

Mutation Detection in Gastrointestinal Stromal Tumors (GISTs)

IDENTIFICATION OF MUTATIONS IN THE KIT OR PDGFR GENES SUPPORTS THE DIAGNOSIS OF GIST AND PREDICTS RESPONSE TO GLEEVEC[®]

Test Highlights

- Molecular analysis of formalin-fixed, paraffin-embedded tumor tissue to identify mutations in the *KIT* and *PDGFR* genes.
- Predicts probability of patient response to Gleevec (imatinib).

Clinical Background

- Previously, patients with stromal tumors of the gastrointestinal tract (GISTs) had few therapeutic options. This situation has changed with the introduction of STI-571 (Gleevec) into clinical practice.
- Gleevec is a phenylaminopyrimidine, which acts as a competitive inhibitor of the *KIT* and *PDGFR* tyrosine kinases. Patients with activating mutations in the tyrosine kinase domains of *KIT* and *PDGFR* have shown partial response and stabilization of disease after Gleevec therapy. This clinical response underscores the need to provide an accurate diagnosis of GIST.
- The presence of mutations in the *KIT* or *PDGFR* genes supports a diagnosis of GIST and predicts response to Gleevec.

Disease Overview

- Historically, the diagnosis of stromal tumors of the gastrointestinal tract has been difficult. Many were originally thought to be of muscle or neural origin but recent data suggests they are derived from multi-potential mesenchymal stem cells.
- The majority of GISTs express the c-kit (CD117) protein, which is detectable by immunohistochemistry.
- While a positive CD117 immunostain suggests the tumor may be correctly diagnosed as a GIST, a negative CD117 immunostain does not rule out the diagnosis of a GIST.
- Approximately 15 percent of GISTs have mutations in *PDGFR* and are usually CD117-negative. Additionally, the CD117 immunostain does not give information about the location and type of mutation, which is critical for predicting responsiveness to Gleevec.

Genetics

- GISTs typically contain activating mutations in either the *KIT* or platelet-derived growth factor receptor-alpha (*PDGFR*) genes. Both genes encode transmembrane tyrosine kinase receptors that undergo dimerization and auto-phosphorylation upon ligand binding. This activates downstream signaling pathways that have critical roles in cell proliferation and differentiation.

- *KIT* and *PDGFR*-activating mutations permit ligand-independent signaling, which appears to be the driving force for oncogenesis in GISTs.

Methodology

- Mutation analysis for GISTs utilizes real-time PCR to amplify *KIT* exons 9, 11, 13, and 17 and *PDGFR* exons 12 and 18.
- High-resolution amplicon melting analysis scans for mutations, which are then confirmed by sequencing.

Indications for Ordering

Patients diagnosed with or suspected of having a GIST based on tumor morphology, location, and CD117 stain.

References

1. Badalamenti G, et al. Gastrointestinal stromal tumors (GISTs): focus on histopathological diagnosis and biomolecular features. *Ann Oncol* 2007;18: Suppl 6:vi136–40.
2. Demetri GD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw* 2007;5:S1–29.
3. Kirsch R, Gao ZH, Riddell R. Gastrointestinal stromal tumors: diagnostic challenges and practical approach to differential diagnosis. *Adv Anat Pathol* 2007;14(4):261–85.

Test Information

2002674 Gastrointestinal Stromal Tumor Mutation

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.