USER MANUAL

16, 32, 48 AND 96 SAMPLES

Research Use Only Components of SOPHiA DDM™ Dx Hereditary Cancer Solution

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

SOPHiA GENETICS™

SUMMARY INFORMATION

Product Name	SOPHiA DDM™ Dx Hereditary Cancer Solution – Research Use Only Components
Product Type	Bundle Solution
Product Family	Molecular diagnostic application (kit + analytics)
Algorithm ID	ILL1XG1G6_CNV
Gene Panel ID	HCS v1.1
Product Version	1.1
Sample Type	Germline DNA isolated from peripheral blood
Sequencer	Illumina - MiSeq
GMDN Description	Reagent kit IVD / Human genomic analysis interpretive software
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RUO

PRODUCT CODES

	FULL PRODUCT CODE	BOX 1	BOX 2	LIBRARY PREPARATION KIT
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	BS0102ILLCGLL01-032	B1.01.0002.C-32	B2.0001.C-32	700232
	BS0102ILLCGLL01-048	B1.01.0002.C-48	B2.0001.C-48	700234
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REVISION HISTORY

DOCUMENT ID/VERSION	DATE	DESCRIPTION OF CHANGE
v1.0	13 November, 2025	• Initial Version

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

The validated function of the SOPHiA DDM™ Dx Hereditary Cancer Solution (HCS) analytics is to analyze raw NGS data generated by an Illumina® MiSeq® instrument with MiSeq® Reagent Kit v3, on germline samples with SOPHiA GENETICS™ DNA Library Prep Kit I.

The SOPHiA DDM™ Dx HCS 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 SOPHiA DDM™ Dx mode and analyzed using the SOPHiA DDM™ Dx HCS application.

SOPHiA DDM™ Dx HCS 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™ Dx platform allows users to: visualize and interpret SNVs and INDELs from 26 genes (including BRCA1, BRCA2) as well as CNVs. Limitations associated with the RUO functions are provided in a subsection within the section - Limitations, Warnings and Precautions, for Research Use Only.

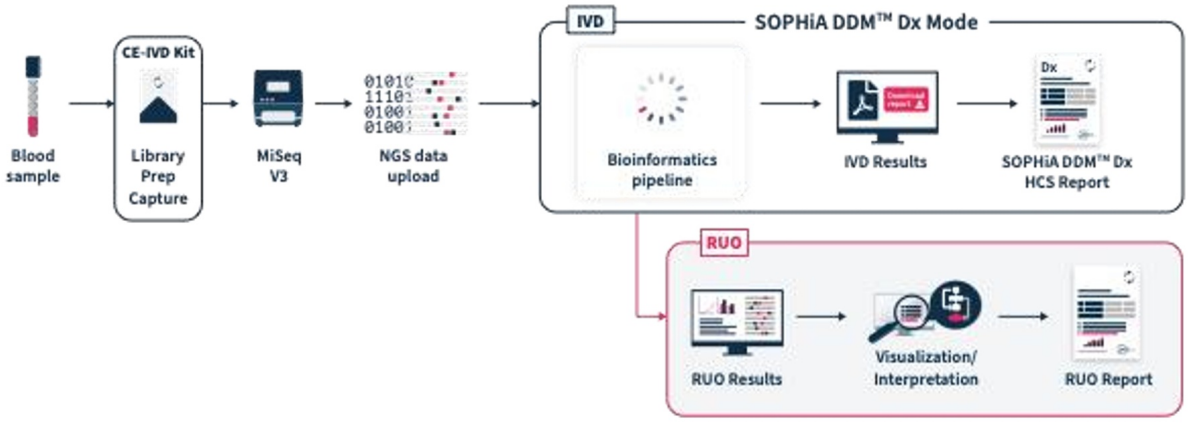

Figure 1: Overview of components of SOPHiA DDM Dx HCS

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)).

HEREDITARY BREAST AND OVARIAN CANCER (HBOC)

Most breast and ovarian cancers are sporadic in nature, however, hereditary syndromes account for an estimated 10% to 15% of breast cancer cases (Collaborative Group on Hormonal Factors in Breast Cancer, Lancet, 2001; Pruthi S et al, Mayo Clin Proc, 2010). Pathogenic mutations in BRCA1 and BRCA2 genes account for approximately 30% of cases of hereditary breast and ovarian cancer syndromes (Couch FJ et al, Science, 2014). Among BRCA mutation carriers, the mean cumulative risk of developing breast cancer by the age of 80 has been estimated at 67-72% in BRCA1 carriers, and 66-69% in BRCA2 carriers (Hartmannn LC et al, NEJM, 2016; Kuchenbaecker KB et al, JAMA, 2017). BRCA1 carriers generally have a higher penetrance for ovarian cancer when compared with BRCA2 carriers. The cumulative risk of developing ovarian cancer by the age of 80 has been estimated at 44-45% in BRCA1 carriers and 12-17% in BRCA2 carriers (Hartmannn LC et al, NEJM, 2016; Kuchenbaecker KB et al, JAMA, 2017).

BRCA1 and BRCA2 genes encode for tumor suppressor proteins, and more than 1,800 and 2,000 distinct variants have been reported for BRCA1 and BRCA2 genes respectively, in the form of intronic changes, missense mutations, and small in-frame insertions and deletions (Couch FJ et al, Science, 2014). Large genomic rearrangements occur relatively more frequently in BRCA1 (~14% of mutations) than in BRCA2 (~3% of mutations), and this is linked to the large number of Alu repeats in the genomic region in the vicinity of BRCA1 (Judkins T et al, Cancer, 2012).

In addition to BRCA1 and BRCA2 genes, pathogenic mutations in ATM, BARD1, CHEK2, PALB2 and RAD51D genes have also been associated with moderately or highly increased risk of breast cancer (Couch FJ et al, JAMA, 2017). Similarly, mutations in ATM, BRIP1, MSH2, MSH6, PALB2, RAD51C, and RAD51D genes have been associated with moderately or highly increased risk of ovarian cancer (Lilyquist J et al, Gynecol Oncol, 2017).

Other cancer predisposition syndromes are also linked to increased risks of developing breast or ovarian cancer. Li-Fraumeni syndrome is characterized by germline mutations in the tumor suppressor gene TP53 and is associated with an estimated ~54% risk of developing breast cancer by age 70 (Sidransky D et al, Cancer Res, 1992). Hereditary diffuse gastric cancer syndrome (HDGC) is characterized by germline mutations in the CDH1 gene encoding for E-cadherin and is associated with an estimated 39% cumulative risk of developing lobular breast cancer (Pharoah PD et al, Gastroenterology, 2001).

HEREDITARY COLORECTAL SYNDROMES

Hereditary syndromes are responsible for an estimated 5-10% of all colorectal cancer cases and have been associated with a 60-100% lifetime risk for developing colorectal cancers.

Two main categories of hereditary colorectal syndromes include intestinal polyposis syndromes and hereditary nonpolyposis colorectal cancer (HNPCC).

Intestinal Polyposis Syndromes

About 1 in 100 individuals of European descent carries a mutation in one of the genes involved in predisposition to an Intestinal Polyposis Syndrome. Key polyposis syndromes include adenomatous polyposis syndromes and hamartomatous polyposis syndromes.

Adenomatous polyposis syndromes include Familial Adenomatous Polyposis (FAP), Attenuated Familial Adenomatous Polyposis (AFAP) and MUTYH-associated Adenomatous Polyposis (MAP).

Familial Adenomatous Polyposis (FAP) is a rare autosomal dominant inherited disorder that is associated with the development of hundreds of colorectal adenomas. FAP carries a lifetime risk of colorectal cancer of virtually 100% if left untreated (Jasperson KW et al, Gastroenterology, 2010). FAP is caused by germline mutations in the APC gene and has an estimated incidence of 1:10,000. Although FAP is a hereditary disorder, up to 30% of FAP cases are due to de novo APC mutations (Samadder NJ et al, Mayo Clin Proc, 2019).

Attenuated FAP (AFAP) is a form of the disease with lower severity, associated with delayed onset and fewer polyps. AFAP is associated with a relatively lower risk of colorectal cancers, estimated at ~70% (Burt RW et al, Gastroenterology, 2004).

MUTYH-associated Adenomatous Polyposis (MAP) is inherited in an autosomal recessive manner. Affected individuals can therefore have either homozygous or compound heterozygous germline MUTYH mutations. The phenotype of MAP is similar to an attenuated polyposis syndrome such as AFAP. Affected individuals have a lifetime risk of colorectal cancer estimated at ~80% (Jenkins MA et al, Cancer Epidemiol Biomarkers Prev, 2006).

Harmartomatous polyposis syndromes include Peutz-Jeghers Syndrome (PJS), Juvenile Polyposis Syndrome (JPS) and PTEN hamartoma tumour syndromes. All three conditions are very rare, each with a prevalence estimated at 1:100,000 (Samadder NJ et al, Mayo Clin Proc, 2019). All three hamartommatous syndromes have autosomal dominant inheritance and are caused by loss of function mutations in their respective tumor suppressor genes: STK11 for Peutz-Jeghers Syndrome, SMAD4 or BMPR1A for Juvenile Polyposis Syndrome, PTEN for PTEN hamartoma tumour syndrome.

Hereditary nonpolyposis colorectal cancer

Lynch syndrome is the most common form of hereditary colorectal cancer, representing 2-4% of all colorectal neoplasias, and about 1 in 800 individuals of European descent carries a mutation in one of the genes involved in predisposition to Lynch syndrome. Affected individuals have a marked increase in lifetime risk of developing colorectal cancer and endometrial cancer, estimated at ~80% and ~60%, respectively (Syngal S et al, Am J Gastroenterol, 2015). Additionally, Lynch syndrome is associated with a predisposition to other extracolonic cancers, including gastric, small bowel, biliary tract, pancreatic, urothelial and ovarian cancers (Watson P et al, Anticancer Res, 1994).

Lynch syndrome results from germline autosomal dominant mutations in one of four genes involved in mismatch repair (MMR): MLH 1, MSH2, MSH6 and PMS2. Additionally, deletions in the non- mismatch repair gene EPCAM have been shown to also cause Lynch Syndrome through loss of MSH2 expression (Kempers MJ et al, Lancet Oncol, 2011).

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

Table 1. Genes targeted by the SOPHiA DDM™ Dx Hereditary Cancer Solution (HCS) and their associated diseases

Breast and Ovarian Cancer	Intestinal Polyposis Syndromes	Lynch Syndrome
ABRAXAS1	APC	MLH1
ATM	MUTYH	MSH2
BARD1	STK11	MSH6
BRCA1	PTEN	PMS2
BRCA2		EPCAM
BRIP1		PMS2CL*

Breast and Ovarian Cancer	Intestinal Polyposis Syndromes	Lynch Syndrome
CDH1		
CHEK2		
MRE11A		
NBN		
PALB2		
PIK3CA		
RAD50		
RAD51C		
RAD51D		
STK11		
TP53		
XRCC2		

* PMS2CL is part of the analysis but not a gene responsible for disease.

It is estimated that about 1 in 300 individuals of European descent carries a mutation in one of the genes in the HCS panel. Most of the individuals who inherit a single pathogenic mutation from one parent carry a high risk of developing cancer, and at an earlier age of onset than the general population.

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™ Dx mode 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 variant below the limits of detection of the assay.

FOR RESEARCH USE ONLY PROCEDURES

Large INDELs

- Large deletions that are longer than approximately 5,000 bp may not map correctly and might be missed.
- Large insertions that are longer than approximately 2/3 of the read length might be missed due to insufficient anchor length 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.
- Alu insertions longer than 2/3 of the read length may be detected if they match at least one sequence in a database of known Alu-sequences. Otherwise, they will be missed.
- 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.
- The SOPHiA DDM™ Dx Hereditary Cancer Solution gene panel involves several genes that have homologous regions in pseudogenes (PMS2, PIK3CA, PTEN, CHEK2). CNVs marked in those genes may therefore indicate either

true CNVs or gene conversion events (exchange of alleles between the gene and the pseudogene). In the main part of the report, exons 12–15 of PMS2 are omitted, since exchange of alleles in those exons are frequent and often not linked together. Possible gene conversion events in exons 11–15 of PMS2 are analyzed separately in the last section of the report.

4. 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"

5. 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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