**ICCR Gastrointestinal Stromal Tumour (GIST) Histopathology Reporting Guide – Biopsy Specimens, 1st edition**

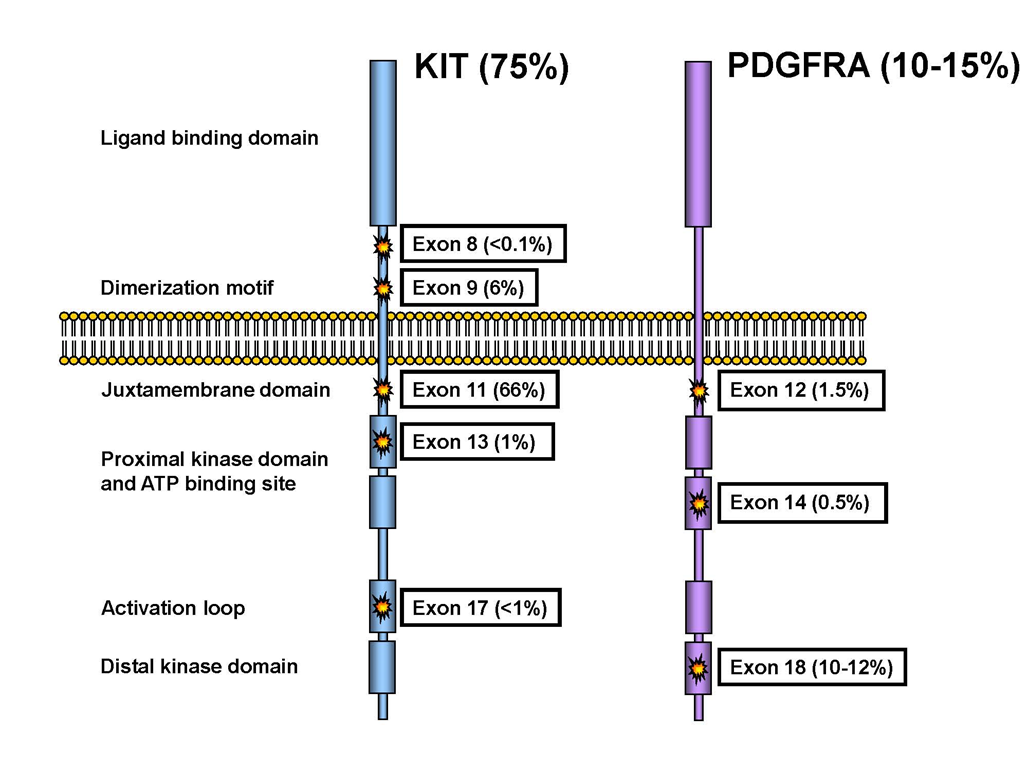
**Elements in black text are CORE Elements in grey text are NON-CORE o indicates single select values □ indicates multi-select values**

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| Definition of 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 evidence1). 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.  **Reference**  1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34. |
| Definition of 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. |
| Scope of this dataset | 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.1  Metastatic GIST specimens are excluded from this dataset. A separate ICCR dataset for soft tissue sarcoma is available.2  **References**  1 International Collaboration on Cancer Reporting (2021). *Gastrointestinal Stromal Tumour (GIST) Histopathology Reporting Guide - Resection Specimens*. Available from: http://www.iccr-cancer.org/datasets/published-datasets/soft-tissue-bone (Accessed 19th April 2021).  2 International Collaboration on Cancer Reporting (2021). *Soft Tissue Sarcoma Histopathology Reporting Guide - Biopsy Specimens*. Available from: http://www.iccr-cancer.org/datasets/published-datasets/soft-tissue-bone (Accessed 19th April 2021). |

| **Core/**  **Non-core** | **Element name** | **Values** | **Commentary** | **Implementation notes** |
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| Core | RELEVANT SYNDROME | * Information not provided * Carney triad * Carney-Stratakis syndrome * Neurofibromatosis type 1 * Familial GIST syndrome * Other, *specify* | 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*).1-4 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.5,6 Clinical behaviour, therapy, and follow-up of GISTs in these syndromes are different from sporadic GISTs.  **References**  1 Maeyama H, Hidaka E, Ota H, Minami S, Kajiyama M, Kuraishi A, Mori H, Matsuda Y, Wada S, Sodeyama H, Nakata S, Kawamura N, Hata S, Watanabe M, Iijima Y and Katsuyama T (2001). Familial gastrointestinal stromal tumor with hyperpigmentation: association with a germline mutation of the c-kit gene. *Gastroenterology* 120(1):210-215.  2 Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, Boikos SA, Ferrando B, Pacak K, Assie G, Baudin E, Chompret A, Ellison JW, Briere JJ, Rustin P, Gimenez-Roqueplo AP, Eng C, Carney JA and Stratakis CA (2008). Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. *Eur J Hum Genet* 16(1):79-88.  3 Andersson J, Sihto H, Meis-Kindblom JM, Joensuu H, Nupponen N and Kindblom LG (2005). NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. *Am J Surg Pathol* 29(9):1170-1176.  4 Miettinen M, Fetsch JF, Sobin LH and Lasota J (2006). Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. *Am J Surg Pathol* 30(1):90-96.  5 Carney JA (1999). Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney Triad): natural history, adrenocortical component, and possible familial occurrence. *Mayo Clin Proc* 74(6):543-552.  6 Zhang L, Smyrk TC, Young WF, Jr., Stratakis CA and Carney JA (2010). Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. *Am J Surg Pathol* 34(1):53-64. |  |
| Core | OPERATIVE PROCEDURE | * Not specified * Core needle biopsy * Endoscopic biopsy * Fine needle aspiration (FNA) biopsy * Other, *specify* | Depending upon the anatomic location, GIST 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. |  |
| Core | TUMOUR SITE | * Not specified * Oesophagus * Gastro-oesophageal junction * Stomach * Duodenum * Small intestine (non-duodenal) * Colon (non-rectal) * Rectum * Other, *specify* | 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.1,2 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.3,4 For this reason, it is critical to specify location as accurately as possible.  **References**  1 Miettinen M, Felisiak-Golabek A, Wang Z, Inaguma S and Lasota J (2017). GIST manifesting as a retroperitoneal tumor: clinicopathologic immunohistochemical, and molecular genetic study of 112 Cases. *Am J Surg Pathol* 41(5):577-585.  2 Miettinen M, Sobin LH and Lasota J (2009). Gastrointestinal stromal tumors presenting as omental masses--a clinicopathologic analysis of 95 cases. *Am J Surg Pathol* 33(9):1267-1275.  3 Miettinen M, Sobin LH and Lasota J (2005). 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* 29(1):52-68.  4 Miettinen M, Makhlouf H, Sobin LH and Lasota J (2006). 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* 30(4):477-489. |  |
| Core | HISTOLOGICAL TUMOUR TYPE | * Spindle cell type * Epithelioid type * Mixed type * Other, *specify* | Histological diagnosis is based on the 2020 World Health Organization (WHO) Classification of Soft Tissue and Bone Tumours, 5th edition.1 GISTs) are most often of spindle cell type, followed by epithelioid type and mixed epithelioid and spindle cell type;1 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)2 or particular syndromes (e.g., Carney triad and Carney-Stratakis syndrome-associated GISTs are usually of epithelioid or mixed type),3 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.4  **References**  1 WHO Classification of Tumours Editorial Board (2020). *Soft Tissue and Bone Tumours. WHO Classification of Tumours, 5th Edition, Volume 3*. IARC Publications, Lyon.  2 Wardelmann E, Hrychyk A, Merkelbach-Bruse S, Pauls K, Goldstein J, Hohenberger P, Losen I, Manegold C, Büttner R and Pietsch T (2004). Association of platelet-derived growth factor receptor alpha mutations with gastric primary site and epithelioid or mixed cell morphology in gastrointestinal stromal tumors. *J Mol Diagn* 6(3):197-204.  3 Zhang L, Smyrk TC, Young WF, Jr., Stratakis CA and Carney JA (2010). Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. *Am J Surg Pathol* 34(1):53-64.  4 Antonescu CR, Romeo S, Zhang L, Nafa K, Hornick JL, Nielsen GP, Mino-Kenudson M, Huang HY, Mosquera JM, Dei Tos PA and Fletcher CD (2013). Dedifferentiation in gastrointestinal stromal tumor to an anaplastic KIT-negative phenotype: a diagnostic pitfall: morphologic and molecular characterization of 8 cases occurring either de novo or after imatinib therapy. *Am J Surg Pathol* 37(3):385-392. | This Value list based on the WHO of Soft Tissue and Bone Tumours (2020).  Note that permission to publish the WHO Classification of Tumours may be needed in your implementation. It is advisable to check with the International Agency for Research on Cancer (IARC). |
| Core | MITOTIC COUNT | \_\_\_ /5 mm2   * Cannot be assessed, *specify* | Mitotic count is the most important feature for the assessment of risk of malignant behaviour.1 The mitotic count should be determined in the most mitotically active area of the tumour. The mitotic count should be reported per 5 mm2. With older microscopes, 5 mm2 is equivalent to 50 high power fields (HPF). However, with most modern microscopes with wider fields, 5 mm2 requires 20 to 25 HPFs using 40X lenses. The number of fields required to be counted to encompass 5 mm2 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.  **Reference**  1 Miettinen M and Lasota J (2006). Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 23(2):70-83. |  |

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| Core | ANCILLARY STUDIES | **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)* | 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.1-3 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.3,4 KIT-negative GISTs (and those with weak or limited staining for KIT) most often harbor *PDGFRA* mutations.5,6 Succinate dehydrogenase (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).7,8 SDHB IHC can therefore be used to confirm the diagnosis of SDH-deficient GIST. SDHA loss is only observed in *SDHA*-mutant GISTs.9 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).10,11 *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 14.12,13 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.14,15  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.16 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.17 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).18 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).19  Other genetic alterations in GIST are rare; these include *BRAF* V600E and *EGFR* mutations; biallelic *NF1* inactivation; and tyrosine kinase receptor gene rearrangements.20,21  **Figure 1 (See the end of document for figure)**  **References**  1 Kindblom LG, Remotti HE, Aldenborg F and Meis-Kindblom JM (1998). Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol* 152(5):1259-1269.  2 West RB, Corless CL, Chen X, Rubin BP, Subramanian S, Montgomery K, Zhu S, Ball CA, Nielsen TO, Patel R, Goldblum JR, Brown PO, Heinrich MC and van de Rijn M (2004). The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. *Am J Pathol* 165(1):107-113.  3 Miettinen M, Wang ZF and Lasota J (2009). DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. *Am J Surg Pathol* 33(9):1401-1408.  4 Liegl B, Hornick JL, Corless CL and Fletcher CD (2009). Monoclonal antibody DOG1.1 shows higher sensitivity than KIT in the diagnosis of gastrointestinal stromal tumors, including unusual subtypes. *Am J Surg Pathol* 33(3):437-446.  5 Debiec-Rychter M, Wasag B, Stul M, De Wever I, Van Oosterom A, Hagemeijer A and Sciot R (2004). Gastrointestinal stromal tumours (GISTs) negative for KIT (CD117 antigen) immunoreactivity. *J Pathol* 202(4):430-438.  6 Medeiros F, Corless CL, Duensing A, Hornick JL, Oliveira AM, Heinrich MC, Fletcher JA and Fletcher CD (2004). KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. *Am J Surg Pathol* 28(7):889-894.  7 Gaal J, Stratakis CA, Carney JA, Ball ER, Korpershoek E, Lodish MB, Levy I, Xekouki P, van Nederveen FH, den Bakker MA, O'Sullivan M, Dinjens WN and de Krijger RR (2011). 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PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J Clin Oncol* 23(23):5357-5364.  14 Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S and Fletcher JA (2003). Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 21(23):4342-4349.  15 Anonymous (2020). Avapritinib approved for GIST subgroup. *Cancer Discov* 10(3):334.  16 Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P and Lasota J (2011). Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. *Am J Surg Pathol* 35(11):1712-1721.  17 Mason EF and Hornick JL (2016). Conventional risk stratification fails to predict progression of succinate dehydrogenase-deficient gastrointestinal stromal tumors: a clinicopathologic study of 76 Cases. *Am J Surg Pathol* 40(12):1616-1621.  18 Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, Boikos SA, Ferrando B, Pacak K, Assie G, Baudin E, Chompret A, Ellison JW, Briere JJ, Rustin P, Gimenez-Roqueplo AP, Eng C, Carney JA and Stratakis CA (2008). Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. *Eur J Hum Genet* 16(1):79-88.  19 Killian JK, Miettinen M, Walker RL, Wang Y, Zhu YJ, Waterfall JJ, Noyes N, Retnakumar P, Yang Z, Smith WI, Jr., Killian MS, Lau CC, Pineda M, Walling J, Stevenson H, Smith C, Wang Z, Lasota J, Kim SY, Boikos SA, Helman LJ and Meltzer PS (2014). 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**Figure**

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