SOPHiA™

SOLID TUMOR SOLUTION™

CE IVD

Profiling cancer genome to optimize solid tumor management

HIGHLIGHTS

- Customizable gene content covering multiple genes associated with solid tumors
- Clinical-grade performance
- Robust solution capable of detecting long Indels, SNVs, MSI and gene amplification
- Short turnaround time
- Optimal cost per sample ratio

The Solid Tumor Solution (STS) by SOPHiA GENETICS is a CE-IVD marked molecular diagnostic application that bundles a capture-based target enrichment kit with the analytical power of SOPHiA™ AI and full access to the SOPHiA DDM™ platform.

The solution was expertly designed to accurately characterize the complex mutational landscape of the major solid tumors such as lung, colorectal, skin and brain cancers.

SMART KIT DESIGN

- Proven probe design ensuring excellent coverage uniformity
- Comprehensive panel of 42 genes expertly selected by leading global institutions
- Streamlined library preparation workflow - 1.5 days

ANALYTICAL POWER

- Unmatched analytical performance
- High-confidence calling of SNVs, Indels, MSI and gene amplification
- Advanced screening of hotspot positions
- Pre-classification of genomic alterations
- Accurate associations between genomic alterations, cancer types and drugs

UNIVERSAL PLATFORM

- Intuitive and user-friendly interface
- Secure storage of anonymized data
- Dedicated features to help data visualization and interpretation
- Display of genomic alterations associated with patient's tumor and available therapies
- Customized reporting

Better diagnosis, better care

SOPHiA GENETICS helps healthcare professionals to achieve better and faster diagnosis of patients worldwide. Experts who use our solutions benefit from:

SOPHiA AI
Over 180 clinical-grade genomic applications supported

Set Up Program
Rapid adoption of genomic applications in routine diagnostics and ISO 15189 accreditation

Data security policy
Full compliance with national privacy laws, GDPR and applicable legislation regarding data privacy

SOPHiA's community
Anonymized and safe knowledge sharing among experts worldwide

GDPR

ISO 13485 Medical Devices Quality Management

ISO/IEC 27001 Information Security Management

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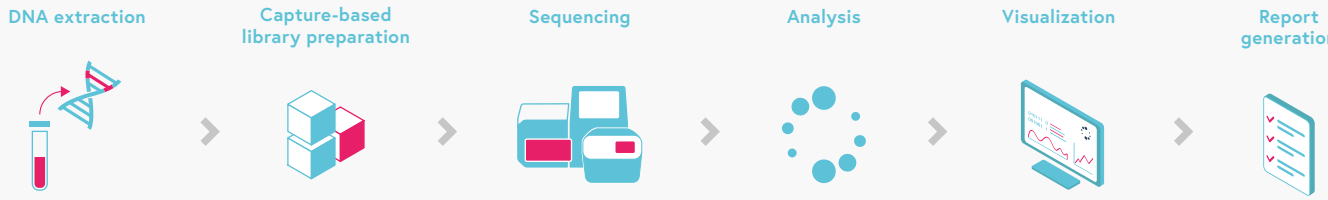
Streamlined workflow from DNA extraction to report generation

STS provides an easy library preparation workflow. Ready to-use sequence target-enriched libraries are generated in 1.5 days, starting from 10 ng of FFPE gDNA samples. Library preparation is compatible with Illumina and Thermo Fisher Scientific sequencing platforms.

Sequencing output files are then analyzed by SOPHiA, that adapts to the specifics of each platform, ensuring clinical-grade performance. Results are displayed on the SOPHiA DDM platform, allowing experts to easily interpret the findings and generate a comprehensive somatic variant report.



Relevant gene content

The STS application 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 highly-optimized to provide exceptional coverage uniformity throughout the entire target region, resulting in superior data quality. If more flexibility is needed, the gene panel 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 (8-12), FGFR1 (13,15), 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*

Measure	FISH	PCR	NGS	STS by SOPHiA GENETICS
Substitutions		✓	✓	✓
Indels		✓	✓	✓
MSI		✓		✓
CNVs	✓			✓
Rearrangements/ fusions	✓			

Smart kit specifications

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

Sequencing and multiplexing recommendations

Sequencers	Flow Cell / Ion Chip Kit	Recommended samples per run (for 1000x median coverage depth)
MiniSeq™	High Output Kit (2x150bp)	24
	Mid Output Kit (2x150bp)	8
MiSeq®	V3 (2x150bp)	24
	V2 (2x150bp)	12
NextSeq® 500/550	Mid Output Kit v2 (2x150bp)	96*
	High Output Kit v2 (2x150bp)	96*
Ion S5™	Ion 530™ Chip	12
	Ion 540™ Chip	48

*Maximum number of indices available. Other platforms available upon request.
CE-IVD mark only applies to MiSeq® sequencer using v3 chemistry.

Excellent coverage uniformity

The STS achieves very high on-target read percentage which assures reliably high coverage uniformity within 0.2x and 5x median $\log_2$ coverage value across all target regions, even in those with high GC-content (Fig. 1A, B).

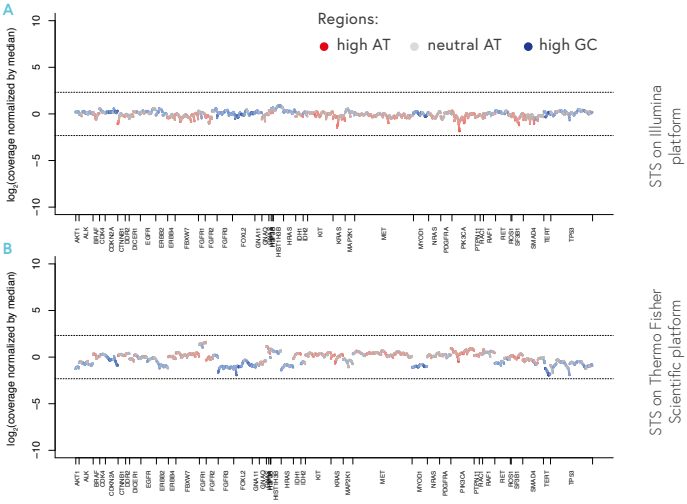


Figure 1: Coverage uniformity profile of a typical clinical FFPE sample. A) on Illumina platform; B) on Thermo Fisher Scientific platform. The X-axis represents the STS genes and the Y-axis the coverage uniformity. The closer the dots are to the 0 line, the more homogeneous are the reads covering each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

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Clinical-grade performance

SOPHiA analyzes complex NGS data by detecting, annotating and pre-classifying SNVs, Indels, MSI and gene amplification to help experts better diagnose patients.

SOPHiA enables clinical-grade performance:

	Observed	Lower 95% CI
Sensitivity	100%	94.82%
Reproducibility	99.97%	99.92%
Repeatability	99.99%	99.95%
Accuracy	100%	95.77%
Precision	100%	93.18%
Coverage uniformity	98.6%	93.5% (5% quantile)

A total of 394 samples were processed on MiSeq® to obtain the above-mentioned metrics. Performance values have been calculated on SNVs and Indels only. The detection of MSI is not part of the CE-IVD claim. 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 accurately detects large deletions such as *MET* gene deletion.

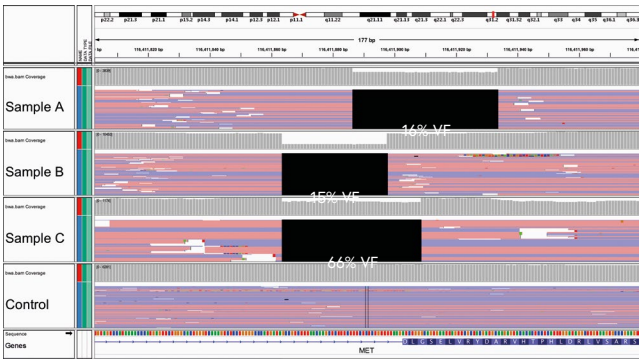

Figure 2: MET exon 14 deletions. The screenshot represents 3 clinical FFPE samples with MET deletions sequenced on an Illumina platform; Control sequenced on an Illumina platform with no MET exon 14 deletion showing excellent quality of the data.

Precise hotspot screening

The absence of a genomic alteration is not synonymous with a wild type position, but can be due to a poorly covered or noisy region. SOPHiA screens specific genomic positions known to be hotspots for mutations such as SNVs, deletions and insertions to verify wether the genomic position is wild

Figure 4: Example of genomic alterations detected by the hotspot screening module.

Excellent detection of MSI in colorectal cancer

MSI status is an important prognostic indicator associated with a more favorable survival rate in multiple tumor types including colorectal and endometrial cancers. SOPHiA 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 defines an MSI score by using read alignment. An alignment profile of one given sample is compared to the reference profile and the differential value between the two profiles is defined as the MSI score in this locus.

	Observed
Sensitivity	100%
Specificity	90%
Limit of detection	20% tumor content

MSI detection using 50ng 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.

SOPHiA decreases the 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 clusters identical reads from the same fragments to establish a consensus read. This allows for the effect of deamination artifacts to be drastically reduced.

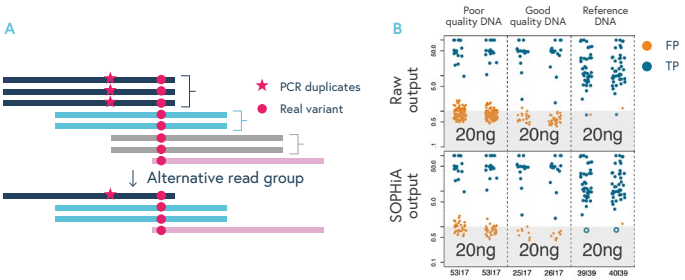

Figure 3: Number of false positive variants decreases when using SOPHiA. A) Alternative read grouping; B) Output of variants using 20ng of DNA from FFPE clinical samples.

Reliable detection of gene amplification

SOPHiA detects gene amplification in 24 genes in the STS application without the need for extra controls, thus maximizing cost-effectiveness. The detection of gene amplification is performed by first 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 (or other predefined large region) are deduced. The genes with increased copy-number levels are then reported.

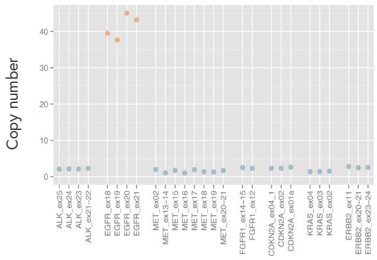

Figure 5: Normalized coverage levels. Blue dots correspond to target regions without gene amplification and orange dots to amplified gene regions.

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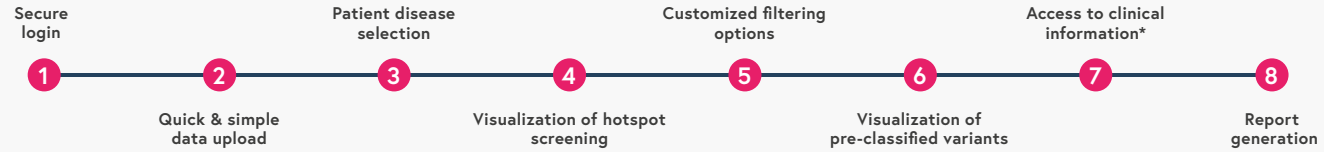
A fast, easy and intuitive workflow for advanced secondary and tertiary analysis

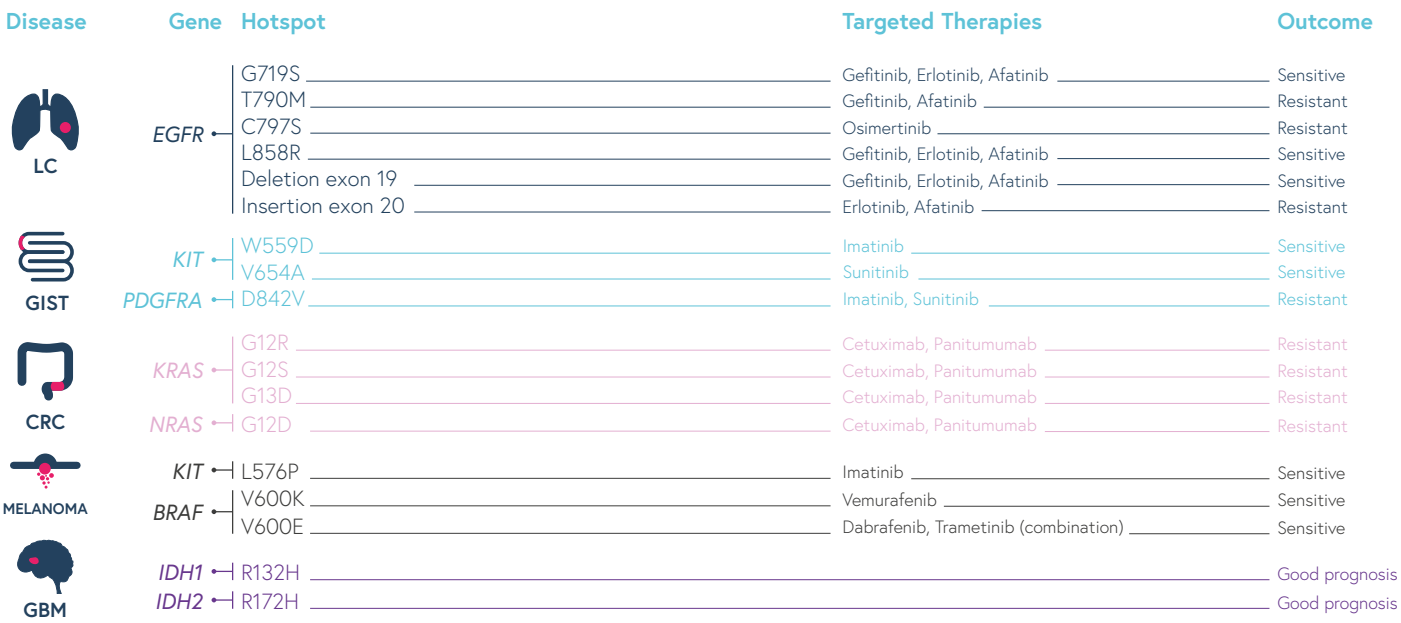
The SOPHiA DDM platform offers a fully integrated workflow. It allows experts to manage genomic data and efficiently explore, characterize and report clinically relevant genomic alterations associated with solid tumors and hematological malignancies. The platform offers several features that make variant analysis more efficient, such as hotspot screening feature which eases visualization of mutated and wild type hotspot positions. With variant pre-classification, experts can easily accelerate the data interpretation process.

SOPHiA DDM also integrates the OncoPortal, a decision support functionality based on precision medicine intelligence. It enables experts to access relevant therapeutic, prognostic and diagnostic databases to determine the actionability and clinical significance of a given genomic alteration. Moreover, the OncoPortal uses inclusion and exclusion criteria to maximize clinical trial matching that may benefit the patient, both locally and at the global level.

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



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



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

Non-exhaustive list

Access SOPHiA's 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 patient privacy and respects national privacy laws, GDPR and applicable legislation regarding data privacy.

Summary

The Solid Tumor Solution by SOPHiA GENETICS is a comprehensive molecular diagnostic application that enables detection of actionable variants associated with multiple tumors, such as lung, colorectal, skin and brain cancers. This capture-based solution enables detection of SNVs, Indels, MSI and gene amplification in one unique and convenient NGS-based application.

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.

List of abbreviations:
VF: Variant Fraction / FP: False Positive / TP: True Positive
LC: Lung Cancer / GIST: Gastrointestinal Stromal Tumors / CRC: Colorectal Cancer / GBM: Glioblastoma Multiforme