SOPHiA GENETICS™

SOLID TUMOR SOLUTION

CE [IVD]

Profiling cancer genome to optimize solid tumor management

SOPHiA Solid Tumor Solution is a CE-IVD marked molecular diagnostic application that bundles a 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 solid tumors, including lung, colorectal, skin, and brain cancers.

SMART KIT DESIGN

- Expertly designed panel, targeting 42 genes involved in the most common solid tumors
- 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

SOPHiA DDM PLATFORM

- Clinical-grade analytical performance
- High-confidence calling of SNVs, Indels, MSI*, and gene amplifications* in one unique assay
- Precise screening of hotspot positions
- Pre-classification of genomic alterations
- Access to the latest scientific evidence on all relevant alterations
- 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

Customization and detection of MSI and gene amplifications are not part of the CE-IVD claim.

GDPR HIPAA COMPLIANCE

Solid Tumor Solution CE IVD

Streamlined workflow from DNA extraction to variant report generation

SOPHiA Solid Tumor Solution provides an easy library preparation workflow. Ready-to-sequence target-enriched libraries are generated in just 1.5 working days, using as little as 10 ng of FFPE DNA samples. Library preparation is compatible with Illumina and Thermo Fisher Scientific sequencing platforms*.

Sequencing output files are then analyzed by SOPHiA DDM™, that adapts to the specifics of each sequencer, ensuring clinical-grade performance. Finally, results are displayed on the platform for a streamlined interpretation and generation of a comprehensive variant report.

DNA EXTRACTION	CAPTURE-BASED LIBRARY PREPARATION	SEQUENCING	ANALYSIS	VISUALIZATION	REPORT GENERATION
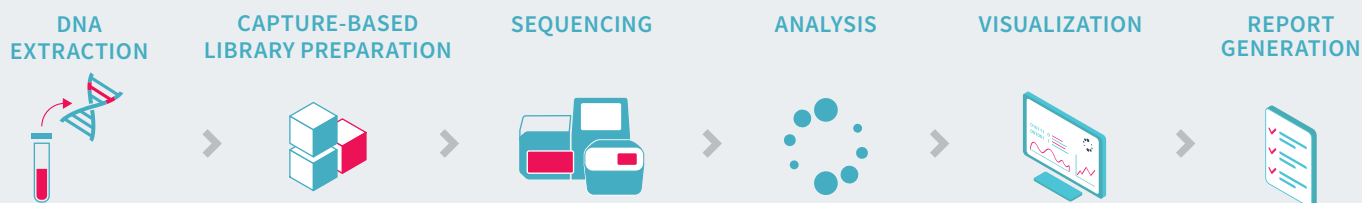
Relevant gene content

The solution covers 42 clinically relevant genes associated with solid tumors, such as lung, colorectal, skin, and brain cancers. It also covers 6 unique loci to detect MSI* status associated with colorectal cancer. 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. For specific needs, the gene content can be fully customized.*

Genes

AKT1 (3), ALK (21-25), BRAF (11,15), CDK4 (2), CDKN2A (1*,2,3), CTNNB1 (3), DDR2 (18), DICER1 (24,25), EGFR (18-21), ERBB2 (8,17,20), ERBB4 (10,12), FBXW7 (7-11), FGFR1 (12,14), FGFR2 (7,12,14), FGFR3 (7,9,14,16), FOXL2 (1*), GNA11 (4,5), GNAQ (4,5), GNAS (8), H3F3A (2*), H3F3B (2*), HIST1H3B (1), HRAS (2-4), IDH1 (4), IDH2 (4), KIT (8-11,13,17,18), KRAS (2-4), MAP2K1 (2,3), MET (2,14-20), MYOD1 (1), NRAS (2-4), PDGFRA (12,14,18), PIK3CA (2*,3,6*,8,10,21), PTPN11 (3), RAC1 (3), RAF1 (7,10,12,13*,14*,15*), RET (11,13,15,16), ROS1 (38*,41*), SF3B1 (15-17), SMAD4 (8-12), TERT (promoter*,1*,8*,9*,13*), TP53 (2-11)

*Hotspots

Smart kit specifications

Parameter	Details
Sample source	FFPE, fresh-frozen tissue*
DNA input requirement	10 ng min (50 ng recommended)
Target region	21.6 kb
Library preparation time	1.5 days

Sequencing and multiplexing recommendations

Sequencer	Flow Cell / Ion Chip Kit	Recommended samples per run (for 1000x median coverage depth)
Illumina MiniSeq™	Mid Output Kit (2x150bp)	8
Illumina MiSeq®*	v3 (2x300bp)†	24
Ion Torrent™ Ion S5™ System	Ion 530™ Chip	12

†2x150-cycle sequencing run (paired-end) is recommended.

*Customization and MSI detection are not part of CE-IVD claim. CE-IVD mark only applies to FFPE samples analyzed on MiSeq® sequencer using V3 chemistry.
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

The application achieves a very high on-target read percentage and excellent coverage uniformity across all the target regions, even in those with high GC-content, including *TERT* gene and promoter (Fig. 1A, B). Equal read coverage in all genes guarantees maximum sample multiplexing capability, resulting in an optimum cost per sample.
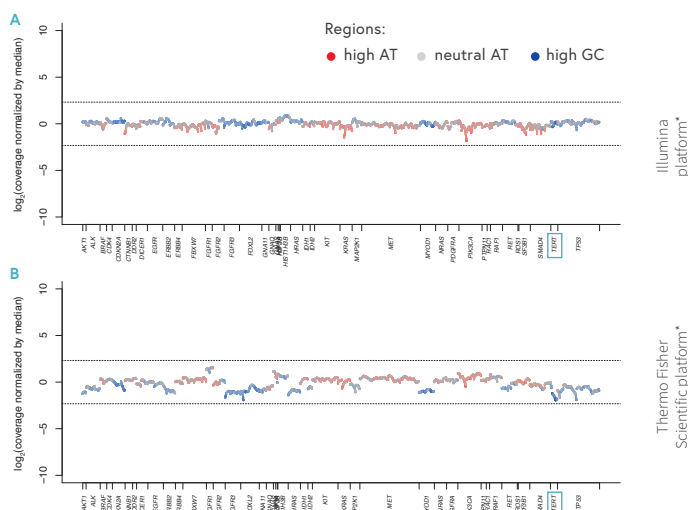

Figure 1: Coverage uniformity profile of a typical clinical FFPE sample on A) Illumina platform; B) Thermo Fisher Scientific platform. The X-axis represents the genes included in the application and the Y-axis the $\log_2$ coverage normalized by the median. The closer the dots are to the 0 line, the more homogeneous are the reads covering each target.

Clinical-grade performance

SOPHiA DDM™ analyzes complex NGS data by detecting, annotating and pre-classifying SNVs, Indels, MSI*, and gene amplifications* to help clinicians better manage solid tumors patients.

SOPHiA DDM™ reaches clinical-grade performance:

	Observed	Lower 95% CI
Sensitivity	98.77%	93.31%
Specificity	100%	99.92%
Accuracy	99.97%	99.85%
Precision	100%	96.25%
Repeatability	96.45%	96.41%
Reproducibility	89.13%	89.05%
Coverage uniformity	98.70%	92.50%[†]

[†]5% quantile

A total of 155 samples were processed on Illumina MiSeq® to obtain the above-mentioned metrics. Performance values have been calculated on SNVs and Indels only.

Analysis time from FASTQ files: 4 hours
Analysis time may vary depending on the number of samples multiplexed and server load.

Accurate detection of large deletions

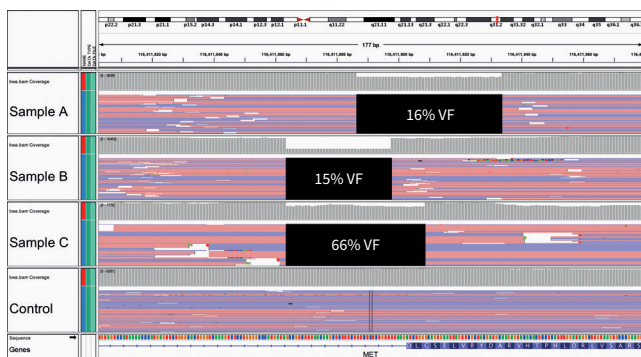SOPHiA DDM™ accurately detects large deletions such as the one in the *MET* gene.

Figure 2: MET deletions. The screenshot represents 3 clinical FFPE samples with MET deletions sequenced on an Illumina platform; Control sample with no MET exon 14 deletion and sequenced on an Illumina platform. VF: Variant Fraction

Precise hotspot screening

Absence of a genomic alteration is not always synonymous with a wild-type position, but can be a false negative due to a poorly covered or noisy region. SOPHiA DDM™ screens specific genomic positions known to be hotspots for mutations such as SNVs and Indels to verify whether the genomic position is wild-type or mutated.

Figure 4: Example of genomic alterations detected by the hotspot screening module. LC: Lung Cancer / GIST: Gastrointestinal Stromal Tumors / CRC: Colorectal Cancer

High confidence calling of MSI in colorectal cancer

Microsatellite Instability (MSI) status is an important prognostic indicator associated with a more favorable survival rate in multiple tumor types. SOPHiA DDM™ detects MSI* status in 6 unique loci associated with colorectal cancer: *BAT-25, BAT-26, CAT-25, NR-21, NR-22* and *NR-27*. SOPHiA DDM™ defines an MSI score by using read alignment. An alignment profile of a given sample is compared to the reference one and the differential value between the two profiles is defined as the MSI score.

	Observed
Sensitivity	100%
Specificity	90%
Minimal tumor content	20% tumor content

MSI detection using 50 ng of input DNA with an MSI score cut-off of 5. A total of 68 clinical FFPE samples were genotyped by both NGS and PCR.

Reduced number of false positives

Formalin fixation causes deamination of nucleic acids in FFPE samples leading to an increase of false positives in NGS analysis.[1] SOPHiA DDM™ clusters identical reads from the same fragments to establish a consensus read. This significantly reduces the effect of deamination artifacts.
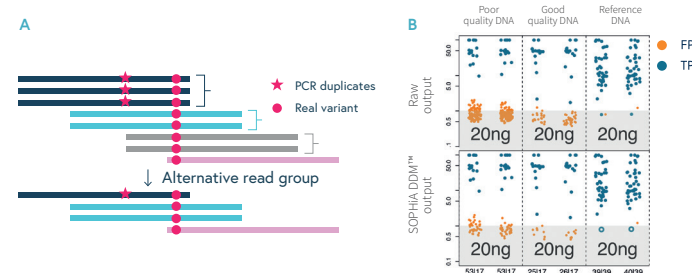
Figure 3: The number of false positive variants decreases when using SOPHiA DDM™. A) Alternative read grouping; B) Output of variants using 20 ng of DNA from FFPE clinical samples. FP: False Positive / TP: True Positive

Reliable detection of gene amplifications

SOPHiA DDM™ detects gene amplifications in 24 genes of the panel without the need for extra controls, thus maximizing cost-effectiveness. The detection is performed by normalizing the coverage levels of the target regions within a sample and across samples of the same run.

Then, the average copy-number levels per gene are deduced and the genes with increased copy-number levels are reported.
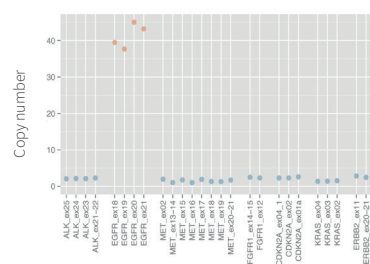
Figure 5: Normalized coverage levels. Blue dots correspond to target regions without gene amplification and orange dots to amplified gene regions.

*The detection of MSI and gene amplifications are not part of the CE-IVD claim.
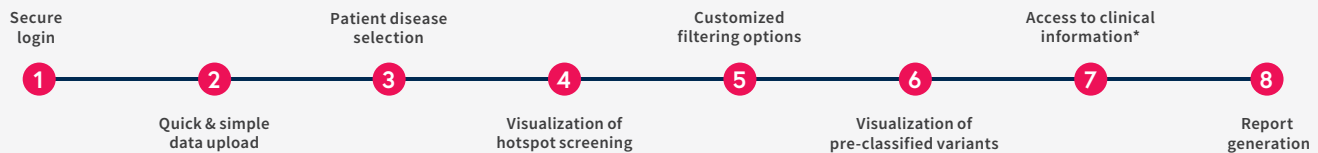
Solid Tumor Solution CE IVD

Fast, easy and intuitive workflow for advanced secondary and tertiary analysis

SOPHiA DDM™ offers a fully integrated workflow, enabling clinicians to manage complex genomic data and efficiently explore, characterize and report clinically relevant genomic alterations associated with solid tumors. The platform offers several features that facilitate the interpretation process, including hotspot screen-ing which streamlines the visualization of mutated and wild type hotspot positions.

SOPHiA DDM™ integrates the OncoPortal, that supports decisions based on the Jax-CKM™ database and CAP / ASCO / AMP guidelines.

End-to-end workflow from raw sequencing data to actionable insights

| 1 Secure login | 2 Quick & simple data upload | 3 Patient disease selection | 4 Visualization of hotspot screening | 5 Customized filtering options | 6 Visualization of pre-classified variants | 7 Access to clinical information* | 8 Report generation |

This is an example of a typical workflow. Some users may require fewer steps.
*including the access to actionable, diagnostic and prognostic information as well as open clinical trials

Disease	Gene	Hotspot	Targeted Therapies	Outcome
LC	EGFR	G719S	Gefitinib, Erlotinib, Afatinib	Sensitive
		T790M	Gefitinib, Afatinib	Resistant
		C797S	Osimertinib	Resistant
		L858R	Gefitinib, Erlotinib, Afatinib	Sensitive
		Deletion exon 19	Gefitinib, Erlotinib, Afatinib	Sensitive
		Insertion exon 20	Erlotinib, Afatinib	Resistant
GIST	KIT	W559D	Imatinib	Sensitive
		V654A	Sunitinib	Sensitive
	PDGFRA	D842V	Imatinib, Sunitinib	Resistant
CRC	KRAS	G12R	Cetuximab, Panitumumab	Resistant
		G12S	Cetuximab, Panitumumab	Resistant
		G13D	Cetuximab, Panitumumab	Resistant
	NRAS	G12D	Cetuximab, Panitumumab	Resistant
MELANOMA	KIT	L576P	Imatinib	Sensitive
	BRAF	V600K	Vemurafenib	Sensitive
		V600E	Dabrafenib, Trametinib (combination)	Sensitive
GBM	IDH1	R132H		Good prognosis
	IDH2	R172H		Good prognosis

Schematic illustration showing a combination of cancer types, genomic alterations, associated therapies and outcomes.

Non-exhaustive list

LC: Lung Cancer, GIST: Gastro Intestinal Stromal Tumor, CRC: Colorectal cancer, GBM: Glioblastoma Multiforme

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 redundantly in secured and private data centers. The platform ensures data protection and respect national privacy laws, GDPR, HIPAA guidelines and applicable legislation regarding data privacy.

Summary

SOPHiA Solid Tumor Solution is a comprehensive molecular diagnostic application enabling the detection of expertly selected somatic alterations associated with solid tumors. By assessing 42 genes in a single assay and leveraging on the clinical-grade analytical power of SOPHiA DDM™, this solution offers a streamlined and standardized workflow that can be easily implemented by any healthcare institution.

References:
[1] Prentice LM, Miller RR et al. Formalin fixation increases deamination mutation signature but should not lead to false positive mutations in clinical practice. PLoS One. 2018 Apr 26;13(4):e0196434. doi: 10.1371/journal.pone.0196434. eCollection 2018.

Somatic gene variant annotations and related content have been powered by, without limitation, The Jackson Laboratory Clinical Knowledgebase (JAX-CKB™).