KIT and PDGFRA testing for diagnosis of gastrointestinal stromal tumors (GISTs)

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Authors' objectives
Gastrointestinal stromal tumors (GISTs) are the most common tumors of mesenchymal origin, although they are rare, with a prevalence of just 10 to 15 per million individuals. GISTs may occur anywhere within the gastrointestinal (GI) tract, with the most common locations being the stomach and jejunum and ileum. The malignancy of GISTs is variable, but is highest for small intestine GISTs at 40% to 50%. GISTs can be detected through clinical symptoms, such as fatigue, dyspepsia, and acute or chronic GI bleeding, or incidentally through surgery, imaging studies, or endoscopy. GISTs are usually found in patients who are 40 years of age or older; however, 5% to 20% are found in younger individuals and are often associated with syndromes such as neurofibromatosis type 1 (NF1), Carney-triad syndrome, Carney-Stratakis syndrome, and familial GIST. The vast majority of GISTs occur sporadically. In the late 1990s it was observed that GISTs typically express the CD117 protein, which is encoded by the v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog gene known as KIT. The CD117 protein is a type III tyrosine kinase receptor and GIST tumors often have sequence variants in the KIT gene that result in a gain of function of the CD117 protein. Most GISTs test positive for CD117 immunostaining, indicating expression of the KIT gene. A second gene associated with GISTs is the platelet-derived growth factor receptor, alpha polypeptide gene (PDGFRA). PDGFRA is located next to KIT on chromosome 4 and may be an ancestral gene duplication of KIT. The PDGFRA protein is also a tyrosine kinase receptor and probably functions similarly to CD117. Sequence variants in KIT and PDGFRA appear to be mutually exclusive, which suggests that sequence variants in these genes are key in the development of the tumors. Some patients have GISTs that do not have KIT or PDGFRA sequence variants and these are called "wild-type" GISTs. Treatment of GISTs is with surgery if the tumor is resectable, with the aim of surgery being to completely remove the tumor and any marginal tissue without rupture. For patients with more advanced disease that has spread to nearby lymph nodes or has metastasized, the tumor may only be partially resectable or might not be resectable at all. GISTs are relatively unresponsive to traditional chemotherapeutic agents. However, treatment of GISTs has been revolutionized by the discovery that the tyrosine kinase inhibitors (TKIs) imatinib mesylate (Gleevec®/Glivec®; Novartis Pharmaceuticals Corp.) and sunitinib malate (Sutent®; Pfizer Inc.) are often effective at increasing survival time of patients with GISTs. GISTs may resemble several other neoplasms, so differential diagnosis of GISTs can be problematic. Diagnosis of GIST is typically based on the tumor location, its histological appearance, and the results of immunostaining tests with antibodies, including CD117, CD34, DOG1, and/or PDGFRA. DOG1 is an abbreviation of Discovered On GIST-1 and the protein is encoded by the ANO1 (anoctamin 1, calcium-activated chloride channel) gene. CD34 is a cell surface antigen that is expressed on human hematopoietic progenitor cells and is encoded by the CD34 gene. This report focuses on the use of KIT and PDGFRA molecular analysis in the diagnosis of GIST.

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Address for correspondence
HAYES, Inc., 157 S. Broad Street, Suite 200, Lansdale, PA 19446, USA. Tel: 215 855 0615; Fax: 215 855 5218 Email: hayesinfo@hayesinc.com

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