

The Case for a Distributable CDx Model

Precision Medicine

The past decade has been an exciting era in healthcare for patients and providers with the increasingly broad adoption of precision medicine in drug development, clinical trials and approvals. The rise of precision medicine means patients have access to targeted, potentially more effective, therapies based on their genetic responses to treatment pathways. At the forefront of this trend is oncology. In oncology alone, by 2019, more than 160 biomarkers were approved for targeted therapy selection by the U.S. Food and Drug Administration (FDA). Further, more than 90 percent of pivotal clinical trials currently underway are to evaluate drugs aimed at specific molecular targets for the treatment of cancer.¹

The trend of precision medicine development particularly in oncology is not only happening in the United States, but also across Europe and Asia Pacific regions. In Japan, for example, the Lung Cancer Genomic Screening Project for Individualized Medicine project (LC-SCRUM) was established in 2013 as a National Cancer Screening Program to screen target genes in lung cancer in an effort to advance the development of new molecular targeted drugs and diagnostics. As of August 2020, LC-SCRUM has expanded to more than 200 institutions in Japan and six institutions in Taiwan. LC-SCRUM is now in phase 4 of its program and continues to expand cancer screening in additional Asian countries.²

Other countries have launched their own precision medicine initiatives as well. In the United Kingdom, the 100,000 Genomes Project was launched to better understand rare diseases and cancer with the aim of integrating personalised data into healthcare delivery.³ The World Economic Forum has also established a precision medicine program to encourage collaboration between governments, industry, academia and patient groups to ensure more patients have access to advances in precision medicine on a global scale.⁴

The Rise of NGS Companion Diagnostics

With the increase in targeted therapies available to patients comes a growing need for companion diagnostics (CDx) to find patients who may benefit from these treatments. Companion diagnostics first emerged more than a decade ago. In 2011, the FDA published draft guidance on CDx development and since then has worked with pharmaceutical companies and diagnostics companies on the development and approval of CDx tests to coincide with new drug launches.⁵

Next-generation sequencing (NGS) has emerged as an ideal solution for CDx development because it enables testing for multiple biomarkers associated with multiple therapies simultaneously from a single sample. Because current targeted therapies available are often approved to treat advanced stage cancer, tissue samples – typically from a small biopsy or cytology specimens – are often not sufficient to be run through multiple single gene tests. Further, single gene testing can be time consuming. As a result, molecular testing is shifting to multiplex genetic tests and pharmaceutical companies are increasingly partnering with testing companies in early stages of drug development to bring NGS CDx tests to market in parallel with new therapies to increase opportunities to reach patients with targeted, potentially more effective treatment.

Over the past five years, more than 20 pharmaceutical companies have announced CDx partnerships with leading NGS companies, including Thermo Fisher Scientific.

The FDA has approved several NGS CDx tests to-date. Most approved CDx tests are designed to be run in centralised reference labs, while in contrast, Thermo Fisher's Oncomine Dx Target Test was designed with a global distribution model in mind to be implemented in any hospital lab.

Distributable NGS CDx Model vs. Centralised Lab Service NGS CDx Model

To reach as many patients as possible, pharmaceutical companies will typically plan for a phased global launch of a targeted therapy, which requires bringing new

targeted therapies and their accompanying CDx tests through regulatory approvals in key regions including the U.S., the European Union, Japan, Latin America and Asia Pacific countries. In each region, regulatory and reimbursement environments vary greatly, and navigating them can be a challenge as pharmaceutical companies seek to reach as many patients as possible through CDx testing.

In the U.S., send-out, or outsourced, testing to centralised reference labs is a well-established model, though there's a much-needed effort underway to bring testing closer to patients at the community level to enable faster turnaround time and broader access to therapies. In addition, centralised testing is often not feasible in regions outside of the U.S. where the financial or logistical burden of centralised testing is too high. Thus, driving patient testing access for a new drug requires a distributable NGS CDx test that can be easily deployed through local laboratory networks based on countries' regulations, payor policies and testing environments. Key factors such as sample send-out challenges, turnaround time and reimbursement economics may result in local environments where a distributable NGS CDx model is favorable over reliance on a centralised lab service-based NGS CDx.

Sample send-out challenge

In Europe, for example, sending samples out of the country to a U.S. centralised lab for CDx testing is generally not an accepted practice. To most efficiently determine patients who may benefit from targeted therapies – and to reach as many patients as possible – a local, distributable CDx testing solution that can be implemented in any hospital in-country is necessary in such scenarios.

Turnaround time

Shorter turnaround times (TAT) are critical to match patients with appropriate targeted therapies without delaying care, especially for patients with aggressive or late-stage cancers. The median life expectancy for stage IV non-small cell lung cancer (NSCLC) is 16 weeks⁶ and guidelines recommend a TAT goal of one week, up to a maximum TAT of two weeks.⁷ Hence, a distributed CDx test

offered at a local lab can offer a significant advantage in faster turnaround time for results versus sending patient samples to a centralised lab that, in some cases, may even be located in another country. This may allow physicians to start patients on effective targeted therapies earlier in their care journey.

Reimbursement economics

Significant progress has been made in the past five years by the U.S. Centers for Medicare and Medicaid Services to expand national coverage to all NGS CDx tests approved by the FDA. However, outside of the U.S., many countries are behind with NGS reimbursement, often with more restricted coverage and substantially lower reimbursement thresholds, which ultimately can result in more of the cost being passed on to patients. By more closely aligning costs with local reimbursement standards, a distributable model allows CDx tests to be much more affordable to patients under local reimbursement payment structures.

CDx in Japan: A Case Study for the Distributed NGS CDx Model

Japan is one country where a localised CDx model has proven invaluable. Japan has been an early adopter of precision medicine, making it an important market for pharmaceutical companies. More than 20,000 patients with advanced solid tumours have participated in SCRUM-Japan, making it the world's largest genomic screening program. The project has directly impacted access to new therapeutic drugs and diagnostics in the country, enabling 11 new drugs (13 indications) and seven in-vitro diagnostics approvals.

As new drugs and diagnostics are developed, the country has also continued to evolve regulatory guidance for the use of CDx and new, targeted therapies. In Japan, CDx test results are required for clinicians to prescribe therapies for patients. The adoption rate of the CDx test has a direct impact on the number of patients that can be identified for therapies. As of 2021, three NGS CDx tests have been approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, including Oncomine Dx Target Test.

Oncomine Dx Target Test, a distributable NGS CDx test, was the first NGS CDx test approved by PMDA in April 2018 as a companion diagnostic for BRAF in NSCLC. In Feb. 2019, PMDA expanded approval for the test as a companion diagnostic for EGFR,



ALK, and ROS1 in NSCLC. The test was then approved by the Ministry of Health, Labour and Welfare (MHLW) for reimbursement in June 2019 and has since been widely adopted in leading commercial labs and hospital labs in Japan. By aligning with local reimbursement thresholds, labs can provide CDx testing services, without incurring large out-of-pocket cost for the patients. As of December 2020, more than 30,000 patients have been tested by the Oncomine Dx Target Test in Japan.

In contrast, a centralised test recently approved as a companion diagnostic for a MET inhibitor has seen slow uptake in Japan due to hospital CDx reimbursement issues. The out-of-pocket cost of centralised companion diagnostic testing is simply too high for medical institutions, which often can only claim reimbursement for far less than the actual costs of these tests. This prompted the Japan Lung Cancer Society and the Japan Lung Cancer Alliance to jointly issue a new guideline recommending using Thermo Fisher's Oncomine Dx Target Test to initially screen patients to see if they are positive for MET exon 14 skip, and to use the centralised CDx as a confirmatory test before putting the patients on therapy.

Conclusions

As pharmaceutical companies determine the best approach for collaborating with a CDx partner, the most important consideration is of course the ability to benefit patients. Local regulations, reimbursement and testing environments have an important impact on identifying patients for treatment. Japan is just one example of a country where a distributable NGS CDx model that fits local reimbursement economics and enables in-country testing is essential to put more patients on targeted therapies. In many regions, a distributable NGS CDx may be far more advantageous than a centralised lab service NGS CDx as a global solution that can be deployed locally, cost effectively and with fast turnaround time to drive the broadest

adoption of targeted therapies and improve patient outcomes.

REFERENCES

1. Albrecht, B., Alfano, S., Keane, H., Yang, G. Delivering innovation: 2020 oncology market outlook, McKinsey (2020)
2. LC-SCRUM ESMO presentation, 2020
3. National Academies of Sciences, Engineering, and Medicine; Division on Earth and Life Studies; Institute for Laboratory Animal Research. Advancing Disease Modeling in Animal-Based Research in Support of Precision Medicine: Proceedings of a Workshop. National Academies Press (US); 2018 May 30. 2, Existing Precision Medicine Initiatives.
4. <https://www.weforum.org/communities/precision-medicine>, visited on 9 July, 2021
5. Mansfield, E. FDA Perspective on Companion Diagnostics: An Evolving Paradigm. Clin Cancer Res. 20(6), 1453-1457 (2014)
6. DiStasio, M. et al. Molecular Testing Turnaround Time for Non-Small Cell Lung Cancer in Routine Clinical Practice Conforms Feasibility of CAP/IASLC/AMP Guideline Recommendations: A Single-center Analysis. Clinical Lung Cancer 18(5), 349-356 (2017)
7. Lindeman, N. et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors. Journal of Thoracic Oncology 8(7), 823-859 (2013)



Jane Li

Jane Li has been serving as Senior Director, Global Companion Diagnostics Commercialization for Thermo Fisher Scientific's Clinical Sequencing Division since 2015. Previously, she was Senior Director, Clinical and Pharma Services for the Clinical Sequencing Division. She also held different roles in corporate strategy, business development, and M&A over the 20 years she's been with Thermo Fisher.