**Protocol for the Examination of Biopsy Specimens From Patients With Gastrointestinal Stromal Tumor (GIST)**

**Version:** 4.3.0.0

**Protocol Posting Date:** December 2022

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

**This protocol may be used for the following procedures AND tumor types:**

|  |  |
| --- | --- |
| **Procedure** | **Description** |
| Biopsy |   |
| **Tumor Type** | **Description** |
| Gastrointestinal stromal tumor  |   |

**The following should NOT be reported using this protocol:**

|  |
| --- |
| **Procedure** |
| Resection |
| Cytologic specimens |

**Authors**

Julie C. Fanburg-Smith, MD, FCAP\*; Julia A. Bridge, MD, FCAP\*; Andrew M. Bellizzi, MD\*; Paari Murugan, MD, FCAP\*; Javier A. Laurini, MD; Markku Miettinen, MD.
With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
\* Denotes primary author.

**Accreditation Requirements**

The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

**Summary of Changes**

**v 4.3.0.0**

* Added Associated Syndrome under Clinical
* Reformatted Tumor Site
* Added BRAF to Special Studies
* Updated Note D Table 1 correction of Gastric moderate rate changed from 10% to 12%

**Reporting Template**

**Protocol Posting Date: December 2022**

**Select a single response unless otherwise indicated.**

**CASE SUMMARY: (GASTROINTESTINAL STROMAL TUMOR (GIST): Biopsy)**

**Standard(s)**: AJCC-UICC 8

*This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.*

**CLINICAL**

**+Associated Syndrome**

\_\_\_ Carney triad

\_\_\_ Carney-Stratakis syndrome

\_\_\_ Neurofibromatosis type1

\_\_\_ Familial GIST syndrome

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**+Prebiopsy Treatment (select all that apply)**

\_\_\_ No known prebiopsy therapy

\_\_\_ Systemic therapy performed (specify type): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Therapy performed, type not specified

\_\_\_ Not specified

**SPECIMEN**

**Procedure**

\_\_\_ Core needle biopsy

\_\_\_ Endoscopic biopsy

\_\_\_ Fine needle aspiration biopsy

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**TUMOR**

**Tumor Site (Note** [**A**](#N10819)**)**

\_\_\_ Esophagus (specify location): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Gastroesophageal junction: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Stomach (specify location): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Small intestine

\_\_\_ Duodenum

\_\_\_ Jejunum

\_\_\_ Ileum (excluding ileocecal valve)

\_\_\_ Meckel diverticulum (site of neoplasm)

\_\_\_ Small intestine, NOS

\_\_\_ Appendix: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Ileocecal valve: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Large intestine

\_\_\_ Cecum

\_\_\_ Ascending colon

\_\_\_ Hepatic flexure of colon

\_\_\_ Transverse colon

\_\_\_ Splenic flexure of colon

\_\_\_ Descending colon

\_\_\_ Sigmoid colon

\_\_\_ Rectosigmoid junction: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Rectum: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Large intestine, NOS

\_\_\_ Retroperitoneum: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Peritoneum / abdomen (specify site): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**Histologic Type**

\_\_\_ Gastrointestinal stromal tumor, spindle cell type

\_\_\_ Gastrointestinal stromal tumor, epithelioid type

\_\_\_ Gastrointestinal stromal tumor, mixed

\_\_\_ Gastrointestinal stromal tumor, other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Histologic Type Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Tumor Size (based on clinicoradiologic estimate)**

\_\_\_ Greatest dimension in Centimeters (cm): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

**+Additional Dimension in Centimeters (cm): \_\_\_\_ x \_\_\_\_ cm**

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Mitotic Rate (Note** [**B**](#N10820)**)**

*The mitotic rate should be determined in 5 mm2 of tumor. With the use of older model microscopes, 50 HPF is equivalent to 5 mm2. Most modern microscopes with wider fields require approximately 20 to 25 HPF to encompass 5 mm2. If necessary, please measure a field of view to accurately determine actual number of fields required to be counted on individual microscopes to encompass 5 mm2.*

\_\_\_ Specify mitotic rate per 5 mm2: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ mitoses per 5 mm2

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Histologic Grade (Note** [**B**](#N10820)**)**

\_\_\_ G1, low grade (mitotic rate less than or equal to 5 per 5 mm2)

\_\_\_ G2, high grade (mitotic rate greater than 5 per 5 mm2)

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ GX, cannot be assessed: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Necrosis**

\_\_\_ Not identified

\_\_\_ Present

**+Extent of Necrosis**

\_\_\_ Specify percentage: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ %

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Treatment Effect (Note** [**C**](#N10823)**)**

\_\_\_ No known prebiopsy therapy

\_\_\_ Not identified

\_\_\_ Present

**+Percentage of Viable Tumor**

\_\_\_ Specify percentage: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ %

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Risk Assessment (Note** [**D**](#N10821)**)**

\_\_\_ None

\_\_\_ Very low risk

\_\_\_ Low risk

\_\_\_ Moderate risk

\_\_\_ High risk

\_\_\_ Overtly metastatic

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Tumor Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**ADDITIONAL FINDINGS**

**+Additional Findings (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**SPECIAL STUDIES (Note** [**E**](#N10822)**)**

*The CAP GIST Biomarker Template can be used for reporting biomarkers.*

**+Immunohistochemical Studies (select all that apply)**

\_\_\_ Not performed

\_\_\_ KIT (CD117)

**KIT (CD117)**

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

\_\_\_ DOG1 (ANO1)

**DOG1 (ANO1)**

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

\_\_\_ SDHA

**SDHA**

\_\_\_ Intact

\_\_\_ Deficient

\_\_\_ Pending

\_\_\_ SDHB

**SDHB**

\_\_\_ Intact

\_\_\_ Deficient

\_\_\_ Pending

\_\_\_ BRAF

**BRAF**

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Molecular Genetic Studies (eg., KIT, PDGFRA, SDHA / B / C / D, RAS or NF1 mutational analysis or BRAF or FGFR1 fusion gene analysis)**

\_\_\_ Performed, see biomarker report: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Performed (specify method(s) and result(s)): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Pending

\_\_\_ Not performed

**COMMENTS**

**Comment(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Explanatory Notes**

**A. Location**

Gastrointestinal stromal tumors may occur anywhere along the entire length of the tubal gut, as well as in extravisceral locations, which include the omentum, mesentery, pelvis, and retroperitoneum.[1,](#R46198)[2,](#R46199)[3,](#R46200)[4,](#R46202)[5,](#R46201)[6](#R46203) Typically, they arise from the wall of the gut and extend inward toward the mucosa, outward toward the serosa, or in both directions. Lesions that involve the wall of the gastrointestinal (GI) tract frequently cause ulceration of the overlying mucosa. Infrequently, lesions invade through the muscularis mucosa to involve the mucosae. Mucosal invasion is an adverse prognostic factor in numerous studies. Because the anatomic location along the GI tract affects prognosis, with location in the stomach having a more favorable prognosis, it is very important to specify anatomic location as precisely as possible.[5,](#R46201)[6](#R46203)

References

1. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459-465.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch. 2001;438(1):1-12.
3. Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol. 2000;13(5):577-585.
4. WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (france): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed; vol. 1).
5. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29(1):52-68.
6. Miettinen M, Felisiak-Golabek A, Wang Z, Inaguma S, Lasota J. GIST Manifesting as a Retroperitoneal Tumor: Clinicopathologic Immunohistochemical, and Molecular Genetic Study of 112 Cases. Am J Surg Pathol. 2017 May;41(5):577-585. PMID: 28288036

**B. Histologic Grade**

Histologic grading in GIST, unlike in soft tissue sarcoma, only takes mitotic rate into account. GIST is generally less proliferative than many other soft tissue tumors and the threshold for separating low from high-grade tumors occurs at 5 mitotic figures per 5 mm2.[1,](#R46204)[2,](#R46205)[3](#R46206)

GX: Grade cannot be assessed

G1: Low grade; mitotic rate ≤5/5 mm2

G2: High grade; mitotic rate >5/5 mm2

The mitotic count should be initiated in an area that on screening magnification reveals the highest level of mitotic activity and be performed as consecutive high-power fields (HPF). Stringent criteria should be applied when counting mitotic figures; pyknotic or apoptotic nuclei should not be regarded as mitosis.

Note: Mitoses should be counted in 5 mm2 of tumor.[2,](#R46205)[3](#R46206) With the use of older model microscopes, 50 HPF is equivalent to 5 mm2. Most modern microscopes with wider fields require approximately 20 to 25 HPF to encompass 5 mm2. If necessary, please measure a field of view to accurately determine actual number of fields required to be counted on individual microscopes to encompass 5 mm2.

References

1. Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23(2):70-83.
3. WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (france): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed; vol. 1).

**C. Treatment Effect**

Gastrointestinal stromal tumors respond well to the newer targeted systemic therapies, imatinib mesylate, and sunitinib malate. The types of treatment effects that have been seen are hypocellularity, myxoid stroma, fibrosis, and necrosis. Nests of viable tumor cells are virtually always observed. Because all of these histologic features can be demonstrated in untreated GIST, it is not possible to know whether these changes are due to treatment or not. As a practical compromise, it is best to report the percentage of viable tumor after treatment.

**D. Risk Assessment**

Biopsies are suboptimally positioned for GIST risk stratification as these may not include sufficient tumor (i.e., 5 mm2) for mitotic counting and may not sample mitotic “hot spots”. Furthermore, the risk for metastasis or tumor related death presumes that the GIST has been removed. On biopsy, one may attempt to risk stratify a GIST, using location, available material for mitotic count, and clinicoradiologic size into account.

Biopsies are more predictive if overtly high mitotic count/high grade/high risk on biopsy, based on mitoses and clinicoradiologic size yet low mitotic count/low grade on biopsy may underestimate actual mitoses on resection and not be accurate due to sampling. Most GIST is now regarded as having at least some potential for distant metastasis. This concept was originally the result of a National Cancer Institute-sponsored consensus conference that was held in 2002.[1](#R46212) More specific data generated by large follow-up studies refined the biologic potential assessment.[2,](#R46208)[3,](#R46209)[4,](#R46210)[5,](#R46207)[6,](#R46211)[7](#R46213) Criteria obtained from those data were adopted in a National Cancer Care Network (NCCN) Task Force report on GIST.[8](#R46214) We have adopted the criteria for risk stratification, as indicated in Table 1.[2,](#R46208)[3,](#R46209)[4,](#R46210)[5,](#R46207)[6,](#R46211)[7](#R46213) The scheme includes anatomic site as a factor because small bowel GIST carries a higher risk of progression than gastric GIST of similar size and mitotic activity. This prognostic assessment applies best to KIT/PDGFRA mutant GIST whereas SDH-deficient GIST is more unpredictable.[9](#R46215) For anatomic sites not listed in this table, such as esophagus, mesentery, and peritoneum, or in the case of “insufficient data,” it is best to use risk criteria for jejunum/ileum.

**Table 1. Guidelines for Risk Assessment of Primary Gastrointestinal Stromal Tumor (GIST)**

|  |  |
| --- | --- |
| **Tumor Parameters** | **Risk of Progressive Disease**#**(%)** |
| ***Mitotic Rate*** | ***Size*** | ***Gastric*** | ***Duodenum*** | ***Jejunum/Ileum*** | ***Rectum*** |
| **≤5 per 5 mm2** | ≤2 cm | None (0%) | None (0%) | None (0%) | None (0%) |
| >2 - ≤5 cm | Very low (1.9%) | Low (8.3%) | Low (4.3%) | Low (8.5%) |
| >5 - ≤10 cm | Low (3.6%) | (Insufficient data##) | Moderate (24%) | (Insufficient data##) |
| >10 cm | Moderate (12%) | High (34%) | High (52%) | High (57%) |
| **>5 per 5 mm2** | ≤2 cm | None | (Insufficient data##) | High | High (54%) |
| >2 - ≤5 cm | Moderate (16%) | High (50%) | High (73%) | High (52%) |
| >5 - ≤10 cm | High (55%) | (Insufficient data##) | High (85%) | (Insufficient data##) |
| >10 cm | High (86%) | High (86%) | High (90%) | High (71%) |

Adapted with permission from Miettinen and Lasota.[5](#R46207) Copyright 2006 by Elsevier.

# Defined as metastasis or tumor-related death.

## Denotes small number of cases.

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GIST from the pre-imatinib era.[2,](#R46208)[3,](#R46209)[4,](#R46210)[6](#R46211)

Note: See Note B, “Histologic Grade,” regarding the number of high-power fields to evaluate

References

1. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459-465.
2. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29(1):52-68.
3. Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. Am J Surg Pathol. 2001;25(9):1121-1133.
4. Miettinen M, Kopczynski J, Makhlouf HR, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. Am J Surg Pathol. 2003;27(5):625-641.
5. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23(2):70-83.
6. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol. 2006;30(4):477-489.
7. Miettinen M, Felisiak-Golabek A, Wang Z, Inaguma S, Lasota J. GIST Manifesting as a Retroperitoneal Tumor: Clinicopathologic Immunohistochemical, and Molecular Genetic Study of 112 Cases. Am J Surg Pathol. 2017 May;41(5):577-585. PMID: 28288036.
8. Demetri GD, Benjamin RS, Blanke CD, et al; NCCN Task Force. 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(Suppl 2):S1-S29.
9. WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (france): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed; vol. 1)

**E. Ancillary Studies**

**Immunohistochemistry**

Because small-molecule kinase inhibitor therapy is highly effective in the treatment of GIST, it has become imperative to distinguish GIST from its histologic mimics, mainly leiomyoma, leiomyosarcoma, schwannoma, and desmoid fibromatosis.[1,](#R46216)[2](#R46217) Immunohistochemistry is instrumental in the workup of GIST. For the initial work up of GIST, a basic immunohistochemical panel including CD117 (KIT), DOG1 (Ano1), Desmin, S100 protein, and CD34 is recommended. GIST is immunoreactive for KIT (CD117) (approximately 95%) and/or DOG1(>99%).[3,](#R46235)[4,](#R46236)[5](#R46237) KIT immunoreactivity is usually strong and diffuse but can be more focal in unusual cases (Figure 1, A and B). It is not unusual for GIST to exhibit dot-like perinuclear staining (Figure 1, C), while less commonly, some cases exhibit membranous staining (Figure 1, D). These patterns do not clearly correlate with mutation type or response to therapy. Most KIT-negative/DOG1-positive GIST is gastric or extra-visceral GIST and almost invariably harbor a platelet-derived growth factor receptor A (PDGFRA) mutation.[6](#R46218) DOG1 expression is not related to mutational status in GIST, and it may be a useful marker to identify a subset of patients with CD117-negative GIST, who might benefit from targeted therapy.[4,](#R46236)[5](#R46237) Approximately 70% of GIST is positive for CD34, 30% to 40% are positive for smooth muscle actin, 5% are positive for S100 protein (usually focal), 5% are positive for desmin (usually focal), and 1% to 2% are positive for keratin (weak/focal).[7](#R46232)

Note: PanTrk immunohistochemistry may be positive in GIST, a tumor typically negative for NTRK fusion and this immunostain is not recommended.

Since succinate dehydrogenase (SDH)-deficient GIST may be familial, have specific implications (see the following), it is recommended that all gastric GIST be screened for loss of SDH by immunohistochemistry, best accomplished by immunostaining for SDHB, which is lost independent of the SDH-subunit that is inactivated.[8,](#R46233)[9,](#R46234)[10,](#R46219)[11](#R46220) Mutations in SDHA are detected in 30% of SDH-deficient GIST and loss of expression of SDHA specifically identifies tumors with SDHA mutations; other SDH-deficient GIST show normal (intact) cytoplasmic staining for SDHA.[12,](#R46221)[13](#R46222) Patients with SDH-deficient GIST should be referred to a genetic counselor for appropriate workup.



**Figure 1**. Patterns of KIT staining in gastrointestinal stromal tumor (GIST). A. Diffuse and strong immunoreactivity in a typical GIST. B. Focal and weak pattern in an epithelioid gastric GIST with a PDGFRA mutation. C. Dot-like perinuclear staining. D. Membranous pattern. (Original magnification X400)

**Molecular Analysis**

Approximately 75% of GIST possess activating mutations in the KIT gene, whereas another 10% have activating mutations in the PDGFRA gene.[14,](#R46223)[15,](#R46224)[16,](#R46225)[17](#R46226) These mutations result in virtually full-length KIT proteins that exhibit ligand-independent activation. KIT and PDGFRA each contain 21 exons. However, mutations cluster within “hotspots”: exons 9, 11, 13, and 17 in KIT, and exons 12, 14, and 18 in PDGFRA (Figure 2). About 5% to 10% of GIST appear to be negative for both KIT and PDGFRA mutations. The most recent NCCN Task Force on GIST strongly encourages that KIT and PDGFRA mutational analysis be performed if tyrosine kinase inhibitors (TKIs) are considered as part of the treatment plan for unresectable or metastatic disease and that mutational analysis be considered for patients with primary disease, particularly those with high-risk tumors. KIT and PDGFRA mutation status can be determined easily from paraffin-embedded tissue. Secondary or acquired mutations can be associated with development of tumor resistance in the setting of long-term imatinib mesylate treatment. These are usually point mutations that occur most commonly in KIT exons 13, 14, and 17.[18](#R46231) The clinical utility of these mutations is an evolving concept, but it is important not to confuse them with the primary or initial mutation in GIST.

Recent studies focusing on the molecular classification of GIST recognized two major subgroups: succinate dehydrogenase (SHD)-competent and SDH-deficient GIST, both of which can arise in the sporadic or familial setting.[8,](#R46233)[9](#R46234) SDH-competent GIST include tumors with mutations of KIT and PDGFRA as well of a subset of wild-type GIST with mutations mainly in NF1 and BRAF genes or rarely fusion gene events involving FGFR1 or BRAF.[19,](#R46245)[20,](#R46246)[21,](wild-type#R46247)[22,](#R46248)[23,](#R46249)[24](#R46252) On the other hand, SDH-deficient GIST includes tumors with a genetic alteration in any of the SDH subunits leading to SDH dysfunction.

SDH-deficient GIST represent approximately 8% of GIST; although, these may arise sporadically.  The majority of pediatric GIST, arise in Carney triad and Carney-Stratakis syndrome and are SDH-deficient. SDH is a mitochondrial enzyme comprising four subunits (SDHA, SDHB, SDHC and SDHD) that is involved in the Krebs cycle. Genetic alteration of any of the four subunits results in SDH dysfunction and subsequent loss of SDHB expression by immunohistochemistry. SDH deficient GIST arise almost exclusively in the stomach, affect predominantly female patients and tend to manifest at a young age. Pathologic features associated with SDH-deficient tumors include multinodular and/or plexiform growth pattern, epithelioid morphology, lymphovascular invasion, nodal involvement and frequent metastasis to the liver and peritoneum. Importantly, germline mutations in the genes coding for any of the SDH subunits can also lead to paraganglioma/pheochromocytoma, SDH-deficient renal cell carcinoma and pituitary tumors in addition to GIST. It is recommended that all gastric GIST be screened for loss of SDHB by immunohistochemistry. All patients with SDH-deficient GIST identified by loss of SDHB immunostain should be referred to a genetic counselor.



**Figure 2.** Locations and frequency of activating KIT and PDGFRA mutations in GIST. Adapted with permission from Heinrich et al.[14](#R46223)  Copyright 2003 by the American Society of Clinical Oncology. All rights reserved.

KIT and PDGFRA are excellent targets for small-molecule tyrosine kinase inhibitors, and two compounds of this class, imatinib mesylate (Gleevec, Novartis Pharmaceuticals, Basel, Switzerland) and sunitinib malate (Sutent, Pfizer Pharmaceuticals, New York, New York), avapritinib (Ayvakit, PDGFRA D842V (exon 18) mutant, may be resistant to standard therapy), regornfenib (3rd line), ripretinib (4th line, Qinlock) have shown efficacy in clinical trials and have been approved by the US Food and Drug Administration for the treatment of GIST.[25,](#R46227)[26,](#R46228)[27,](#R46229)[28](#R46250) SDH-deficient GIST are usually resistant to imatinib but may have a higher probability of response to sunitinib.[8,](#R46233)[29](#R46251) Because different tyrosine kinase inhibitors (TKIs) may have differential efficacy depending on the type of mutation present in GIST, oncologists may want to know the mutation status of each GIST[30](#R46230), because this may influence which drug the patient receives.[14](#R46223) Secondary resistance mutations may also affect drug selection as their significance is further defined.

References

1. Hornick JL, Fletcher CD. Immunohistochemical staining for KIT (CD117) in soft tissue sarcomas is very limited in distribution. Am J Clin Pathol. 2002;117(2):188-193.
2. Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol. 2000;13(10):1134-1142.
3. Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, Miettinen M. CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol. 1998;11(8):728-734.
4. Espinosa I, Lee CH, Kim MK, et al. A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. Am J Surg Path. 2008;32(2):210–218.
5. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol. 2009;33:1401–1408.
6. Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. Am J Surg Pathol. 2004;28(7):889-894.
7. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459-465.
8. Mei L, Smith SC, Faber AC, et al. Gastrointestinal Stromal Tumors: The GIST of Precision Medicine. Trends Cancer. 2018;4:74-91.
9. Gill AJ. Succinate dehydrogenase (SDH) and mitochondrial driven neoplasia. Pathology. 2012 Jun;44(4):285-92.
10. Gill AJ, Benn DE, Chou A, et al. Immunohistochemistry for SDHB triages genetic testing of SDHB, SDHC, and SDHD in paraganglioma-pheochromocytoma syndromes. Hum Pathol. 2010 Jun;41(6):805-14.
11. Doyle LA, Nelson D, Heinrich MC, et al. Loss of succinate dehydrogenase subunit B (SDHB) expression is limited to a distinctive subset of gastric wild-type gastrointestinal stromal tumours: a comprehensive genotype-phenotype correlation study. Histopathology. 2012;61(5):801-809.
12. Wagner AJ, Remillard SP, Zhang YX, et al. Loss of expression of SDHA predicts SDHA mutations in gastrointestinal stromal tumors. Mod Pathol. 2013;26(2):289-294.
13. Dwight T, Benn DE, Clarkson A, et al. Loss of SDHA expression identifies SDHA mutations in succinate dehydrogenase-deficient gastrointestinal stromal tumors. Am J Surg Pathol. 2013;37(2):226-233.
14. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21(23):4342-4349.
15. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003;299(5607):708-710.
16. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279(5350):577-580.
17. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res. 2001;61(22):8118-8121.
18. Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol. 2006;24(29):4764-4774.
19. Dare AJ, Gupta AA, Thipphavong S, Miettinen M, Gladdy RA. Abdominal neoplastic manifestations of neurofibromatosis type 1. *Neurooncol Adv.* 2020 Jun 25;2(Suppl 1):i124-i133. doi: 10.1093/noajnl/vdaa032. PMID: 32642738.
20. Lasota J, Kowalik A, Felisiak-Golabek A, Zięba S, Wang ZF, Miettinen M. New Mechanisms of mTOR Pathway Activation in KIT-mutant Malignant GISTs. *Appl Immunohistochem Mol Morphol*. 2019 Jan;27(1):54-58. PMID: 28777148.
21. Shi E, Chmielecki J, Tang CM, et al. FGFR1 and NTRK3 actionable alterations in“wild-type” gastrointestinal stromal tumors. *J TranslMed*. 2016;14(1):339.
22. Pantaleo MA, Urbini M, Indio V, et al. Genome-wide analysis identifies MEN1 and MAX mutations and a neuroendocrine-like molecularheterogeneity in quadruple WT GIST. *Mol Cancer Res*. 2017;15(5):553-562.
23. Charo LM, Burgoyne AM, Fanta PT, Patel H, Chmielecki J, Sicklick JK, McHale MT. A Novel PRKAR1B-BRAF Fusion in Gastrointestinal Stromal Tumor Guides Adjuvant Treatment Decision-Making During Pregnancy. *J Natl Compr Canc Netw* 2018;16:238-42.
24. Torrence D, Xie Z, Zhang L, Chi P, Antonescu CR. Gastrointestinal stromal tumors with BRAF gene fusions. A report of two cases showing low or absent KIT expression resulting in diagnostic pitfalls. *Genes Chromosomes Cancer.* 2021 Dec;60(12):789-795.
25. Demetri GD, Benjamin RS, Blanke CD, et al; NCCN Task Force. 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(Suppl 2):S1-S29.
26. Demetri GD. Targeting the molecular pathophysiology of gastrointestinal stromal tumors with imatinib: mechanisms, successes, and challenges to rational drug development. Hematol Oncol Clin North Am. 2002;16(5):1115-1124.
27. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329-1338.
28. Kelly CM, Gutierrez Sainz L, Chi P. The management of metastatic GIST: current standard and investigational therapeutics. *J Hematol Oncol* 14:2, 2021.
29. Glod J, Arnaldez FI, Wiener L, Spencer M, Killian JK, Meltzer P, Dombi E, Derse-Anthony C, Derdak J, Srinivasan R, Linehan WM, Miettinen M, Steinberg SM, Helman L, Widemann BC. A Phase II Trial of Vandetanib in Children and Adults with Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumor. *Clin Cancer Res*. 2019 Nov 1;25(21):6302-6308. Epub 2019 Aug 22. PMID: 31439578.
30. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol. 2005;23(23):5357-5364.