be able to use the biomarker information if they need to. When it becomes clear that a biomarker approach is required because of a lack of efficacy in a non-selected patient population, the focus turns to identifying the ideal diagnostic tool that can secure regulatory approval and help bring the product to market.

Historically, these decisions have been based on identifying global in vitro diagnostic (IVD) players with validated technologies with well-worn pathways through the FDA, such as polymerase chain reaction (PCR), immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), etc. Relatively little consideration is given to whether this regulatory-focused diagnostic tool will meet the needs of an evolving testing marketplace. Therefore commercial teams often struggle to determine how to make the best out of what they have by leveraging a partnership with a global IVD player, identifying local IVD partners, and in many cases engaging local labs to create test offerings that align with the demands of the physician community.

Not much thought is given to whether the diagnostic assay could be a differentiator in the marketplace because the markets are still nascent with limited offerings. Additionally, if a company did want to stake a claim to some virgin territory, their ownership of the space would quickly be eroded by others developing data and launching similar assays in the same space. Competitors are able to do this in part because no one has owned the intellectual property (IP) around the biomarker – the Supreme Court case that the Association for Molecular Pathology (AMP) brought against Myriad on BRCA testing meant the end to gene patents. Now if anyone wants to offer BRCA testing and they have a lab and available instrumentation, they can launch their own test offering.

Potential Value of a Proprietary Dianostic?

This raises the question about whether there is a better and more thoughtful approach to working with predictive biomarker tools. Is there a way that a pharma or diagnostics company could create a proprietary biomarker tool that would identify a unique subpopulation of patients with a critical unmet medical need that traditional tools would not be able to find? Could then this assay be successfully commercialized to not only gain access to a patient subpopulation but also exclude other companies from marketing their products to this patient group?

Recent technological developments in diagnostics have included more innovative methods. These tools utilize a combination of diagnostic methods, software, and algorithms, which would be much more difficult for another entity to duplicate relative to a simple individual biomarker test. We now see partnerships between diagnostic and pharmaceutical companies to develop custom tools that tailor therapies to the patient's clinical profile. These types of partnerships may present unique opportunities to carve out distinct and enduring value in the markets for both the diagnostic and the therapeutic.

Below are just a few examples of companies with proprietary diagnostic platforms that have the potential to create clinically and commercially differentiated value:

Adaptive Biotechnologies

Adaptive Biotechnologies, Immunosequencing, has developed an immune profiling platform which leverages computational biology, software and machine learning to read the diverse genetic code of a patient's immune system. It relies on next-generation sequencing (NGS) to assess single chains of "Y-shaped" T-cell or B-cell receptors.

The company has partnered with Genentech to leverage its proprietary T-cell receptor discovery and immune profiling platform (TruTCR™) to create tailored cellular therapies targeting neoantigens in cancer patients. The company has also partnered with Microsoft to map the genetics of the human immune system, or immunome.

Path AI

Path AI, Digital Pathology AI, is a digital pathology player, applying artificial intelligence (AI) and machine learning solutions to extract more information and value from tissue analyses.

ClearView
Healthcare Partners

The Company has also formed partnerships with Bristol-Myers Squibb (BMS) and Novartis that are using the technology to analyze clinical trial tissue samples to better understand which patients respond to therapy.

Natera

Natera, Signatera is a prenatal genetic screening company that has just recently entered the cancer space. Their lead offering, Signatera, involves identification of a unique genetic signatures (~16 somatic variants that are individualized to each patient's tumor) that can then be monitored throughout the course of a patient's care. According to Natera, Signatera is the first circulating tumor DNA (ctDNA) molecular monitoring tool.

Natera has entered into an agreement with BMS to use the tool in a Phase 2 study in adjuvant non-small cell lung cancer (NSCLC). The study is the first prospective trial that will use the assay to select patients who have minimal residual disease (MRD) after surgical resection to receive adjuvant standard of care with or without Opdivo.
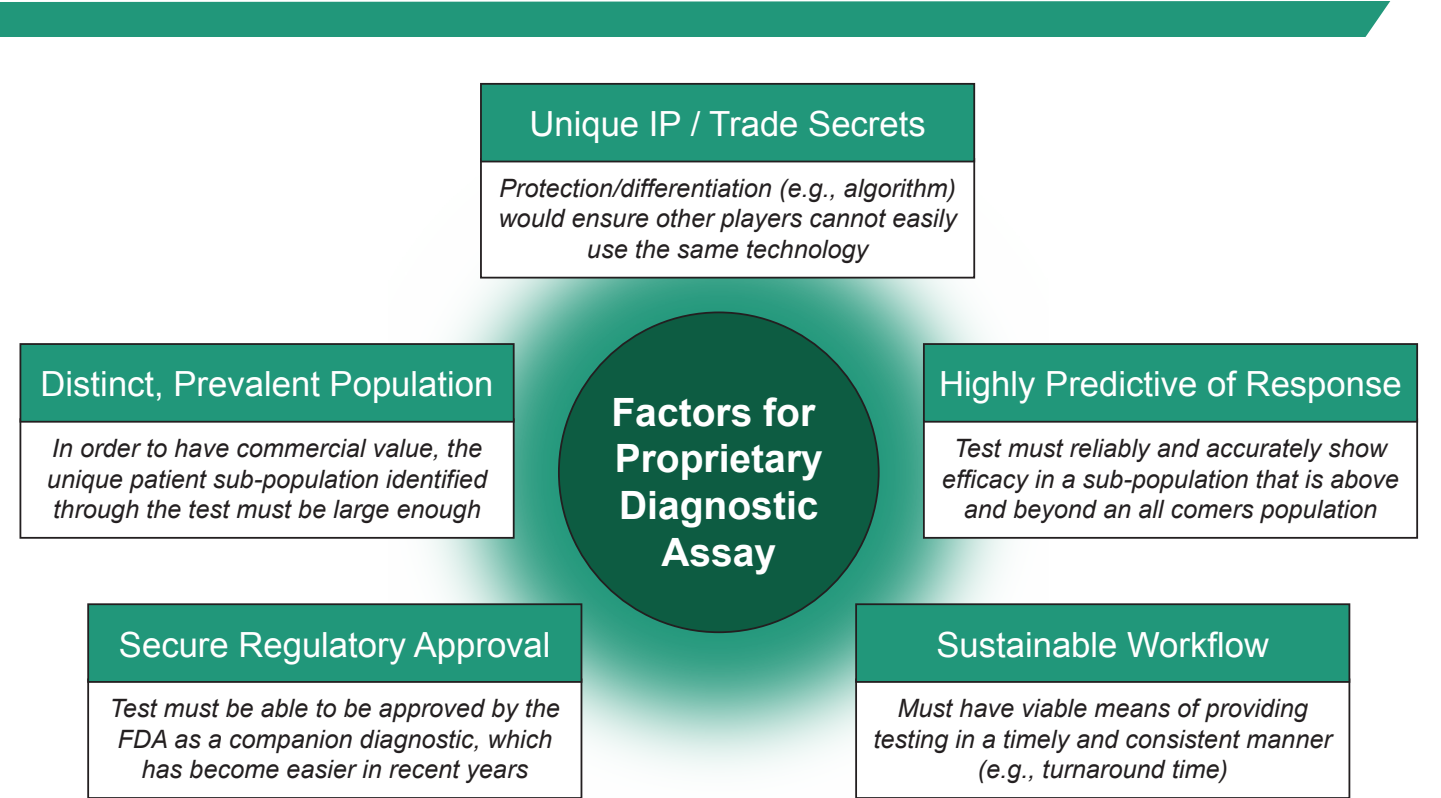
Key Considerations of a Proprietary Diagnostic Assay

Successful development of a propriety diagnostic assay hinges on several key factors worth noting. First and foremost, the one critical feature is that the assay should use a unique technology or method that is not readily duplicated.
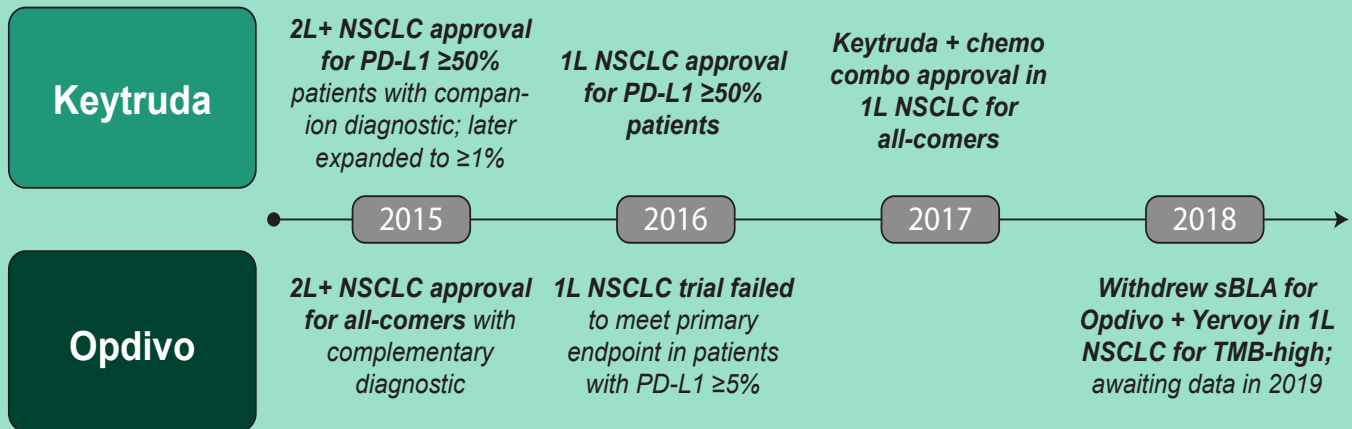
Have unique IP / trade secrets

Intellectual property (IP) protection would ensure that other players cannot easily recreate the assay and compete in the same space. This would have to go beyond traditional single gene biomarker approaches such as KRAS and BRAF, or even multi-marker methods such as TMB and MMR/MSI, as any laboratory can create their own versions of these assays. In order to prevent competitors from replicating it in the market, the assay would have to involve unique and proprietary algorithms and methodology. For instance, the assay can involve a unique integration of multiple methods such as genomics, proteomics, and metabolomics, and utilize proprietary algorithms to assess the relationship between these biomarkers.

FIGURE 1 - Hallmarks of a Proprietary Diagnostic

Unique IP / Trade Secrets

Protection/differentiation (e.g., algorithm) would ensure other players cannot easily use the same technology

Distinct, Prevalent Population

In order to have commercial value, the unique patient sub-population identified through the test must be large enough

Factors for Proprietary Diagnostic Assay

Highly Predictive of Response

Test must reliably and accurately show efficacy in a sub-population that is above and beyond an all comers population

Secure Regulatory Approval

Test must be able to be approved by the FDA as a companion diagnostic, which has become easier in recent years

Sustainable Workflow

Must have viable means of providing testing in a timely and consistent manner (e.g., turnaround time)

Case Study: Evolution of Biomarker Testing in Lung Cancer

Keytruda

2L+ NSCLC approval for PD-L1 ≥50% patients with companion diagnostic; later expanded to ≥1%

1L NSCLC approval for PD-L1 ≥50% patients

Keytruda + chemo combo approval in 1L NSCLC for all-comers

2015 — 2016 — 2017 — 2018 →

Opdivo

2L+ NSCLC approval for all-comers with complementary diagnostic

1L NSCLC trial failed to meet primary endpoint in patients with PD-L1 ≥5%

Withdrew sBLA for Opdivo + Yervoy in 1L NSCLC for TMB-high; awaiting data in 2019

The battle between the immune-oncology giants such as Merck, BMS, and Astratzenca, for market share in lung cancer helps illustrate the evolution of the pharmacodiagnostics landscape. Originally it appeared that Merck would focus on patients with high PD-L1 expression which made it more difficult for them to gain uptake in the 2nd line due to the inconvenience of having to do additional testing. However, when the products began pursuing 1st line indications, they were able to secure a monotherapy approval, while Opdivo failed its all-comers trial. Eventually, Merck was able to show efficacy of Keytruda in combination with chemotherapy in all patients thus propelling them to preferred positioning in the market place. Now, BMS and AstraZeneca are exploring the use of tumor mutational burden (TMB) as a potential means of sub-stratifying the population. However, one of the challenges with TMB is that even if BMS or AZ are ultimately success they will face the challenge in the future because others will seek to leverage the widespread availability of TMB, thus precluding exclusive access to this subset of the patient population. If a company were to leverage a novel proprietary technology, however, they could carve out a unique piece of the eligible population that others would not be able to quickly duplicate.

However, simply being proprietary does not mean the assay will be commercially successful. It is also important to consider the assay's overall feature set which helps determine the viability of the testing tool in clinical practice. The following considerations may be particularly important for a proprietary test.

Highly predictive of therapeutic response

For the assay to be valuable it must provide efficacy information which heretofore was unobtainable by other biomarker methods. Innovators should focus their efforts on certain parts of the disease treatment paradigm where there are not only limited and inferior treatment options but also limited diagnostics tools. For this diagnostic to have value, it must be highly informative of therapeutic response. Take for instance 2nd line NSCLC: what crucially limited the value of PD-L1 in determining Opdivo's response was that it was really just a "good to great" story – the drug worked well in all-comers but was only somewhat better in the biomarker-selected subgroup (see above Case Study).

Identifies a distinct and sizable prevalent population

In a similar vein, if the biomarker identifies a highly responsive patient subgroup but the size of that subgroup is exceptionally small, it will mute enthusiasm for testing and inherently limit demand. Part of the reason for the slow adoption of ALK testing associated with Xalkori use was not only the limitations and challenges of leveraging a FISH test but also the low biomarker prevalence of merely ~5%. Motivating community oncologists to look for this "needle in the haystack" proved to be quite challenging.

Sustainable technology workflow

Even if all the hallmarks just discussed have been met (i.e., an IP-protected, highly predictive assay identifying a distinct patient population), the assay is only commercially viable if it proves to be practically feasible in the real world. Most physicians simply won't bother with an assay that is only available in one lab in the world

and requires four weeks to turnaround testing results. Ideally, the assay would comprise instrumentation and software that can reduce logistical burden – potentially by performing more straightforward wet analytics locally while keeping the "black box" elements centralized but easily accessible through advanced computing.

Able to secure regulatory approval

Finally, another part of assuring access to the assay is being able to secure a pathway to regulatory approval. If the test can only be performed in a research context, it will have limited utility for clinical care. Interestingly this is becoming less of a barrier in recent years as the FDA has shown increasing flexibility in creating novel approval pathways for advanced diagnostic tools. This includes approval of pan-cancer biomarkers and NGS technologies. The FDA has also published documents offering guidance around the use of AI, algorithms, and machine learning tools in medical products.

Value for Diagnostic, Pharmaceutical, and Payer Stakeholders

Once a unique opportunity has been identified, all stakeholders (pharma, diagnostics innovators, physicians, payers, and patients) will want to see the promised value be transformed into reality through incorporation into everyday practice. Key to this will be balancing widespread access to testing with uniformity in test execution. Strategies aimed at mitigating the risks associated with development and launch of the assay should focus not only on assay design and validation but also on securing regulatory approval, commercialization viability, and the ability to drive adoption. This includes understanding the current market landscape, taking a deep dive into testing/tissue journey, developing test quality/market authorization strategy, identifying pathways to sustainable reimbursement, and dividing roles and responsibilities between pharma and its partners. However, if these challenges can be successfully navigated, the payoffs could be considerable.

If a pathway to market can be identified for a proprietary assay, the question then becomes how to capture the value of this innovation. At a high level, there are really just two key pathways: through the diagnostic test or through the associated drug.

Through the Test: Historically, diagnostic innovators have focused on creating tools that could help clinicians determine which patients might benefit from existing expensive therapies. The idea is this could reduce a trial-

and-error approach to treatment and provide significant cost-savings to payers, thus smoothing the pathway to reimbursement. However, diagnostic players should be aware that although this value story will help them secure payer coverage, payers have been reluctant to impose restrictions to novel therapies based on testing. This is in part due to the limited data supporting use of the assays, which are largely derived solely from clinical trials conducted by the pharmaceutical company. It is therefore unlikely that the most value will be secured through the launch of a reimbursed diagnostic test.

Through the Drug: Alternatively, a proprietary assay in an underserved portion of the care paradigm could provide disproportionate value for the pharma stakeholder manufacturing the associated therapy. In certain cases, to the drug manufacturer, the value created by accessing a unique patient population in a differentiated way may be well worth creating an alternative revenue-sharing model with a diagnostics partner. This has not happened historically because the diagnostic component has not brought enough value to the equation. However, if the principles for proprietary assays outlined above are followed, then that equation may change. Opportunities for application are not limited to oncology, and can include other disease areas where it has been challenging to define patient response (e.g., rheumatology) or where complex signatures are being explored (e.g., microbiome).

To definitively carve out unique territory, innovators should continue to explore the possibilities for novel proprietary biomarkers and tests in oncology. The introduction of new tools such as gene signatures, methods based on advanced imaging, or means to detect neoantigens suggest it is now viable to launch diagnostic methods that cannot be readily duplicated. Additionally, advances in FDA approval and business model/commercialization approaches suggest there is now a pathway being created to make this successful. Though no companies have yet to produce a true proprietary assay, development activities over the years have helped shape an oncology diagnostic landscape that is ripe for the introduction of innovative testing. ▬

CLEARVIEW
Healthcare Partners

About ClearView Healthcare Partners

Founded in 2007, ClearView Healthcare Partners is a global strategy consulting firm serving the life science sector.

The firm combines international industry knowledge and deep scientific expertise across a range of therapeutic areas with an extensive network of external stakeholders to deliver practical and actionable recommendations to our clients' most complex challenges. The firm's projects include cross-functional support at the corporate, franchise, and product levels for pharmaceutical, biotech, medtech and digital, and diagnostics companies worldwide.

About the author(s)

Charles Mathews
Principal, Boston
charles.mathews@clearviewhcp.com

Owen Im
Engagement Manager, Boston
owen.im@clearviewhcp.com