EXECUTIVE INSIGHTS

Move Precision Medicine Beyond Oncology: Keys to Successful Enterprise-Level Strategy

Fully integrated precision medicine (PM) strategies are increasingly critical to the success of drug development across therapeutic areas (TAs). At the epicenter of a successful PM strategy within oncology are the application of biomarkers and diagnostic testing, which generate scientific insights, improve clinical trial efficiency and improve health outcomes for patients and payers. These benefits in turn accelerate drug development and differentiate approved products.

There has been a notable acceleration of U.S. Food & Drug Administration (FDA) approvals for companion diagnostic (CDx)-guided precision oncology agents, with more than 30 new drug approvals over the past 10 years[1] (see Figure 1). FDA-approved diagnostics now support use cases that span the patient journey — particularly in oncology, from screening to prognosis/risk assessment to therapy guidance to monitoring. Examples of these diagnostics include Cologuard (screening), FoundationOne CDx (therapy guidance) and clonoSEQ (monitoring).

Because PM approaches have succeeded in driving R&D efficiency and improving patient outcomes in oncology, PM strategies are increasingly critical to success in TAs beyond oncology (e.g., neurology, immunology and cardiovascular disease (CVD)). For example, neurodegenerative diseases and CVD have historically been burdened by highly heterogeneous patient populations leading to:

- Large, expensive clinical trials
- Modest effect sizes and low clinical success rates
- Challenges in securing reimbursement[2]

Figure 1
Approvals for companion diagnostic-guided precision oncology therapies (2000-2021)

Source: L.E.K. analysis of 1998-2021 FDA approval letters for drugs with CDx (e.g., Herceptin, GLEEVEC, Tarceva, ERBITUX, Iressa, TASIGNA, LYNPARZA, XALKORI, Zelboraf, GILOTRIF, KADCYLA, ZYKADIA, KEYTRUDA, VENCLEXTA, Rubraca, TECENTRIQ, ALECENSA, IDHIFA, RYDAPT, NERLYNX, ALUNBRIG, ZEJULA, GAVRETO, PIQRAY, LIBTAYO, LORBRENA, EXKIVITY, LUMAKRAS, JEMPERLi)

Advances in technology, including blood-based diagnostics for neurodegenerative diseases and broad, consumer-focused genetic testing for CVD risk factors, are creating new opportunities to identify and define addressable patient segments within these diseases. By targeting these addressable segments, new therapies can achieve the clinically relevant effect size to support approval and market access. Biopharma companies must continue to evolve their approach to PM to capture the benefits already realized in precision oncology.

Challenges to precision medicine beyond oncology

In order to successfully implement PM strategies for additional TAs, organizations must prepare for emerging critical scientific, regulatory and commercial challenges while avoiding common organizational pitfalls.

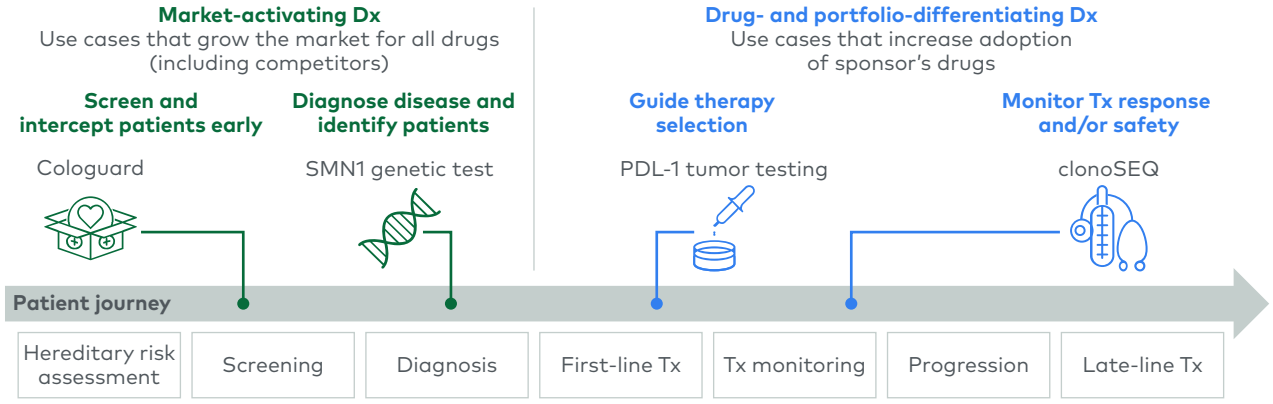
External challenges: technology and market access

- **Beyond oncology, many diagnostic partners may lack channel/technology capabilities to drive success.**
  Historically, pharma companies with limited PM capabilities have relied on diagnostics partners to drive testing. However, beyond oncology, many potential partners have never supported a clinical diagnostic before and therefore may lack scale, channel, regulatory and other "above the test" capabilities that will be critical to success in larger indications

with diffuse call points (e.g., sample access and logistical support). As PM expands beyond oncology, biopharma will need to play a larger role in driving market development with strategic investments rather than relying entirely on diagnostics partners for technology and commercial field force.

- **Emergent "market-activating" diagnostics may require biopharma to evolve its customer-engagement models.**
  The rise of these diagnostic testing nodes earlier in the patient journey is creating a new category of market-activating diagnostic use cases that may not be therapy- or prescriber-channel-specific (see Figure 2). Unlike therapy guidance or monitoring tests, these use cases can grow the market for all potential competitors within an indication and often require engaging a broader set of healthcare providers. In one example, screening tests that identify early-stage neurodegenerative patients may necessarily require drugmakers to expand channel strategy beyond geriatricians and neurologists and into routine primary care, where early screening occurs.

Figure 2
Diagnostic testing nodes are emerging earlier in the patient journey, creating market-activating Dx use cases



Source: L.E.K. research and analysis

- **Competitors are proactively pursuing PM.**
  Competitor activity will also create significant portfolio risk for PM laggards by raising barriers to entry and, potentially, encouraging market access and reimbursement gatekeepers to require PM solutions. For example, Eli Lilly's ERBITUX (Cetuximab) was approved by the European Medicines Agency (EMA) for use in patients with metastatic colorectal cancer agnostic of KRAS biomarker status.[3] However, the EMA restricted the use of ERBITUX to patients with exon 2 wild-type KRAS following the approval of Amgen's

Vectibix (panitumumab), which was approved in the narrower wild-type KRAS patient subpopulation, given strong patient response data.[4,5] The FDA promptly followed suit and recommended restricting both drugs to wild-type KRAS patients.[6] Competitors' PM strategies can significantly impact a company's portfolio opportunities and leave the organization at a competitive disadvantage (i.e., lacking compelling biomarker data to drive market access and reimbursement).

Internal challenges: organizational pitfalls

- **Taking a reactive approach to PM**
  Many organizations enter clinical development with a default "all comers" approach to trial design and are forced to incorporate a nuanced PM strategy only after failure to meet critical endpoints with the all-comers trial. However, by this point in development timelines, the time for collecting relevant samples may have passed and there is insufficient time to properly assess the optimal PM approach; this can lead to errors such as deploying subpar diagnostic tests, rushing partner selection or failing to consider global commercial needs for successful launch. This challenge is compounded in crowded indications, where competitors are actively designing development programs around PM strategies.

- **Lacking or siloed expertise (often limited to one brand or TA)**
  Historically, PM resources have been either absent, siloed within oncology business units (e.g., Novartis) or nested within a major development program (or brand) with significant PM needs (e.g., Merck's KEYTRUDA). This structure can be problematic for other development/brand teams that need PM resources but lack their own budgets, experts and capabilities. These resource constraints can drive many promising PM activities to "die on the vine" without PM advocates within those other business units.

- **Limited coordination of functions across value chain**
  PM and diagnostics resources are often split between research/biomarker teams and late development/commercial teams, which often leads to poor cross-functional coordination and clunky handoffs as candidate programs move from discovery into clinical development. Cross-functional coordination is further inhibited by limited (or late) communication about PM opportunities. Product development and commercialization stage-gating committees rarely discuss PM opportunities or diagnostic needs, which leaves many stakeholders without a venue to provide input.

Six steps to develop a precision medicine organizational transformation roadmap

Success in PM beyond oncology requires organizational commitment, coordination of resources and advanced planning. L.E.K. Consulting has developed a PM transformation roadmap to help organizations prepare and implement a successful enterprise-level PM strategy.

1. **Adopt a "PM as default" mindset**
   The first step is to reorient the organization's mindset to embrace PM with a top-down executive mandate for PM excellence. The goal should be for PM to be integrated into the DNA of the company, with organizationwide understanding of PM as a critical value enabler. Organizations should strive toward a PM-as-default mindset, where PM is the assumed approach for all programs. Companies with this mindset expect all programs to consider PM strategies early (e.g., What biomarkers might we need? How will we measure them?) and continually assess potential diagnostic needs throughout the program life cycle.

2. **Determine testing needs for each treatment**
   Next, companies must build a portfolio-level view of PM needs. This step involves assessing the current and future patient journeys for key portfolio indications to understand factors such as when and where the patient presents, who the managing providers are, what management decisions are made at each intervention point and what unmet needs remain to be addressed. When defining potential testing needs, organizations need to assess not only the role of the test in patient management (e.g., screening, therapy guidance, monitoring), but also the potential nature of the diagnostic required (modality, performance, sample, etc.). Often, organizations are surprised by the breadth of potential PM needs across their portfolios and the implications for cross-functional planning and resourcing required to succeed.

3. **Assess potential areas of test leakage**
   Understanding potential areas of test leakage, defined as aspects of test performance or the testing ecosystem that may result in failure to identify patients, is critical. L.E.K.'s diagnostic testing pain point and leakage framework (see Figure 3) can help identify barriers that an organization's PM strategy must address. Leakage can occur with testing directly (e.g., insufficient sample collection, analytical failure of a test such as a false negative) or within the broader ecosystem (e.g., limited awareness of need to test). By aggregating a view of potential pain points and leakage areas across the portfolio, an organization can identify the functional capabilities that will be required to drive a successful PM strategy.

Figure 3
Framework for assessing potential diagnostic testing pain points and key leakage areas

Leakage point		Factors to consider (current, evolution)
Testing	Pre-analytical	• Sample type and amount • Sample stability
	Analytical	• Analytical performance (sensitivity, failure rate) • Test interpretation
Market development	Awareness and incentives to test	• Diagnostic work-up/algorithm • Dx modality utilization
	Biopharma competitors	• Therapy pipeline • Biomarker/patient segmentation/diagnostics strategies • Pre-competitive activities (e.g., consortia)
	Diagnostic company interest and ability	• Channel presence (in testing ecosystem) • Company scale
Market access	Lab access	• Lab concentration • Sample flow patterns • Testing site economics
	Test reimbursement	• Policies/level • Requirements for therapy access

Source: L.E.K. research and analysis

4. Determine capabilities needed

Following an audit of patient leakage across the portfolio, an organization can identify common themes and clusters of potential failure points. Focused discussions with internal and external stakeholders, including lab directors, physicians and patients, can identify capabilities (technological and organizational) and best practices that can address these potential failure points. Key capabilities to consider include biospecimen access for biomarker discovery and validation, longitudinal patient sample collection and biobanking for clinical trials, diagnostics-specific regulatory and reimbursement expertise, diagnostics-specific medical affairs and field personnel, and above-the-test services (e.g., sample collection support, reimbursement support, sponsored testing) for commercial diagnostic tests.

5. Assess capability gaps and determine how to address

A successful PM strategy will include a mapping of current PM capabilities across functions to identify potential capability/capacity gaps. A highly cross-functional team is required for this gap assessment, as the expertise required for PM excellence is often siloed, insufficiently linked between business units or lacking altogether. Next, a strategic options assessment can inform whether the organization should build capabilities in-house, outsource/partner or execute strategic M&A to address the gaps.

6. **Implement change: Create a PM transformation management office**
   Finally, companies should implement change through a fit-for-purpose PM transformation management office. The remit of this office will depend on the organization's current PM capabilities, breadth of future PM needs and specific new capabilities required.

Best practices for precision medicine enterprise strategy

While the optimal capability set and organizational structure will be company-specific, there are select best practices for PM enterprise strategy that apply across companies. Namely, a successful PM strategy requires seamless integration of PM personnel, capabilities and knowledge into all critical functions across the value chain. Successful integration should also ingrain PM into key processes and decision-making forums, including asset development stage-gates, budgeting and long-range planning. For example, some leading PM companies require candidate target product profiles to include discussion of potential diagnostic opportunities (e.g., potential biomarkers and implications for technology platform partners). Integrating PM efforts across functions naturally reinforces the "start early and reevaluate often" decision-making paradigm that drives PM excellence.

Going forward, companies seeking to deploy PM strategies beyond oncology will struggle to succeed if they benchmark solely against best practices for precision oncology. Instead, companies should aspire to develop fit-for-purpose PM strategies and supporting organizations suited to the capabilities they will need in order to deploy winning PM solutions that help improve the lives of the patients they serve. Now is the time to leverage the power of precision medicine to unlock the next wave of innovative therapeutics in neurology, immunology, cardiology and other high-need therapeutic areas.

For more information, contact lifesciences@lek.com.

Endnotes

[1]L.E.K. analysis of 1998-2021 FDA approval letters for drugs with CDx (e.g., Herceptin, GLEEVEC, Tarceva, ERBITUX, Iressa, TASIGNA, LYNPARZA, XALKORI, Zelboraf, GILOTRIF, KADCYLA, ZYKADIA, KEYTRUDA, VENCLEXTA, Rubraca, TECENTRIQ, ALECENSA, IDHIFA, RYDAPT, NERLYNX, ALUNBRIG, ZEJULA, GAVRETO, PIQRAY, LIBTAYO, LORBRENA, EXKIVITY, LUMAKRAS, JEMPERLI)

[2]Example: PCSK9 inhibitors, a class of drugs intended to reduce the risk of cardiovascular events by lowering LDL cholesterol that includes Amgen's PRALUENT (alirocumab) and Repatha (evolocumab) were subject to intense access and reimbursement negotiations. The German Health Technology Assessment body found "no added benefit" for both drugs in this class, leading to reimbursement restrictions in Germany and other EU countries.

[3]Cancer Network, "Erbitux gains expanded approval in Europe," https://www.cancernetwork.com/view/erbitux-gains-expanded-approval-europe

[4]Fierce Pharma, "European Commission Approves Update of Erbitux Metastatic Colorectal Cancer Labeling to Patients with RAS Wild-Type Tumors," https://www.fiercepharma.com/pharma/european-commission-approves-update-of-erbitux-metastatic-colorectal-cancer-labeling-to

[5]Amgen press release, "Vectibix® (Panitumumab) Granted Approval for Expanded Indications in the European Union," https://www.amgen.com/newsroom/press-releases/2011/11/vectibix-panitumumab-granted-approval-for-expanded-indications-in-the-european-union

[6]Atreya et al., "Expanded RAS: Refining the Patient Population," Journal of Clinical Oncology (2015)

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