Neuroblastoma RAS Viral Oncogene (NRAS) testing to predict treatment response in colorectal cancer

Record Status
This is a bibliographic record of a published health technology assessment. No evaluation of the quality of this assessment has been made for the HTA database.

Citation

Authors' conclusions
Background Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in the United States. When diagnosed in its early stages, CRC can often be cured by surgical resection. However, CRC that has spread beyond the lymph nodes is much more difficult to treat. While the 5-year survival rate for patients with cancer localized to the colon or rectum is approximately 90%, it is less than 12% for those with distant metastases. Four types of treatment are used in patients with CRC: surgery, chemotherapy, radiation therapy, and targeted therapy (treatments designed to target specific molecules involved in tumor growth and progression). Because of its role in the activation of signaling cascades known to be dysregulated in CRC, the epidermal growth factor receptor (EGFR) has been an important target for the development of new anti-cancer therapies. Cetuximab (Erbitux®; ImClone Systems Inc.) and panitumumab (Vectibix®; Amgen Inc.) are monoclonal antibodies designed to bind and inactivate EGFR. While these antibodies generate a significant tumor response in up to 30% of treated patients, approximately 70% of patients do not benefit from treatment with this therapy. Therefore, recent pharmacogenetic studies have been performed in order to identify predictive markers that may allow for patient-tailored treatment strategies. Recently developed tests include assays to identify specific sequence variants in genes involved in RAS signaling pathways. The RAS genes, which include the Kirsten rat sarcoma viral oncogene homolog (KRAS), the Harvey rat sarcoma viral oncogene homolog (HRAS), and the neuroblastoma rat sarcoma viral oncogene homolog (NRAS), encode signal transduction molecules that link cell surface receptors, such as EGFR, with intracellular effector pathways. The binding of growth factors to EGFR leads to activation of the RAS protein, which then triggers downstream signaling cascades that play a role in the regulation of cell growth, proliferation, differentiation, and survival. Gene variants leading to the constitutive activation of pathways downstream of EGFR are believed to be responsible for the lack of response in some patients treated with anti-EGFR monoclonal antibodies. Variants in the KRAS gene are now known to be predictive of anti-EGFR treatment response, while the BRAF (v-RAF murine sarcoma viral oncogene homolog B1) gene appears to be useful for identifying potential nonresponders in KRAS-negative individuals. Another gene being evaluated as a predictive marker of anti-EGFR response is the NRAS gene, which maps to chromosome 1 at band p13.2. Like other RAS genes, NRAS encodes a guanosine triphosphate (GTP)-binding protein that may function downstream of EGFR. It has been estimated that approximately 2% of cancers involving the colon harbor activating sequence variants in the NRAS gene, typically, variants involving 12, 13, or 61. This assessment focuses specifically on data regarding the NRAS gene and its usefulness as a predictive marker of CRC treatment response. Additional GTE reports are available for the use of KRAS and BRAF gene tests to predict response to anti-EGFR monoclonal antibodies.

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