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SAMPLE INFORMATION

Name	-	**Date Sp. Extracted**	-
ID/Medical ID	-	**Req. Physician**	-
Date of Birth	-	**Report No**	26xxxxxGR
Material #1	PARAFFIN EMBEDDED TISSUE-BLOCK	**Date Received**	-
Material #2	-	**Date of Report**	-
Sample #1 ID	-	**Tumor type**	GASTROINTESTINAL STROMAL TUMOR

Com.Pl.i.t. Dx (17 genes, 9 fusions) | Comprehensive Panel for Individualized Treatment

1. Clinically Significant Biomarkers*

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance	Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off label/ Investigational therapies (Level C)	
KIT	Exon 11 p.W557_K558del VAF: 39.9%	Imatinib Sunitinib Regorafenib Ripretinib	-	-	-
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-

*Note: Variants' Level of Evidence (LoE) (e.g. A, B, C etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1

^ The analysis of selected biomarkers included in the present multigene panel is performed within the scope of accreditation according to ELOT EN ISO 15189:2022 (see «Methodology» section). Accreditation according to ELOT EN ISO 15189:2022 applies exclusively to the analytical determination of the selected biomarkers. Interpretations related to the prediction of therapeutic response are not included in the scope of accreditation.

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George Nasioulas, PhD Molecular Biologist, Scientific Director, Medical ID:26025301255

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2. Methodology

DNA is extracted from the sample under investigation using the Qiamp DNA FFPE Kit (Qiagen). A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology Multi-Gene Variant Assay (GenePlus) which is a qualitative in vitro diagnostic test. The analysis includes the entire exon regions and CNVs of 17 genes and introns/promoters/fusion breakpoint regions of 9 genes. The test also reports on Microsatellite Instability (MSI) status.

Sequencing was carried out on the DNBSEQ-T7 NGS platform (MGI). Sequencing data are analyzed through bioinformatics pipeline for variant calling and interpretation using the Gene+Box data analysis and management system. Alteration- and tumor type-specific therapeutic implications are classified using the OncoKB Levels of Evidence system, which assigns clinical actionability to individual mutational events. For additional details about the OncoKB curation process, please refer to the version-controlled OncoKB Curation Standard Operating Procedure.

Genes Analyzed

17 Gene Alterations									
ARID1A*	ATRX*	BRAF*	ERBB2*	KIT*	KRAS*	NF1*	PDGFRA*	PIK3CA*	PTEN*
RB1*	SDHA*	SDHAF2*	SDHB*	SDHC*	SDHD*	TP53*			
9 Fusion Genes									
ALK	FGFR1	FGFR2	FGFR3	NTRK1	NTRK2	NTRK3	RET	ROS1	
MSI									

*CNV (amplification/deletion) analysis is included for these genes

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Biomarkers within the scope of accreditation (ISO15189:2022)

-*BRAF, ERBB2, KRAS, KIT, PIK3CA* (SNV/indel detection by NGS)
-*ALK, ROS1, RET, FGFR1,2,3, NTRK1,2,3* (Fusion detection by NGS)

Sensitivity: Positive reference standards are tested with the assay, all corresponding mutation sites can be accurately detected, and the positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs) assessed was 100%.
Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 100%.
Limit of Detection (LoD): The limit of detection (LoD) of this assay is listed in the table below. The LoD is based on as low as 50 ng of gDNA input for library preparation. The assay can also be used to test microsatellite instability (MSI) with a tumor cell content as low as 10%.

The performance characteristics of the assay are summarized in the following table:

Variant Type	Limit of Detection
Single nucleotide variations (SNV)	Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%
Insertions/deletions (Indel)	Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%
Fusion (or rearrangement)	VAF ≥2%

Disclaimer

1. This test is mainly used to assist clinical decision-making, and the result does not represent clinical decision.

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2. The test should be interpreted by combining the actual patient context. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.
3. The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: https://clinicaltrials.gov/.
4. As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
5. Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follow guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).
6. Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phaseIII-ucsc), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (2013-12-06), Clinvar (2018-8) and Cosmic(V80).

Limitations

1. The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
2. Limited tissue detection may not represent the whole DNA variations of lesions because of tumor heterogeneity.
3. Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
4. Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
5. The detection method cannot distinguish between somatic mutations and germline mutations effectively without control sample analysis.
6. Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.
7. Improper sample collection, transportation and storage may lead to compromised or invalid results.

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3. Quality Control Results

Quality Control Index		Result	Criterion
Sequencing Quality Assessment	Average effective sequencing depth[1]	**893**	≥500
	Fraction of target covered with ≥50x[2]	100%	≥90%
	Fraction of base quality ≥Q30[3]	99%	≥80%
Tumor cell content[4]		40%	≥20%
Overall Assessment[5]		PASS	

Note :

1. Average effective sequencing depth: Average sequencing depth on target without duplicated reads.
2. Fraction of target covered with ≥ 50x: The proportion of bases that sequencing depth reach or above 50x on target, this index reflecting the coverage uniformity of sequencing.
3. An overall tumor cell content percentage of ≥ 20% is recommended for the efficient detection of somatic alterations in the sample analyzed.
4. Fraction of base quality ≥ Q30: The proportion of base quality in sequencing data that reach or above Q30, that is the probability of base recognition accuracy rate exceeds 99.9%.
5. Overall Assessment: The quality control overall assessment results are divided into two levels: "PASS" and "RISK". When the overall quality assessment result is "RISK", 94-96% of coverage was achieved in the genes analysed, hence there is a small range where clinical actionable variations could be undetected.

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4. Important biomarkers findings

Gene	Finding (VAF)	Gene	Finding (VAF)
*BRAF*_V600E	Not Detected	*MSI* status	**MSS**
ERBB2 amplification	Not Detected	*PDGFRA* mutation	Not Detected
KIT mutation	**p.W557_K558del (39.9%)**	*RET* rearrangement	Not Detected
NTRK1/2/3 rearrangement	Not Detected		

5. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant	Result	Clinical Interpretation
Treatment effect - positive correlation		
MSI status	MSS	-
TP53 mutation	Not Detected	-
Treatment effect - negative correlation		
ALK rearrangement	Not Detected	-
PTEN inactivating mutation	Not Detected	-

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6. Interpretations for targeted therapies

Genetic Variation:	*KIT*: c.1669_1674del (p.W557_K558del)	VAF*: 39.9%	OncoKB

Treatment Information

The multikinase KIT and PDGFRA inhibitors imatinib, sunitinib, regorafenib and ripretinib are FDA-approved for the treatment of patients with gastrointestinal stromal tumors (GISTs) harboring KIT exon 11 alterations, such as KIT W557_K558del.

Gene information

The proto-oncogene KIT encodes a type 3 transmembrane receptor tyrosine kinase. The receptor is activated through dimerization and autophosphorylation upon binding by its ligand, stem cell factor (SCF) also known as mast cell growth factor (MGF) (PMID: 9438854). KIT activation results in increased intracellular signaling through several pathways including PI3K, MAPK and STAT, ultimately leading to cell proliferation and survival (PMID: 17546049, 11896121, 22089421). For patients with wildtype gastrointestinal stromal tumors (GIST; no KIT or PDGFRA mutations), NCCN recommends testing for germline succinate dehydrogenase (SDH) mutations. About 10-15% of GISTs are wildtype; thus, the absence of a mutation does not exclude the diagnosis of GIST. In patients without KIT mutations, a subset of those with advanced GISTs benefit from imatinib (0-45% of patients) (NCCN Soft Tissue Sarcoma v.2.2017). Activating KIT mutations occur in 80 - 90% of GISTs and are distributed over multiple exons with different frequencies (exons 11 (66.1%), exon 9 (13%), exon 13 (1.2%), and exon 17 (0.6%)) (PMID: 15365079, 17268243, 11719439). There are at least eight small molecule tyrosine kinase inhibitors (TKIs) targeting KIT that have been approved by the US Food and Drug Administration with the efficacy of each TKI strongly depending on the location of the activating KIT mutation (PMID: 2427414, 18955458, 19164557).

Variant Information

The KIT W557_K558del mutation is located in the juxtamembrane domain in exon 11 of the protein. This mutation has been found in gastrointestinal stromal tumors (GIST) (PMID: 17699867, 14645423, 25239608). Biological characterization of this variant in Ba/F3 and CHO cells demonstrated it is activating and promotes growth, as demonstrated by pathway activation and factor-independent proliferation (PMID: 17699867, 14645423, 25239608). In vitro studies have suggested that this mutation is sensitive to tyrosine kinase inhibitors, including imatinib, dasatinib, nilotinib, sorafenib and ponatinib as evidenced by pathway activation and cell viability (PMID: 25239608, 17699867, 14645423). Two patients with GIST whose tumors harbored the KIT E557_K558del mutation had partial responses to treatment with imatinib before acquiring secondary resistance (PMID: 16954519, 15930355). The KIT W557_K558del alteration is known to be pathogenic.

Imatinib DrugBank

Imatinib is a small molecule inhibitor of KIT and other kinases that is FDA-approved for adult patients with gastrointestinal stromal tumors (GISTs). FDA approval was based on the Phase II trial of imatinib in 147 patients with malignant or unresectable GIST in which 56 patients across two dose levels had a partial response, giving an overall response rate of 38% (95% CI= 30-46) (PMID: 12181401). Two further Phase III studies of imatinib in 946 or 694 patients, respectively, with KIT-expressing malignant or unresectable GIST demonstrated a greater response rate in patients given 800mg imatinib versus 400mg, with complete response rates ranging from 44.6%-48.1% at the 800 mg dose versus 5.2%-5.3% at the 400mg dose (PMID: 18235122, 18955451). Long-term follow-up of these patients demonstrated a ten-year overall survival across both study arms of 22% (95% CI= 19.0-26.0), with patients harboring KIT exon

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9 mutations having significantly shorter overall survival on imatinib than patients with KIT exon 11 mutations (p=0.0013) (PMID: 28196207).

Sunitinib

DrugBank

Sunitinib is a small molecule inhibitor of KIT and other kinases that is FDA-approved for use in gastrointestinal stromal tumors (GIST) after disease progression on or intolerance to imatinib mesylate. FDA approval was based on the randomized, double-blind Phase III study of sunitinib versus placebo in 312 patients with imatinib-resistant, unresectable GIST in which median time to progression was 27.3 weeks versus 6.4 weeks (HR = 0.33; p<0.0001) in the sunitinib versus placebo groups, respectively (PMID: 17046465). In the sunitinib group, 7% (n=14), 58% (n=120) and 19% (n=39) of patients had a partial response, stable disease or progressive disease, while 0%, 48% (n=50) and 37% (n=39) of patients in the placebo group had a partial response, stable disease or progressive disease, respectively (PMID: 17046465).

Regorafenib

DrugBank

Regorafenib is a small molecule inhibitor of KIT and other kinases (e.g. VEGFR2 and -3, PDGFR) that is FDA-approved for patients with advanced, unresectable gastrointestinal stromal tumors (GIST) that no longer respond to imatinib and sunitinib. FDA approval was based on results from the randomized, double-blind Phase III trial of regorafenib versus placebo in 199 patients with unresectable GIST that progressed on imatinib and sunitinib in which the progression-free survival was 4.8 months on regorafenib versus 0.9 months on placebo (HR=0.77; p < 0.0001) and the disease control rates were 53% and 9%, respectively (PMID: 23177515). For patients with KIT exon 11 (n=51) or exon 9 (n=15) mutations, the hazard ratios were 0.212 (95% CI =0.098-0.458) and 0.239 (95% CI= 0.065-0.876), respectively, in favor of regorafenib (PMID: 23177515).

Ripretinib

DrugBank

Ripretinib is a small molecule inhibitor of KIT and PDGFRA kinases that is FDA-approved for adult patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with three or more kinase inhibitors. FDA approval was based on the results of the international, multi-center, randomized (2:1), double-blind, placebo-controlled trial (NCT03353753) of ripretinib in 129 patients with advanced, pretreated GIST in which the overall response rate was 9% (95% CI= 4.2, 18), the median progression-free survival was 6.3 months (95% CI= 4.6, 6.9), and the median overall survival was 15.1 months (95% CI= 12.3, 15.1) (PMID: 32511981).

*VAF: Variant Allele Frequency

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7. Clinical Trials to consider

KIT associated clinical trials

NCT04771520	PHASE2
Title	Avapritinib for the Treatment of CKIT or PDGFRA Mutation-Positive Locally Advanced or Metastatic Malignant Solid Tumors
Treatment	Avapritinib
Location	United States

NCT05159245	PHASE2
Title	The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs
Treatment	Alectinib | Cobimetinib | Vismodegib | Trastuzumab+Pertuzumab | Entrectinib | Atezolizumab | Vemurafenib | Regorafenib | Apalutamide | Abemaciclib | Tepotinib | Dabrafenib | Trametinib | Dabrafenib+Trametinib | Pemigatinib
Location	Finland

NCT02029001	PHASE2
Title	Adapting Treatment to the Tumor Molecular Alterations for Patients With Advanced Solid Tumors: MyOwnSpecificTreatment
Treatment	Nilotinib (400 mg BID) | Everolimus (10 mg QD) | Sorafenib (400 mg BID) | Lapatinib (1500 mg QD) | Pazopanib (800 mg QD) | Olaparib (300 mg BID) | Durvalumab + Tremelimumab
Location	France

NCT05366816	PHASE2
Title	ctDNA-Guided Sunitinib And Regorafenib Therapy for GIST
Treatment	Sunitinib | Regorafenib
Location	United States

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NCT05009927	PHASE2
Title	Efficiency of Imatinib Treatment After 10 Years of Treatment in Patients With Gastrointestinal Stromal Tumours (GIST) (Gist-Ten)
Treatment	Imatinib tablets
Location	France

NCT06630234	PHASE1 | PHASE2
Title	A Master Protocol to Evaluate DCC-3009 in Gastrointestinal Stromal Tumor (GIST)
Treatment	DCC-3009
Location	United States

NCT06805825	PHASE1
Title	A Study of the c-Kit Specific Antibody-Drug Conjugate NN3201 for Advanced and/or Metastatic Solid Tumors Known to Express c-Kit
Treatment	NN3201
Location	United States

NCT07171203	PHASE1
Title	Preoperative Imatinib and Fampridine in KIT Mutant Gastrointestinal Stromal Tumor
Treatment	Imatinib | Fampridine
Location	United States

Press here for a live search of clinical trials for KIT

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8. Appendix

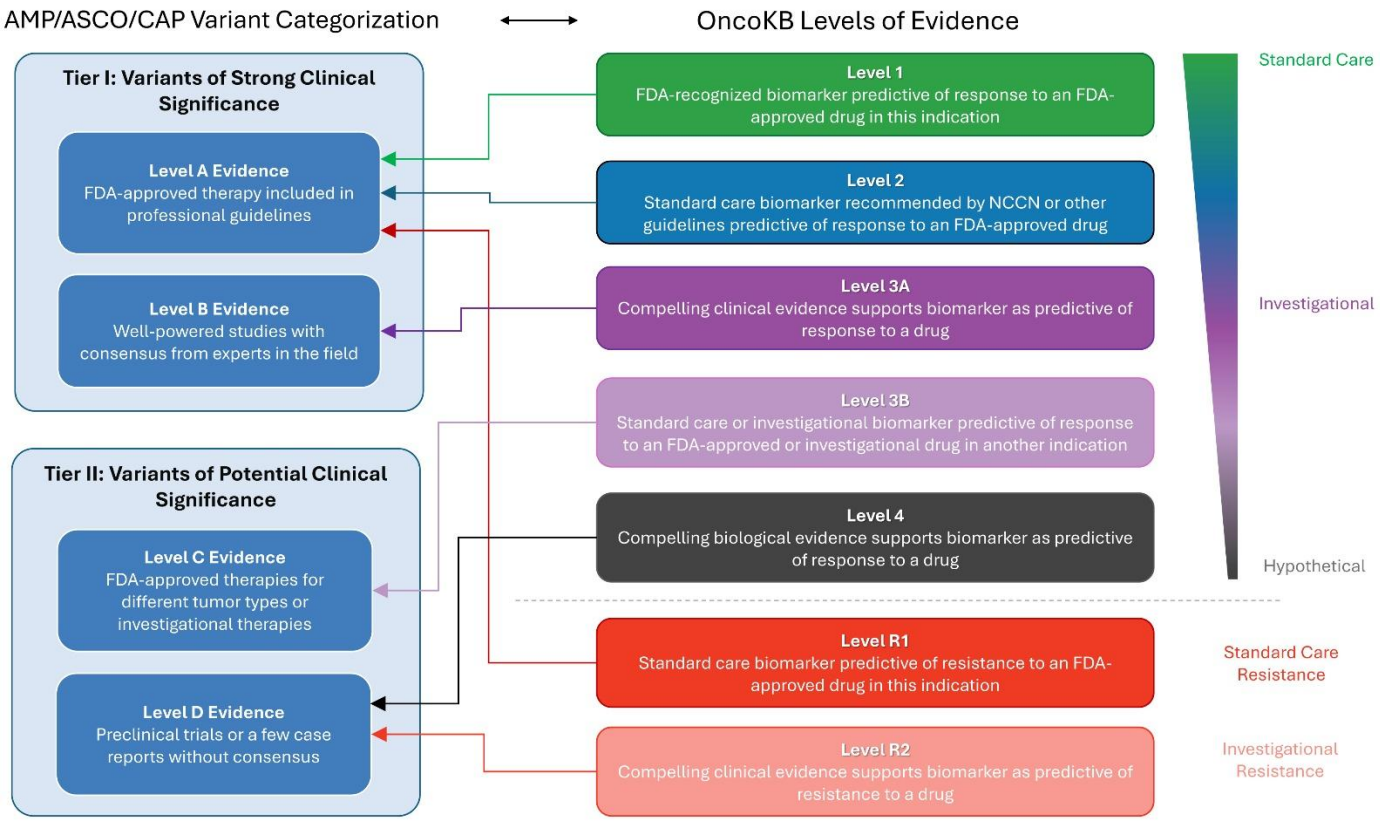

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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Microsatellite Instability (MSI)

Microsatellite instability (MSI) is a condition of genetic hypermutability resulting from impaired DNA mismatch repair (MMR) mechanisms. It is characterized by the accumulation of mutations in short repetitive DNA sequences known as microsatellites. MSI-H is found across multiple cancer types, most notably in colorectal, endometrial, gastric, and ovarian cancer. It can arise sporadically or as part of Lynch syndrome, a hereditary condition caused by germline mutations in MMR genes (MLH1, MSH2, MSH6, PMS2).

The results of MSI are divided into three types: MSI-H, which means microsatellites are highly unstable; MSS, which means microsatellites are stable; MSI-U, which means that the sample does not meet the MSI evaluation conditions (tissues or pleural fluid samples may not have passed the MSI indicator calculation quality control due to the low DNA and/or content of tumor cells).

Pembrolizumab has received full FDA approval for adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors((PMID: 35680043, 33264544) — representing the first full approval for an immunotherapy based on a predictive biomarker, regardless of solid tumor type. This approval applies to patients who have progressed after prior treatment and have no satisfactory alternative options. Beyond the tumor-agnostic indication, specific approvals have been granted for tumor types such as endometrial and colorectal cancer.

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9. Biomarker findings across all Levels of evidence (A-D)

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance		Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off label/ Investigational therapies (Level C)	Therapies in pre-clinical trials (Level D)	
KIT	Exon 11 c.1669_1674del (p.W557_K558del) VAF: 39.9%	Imatinib Sunitinib Regorafenib Ripretinib	-	-	-	-

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