

Precision Medicine: Key Applications and Considerations for Commercial Success & Market Access

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PRECISION MEDICINE

Precision Medicine [1-3] is an approach to discovering and developing medicines and vaccines that deliver superior outcomes for patients, by integrating clinical and molecular information to understand the biological basis of disease creating a GPS map of human disease. This approach should lead to selection of better drug targets and identification of patient populations that have better clinical outcomes due to higher likelihood of response or lack of adverse events. When appropriate, these new treatments are focused on a particular subgroup of patients with certain phenotypic or genetic hallmarks that make them more likely to respond beneficially.

STRATEGIC APPLICATION OF PRECISION MEDICINE

One of the emerging challenges in the access and uptake of pharmaceuticals developed by the traditional drug development model is the inability to accurately pinpoint the specific population, in which the drug is supposed to be used for optimal benefit. This is particularly relevant for certain primary care diseases (e.g., hypertension, mild asthma, seasonal allergy, upper respiratory infections etc) where generic versions of effective treatments are increasingly available and unmet need is generally lower than in specialty and oncology areas. Increasingly, payers and reimbursement agencies around the world require submission of data cuts on the subpopulation, where many of the existing treatments may not be effective, and as such reimbursement and utilization of a novel treatment would be appropriate.

Treatments developed using the Precision Medicine approach may be perfectly suited for these types of situations, as the predictability of response can be significantly im-

proved by using appropriate biomarkers or diagnostics, to determine eligibility prior to administration of treatment. As such, therapies developed using the Precision Medicine approach may be able to command a higher price, driven by a greater value provided to each treated patient, and by reducing waste associated with treating patients not gaining benefit from the therapy. In addition, from a regulatory perspective, there may be fewer adverse events and therefore less potential for market withdrawal and fewer label restrictions; as well from a payer perspective, reimbursement hurdles may be lower due to elimination of costs associated with non-response to therapy.

The success of Precision Medicine is dependent on the appropriate selection of projects that benefit from its application. Ideally the following criteria are fulfilled:

- Strong human biology data package indicating that the drug target is a critical driver of disease and modulation of its activity is likely to produce a significant clinical benefit.
- Evidence of downstream pharmacodynamic effects as a consequence of engaging the target.
- Efficacy or safety biomarkers predictive of clinical benefit, allowing population stratification and diagnostics development if appropriate.

Biomarkers for patient stratification are typically not validated until phase II clinical trials, although it is ideal if they are available earlier. For the biomarker to be validated for use in patient selection, a clinically significant improvement in outcome (therapeutic index) associated with the biomarker is required. Validated biomarkers may be translated into a companion diagnostic used to identify a subpopulation that should (or should not) receive treatment if appropriate.

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Ideally, a drug and its companion diagnostic are developed and filed for approval contemporaneously based on the clinical relevance and technical performance criteria established using data from the clinical development program (as was done for Herceptin[®], Xalkori[®], and Zelboraf[®]). Contemporaneous development of a distinct FDA approved companion diagnostic with each single precision medicine is a cumbersome and expensive task that can slow the advance and uptake of novel life saving drugs. The recent progress in regulatory clearance of DNA sequencing platforms, opens the door for simpler development of multiplexed companion diagnostic assays for novel targeted treatments e.g., cancer drugs against mutationally activated oncogenes.

PRECISION MEDICINE CASE STUDIES

Example #1. Developing a cancer therapeutic for a targeted population: Xalkori[®]

Oncology constitutes the frontier of Precision Medicine, with patient selection defined by gene fusions (e.g. Gleevec[®], Xalkori[®]), somatic mutations (e.g. Zelboraf[®]) or protein over-expression (e.g. Herceptin[®]). Xalkori[®] a.k.a. Crizotinib was originally developed as a cMET kinase inhibitor, but also inhibits ALK and ROS kinases. In 2007 it was discovered that ~ 5% of patients with non-small cell lung cancer (NSCLC) express an EML4-ALK fusion protein in which ALK kinase is constitutively active [4]. Phase I clinical trials were rapidly amended to include a molecularly defined EML4-ALK cohort. Impressive efficacy (~ 60% ORR) allowed rapid progress from Phase I directly to Phase III. Contemporaneous FDA approval of Xalkori[®] and a diagnostic FISH test (Vysis) was achieved in August 2011 in a record five years after the start of the first clinical studies, and with relatively few patients. Had the clinical trials been conducted in a non-selected NSCLC patient population, the strong clinical efficacy would not have been evident (number needed to treat (NNT) of ~ 40 for the broad population vs. ~ 2 for the EML4-ALK population), and this compound most likely would never have become a medicine.

Unfortunately most patients become resistant to Xalkori[®] (and other targeted therapies). Resistance mutations can be identified by next generation sequencing (NGS) and used to inform the design of second generation compounds. Furthermore, combining chemotherapy or targeted therapies with harnessing the

immune system with “checkpoint modulators” or by potentiating patient T Cells with recombinant proteins or gene therapy promises to dramatically increase the number of patients that obtain real cures using Precision Medicine. The use of “liquid biopsies” e.g. circulating tumor cells for early detection of cancer and monitoring of response as well as more precise diagnostics such as standard sequencing of the tumor and monitoring the state of tumor infiltrating lymphocytes also promise to further improve outcome for patients. At the point of care multiplexed diagnostic assays particularly those employing NGS technology will become increasingly important due to limited sample availability and the practicality of only one or a few diagnostic tests.

Example #2. Leveraging insight from human genetics: PCSK9

The rapid progress in human genetics enables easy identification of the genetic cause for many diseases with “extreme phenotypes”. For example, individuals with a mutation in the PCSK9 gene have very low LDL-cholesterol and significantly reduced incidence of CV disease but are otherwise normal [5]. Based on these findings several companies are developing anti-PCSK9 antibodies. One such antibody, RN316, shows significant and long lasting declines in LDL-cholesterol in many patients with elevated LDL-cholesterol. Another application of genetics is in functional analysis of gene variants identified by genetic studies. Differentiated iPS cell lines with distinct variants of the target gene introduced by genome editing (with TALEN, CRISPR or similar approaches) is becoming a main stream tool for interrogating the functional consequences of gene variants in a physiologically relevant setting.

Example #3. Understanding the molecular basis of adverse drug events to create safer therapeutics: Tysabri[®]

Precision Medicine can be employed to deliver better clinical outcomes by selecting patients for treatment to avoid drug-related adverse events. An analysis of drugs with pharmaco-genomic Biomarkers in their label demonstrated that 62% of the biomarkers are used for exclusion of patients or dose adjustment to avoid certain adverse events [6]. The majority of safety biomarkers detect polymorphisms in genes for metabolizing enzymes or drug transporters in order to ensure adequate drug exposure. Other safety biomarkers focusing on idiosyncratic toxicity frequently measure enzyme deficiencies or immune response (e.g. HLA genes). A parti-

cular impactful example is that of Tysabri®, an immunosuppressive α 4-integrin antibody for treatment of Multiple sclerosis. The rare and sometimes fatal occurrence of PML caused by JC Virus was threatening this multi-billion dollar franchise and the availability of an effective therapeutic to patients. The finding that 99% of PML cases could be predicted by anti-JC virus antibodies provided an effective way of excluding patients that may experience PML [7].

Example #4. Importance of aligning therapeutic and diagnostic test with clinical practice for achieving commercial success: Celsentri/Selzentry®

Celsentri® belongs to a class of anti-retrovirals referred to as CCR5 antagonists. CCR5 antagonists prevent the binding of HIV to the CCR5 co-receptor present on the surface of the CD4⁺ T cell, thereby preventing the virus from entering these cells and the resultant viral replication. Celsentri®'s targeted activity against CCR5 tropic virus requires that patient responders be identified via a tropism diagnostic prior to therapy initiation. When the product was first launched, the only validated tropism diagnostic was offered by a single diagnostic manufacturer. Even though Celsentri® was a very targeted therapy with proven efficacy, the implication of having the tropism assay done by a single assay manufacturer, resulted in a logistical challenge of having a blood sample drawn, having it shipped across continents and waiting for confirmation prior to administration of treatment; this resulted in limited uptake and commercial success. This identified limitation points to the inherent need for a diagnostic-drug combination that can be co-administered, with the drug administration following confirmation of diagnosis by the companion diagnostic that is available widely and conducted with minimal logistical hurdles, ensuring compatibility with clinical practice.

COMMERCIAL AND MARKET ACCESS CONSIDERATIONS

Commercial development of therapeutics developed with a Precision Medicine approach requires careful thought. They may command an attractive price and greater reimbursement due to enhanced value to patients and payers, improved patient compliance and fewer failures. There may also be less adverse events and hence decreased potential for market withdrawal and label restrictions. These advantages, however, are balanced by a more fragmented market that may limit sales potential.

For these reasons, it is critical to build a convincing case for the clinical benefit and therapeutic index of the medicine in the defined patient population. Such a case could be strengthened through the health economic and/or health technology assessments increasingly used by public health bodies to support reimbursement recommendations for medicines and devices. From a payer perspective, there are many potential benefits of Precision Medicine that might increase the value. Benefits include improved risk estimates and optimized treatment as well as diagnostics or other tests that can identify high risk patients at an early stage of disease. Importantly, the ability to identify the patients who are more likely to respond to treatment or less likely to experience adverse events will be a strong driver of value as payers balance mounting healthcare costs versus healthcare funding constraints and decreasing budgets.

Even though the promise of Precision Medicine is certainly there, there are significant hurdles that need to be overcome from a policy and infrastructure perspective, for the promise to be realized:

First of all, evaluation of the diagnostic and therapy are currently conducted separately by regulatory and reimbursement agencies. This results in disconnect in the assessment, and creates a potential hurdle for the full realization of synergistic value from a precision medicine approach, as diagnostics by themselves may not be cost-effective. In addition, the pathway for assessment of diagnostics is relatively unclear, leading to sometimes protracted time for approval and delay in the medicine reaching the appropriate patient.

Second, current Health Technology Assessment methods and reimbursement models do not have a mechanism of uniformly assessing diagnostics, and appropriately linking payment for diagnostics to the value generated. This has been apparent due to lack of or in some cases reduction in reimbursement rates for diagnostics measures or scans (e.g. bone density scans), with the pharmaceutical manufacturer picking up the costs for diagnostic testing in many cases (e.g. KRAS tests).

Third, in absence of a clear direction and incentive to simultaneously develop the medicine and the diagnostic, pharmaceutical manufacturers have been reticent to setup co-development platforms and infrastructure, which would facilitate the development and value demonstration of the diagnostic-medicine package.

Fourth, lack of clear intellectual property designations for diagnostic tests has resulted in limited interest on behalf of diagnostic ma-

nufacturers, to comprehensibly develop and demonstrate value of the tests.

Finally, today's episode-of-care based reimbursement systems do not create appropriate incentives for adopting a targeted approach to treatment in clinical practice; a move towards outcome-based reimbursement would be required for adoption of diagnostics and

the full benefits of Precision Medicine to be realized.

Precision Medicine certainly holds a lot of promise to change the way pharmaceuticals are developed and delivered; however, a lot of progress still needs to be made within the regulatory, reimbursement and policy framework for this promise to become a reality.

REFERENCES

1. Desmond-Hellman S. Toward precision medicine: a new social contract? *Sci Transl Med* 2012; 4:1-2; <http://dx.doi.org/10.1126/scitranslmed.3003473>
2. Toward precision medicine: Building a knowledge network for biomedical research and a new taxonomy of disease. Washington, DC: The National Academies Press, 2011
3. Sogaard M, Dolsten M. Precision medicine: an approach to R&D for delivering superior medicines to patients. *Clinical and Translational Medicine* 2012; 1: 7; <http://dx.doi.org/10.1186/2001-1326-1-7>
4. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2013; 448: 561-6; <http://dx.doi.org/10.1038/nature05945>
5. Pacanowski MA, Zineh MA. Pharmacogenomic strategies in drug safety. *Drug Discov Today: Therapeutic Strategies* 2012; 9: e67-e74; <http://dx.doi.org/10.1016/j.ddstr.2011.04.002>
6. Cohen JC, Boerwinkle E, Mosley TH Jr, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006; 354: 1264-72; <http://dx.doi.org/10.1056/NEJMoa054013>
7. Subramanyam M, Belachew S, Compton T. More on JC Viremia in Natalizumab-Treated Patients with Multiple Sclerosis. *N Engl J Med* 2013; 369: 1279-80; <http://dx.doi.org/10.1056/NEJMc1308784>