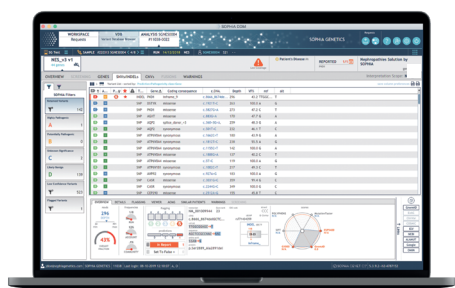


NEPHROPATHIES SOLUTION

Getting upstream to the source of hereditary nephropathies



SOPHiA DDM™ Nephropathies Solution bundles a smart capture-based target enrichment kit with the analytical performance and advanced features of the SOPHiA DDM™ Platform. Expertly designed in collaboration with Ospedale Pediatrico Bambino Gesù in Italy, the solution targets 44 genes associated with the most prevalent hereditary nephrology disorders.

SMART KIT DESIGN



- Expertly designed panel targeting 44 genes linked to the major hereditary nephrology disorders
- High affinity probe design, ensuring high on-target rate and 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 (i.e. 100% sensitivity and accuracy)
- High-confidence calling of SNVs, Indels, and CNVs in all the genes of the panel
- Efficient differentiation of gene and pseudogene variants in *PKD1**
- Intuitive features for simplified data visualization and interpretation
- Customizable report
- Secure storage of anonymized data

*Due to high gene conversion rates, a definite location in *PKD1* and its pseudogenes cannot be assigned in homologous regions of exon 5.

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

Dedicated pipelines covering Oncology, Rare and Inherited Disorders, 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

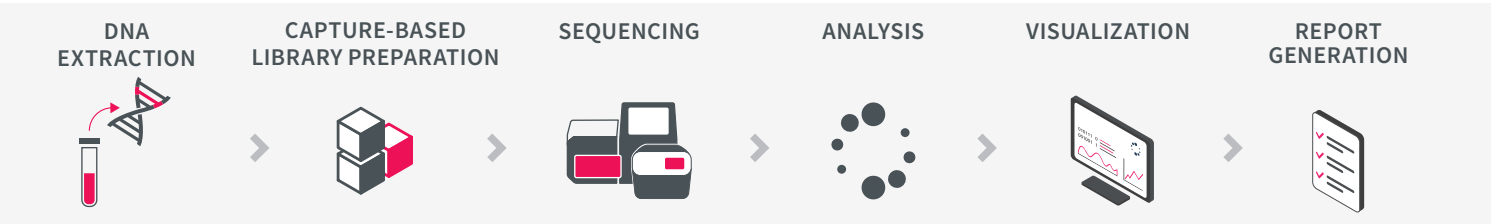
Anonymized and safe knowledge sharing among experts worldwide

Nephropathies Solution

Streamlined workflow from DNA extraction to variant report generation

SOPHiA DDM™ 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 sequencing platforms. Sequencing output files are then analyzed by SOPHiA DDM™, which adapts to the specifics of each sequencer to ensure advanced analytical performance. Finally, results are displayed on the platform for streamlined interpretation and generation of a comprehensive variant report.



Relevant gene content

SOPHiA DDM™ Nephropathies Solution covers the complete coding sequence (\pm 5bp of exon-flanking regions) of 44 genes related to a broad range of nephropathies such as nephrotic syndromes, polycystic kidney disorders, 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

SOPHiA DDM™ Nephropathies Solution achieves a very high on-target read percentage, which assures reliably high coverage uniformity within 0.2x and 5x the median coverage value across all 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.

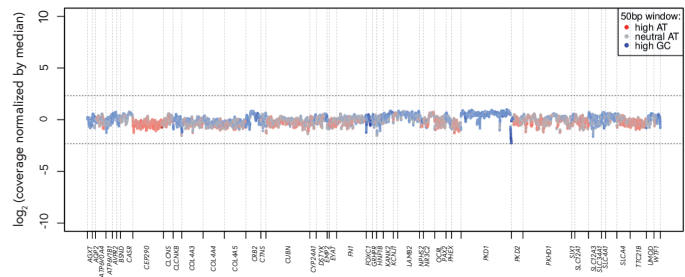


Figure 1: Coverage uniformity profile of a typical sample analyzed with SOPHiA DDM™ Nephropathies Solution.
The X-axis represents the genes included in the application and the Y-axis the \log_2 coverage normalized by the median. The closer the dots are to the 0 line, the more homogenous the reads are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



Nephropathies Solution

Advanced analytical performance

SOPHiA DDM™ 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 DDM™ 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 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 diseases¹. For example, a whole gene deletion of *PKD1* is known to cause polycystic kidney disease².

SOPHiA DDM™ detects CNVs in all covered 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 DDM™ 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 DDM™ Nephropathies Solution reduces the need for additional assays by allowing the simultaneous 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.

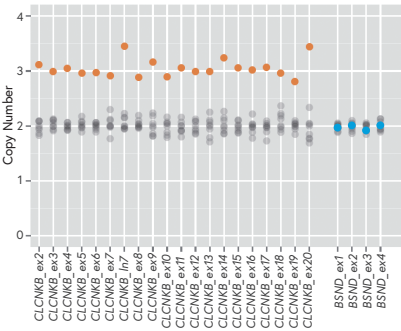


Figure 2: Normalized coverage levels of Copy Number status. Plot shows the normalized coverage levels in a given sample (blue and orange dots) compared to the reference coverage levels (grey dots). Blue dots correspond to target regions without CNVs, orange dots to duplications. Solid dots represent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

Very high reproducibility and repeatability

Repeatability and reproducibility are required elements for establishing precision of any NGS-based application, and are determined by sequencing the same sample several times under either the same (i.e. intra-run replicates) or different (i.e. inter-run

replicates) conditions, respectively. SOPHiA DDM™ Nephropathies Solution has been tested extensively, ensuring almost 100% repeatability and reproducibility (Fig. 3), giving genomic experts confidence in their NGS sequencing.

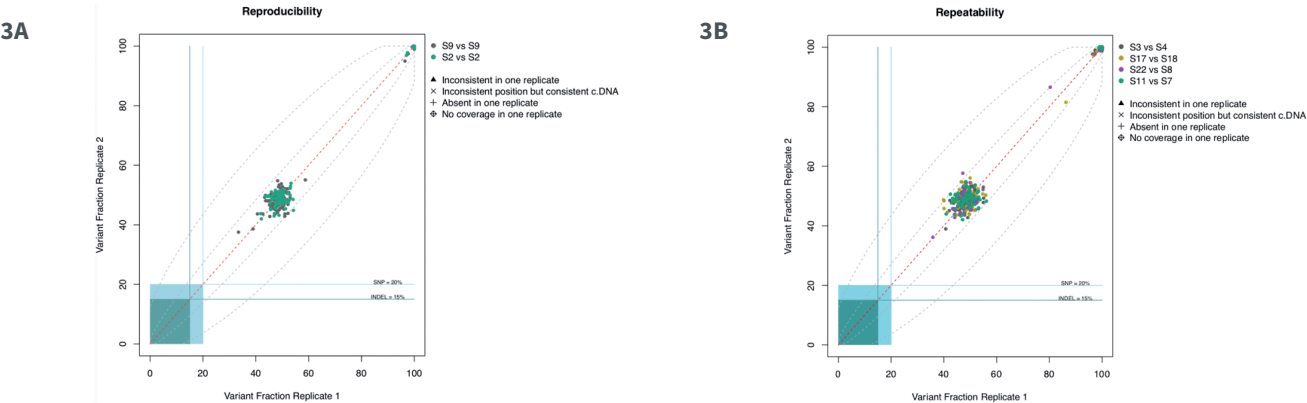


Figure 3: SOPHiA DDM™ Nephropathies Solution reaches high reproducibility (3A) and repeatability (3B). The variant fractions, depicted by colored dots, are typically 0.5 (heterozygous) or 1.0 (homozygous), as expected for germline variants. The grey dotted lines represent the 5% and 10% standard deviation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



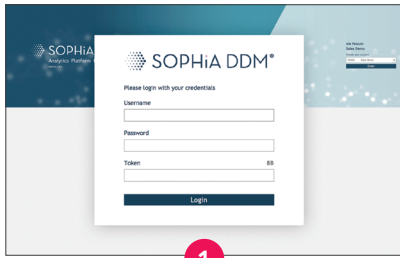
Nephropathies Solution

Integrated features for efficient variant prioritization and interpretation

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

The Platform enables researchers to explore and interpret genomic variants and to report significant findings. Users can also have

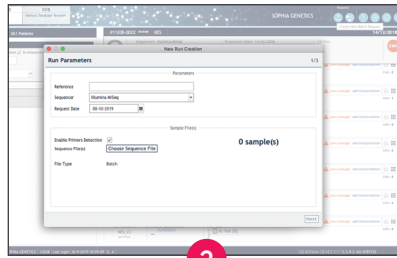
access to Alamut™ Visual Plus, a full-genome browser that integrates numerous curated genomic and literature databases, guidelines, and missense and slicing predictors, enabling a deeper variant exploration.



1

Secure login

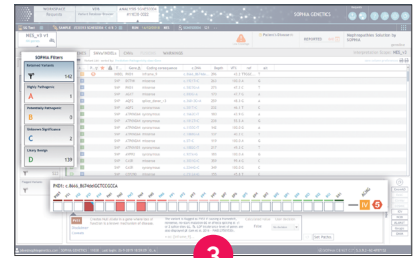
Access to SOPHiA DDM™ is restricted to registered users only. Log in features a 2-step verification procedure.



2

Quick and simple data upload

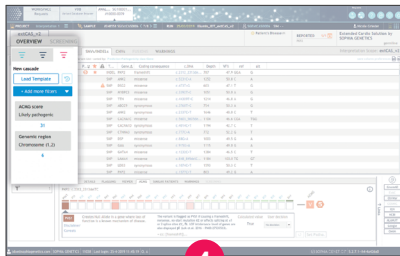
Once sequencing output files are uploaded, all relevant information is automatically extracted and displayed, saving time and avoiding human error from manual insertion.



3

Dual variant pre-classification

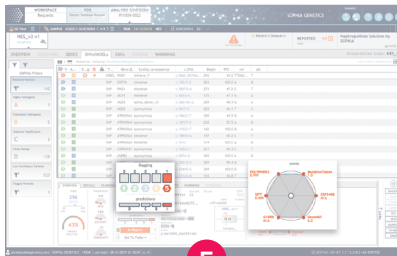
Detected variants are displayed by variant type (SNVs, Indels and CNVs). Users can easily visualize an overview of major variants pre-classified through machine learning-based pathogenicity classes and ACMG scores.



4

Cascading filters

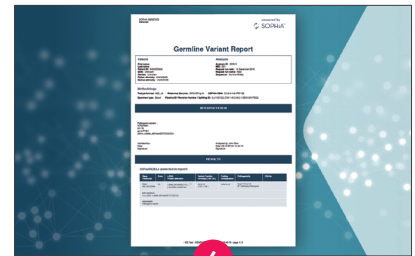
Apply custom filtering options for quicker screening of relevant variants and save strategies for future analyses and inclusion in reports.



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, 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.

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 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 DDM™ Nephropathies Solution is a comprehensive genomic application that 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 DDM™. As a result, the solution globally offers a streamlined and standardized workflow, that can be easily implemented by any healthcare institution.

References:

- ¹ Sanna-Cherchi S, et al. 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.

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