USER MANUAL

16, 32, 48 AND 96 SAMPLES

Research Use Only Components of SOPHiA DDM™ Dx Myeloid Solution

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

SOPHiA GENETICS™

SUMMARY INFORMATION

Product Name	SOPHiA DDM™ Dx Myeloid Solution – Research Use Only Components
Product Type	Bundle Solution
Product Family	Molecular diagnostic application (kit + analytics)
Algorithm ID	ILL1XG1S9_CNV
Gene Panel ID	MYS_v1
Product Version	1.0
Sample Type	Somatic DNA isolated from blood
Sequencer	Illumina - MiSeq
GMDN Description	Reagent kit IVD / Human genomic analysis interpretive software
Document ID	SG-08859
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EC REP

REF

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BS0103ILLCSML01-048
BS0103ILLCSML01-96

RUO

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

PRODUCT CODES

	FULL PRODUCT CODE	BOX 1	BOX 2	LIBRARY PREPARATION KIT
REF	BS0103ILLCSML01-016	B1.01.0003.C-16	B2.0003.C-16	700232
	BS0103ILLCSML01-032	B1.01.0003.C-32	B2.0003.C-32	700232
	BS0103ILLCSML01-048	B1.01.0003.C-48	B2.0003.C-48	700234
	BS0103ILLCSML01-96	B1.01.0003.C-96	B2.0003.C-48	700234

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REVISION HISTORY

DOCUMENT ID/VERSION	DATE	DESCRIPTION OF CHANGE
SG-08859 -1.0	January 2026	• Initial Version

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

The validated function of the SOPHiA DDM™ Dx Myeloid Solution (MYS) analytics is to analyze raw NGS data generated by an Illumina MiSeq® instrument with MiSeq® Reagent Kit v3, on somatic samples isolated from blood with the KAPA® Library Amplification Kit and SOPHiA GENETICS™ DNA Library Prep Kit I (QIAseq® FX DNA Library Kit OEM-licensed from QIAGEN).

The SOPHiA DDM™ Dx MYS involves three main steps. The first step is to qualify the DNA sample from blood 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™ platform and analyzed using the SOPHiA DDM™ Dx MYS application.

SOPHiA DDM™ Dx MYS also offers an additional component via the SOPHiA DDM™ Desktop App platform that allows users to visualize, interpret and report research use only (RUO) 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 30 genes as well as CNVs. Limitations associated with the RUO functions are provided in a subsection within the section 3 – RUO Limitations, Warnings and Precautions.

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)).

LEUKAEMIA

Acute myeloid leukaemia (AML) is the most common acute leukaemia in adults, with around 20,000 new cases annually of AML in the US. AML is still fairly rare overall, accounting for only about 1% of all cancers. AML is caused by defective regulation of the differentiation and self-renewing programs of multipotent hematopoietic stem cells (HSCs), resulting in the bone marrow expansion of myeloid precursors with limited or abnormal differentiation capacity, which disseminate to the periphery. On average, there are 13 genes mutated per AML case with the top mutated genes being FLT3, NPM1, DNMT3A, IDH1, IDH2, TET2, RUNX1, TP53, NRAS, CEBPa and WT1. NPM1-mutated AML is the largest patient group with more than 70% of patients also carrying mutations in other genes, such as DNMT3A, IDH1, IDH2(R140), and TET2. The second largest group contains patients with mutations in genes regulating RNA splicing (SRSF2, SF3B1, U2AF1, ZRSR), chromatin structure (ASXL1, STAG2, BCOR, MLL-PTD, EZH2, PHF6), or transcription (RUNX1) (Papaemmanuil et al. 2016). Germline disorders include telomere biology disorders involving the TERC or TERT genes, familial AML with mutated CEBPa, familial myelodysplastic syndromes or familial AML (GATA2), and familial platelet disorders with propensity to myeloid malignancy.

MYELOPROLIFERATIVE NEOPLASMS (MPN)

Myeloproliferative Neoplasms (MPNs) are characterized by an excessive production of terminally differentiated myeloid cells clonally derived from a single mutated hematopoietic stem cell (HSC). The most frequent MPNs comprise of chronic myeloid leukemia (CML), essential thrombocytemia (ET), Polycytemia Vera (PV) and primary myelofibrosis (PMF). Aside from these malignancies, MPNs include other rare entities such as chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL), not otherwise specified (NOS) and unclassifiable MPNs. These four MPNs are further divided into CML and BCR-ABL1 negative or

Philadelphia negative MPNs. In MPNs a single somatic mutation might be associated with different phenotypes which include the driver genes JAK2, CALR, MPL. In contrast, mutations associated with Philadelphia negative MPNs are not specific to a single MPN entity and therefore cannot be used alone for MPN diagnosis. However, specific recurrent mutations can be found in a very high proportion of MPN patients in genes such as JAK2, CALR or MPL for essential thrombocytemia, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2 or SF3B1 for primary myelofibrosis and CSF3R for chronic myeloid leukemia.

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDS/MPN)

Myelodysplastic diseases/myeloproliferative neoplasms (MDS/MPN) represent a distinct category of myeloid disorders that possess both dysplastic and proliferative features. These disorders are not properly classified as either MDS or MPN because they have some features of both MDS and MPNs. MDS/MPN share with MPNs an excessive production of myeloid cells and signs of myeloid cell dysplasia and/or cytopenia with MDS. The MDS/MPN category includes three major myeloid disorders: chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (jMML) and atypical chronic myeloid leukemia (aCML). The diagnosis may sometimes be difficult, and exclusion of other chronic myeloid malignancies is often necessary.

Most mutations identified in MDS/MPN are not specific to a single entity. However, the frequencies at which individual genes are mutated vary significantly across the different subtypes. SF3B1 mutations are associated with MDS criteria; JAK2, CALR and MPL mutations with MPNs; CSF3R with CNL; any clonal evidence with CMML; and SETBP1 or ETNK1 mutations with aCML.

The following table shows genes that are targeted by the SOPHiA DDM™ Dx Myeloid Solution (MYS) and the diseases that are associated with those genes.

Table 1. Genes targeted by the SOPHiA DDM™ Dx Myeloid Solution (MYS) and their associated diseases

Leukemia	MPN	MDS/MPN
ASXL1	ABL1	ABL1
BRAF	ASXL1	AXSL1
CBL	CALR	CALR
CEBP*a*	CBL	CBL
DNMT3A	DNMT3A	CSF3R
EZH2	ETV6	DNMT3A
FLT3	EZH2	EZH2
HRAS	FLT3	JAK2
IDH1	IDH1	KRAS
IDH2	IDH2	MPL
KIT	JAK2	NRAS
KRAS	MPL	PTPN11
NPM1	NRAS	RUNX1
NRAS	RUNX1	SETBP1
PTPN11	SF3B1	SF3B1
RUNX1	SRSF2	SRSF2
SF3B1	TET2	TET2
SRSF2	TP53	ZRSR2
TET2	U2AF1	-
U2AF1	-	-
WT1	-	-
ZRSR2	-	-

3. PRODUCT COMPONENTS

SOPHiA DDM™ Dx MYS 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 blood samples suitable for sequencing on an Illumina® MiSeq® sequencer. The NGS kit allows users to generate targeted sequencing data. The elements are described in the SOPHiA DDM™ Dx MYS Instructions for Use (IFU).

- The bioinformatics pipeline ("MYS pipeline") processes the raw NGS data via algorithms capable of assessing genomic integrity.

- 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 the SOPHiA DDM™ Dx MYS Instructions for Use (IFU) for applicable limitations.

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.

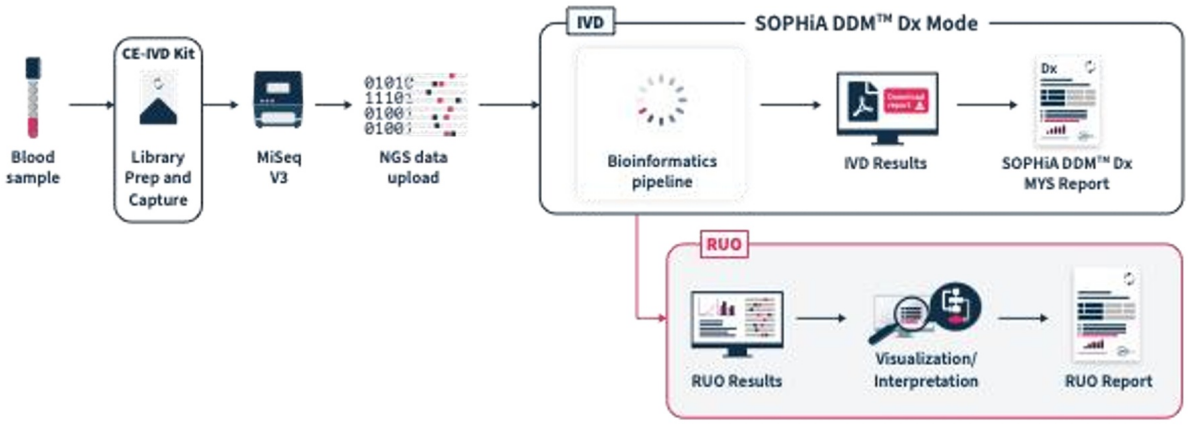

Figure 1: Components of SOPHiA DDM Dx MYS

3. LIMITATIONS, WARNINGS AND PRECAUTIONS

GENERAL WARNINGS

- If any part of the handling, protocol, sequencer, multiplexing etc. is changed, the analyzes are not covered by the described instructions for use.
- The data provided in the Quality Report (available for download from the SOPHiA DDM ™ Platform is for information only and is not intended to be used for diagnosis.
- The accuracy of the results of the analysis cannot be guaranteed. Sequencing laboratories need to fulfill quality checks of the samples and flag the unqualified samples. Unqualified samples (e.g. insufficient biopsy sample) could lead to compromised results. SOPHiA GENETICS is not liable for the results and consequent decisions taken on the basis of these results.
- Good laboratory practice standards and procedures in addition to strictly following the IFU is required in order to obtain proper performance of the product. For specific safety information, please refer to the corresponding Material Safety Data Sheets (MSDS) provided with each component of the product.
- Physically separated pre- and post- PCR rooms should be defined to prevent DNA sample contamination. Always use fresh reagents, correctly extracted and stored DNA. For details on DNA quality and integrity see IFU Section 5. Kit Materials and Methods - Section 5.2.1 Genomic DNA Preparation.
- Correctly calibrated pipettes and proper lab equipment should be used to perform the experiment.
- Different lot numbers of reagents should not be mixed.
- Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community.

GENERAL LIMITATIONS

- Poor quality of the data due to issues in the sample preparation or sequencing step can confound the data analysis and cause False Positives and/or False Negatives.
- The absence of a variant in the report does not rule out the presence of a variation below the limits of detection of the assay.

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 2/3 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.
- Large INDELs, such as FLT3 ITD, below 10% variant fraction may not be detected. The reported Limit of detection of 2.5% does not include FLT3 ITD.
- Quantification of insertions longer than read length can increase the risk of overestimating variant fractions.

Copy Number Variants

- 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.
- The performance of the CNV module is generally higher for longer CNVs than for shorter CNVs and also higher for deletions than for duplications (insertions).
- The first exons of genes frequently have higher coverage fluctuations due to their higher GC content. As a consequence, the performance of the CNV detection is lower for the starting exons of the genes.
- In case of a target region covered by only one probe, a deletion may be called in case of insertions or deletions (INDELs) in the probe region if they are sufficiently large to suppress probe binding.
- The CNV detection algorithm only reliably detects CNVs with whole (or almost whole) target regions deleted or duplicated. In case of CNVs with breakpoints inside target regions, the boundaries of such CNVs may be determined incorrectly.
- 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 Myeloid Solution, the algorithm is designed to detect somatic CNVs. Copy numbers may be fractional, with the resolution of 0.1. The precision of the copy-level estimates is also about 0.1. Small deviations from the normal coverage level (typically, 10% or smaller) may be missed.
- Four regions are excluded from the CNV detection due to typically high noise level: CEBPA_ex1_1, RUNX1_ex4, SRSF2_ex1, RUNX1_ex9.
- This panel contains one gene from the X chromosome (ZRSR2). For a reliable CNV detection in this gene, the sex of the patient needs to be determined. The current version of the algorithm can deduce the sex of the patient from the ratio of the coverage in the X chromosome and in the autosomes. This method may produce inaccurate results, and it is recommended to check the automatically determined sex value against the actual patient data

9. SYMBOLS

Symbol	Title
	Consult instructions for use
	Catalog number
	Batch code (Lot Number)
	Caution
	Manufacturer
	Temperature Limit
	Use-by date
	European Conformity
	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"

10. 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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