Gastrointestinal Stromal Tumour (GIST) Histopathology Reporting Guide Biopsy Specimens

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

RELEVANT SYNDROME (Note 1)

- ◯ Information not provided
- ◯ Carney triad
- ◯ Carney-Stratakis syndrome
- ◯ Neurofibromatosis type 1
- ◯ Familial GIST syndrome
- ◯ Other, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- ◯ Not specified
- ☐ Core needle biopsy
- ☐ Endoscopic biopsy
- ☐ Fine needle aspiration (FNA) biopsy
- ☐ Other, *specify*

TUMOUR SITE (select all that apply) (Note 3)

- ◯ Not specified
- ☐ Oesophagus
- ☐ Gastro-oesophageal junction
- ☐ Stomach
- ☐ Duodenum
- ☐ Small intestine (non-duodenal)
- ☐ Colon (non-rectal)
- ☐ Rectum
- ☐ Other, *specify*

HISTOLOGICAL TUMOUR TYPE (Note 4)

- ◯ Spindle cell type
- ◯ Epithelioid type
- ◯ Mixed type
- ◯ Other, *specify*

MITOTIC COUNT (Note 5)

/5 mm^2

- ◯ Cannot be assessed, *specify*

ANCILLARY STUDIES (Note 6)

Immunohistochemistry

- ◯ Not performed
- ◯ Performed
  - ☐ KIT (CD117), *record results*
  - ☐ DOG1 (ANO1), *record results*
  - ☐ SDHB, *record results*
  - ☐ Other (e.g., SDHA), *specify test(s) and result(s)*

Molecular genetic testing

- ◯ Not performed
- ◯ Performed, *record methodology and result(s)*

Other ancillary studies

- ◯ Not performed
- ◯ Performed, *specify test(s) and result(s)*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the Dataset Authoring Committee.

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Scope

The dataset has been developed for the pathology reporting of biopsy specimens for gastrointestinal stromal tumour (GIST). A separate International Collaboration on Cancer Reporting (ICCR) dataset is available for reporting of resection specimens of GIST.[2]

Metastatic GIST specimens are excluded from this dataset. A separate ICCR dataset for soft tissue sarcoma is available.[3]

The authors of this dataset can be accessed here.

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Note 1 – Relevant syndrome (Core)

Gastrointestinal stromal tumours (GISTs) may arise in the setting of familial or non-familial syndromes. Familial syndromes include Carney-Stratakis syndrome (germline mutations in *SDHX* genes; affected patients develop gastric GISTs and extra-adrenal paragangliomas), neurofibromatosis type 1 (germline mutation in *NF1*; most GISTs in this setting arise in the small intestine), and familial GIST syndrome (germline mutation in *KIT* or *PDGFRA*).[4-7] Carney triad is a non-familial syndrome most often driven by *SDHC* promoter hypermethylation; this syndrome usually affects young women and is characterised by succinate dehydrogenase (SDH)-deficient gastric GIST, extra-adrenal paragangliomas, and pulmonary

chondromas.[8,9] Clinical behaviour, therapy, and follow-up of GISTs in these syndromes are different from sporadic GISTs.

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Note 2 – Operative procedure (Core)

Depending upon the anatomic location, GISTs may be first sampled by core needle biopsy, fine needle aspiration (FNA) biopsy, or, for superficially located tumours, endoscopic biopsy. It is important that sufficient tumour tissue is obtained from the biopsy for immunohistochemistry (IHC) and molecular genetic analysis. If an FNA biopsy is obtained, a cell block should be prepared for IHC. It is not uncommon for endoscopic biopsies to obtain only uninvolved mucosa and/or ulcer bed without diagnostic tumour tissue; a repeat biopsy (or resection) may be required for definite diagnosis.

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Note 3 – Tumour site (Core)

Gastrointestinal stromal tumours (GISTs) most often arise in the stomach and non-duodenal small intestine, followed by the rectum and duodenum; primary GISTs of the oesophagus and colon are rare. Other sites may include the appendix and pancreas; however, these locations are exceptionally rarely involved. It is often difficult (or impossible) for the surgeon and the pathologist to distinguish between the jejunum and ileum, and there is no known prognostic difference for tumours arising at these sites; for these reasons, 'small intestine (non-duodenal)' is applied instead of jejunum or ileum.

So-called extragastrointestinal stromal tumours (EGISTs) are exceptionally rare and may present in the omentum, mesentery, or retroperitoneum; in some cases, attachment to the stomach or small intestine can be documented, whereas in other cases, no connection can be identified.[10,11] Many EGISTs likely represent gastric or small intestinal GISTs that arose from the outer layer of the wall and lost attachment to the respective organ.

Primary anatomic site is an important prognostic parameter; for example, gastric primary GISTs generally have a lower risk of metastasis than small intestinal GISTs.[12,13] For this reason, it is critical to specify location as accurately as possible.

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Note 4 – Histological tumour type (Core)

Histological diagnosis is based on the 2020 World Health Organization (WHO) Classification of Soft Tissue and Bone Tumours, 5th edition.[14] GISTs are most often of spindle cell type, followed by epithelioid type and mixed epithelioid and spindle cell type;[14] the latter two histological types are most common in the stomach. The histological tumour type may be associated with mutational status (e.g., most *PDGFRA*-mutant GISTs are of epithelioid type)[15] or particular syndromes (e.g., Carney triad and Carney-Stratakis syndrome-associated GISTs are usually of epithelioid or mixed type),[9] although this is not always the case.

Pleomorphic morphology in GIST is rare (<2%). Dedifferentiated GIST, defined as the abrupt transition from conventional spindle cell or epithelioid GIST to an anaplastic sarcomatous appearance, usually accompanied by loss of the expression of lineage markers (e.g., KIT and ANO1/DOG1), is exceptionally rare.[16]

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Note 5 – Mitotic count (Core)

Mitotic count is the most important feature for the assessment of risk of malignant behaviour.[17] The mitotic count should be determined in the most mitotically active area of the tumour. The mitotic count should be reported per 5 mm^2. With older microscopes, 5 mm^2 is equivalent to 50 high power fields (HPF). However, with most modern microscopes with wider fields, 5 mm^2 requires 20 to 25 HPFs using 40X lenses. The number of fields required to be counted to encompass 5 mm^2 should be calculated on individual microscopes.

In limited biopsy specimens, mitotic count often cannot be reliably assessed. In such cases, it is appropriate to include a disclaimer statement to that effect; for example: "accurate assessment of mitotic count cannot be made based on this limited biopsy sample and is deferred to surgical resection." However, if the mitotic count in a limited biopsy sample is high, that information is helpful for prognostication.

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Note 6 – Ancillary studies (Core)

Immunohistochemistry (IHC) plays a critical role in confirming the diagnosis of GIST. The tyrosine kinase receptor KIT (CD117) and the chloride channel ANO1 (DOG1), markers of interstitial cell of Cajal lineage, are highly sensitive and specific markers for GIST.[18-20] KIT expression is observed in 95% of cases, most often with a cytoplasmic staining pattern; a paranuclear dot-like or membranous pattern may also be seen. DOG1 is helpful to confirm the diagnosis in KIT-negative GISTs and those with weak or limited staining.[20,21] KIT-negative GISTs (and those with weak or limited staining for KIT) most often harbor *PDGFRA* mutations.[22,23] SDH-deficient GISTs show loss of staining for SDHB, irrespective of which *SDHX* gene is mutated (or if there is SDHC promoter hypermethylation; see below).[24,25] SDHB IHC can therefore be used to confirm the diagnosis of SDH-deficient GIST. SDHA loss is only observed in *SDHA*-mutant GISTs.[26] Despite the lack of *KIT* mutations, SDH-deficient GISTs are typically strongly positive for KIT (and DOG1).

KIT mutations are found in about 75% of GISTs, most often in exon 11 (66% overall) and exon 9 (6%); mutations in exon 13, exon 17, and other locations are rare (see Figure 1).[27,28] *PDGFRA* mutations are identified in 10-15% of GISTs, most often in exon 18 (10-12% overall; the most common is p.D842V), rarely in exons 12 or exon 14.[29,30] Molecular genetic testing is typically performed when systemic tyrosine kinase inhibitor therapy is being considered (e.g., moderate-to-high risk primary or metastatic GIST). Genotype predicts response to tyrosine kinase inhibitor therapy; for example, *KIT* exon 11-mutant GISTs have the best response to imatinib mesylate, whereas GISTs with *PDGFRA* D842V mutations show primary imatinib resistance, although such tumours respond to the tyrosine kinase inhibitor avapritinib.[31,32]

SDH-deficient GISTs account for about 5% of GISTs overall, including the majority of gastric GISTs that lack *KIT* and *PDGFRA* mutations and most tumours occurring in paediatric patients.[33] SDH-deficient

GISTs typically show indolent behaviour with often late and slowly progressive metastases and show limited response to imatinib. As mentioned previously, conventional risk stratification systems do not apply to SDH-deficient GISTs.[34] SDH-deficient GISTs are often associated with germline mutations in *SDHA*, *SDHB*, *SDHC* or *SDHD*; these mutations are sometimes associated with Carney-Stratakis syndrome (the dyad of gastric GIST and paraganglioma).[5] SDH-deficient GISTs that lack *SDHX* mutations usually show hypermethylation of the *SDHC* promoter; this epigenetic dysregulation is characteristic of Carney triad (SDH-deficient GIST, paraganglioma, and pulmonary chondroma).[35]

Other genetic alterations in GIST are rare; these include *BRAF* V600E and *EGFR* mutations; biallelic *NF1* inactivation; and tyrosine kinase receptor gene rearrangements.[36,37]

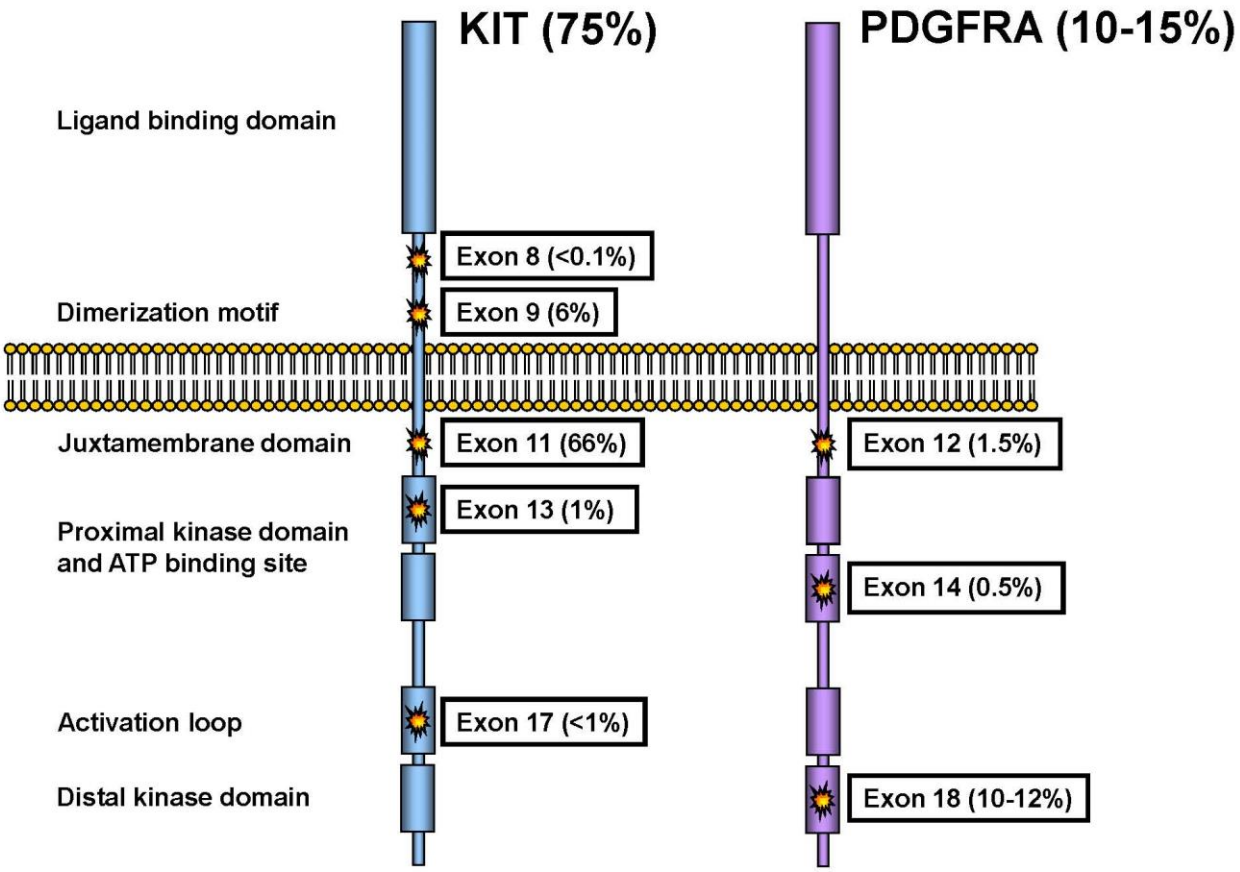

Figure 1: Distribution of *KIT* and *PDGFRA* mutations in gastrointestinal stromal tumours. *Permission courtesy of Professor Jason L. Hornick.*

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