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PATHOLOGISTS

## Template for Reporting Results of Biomarker Testing of Specimens From Patients With Gastrointestinal Stromal Tumors

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## **CAP Gastrointestinal Stromal Tumor Biomarker Template Revision History**

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### **Version Code**

The definition of the version code can be found at [www.cap.org/cancerprotocols](http://www.cap.org/cancerprotocols).

**Version:** GISTBiomarkers 1.0.0.0

### **Summary of Changes**

This is a new template.

## GIST Biomarker Reporting Template

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Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient's medical record and thus readily available to the treating clinical team.

### GASTROINTESTINAL STROMAL TUMOR (GIST)

Select a single response unless otherwise indicated.

**Note:** Use of this template is optional.

#### + RESULTS

##### + Immunohistochemical Studies (Note A)

- + \_\_\_ KIT (CD117)#
  - + \_\_\_ Positive
  - + \_\_\_ Negative
- + \_\_\_ DOG1 (ANO1)#
  - + \_\_\_ Positive
  - + \_\_\_ Negative
- + \_\_\_ SDHB
  - + \_\_\_ Intact
  - + \_\_\_ Deficient
- + \_\_\_ SDHA
  - + \_\_\_ Intact
  - + \_\_\_ Deficient
- + \_\_\_ Other (specify): \_\_\_\_\_
  - + \_\_\_ Positive
  - + \_\_\_ Negative

# Note: Duplicate testing/reporting of KIT (CD117) and DOG is not required if previously performed.

##### + Molecular Genetic Studies (eg, KIT, PDGFRA, BRAF, SDHA/B/C/D, or NF1 mutational analysis)

- + \_\_\_ Submitted for analysis; results pending
- + \_\_\_ Performed, see separate report: \_\_\_\_\_
- + \_\_\_ Performed
  - + Specify method(s) and results: \_\_\_\_\_
- + \_\_\_ Not performed

##### + KIT Mutational Analysis (Note B)

- + \_\_\_ No mutation detected
- + \_\_\_ Mutation identified (specify): \_\_\_\_\_
- + \_\_\_ Cannot be determined (explain): \_\_\_\_\_

**+ PDGFRA Mutational Analysis (Note C)**

- +  No mutation detected
- +  Mutation identified (specify): \_\_\_\_\_
- +  Cannot be determined (explain): \_\_\_\_\_

**+ BRAF Mutational Analysis (Note D)**

- +  No BRAF mutation detected
- +  BRAF V600E (c.1799T>A) mutation
- +  Other BRAF mutation (specify): \_\_\_\_\_
- +  Cannot be determined (explain): \_\_\_\_\_

**+ SDHA/B/C/D Mutational Analysis (Note E)**

- +  No mutation detected
- +  Mutation identified (specify): \_\_\_\_\_
- +  Cannot be determined (explain): \_\_\_\_\_

**+ NF1 Mutational Analysis (Note F)**

- +  No mutation detected
- +  Mutation identified (specify): \_\_\_\_\_
- +  Cannot be determined (explain): \_\_\_\_\_

**+ METHODS****+ Dissection Method(s) (select all that apply) (Note G)**

- +  Laser capture microdissection
- +  Manual under microscopic observation
- +  Manual without microscopic observation
- +  Cored from block
- +  Whole tissue section (no tumor enrichment procedure employed)

**+ KIT Mutational Analysis****+ Exons Assessed** (select all that apply)

- +  Exon 9
- +  Exon 11
- +  Exon 13
- +  Exon 14
- +  Exon 17
- +  Other (specify): \_\_\_\_\_

**+ Testing Method(s)#**

- + Specify name of method used and exons tested: \_\_\_\_\_

# Please specify if different testing methods are used for different exons.

**+ PDGFRA Mutational Analysis****+ Exons Assessed** (select all that apply)

- +  Exon 12
- +  Exon 14
- +  Exon 18
- +  Other (specify): \_\_\_\_\_

† Data elements preceded by this symbol are not required.

+ Testing Method(s)#

+ Specify name of method used and exons tested: \_\_\_\_\_

# Please specify if different testing methods are used for different exons.

**+ BRAF Mutational Analysis (Note D)**

+ Exons Assessed

+ \_\_\_ Exon 15

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

+ Testing Method(s)

+ Specify name of method used and exons tested: \_\_\_\_\_

**+ SDH A/B/C/D Mutational Analysis (Note E)**

+ \_\_\_ Exons assessed (specify): \_\_\_\_\_

+ Testing Method(s)#

+ Specify name of method used and exons tested: \_\_\_\_\_

# Please specify if different testing methods are used for different exons.

**+ NF1 Mutational Analysis (Note F)**

+ Exons assessed (specify): \_\_\_\_\_

+ Testing Method(s)#

+ \_\_\_ Sanger

+ \_\_\_ NGS

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

+ Specify name of method used: \_\_\_\_\_

# Please specify if different testing methods are used for different exons.

**+ COMMENT(S)**

\_\_\_\_\_

\_\_\_\_\_

*Note: Fixative type, time to fixation (cold ischemia time), and time of fixation should be reported if applicable in this template or in the original pathology report.*

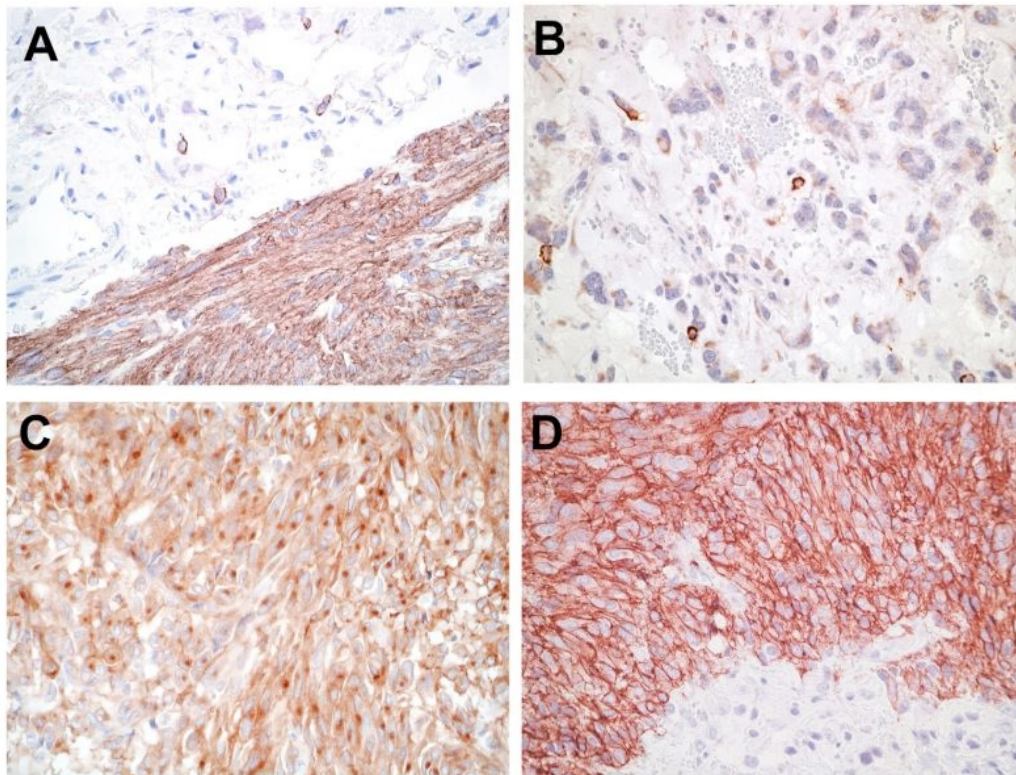
*Gene names should follow recommendations of The Human Genome Organisation (HUGO) Nomenclature Committee ([www.genenames.org](http://www.genenames.org); accessed October 29, 2014).*

*All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society ([www.hgvs.org/rec](http://www.hgvs.org/rec); accessed October 29, 2014).*

## Explanatory Notes

### A. Immunohistochemical Analysis

Because of the advent of small-molecule kinase inhibitor therapy for the treatment of GIST (see the following), it has become imperative to distinguish GIST from its histologic mimics, mainly leiomyoma, leiomyosarcoma, schwannoma, and desmoid fibromatosis.<sup>1,2</sup> Immunohistochemistry is instrumental in the workup of GIST. Approximately 95% of GISTs are immunoreactive for KIT (CD117).<sup>3</sup> Most KIT-negative GISTs are gastric or omental tumors that harbor mutations in platelet-derived growth factor receptor A (*PDGFRA*).<sup>4</sup> KIT immunoreactivity is usually strong and diffuse but can be more limited in extent in some cases (Figure 1, A and B). It is not unusual for GISTs 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. DOG1 is another highly sensitive and specific marker for GIST, which was discovered by gene expression profiling.<sup>5,6</sup> DOG1 (also known as anoctamin 1, ANO1) is particularly useful for KIT-negative tumors and those with limited KIT expression; DOG1 is more sensitive than KIT for gastric epithelioid GISTs.<sup>7</sup> Approximately 70% of GISTs are positive for CD34, 30% to 40% are positive for smooth muscle actin, 5% are positive for S100 (usually focal), 5% are positive for desmin (usually focal), and 1% to 2% are positive for keratin (weak/focal).<sup>8</sup>



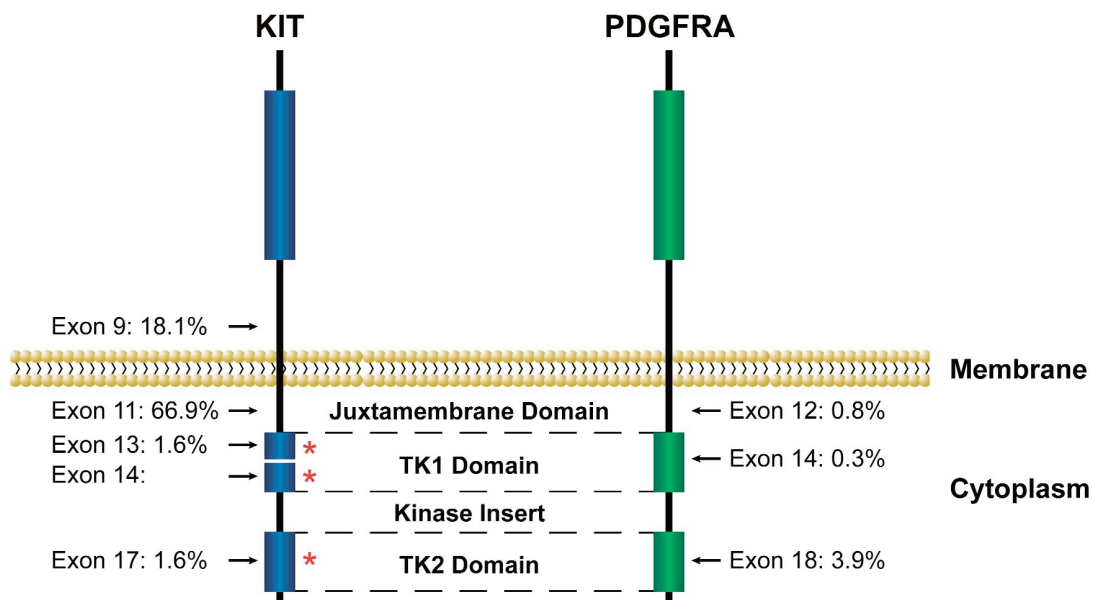
**Figure 1.** Patterns of KIT staining in gastrointestinal stromal tumor (GIST). A, Diffuse and strong immunoreactivity in a typical GIST. B, Focal and weak pattern in an epithelioid gastric GIST with a *PDGFRA* mutation. C, Dot-like perinuclear staining. D, Membranous pattern. (Original magnification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

Approximately 8% of gastric GISTs are characterized by dysfunction of the mitochondrial succinate dehydrogenase (SDH) complex, known as “SDH-deficient GISTs.”<sup>9</sup> This clinically and pathologically distinctive subset of GISTs, which can be recognized by multinodular/plexiform architecture, has a predilection for children and young adults, is usually dominated by epithelioid cytomorphology, often metastasizes to lymph nodes (an exceeding rare occurrence in conventional GIST), and pursues a relatively indolent clinical course when metastatic.<sup>10</sup> Approximately 50% of SDH-deficient GISTs have

mutations in one of the SDH subunit genes (see the following). The diagnosis of SDH-deficient GIST can be confirmed by demonstrating loss of expression of SDHB by immunohistochemistry, which is observed irrespective of the presence of an identifiable SDH mutation (or the particular mutation type). Other genetic groups of GIST (eg, those with mutations in *KIT* or *PDGFRA*) show granular cytoplasmic staining for SDHB.<sup>11</sup> Mutations in *SDHA* are detected in 30% of SDH-deficient GISTs; *SDHA* is the most commonly mutated gene in this class of tumors (see below). Loss of expression of *SDHA* specifically identifies tumors with *SDHA* mutations<sup>12,13</sup>; other SDH-deficient GISTs show normal (intact) cytoplasmic staining for *SDHA*. Immunohistochemistry for SDHB and *SDHA* can therefore be used to triage patients for genetic testing. Immunohistochemistry for SDHB and *SDHA* need not be performed on all GISTs, but only to confirm the diagnosis in a resection of a gastric GIST with multinodular architecture, and to screen small biopsies of gastric GISTs with epithelioid cytology (particularly in younger patients).

### Molecular Analysis

Most GISTs are driven by oncogenic mutations in one of two receptor tyrosine kinases, *KIT* (75%) and *PDGFRA* (10%).<sup>14,15</sup> These mutations result in constitutive ligand independent activation of full-length proteins. Mutations cluster within “hot spots” exons 9, 11, 13, 17 in *KIT* and exons 12, 14, 18 in *PDGFRA* (Figure 2). *KIT* and *PDGFRA* mutations are mutually exclusive. Multiple phase I, II, and international phase III trials have established the efficacy of tyrosine kinase inhibitors such as imatinib, sunitinib, and regorafenib in metastatic tumors and in the adjuvant setting.<sup>16-20</sup> Imatinib was originally granted accelerated approval for the treatment of advanced or metastatic GIST in 2002. In 2012, the Food and Drug Administration (FDA) approved the use of imatinib for GIST in the adjuvant setting. The most recent National Comprehensive Cancer Network (NCCN) task force on GIST strongly encourages that *KIT* and *PDGFRA* mutational analysis be performed if imatinib therapy is begun for unresectable or metastatic disease and that mutational analysis to be considered for patients with primary disease, particularly those with high-risk tumors. In the setting of long-term imatinib therapy, secondary or acquired mutations occur in *KIT* exons 13, 14, and 17 and *PDGFRA* exon 18.<sup>21</sup>



\* Refers to exons involved most frequently by secondary/acquired mutations.

**Figure 2.** Locations and frequency of activating *KIT* and *PDGFRA* mutations in GIST. Adapted with permission from Heinrich et al.<sup>14</sup> Copyright 2003 by the American Society of Clinical Oncology. All rights reserved.



**B. KIT Mutational Analysis**

The most common mutations affect the juxta membrane domain encoded by exon 11 (two-thirds of GIST). These mutations include in-frame deletions, substitutions, and insertions. Deletions (in particular codon 557 and/or 558) are associated with shorter progression free and overall survival.<sup>22-25</sup> About 7% to 10% of the tumors harbor mutations in the extracellular domain encoded by exon 9 (most commonly insAY502-503).<sup>26</sup> Primary mutations in the activation loop (exon 17) and ATP binding region (exon 13) are uncommon (1%). Majority of these mutations are substitutions.<sup>27</sup> *KIT* exon 8 mutations are extremely rare (0.15%).<sup>28</sup> Secondary or resistance mutations occur commonly in tumors harboring primary exon 11 mutations. The newly acquired secondary mutations are always located in exons encoding tyrosine kinase domain (exons 13, 14, 17).<sup>29</sup>

**C. PDGFRA Mutational Analysis**

More than 80% of *KIT*-negative GISTs have *PDGFRA* mutations. Activation of *PDGFRA* is seen in GISTs harboring mutations in juxta membranous domain (exon 12), the ATP binding domain (exon 14), or the activation loop (exon 18).<sup>30</sup> Mutations include substitutions and deletions. Primary resistance to imatinib is seen with the most common *PDGFRA* exon 18 D842V mutation.

**D. BRAF Mutational Analysis**

Activating mutations of *BRAF* (V600E) has been identified in a small subset (7%) of *KIT*/*PDGFRA* wild-type GISTs. These tumors show a predilection for small bowel location.<sup>31</sup>

**E. SDH A/B/C/D Mutational Analysis**

The succinate dehydrogenase (SDH) complex (mitochondrial complex II) participates in both the Krebs cycle and the electron transport chain of oxidative phosphorylation. About 8% of gastric GISTs (all lacking mutations in *KIT* and *PDGFRA*) are caused by dysfunction of the SDH complex ("SDH-deficient GISTs"). Around 50% of patients affected by such tumors harbor germline mutations in one of the SDH subunit genes (*SDHA/B/C* or *D*). *SDHA*-inactivating mutations are most common, detected in about 30% of SDH-deficient GISTs. Mutations involve exons 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14 of *SDHA*; exons 1, 2, 3, 4, 6, 7 of *SDHB*; exons 1, 4, 5 of *SDHC*; and exons 4 and 6 of *SDHD*. While the majority of the mutations are substitutions, deletions, splice-site mutations, frame shift, and duplications have also been reported.<sup>9,11,13,32</sup>

**F. Neurofibromatosis Type 1 (NF1) Mutational Analysis**

NF1 is an inherited, autosomal dominant disease characterized by multiple café au lait spots, Lisch nodules, freckling, and development of neurofibromas. GISTs in NF1 patients arise predominantly from the small intestine and can be multicentric and lack *KIT* and *PDGFRA* mutations. Until now, no specific genetic alterations have been found in NF1-related GIST.<sup>32</sup>

**G. Dissection Method:**

While in majority of cases GIST samples show tumor percentage (%) well above the analytical sensitivity of Sanger sequencing (>50% neoplastic cell percentage/20% to 25% mutant allele percentage), in cases of mutation analysis of treated samples, careful macro/microdissection may be necessary to avoid false negative results.

**H. Reporting Nomenclature**

Consistent gene mutation nomenclature is essential for efficient and accurate reporting.<sup>33</sup> Following are examples as recommended by Human Genome Variation Society (HGVS) for description of variant changes.<sup>34</sup> It is also preferred that protein alterations are mentioned in the report in addition to genomic coordinates.

DNA, RNA and Protein

DNA: A, G, C, T (example: c.957A&gt;T)

RNA: a, g, c, u (example: r.957 a&gt;u)

Protein: three/one letter amino acid code, X= Stop codon (example: p. Glu78Gln)

| <u>Types of Variation</u>   | <u>Examples</u>                                 |
|-----------------------------|---|
| Substitution                | c.123A>G  |
| Deletion                    | c.123delA, c.586_591delTTGGTCA or c.586_591del6 |
| Duplication                 | c.123dupA, c.586_591dupTTGGTCA or c.586_591dup6 |
| Insertion                   | c.123_124insC, c.1086_1087insGCGTGA             |
| Frame shift                 | p. Arg83 fs or p. Arg83Ser fsX15                |
| Deletion/insertions "indel" | c.112_117delAGGTCAinsTG                         |

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