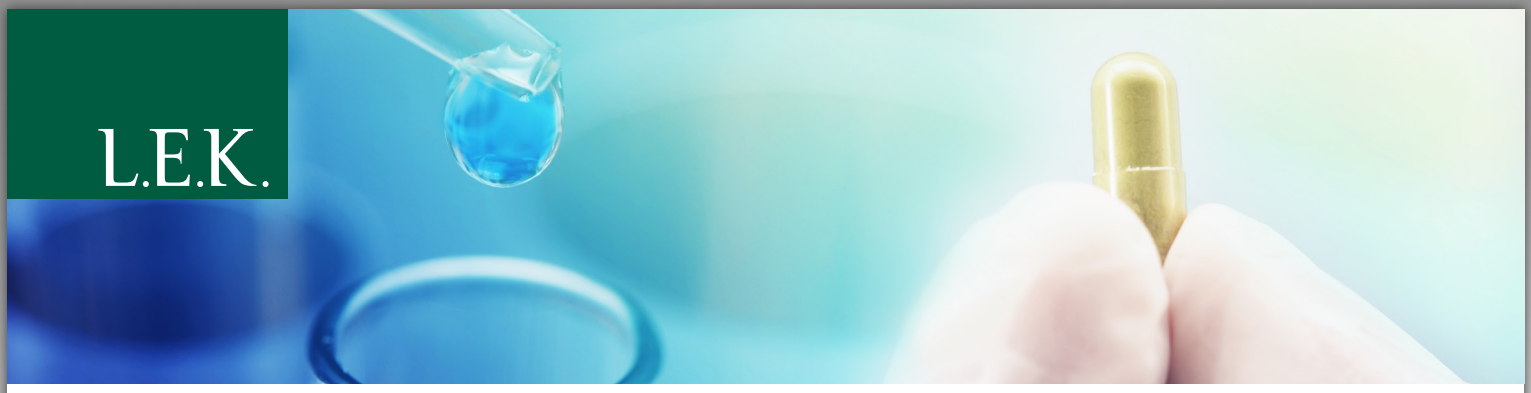

L.E.K.

EXECUTIVE INSIGHTS

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Working with Reference Laboratories to Support CDx Commercialization

Companion diagnostic (CDx) tests are indispensable to personalized medicine, but the commercialization of these tests raises challenges for biopharmaceutical companies, whose main objective is to ensure patients' unfettered access to the tests. Biopharmaceutical companies typically partner with global in vitro diagnostic (IVD) companies to complete the steps on the path to a successful CDx test: development, regulatory approval and commercialization. Generally, IVD companies help biopharmaceutical companies accomplish the first two steps, they often lack the incentives and resources required to drive the broad commercialization that biopharma companies expect.

We believe opportunities exist to work closer with reference laboratories to address CDx-related commercialization challenges and in some instances replace the need for IVD partnerships altogether.

Figure 1

Key CDx Development and Commercialization Steps and Partner Types

	Early stage			Late stage	
	Biomarker discovery	RUO test deployment[1]	IUO test deployment[2]	Regulatory test deployment	Commercial test deployment
Definition	Discovery and validation of relevant biomarkers (e.g., genomic, proteomic)	Diagnostic test for research use only	Diagnostic test used for early clinical trials (e.g., Phase 1) in CLIA-certified lab	Diagnostic test used in drug's pivotal trial to support FDA PMA approval	Includes regulatory tests, "follow on" IVD[3] tests and LDTs[4] used for patient testing
	Potential partners				
IVD manuf.	Test development			Test validation and regulatory submission	Test commercialization
Ref. lab			CLIA lab access		
Tools company	Novel technology access				
CROs		Clinical trial testing			
AMCs	Scientific expertise				

[1]Research use only. [2]Investigational use only. [3]An IVD test is a diagnostic test approved/cleared by the FDA for clinical use; it can be sold and distributed by its manufacturer. [4]An LDT test is a "home brewed" diagnostic test developed in-house by a CLIA-certified laboratory for clinical use; it is used solely in the laboratory that developed it and cannot be distributed or sold commercially

Sources: FDA, L.E.K. analysis

Working with Reference Laboratories to Support CDx Commercialization was written by **Brian Baranick** and **Alex Vadas**, managing directors in L.E.K. Consulting's Biopharma and Life Sciences practice. Brian and Alex are based in Los Angeles. For more information, please contact lifesciences@lek.com.

IVD Companies Are Key Partners for CDx Test Development

Biopharmaceutical companies continue to adopt personalized medicine approaches that leverage patient-specific biomarkers to identify and stratify patients. To deploy personalized medicine approaches, these companies must navigate multiple steps on the path to successful companion diagnostic (CDx) development, regulatory approval and commercialization (see Figure 1).

Most biopharmaceutical companies lack internal diagnostic capabilities for CDx testing, so they partner with a variety of third parties to access needed expertise as the CDx test progresses along its development path. Typically, biopharmaceutical companies partner with IVD manufacturers that play a significant role in supporting development of the regulatory test used in the associated drug's pivotal clinical trial. The IVD partner also coordinates regulatory filing and submission of the test in lockstep with the associated drug and takes on the primary role of commercializing the CDx test.

Until 2015, most of the CDx tests the FDA approved or cleared were for oncology to select for targeted therapies (see Figure 2). These success stories typically involve a single partnership between the biopharmaceutical company and a global IVD manufacturer (a couple of notable exceptions will be discussed).

Commercialization Challenges

IVD partners are well-suited to develop a CDx test, take it through regulatory approval, and even manufacture and distribute the test for global usage. For the following reasons, however, they may understandably struggle to provide the breadth of commercial support needed to ensure broad test access:

- CDx test market opportunities have historically been rather small (less than $50 million) and partnerships are often non-exclusive, thereby limiting incentives for IVD partners to put significant resources against commercialization

- IVD companies may lack the capabilities and resources required for test commercialization because they have:
  - Historically focused on placing instruments in clinical laboratories and often promote the instrument menu versus a specific CDx test
  - Small sales forces (10s of sales reps) with limited influence across stakeholders (e.g., providers, payers) outside those laboratories; in addition, selected stakeholders may not be contacted by biopharmaceutical sales reps thereby leaving a coverage gap

Figure 2
Approved Personalized Medicine Oncology Drugs as of 2014[1]

Drug Name	Drug Manufacturer	Therapeutic Area	Biomarker(s)	IVD Partner
Gilotrif	Boehringer Ingelheim	Oncology (NSCLC)	EGFR	Qiagen
Gleevec	Novartis	Oncology (leukemia and GIST)	C-Kit	Agilent (Dako)
Herceptin	Roche	Oncology (breast)	HER-2/Neu	Agilent (Dako)
Tafinlar and Mekinist	GSK	Oncology (melanoma)	BRAF V600E and V600K	bioMerieux
Tarceva	Roche	Oncology (NSCLC)	EGFR	Roche Molecular Systems
Vectibix[2]	Amgen	Oncology (colorectal)	KRAS	Qiagen
			EGFR	Agilent (Dako)
Xalkori	Pfizer	Oncology (NSCLC)	ALK	Abbott Molecular
Zelboraf	Roche	Oncology (melanoma)	BRAF V600E	Roche Molecular Systems

Notes: [1]Based on List of Cleared or Approved Companion Diagnostic Devices by FDA in December 2014. [2]Similar tests are approved for Erbitux
Sources: FDA, L.E.K. analysis

CDx Patient Leakage Can Be Significant

We have found that biopharmaceutical companies may fail to fully appreciate IVD partner constraints and may even tend to rely too much on their IVD partner for successful CDx test commercialization. These issues can lead to commercial challenges that often result in CDx-related patient leakage, in which potentially eligible patients fail to be tested. Patient leakage can occur at many places in the care continuum for a variety of reasons (see Figure 3), and while each driver may be a minor contributor, the aggregate impact can be significant (we have estimated leakage of up to 33% in selected cases).

The overall impact of CDx-related patient leakage can be highly detrimental to a launched therapy, especially if the test is required to determine a patient's candidacy. We expect leakage barriers could actually intensify in the coming years, driven by the following:

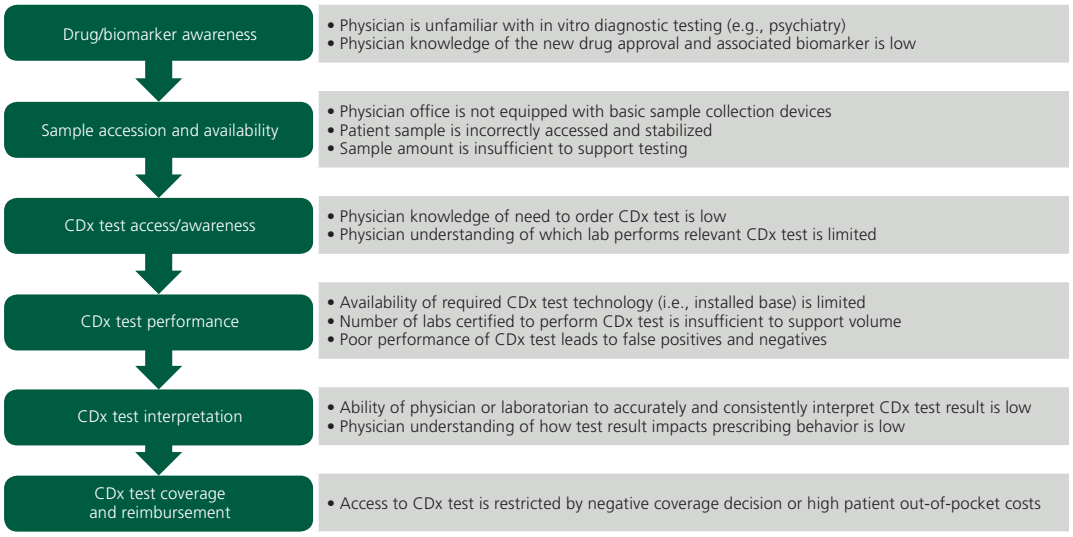
- Emergence of CDx outside oncology, especially in areas with low diagnostics usage today (i.e., stakeholders less familiar with all the requirements to successfully test patients)
- Inability of physicians to keep pace with the increasing number of biomarkers and launched CDx tests
- Increased competition for patient samples as more tests are launched in a given indication
- Increased complexity of CDx testing (driven by need to include multiple biomarkers or to leverage novel technologies), which may limit the number of reference labs with suitable competencies

How Reference Labs Can Help

Although reference labs already perform a significant portion of CDx testing (using solutions provided by IVD companies), biopharmaceutical companies rarely formally engage these labs to support CDx programs. In two notable exceptions, a biopharma company engaged a reference lab — Pfizer with Monogram and AstraZeneca with Myriad — and in both instances, these were specialty labs offering novel tests.

Large reference labs, on the other hand, have significant capabilities that biopharmaceutical companies can leverage to enhance test commercialization efforts including physician-oriented field forces, phlebotomy centers, sample logistics capabilities, test reporting, test utilization and biomarker data, and test reimbursement support capabilities (see Figure 4 for examples). The partnership model between biopharma companies and reference labs has not been relevant to the U.S.

Figure 3
Examples of Drivers of CDx-Related Patient Leakage

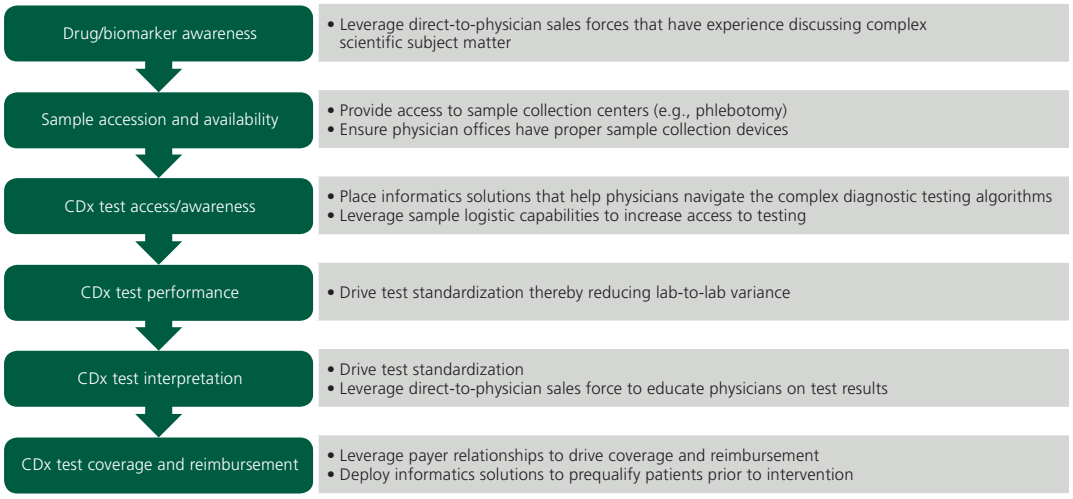


Source: L.E.K. analysis

market historically, but the number of opportunities outside the U.S. is increasing as reference labs (e.g., Sonic, Quest) globalize and regional labs (e.g., Labco, Unilabs) gain scale.

As biopharmaceutical companies continue to develop and commercialize CDx tests, we encourage them to better understand their IVD partners' capabilities, economics and incentives and to consider all the issues that can lead to CDx-related patient leakage. These companies should consider working with reference labs to improve CDx planning and commercialization. Many leading biopharmaceutical companies work with a trusted advisor that understands their program-specific needs and can develop commercialization and partnering strategies involving IVD companies, reference laboratories and other potential enablers.

Figure 4
Examples of How Reference Labs Can Support CDx Commercialization



Source: L.E.K. analysis

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