Gastrointestinal Stromal Tumour (GIST)
Histopathology Reporting Guide
Resection 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

NEOADJUVANT THERAPY (Note 1)

- ◯ Information not provided
- ◯ Not administered
- ◯ Administered, *describe*

RELEVANT SYNDROME (Note 2)

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

OPERATIVE PROCEDURE (select all that apply) (Note 3)

- ◯ Not specified
- ☐ Resection, *specify type*
- ☐ Lymph nodes, *specify site(s)*
- ☐ Other, *specify*

TUMOUR SITE (select all that apply) (Note 4)

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

TUMOUR FOCALITY (Note 5)

- ◯ Cannot be assessed
- ◯ Unifocal
- ◯ Multifocal
  - Specify number of tumours
  - Specify site(s)

MAXIMUM TUMOUR DIMENSION (Note 6)

mm

OR

mm to mm [a]

- ◯ Cannot be assessed, *specify*

[a] *Include the range of sizes for multifocal tumours.*

HISTOLOGICAL TUMOUR TYPE (Note 7)

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

MITOTIC COUNT (Note 8)

/5 mm^2

- ◯ Cannot be assessed, *specify*

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NECROSIS (Note 9)

- ◯ Cannot be assessed
- ◯ Not identified
- ◯ Present
  - % _____

TUMOUR RUPTURE (Note 10)

- ◯ Not identified
- ◯ Present

RISK ASSESSMENT (Note 10)

- ◯ Not applicable
- ◯ No risk
- ◯ Very low risk
- ◯ Low risk
- ◯ Moderate risk
- ◯ High risk
- ◯ Overtly malignant/metastatic
- ◯ Cannot be assessed, *specify*

LYMPHOVASCULAR INVASION (Note 11)

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

RESPONSE TO NEOADJUVANT THERAPY (Note 12)

- ◯ No prior treatment
- ◯ No response
- ◯ Response, *describe*
- ◯ Cannot be assessed, *explain reasons*

MARGIN STATUS (Note 13)

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour from closest margin _____ mm
  - Specify closest margin, if possible
- ◯ Involved
  - Specify margin(s), if possible

LYMPH NODE STATUS (Note 14)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found
- Number of lymph nodes examined
- ◯ Not involved
- ◯ Involved
  - Number of involved lymph nodes
  - ◯ Number cannot be determined

COEXISTENT PATHOLOGY (Note 15)

- ◯ None identified
- ◯ Present, *specify*

ANCILLARY STUDIES (Note 16)

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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HISTOLOGICALLY CONFIRMED METASTASES (Note 17)

- ◯ Not identified
- ◯ Present, *specify site(s)*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[b] (Note 18)

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

Primary tumour (pT)

- ◯ Inadequate specimen for assessment
- ◯ TX Primary tumour cannot be assessed
- ◯ T0 No evidence for primary tumour
- ◯ T1 Tumour 2 cm or less
- ◯ T2 Tumour more than 2 cm but not more than 5 cm
- ◯ T3 Tumour more than 5 cm but not more than 10 cm
- ◯ T4 Tumour more than 10 cm in greatest dimension

Regional lymph nodes (pN)

- ◯ No nodes submitted or found
- ◯ NX Regional lymph nodes cannot be assessed[c]
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

[b] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 6th October 2020).*

[c] *Regional lymph node involvement is rare for GISTs, so that cases in which the nodal status is not assessed clinically or pathologically could be considered N0 instead of NX or pNX.*

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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 resection specimens for gastrointestinal stromal tumour (GIST). A separate International Collaboration on Cancer Reporting (ICCR) dataset is available for reporting of biopsy 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 – Neoadjuvant therapy (Non-core)

In some cases, resection of GIST will be performed following neoadjuvant therapy with tyrosine kinase inhibitors (e.g., imatinib mesylate). Such approaches may be used for reducing tumour size to facilitate resection.

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Note 2 – 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 3 – Operative procedure (Core)

The type of resection varies based on the anatomic site of involvement. Gastric primary GISTs may often be managed by a local or wedge resection with excision of limited uninvolved stomach; for large tumours, subtotal or total gastrectomy or oesophago-gastrectomy may be required, depending upon the specific location. GISTs of the small intestine (non-duodenal) are typically managed by segmental resection. Duodenal primary GISTs may require pancreatoduodenectomy (i.e., Whipple procedure). Depending upon the tumour size and precise location, rectal primary GISTs may be managed by local excision, low anterior resection, or abdominoperineal resection. Rare primary colonic GISTs may be managed by right colectomy or segmental colectomy of other parts of the colon. Oesophageal primary GISTs may be managed by local excision (for small tumours) or oesophagectomy. The dataset should also document other resected organs. Preoperative therapy may facilitate more limited resection, especially for oesophageal, duodenal and rectal tumours.

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Note 4 – 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 5 – Tumour focality (Core)

Multifocal tumours are often associated with syndromic predisposition, such as neurofibromatosis type 1, Carney triad, and familial GIST syndrome.[4-7] However, minute gastric GISTs (so-called 'microGISTs' <1 centimetres (cm)) are common in the general population,[14,15] and may therefore accompany GISTs that present clinically in the absence of a tumour syndrome. Tumour focality is determined based on combined macroscopic and microscopic assessment. In the case of multiple synchronous tumours, the number of tumours should be recorded. A single dataset should be completed, in which the site and dimensions of the individual tumours are recorded; staging should be based on the largest tumour.

In some cases, it may be difficult to distinguish multifocality from metastatic disease; multifocal tumours most often arise in the muscularis propria, whereas metastases usually present on the serosa or within the mesentery or omentum.

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Note 6 – Maximum tumour dimension (Core)

Tumour size is a critical parameter for assessment of risk of malignant behaviour. For multifocal tumours, a range of sizes should be reported.

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Note 7 – Histological tumour type (Core)

Histological diagnosis is based on the 2020 World Health Organization (WHO) Classification of Soft Tissue and Bone Tumours, 5th edition.[16] GISTs are most often of spindle cell type, followed by epithelioid type and mixed epithelioid and spindle cell type;[16] 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)[17] 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.[18]

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Note 8 – Mitotic count (Core)

Mitotic count is the most important feature for the assessment of risk of malignant behaviour.[19] 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.

Effective neoadjuvant tyrosine kinase inhibitor therapy limits the ability to accurately determine mitotic count; in such cases, it is appropriate to use 'cannot be assessed' with an explanation.

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Note 9 – Necrosis (Non-core)

The presence of necrosis is not associated with clinical behaviour in GIST. Neoadjuvant therapy may be associated with necrosis; however, most often, treated tumours show decreased cellularity and extensive hyalinized fibrotic or myxoid stroma.

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Note 10 – Tumour rupture (Core) and Risk assessment (Core)

The risk of malignant behaviour in GIST is associated with anatomic site, mitotic rate, and tumour size. Tumour rupture is associated with a particularly high risk of recurrence.[20] Risk assessment plays a critical role for predicting metastatic potential in the management and follow-up of patients with GIST.[21] For example, patients with GISTs that are determined to be of moderate or high risk are often treated with adjuvant imatinib mesylate, following resection of localised primary tumours.

The most widely used risk assessment system was developed by Miettinen and Lasota (2006) (see Table 1),[19] which has been adopted by the WHO and many other organisations. Alternative risk assessment systems include prognostic nomograms and contour maps, which are quite often used by clinicians.[21-23]

This risk assessment system should not be applied to SDH-deficient GISTs[24] or GISTs in patients with neurofibromatosis type 1 or other syndromes (*PDGFRA*-mutant syndrome, *KIT*/*PDGFRA* germline mutations, *BRAF* mutation).

Risk assessment cannot be determined following neoadjuvant therapy, since the mitotic count cannot be accurately determined in this context. It is also inappropriate to apply risk assessment to metastatic tumours.

Table 1: Risk assessment for primary gastrointestinal stromal tumours.

Tumour parameters		Risk of progressive disease[a] (%)			
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)[b]	Moderate (24%)[b]	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 per 5 mm²	≤2 cm	None[b]	(Insufficient data)	High[b]	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%)

[a] Defined as metastasis or tumour-related death.
[b] Denotes small number of cases.

Modified version reprinted from Semin Diagn Pathol, 23(2), Miettinen M and Lasota J, Gastrointestinal stromal tumors: pathology and prognosis at different sites, Pages 70-83 (2006), with permission from Elsevier.[19]

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Note 11 – Lymphovascular invasion (Non-core)

Lymphovascular invasion is most often seen in SDH-deficient GIST;[25] this finding is rare in *KIT* and *PDGFRA*-mutant GISTs.

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Note 12 – Response to neoadjuvant therapy (Non-core)

Effective neoadjuvant tyrosine kinase inhibitor therapy is typically associated with markedly decreased cellularity and the presence of extensive hyalinized fibrotic or myxoid stroma;[26] less often, necrosis is seen. Highly cellular, mitotically active tumour is an indicator of no response; this may be seen as a clonal event within a tumour that otherwise shows extensive treatment effect. Such a finding should be documented.

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Note 13 – Margin status (Core)

Gastrointestinal stromal tumours (GISTs) rarely recur locally at precisely the surgical site, even following excision with narrow margins. Surgical margins vary based on primary anatomic site for GISTs, in large part owing to anatomic constraints and surgical approaches. For example, narrow margins (several millimetres) are adequate for gastric GISTs; wedge resections are often sufficient for GISTs in the stomach. Since small intestinal GISTs are managed by segmental resection, the margins in such cases are typically greater. Because of anatomic constraints around the duodenum, a Whipple procedure (with wide surgical margins) is sometimes required. Resection of primary rectal GISTs often results in narrow circumferential (radial) margins; GISTs at this site are associated with a higher risk of local recurrence in the pelvis.

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Note 14 – Lymph node status (Non-core)

Lymph node metastases are rarely observed in GIST, other than for SDH-deficient tumours; such tumours frequently spread to regional lymph nodes.[24,25] Finding lymph node metastases should prompt evaluation for SDH deficiency.

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Note 15 – Coexistent pathology (Non-core)

Coexistent pathology might include inflammatory conditions of the stomach, such as *Helicobacter pylori* gastritis or chronic atrophic (autoimmune) gastritis.

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Note 16 – 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.[27-29] 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.[29,30] KIT-negative GISTs (and those with weak or limited staining for KIT) most often harbor *PDGFRA* mutations.[31,32] 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).[33,34] SDHB IHC can therefore be used to confirm the diagnosis of SDH-deficient GIST. SDHA loss is only observed in *SDHA*-mutant GISTs.[35] 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).[36,37] *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.[38,39] 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.[40,41]

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.[25] 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.[24] 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).[42]

Other genetic alterations in GIST are rare; these include *BRAF* V600E and *EGFR* mutations; biallelic *NF1* inactivation; and tyrosine kinase receptor gene rearrangements.[43,44]

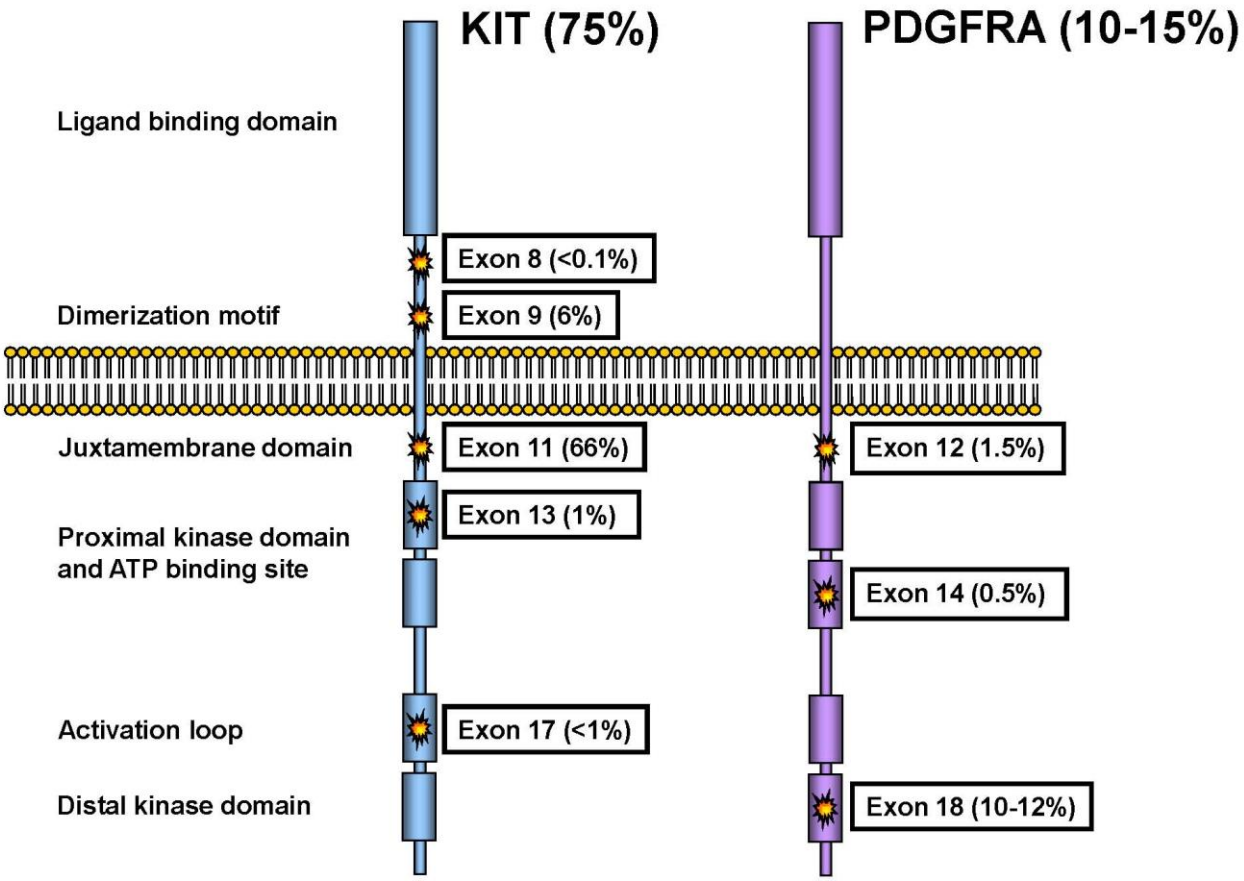

Figure 1: Distribution of *KIT* and *PDGFRA* mutations in gastrointestinal stromal tumours. *Permission courtesy of Professor Jason L. Hornick.*

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Note 17 – Histologically confirmed metastases (Core)

Gastrointestinal stromal tumour (GIST) most often metastasizes to the peritoneum (serosa or omentum) and liver. Spread to other distant sites is rare outside of the setting of advanced, longstanding disease.

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Note 18 – Pathological staging (Non-core)

The primary tumour T category in the TNM classification of the Union for International Cancer Control (UICC)[45] and the American Joint Committee on Cancer (AJCC)[46] includes the same size cut-offs as the risk assessment system developed by Miettinen and Lasota (2006).[19]

Lymph node metastases are often associated with SDH-deficient GISTs but are rarely seen with *KIT* or *PDGFRA*-mutant GISTs.

Gastrointestinal stromal tumours (GISTs) most often metastasize to the liver and peritoneum. Other distant metastatic sites are rare, other than in patients with longstanding, advanced disease.

This staging system should not be applied to syndromic GISTs, which are often multifocal at presentation and usually show indolent behaviour.

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