Mutation in the BCR-ABL1 Fusion Gene
Conferring Resistance to Tyrosine Kinase Inhibitor Drugs

Sanger sequencing can detect mutation in the kinase domain of the BCR-ABL1 fusion gene associated with resistance to tyrosine kinase inhibitor drugs.

Biology of the disease: A tyrosine kinase inhibitor is usually the drug of choice for patients with chronic myelogenous leukemia (CML). The inhibitor works by binding and stabilizing the inactive form of BCR-ABL1, thus inhibiting its phosphorylation function and downstream effects on various substrates. Some patients either fail to respond, or initially respond and later have rising BCR-ABL1 mRNA levels (>10-fold increase), suggesting drug resistance. The most common mechanism of resistance is ABL1 mutation in the kinase domain that interferes with drug binding or masks its effect. Depending on which mutation is detected, increasing the dose of drug or switching to another drug may restore control over cell proliferation. NCCN guidelines (cited below) contain further information on drug selection in the context of particular mutations.

Clinical Indications for the ABL1 drug resistance mutation test:
CML patients who either fail to respond to tyrosine kinase inhibitor or who initially respond and later have a >10-fold rise in BCR-ABL1 mRNA levels to above 0.1 IS% ratio.

Laboratory testing for ABL1 drug resistance mutations: The preferred sample is EDTA-anticoagulated blood (3mL purple top) or bone marrow (1mL) with amplifiable BCR-ABL1 by QrtPCR. RNA is converted to cDNA and PCR-amplified, and products are Sanger sequenced across the ABL1 kinase domain, including the P-loop, catalytic domain, and activation loop. Results are interpreted by a pathologist. The assay detects mutation in as few as 20% of nucleated cells.

References:
3. NCCN Clinical Practice Guidelines in Oncology, Chronic Myelogenous Leukemia.

To consult a pathologist about indications for testing or the significance of a result, call the Molecular Genetics Lab at (984) 974-1825, Dr. Weck at (984) 974-1825 or Dr. Gulley at (919) 843-4595. E-mail: Karen.Weck@unchealth.unc.edu or margaret_gulley@med.unc.edu


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