



## Companion Diagnostics Leakage in Oncology

Biopharmaceutical companies continue to adopt personalized medicine approaches that leverage patient-specific biomarkers to stratify patients. Companion diagnostic (CDx) tests are indispensable to personalized medicine, which relies on accurate, reliable and clinically meaningful tests to identify the appropriate drugs for each patient.

The commercialization of these tests raises challenges for biopharmaceutical companies, which strive to provide patients access to drugs. Biopharmaceutical companies typically partner with global in vitro diagnostic (IVD) companies to complete the steps that lead to a successful CDx test: development, regulatory approval (often sought during the drug's pivotal trial), commercialization and widespread distribution into laboratories. Local or central laboratories often process collected samples, perform the tests (from the IVD partner) and report test results back to physicians. Laboratories might also create their own "homebrews" or laboratory-developed tests (LDTs) to reduce input costs.

### Leakage points exist despite successful commercialization

Most biopharmaceutical companies that launch products with companion diagnostics inevitably face CDx-related patient leakage, or the failure of eligible biomarker-positive patients to receive

appropriate targeted therapy. Patient leakage occurs throughout the test workflow from the collection of a sample/biopsy through the receipt of an actionable test report (see Figure 1). While sample access issues are well known (especially in sample-constrained environments such as NSCLC) in this *Executive Insights*, L.E.K. Consulting focuses on issues during test ordering, test performance and results reporting that can lead to patient leakage.

### Test ordering issues

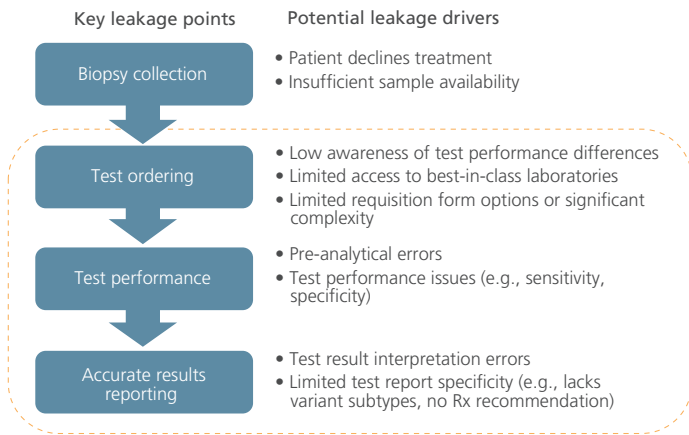
Most physicians — especially outside of oncology — have a limited understanding of the technical nature of laboratory medicine. They often rely on their local/national labs to offer the appropriate testing and testing algorithms, select the best technologies and report results accurately. Although labs have patients' best interests in mind, it may not be feasible for them to offer the most ideal test or testing algorithm.

A patient's failure to receive the appropriate test or most comprehensive testing algorithm for a given biomarker is a key source of patient leakage. We have found that two converse factors drive ordering-related patient leakage: (1) the availability of too many options, which makes it difficult for physicians to choose the most appropriate option for a given patient situation; and (2) the availability of too few options, which may not include the optimal one. One of the leading national reference labs is an example of a lab that offers a vast array of options — in this case, multiple tests and algorithms for HER2, which are used as companion diagnostics for Herceptin (see Figure 2).

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**Figure 1**  
CDx leakage



Source: L.E.K. analysis

This vast array of testing options is ideal only if the ordering physician has in-depth knowledge of laboratory medicine and, as previously stated, most do not. Inappropriate test ordering may lead to suboptimal HER2 tests or algorithms and subsequent false negatives, thereby preventing eligible patients from receiving beneficial therapy.

## Test performance issues

Assuming the optimal test and algorithm were selected, patient leakage can still occur due to variance in analytical test performance. Analytical test performance often varies by test modality (e.g., PCR, IHC, FISH) and by vendor, and a broad array of technical factors (e.g., variant coverage, probe specificity, antibody sensitivity) can influence such performance. Peer-reviewed studies suggest that sensitivity-related issues can lead to false negative

**Figure 2**  
Tests and diagnostics for HER2

Modality	Test name	Description
IHC	HER2 (HercepTest®), IHC	Dako (Agilent) HercepTest for HER2
	InScape® HER2, Quantitative, IHC	IHC for HER2
	InScape® ER/PR/HER2, Quantitative, IHC	IHC for ER, PR and HER2
ELISA	HER2, ELISA	ELISA for HER2 quantitation
Multiple	ER/PR/DNA/HER2 with Reflex to HER2, FISH	Flow cytometry for DNA cell cycle, IHC for ER and PR, and reflexes to FISH if IHC result is 2+
	ER/PR/HER2 with Reflex to HER2, FISH	IHC for ER, PR, HER2 and reflexes to FISH if IHC result is 2+
	FISH, HER2/neu with Reflex to IHC	Uses FISH for HER2 and reflexes to IHC if FISH is equivocal

Source: Quest Diagnostics

rates of 4-10% for approved molecular diagnostic tests, but L.E.K. research has observed situations where a confluence of factors can make them as high as 25%.

Pathology tests (e.g., IHC, FISH) may also face additional interpretation challenges, given that these tests' results are often subjective. Test interpretation typically requires a highly skilled and trained pathologist but pathology tests' subjective nature can lead to significant variation between pathologists and labs. In an effort to reduce interpretation variance, most IVD manufacturers often develop "test interpretation manuals," which provide a form of test interpretation standardization (see Figure 3).

Some studies have attempted to quantify the true impact of subjective interpretation, reporting false-positive rates as high as 26% for locally tested samples re-tested by central labs where pathologists may be more familiar with the tests. A recent study found that 4% of locally tested negative HER2 patients were actually found to be positive upon central lab testing, suggesting that approximately 7,000 U.S. patients were not receiving appropriate HER2 therapy.<sup>1</sup>

## Results reporting issues

Test reporting forms may contribute to patient leakage and inadvertently lead a physician to misunderstand a patient's true biomarker status or make suboptimal therapy selection decisions. Reporting can be heterogeneous, with some reports including a simple "biomarker negative/positive" (e.g., EGFR mutation positive or EGFR mutation negative), or it can provide mutation-specific differences (e.g., EGFR positive with exon 19 deletions) within a given biomarker.

As a case study, we investigated EGFR in lung adenocarcinomas. In this specific context, a simple EGFR negative/positive report is insufficient to make informed therapy selection decisions. Studies have shown that susceptibility to the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib can vary greatly depending on the specific EGFR mutation pattern (see Figure 4).

## TKI susceptibility

In the case of EGFR, it is important that labs use a testing modality capable of interrogating the various mutations. It is equally important for the associated report to provide, at a minimum, the mutation status for each specific EGFR mutation. Ideally, the report should arm the physician with the medical information needed to make informed therapy selection decisions.

We have not seen specific studies that quantify the impact of high-quality lab reports on patient leakage, but our experience suggests that a meaningful percentage of patients can be lost due to variance in lab reporting.

# Executive Insights

## It will get better and worse going forward

The industry is working to improve the situation in the following ways:

- Increasing genetic education in medical schools and through CME
- Adopting technologies with very high sensitivity (e.g., NGS, digital PCR), which can improve sensitivity
- Using technologies that have broad variant coverage (e.g., NGS)
- Adopting digital pathology solutions that help standardize interpretation
- Increasing regulatory oversight and guidance

**Figure 3**

**Dako HercepTest interpretation manual breast cancer**

Score to Report	Her2 Protein Overexpression Assessment	Staining Pattern
0	Negative	No staining is observed, or membrane staining is observed in <10% of the tumor cells.
1+	Negative	A faint/barely perceptible membrane staining is detected in > 10% of tumor cells. The cells exhibit incomplete membrane staining.
2+	Weakly Positive	A weak to moderate complete membrane staining is observed in >10% of tumor cells
3+	Positive	A strong complete membrane staining is observed in >10% of tumor cells

Source: Dako HercepTest

**Figure 4**

**TKI susceptibility**

Sensitive / Responders	Possible Response / Limited Data	Nonresponse / Resistance
Exon 19 deletions	Exon 18 point mutations	Exon 20 insertion
Exon 21 L858R point mutation	Exon 21 L861Q	Exon 20, S768I single mutation
	Dual mutations exon 19 or 21 mutations with exon 20, S768I	Exon 20 T790M

Source: Dako HercepTest

Despite these efforts, we expect continuing increases in the number of biomarkers, number of test offerings, number of test algorithms and overall test complexity to lead to more patient leakage during test ordering, test performance and results reporting.

## Potential solutions

Biopharma companies need to be aware that launching a drug with a CDx test that has regulatory approval does not guarantee access. Even with a successful commercialization strategy, a CDx test is not necessarily immune to patient leakage due to test ordering, test performance and results reporting issues, which can lead to lower-than-expected drug revenues and reduced clinical benefit for patients. Potential strategies to minimize patient leakage and maximize access to drugs with a CDx may include:

- Characterizing and quantifying leakage points and how they vary by situation (care setting, region, patient specific)
- Identifying contributing forces to leakage and developing plans to address those forces by stakeholder (e.g., pathologist, physician, payer, provider, patient)
- Developing commercial strategies to address leakage points and contributing factors
- Developing CDx life cycle strategies
- Outlining new partnering strategies that can help reduce patient leakage

<sup>1</sup> Kaufman et al., *Cancer* 2014; 120:2657-64

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## About the Authors



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