L.E.K.

EXECUTIVE INSIGHTS

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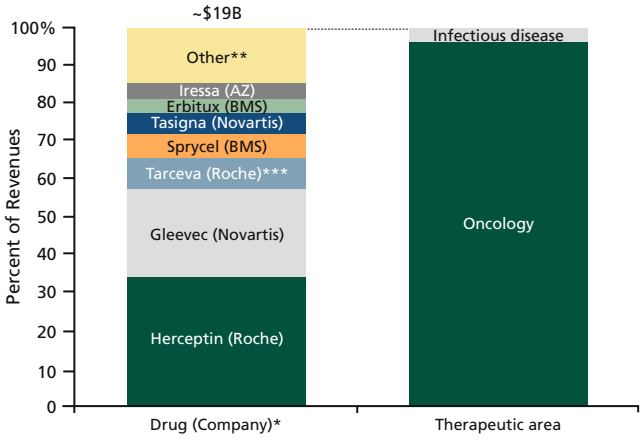
Partnering on Novel Technologies for Companion Diagnostics

The past 10 years have seen a paradigm shift toward personalized medicine strategies that leverage biomarkers and associated companion diagnostics (CDx) to stratify patients. Biopharmaceutical companies have typically partnered with well-established in vitro diagnostic (IVD) companies to develop CDx tests, and this model has generally proven effective. However, a number of drivers in personalized medicine are rapidly reshaping the CDx landscape, prompting the need for biopharmaceutical companies to thoroughly assess novel CDx technologies and carefully plan for their adoption.

Figure 1

Worldwide CDx-Informed Drug Revenue 2013*



Note: *2013 revenues are actual or analyst estimates; products include those with labels that require/recommend CDx tests for candidacy, **Other includes Mekinist, Bosulif, Tafinlar, Vectibix, Selzentry, Kadcyla, Xalkori, Tykerb/Tyverb, Perjeta, Zelboraf and Victrelis, ***Includes all Tarceva revenues

Source: Company websites, press releases and annual reports, EvaluatePharma, L.E.K. analysis

CDx Partnerships: Building on What Works

To date, most personalized medicine strategies have been deployed in oncology (see Figure 1). The majority of the oncology CDx-informed therapeutics deployed a one-drug, one-test approach for therapy selection.

In addition, most biopharmaceutical companies have followed a well-established path to execute their personalized medicine strategies.

Since they generally lack in-house expertise to develop and commercialize diagnostics, most biopharmaceutical companies choose to partner with IVD companies. Not surprisingly, the vast majority of CDx partnerships associated with launched therapies involve global oncology diagnostic companies (such as Abbott Molecular, Dako/Agilent, Qiagen and Roche) that supply polymerase chain reaction (PCR), immuno-histochemistry (IHC) and fluorescence in-situ hybridization (FISH) in vitro diagnostic tests.

Here, the primary goal for biopharmaceutical companies is to reduce the development, and commercial risk associated with co-development, of a drug and CDx test. It is no surprise that most seek out partnerships that:

Partnering on Novel Technologies for Companion Diagnostics 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.

- Involve diagnostic companies with **demonstrated CDx development experience**, which suggests the partner can meet deadlines, coordinate development and successfully navigate regulatory pathways

- Leverage **established technologies** with a broad installed base, thereby reducing regulatory and commercial risk (via broad access to testing)

- Include **large and well-capitalized partners** that offer global commercialization capabilities and financial stability

But while this model historically has met biopharma needs, we believe that rapid advances in personalized medicine are changing CDx test requirements and technology needs.

Trends Driving the Need for Novel CDx Technologies

A number of drivers, both within and outside of oncology, are reshaping the partnering landscape for personalized medicine:

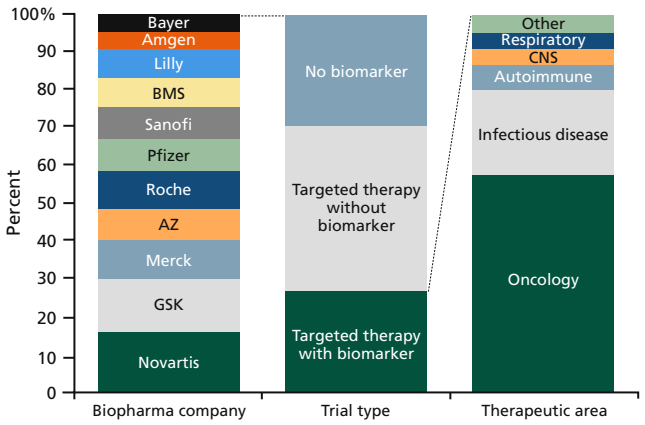
- **Broader adoption of personalized medicine outside of oncology.** Our recent assessment of late-stage clinical trials from leading biopharmaceutical companies indicates that more than 27% of trials across all therapeutic areas incorporate a biomarker to enroll a patient in the trial and/or measure efficacy or safety as a clinical endpoint. Interestingly, oncology has been joined by infectious disease as well as autoimmune, central nervous system and other disease areas in incorporation of biomarkers within their clinical development plans (see Figure 2).

  As personalized medicine adoption continues to move beyond oncology, new diagnostic technologies will be needed to interrogate different sample types and measure non-genomic biomarkers.

- **Increased competition in oncology.** As more targeted therapies and more biomarkers are launched in oncology, competition is increasing to enroll patients in clinical trials, access their biopsy samples and clinically differentiate the drug therapy.

Figure 2

Late-Stage Clinical Trial Pipeline by Trial Type and Therapeutic Area



Note: Analysis performed in March 2014. We identified 570 late stage clinical trials (PII+) of which 154 included a targeted therapy with a biomarker

Source: Pipeline, ClinicalTrials.gov, company websites, L.E.K. analysis

However, enrolling patients in clinical trials is increasingly challenging, as biopharmaceutical companies continue to deploy drugs in similar patient populations (e.g., Xalkori, Tarceva, Gilotrif in NSCLC), and in smaller patient populations where the prevalence of the biomarker is low (e.g., ALK's approximately 5% prevalence in NSCLC). Highly multiplexed technologies, especially when used in coordinated clinical trials (e.g., Lung Master Protocol), have the potential to identify patients and more quickly link them to biomarker-specific trials.

Sample access issues have already been demonstrated in NSCLC, where pathologists are struggling to analyze multiple biomarkers in fine needle aspirates. Seeking to address the sample availability issue, biopharmaceutical companies are leveraging multiplexed technologies capable of interrogating multiple biomarkers from the same sample (e.g., NGS) as well as pursuing liquid biopsy approaches that can measure biomarkers in either circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA).

Biopharmaceutical companies are also looking broadly for ways to improve the predictive power of their CDx tests, including the ability to profile multiple biomarkers (e.g., KRAS and NRAS) and to include additional mutations (e.g., moving beyond inherited BRCA mutations to also include somatic BRCA mutations).

- **Movement to monitor therapy response or disease recurrence in oncology.** With personalized medicine approaches to monitor disease recurrence or therapeutic response in oncology, oncologists are able to either intervene earlier or augment therapy faster; both may improve patient outcomes and treatment economics. Better still, CTC and ctDNA liquid biopsies promise to enable less-invasive, more cost-effective monitoring approaches.

- **Exploration of nuanced cancer biology for biomarker discovery.** Biopharmaceutical companies continue to invest heavily in biomarker discovery and explore novel biology in rapidly evolving therapeutic areas, such as immunotherapy in oncology. Companies are analyzing small subpopulations of cells or single cells, small-fold changes (e.g., DNA copy-number variation, gene expression), multi-omic biomarkers, more biologically relevant biomarkers (e.g., RNA versus DNA surrogates), and nucleic acid or protein modifications. Novel technologies will be needed to test for these emerging biomarkers/profiles.

Many innovative companies are developing novel tools to address these technology needs, and are candidates to become enabling partners for biopharmaceutical companies (see Figure 3).

Novel Technology Partnerships Move Into CDx

Biopharmaceutical companies are exploring ways to incorporate novel technologies into pivotal trials and may move forward to commercialize CDx tests based on these technologies.

We saw evidence of this shift when looking at partnerships formed between 2011 and 2014. Our analysis identified 95 partnerships involving a novel technology. Surprisingly, more than half these novel technology partnerships were outside the biomarker discovery arena, being focused rather on CDx test development and commercialization (see Figures 4 and 5).

Figure 3
Novel CDx Tools

Technology		Description	Example technology players	
Proteomic/multi-omic	**Proteomic arrays**	Quantitative detection of protein biomarkers via a single antibody in multiple samples fixed to a solid substrate (e.g., slide, bead)	• Luminex	• Meso Scale
	Mass spec	Semi-quantitative analysis and identification of multiple protein biomarkers	• Thermo	• Agilent
	Multiplexed histology	Multiparametric and semi-quantitative IHC	• Roche	• GE/ Clarient
Multiplexed genomic	**NGS**	Quantitative and qualitative detection of nucleic acids using high-throughput massively parallel sequencing	• Illumina • Thermo	• PacBio
	Multigene expression	Quantitative detection of gene expression levels across multiple gene targets	• nanoString • Thermo	• Seegene
High sensitivity	**Digital PCR (dPCR)**	Absolute quantitation of nucleic acids using parallel amplification of PCR reactions in microwells	• Thermo • Bio-Rad	• Raindance • Fluidigm
	Digital immunoassay	Quantitative detection of protein biomarkers at the femtomolar or single-molecule level	• Quanterix • Singulex	
Liquid biopsy	**CTCs**	Qualitative characterization and semi-quantitative detection of rare cells (including circulating tumor cells) in blood	• EPIC Sciences	• Veridex
	ctDNA	Capture and interrogation of cell-free tumor DNA	• Inostics (Sysmex) • S and dPCR vendors	
Other	**RNA-ISH**	Semi-quantitative detection and visualization of RNA sequences using fluorescently labeled probes	• ACD	• Affymetrix

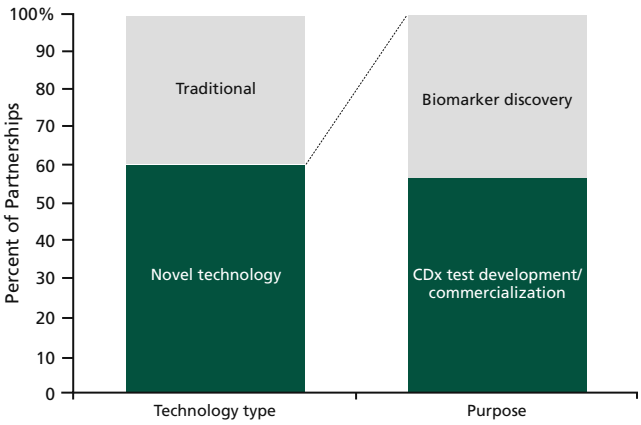
Source: Company websites, L.E.K. analysis

Assessing the Benefits and Risks of Novel Technology Adoption

Adoption of novel technologies for CDx purposes is complex and carries considerable risks that must be fully appreciated, and that demand strategic planning. These risks are often compounded by companies' limited resources and experience in test development and commercialization. Among the challenges:

- **Limited resources**
  - Lack of financial resources
  - Narrow geographic footprint
- **Challenging CDx test development**
  - Lack of familiarity with biopharmaceutical development timelines
  - Limited in-house regulatory expertise or experience attaining PMA-level approvals typically required for CDx
  - Lack of clear regulatory precedence for the novel technology

Figure 4
Partnerships on Novel CDx Technologies



Note: Biopharma novel CDx partnerships (2011-2014). We identified 156 partnerships of which 95 involved a novel technology

Source: L.E.K. analysis

Figure 5
Examples of Novel Technology Partnerships

PM trends		Biopharma company(ies)	Partner	Description
Adoption of PM outside oncology		Takeda	Quest Diagnostics	Genotyping test for APOE status and TOMM40 polymorphism for Alzheimer's
		Merck	Luminex	Immunoassay for Amyloid 42 and tau in mild cognitive impairment
Increased competition in oncology	**More efficient clinical trial enrollment**	Amgen, Genentech, Pfizer, AZ	Foundation Medicine	Lung Cancer Master Protocol collaboration
	Improved sample access	AstraZeneca	Qiagen	Liquid biopsy approaches in a sample constrained environment
		Bayer	Sysmex	
		Merck KGaA		
	Improved CDx predictive power	Amgen	Illumina	NGS panel test for KRAS and NRAS
		GSK	BioMerieux	PCR panel test for V600E and V600K
Movement beyond oncology therapy selection to monitoring		Arno Therapeutics	Veridex	Enables disease/therapy monitoring
		Novartis		
Exploration of nuanced cancer biology		Eli Lilly	Qiagen	Detection of both DNA and RNA biomarkers for oncology
		BMS	IncellDx	Multimodal technology for cell-based protein and gene expression analysis

Source: Company press releases, company websites, annual reports, GenomeWeb, L.E.K. analysis

- **Complex CDx commercialization**
  - Confined installed base for the technology
  - Limited reimbursement expertise
  - Small commercial sales force

Over the past few years, L.E.K. Consulting has worked with several biopharmaceutical companies to understand the drug development program requirements for both R&D and commercialization, create roadmaps for successful implementation, and develop risk mitigation strategies for novel CDx technologies.

As new personalized medicine approaches are rapidly adopted, we believe these novel technologies will play an increasingly important role, and we encourage biopharmaceutical companies to thoroughly assess them and carefully plan for their adoption.

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