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## **New DNA Sequencing Test for BCR-ABL Kinase Domain Mutations Mediating Imatinib Resistance in Chronic Myeloid Leukemia**

### **In CML / ALL patients treated with imatinib:**

- Resistance to targeted imatinib therapy is often the result of acquired mutations in the BCR-ABL kinase domain that abrogate imatinib's inhibitory effects.
- Patients who fail to initially respond to imatinib therapy may also have acquired ABL mutations (although less frequently).

### **Patients Who May Benefit From Imatinib Resistance Testing Include Those With:**

- Rising disease burdens despite continued imatinib therapy - usually detected by:
  - Rising levels of BCR-ABL RNA by RQ-PCR  
2-fold rise in BCR-ABL RNA levels is 97% sensitive for predicting ABL resistance mutations.
  - Loss of complete cytogenetic or hematologic response.
- Failure to respond to imatinib therapy by hematologic, cytogenetic, or molecular criteria.

### **Clinical Relevance of ABL Kinase Domain Resistance Mutations:**

- Alternative second-generation targeted kinase inhibitor drugs are active against almost all ABL kinase mutants so far discovered (except T315I).
- If serial RQ-PCR's are closely monitored, therapy changes can be made before frank hematologic or cytogenetic relapse.

### **Testing Information:**

- RT-PCR of entire ABL kinase domain followed by direct DNA sequencing.
- Sequencing will detect all known mutations associated with drug resistance.
- Assay sensitivity ~20%; mutant clones at lower abundance may not be detected .
- Data generated, reviewed, and clinically interpreted by a board-certified physician within 1-2 weeks - within a licensed, accredited clinical diagnostic lab.

### **Sample Requirements:**

- 10-20 mL of blood or bone marrow — yellow (ACD) or purple (EDTA) tube (mixed thoroughly).
- Ship COLD (not frozen) to lab shipping address above; must arrive within 24 hours of collection.
- If our lab is used to monitor the patient's BCR-ABL RNA levels (by RQ-PCR), the same sample that was used for quantitative PCR can also be used for sequencing. We routinely store these samples (stabilized) for several weeks after RQ-PCR reporting. Just call us to order sequencing.
- PCR-based DNA sequencing will likely not be technically feasible if the BCR-ABL RNA level is more than ~2.5 logs below the baseline (ie, a BCR-ABL to G6PDH RNA ratio below ~0.02%)

For more information about this and other tests offered by the Molecular Diagnostic Center go to [www.ohsulabs.com](http://www.ohsulabs.com) or call the phone numbers listed above.