SOPHiA™

NEPHROPATHIES SOLUTION

Getting upstream to the source of hereditary nephropathies

HIGHLIGHTS

- Customizable gene content, covering more than 20 inherited kidney disorders
- Advanced analytical performance
- Robust detection of multiple types of variants, including CNVs
- Effective differentiation between gene and pseudogene variants
- High workflow productivity with short turnaround time

SOPHiA Nephropathies Solution is a genomic 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 in collaboration with Ospedale Pediatrico Bambino Gesú (Italy) to target 44 genes associated with the most prevalent hereditary nephrology diseases.

SMART KIT DESIGN

- High affinity probe design ensuring extremely uniform coverage of the target region
- Comprehensive application targeting 44 genes
- Automated workflow available on leading liquid handling robots for high-throughput library preparation

Ai ANALYTICAL POWER

- Advanced analytical performance (i.e. 100% sensitivity and accuracy)
- High-confidence calling of SNVs, Indels and CNVs in all the genes
- Efficient differentiation of gene and pseudogene variants in *PKD1*

UNIVERSAL PLATFORM

- Intuitive and user-friendly interface
- Secure storage of anonymized data
- Dedicated features for simplified data visualization and interpretation
- Fully customizable report

Democratizing Data-Driven Medicine

SOPHiA GENETICS helps clinical researchers better analyze and interpret genomic data. Experts who use our solutions benefit from:

SOPHiA AI
Over 200 genomic applications supported

Set Up Program
Rapid adoption of genomic applications

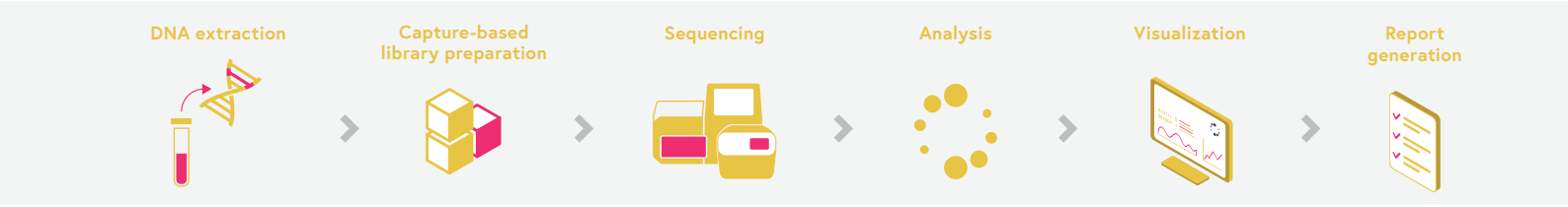
Data security policy
Compliance with national privacy laws, GDPR, HIPAA guidelines and applicable legislation

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

Nephropathies Solution

Streamlined workflow from DNA extraction to variant report generation

SOPHiA Nephropathies Solution provides a straightforward library preparation workflow: ready-to-sequence target-enriched libraries are generated in just 1.5 working 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, that adapts to the specifics of each sequencer, always ensuring advanced performance. Finally, results are displayed on the SOPHiA DDM platform where clinical researchers can easily interpret them and generate a complete variant report.



Relevant gene content

The solution covers the complete coding sequence (± 5bp of exon-flaking regions) of the 44 most relevant genes related to a broad range of nephropathies, such as nephrotic syndromes, polycystic kidney diseases, Bartter syndromes, Alport syndrome, CAKUT and tubulopathies. Probe design is optimized to provide high coverage uniformity throughout the entire target region, resulting in valuable data quality. For specific needs, the gene content can be fully customized.

44 genes

AGXT, AQP2, ATP6V0A4, ATP6V1B1, AVPR2, BSND, CASR, CEP290, CLCN5, CLCNKB, COL4A3, COL4A4, COL4A5, CRB2, CTNS, CUBN, CYP24A1, DSTYK, EMP2, EYA1, FN1, FOXC1, GRHPR, HNF1B, KANK2, KCNJ1, LAMB2, NPHS2, NR3C2, OCRL, PAX2, PHEX, PKD1, PKD2, PKHD1, SIX1, SLC12A1, SLC12A3, SLC34A1, SLC4A1, SLC4A4, TTC21B, UMOD, WT1

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

Sequencers	Flow Cell / Ion Chip Kit	Recommended samples per run (for 250x median coverage depth)
MiSeq®	v3 (2x300 bp)	32
	v2 (2x250 bp)	24
NextSeq® 500/550	Mid Output Kit v2 (2x125 bp)	96*
	High Output Kit v2 (2x150 bp)	96*
Ion Proton™	Ion P1	32
Ion S5™	Ion 540	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.

Extremely uniform coverage

The application 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 and precise CNV detection.

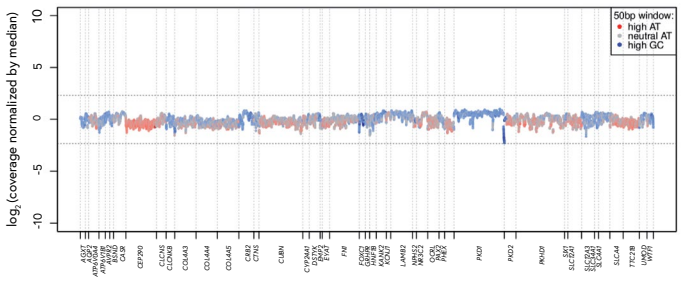


Figure 1: Coverage uniformity profile of a typical sample analyzed with SOPHiA Nephropathies Solution.
The X-axis represents the genes included in the application and the Y-axis the log_2 coverage normalized by the median. The closer the dots are to the 0 line, the more homogenous the reads are covering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

Nephropathies Solution

Advanced analytical performance

SOPHiA analyzes complex NGS data by detecting, annotating and pre-classifying SNVs, Indels and CNVs in all the genes covered by the solution in a single experiment.

SOPHiA reaches advanced analytical performance:

	Observed	Lower 95% CI
Sensitivity	100%	82.21%
Reproducibility	100%	100%
Repeatability	100%	100%
Accuracy	100%	84.21%
Precision	99.99%	99.97%
Coverage uniformity	99.99%	99.97%
Average on-target rate*	75%	
Coverage uniformity	97.55%	
Average percentage of target region with depth >200x	95.09%	

*The number of off-target high coverage regions is particularly high because of the presence of pseudogenes in the panel.

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 Copy Number Variations

Copy Number Variations (CNVs) have been reported to play a role in many kidney diseases[1]. For example, whole gene deletions of *PKD1* is known to cause polycystic kidney disease[2]. SOPHiA detects CNVs in all genes at a resolution of 1 exon (Fig. 2). This analysis is performed by evaluating the coverage levels of the target regions across all samples within the same sequencing run. For each sample, SOPHiA automatically selects a set of reference samples from the same run, based on the similarity of coverage patterns. Subsequently, the coverage is normalized by sample and target region using the reference samples, enabling CNV calling.
Thanks to its accuracy, SOPHiA Nephropathies Solution reduces the need for additional assays by allowing the detection of SNVs, Indels and CNVs in a single experiment. In addition, the number of samples multiplexed in a run can be increased by avoiding supplementary reference samples. The result is a fast, nimble and more cost-effective workflow.

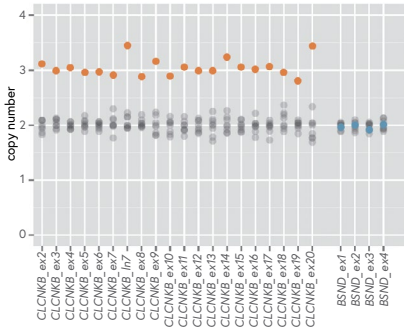
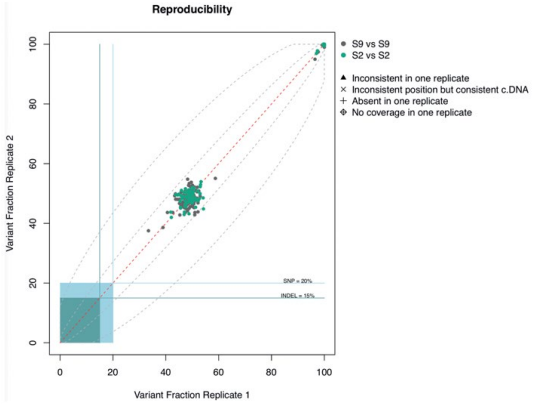


Figure 2: Normalized coverage levels of Copy Number status.
Plot shows the normalized coverage levels in a given sample (blue and orange dots) compared to the reference coverage levels (grey dots). Blue dots correspond to target regions without CNVs, orange dots to duplications. Solid dots represent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

Very high reproducibility and repeatability

Required elements for establishing precision of any NGS-based application, repeatability and reproducibility must be determined by sequencing the same sample several times under same conditions (i.e. intra-run replicates) or under different conditions (i.e. inter-run replicates) respectively. SOPHiA Nephropathies Solution has been tested extensively, ensuring almost 100% repeatability and reproducibility (Fig. 3), giving genomic experts confidence in NGS sequencing.

3A



3B

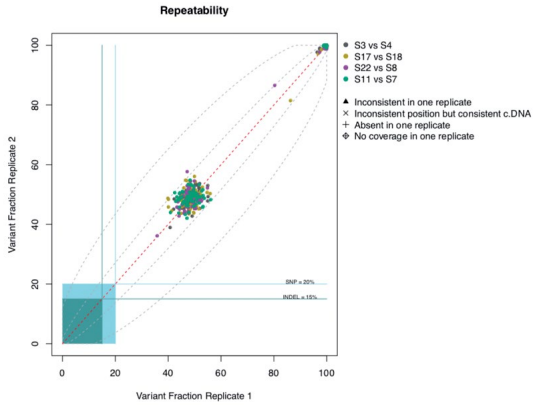


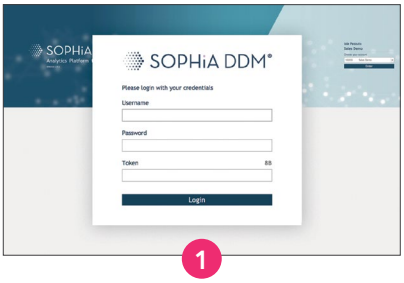
Fig.3: SOPHiA Nephropathies Solution reaches high reproducibility (Fig. 3A) and repeatability (Fig. 3B). The variant fractions, depicted by colored dots, are typically 0.5 (heterozygous) or 1.0 (homozygous), as expected for germline variants. The grey dotted lines represent the 5% and 10% standard deviation from identity (diagonal = red dashed line). The blue and green squares represent the low variant fraction cut-off (SNP=20%, Indel=15%). 3A) The replicated samples show an almost perfect match in variant fractions between 2 runs. 3B) The replicated samples show almost perfect match in variant fraction between the 2 replicates.

Nephropathies 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.

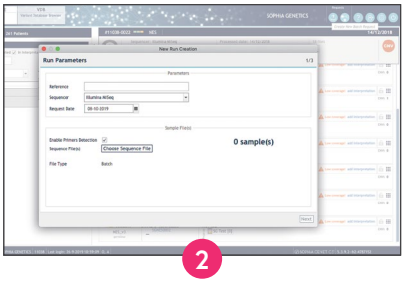
The platform enables clinical researchers to explore and interpret genomic variants and also report significant findings.



1

Secure login

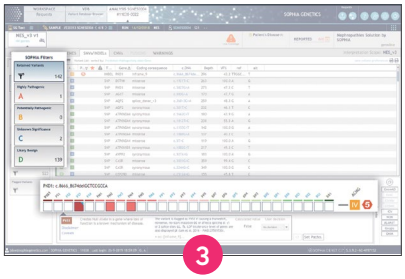
Access to SOPHiA DDM is restricted to registered users only. Login features a 2-step verification procedure.



2

Quick and simple data upload

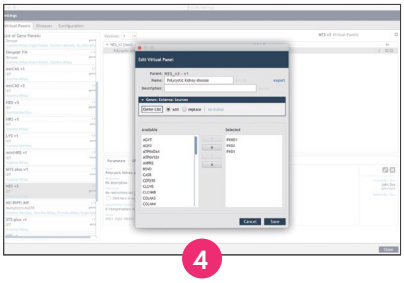
Once sequencing output files are uploaded, all relevant information is automatically extracted and displayed, saving time and avoiding human error from manual insertion.



3

Dual variant pre-classification (ACMG score and SOPHiA's prediction)

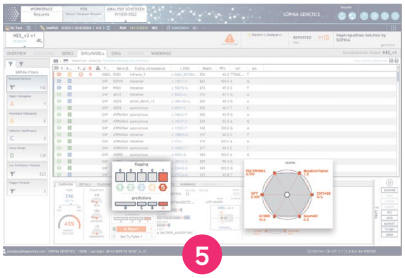
Detected variants are displayed by variant type (SNVs, Indels and CNVs). Users can easily visualize an overview of the major SNVs and Indels pre-classified by level of pathogenicity according to both ACMG guidelines and SOPHiA's predictions.



4

Customized filtering

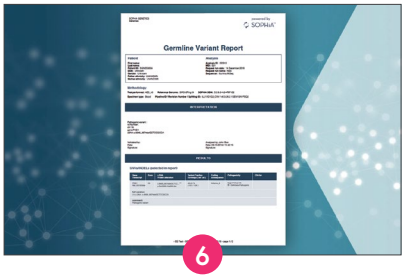
Virtual Panels can be created to limit the interpretation to a subset of genes available in the panel for quicker screening of relevant variants.



5

Variant flagging

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



6

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 user.

Access to 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.

Respect data 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 respects national privacy laws, GDPR, HIPAA guidelines and applicable legislation regarding data privacy.

Summary

SOPHiA Nephropathies Solution is a comprehensive genomic application that detects and characterizes germline variants associated with the most prevalent nephropathies. It enables the assessment of multiple types of variants in 44 genes within a single assay, leveraging the advanced analytical power of SOPHiA. As a result, the solution globally offers a streamlined and standardized workflow, that can be easily implemented by any healthcare institution.

References:
[1] *Copy-Number Disorders Are a Common Cause of Congenital Kidney Malformations. Am J Hum Genet. 2012 Dec 7; 91(6): 987–997.*
[2] *The European Polycystic Kidney Disease C. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. Cell. 1994;77(6):881-94.*