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Pharma's Progress In Precision Medicine

by Nancy Dvorin

Precision medicine is significantly impacting pharma dealmaking, R&D and market access, according to a new report from Datamonitor Healthcare.

Precision medicine is about more than molecularly targeted treatments. It increasingly refers to a far broader notion of getting the right therapy to the right patient at the right time, using any one or more of a multitude of tools and technologies. It is about getting better data about patients' conditions, needs and lifestyles in order to allow the most appropriate treatment, and, ultimately, effective prevention strategies.

Precision Medicine and The Future of Healthcare , a new report from Informa's *Datamonitor Healthcare* division, indicates that the practice of precision medicine remains rare, for now. Its implementation demands robust data infrastructure as well as cultural changes.

But the report, authored by frequent *In Vivo* contributor Melanie Senior, reveals that precision medicine is already significantly impacting pharma R&D and commercialization. Scientists' growing understanding of disease biology is driving the identification of new disease subtypes, and thus the development of more specialist treatments, designed for more specific patient groups. In 2015, over a quarter of all new drugs approved by the FDA were personalized medicines, according to the Personalized Medicine Coalition, which defines such treatments as including reference to a specific biomarker in the label, identified by a diagnostic. These more targeted medicines are supported by smaller, potentially shorter clinical trials with far more precisely defined patient selection criteria. Thus trial recruitment strategies and trial design are changing.

Pipelines Filling Diagnostic-Linked Candidates

A growing number of development programs include biomarkers and biopharma firms believe the number of personalized medicines in development will *increase by almost 70% between 2015 and 2020*, according to a Tufts Center for the Study of Drug Development report in 2015. *AstraZeneca PLC*, for instance, expects half of its new drug launches to include companion

diagnostics by 2020. The big pharma's lung cancer drug *Tagrisso* (osimertinib) is an example of a next-generation targeted treatment: it is aimed at patients with a very specific mutation that confers resistance to an older kind of less narrowly targeted therapy, epidermal growth factor receptor inhibitors such as *Roche*'s *Tarceva* (erlotinib) or AstraZeneca's own *Iressa* (gefitinib).

This new, vastly more complex disease taxonomy and increasingly targeted medicines are forcing new kinds of trial design and recruitment strategies. Patients have to be carefully pre-selected less in terms of age, race and co-morbidities and more according to the genetic profile of their disease. Novartis' Signature Trial, for instance, matches experimental therapies to specific mutations found in some cancer patients' tumors Recently listed *Blueprint Medicines Corp.* uses genomic profiling to match compounds from a library of kinase inhibitors with the cancers they are most likely to treat; the company attracted a multi-program licensing deal from Roche in March 2016.

This pre-selection means suitable study patients may take longer to find, yet they are also those most likely to respond to the treatment. This selection reduces development risk, and may indeed reduce costs, too, by allowing efficacy to be demonstrated via far smaller, potentially shorter clinical trials. AstraZeneca's Tagrisso took only two years to get from human trials to approval, and was tested in just over 400 patients; Iressa took over three times that, and was tested in 3,000 patients.

Targeted Drugs May Lower Reimbursement Risk

These new patient selection strategies may also reduce reimbursement risk by offering payers more compelling efficacy data among a more narrowly defined patient subgroup. Indeed, most payers appear to prefer reimbursing drugs designed for specific high-responder subgroups, according to a forthcoming Datamonitor Healthcare study of payers and payer-advising key opinion leaders on reimbursement of non-small cell lung cancer (NSCLC) agents. In the US, *Merck & Co. Inc.*'s *Keytruda* (pembrolizumab) is approved for NSCLC patients who overexpress the PD-L1 marker, whereas *Bristol-Myers Squibb Co.*'s *Opdivo* (nivolumab) can be used regardless of PD-L1 status.

Clear markers of effectiveness among a manageable patient group could also make outcomes-linked pricing deals more practicable than they have proven to date – and shorten the time frame to convince payers of a drug's real-world efficacy.

Higher Sales Not Guaranteed

Payers' Perspectives

- "From a payer's perspective, the more targeted a therapy can be, the more desirable it is for us because if it is

Still, although narrowing the target population for a drug may improve the economics of its R&D and please payers, it also risks reducing its overall commercial potential (assuming a cap on the extent to which prices can be raised). There are some high-profile examples of targeted medicines that have become blockbusters: Roche's breast cancer drug *Herceptin* (trastuzumab), for instance, or *Novartis AG*'s leukemia treatment *Gleevec* (imatinib), both of which are used in conjunction with diagnostic tests.

But there is little evidence so far that more targeted medicines are systematically more commercially successful. It appears, for now, that the opposite is just as likely to be true. Until its recent Phase III failure at least, Bristol-Myers Squibb's lung cancer drug Opdivo, which does not require concurrent diagnostic testing, has fared better than its same-class competitor, Keytruda, despite payer preference for personalized agents. This example highlights one of the hurdles facing more widespread molecular precision medicine: it takes time to order a test and wait for the results, so if a similarly effective therapy is available that does not require these extra steps, it will have an edge in terms of uptake.

targeted toward those who overexpress a particular marker or underexpress a particular marker, that allows us to target a population more closely and manage it [just like the melanoma drugs with BRAF mutation and V600E]." US payer

- "I think [clinical trials for PD-L1-positive patients] will reassure the health authorities to have more targeted access. I am in favor of targeting the access to patients with positive biomarkers." French payer-advising key opinion leader
- "We prefer if possible to extract a highly responsive subgroup of patients, so that we can get the optimal response to selecting that patient group." UK payer-advising key opinion leader

Digital Technologies Encourage Patient-centric, Personalized Solutions

Scientific and technological advances mean pharma will continue to develop more specialist, targeted therapies. Yet the conjunction of digital technologies and patient empowerment are also compelling it to develop other kinds of more patient-centric solutions that may, too, ultimately amount to precision medicine. Many of these solutions may expand beyond pharmacological therapies to include tools and services to aid compliance or support healthier lifestyles. (*(Also see "How Patients Are Transforming Pharma R&D*" - In Vivo, 9 May, 2016.).)

There are challenges facing digital medicines, just as there are facing diagnostic-linked treatments. Yet the forces driving both – the quest for more efficient R&D, for drug prices that reflect value, for better outcomes and for greater patient involvement – are unstoppable, leaving pharma with little choice but to embrace precision medicine in all its flavors.

Partnerships Critical

Embracing precision medicine, whether driven by molecular or other kinds of tools, requires pharma to collaborate. It must partner both with traditional health care stakeholders, and also with experts from other sectors, including for instance technology, data analytics and consumer care-focused groups.

> ***Pharmas will need to engage more collaboratively with payers and providers to work out how to collect the outcomes data that are increasingly necessary to support the prices of targeted therapies.***

Roche is an outlier among pharma firms in its investment in diagnostics to date; its largest recent deal, in early 2015, was acquiring a 57% stake in cancer profiling firm *Foundation Medicine Inc.* (*(Also see "Which Path Forward For Foundation Medicine?*" - In Vivo, 17 Jun, 2015.).) But others are now accessing diagnostics expertise, too, as they embrace precision medicine. AstraZeneca in June 2016 tied up with Foundation Medicine to develop a companion diagnostic for cancer drug *Lynparza* (olaparib), in order to expand the use of the drug in further cancer types beyond ovarian and peritoneal, where it is currently approved. *Astellas Pharma Inc.* in 2015 struck a deal with Roche's *Ventana Medical Systems Inc.* to develop a companion diagnostic for the Japanese firm's Phase I cancer candidate.

And not all deals are in cancer: AstraZeneca in 2015 announced a deal with *Abbott Laboratories Inc.* to develop a diagnostic to test which patients might respond to a late-stage asthma drug, and with scientists at the Montreal Heart Institute, who will screen thousands of patients to find genetic traits linked to heart disease and diabetes. In 2014, *Eli Lilly & Co.* and *Janssen Pharmaceutical Cos.* both struck broad diagnostics deals with, respectively, *Qiagen NV* and *Adaptive Biotechnologies Corp.[See Deal][See Deal]*

The number of acquisitions and licensing deals among big pharma and diagnostics firms has remained relatively stable over the last three years, according to Informa's *Strategic Transactions*. But big pharmas are not the only players looking for diagnostics expertise. Engineering giant *Siemens AG*, for instance, is buying into molecular diagnostics as it positions itself as a partner to providers seeking improved outcomes and lower costs. Siemens in May 2016 bought German start-up NEO New Oncology GMBH, which launched *NeoLiquid*, a blood-based cancer test, in November 2015. The start-up claims the test can detect all therapeutically relevant genetic

changes in circulating tumor DNA.

Pharma firms have begun to collaborate with one another to test the viability of certain treatment combinations, particularly in cancer. They will need to engage more collaboratively with payers and providers to work out how to collect the outcomes data that are increasingly necessary to support the prices of targeted therapies. Examples of such pay-for-performance deals are emerging, for instance around Novartis' heart drug *Entresto*, though they remain exceptional. Pharma must also maintain regular dialogues with regulators as new trial designs and treatment characteristics emerge.

A Long-Term Game

The scientific, regulatory, commercial and cultural hurdles will take time to overcome, but they are surmountable and many are already being addressed. Science and market forces have driven biopharma firms toward more targeted drug development and several are using new trial recruitment approaches to facilitate that. Insurers have started to reimburse genome sequencing tests

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The moves toward precision medicine are also forcing diagnostics issues into the limelight. Several US payers, including [United Healthcare Services Inc.] and Independence Blue Cross have started to reimburse whole-genome sequencing, albeit for now only in a limited number of late-stage cancer patients. Evidence demonstrating the clinical utility of whole-genome sequencing is not exactly overwhelming, "but payers can't stay on the sidelines. Five years from now, everyone will be using [next-generation sequencing tests], so we need to learn as much as we can today about it," opines Anthony Coletta, EVP and president of facilitated health networks at Independence Blue Cross.

There are calls for Medicare and Medicaid to do the same. There is no evidence yet that this approach will help patients. But in principle, payers and providers would prefer to use multiplex tests that pick up several gene mutations in one go, rather than paying for a series of tests for individual mutations. Such multiplex tests are emerging — though their accuracy, and economics, remain unclear.

As diagnostics gain in prominence, along with clinicians' understanding of how to best use them, the "treat" mind-set will begin to be challenged, especially as empowered patients demand more information and choice on their options, and as the quest for cost-effective outcomes continues.

Most importantly perhaps, the number of health systems and practices trying to implement precision medicine is growing. Many of these experiments are occurring within integrated health systems (also known as integrated delivery networks). These, coupled with several of the top, best-funded research-focused hospital systems, are, by and large, leading the way in precision medicine. Some already have access to electronic health records and more comprehensive patient data. Some are attempting to integrate data from across a further variety of sources. Several of the US precision medicine efforts are funded by philanthropists, such is the promise of precision medicine to transform health care – and the challenge of accelerating it using only government and industry funding. As more providers become part of accountable care organizations (ACOs), groups of hospitals and doctors incentivized to offer high-quality, coordinated care, there will be more interest in the potential efficacy gains from precision medicine. But for now, most ACOs – themselves still a minority among health care providers in the US – are still struggling to integrate, to provide coordinated care and to generate savings from standard medicine. For the vast majority of US health care providers, precision medicine is tomorrow's, not today's, challenge.

And it may, even then, only be a challenge in select disease areas, most obviously cancer. Molecularly based precision medicine is not likely to be practicable or affordable across all therapy areas, and all health systems, at least not in the foreseeable future. For chronic conditions like diabetes or heart disease, digitally enabled precision medicine, supported (for example) by new wearable technologies, is probably a far more scalable and nearer-term solution to providing more personalized care. Not all medicines can or will become more targeted in themselves; health systems, at least in their current guise, cannot afford to pay for hundreds of targeted therapies for ever-smaller population groups. Instead, many therapies may be prescribed and administered in a more focused fashion. (*(Also see "Digital Health Is Changing Health Care. Is it Changing Pharma?*" - In Vivo, 16 Jun, 2014.).) So for example, new data sources may allow patients to be segmented by lifestyle or behavior patterns, with treatment plans tailored accordingly. Population-based care paradigms will continue to be paramount, with precision medicine approaches enhancing these in selected therapy areas and health care systems.

However challenging its progress and adoption, precision medicine is here to stay. Genomic sequencing is more affordable, data are more easily shared, and patients are becoming advocates for their own cures and care. When those elements combine – genomics, technology and passion, it's unstoppable, opines Multiple Myeloma Research Foundation founder Kathy Giusti. As in so many areas, "it's the old structures and systems that are stopping this. Not individuals or technology."

For more information on Datamonitor Healthcare's August 2016 report, Precision Medicine and the Future of Healthcare, contact reportstoreleads@informa.com.