

## Mutation Analysis for *PTEN* in Breast and Colorectal Cancer

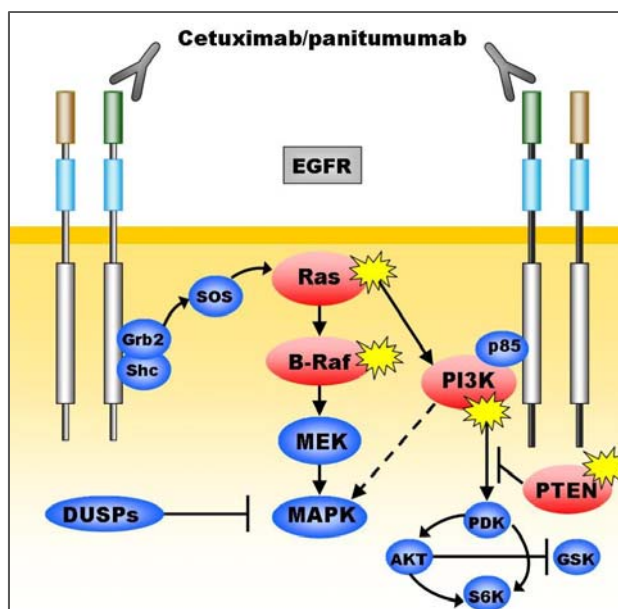
Multiple biomarkers representing the integrity of genes considered critical in oncogenic pathways can be identified by performing a variety of genomic tests on tumor tissue. Identification of these molecular biomarkers is proposed to better predict and “personalize” chemotherapy response in terms of efficacy and/or toxicity. *PTEN* somatic gene changes, identified mainly by immunohistochemical staining (IHC) of the protein product of the *PTEN* gene in tumor tissue, have been explored as a predictive marker of response to chemotherapeutic drugs for breast, colorectal and other cancers.

**Summary: Evidence does NOT support the utility of immunohistochemical staining or other genetic tests of *PTEN* gene status on tumor tissue for prognostication or predictive response to chemotherapeutic drugs in breast, colorectal or other cancers.**

### *PTEN* Role in the Oncogenic Pathway

The *PTEN* (protein and tensin homologue deleted on chromosome 10) gene encodes for a major tumor suppressor (protein) that is a dual specificity phosphatase and an integral part of the *PI3K/AKT/PTEN* pathway. *PTEN* and PI3-kinase are major negative and positive regulators, respectively, of the PI3-kinase pathway, which regulates growth, survival, and proliferation. These key signaling components are two of the most frequently mutated proteins in human cancers, resulting in unregulated activation of PI3K signaling thus playing a central role in tumor genesis. *PTEN* regulates PI3K signaling, but may have additional phosphatase-independent activities, as well as other functions in the nucleus. *PTEN* appears to diffuse easily from the cytoplasm to the nucleus of the cell. *PTEN* activity also enhances centromeres, genomic stability, and apoptosis.

*PTEN* expression can be lost either by mutation, deletion, or promoter methylation so testing can be performed by sequencing (for mutations), deletion/duplication analysis, or methylation analysis. Genetic abnormalities may or may not be the same in the primary versus secondary tumors. The genetic abnormality usually creates a truncated protein that can be detected with high sensitivity by the IHC test.



### Proposed indications for use in chemotherapeutic decision-making

Colon and rectal cancer. *PTEN* somatic testing can be used either for prognostic or predictive decisions. Prognostic value helps determine patients’ outcomes independent of treatment and predictive value helps determine which patients are likely or unlikely to benefit from a particular drug (regimen).

Since the *PI3K/AKT/PTEN* pathway is downstream of the initiating EGFR pathway, *PTEN* status (as well as PI3K/AKT markers) has been proposed as a predictor of anti-EGFR (eg, cetuximab) treatment response;

to help further stratify KRAS mutation negative patients to determine which of these patients are (not) likely to respond to these drugs. However, given the complexities of the EGFR and *PI3K/AKT/PTEN* subpathways, it may be that *PTEN* status will become more important as drugs developed specifically to target the *PI3K/AKT/PTEN* pathway; especially tyrosine kinase and signal transduction inhibitors, come into practice. *PTEN* expression may also be considered as a prognostic marker of CRC outcome.

**Breast Cancer.** As with CRC, *PTEN* status may be considered for either prognostic or predictive use. *PTEN* gene or protein status is being explored as a predictive marker for a variety of anti-neoplastic drugs, including lapatinib and trastuzumab. It is also being considered as a predictor for adjuvant therapy; eg, the success/failure of Tamoxifen. (Anti-EGFR drugs are not used in treating breast cancer thus *PTEN* status would not be relevant for this class of drugs.) *PTEN* status may also play a role as a prognostic marker in much the same way as OncotypeDx and MammaPrint; however, evidence for this role is immature. Determination of somatic *PTEN* status may become part of a companion diagnostic strategy accompanying the emerging tyrosine kinase and signal transduction inhibitor drugs currently in development.

**Testing Options:**

Tissue tested: Tumor specimen

Testing available: ARUP Immunohistochemistry stain for PTEN  
Myriad Genetics (-information pending)

**ASCO Provisional Clinical Opinion (PCO 2009)** —“this PCO is limited to the current state of knowledge about the treatment of metastatic colorectal carcinoma and does not address the use of anti-EGFR MoAbs for adjuvant therapy in colorectal carcinoma, the use of small molecule tyrosine kinase inhibitors in metastatic colorectal carcinoma, or assays for other alterations that have been reported to affect response to anti-EGFR MoAbs (eg, mutation in BRAF, PI3K, or ***PTEN* genes and loss of expression of *PTEN*** that may indicate resistance; amplification of EGFR, **lack of amplification of *PTEN***, and expression of epiregulin or amphiregulin that may indicate response). These subjects are either the focus of current research, or there are insufficient data to justify an opinion at present.”<sup>1</sup>

***PTEN* testing on tumor tissue for the purpose of making treatment decisions for either colorectal or breast cancer is NOT covered by SelectHealth. However, *PTEN* germ-line mutation analysis in limited circumstances as a diagnostic tool is covered. Please refer to the GeneInfo sheet on *PTEN* in Familial Cancer Syndrome: Cowden syndrome.**

**Resources:**

1. [ASCO Provisional Clinical Opinion: Testing for KRAS Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy](http://jco.ascopubs.org/cgi/reprint/JCO.2009.21.9170v1). (<http://jco.ascopubs.org/cgi/reprint/JCO.2009.21.9170v1>)
2. GeneInfo sheets on Tumor markers: [KRAS](#) and [BRAF](#)
3. GeneInfo sheet on *PTEN* in Familial Cancer Syndromes: Cowden syndrome (under construction)