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 Q-rtPCR. 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:

1. Jain P, Kantarjian H, Cortes J. Chronic myeloid leukemia: overview of new agents and comparative analysis. Curr Treat Options Oncol. 14:127-43, 2013. PMID: 23572291
2. Jones D, Kamel-Reid S, Bahler D, Dong H, Elenitoba-Johnson K, Press R, Quigley N, Rothberg P, Sabath D, Viswanatha D, Weck K, Zehnder J: Laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations in chronic myelogenous leukemia and acute lymphoblastic leukemia: a report of the Association for Molecular Pathology. J Mol Diagn 11:4-11, 2009.
3. NCCN Clinical Practice Guidelines in Oncology, Chronic Myelogenous Leukemia.
4. Baccarani M, Dreyling M; ESMO Guidelines Working Group. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 23 Suppl 7:vii172-77, 2012.
5. Deininger MW. Diagnosing and managing advanced chronic myeloid leukemia. Am Soc Clin Oncol Educ Book. 2015;35:e381-8.

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

Website, http://www.uncmedicalcenter.org/uncmc/professional-education-services/mclendon-clinical-laboratories/directory/molecular-pathology-and-genetics