SOPHiA™

CLINICAL EXOME SOLUTION

The big panel to answer big questions in genomic diagnostics

HIGHLIGHTS

- Customizable gene content covering the majority of inherited diseases
- Advanced analytical performance
- Robust solution designed to detect all types of genomic variants (SNVs, Indels, CNVs) in one single experiment
- Exceptional CNV calling capabilities
- Exomes dedicated variant filtering options
- Fully automated Familial Variant Analysis (Trio-analysis)

Exome sequencing is widely used when other alternatives fail to identify alterations in genes associated with hereditary and rare diseases. The Clinical Exome Solution (CES) by SOPHiA GENETICS is a molecular diagnostic application that bundles a smart 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 provide a comprehensive coverage of all types of genomic variants in nearly 4'500 disease-related genes, and represents a powerful solution to improve patient's diagnosis.

SMART KIT DESIGN

- High affinity probe design ensuring unmatched coverage uniformity
- Comprehensive panel of 4'490 genes carefully selected by experts from several leading institutions worldwide
- Automated workflow available on leading liquid handling robots for high-throughput library preparation

Ai ANALYTICAL POWER

- Exceptional analytical performance
- High-confidence calling of SNVs and Indels for all genes of the panel
- CNVs detection available for 4'408 genes (98.1% of the panel)

UNIVERSAL PLATFORM

- Intuitive and user-friendly interface
- Full control over accessibility with secure data storage
- Dedicated features facilitating data visualization, filtering and interpretation of large sets of variants
- Customized reporting

Better diagnosis, better care

SOPHiA GENETICS helps healthcare professionals achieve faster, better diagnoses for patients worldwide. When choosing our solutions, clinicians 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 GDPR and national privacy laws for maximum patient privacy

SOPHiA's community
Safe and anonymized knowledge sharing among leading global genomic experts

GDPR

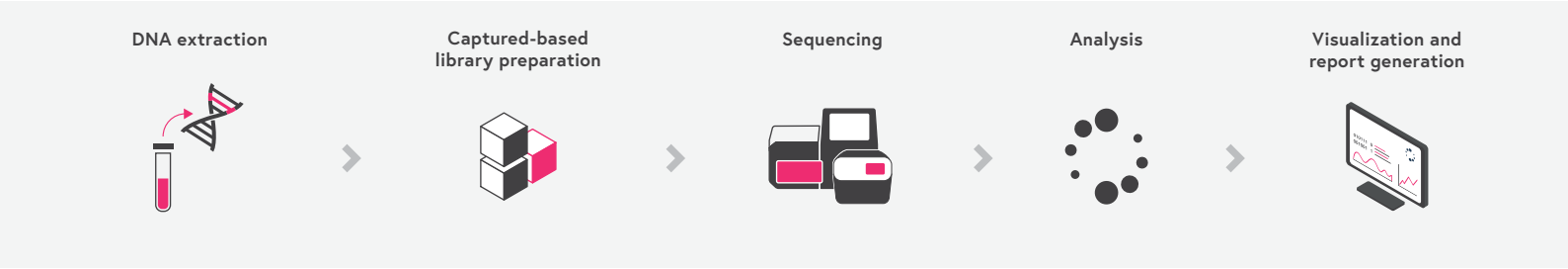
ISO 13485 Medical Devices Quality Management

ISO/IEC 27001 Information Security Management

Clinical Exome Solution

Streamlined workflow from DNA extraction to variant report generation

CES provides straightforward library preparation for ready-to-sequence target-enriched libraries in just 2 working days. 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 analyzed by SOPHiA AI, that adapts to the specificity of each sequencer, always providing clinical-grade performance. Results are displayed on the SOPHiA DDM platform where clinicians can easily interpret the results and generate a complete variant report.



Relevant gene content

The CES panel spans 12 Mb of target region covering the coding regions (± 5bp of exon-flanking regions) of 4'490 genes associated with the vast majority of inherited diseases*, in different disease area. Capture probes are highly-optimized to provide exceptional coverage of the targeted regions, resulting in superior data quality. For specific needs, the gene panel can be customized.

*complete list of genes available at: https://www.sophiagenetics.com/fileadmin/documents/Solutions/CES/ces_v2_genes.xlsx

Smart kit specifications

Parameter	Details
Sample source	Blood
DNA input requirement	200 ng
Target region	12'026'039bp
Turnaround time library preparation	2 days

Sample throughput recommendations

Sequencers	Flow Cell / Ion Chip Kit (sequencing run)	Recommended samples per run (for 250x coverage depth)
HiSeq®3000/4000	High Output (2x100bp)	24 (per lane)
	High Output (2x150bp)	32 (per lane)
HiSeq®2500	High Output (2x125bp)	24 (per lane)
	Rapid run mode (2x150bp)	16 (per lane)
MiSeq®	v3 (2x300bp)	4
NextSeq® 500/550	Mid Output Kit (2x150bp)	16
	High Output Kit (2x150bp)	48
Ion Proton™	Ion P1 v3	4
Ion S5™	Ion 540	4

Excellent coverage uniformity

CES achieves impressive high on-target read percentage, for a large panel, which assures reliable high coverage uniformity value across all the target regions even those with high GC-content (Fig. 1). This unique coverage uniformity is of crucial importance for the precise identification of different types of variations including CNVs.

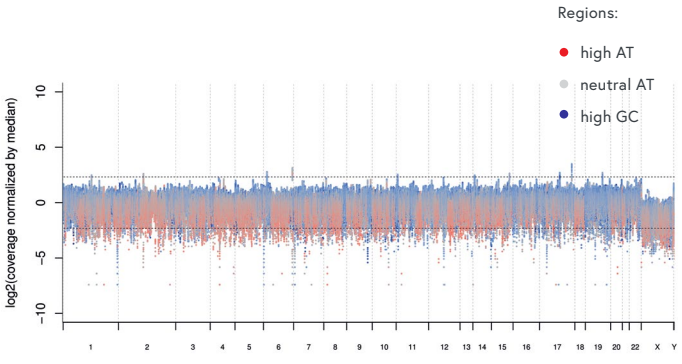


Figure 1: Coverage uniformity profile of a typical clinical sample.
The X-axis represents the chromosomic positions targeted by CES and the Y-axis the log2 coverage normalized by the median. The closer the dots are to the 0 line, the more homogenous the reads are covering each target. Dashed lines represent 20% (lower line) and 500% (upper line) of the median coverage. Coverage on the X chromosome is lower because the sample comes from a male patient.

Advanced analytical performance

SOPHiA analyzes complex genomic NGS data by detecting, annotating and pre-classifying SNVs, Indels and CNVs in all the genes of the panel** to help clinicians better diagnose their patients.

SOPHiA leads to excellent analytical performance:

	Observed
Sensitivity	> 99%(1)
Precision	> 99%(1)
Repeatability	> 99%
Reproducibility	> 99%
Average on-target rate	> 90%
Coverage uniformity	> 98%
Average % of target region > 50x	> 96%

*** CNVs detection is available for 98.1% of the panel*
(1) Performance metrics are based on high confidence regions in a reference sample. Values have been calculated on a reference sample and 20 M reads per sample on a HiSeq® instrument (300bp read length)

Unique detection of Copy Number Variations

Copy Number Variations (CNVs) play an important role in a broad range of genetic disorders[1]. Accurate CNVs detection via exome-based profiling can then result in increased diagnostic yield. However, classical large gene panel settings render the detection of CNVs very difficult due to the extended target regions and the increased depth of sequencing that one needs to perform in order to reliably detect CNVs.

Thanks to its unique coverage uniformity, along with the superior analytical performance of SOPHiA, CES overcomes the hurdle of CNVs detection in large gene panels without the need of an extreme sequencing depth and offers a unique opportunity for simultaneous calling of all types of genomic variations***. In particular, CNVs are precisely detected by comparing the coverage levels of the target regions across all samples within the same sequencing run. The background noise of each sample is then individually adjusted by removing any artefacts coming from library preparation and sequencing workflow. Through its unique detection capabilities, CES omits the need for any additional CNV specific assay, and allows clinicians to save a tremendous amount of turnaround time, money and complexity, bringing them closer to single-test genomic diagnostics.

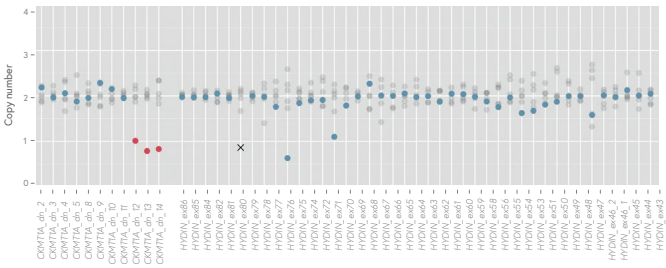


Figure 2: Normalized coverage levels of Copy Number status.
Plot shows the normalized coverage levels in a given sample (blue and red dots) compared to the reference coverage levels (grey dots). Blue dots correspond to target regions without CNVs, red dots to deletions. Solid dots represent high-confidence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

*** Accurate CNV calling requires at least 8 co-captured samples*

Enhanced variant visualization and interpretation

Powered by SOPHiA, the SOPHiA DDM platform features intuitive variant filters, and flexible classification and reporting functionalities to simplify data visualization and interpretation. The platform enables clinicians to explore and interpret genomic variants and also report clinically significant findings.

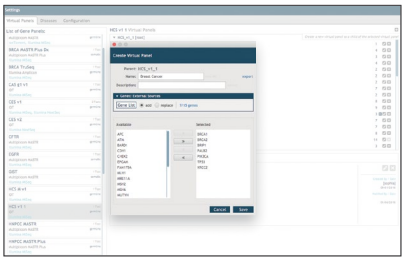
1. Secure login
2. Quick and simple data upload
3. Variant detection and pre-classification
4. Customized filtering options
5. Variant flagging
6. Variant report generation

Clinical Exome Solution

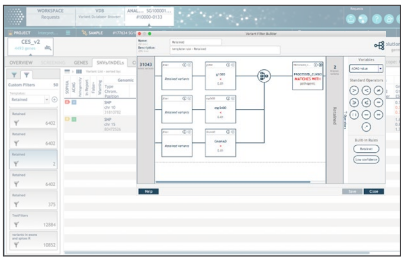
Integrated features for efficient variant prioritization and interpretation

KEY ADVANTAGES

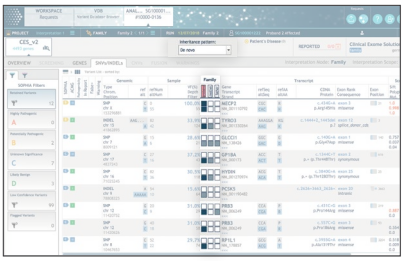
- Narrow the number of variants down to the most relevant ones
- Increase diagnostic yield
- Shorten turnaround time



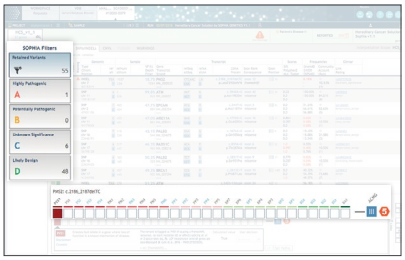
Virtual Panel
Limit the interpretation to a subset of genes based on patient's phenotype.



Variant Filter Builder
Create custom filtering strategies for quicker screening of relevant variants.

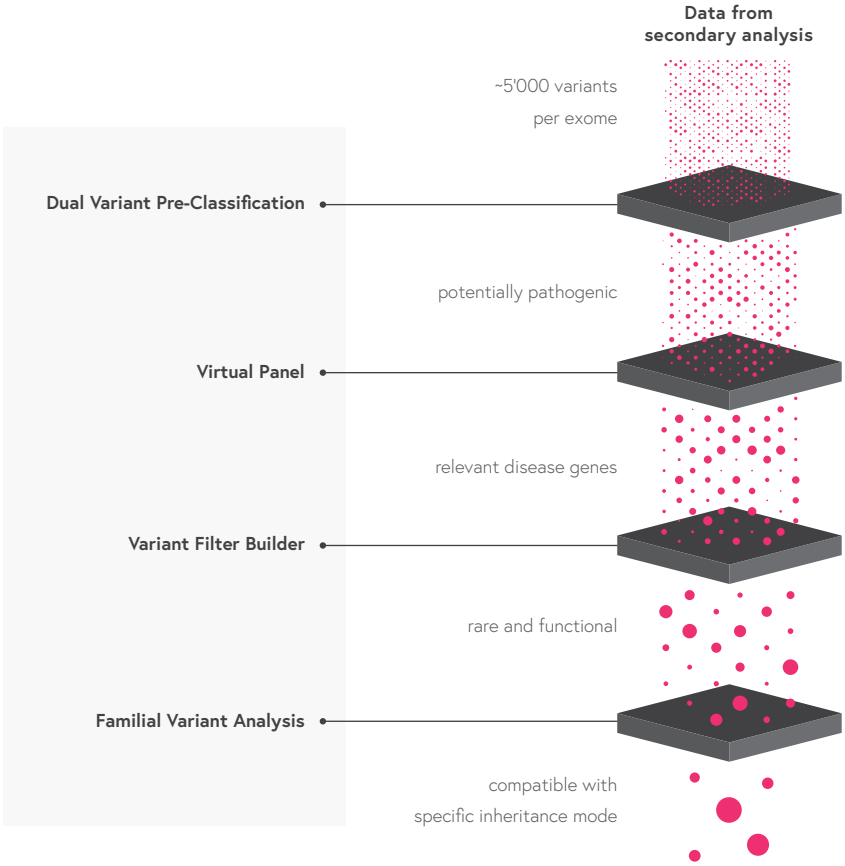


Familial Variant Analysis (trio analysis)
Quickly identify causative variants by selecting different inheritance modes with a single mouse click and reducing the candidate variant list accordingly.



Dual variant pre-classification (ACMG score and SOPHiA's prediction)
Pre-classify variants according to both ACMG guidelines and SOPHiA's prediction to offer a complete set of information to clinicians for improved assessment of variants pathogenicity.

Clinical utility



Access to SOPHiA's community

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

Respect 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 the European General Data Protection Regulation (GDPR) as well as national privacy laws.

Summary

The Clinical Exome Solution by SOPHiA GENETICS is a comprehensive molecular diagnostic application enabling the detection of all types of genomic variants associated with the most common inherited disorders. It assesses 4'490 genes in a single assay and leverages the unmatched analytical power of SOPHiA combined with the dedicated features of SOPHiA DDM. This solution allows clinicians to accurately diagnose hereditary and rare diseases and answer big questions in genomic diagnostics.

References:
1. Pfundt R†, et al. Detection of clinically relevant copy-number variants by exome sequencing in a large cohort of genetic disorders. Genet Med. 2017 Jun;19(6):667-675. doi: 10.1038/gim.2016.163. Epub 2016 Oct 27.