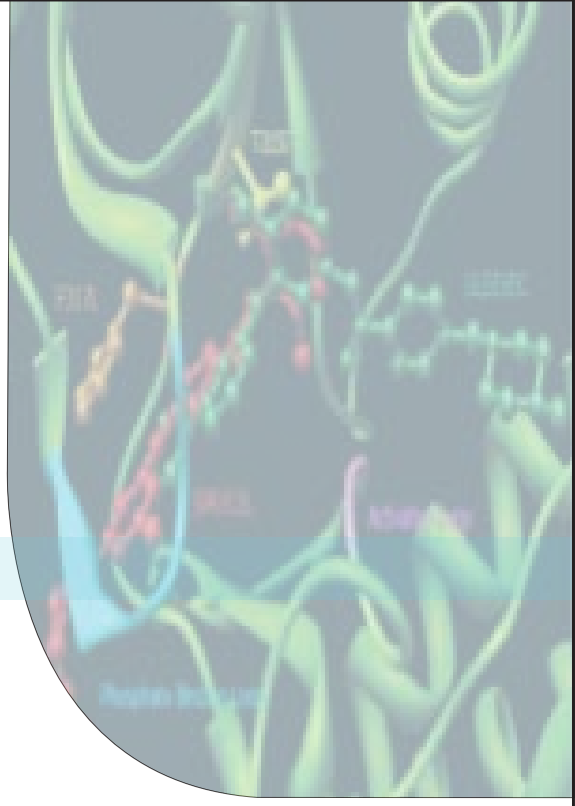
Unipath
SPECIALTY LABORATORY Ltd.

ABL KINASE DOMAIN MUTATION TESTING

Department of Molecular Biology



INDICATION OF TESTING:

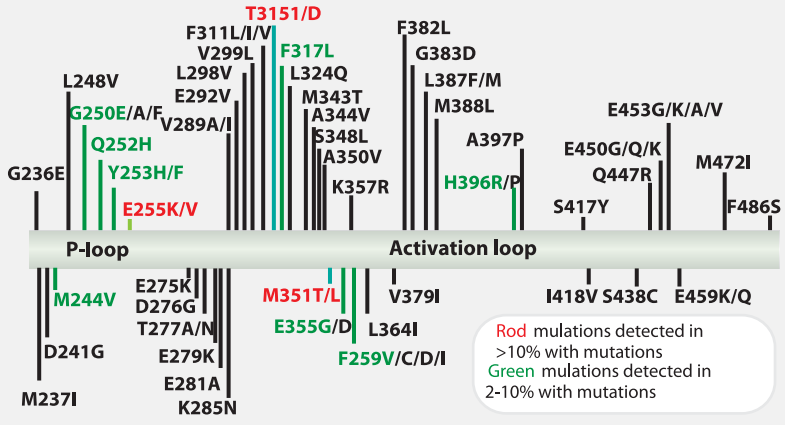
This test is intended to evaluate the patients with chronic myeloid leukemia and Philadelphia chromosome positive B-cell acute lymphoblastic leukemia receiving tyrosine kinase inhibitor (TKI), therapy, who is apparently failing treatment.

BACKGROUND INFORMATION:

Chronic myeloid leukemia (CML) is characterized by the presence of the t(9:22) BCR-ABL abnormality, resulting in formation of a fusion BCR-ABL mRNA and protein. The ABL component of this oncoprotein contains tyrosine kinase activity and is thought to play a central role in the proliferative phenotype of this leukemia.

Recent advances have resulted in a number of therapeutic drugs that inhibit the ABL tyrosine kinase, as well as other protein tyrosine kinases. Imatinib mesylate (Gleevec, Novartis) is the prototype of these tyrosine kinase inhibitors (TKIs), which are capable of inducing durable hematologic and (in most patients) cytogenetic remissions. Unfortunately, a significant subset of patients can develop functional resistance to TKIs, due in a large number of tumors to the acquisition of point mutations in the kinase domain (KD) of the chimeric ABL gene. To date, over 50 distinct mutations have been described, although 15 of these account for more than 80% of the mutations encountered and have well documented in vitro or clinical resistance to TKIs.

Imatinib Resistance-Associated Bcr-Abl Mutations in CML



CLINICAL SIGNIFICANCE

Recognition of TKI resistance is important in CML, as the effect of some mutations can be overcome by increasing imatinib dosage, whereas others require switching to either a different (second-generation) TKI, or alternative therapy. The common T315I KD mutation is particularly important, given that this alteration confers pan-resistance to all currently employed TKIs. Typically, TKI resistance is suspected in a CML patient who shows loss of initial therapeutic response (eg, cytogenetic relapse), or a significant and sustained increase in molecular BCR-ABL quantitative levels. Similar considerations are also present in patients with Philadelphia chromosome positive B-cell acute lymphoblastic leukemia, who can also be treated using TKI therapy.

METHEDOLOGY

Point mutations in ABL are typically detected by direct sequencing of PCR products,following RT-PCR amplification of the BCR-ABL mRNA transcript from a peripheralblood specimen. However, direct sequencing has limited analytic sensitivity(approximately 20%-30% mutant alleles).

TEST NAME	METHOD	SPECIMEN	REPORTING TIME
ABL Kinase Domain Mutations	PCR – SEQUENCING	EDTA Blood	15 Days

ISO 9001 International Standard Certification LIC No QAC/R91/3585
NABL M-0520

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