The SOPHiA DDM™ Exome Solutions include two genomic applications, Clinical and Whole Exome, that both combine a capture-based target enrichment kit with the analytical capabilities and advanced features of the SOPHiA DDM™ Platform.

Expertly designed, these applications provide comprehensive coverage of multiple types of genomic variants in up to 19,425 genes, enabling data-informed decision making.

**SMART KIT DESIGN**
- High affinity probe design, ensuring high on-target rate and coverage uniformity throughout the target regions
- Whole Exome Solution v2: Targeting 19,425 genes and the entire mitochondrial genome
- Clinical Exome Solution v3: Targeting 4,727 genes, the entire mitochondrial genome, and ~200 non-coding variants with known pathogenicity in deep introns/enhancer/promoter genes
- Automated workflow available on leading liquid handling robots for high-throughput library preparation for optimal cost per sample

**SOPHiA DDM™ PLATFORM**
- Advanced analytical performance (i.e. >99% sensitivity and precision)
- High-confidence calling of SNVs and Indels
- Efficient CNV detection available for:
  - 97% of covered genes
- Intuitive features for simplified data visualization and interpretation
- 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**
  - 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

For Research Use Only. Not for use in diagnostic procedures.
SOPHiA DDM™ Exome Solutions provide a straightforward library preparation workflow. Ready-to-sequence target-enriched libraries are generated in just 2 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 of both applications 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, ensuring 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™ Clinical Exome Solution v3 covers the coding regions (±5bp of intronic regions) of 4,727 genes*, the entire mitochondrial genome, and ~ 200 non-coding variants with known pathogenicity in deep introns/enhancers/promoters associated with rare and inherited disorders (probe footprint of 16 Mb). SOPHiA DDM™ Whole Exome Solution v2 covers 19,425 genes and the entire mitochondrial genome, enabling an exome-wide investigation. Probe design is highly optimized to guarantee a high on-target reads percentage and coverage uniformity even in GC-rich regions, including the first exon. For specific needs, the gene content can be customized.

*SComplete list of genes available upon request.

**Smart kit specifications**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample source</td>
<td>Blood</td>
</tr>
<tr>
<td>DNA input requirement</td>
<td>200 ng</td>
</tr>
<tr>
<td>Target region</td>
<td>16 Mb (Clinical Exome) 34 Mb (Whole Exome)</td>
</tr>
<tr>
<td>Hands-on library preparation time</td>
<td>8 hours</td>
</tr>
</tbody>
</table>

**Sequencing and multiplexing recommendations**

<table>
<thead>
<tr>
<th>Sequencers</th>
<th>Flow Cell / Ion Chip Kit</th>
<th>Recommended samples per run (for &gt;50x coverage depth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illumina NovaSeq® 6000</td>
<td>SP</td>
<td>Clinical Exome: 48 (per lane) Whole Exome: 12 (per lane)</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>Clinical Exome: 96 (per lane) Whole Exome: 24 (per lane)</td>
</tr>
<tr>
<td></td>
<td>S2</td>
<td>Clinical Exome: NA Whole Exome: 56 (per lane)</td>
</tr>
<tr>
<td>Illumina HiSeq® 2500</td>
<td>High Output (2x125bp)</td>
<td>NA (per lane)</td>
</tr>
<tr>
<td></td>
<td>Rapid Run Mode (2x150bp)</td>
<td>NA (per lane)</td>
</tr>
<tr>
<td>Illumina NextSeq® 500/550</td>
<td>Mid Output Kit v2 (2x150bp)</td>
<td>16 (per lane)</td>
</tr>
<tr>
<td></td>
<td>High Output Kit v2 (2x150bp)</td>
<td>48 (per lane)</td>
</tr>
</tbody>
</table>

**Extremely uniform coverage**

SOPHiA DDM™ Exome Solutions achieve very high on-target rates, which ensure reliable coverage uniformity values across all the target regions, even in GC-rich regions (Fig. 1). Equal read coverage is of crucial importance for the precise identification of multiple types of variations, including CNVs.
**Exome Solutions**

### 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 applications, in a single experiment.

*CNV detection is available for 97% of the covered genes

<table>
<thead>
<tr>
<th>Analysis time from FASTQ files</th>
<th>Clinical Exome Solution v3</th>
<th>Whole Exome Solution v2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOPHiA DDM™</td>
<td>6 hours</td>
<td>Overnight</td>
</tr>
</tbody>
</table>

Analysis time may vary depending on the number of samples multiplexed and server load.

1SNV and Indel performance metrics are based on more than 6,100 variants. There were 16.25M reads per sample. Sequencing was performed using an Illumina NextSeq® instrument.

2Analytical performance for CNVs was calculated on 80 CNVs, sequenced using an Illumina NextSeq® instrument.

3Sensitivity for mitochondrial SNVs/Indels was calculated on 96 variants (93 SNPs and 3 Indels), sequenced using an Illumina NextSeq® instrument.

4Sensitivity metrics are based on high confidence regions in 4 reference samples, with 81M reads per sample. Sequencing was performed using an Illumina NextSeq® 550 instrument (300 bp read length).

5Analytical performance for CNVs was calculated from 4 samples, with 102M reads per sample. Sequencing was performed using an Illumina NovaSeq® instrument.

### Sensitive CNV calling

Copy Number Variations (CNVs) play an important role in a broad range of genetic disorders1. Accurate CNVs detection via exome-based profiling can result in increased analytical yield. However, classical extended exome application settings render the detection of CNVs very difficult due to the extended target regions and the increased depth of sequencing needed to reliably identify CNVs.

SOPHiA DDM™ detects CNVs* at a resolution of 2-5 exons (Fig. 2) in both applications. 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.

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

Thanks to its accuracy, the use of both applications reduces the need for additional assays by allowing the simultaneous detection of SNVs, Indels and CNVs. The result is a fast, nimble and cost-effective workflow.

![Figure 2: Example of normalized coverage levels of Copy Number status for SOPHiA DDM™ Clinical Exome Solution v3 on the SOPHiA DDM™ Platform. 90% sensitivity of CNV detection was observed in two consecutive regions (exons) with 40 million fragments (80 million reads). Comparable results are observed with SOPHiA DDM™ Clinical Exome Solution v3 on the SOPHiA DDM™ Platform. *Accuracy CNV calling requires at least 8 co-captured samples.

### Full coverage of the mitochondrial genome by the SOPHiA DDM™ Exome Solutions

The SOPHiA DDM™ Exome Solutions’ panel design and sophisticated algorithms address the unique challenges associated with the mitochondrial genome, such as the high and variable amount of mitochondrial DNA and heteroplasmy, to provide coverage uniformity and to accurately and confidently identify mitochondrial variants in a streamlined analytical workflow. The applications provide coverage of the entire mitochondrial genome, with 100% sensitivity for mitochondrial SNVs/Indels down to 5% variant frequency (Fig. 3).

![Figure 3: Sensitivity and precision of mitochondrial analysis for the SOPHiA DDM™ Clinical Exome Solution v3 on the SOPHiA DDM™ Platform, according to expected variant frequency. Metrics were calculated on 96 variants (93 SNPs and 3 Indels), sequenced using an Illumina NextSeq® instrument (data on file).](image-url)
Exome Solutions

Integrated features for efficient variant visualization and interpretation

The SOPHiA DDM™ Platform enables clinical researchers to explore and interpret genomic variants and report significant findings. The Platform uses complete GRCh38/hg38-based analytics for variant annotation, performs comprehensive transcript annotation with MANE, and features variant prioritization options to streamline interpretation and help reduce turnaround time.

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™ Exome Solutions are comprehensive genomic applications enabling the detection of multiple types of variants associated with rare and inherited disorders. They enable the assessment of up to 19,425 genes in a single assay by leveraging the advanced analytical power of SOPHiA DDM™. As a result, these applications globally offer a streamlined and standardized workflow that can be easily implemented by any healthcare institution.

References:

All product and company names are trademarks™ or registered® trademarks of their respective holders. Use of them does not imply any affiliation with or endorsement by them.