

***KIT* Mutations Conferring Drug Susceptibility**

The UNC Hospitals Molecular Genetics Laboratory performs DNA sequencing to detect *KIT* gene mutations associated with responsiveness to the tyrosine kinase inhibitor drug, imatinib (Gleevec) in patients with melanoma or gastrointestinal stromal tumor.

Biology of the process: *KIT* is a tyrosine kinase that, when activated by acquired mutation, contributes to malignant cell proliferation. Drugs such as imatinib that inhibit *KIT* tyrosine kinase activity are now available and can be considered for use in patients whose tumor appears to be driven, at least in part, by *KIT* activation as assessed by mutation of the *KIT* gene. The relevant tumors include melanoma and gastrointestinal stromal tumor (GIST). Among melanomas, *KIT* mutation frequency appears to be higher in those that arise in mucosa (e.g. ano-rectal), acral skin, and chronically sun-damaged skin where mutation rates of up to 21% are seen. The relevant mutations include in-frame insertions, deletions, and point mutations in exons 9, 11, 13, 17, and 18. Secondary mutations may be associated with acquired resistance or initial non-responsiveness to therapy. This assay does not test for gene amplification or alternate mechanisms of tyrosine kinase activation (e.g. *PDGFRA* mutation in GIST).

Clinical Indications for *KIT* mutation testing: Patients with GIST or melanoma (mucosal, acral or arising in sun-damaged skin) who are candidates for imatinib therapy.

Laboratory testing for *KIT* mutations: The preferred sample is a formalin-fixed, paraffin-embedded block containing at least 50% malignant cells representing either primary or metastatic melanoma or GIST, or five 10um unstained paraffin sections on plain glass slides plus an H&E-stained slide. A copy of the pathology report is requested. Tumor cells are enriched by macrodissection if needed, and extracted DNA is PCR-amplified across exons 9, 11, 13, 17, and 18 of the *v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT)* gene, followed by DNA sequencing to identify sequence variants. The limit of detection is 20%, implying that the mutated allele must comprise at least 20% of *KIT* alleles. Results are interpreted by a pathologist.

References:

1. Hodi, FS, et al. Major Response to Imatinib Mesylate in *KIT*-Mutated Melanoma. *J Clin Onc.* 2008, 26:2046-2051.
2. Holden, JA, Wilmore-Payne, C, Layfield, LJ. Tyrosine kinase activating mutations in human malignancies: Implications for diagnostic pathology. *Exp Mol Path,* 2008, 85: 68-75.

Questions? Consult a pathologist in the Molecular Genetics Lab at (919) 966-4408 or email Dr. Margaret L. Gulley at Margaret_gulley@med.unc.edu
http://labs.unchealthcare.org/directory/molecular_pathology/index_html