SOPHiA GENETICS™

HEREDITARY CANCER SOLUTION

Confidently assessing genetic variants associated with hereditary cancers

SOPHiA DDM™ Hereditary Cancer Solution is a genomic application that bundles a smart capture-based target enrichment kit with the analytical performance and advanced features of the SOPHiA DDM™ platform.

The solution was expertly designed to accurately characterize the complex mutational landscape of the major hereditary cancer syndromes such as Hereditary Breast and Ovarian Cancer (HBOC), Lynch and intestinal polyposis syndromes.

SMART KIT DESIGN

- Expertly designed panel, targeting 26 genes predisposing to the major hereditary cancer syndromes
- High affinity probe design, ensuring high on-target rate and excellent coverage uniformity throughout the entire target regions
- Ready-to-sequence target-enriched libraries generated in just 1.5 days
- Optimal cost per sample ratio, due to the ability to multiplex more samples per run
- Automated workflow available on leading liquid handling robots for high-throughput library preparation needs

SOPHiA DDM™ PLATFORM

- Advanced analytical performance
- High-confidence calling of SNVs, Indels, and CNVs in all genes of the panel
- Reliable detection of *Alu* insertions and Boland inversion
- Identification of *PMS2*- and *PMS2CL*-like alleles
- Customizable report
- Secure storage of anonymized data

Discover the full power of your genomic data

The SOPHiA DDM™ platform helps to increase your productivity, enabling high-throughput assessment of genomic data. Designed to be secure, the platform offers a streamlined end-to-end workflow (from raw data to variant report) with machine learning-patented algorithms and intuitive features to detect, annotate and classify multiple types of variants in a single assay with a high level of accuracy.

Universal platform
Over 330 pipelines covering Oncology, Rare and Inherited Diseases, Cardiology, Metabolism and Neurology

Set Up Program
Assistance with assay set up for fast and worry-free transition to routine testing

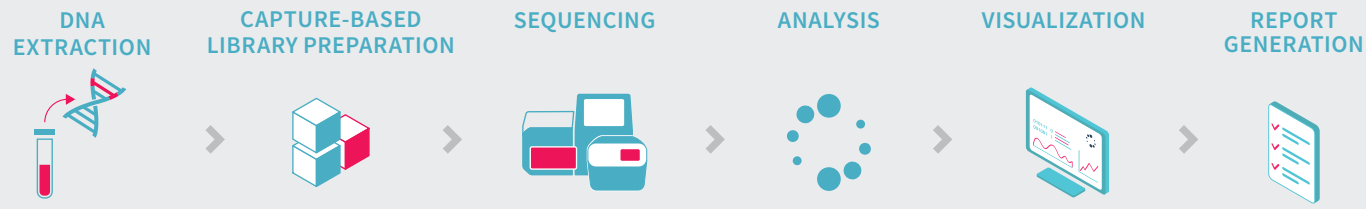
Data security policy
Compliance with national privacy laws, GDPR, HIPAA guidelines and applicable legislation

SOPHiA GENETICS community
Anonymized and safe knowledge sharing among experts worldwide

Hereditary Cancer Solution

Streamlined workflow from DNA extraction to variant report generation

SOPHiA DDM™ Hereditary Cancer Solution provides an easy library preparation workflow. Ready-to-sequence target-enriched libraries are generated in just 1,5 days, starting from 200 ng of DNA. For high-throughput needs, DNA extraction and library preparation can be fully automated using pre-optimized protocols for a variety of liquid handling robots. Library preparation is compatible with Illumina and Thermo Fisher Scientific platforms. Sequencing output files are then analyzed by SOPHiA DDM™, that adapts to the specifics of each sequencer, ensuring advanced analytical performance. Finally, results are displayed on the platform for a streamlined interpretation and generation of a comprehensive variant report.



Relevant gene content

The solution covers complete coding sequences of the 26 most relevant genes associated with hereditary cancers. Probe design is optimized to provide high coverage uniformity throughout the entire target regions, resulting in high data quality, and ability to multiplex more samples per run. Expanded community panels are also available, covering an extended range of cancer genes (from 38 to 143). For specific needs, the gene content can be fully customized.

Disease	Genes
Hereditary Breast & Ovarian Cancer	*ABRAXAS1, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11, NBN, PALB2, PIK3CA, RAD50, RAD51C, RAD51D, TP53* and *XRCC2*
Lynch Syndrome	*EPCAM, MLH1, MSH2, MSH6, PMS2* and *PMS2CL**
Intestinal Polyposis Syndromes	*APC, MUTYH, PTEN* and *STK11*

**Extra probes for the pseudogene PMS2CL are included in the design to provide information to help you investigate whether identified variants could be in the inactive pseudogene or the active gene.*

Smart kit specifications

Parameter	Details
Sample source	Blood
DNA input requirement	200 ng
Target region	105 kb
Library preparation time	1.5 days

Sequencing and multiplexing recommendations

Sequencer	Flow Cell / Ion Chip Kit	Recommended samples per run (for 250x median coverage depth)
MiniSeq™	High Output Kit (2x150bp)	32
	Mid Output Kit (2x150bp)	12
MiSeq®	v3 (2x300bp)	48
	v2 (2x250bp)	24
NextSeq® 500/550	Mid Output Kit (2x150bp)	96†
Ion Proton™	Ion P1™ v3	Up to 48
Ion Torrent™ Ion S5™System	Ion 530™	Up to 16
	Ion 540™	Up to 48

†Maximum number of indices available
Sequencing recommendations and specifications for other sequencing kits and instruments available upon request. Delivery time may vary according to the selected sequencing platform.

Excellent coverage uniformity

SOPHiA DDM™ Hereditary Cancer Solution achieves very high on-target read percentage, which assures reliably high coverage uniformity within 0.2x and 5x the median coverage value across all the target regions, even in those with high GC content *(Fig. 1)*. Equal read coverage in all genes guarantees maximum sample multiplexing capability, resulting in an optimum cost per sample.

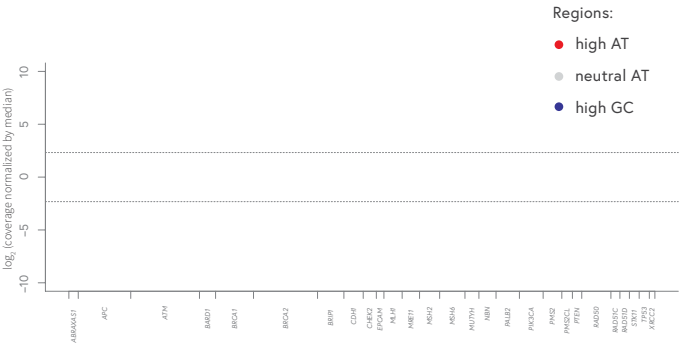


Figure 1: Coverage uniformity profile of a typical sample.
The X-axis represents the genes included in the application and the Y-axis the $\log_2$ coverage normalized by the median. The closer the dots are to the 0 line, the more homogenous the reads are covering each target. Dashed lines represent 20% (lower line) and 500% (upper line) of the median coverage.

Hereditary Cancer Solution

Advanced performance

SOPHiA DDM™ analyzes complex NGS data by detecting, annotating and pre-classifying SNVs, Indels and CNVs in all the genes of the panel. The solutions reaches advanced analytical performance:

	Observed	Lower 95% CI
Sensitivity	100%	99.20%
CNV Sensitivity	99.28%*	
Specificity	100%	99.99%
Accuracy	100%	99.99%
Precision	99.86%	96.42%
Repeatability	99.98%	99.98%
Reproducibility	99.93%	99.93%
Average on-target rate	79.39%	
Coverage uniformity	99.72%	
Average % of target region > 200x	99.95%	

Values were calculated for SNVs and Indels only, on a total of 159 samples processed on a MiSeq®.
**CNV sensitivity was calculated on a total of 321 samples processed on a MiSeq® instrument, with 139 confirmed CNVs.*

Analysis time from FASTQ files: 4 hours

Analysis time may vary depending on the number of samples multiplexed and server load.

High-confidence calling of CNVs

Copy Number Variations (CNVs) have been reported to disrupt genes known to be involved in breast cancer susceptibility, including *BRCA1*, *BRCA2*, *TP53* and *CHEK2*[1] and could similarly alter other genes predisposing to hereditary cancer syndromes. SOPHiA DDM™ detects CNVs down to a fraction of 0.1 copies. The CNV detection is performed by analyzing the coverage levels of the target regions across all samples within the same sequencing run. Background noise is then adjusted individually for each sample, removing any artefacts coming from the library preparation and sequencing workflow *(Fig. 2)*. Thanks to its accuracy, SOPHiA DDM™ Hereditary Cancer Solution reduces the need for additional assays to detect CNVs. The result is a fast, nimble and cost-effective workflow.

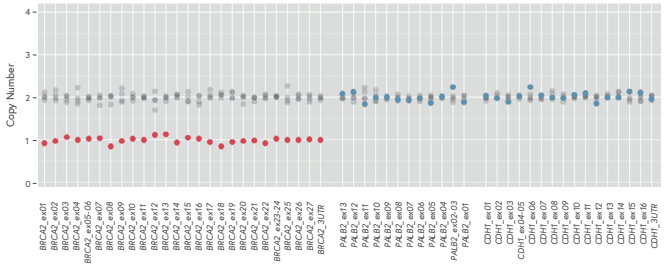


Figure 2: Normalized coverage levels of Copy Number status.
Plot shows the normalized coverage levels in a given sample (blue and red dots) compared to the reference coverage levels (grey dots). Blue dots correspond to target regions without CNVs, red dots to deletions. Solid dots represent high-confidence CNV predictions.

Reliable detection of *Alu* insertions and Boland inversion

Alu elements are the most abundant transposable elements in the human genome and are implicated in several genetic diseases and cancers. Especially in *BRCA1, BRCA2* and *MSH2* genes, rearrangements caused by *Alu* insertions occur quite frequently[2,3]. Normally, *Alu* elements create insertions of ~300bp long that cannot be fully covered by a single sequencing read. SOPHiA DDM™ harnesses the "soft-clipping" signals (mismatched reads) to accurately detect and annotate different types of *Alu* insertions *(Fig. 3)*.

SOPHiA DDM™ allows you to identify an inversion of exons 1-7 in *MSH2* gene. This change known as Boland inversion is a frequent cause of otherwise unexplainable Lynch Syndrome.

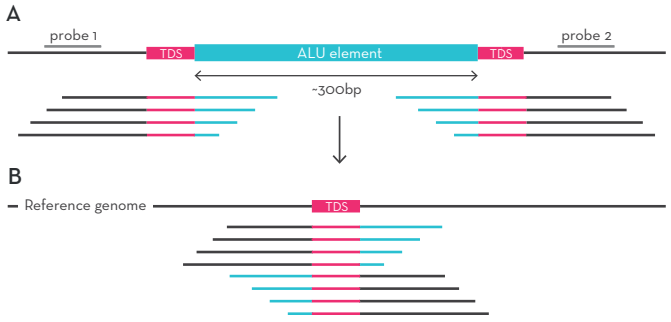


Figure 3: Advanced detection of Alu insertions by SOPHiA DDM™.
(A) Illustration of an Alu element insertion with its tandem duplication sites (TDS). Reads pulled out by capture probes only cover the beginning or the end of the Alu element. (B) Alignment of the reads with the Alu elements to the reference genome. Bases corresponding to the Alu element are soft-clipped and matched against the platform's curated database referring to a list of 800 different Alu sequences. Best match is reported on SOPHiA DDM™.

Investigating *PMS2* versus *PMS2CL* variants

The detection of germline variants in *PMS2* is complicated by the presence of pseudogenes[4]. SOPHiA DDM™ provides information to help you investigate variants that are *PMS2* gene-like or *PMS2CL* pseudogene-like in highly homologous and polymorphic regions (exons 11-15 of *PMS2*). Through a specific gene-conversion add-on, SOPHiA DDM™ analyzes coverage in exons 11-15 of *PMS2* and in the corresponding exons of *PMS2CL*.

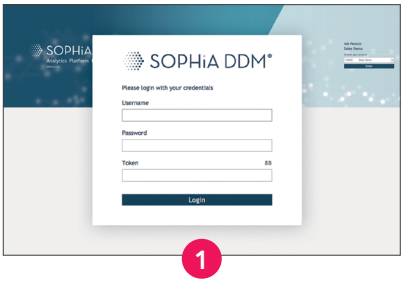
Using cross-sample comparison, SOPHiA DDM™ determines the number of gene-like and pseudogene-like alleles at each location and identifies sequences in *PMS2* and *PMS2CL*. This information facilitates the investigation of unusual gene-conversion events and also CNVs in those highly homologous regions.

Hereditary Cancer Solution

Enhanced variant visualization and interpretation

The SOPHiA DDM™ platform features intuitive variant filters, dual variant pre-classification and reporting functionalities to simplify data visualization and interpretation.

The platform enables clinical researchers to explore and interpret genomic variants and also to report significant findings.



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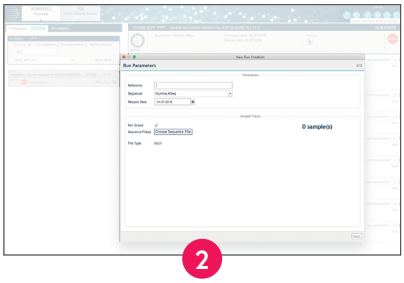
Secure login

Access to SOPHiA DDM™ is restricted to registered users only. Login features a 2-step verification procedure.



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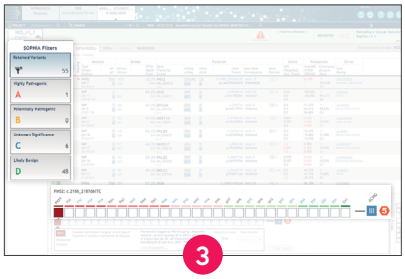
Quick and simple data upload

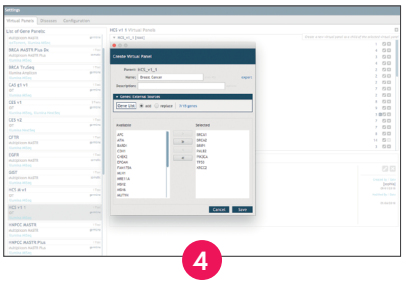
Once sequencing output files are uploaded, all relevant information is automatically extracted and displayed, saving time and avoiding human error from manual insertion.



3

Dual Variant Pre-Classification

Detected variants are displayed by variant type (SNVs, Indels and CNVs). Clinical researchers can easily visualize an overview of the major variants pre-classified through machine learning-based pathogenicity classes and the ACMG's scores.



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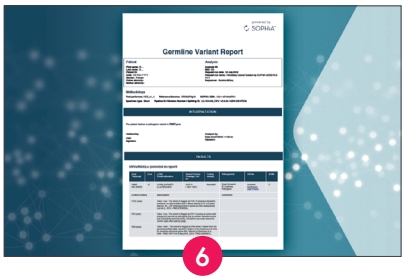
Customized filtering

Virtual Panels can be created to limit the interpretation to a subset of genes available in the panel for quicker screening of relevant variants.

5

Variant flagging

Users can flag the pathogenicity of variants. Flagging decisions are greatly supported by the shared knowledge of the SOPHiA GENETICS global community and a wide range of databases, combining relevant information on variants (e.g., population frequency, pathology significance and others).



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Variant report generation

After interpretation, a variant report is generated. The report is fully customizable and includes information on variants that have been selected by the clinical researcher.

SOPHiA GENETICS community

In SOPHiA DDM™, experts from hundreds of healthcare institutions interpret the results and flag the pathogenicity level of variants according to their knowledge and experience. This highly valuable information feeds the variant knowledge base and is anonymously and safely shared among the members of the community.

Guarantee patient privacy

SOPHiA DDM™ encrypts all data to the highest industry standards before storing it in secured and private data centers. The platform ensures data protection and respects national privacy laws, GDPR, HIPAA guidelines and applicable legislation regarding data privacy.

Summary

SOPHiA DDM™ Hereditary Cancer Solution is a comprehensive genomic application enabling the detection of expertly selected germline variants associated with hereditary cancers. By assessing 26 genes in a single assay and leveraging the analytical power of SOPHiA DDM™, this solution offers a streamlined and standardized workflow, that can be easily implemented by any healthcare institution.

References:
1) Kuiper R.P. et al. Germline copy number variation and cancer risk. Curr Opin Genet Dev. 2010;20(3):282–9.
2) Smith T.M. et al. Complete Genomic Sequence and Analysis of 117kb of Human DNA Containing the Gene BRCA1. Cold Spring Harbor Laboratory Press (1996). ISSN1054-9803/96.
3) Kovac MB et al. High-resolution breakpoint analysis provides evidence for the sequence-directed nature of genome rearrangements in hereditary disorders. Hum Mutat. 2015 Feb;36(2):250-9.
4) Vaughn CP et al. Clinical analysis of PMS2: mutation detection and avoidance of pseudogenes. Hum Mutat. 2010 May;31(5):588-93.