

## Next Generation Sequencing of Gastrointestinal Stromal Tumours (GISTs)

### Overview

Gastrointestinal stromal tumours (GISTs) are rare type of sarcoma (cancer of the connective tissue) and can be found anywhere in the digestive system, although around 50% are found in the stomach <sup>(1)</sup>.

Some GISTs are benign but can become cancerous if not treated. Surgery is the most common treatment, but larger tumours cannot always be completely removed. Tyrosine kinase inhibitor (TKI) drugs slow or stop GISTs growth by blocking the chemical signals required for cancer cell growth. They have shown to dramatically increase survival and are most effective for patients with tumours harbouring a variant in the KIT or PDGFRA genes<sup>(2,3)</sup>. Variants in these genes are mutually exclusive; around 85% of GISTs have a variant in the KIT gene, and then around one third of tumours with a normal KIT<sup>(4)</sup> (no variant) have a variant in PDGFRA (5% of all GISTs).

NICE recommends the use of targeted TKI drug therapies for patients with variants in KIT and PDGFRA:

<https://www.nice.org.uk/search?q=GIST>

Approximately 1.9% of GISTs have NTRK3 fusions and this enables access to selective TRK tyrosine kinase inhibitors (TKIs), including larotrectinib and entrectinib<sup>(5,6,7)</sup>.

### Test Information

The All Wales Genomics Laboratory utilises the Illumina TruSight Oncology 500 High Throughput DNA/RNA assay for next generation sequencing using the Illumina NovaSeq 6000™ to identify nucleotide variants and gene rearrangements (fusions) in patients with solid tumours. More information on this service is available [here](#).

**Table 1. GIST DNA Gene Panel**

Gene	Hotspots/Screen	Regions covered
<b>KIT</b>	Hotspots	Exons 9, 11, 13, 14 & 17
<b>PDGFRA</b>	Hotspots	Exons 12, 14 & 18

**Table 2. GIST RNA Gene Panel**

Gene	Regions covered
NTRK1 NTRK2 NTRK3	Whole gene

**NTRK1** (OMIM 191315), **NTRK2** (OMIM 600456), and **NTRK3** (OMIM 191316) genes fusion testing is also available by RNA NGS.

### Interpretation

A fully interpreted report will be issued for the genes in Table 1.

Please be aware that variants of uncertain significance (VUS) may be identified with this test, these will be further investigated if they are in clinically relevant gene regions and reported as appropriate.

This test is performed to evaluate somatic variants within tumour samples and is not designed to assess for germline variants within the targeted genes.

DNA assay sensitivity/specificity may be reduced in specimens containing <10% tumour nuclei.

RNA assay sensitivity/specificity may be reduced in specimens containing <30% tumour nuclei.

## Specimen Requirements

For information on sending FFPE samples refer to the [CYSGODI service information sheet](#).

Please use the [FFPE solid tumour request form](#) and complete all fields.

## References

- 1) Judson, I., Bulusu, R., Seddon, B. et al. UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST). *Clin Sarcoma Res* 7, 6 (2017). 10:20-4. Review.
- 2) DeMatteo R.P. (2002): The GIST of targeted cancer therapy: A tumour (gastrointestinal stromal tumour), a mutated gene (c-kit) and a molecular inhibitor (STI571) *Ann Surg Oncol*. 9(9):831-9. Review.
- 3) Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. *Lancet*. 2007 May 19;369(9574):1731-41. Erratum in: *Lancet*. 2007 Aug 4;370(9585):388.
- 4) Fletcher J.A. et al. (2007): KIT mutations in GIST. *Curr Opin Genet Dev*. 17(1):3-7. Epub 2007 Jan 8.
- 5) Gopie P, Mei L, Faber AC, Grossman SR, Smith SC, Boikos SA. Classification of gastrointestinal stromal tumor syndromes. *Endocr Relat Cancer* (2018) 25(2):R49–58.
- 6) Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378:731–739.
- 7) Chen Y, Chi P. (2018) *J Hematol Oncol* 11: 78 (available in <https://oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/targeting-ntkr-gene-fusions/overview-of-cancers-with-ntkr-gene-fusion/ntkr-gene-fusions-as-oncogenic-drivers/epidemiology-of-cancers-with-ntkr-gene-fusion>).

### Links for further information

Orphanet [www.orpha.net](http://www.orpha.net)

OMIM [www.omim.org](http://www.omim.org)

Genetic Test Directory <https://www.england.nhs.uk/publication/national-genomic-test-directories/>

### GIST specific links

<https://www.gistcancer.org.uk/>

<https://www.nice.org.uk/search?q=GIST>

Consent for genetic testing and DNA storage is assumed when a test request and samples are received.