USER MANUAL

16, 32, 48 AND 96 SAMPLES

Research Use Only Components of SOPHiA DDM™ Dx Solid Tumor Solution

For Research Use Only (RUO)
Not for use in diagnostic procedures

SOPHiA GENETICS™

SUMMARY INFORMATION

Product Name	SOPHiA DDM™ Dx Solid Tumor Solution, Research Use Only Components
Product Type	Bundle Solution
Product Family	Molecular diagnostic application (kit + analytics)
Algorithm ID	ILL1XG1S8_FFPE_CNV
Gene Panel ID	STS_v1
Product Version	1.0
Sample Type	Somatic DNA isolated from formalin-fixed, paraffin embedded (FFPE) tumor tissue specimens
Sequencer	Illumina - MiSeq
GMDN Description	Reagent kit IVD / Human genomic analysis interpretive software
Document ID	SG-08858
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RUO

Research Use Only Components of SOPHiA DDM™ Dx SOLID TUMOR SOLUTION. FOR RESEARCH USE ONLY.

PRODUCT CODES

	FULL PRODUCT CODE	BOX 1	BOX 2	LIBRARY PREPARATION KIT
REF	BS0105ILLCSML03-016	B1.01.0005.C-16	B2.0005.C-16	_
	BS0105ILLCSML03-032	B1.01.0005.C-32	B2.0005.C-32	
	BS0105ILLCSML03-048	B1.01.0005.C-48	B2.0005.C-32	

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REVISION HISTORY

DOCUMENT ID/VERSION	DATE	DESCRIPTION OF CHANGE
SG-08858 1.0	January 2026	• Initial Version

TABLE OF CONTENTS

1. GENERAL STATEMENT OF THE TEST PRINCIPLE(S)/ PROCEDURE

The validated function of the SOPHiA DDM™ Dx Solid Tumor Solution (STS) analytics is to analyze raw NGS data generated by an Illumina® MiSeq® instrument with MiSeq® Reagent Kit v3, on somatic samples (FFPE) with the KAPA™ Library Amplification Kit and KAPA™ HyperPlus Kit.

The SOPHiA DDM™ Dx STS involves three main steps. The first step is to qualify the DNA sample that can be used for the test. The second is to manually prepare the samples for sequencing, which is called library preparation. Library preparation consists of seven key steps: DNA fragmentation, adapters ligation, PCR amplification of individual libraries, library pooling, probes hybridization, capture, and post- capture PCR amplification. The third procedure is to sequence the prepared sample using SBS (sequencing by synthesis) chemistry on the Illumina® MiSeq® sequencer.

For analysis, the results should be uploaded to the SOPHiA DDM™ Dx mode platform and analyzed using the SOPHiA DDM™ Dx STS application.

2. SUMMARY AND EXPLANATION OF THE TEST

Note that the results of a genetic analysis should only be interpreted by a qualified expert in molecular genetics: (such as a European registered Clinical Laboratory Geneticist (ErCLG) certified by the European Board of Medical Genetics (EBMG)).

The following table shows genes that are targeted by the SOPHiA DDM™ Dx Solid Tumor Solution (STS) and the tumor types that are associated with those genes.

Table 1. Genes targeted by the SOPHiA DDM™ Dx Solid Tumor Solution (STS) and their associated tumor types

GENE	CLINICAL ASSOCIATIONS
AKT1	Breast, endometrial, appendiceal, head and neck, uterine sarcoma, colorectal (CRC), ovarian, prostate, non-hodgkin lymphoma
ALK	Non-small cell lung cancer (NSCLC)
BRAF	Melanoma, thyroid, CRC, NSCLC, pancreatic, non-Hodgkin lymphoma, embryonal
CDK4	Small cell lung cancer (SCLC), melanoma, NSCLC, bladder, liposarcoma
CDKN2A	Melanoma, familial melanoma, skin non-melanoma, esophagogastric, glioblastoma and pancreatic cancer
CTNNB1	Endometrial, hepatobiliary, melanoma, prostate, bladder, NSCLC, pancreatic
DDR2	Esophagogastric, glioma, NSCLC, CRC
DICER1	Endometrial, thyroid, melanoma, esophagogastric, mesothelioma, soft tissue cancer
EGFR	NSCLC, glioma
ERBB2	Bladder, breast, esophagogastric and endometrial cancers
ERBB4	Melanoma, skin non-melanoma, uterine sarcoma, CRC, soft tissue sarcoma, breast, glioma
FBXW7	Endometrial, CRC, bladder, appendiceal, head and neck, esophagogastric, mesothelioma, NSCLC
FGFR1	Soft tissue sarcoma, glioma, skin non-melanoma, prostate, breast, CRC, NSCLC
FGFR2	Bladder, cholangiocarcinoma, hepatobiliary, endometrial, head and neck, melanoma, esophagogastric, breast cancer, CRC
FGFR3	Bladder, head and neck, skin non-melanoma, glioma
FOXL2	Small cell lung, prostate, CRC, NSCLC, adult granulosa cell tumors
GNA11	Uveal melanoma
GNAQ	Uveal melanoma, germ cell tumor
GNAS	Appendiceal, pancreatic, CRC, esophagogastric
H3F3A	Glioma, soft tissue sarcoma
H3F3B	Chondroblastoma and giant cell tumour of bone
HIST1H3B	Glioma
IDH1	Glioma, hepatobiliary, bone, melanoma

GENE	CLINICAL ASSOCIATIONS
IDH2	Non-Hodgkin lymphoma, glioma, hepatobiliary, salivary gland, bone
KIT	Gastrointestinal stromal tumors (GIST), melanoma
KRAS	CRC
MAP2K1	Melanoma, CRC, non-Hodgkin lymphoma, NSCLC, hepatobiliary
MET	NSCLC, renal cell carcinoma, bladder
MYOD1	Soft tissue sarcoma
NRAS	Melanoma, thyroid cancer, CRC
PDGFRA	GIST, embryonal, glioma, endometrial, NSCLC, soft tissue sarcoma
PIK3CA	Endometrial, breast, bladder, head and neck, CRC, skin non-melanoma, glioma, ovarian, salivary gland, appendiceal, esophagogastric, thyroid, renal cell carcinoma, cervical cancers
PTPN11	Glioma, embryonal cancer, salivary gland cancer, skin non-melanoma, esophagogastric, germ cell, breast cancer, leukemia
RAC1	Melanoma, germ cell, skin non-melanoma,
RAF1	Melanoma, bladder, esophagogastric, head and neck, CRCs
RET	Thyroid, NSCLC, esophagogastric, head and neck, prostate, CRC
ROS1	Salivary gland, NSCLC, ovarian, mesothelioma, Soft tissue sarcoma
SF3B1	Breast and uveal melanoma
SMAD4	Pancreatic, appendiceal, CRC, hepatobiliary, Esophagogastric, skin non- melanoma, NSCLC
TERT	Bladder, glioma, thyroid, skin non-melanoma, head and neck, hepatobiliary, renal cell carcinoma, bone, NSCLC, ovarian
TP53	Wide variety of cancers

3. PRODUCT COMPONENTS

SOPHiA DDM™ Dx STS is composed of two components: the NGS kit and the bioinformatics pipeline used in combination with an IVD accessory, the cloud-based SOPHiA DDM™ Dx mode.

- The purpose of the NGS kit is to prepare and enrich DNA libraries from somatic samples (FFPE) suitable for sequencing on an Illumina® MiSeq® sequencer. The NGS kit allows users to generate targeted sequencing data. The elements are described in the following section 5. Kit Materials and Methods - 5.1. Initial Considerations - 5.1.1 Kit Content.

- The bioinformatics pipeline ("STS pipeline") processes the raw NGS data via algorithms capable of detecting variants in tumor-related gene.

- SOPHiA DDM™ Dx mode is a front-end web-based application available as a "software-as-a-service" (SaaS) used to generate a downloadable report for genes mentioned in Table 1 for SNVs and INDELs. Limitations apply - please see section 7 - Limitations, Warnings and Precautions.

SOPHiA DDM™ Dx STS also offers an additional component via the SOPHiA DDM™ Desktop App platform that allows users to visualize, interpret and report Research Use Only (RUO) results computed by the bioinformatics pipeline. The key RUO features supported by the SOPHiA DDM™ platform allows users to: visualize and interpret SNVs and INDELs from 42 genes as well as gene amplifications. Furthermore an MSI report is provided. Limitations associated with the RUO functions are provided in a the Limitations, Warnings and Precautions section.

Note: To access RUO functions the SOPHiA DDM™ Desktop App is required which can be downloaded and installed separately. Access to the SOPHiA DDM™ Desktop App will be granted at the same time as access to SOPHiA DDM™ Dx mode.

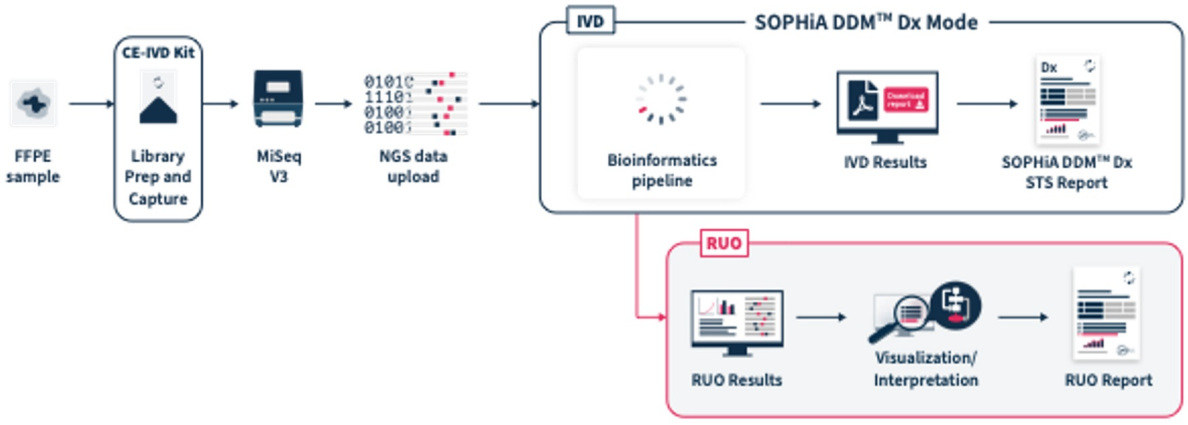

Figure 1: Overview of components of SOPHiA DDM Dx STS

4. LIMITATIONS, WARNINGS AND PRECAUTIONS FOR RESEARCH USE ONLY APPLICATIONS

Large INDELs

- Deletions that are longer than approximately 5,000 bp may not map correctly and might be missed.
- Insertions that are longer than approximately 1/2 of the read length may be missed due to insufficient anchor length needed for the identification of the insertion site.
- Duplications that are not fully covered by complete reads (including the reference sequence that is duplicated) might be missed.
- In the event of a tandem duplication of length more than 1/3 of the read length, the exact number of tandem repeats may not be determined.
- Quantification of insertions longer than read length can increase the risk of overestimating variant fractions.
- Large INDELs below 10% variant fraction may not be detected. We recommend caution in interpretation of variants reported at 1-5% allelic fraction.

Amplification Detection

- In order to provide the optimal performance of the CNV module, it is essential that all the samples in the batch are processed under the same laboratory condition. For processing involving PCR amplification, it is strongly recommended that only samples processed together at the PCR amplification step are combined in one batch.
- At the PCR step of library preparation, temperature gradients should be avoided as much as possible (e.g., by not using the outer rows of PCR plates). Temperature gradients may produce false positive CNV calls.
- For a reliable determination of the reference coverage level, a sufficient number of reference samples is needed. For a good performance, it is recommended to have at least 20 samples in a batch (and 8 samples as an absolute minimum).
- The CNV module is optimized to reduce the occurrence of false negatives (missed CNVs). As a consequence, one should expect a certain number of false positives and rejected regions. We recommend re-checking such cases with an independent test (possibly using a different technology).
- Samples may get rejected for two reasons: either because of quality problems in the library preparation (e.g., failed PCR) or because of a different coverage pattern from the rest of the samples (for any reason). If the total number of non-rejected samples in the batch is below 4, the whole batch gets rejected.
- The algorithm is based on the statistical inference of CNVs from comparing samples to each other. Therefore, it assumes that, for each region, the CNV are only present in a small fraction of samples. It may fail to detect a CNV in batches with a large fraction of samples having CNVs at the same position.
- In the presence of a novel pseudogene with sufficient sequence identity to be amplified, i.e., a pseudogene that is not present in the reference genome, reads coming from the pseudogene will be attributed to the parent gene. In this case the CNV module might over-estimate the copy number of the affected gene. In the case the pseudogene is further amplified, this will increase the estimated copy number even further.

- For the SOPHiA DDM™ Dx Solid Tumor Solution, the CNV detection works in the gene-amplification mode: only whole-gene duplications with a sufficiently large average copy number (above 3.25) are reported, in order to confidently detect amplification levels of 6 copies and higher. Depending on the quality of the DNA material, the reported amplification levels between 3.25 and 6.0 may include a considerable fraction of false positives. The reported copy numbers are very approximate and may have an error as high as 50%.
- Deletions and CNVs affecting only parts of genes are ignored.
- The gene-amplification analysis includes 24 genes: NRAS, ALK, SF3B1, RAF1, PIK3CA, FGFR3, PDGFRA, KIT, FBXW7, TERT, ROS1, EGFR, MET, BRAF, FGFR1, CDKN2A, RET, FGFR2, HRAS, MYOD1, KRAS, CDK4, TP53, ERBB2. The coverage levels used for gene-amplification detection include a linear GC correction deduced from all the regions included in the panel.

MSI status

- The MSI algorithm module relies heavily on the read alignments to the six homopolymer regions. Higher coverage (i.e., having more reads in these regions) eases the detectability and reliability of the microsatellite length differences.
- Two microsatellite stable profiles (run-specific and global) are used for comparisons. The user should interpret the overall results carefully in the case of differences between run-specific and global one. If too few samples are used per run (e.g., less than 8) or if a large proportion of samples with MSI are sequenced in one run, the run-specific profile can be biased and might not represent a stable microsatellite profile accurately. However, in such cases, the global microsatellite instability score will be more accurate since it is obtained from an independent clinical sample sets.

5. SYMBOLS

Symbol	Title
	Consult instructions for use
	Catalog number
	Batch code (Lot Number)
	Caution
	Manufacturer
	Temperature Limit
	Use-by date
	Research Use Only
	Authorized Representative in the European Community
	Research Use Only
	Contains sufficient for <n> tests
	Importer
	Date of manufacture
	Refer to **Warnings and Precautions** in "Section 5. Kit Materials and Methods"
	Refer to **Warnings and Precautions** in "Section 5. Kit Materials and Methods"

6. SUPPORT

In case of difficulty using SOPHiA DDM™ Dx mode, please consult the troubleshooting section of the SOPHiA DDM™ Dx mode User Manual available on SOPHiA DDM™ Dx mode or contact our support line by telephone at +41 21 694 10 60 or e-mail support@sophiagenetics.com. Please visit www.sophiagenetics.com for further details. Support may also be reached via web request from the Dashboard screen in the Support section of SOPHiA DDM™ Dx mode.

Document Approvals

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