

# White Paper: Molecular Markers in Solid Tumors - Breast, Lung and Colorectal Cancer

For Health Plans, Medical Management Organizations and TPAs

## Executive Summary

Emerging molecular testing technologies offer the promise of increased personalization of cancer care. One of the challenges to adopting new molecular markers in oncology, however, is the lack of a standardized validation process due to the heterogeneity of tumor types, treatments, and the tests themselves. A molecular marker validated as prognostic or predictive of response to a specific drug in one malignancy may not be similarly prognostic in other types of tumors or predictive with related drug classes. In addition, the clinical utility of predictive markers also depends on the efficacy of available therapeutic agents—a marker is only as good as the treatment whose benefit it predicts. Ultimately, the study and evolution of molecular markers may accelerate new drug development, offering the promise of individualized treatment for patients with cancer and presenting physicians with the challenge of keeping up with rapidly evolving advances.

Independent medical review facilitates the evaluation of medical need for molecular marker testing in the diagnosis and management of cancer, which requires reviewers who have in-depth training and understanding of not only the field and its technologies, but also the clinical course and findings of cancer and the available treatment options. The process also avoids conflicts of interest, which can relate to economics, lack of specialists to review cases, or having the same doctor who denied a care review an appeal.

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## Introduction

According to estimates of the American Cancer Society (ACS), cancer accounts for nearly one fourth of deaths in the United States, with breast, lung, and colon cancers among the most common forms of cancer. Significant progress in diagnosing certain cancers at an earlier stage and improvements in treatment, however, are clearly reflected in the recent general steady decline in the death rate for cancer and in increased 5-year relative survival rates.

Advances in the molecular biology of tumors have propelled the evolution of medical oncology, allowing early assessment of prognosis and response to treatments. Testing for molecular markers allows more accurate and definitive diagnoses, and identifies patients most likely to respond to therapy, those most likely to experience disease recurrence, or those most likely to suffer toxicity.

## Molecular Tumor Markers

Tumor markers are identifiable molecular characteristics (DNA, RNA, or protein) produced by tumor cells or by other cells within the body in response to cancer. Molecular tumor markers can be static measurements, such as those used to diagnose cancer and identify toxicities to certain chemotherapeutic agents, and they can also be dynamic measurements that correlate with tumor growth or regression over time. These markers may be detected as circulating agents within the peripheral blood plasma or in body fluids (e.g., urine, saliva, sputum, cerebrospinal fluid, effusions). Although an abnormal level of these markers may suggest cancer, their presence does not confirm a diagnosis of cancer. Measurements of these markers are combined with other diagnostic tests (e.g., biopsy, imaging) to confirm a diagnosis of cancer.

## *Prognostic vs. Predictive Molecular Markers*

A prognostic biomarker provides information about the patient's overall cancer outcome, regardless of therapy. The presence or the absence of such a prognostic marker can be useful for the selection of patients for a certain treatment, but does not predict the response to this treatment. A predictive marker gives information on the effect of a therapeutic intervention in a patient, and it can also be a target for therapy.

## Specific Tumor Markers

### Breast Cancer

#### *Hormone Receptors*

Hormone receptor testing for the estrogen receptor (ER) and progesterone receptor (PR) by immunohistochemistry is an established standard of care, with 70% to 80% of breast cancer tumors being ER and/or PR positive. Guidelines established by the National Comprehensive Cancer Network (NCCN) recommend the determination of ER and PR tumor status for all newly diagnosed invasive breast cancers.

#### *HER2*

Assays to identify amplification of the human epidermal growth factor receptor-2 (HER2) gene or elevated levels of this protein in breast cancer tissue have both prognostic and predictive value. The NCCN guidelines recommend HER2 testing in all new cases of invasive breast cancer. HER2-positive breast cancer, which accounts for about 20% of breast cancers, is generally associated with higher-grade tumors that are more likely to metastasize, indicating a worse prognosis in the absence of therapy. HER2 is also an important predictive marker for response to HER2-targeted treatments such as trastuzumab and lapatinib.

#### *Oncotype DX Breast Cancer Assay*

The Oncotype DX breast cancer assay provides an individual, quantitative assessment of the likelihood of disease recurrence. The test results are provided in the form of a "recurrence score," which is an analysis of 21 genes in a breast cancer tumor that correlates to a specific likelihood of breast cancer recurrence within 10 years of initial diagnosis. Studies have shown that the 21-gene signature is predictive of recurrence risk in patients who have lymph-node-negative, ER-positive breast cancer. To date, the NCCN guidelines do not recommend the use of the Oncotype DX assay in patients with node-positive disease.

#### *MammaPrint*

MammaPrint analyzes 70 genes in an early-stage breast cancer tissue sample to determine risk of breast cancer recurrence within 10 years of initial diagnosis. This 70-gene signature, which is not currently recommended in the NCCN guidelines, has demonstrated prognosis value independent of conventional clinicopathologic features but has not yet been validated as a predictive marker of chemotherapy benefit.

#### *BRCA Mutations*

BRCA1 and BRCA2 are genes involved in cell growth, cell division, and repair of damage to DNA. A BRCA mutation can cause DNA damage in cells to go unrepaired, which increases the chance that cancer will occur. Individuals with BRCA mutations may get cancer at an early age, they may develop breast cancer in both breasts, or they may develop more than one type of cancer. Although the most common type of cancer associated with BRCA1 and BRCA2 changes is

breast cancer, mutated forms of BRCA genes are linked to other cancers as well. Please see Table 2 for the risks associated with BRCA gene mutations.

Most breast cancers are not due to inherited changes in genes. Of those that are, about one third are due to mutations in the BRCA1 gene. Another third of breast cancers that run in families are linked to mutations in the BRCA2 gene.

**Table 1. Risks Associated With BRCA Gene Mutations**

BRCA1 Mutation	BRCA2 Mutation
<ul style="list-style-type: none"><li>▶ Increased risk for breast and ovarian cancer in women</li><li>▶ 50% to 85% risk of developing breast cancer by age 70</li><li>▶ 40% to 60% risk of developing ovarian cancer by age 85</li></ul>	<ul style="list-style-type: none"><li>▶ Increased risk for breast cancer in both men and women</li><li>▶ Increased risk for prostate cancer in men</li><li>▶ 16% to 17% risk of developing ovarian cancer by late age in women</li><li>▶ Increase risk for pancreatic cancer and melanoma in both men and women</li></ul>

## Lung Cancer

### *KRAS*

The KRAS gene makes the KRAS protein, which is involved in cell signaling pathways, cell growth, and apoptosis (cell death). KRAS mutation is present in about 20% to 30% of non-small cell lung cancer (NSCLC) tumors and adenocarcinomas, as well as smokers, is associated with worse prognosis, and is a predictive factor for a lack of response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as erlotinib. In addition, recent studies indicate that patients with KRAS mutations may not respond to adjuvant chemotherapy. Currently, the association of KRAS mutations with response to cetuximab remains unclear. KRAS and EGFR mutations are mutually exclusive in patients with lung cancer.

### *EGFR*

EGFR is a receptor with growth-promoting effects, and EGFR overexpression has been shown to positively predict response to EGFR-targeted TKIs. More than 70% of patients with EGFR mutation respond to treatment with either erlotinib or gefitinib. The incidence of EGFR mutation is about 50% in Asian patients vs. 10% in Western patients, most frequently occurring in women and nonsmokers, and in non-mucinous tumors. Patients with EGFR mutation have a progression-free survival of about 5 months, but no overall survival benefit. The NCCN guidelines recommend that EGFR mutation status be considered when selecting first-line therapy for patients with metastatic or recurrent NSCLC, including patients with poor performance status. The guidelines also recommend erlotinib as first-line therapy for patients with EGFR mutation.

### *EML4-ALK*

Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) is a fusion protein that produces a kinase with oncogenic activity. Patients with EML4-ALK fusion gene mutations share many of the clinical features of NSCLC patients likely to have EGFR mutations, but the two mutations are, for the most part, mutually exclusive. EML4-ALK mutations are found in only 3% to 5% of patients with NSCLC, and tend to occur more frequently in men

and younger patients, in adenocarcinomas, and in never/light smokers. Patients with ALK-positive NSCLC do not have mutations in EGFR or KRAS and are resistant to TKIs. The NCCN guidelines recommend EGFR and KRAS testing, with no EML4-ALK testing if EGFR mutation is present.

## Colorectal Cancer

### KRAS

Mutations in codons 12 and 13 of the KRAS gene in colorectal tumors predict lack of response to the monoclonal antibodies cetuximab and panitumumab, which target EGFR. Patients with the wild-type (non-mutated) KRAS gene will respond to these agents. The NCCN guidelines recommend KRAS mutation analysis in all patients with metastatic colorectal cancer at the time of diagnosis of stage IV disease. Early establishment of the patient's KRAS status is not meant to indicate a preference regarding first-line treatment selection, but it is appropriate in order to plan for the treatment continuum while other treatment options exist. KRAS mutations occur early in colorectal cancer formation, and the mutation status in the primary tumor has been shown to correlate with that in the metastases.

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### BRAF V600E

BRAF V600E mutation may be associated with poor prognosis. Some studies have suggested potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status. Patients with non-mutated KRAS tumors with BRAF mutation may not respond to cetuximab and/or panitumumab. Limited available data suggest a lack of anti-tumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a patient has progressed on first-line therapy. The latest NCCN guidelines recommend considering BRAF mutation testing for patients diagnosed with KRAS non-mutated colorectal cancer.

### Microsatellite Instability and Mismatch Repair Protein

Microsatellite instability (MSI) is a mutation found in colorectal cancers that result from the inactivation of the DNA mismatch repair protein (MMR), with high levels of MSI indicating a deficiency in MMR function. Tumors showing the presence of MSI are classified as MSI-high (MSI-H) or MSI-low (MSI-L), depending on the extent of instability in the markers tested; tumors without the presence of MSI are classified as microsatellite-stable (MSS). Patients with MSI-H tumors may not benefit from adjuvant fluorouracil-based (5-FU-based) chemotherapy. The NCCN guidelines for colon cancer recommend considering testing for MMR in all patients less than 50 years of age.

### Oncotype DX Colon Cancer Assay

The Oncotype DX colon cancer assay, which uses technology similar to the Oncotype DX breast cancer assay, is a 12-gene diagnostic test used to assess the risk for recurrence in patients with stage II colorectal cancer following surgery. The current NCCN guidelines for colon and rectal cancer do not include any recommendations for the use of this test.

## Role of Independent Medical Review for Molecular Marker Testing

Practice guidelines are continually changing to reflect the advances in molecular marker technologies, which often complicates the process of establishing evidence-based criteria for practice guidelines and reimbursement for new procedures and treatments. An independent medical review, which is normally used by healthcare payers, looks at whether or not a specific procedure was medically necessary.

The specialty match that an independent review organization (IRO) provides is especially important for molecular marker testing since results from ongoing clinical trials lead to the continual emergence of new diagnostic and prognostic tools, treatment strategies, and therapeutic agents. The board-certified physician specialists who work with IROs keep up-to-date with the latest medical research literature and with the latest standard of care. Physicians who review cases for IROs stay on top of continually evolving technology and treatments as they are studied more extensively and potentially accepted into clinical guidelines.

Independent medical reviews also avoid conflicts of interest, which can relate to economics, lack of specialists to review cases, or having the same doctor who denied a case review an appeal. Independent medical review facilitates effective treatment of patients with cancer, which requires an in-depth understanding of molecular marker developments so that disease management can be individualized for each patient.

## Conclusions

Recent advances in the molecular biology of cancer allow physicians to not only establish more accurate and definitive diagnoses, but also gather information that can be used to guide therapy and predict response to various treatments. Despite significant research efforts and the identification of many promising prognostic and predictive markers, the results to date have been somewhat limiting in that there is no single tumor biological factor for clinical use that can accurately predict the clinical course of disease or treatment response. Difficulties can arise in integrating innovations into routine practice, guidelines, and coverage, as healthcare policy-makers and providers attempt to keep pace with the onslaught of new data.

An IRO can provide ready access to specialists, which healthcare plans may lack internally, allowing for timely determination of whether the requested tests fall under medical necessity guidelines. Independent medical reviews provide unbiased evaluation of medical need for molecular marker testing, thereby facilitating the optimization of care for patients with cancer.

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