USER MANUAL

Research Use Only Components of SOPHiA DDM™ Dx Homologous Recombination Deficiency Solution

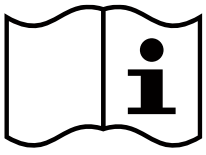
For Research Use Only (RUO)
Not for use in diagnostic procedures

SOPHiA DDM™

SUMMARY INFORMATION

Product Name	SOPHiA DDM™ Dx Homologous Recombination Deficiency Solution – Research Use Only Components
Product Type	Bundle Solution
Product Family	Molecular diagnostic application (kit + analytics)
Algorithm ID	ILL1XG1S7_FFPE_CNV_NextSeq_2
Sequencer	Illumina® - NextSeq® 500/550
Gene Panel ID	HRD_v1
Product Version	v1.0
Sample Type	Somatic DNA isolated from formalin-fixed, paraffin embedded (FFPE) tumor tissue specimens
Release Version	SOPHiA DDM™ Core: v6.4.0 / SOPHiA DDM™ Dx mode: v2.4.0
Document ID	SG-08830
Document Version	v1.0
Revision Date	January 2026

This Instructions For Use (IFU) is applicable for all SOPHiA DDM™ versions.
Please read the IFU thoroughly before using this product.



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PRODUCT CODES

	FULL PRODUCT CODE	BOX 1	BOX 2	LIBRARY PREPARATION KIT
REF	BS0121ILLCSMY08-32	B1.H1.0021.C-32	B2.0021.C-32	5C0232 (x 2)

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REVISION HISTORY

DOCUMENT ID/ VERSION	DATE	DESCRIPTION OF CHANGE
SG-08330 – 1.0	Jan 2026	• Initial release

TABLE OF CONTENTS

1 GENERAL STATEMENT OF THE TEST PRINCIPLES AND PROCEDURE

This document does not include wet lab protocols or IVD analysis procedures. All wet lab protocols and IVD analysis instructions are provided separately in document SG-00661, Instructions for Use, SOPHiA DDM™ Dx Homologous Recombination Deficiency Solution.

The SOPHiA DDM™ Dx HRD Solution allows users to detect Homologous Recombination Deficiency (HRD) via the observation of genomic integrity as a validated marker, for In-Vitro Diagnostics. Furthermore, the product contains a Research Use Only (RUO) component via the SOPHiA DDM™ Desktop App.

The Research Use Only components include the detection of somatic and germline SNP and INDELs as well as gene amplifications in BRCA1, BRCA2 and in other genes involved in Homologous Recombination Repair (HRR). The pipeline computes a proposed BRCA status and conjointly uses the GI status computed in SOPHiA DDM™ Dx mode, to compute the proposed Research Use Only SOPHiA DDM™ HRD status. For research use only components, the SOPHiA DDM™ Desktop App allows visualization of these results and permits the end user to review and, if needed, overwrite, the proposed BRCA, GI and SOPHiA DDM™ HRD statuses. SOPHiA DDM™ Desktop App also allows the user to assess and report the status of non-BRCA genes involved in HRR as well as the CCNE1 gene amplification status.

2 PRODUCT COMPONENTS

All Research Use Only (RUO) results are automatically computed by the bioinformatics pipeline hosted by SOPHiA DDM™ Dx mode by processing the same NGS data used for IVD analysis. RUO results are obtained by analyzing NGS reads mapping to the genomic regions targeted by the gene panel of the SOPHiA DDM™ Dx HRD Solution. RUO results computed by bioinformatics pipeline includes:

- SNPs/INDELs
- CNVs
- Proposed BRCA status
- Proposed GI status
- Proposed RUO SOPHiA DDM™ HRD status (obtained by combining the proposed BRCA status and GI status computed in SOPHiA DDM™ Dx mode).

All RUO results are made available via the SOPHiA DDM™ Desktop App.

All reference to HRD status in this appendix is solely for RUO purposes.

The instructions for use (IFU) for the NGS Kit and the SOPHiA DDM™ Dx mode platform are available in the Instructions for Use (IFU) of the SOPHiA DDM™ Dx HRD Solution, and is out of scope of this Research Use Only User Manual for SOPHiA DDM™ HRD.

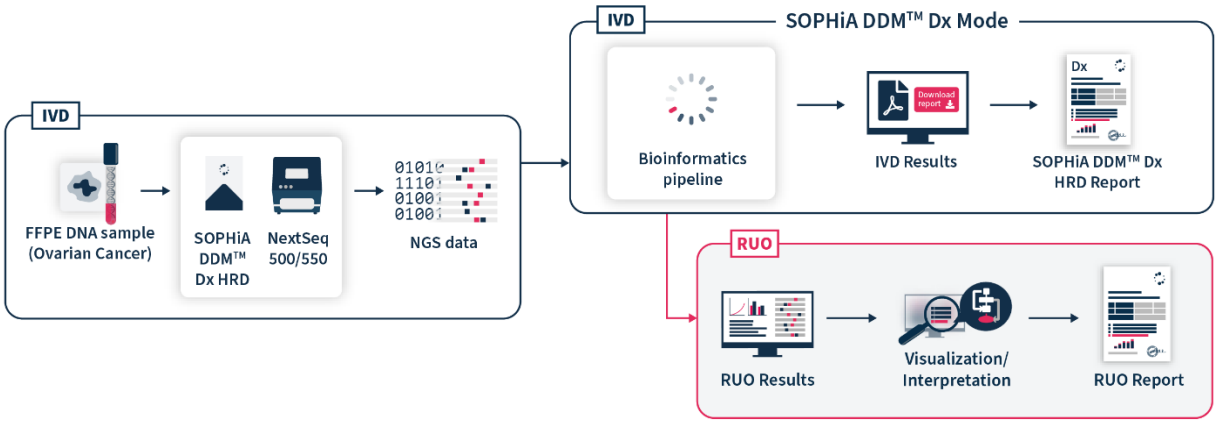


Figure 1. Overview of the different components of SOPHiA DDM™ Dx HRD Solution, with research use only functionality highlighted in pink.

The SOPHiA DDM™ Dx HRD Solution also includes the QA report as research use only, which can be used with the SOPHiA DDM™ Desktop App, to allow users to visualize, interpret and report RUO results computed by the bioinformatics pipeline via targeted deep sequencing data analysis. The key RUO features supported by the SOPHiA DDM™ Desktop App allow users to visualize and interpret SNPs and INDELs from 28 genes (including BRCA1 and BRCA2), define the sample BRCA status, and combine it with genomic integrity results to establish the RUO SOPHiA DDM™ HRD status. All details about the RUO features and results for SOPHiA DDM™ HRD RUO analyzes are available in this document.

3 HOW TO PERFORM A RESEARCH USE ONLY SOPHIA DDM™ HRD ANALYSIS

After completion of the bioinformatics analysis hosted by SOPHiA DDM™ Dx mode, users can perform a RUO SOPHiA DDM™ HRD analysis via the SOPHiA DDM™ Desktop App. To create a RUO SOPHiA DDM™ HRD (also abbreviated as RUO-HRD) interpretation please refer to the SOPHiA DDM™ Desktop App Operation Manual.

The proposed HRD status is displayed on the lower left corner of the Overview tab of the interpretation (*Figure 2*). To access the HRD review window (*Figure 3*), click on the HRD status button.

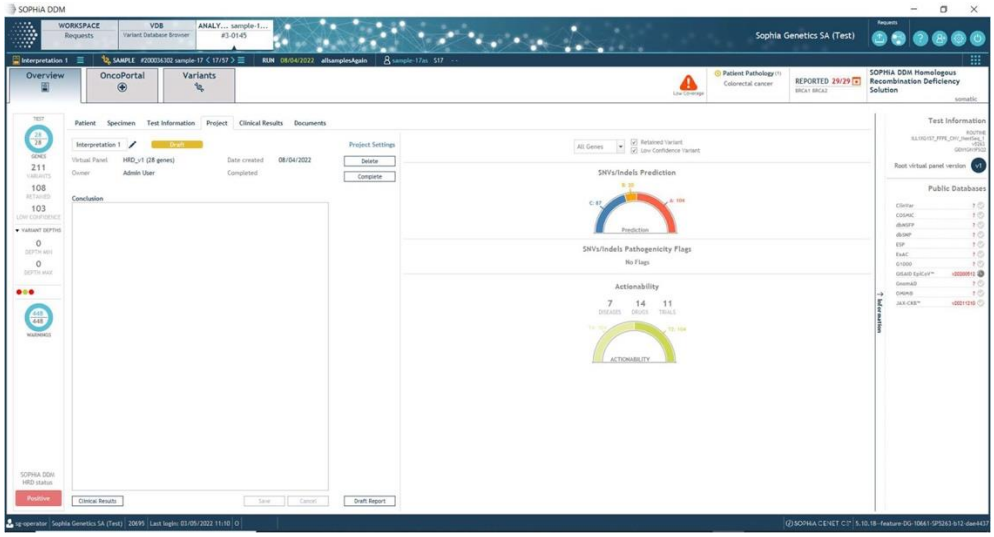


Figure 2. Interpretation overview window with the HRD status indicator.

3.1 Review/Edit the Research Use Only SOPHiA DDM™ HRD Status

The Research Use Only SOPHiA DDM™ HRD status edit/review window displays:

- The HRD status. By default, the final status is based on the proposed HRD status computed by the pipeline.
- A Proposed HRD status computed by the pipeline following the rules described in *Table 9*.
- The HRD supporting Genomic Integrity Index (GII), BRCA, HRR and CCNE1 status. By default, only the GII and BRCA status are selected to be reported together with HRD.

To edit the final HRD status, click on “edit” and select the status value. To review or edit any of the HRD supporting status es, click “view” (Figure 3).

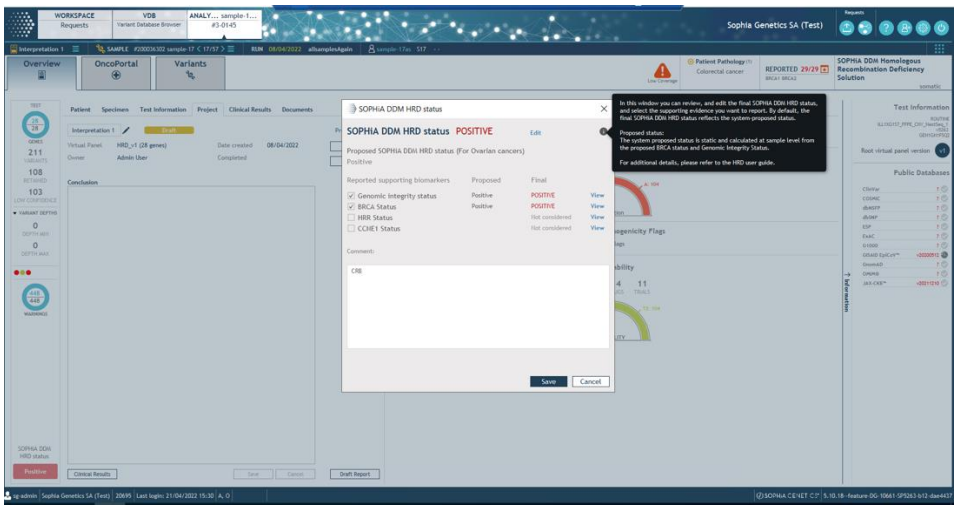


Figure 3. Research Use Only SOPHiA DDM™ HRD status edit/review window.

The BRCA status window (*Figure 4*) displays:

- The final BRCA status. By default, the final status is based on the proposed BRCA status following the rules described in *Table 1*.
- A proposed BRCA status computed by the pipeline which can be edited.
- The list of BRCA variants supporting the proposed status (only high confidence variants with positive, predicted positive, complex case or undetermined BRCA variant score will be prepopulated; these variants are reported if the BRCA status is selected for report). A comment supporting the final BRCA status can also be added.

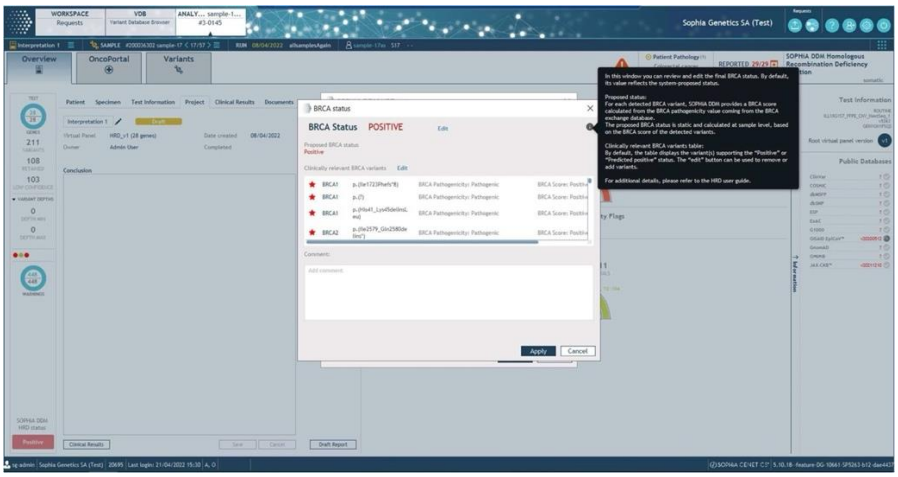


Figure 4. The BRCA Status edit/review window.

Table 1. Translation of the proposed BRCA status into the default final BRCA status.

PROPOSED BRCA STATUS	FINAL BRCA STATUS
Positive	Positive
Predicted positive	Positive
Complex case	Undetermined
Undetermined	Undetermined
Inconclusive	Undetermined
Predicted negative	Negative
Negative	Negative

The BRCA window can also display warnings to inform users of:

1. **False negative risk:** Less than 99% of the BRCA1, BRCA2 regions targeted by the panel is covered by >100x unique molecules. In this case, users should check low coverage regions to judge if the quality of the data is sufficient to confidently report a final BRCA status. User can quickly check the % of BRCA1, BRCA2 regions covered by >100x unique molecules through the dedicated quality indicator (*Figure 5*).

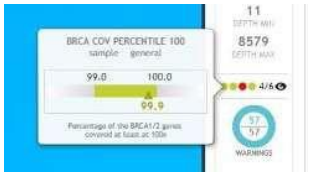


Figure 5. BRCA coverage indicator.

2. **Review clinical interpretation:** High confidence variants supporting a complex case or undetermined BRCA status were detected, requiring clinical review.

3. **Review low confidence variants:** Some relevant BRCA variants have been detected by the pipeline with a low confidence warning. In this case, users may want to check those and bring them up for BRCA interpretation.

To edit the final BRCA status, click on “edit” and select the status value.

To add or remove variants from the list of supporting BRCA variants, click on “edit”. The displayed panel (*Figure 6*) shows all detected BRCA variants and allows users to add or remove them from report. Alternatively, the variants can also be accessed in the variant table.

Note: if the users choose to restrict the interpretation using a virtual panel that excludes BRCA genes, then the BRCA status is disabled.

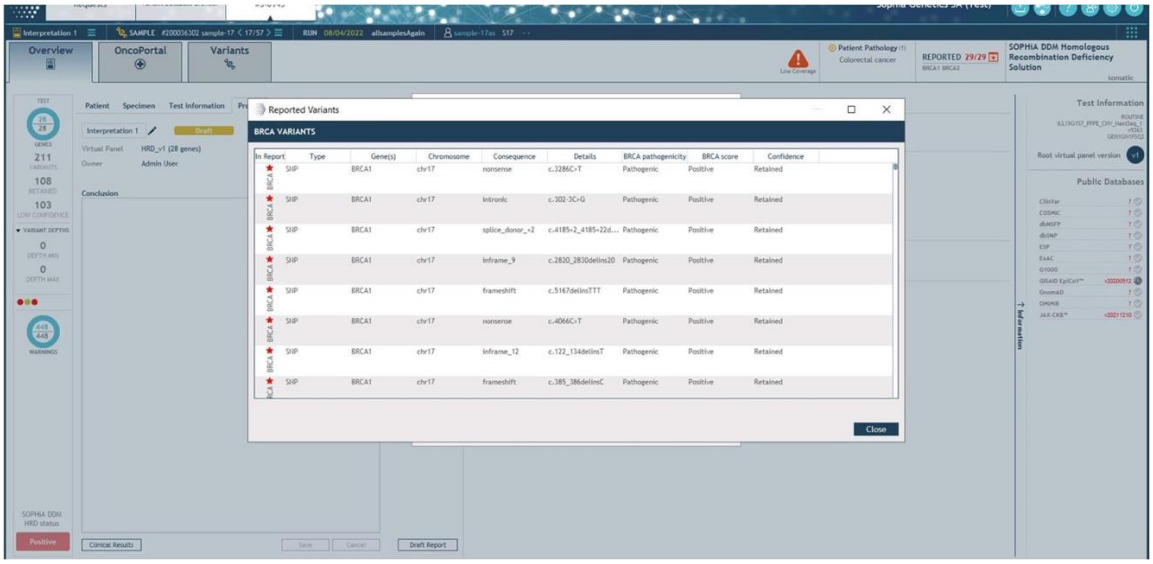


Figure 6. Overview of BRCA variants.

Note: The functionality shown in *Figure 6* of selecting BRCA variants for the report only extends to adding or removing SNPs and INDELs. To add variants of other types (e.g., CNVs) to the report, the "Comment" field in the BRCA Status edit/review window (see *Figure 4*) must be used.

3.2 Review/Edit the Genomic Integrity Status

The GI status computed in SOPHiA DDM™ Dx mode will be available here as a proposed GI status. The GIS edit/review window (*Figure 7*) displays:

- The final GI status. By default, the final status is based on the proposed GI status following the rules described in *Table 2*.
- The proposed GI status for Ovarian Cancer as computed by SOPHiA DDM™ Dx mode.
- The Genomic integrity index as computed by SOPHiA DDM™ Dx mode. The Genomic integrity index is not shown for samples that are "Rejected" or "Inconclusive".
- The Genomic integrity QA status as computed by SOPHiA DDM™ Dx mode.
- The low-pass WGS (lpWGS) coverage profile, showing the data used to compute the GI index.

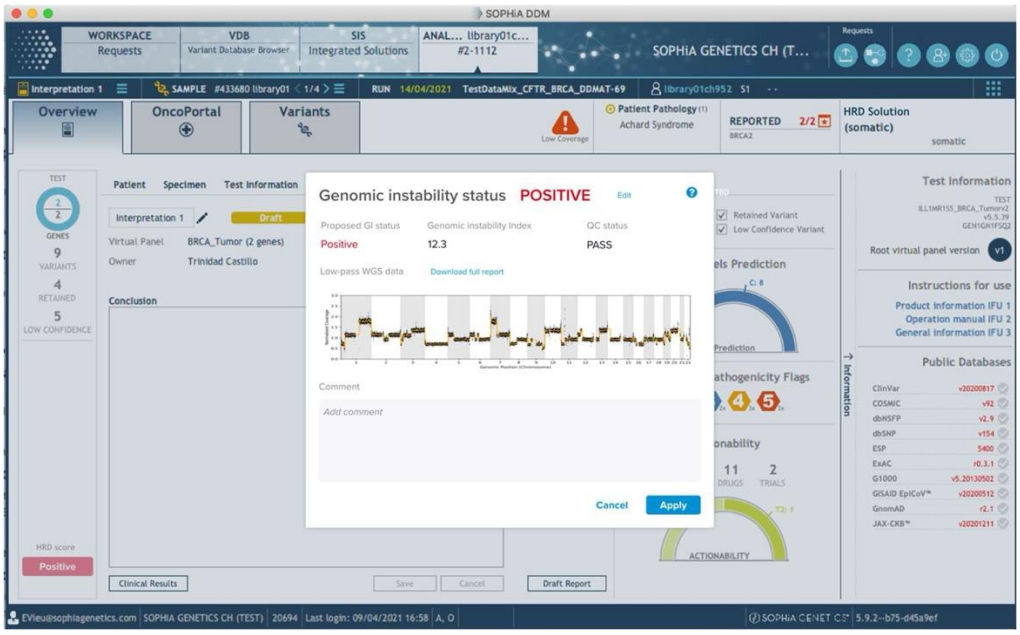


Figure 7. Overview of GIS edit/review window.

Table 2. Translation of the proposed GI status into the default final GI status.

PROPOSED GI STATUS	FINAL GI STATUS
Positive	Positive
Negative	Negative
Negative*	Negative
Inconclusive	Undetermined
Rejected	Undetermined

To edit the final GI status, click on the “edit button”.

Click on “Download full report” to access the PDF GI report where additional QC metrics are reported. It is useful to further investigate GI undetermined samples and understand why a sample has been rejected.

3.3 Define HRR Status

Using the SOPHiA DDM™ Dx HRD Solution, users can report non-BRCA variants which are considered relevant for HRD assessment.

The HRR edit/review window (*Figure 8*) displays:

- The final HRR gene status. By default, the value is set to “Undetermined”, the pipeline does not compute a proposed status.

- The list of HRR gene status supporting variants. This list contains all variants reported by the user within the scope of HRR gene status determination. By default, this list is empty as the system does not pre- populate HRR variants.
- To edit the final HRR gene status, click on the “edit” button.

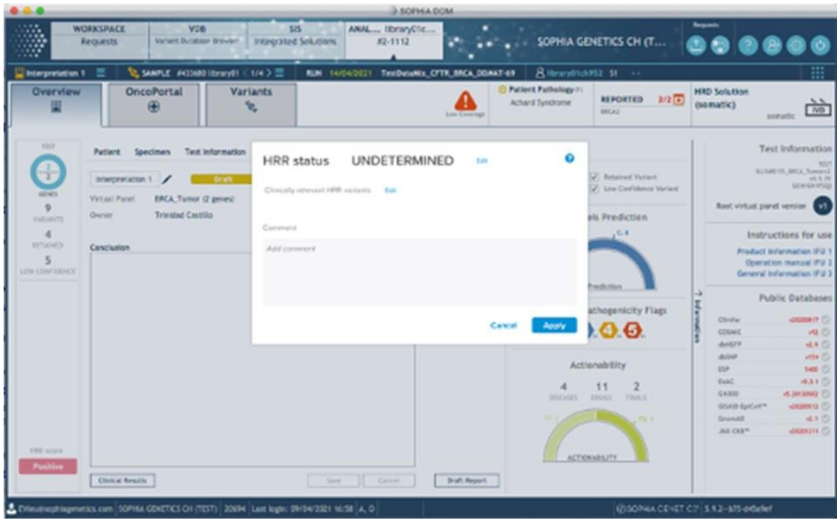


Figure 8. Overview of HRR edit/review window.

Note: A CNV detected in a non-BRCA gene may be included in the HRR status report by entering the relevant information in the “Comment” field in the HRR status window.

3.4 Define CCNE1 Gene Amplification Status

Using the SOPHiA DDM™ Dx HRD Solution, users can also report the presence of CCNE1 gene amplifications. The CCNE1 amplification status edit/review window (*Figure 9*) displays:

- The final CCNE1 status defined by the user. By default, the value is set to “Undetermined”. The bioinformatics pipeline does not compute a proposed CCNE1 gene amplification status.
- The CCNE1 effective copy number detected by the combined Gene-Level and Exon-Level CNV module
- For samples with a CN>3.25 (i.e., if a gene amplification is reported), the user can further interpret the magnitude of the CCNE1 copy number gain by visually inspecting the lpWGS CCNE1 copy number profile plot. The plot is not available for samples with a GI rejected status.

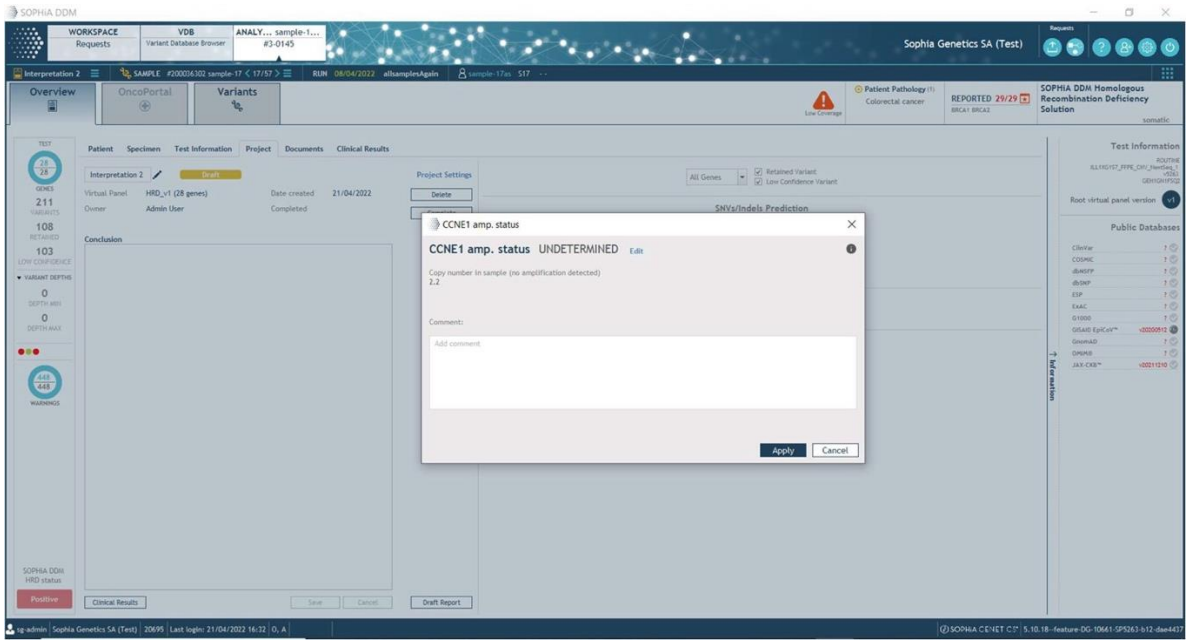


Figure 9. Overview of CCNE1 gene amplification edit/review window.

3.5 Report Variants in Scope

Using the SOPHiA DDM™ Dx HRD Solution, users can report variants as relevant for BRCA or HRR status assessment. In the variant detail view of the variant table, click on “Add to report”, then select the scope between BRCA, HRR and Other (*Figure 10*).

Variants reported in scope of BRCA and HRR will appear in the BRCA/HRR supporting variants table in the BRCA/HRR edit/review window. Variant reported as “Other” will be displayed in a separated section of the report.

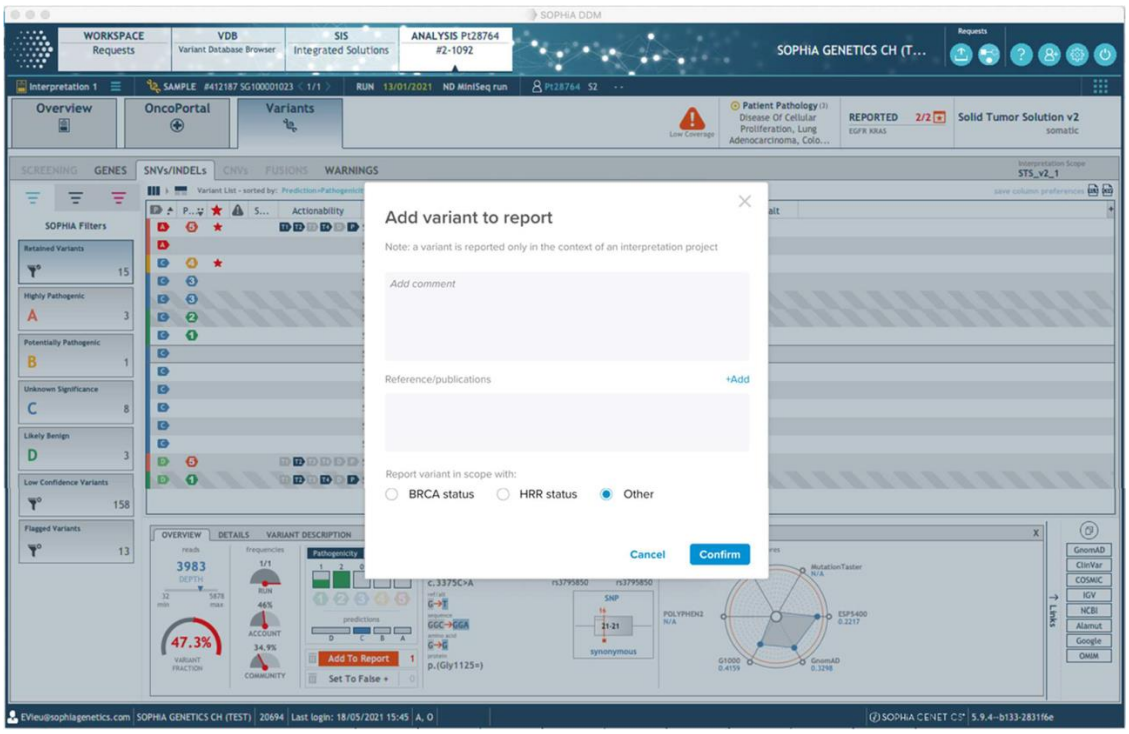


Figure 10. Reporting variant in scope with HRR or BRCA.

3.6 Generate Research Use Only SOPHiA DDM™ HRD report

To generate the Research Use Only SOPHiA DDM™ HRD report, please refer to the SOPHiA DDM™ Desktop App Operation Manual. It is to be noted that the report is for research use only. It is not intended as a primary diagnostic tool.

- The first part of the report is dedicated to the display of HRD, GI and BRCA statuses (if selected).
- The second part of the report is dedicated to HRR and CCNE1 statuses (if selected).
- The third part of the report is dedicated to any additional variants that might be reported out of scope of HRD.

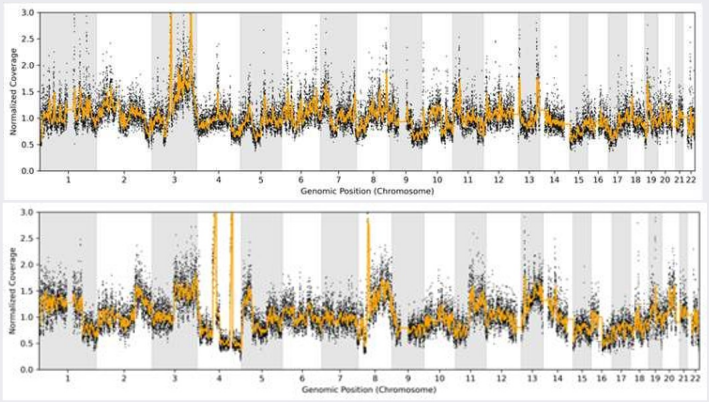
4 CONSIDERATIONS REGARDING INCONCLUSIVE RESULTS

4.1 GI Rejected status

In case of a GI rejected status, we suggest the user to consult the sample QA metrics (available in the pipeline GI report) a s well as Table 3 to identify the underlying cause.

Table 3. Recommendations in case of GI Rejection.

ROOT CAUSE	HOW TO IDENTIFY THE ROOT CAUSE	RECOMMENDATION
Insufficient coverage due to issues in balancing WGS with capture.	• Check the Sample QA section of the pipeline GI report. A sample is rejected when the number of WGS fragments is below 4M. • The Sample QA section of the pipeline GI report shows the percentage of WGS fragments. Compare this metric for all samples that were in the same capture pool. Identify if all the samples in the pool have an unusually low value (<50% of WGS fragments).	The WGS pool was not sequenced to the sufficient depth. We recommend resequencing the sample pool. If needed adjust the ratio between capture and WGS pool to obtain enough WGS reads.
Insufficient coverage due to issues balancing the samples multiplexed in the same run.	• Check the Sample QA section of the pipeline GI report. A sample is rejected when the number of WGS fragments is below 4M. • Check the Sample QA section of the pipeline GI report. Compare the number of WGS fragments (M) between samples in the same run. Check if the reads distribution in the run is balanced, or if there are outliers with very few or too many reads (3-fold).	If you observe a strong imbalance in the sequencing run: We recommend resequencing your samples, ensuring to quantify your libraries carefully and to adjust all samples to the same molarity before pooling.
Insufficient coverage due to poor yield of the sequencing run.	• Check the Sample QA section of the pipeline GI report. A sample is rejected when the number of WGS fragments is below 4M. • Go to the pipeline QA report and check the total number of reads produced by the sequencing run. Compare this with the expected number of reads (~260M reads for a NextSeq Mid Output run, ~800M reads for a NextSeq High Output run).	Repeat the sequencing run adjusting the final sequencing library loading concentration to avoid under- or over-clustering of the run.
Excess of residual noise	• Check the Sample QA section of the pipeline GI report. Residual noise >= 0.17 leads to sample rejection if purity-ploidy ratio is not detected. *Examples of lpWGS coverage profiles with excessive residual noise, in which PPR was not detected.*	High levels of noise can be a sign of low-quality input DNA, possibly resulting from poor DNA extraction To improve the library preparation efficiency, repeat the library preparation, doubling the amount of input DNA and, if possible, starting with a new DNA extraction

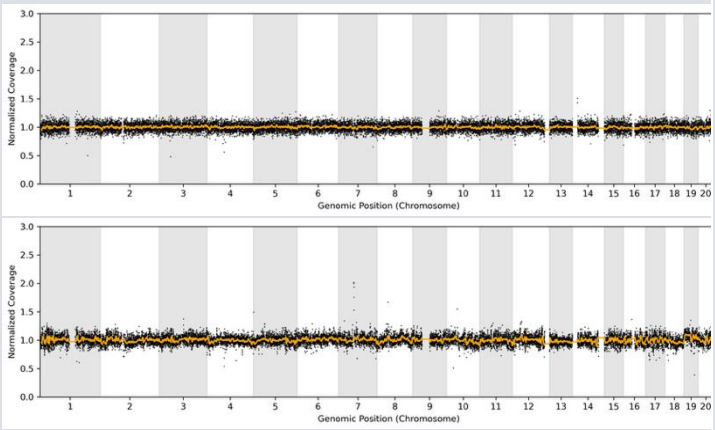
ROOT CAUSE	HOW TO IDENTIFY THE ROOT CAUSE	RECOMMENDATION
		
High proportion of coverage outliers	• Check the Sample QA section of the pipeline GI report. A sample is rejected if the proportion of coverage outliers is larger or equal to 20%. • A high proportion of coverage outliers affecting the lpWGS coverage profile may result from sub-optimal execution of the capture step or from low DNA quality. • To distinguish the two scenarios, compare the proportion of coverage outliers for all samples that were in the same capture pool. Identify if all samples in the pool have an unusually high value (>=20%).	• In case all samples in the pool are rejected due to coverage outliers we recommend repeating the entire workflow for the sample pool paying close attention to the capture instructions. • In case only a minority of the samples in the pool are rejected due to coverage outliers, we recommend repeating the entire workflow only for the rejected samples, doubling the amount of input DNA.

4.2 GI Inconclusive status

In case of a GI inconclusive status, we suggest the user to consult the sample QA metrics (available in the pipeline GI report) as well as *Table 4* to identify the underlying cause.

Table 4. Recommendations in case of GI Inconclusive.

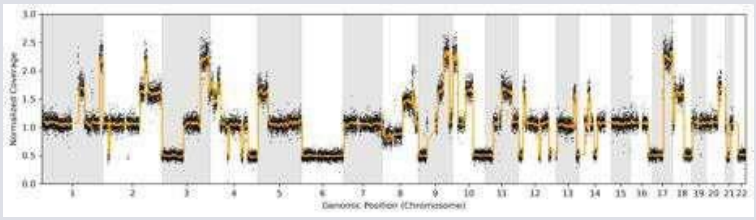
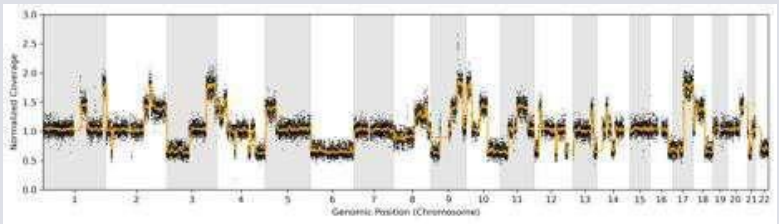
ROOT CAUSE	HOW TO IDENTIFY THE ROOT CAUSE	RECOMMENDATION
The sample does not feature large copy number aberrations	• Check the Sample QA section of the pipeline GI report. A sample is classified GI inconclusive if signal to noise ratio is insufficient (i.e. SNR smaller than 0.55). • Perform a visual inspection of the lpWGS profile in the GI report. The smoothed coverage profile (orange line) should be flat, with no sign of large CN aberrations. The insufficient SNR is due to an absence of signal which could result either from: i) the absence of CN changes in the sample or, ii) from extremely low tumor content. *Examples of lpWGS coverage profiles without large CN aberrations*	• If the sample tumor content is larger than 30%, it is likely that the sample does not feature large copy number aberrations. Repeating the experiment will not affect the results of the GI analysis.

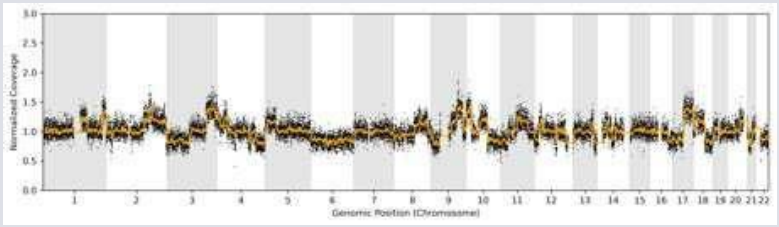
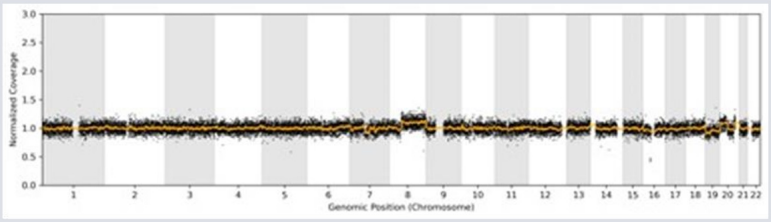
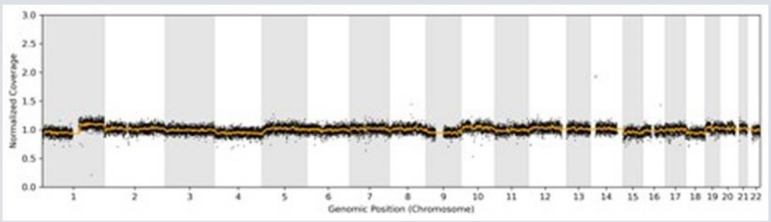
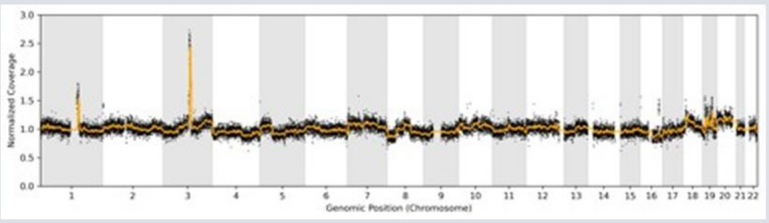
ROOT CAUSE	HOW TO IDENTIFY THE ROOT CAUSE	RECOMMENDATION
		• If there are doubts about the sample tumor content, we recommend repeating the entire wetlab workflow, starting with a sample with higher tumor content.

4.3 GI Negative* Status

GI Negative* statuses are medium confidence negative calls with increased false negative risk. GI Negative* calls result from low signal-to-noise ratio in the NGS data, possibly reflecting insufficient sample tumor content. *Table 5* illustrates how insufficient tumor content impacts SNR.

Table 5. Considerations regarding case of GI* statuses.

ROOT CAUSE	HOW TO IDENTIFY THE ROOT CAUSE	RECOMMENDATION
Insufficient tumor content	• Verify that sample tumor content estimated before processing the DNA sample is larger than 30%. • Check the GI report and confirm that the PPR was either lower than 0.1 or not detected. • Note that GI analysis does not perform tumor content estimation. *Illustration of lpWGS profile obtained by decreasing sample tumor content. The magnitude of the coverage changes between segments decreases, with decreasing tumor content.* Tumor Content=100%  Tumor Content=66%  Tumor Content=33%	If there are doubts about the sample tumor content, we recommend repeating the entire wetlab workflow, starting with a sample with higher tumor content.

ROOT CAUSE	HOW TO IDENTIFY THE ROOT CAUSE	RECOMMENDATION
	 *Examples of lpWGS coverage profiles for insufficient tumor content samples in which PPR was not detected.*   	

4.4 BRCA Inconclusive status and FN risk warning

Assess the severity of the FN risk by checking the % of the BRCA1/2 regions covered with >100x unique molecules. This can be done by looking at the quality indicator “BRCA Cov Percentile 100” that is showed as a traffic light in SOPHiA DDM™ (see description in the quality indicators section, as well as *Figure 5*). A good sample is expected to have a score of at least 99%.

Note: When reading the troubleshooting guidelines below, (*Table 6*) multiple root causes can apply. Make sure to read the entire guide and identify the most relevant cause.

Table 6. Recommendations in case of BRCA undetermined associated with a warning of FN risk.

ROOT CAUSE	HOW TO IDENTIFY THE ROOT CAUSE	RECOMMENDATION
Poor coverage uniformity	• Check the coverage heterogeneity (<0.01) in the pipeline QA report • Identify if the coverage uniformity is low in all samples of the capture pool or just in individual samples.	• If you observe a pool effect: The capture efficiency is low, we recommend repeating the entire batch of samples, and pay close attention to the IFU section describing the hybridization and capture procedure. • If you observed the effect in an individual sample: The library preparation efficiency and/or sample quality is low. To improve the library quality, we recommend doubling the amount of input DNA and repeating the entire workflow, starting with a new DNA extraction, if possible.
Insufficient number of fragments mapping to the target regions of the panel	• Check the Sample QA section of the pipeline GI report. Calculate the number of fragments (M) on the target regions of the panel by subtracting the number of WGS fragments from the total number of fragments. Each sample should have at least 2M fragments mapping to the target regions of the panel. • Identify if the number of fragments mapping to the target regions of the panel is low in all samples of the capture pool or just in individual samples. • Check if the reads distribution in the capture is balanced, or if there are outliers with very few or too many reads (3-fold difference).	• If you observe a pool effect: The capture pool was not sequenced to the sufficient depth, we recommend resequencing the sample pool. If needed, adjust the ratio between capture and WGS pool to obtain enough reads mapping to the target regions. • If you observed the effect in an individual sample: Repeat the entire workflow for the sample and ensure to quantify your libraries carefully before pooling and capture. • If you observe a strong imbalance in the capture pool: Ensure to quantify your libraries carefully before pooling and capture. If you know the quality of your input DNA, you can improve the reads balance by pooling similar quality samples in the same pool. *Warning: The first two scenarios only apply if the coverage uniformity of the samples was of sufficient quality.*
Poor library diversity	• Check the Mapping Statistics in the pipeline QA report to determine the duplicate fraction in the sample. PCR duplicates should be similar for all your samples.	• High percentages of PCR duplicates suggest low library preparation efficiencies. We recommend repeating the entire workflow and, if possible, by doubling the amount of input DNA.
Small library fragment size	• Check if the library size is unusually low in comparison with the other samples processed. You can obtain the average library fragment size via high-resolution capillary electrophoresis, which is used to check the library quality at the end of the library preparation workflow.	• Small library sizes of individual samples can be a sign of low- quality input DNA (assuming multichannel pipettes were used to process samples according to good laboratory practice). To improve the library preparation efficiency, we recommend doubling the amount of input DNA.

5 ANALYSIS DESCRIPTION AND PARAMETERS

5.1 Raw Data Pre-Processing

5.1.1 Preprocessing

- Collect quality metrics based on the raw fastq files.
- Truncate the fastq files to a maximum size of 2500MB.

5.1.2 Alignment

- Cut adapters and trim low-quality ends from reads (base quality below 20).
- Align reads to the hg19 reference genome in paired end mode.
- Compute alignment statistics and coverage metrics on the raw alignment files.
- Trim overhanging adapters sequences.
- Remove reads that have low mapping quality or low average base phred scores. A threshold of <30 is used in both cases.
- Local coverage at any position within the target regions is limited to 30,000x and to 10,000 outside target regions. Excessive coverage is removed following a random down sampling.
- Remove chimeric reads with hairpin loops.
- Realign soft clips.
- Assign reads to read groups based on start-end coordinates.
- Annotate low coverage regions based on a threshold of 100 molecules (read groups).
- Calculate statistics and coverage metrics on the processed alignment file.

5.2 Quality Indicators

For each analyzed sample, a panel of traffic-light-like quality indicators are displayed in SOPHiA DDM™ to inform on specific quality metrics of the sample. Each indicator is colored in green when the corresponding quality metric is within the expected range, or in red vice versa. The following indicators are displayed for each sample:

- Panel_cov_percentile_100: The percentage of the gene panel covered at >100x molecules. The expected range for this metric is between 95% and 100%
- BRCA_cov_percentile_100: The percentage of the on-target BRCA1 and BRCA2 regions covered at >100x molecules. The expected range for this metric is between 99% and 100%. Whenever this indicator fails (ie., below 99%) a FN risk warning will be triggered in the context of BRCA status analysis.

- BRCA_cov_unif: The coverage uniformity in the on-target BRCA1 and BRCA2 regions. Coverage uniformity is defined as the fraction of the genomic regions that have coverage within 5 and 1/5 of the median coverage. The expected range for this metric is between 0.9 and 1.
- Group_size: The group size is defined as the median number of reads in each read group. A high group size reflects low library conversion rate and high rate of duplications. The expected range for this metric is between 1 and 10.
- DeamScore: The deamination score is a score devised to reflect the rate of artificial deamination in a given FFPE sample. The expected range of this score is between 0 and 0.8.
- FragLength: The median DNA fragment length in a sample. The expected range for this metric is between 75 and 250.

5.3 SNVs/INDELs

The SNV/INDEL detection modules include local realignment algorithms, variant calling software that apply statistical tests to identified mismatches versus the reference genome, variant regularization functions, variant quantification functions, and variant filtering functions.

5.4 Variant Calling

- Identify variants (SNVs and indels) by selecting positions in which the signal supporting the alternative allele is significantly different from background noise.
- Perform dedicated variant calling for long duplications and long insertions that cannot be identified by pileup of reads.
- Merge variants together if they are on the same allele (phasing).
- Quantify the variant fraction considering all the haplotypes in the neighboring region.
- Unify homopolymer annotation to long anchor standards.

5.4.1 Variant Filtering

- Filter variants below the background noise level of the panel and sequencer (filter = high_background_noise).
- Filter variants with variant fraction below 4 % (filter = low_variant_fraction).
- Filter variants with high-quality read coverage below 30 (filter = low_coverage).
- Filter variants outside of the target regions (filter = off_target).
- Filter Indels in homopolymers of length equal or higher than 10 (filter = homopolymer_region).
- Calculate a score based on the fraction of C:G>T:A variants with low molecular support and apply a differentiated threshold depending on the sample specific low/high score (filter = low_molecular_support).
- Remove variants beyond the target regions with a padding of 500bp.
- Remove duplications longer than 500bp.

- Filter variants with confidence score below 0 (filter = low_quality).

Variants without any filter associated to them are considered as “high confidence” calls and are the ones used for the assessment of analytical performance. Variants labeled with any of the filters mentioned above are considered “low confidence” and are shown with the sole purpose of helping the interpretation of all the weak signals present in the bam file.

5.4.2 Variant Annotation

The annotation system computes transcript-specific annotations following HGVS coordinate normalizations and notation guidelines (c.DNA and protein notation). This module also provides functional information for the variant’s coding consequence; along with positional and contextual information such as rank and distance to of the closest exon, ref and alt codon sequence, ref and alt amino acid sequence. Transcript- (RefSeq identifiers) and gene-level (HGNC symbol, OMIM gene number) information is also provided at that stage. The annotation system then queries external databases, via genomic-coordinates matches, to retrieve variant-level information including dbSNP identifier, allele frequencies from GnomAD, 1000 genome project, ExAC, ESP5400, CG69, prediction scores from dbNSFP (SIFT, PolyPhen2, MutationTaster) and clinical significance assertions from ClinVar. The system finally annotates variants with licensed catalogs such as OMIM, CKB (actionable evidence displayed in OncoPortal) and the BRCA Exchange databases.

Note: the BRCA1 and BRCA2 variants are annotated as per “BRCA_pathogenicity”; this score is obtained by aggregating the BRCA exchange’s “Pathogenicity_expert” and “Pathogenicity_all” fields, following the set of rules detailed in *Table 7*.

Table 7. Rules followed for aggregating BRCA_Exchange information into the “BRCA_Pathogenicity” displayed in the variant table.

RULES FOLLOWED FOR AGGREGATING BRCA_EXHCANGE INFORMATION INTO THE “BRCA_PATHOGENICITY” DISPLAYED IN THE VARIANT TABLE
The BRCA_pathogenicity is assigned per variant, via classification rules consuming the "Pathogenicity_expert" and "Pathogenicity_all" attributes retrieved from BRCA exchange and applying rules according to the following precedence order:
1: Any variant annotated with 'pathogenic', 'likely pathogenic', 'risk factor', 'probable pathogenic' in **Pathogenicity_expert** gets a “BRCA_pathogenicity” as “pathogenic”.
2: Any variant annotated with 'likely benign', 'benign', 'probably not pathogenic', 'benign / little clinical significance' in **Pathogenicity_expert** gets a “BRCA_pathogenicity” as “benign”.
3: Any variant annotated with 'pathogenic', 'likely pathogenic', 'risk factor', 'probable pathogenic' in **Pathogenicity_all** gets a “BRCA_pathogenicity” as “pathogenic”
4: Any variant annotated with 'likely benign', 'benign', 'probably not pathogenic', 'benign / little clinical significance' in **Pathogenicity_all** gets a “BRCA_pathogenicity” as “benign”.
5: Any variant with conflict between rules 3 and 4 gets a “BRCA_pathogenicity” as “unclear”.
6: Any variant without any “BRCA_pathogenicity” assigned as per rules 1 to 5; and annotated with 'uncertain significance', 'no known pathogenicity', 'variant of unknown significance' in **Pathogenicity_all** gets a “BRCA_pathogenicity” as “unclear”.
Rule traceability: The “pathogenic” and “benign” values, are further prefixed either with ‘ex:’ (expert) when

RULES FOLLOWED FOR AGGREGATING BRCA_EXHCANGE INFORMATION INTO THE “BRCA_PATHOGENICITY” DISPLAYED IN THE VARIANT TABLE
they originate from priority rules 1 and 2 or with 'ag:' (aggregated) when they are generated by rules 3 and 4. As a result, the final available values for the “BRCA_pathogenicity” field are: • ex:pathogenic • ag:pathogenic • ex:benign • ag:benign • unclear • “” (in case there is no entry in BRCA exchange).

5.5 Combined Gene-Level and Exon-Level (GLEL) CNV Analysis

Copy-number variations (CNVs) are structural changes in DNA that result in variations in the number of copies of affected DNA segments. The CNV module detects copy number variations based on an analysis of coverage levels of DNA regions targeted by the gene panel. This version of the CNV module is designed for the analysis of FFPE samples.

Note: A minimum of 8 distinct samples per sequencing run (not counting possible relatives or replicates) is required for CNV detection.

The genes targeted by the solution are divided into two groups:

1. GL genes: *CCNE1*, *FGFR1*, *FGFR2*, *FGFR3*, *PIK3CA*
2. GLEL genes: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCA*, *FANCD2*, *FANCL*, *MRE11*, *NBN*, *PALB2*, *PPP2R2A*, *PTEN*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, *TP53*

For GL genes and GLEL genes, the purpose of the CNV analysis differs:

1. GL genes: CNV analysis only aims to detect whole-gene amplifications.
2. GLEL genes: CNV analysis aims to detect whole-gene gains and losses as well as intragenic gains and losses.

Appendix III in this document provides a list of target regions used for Gene-Level and Exon-Level CNV analysis.

The technical details of the GLEL module are documented in the GLEL Manual (SG-08061), which describes the module independently of the application. Table 8 provides the parameter values used for this specific application.

Table 8. Parameters of the Combined Gene-Level and Exon-Level CNV module

TAG	SCOPE	NAME	DESCRIPTION	VALUE
QA1	QA	GLEL coverage threshold	Samples whose average number of fragments in genomic regions is lower than the threshold will be rejected.	30
QA2	QA	GL residual noise threshold	Gene-level CNV analysis residual noise threshold.Samples whose corresponding exceeds this threshold will be rejected.	0.25
QA3	QA	GLEL gene residual noise threshold	Gene-level and exon-level CNV analysis gene residual noise threshold. Genes whose corresponding values exceeds this threshold will have their CNV calls rejected.	0.15

TAG	SCOPE	NAME	DESCRIPTION	VALUE
QA4	QA	GLEL sample residual noise threshold	Gene-level and exon-level CNV analysis sample residual noise threshold. Samples whose corresponding values exceed this threshold will be rejected.	Not applied
Th1	GL CNV calling	GL gain threshold	Gene-level coverage signal gain threshold. Genes whose coverage signal is equal to or above the threshold will be annotated as Gain	3.25
Th2	GL CNV calling	GL suspected loss threshold	Gene-level coverage signal suspected loss threshold. Genes whose coverage signal equal to or below the threshold will be annotated as Suspected loss	1.2
Th3	GL CNV calling	GL loss threshold	Gene-level coverage signal loss threshold. Genes whose coverage signal is equal to or below the threshold will be annotated as Loss.	0.9

5.6 lpWGS CCNE1 Gene Amplification Plot

The copy number levels reported by the CNV module quantify the copy number in the DNA sample (effective CN) and not the absolute copy number of the tumoral DNA present in the sample. The lpWGS CCNE1 amplification plots are designed to help the users estimate the absolute copy number of the tumoral DNA present in the sample, upon visual inspection (see *Figure 11* and *Figure 12*).

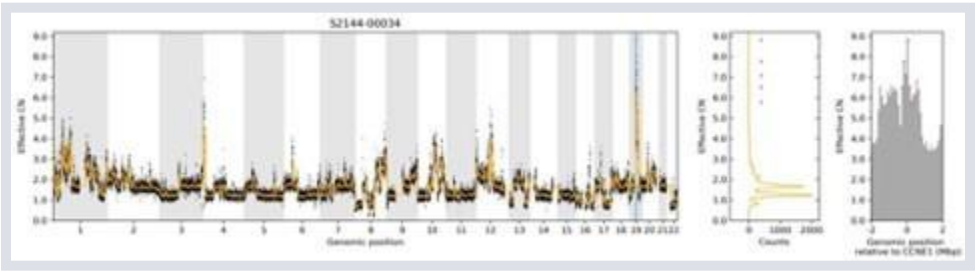


Figure 11. Example of CCNE1 amplification plot with a strong amplification.

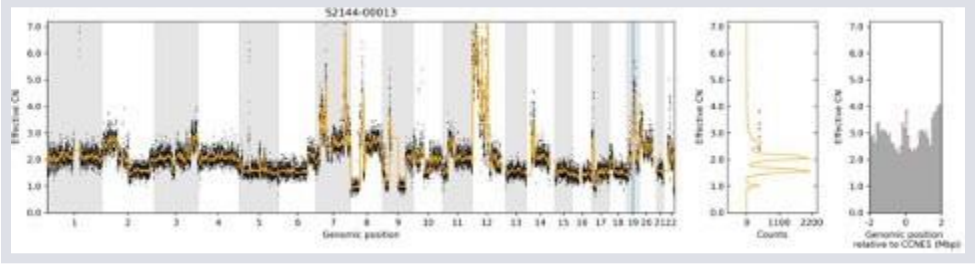


Figure 12. Example of CCNE1 amplification plot with a weak copy number gain.

The left panel shows the lpWGS coverage profile after normalization (black: raw data at 100kb resolution, orange: smoothed version of raw data), with the vertical blue line showing the genomic position of CCNE1.

The middle panel shows: i) Orange: the histogram of the smoothed lpWGS coverage profile shown in the left panel; ii) Red dots: the value of the normalized lpWGS coverage profile measured around the CCNE1 gene (±300Kbp of CCNE1 genomic position). Distinct peaks in the histogram correspond to distinct copy number levels present in the tumor DNA. The position of the red dots with respect to the histogram peaks allows the user to interpret the magnitude of the CCNE1 CN gain present in the tumor DNA. In *Figure 11*, the red dots are far away from all histogram peaks, suggesting the presence of a strong copy number gain in CCNE1. In *Figure 12*, the red dots overlap with some histogram peaks, suggesting the presence of a weak copy number gain in CCNE1.

The right panel provides a zoomed-in view of the lpWGS coverage profile after normalization (same data as in left panel) around the CCNE1 genomic location (±2Mbp). The regions within ±300Kbp of CCNE1 are highlighted by red dots (same red dots as shown in the middle panel).

5.7 Proposed Research Use Only SOPHiA DDM™ HRD Status

The proposed Research Use Only SOPHiA DDM™ HRD status is computed from the aggregation of the "Proposed GI status" and the "Proposed BRCA status". The set of rules that determine the "Proposed Research Use Only SOPHiA DDM™ HRD status", represented in the table cells, are described in *Table 9*, where the "Proposed GI status" is represented along the input row and the "Proposed BRCA status" is represented along the input column.

HRD negativity is constrained by the type of genomic aberrations that are covered by the product. See limitations of proposed BRCA status determination.

Table 9. Proposed Research Use Only SOPHiA DDM™ HRD Status Computation

Proposed GI Statuses	Proposed BRCA Status						
	Positive	Predicted positive	Complex case	Undetermined	Predicted negative	Negative	Inconclusive
Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Inconclusive	Positive	Positive	Undetermined	Undetermined	Undetermined	Undetermined	Undetermined
Rejected	Positive	Positive	Undetermined	Undetermined	Undetermined	Undetermined	Undetermined
Negative*	Positive	Positive	Undetermined				Undetermined
Negative	Positive	Positive	Undetermined				Undetermined

5.8 Proposed BRCA status

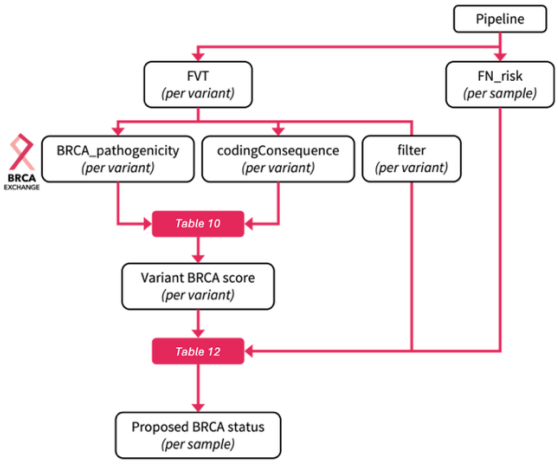
The "Proposed BRCA status" exposes the user to state-of-the-art clinical knowledge for BRCA1/2 variants, while transparently conveying uncertainty in the variant detection and calling. The Proposed BRCA status thus combines clinical knowledge and variant detection metrics gathered at the variant and sample levels.

The system proceeds sequentially by:

1. Establishing the functional impact and clinical relevance of each BRCA1/2 variant detected in the sample
2. Establishing the functional status of BRCA1/2, at the sample level, via a "Proposed BRCA status"

The present section exposes the data flow, rules and intermediate steps involved in establishing the "Proposed BRCA status".

Note: The BRCA status computation only considers SNPs and INDELs.



The analysis starts with the Full Variant Table (columns "BRCA_pathogenicity" and "codingConsequence"). The system establishes the functional impact (i.e., coding consequence) and clinical relevance (i.e., BRCA pathogenicity) of each variant detected in the sample. As a result, each BRCA variant gets assigned a "variant BRCA score" as per rules detailed in *Table 10* (with nomenclature and conventions listed in *Table 11*). Those rules classify each BRCA1/2 variant into:

- Positive: variant known as pathogenic as per clinical knowledge
- Predicted positive: variant with coding consequence predictive of loss-of-function
- Complex case: VUS with coding consequence requiring further inspection by end user
- Predicted Negative: variant with coding consequence predictive of no functional alteration
- Negative: variant known as benign as per clinical knowledge
- Undetermined: otherwise.

The system reports an "NA" category in case of absence of detected variant in BRCA.

Table 10. Rules used to establish the variant BRCA score.

Coding consequence	BRCA pathogenicity flags			
	ex:pathogenic OR ag:pathogenic	ex:benign OR ag:benign	unclear	NA
3'UTR	Positive	Negative	Undetermined	Predicted negative
5'UTR	Positive	Negative	Undetermined	Predicted negative
intronic	Positive	Negative	Undetermined	Predicted negative
synonymous	Positive	Negative	Undetermined	Predicted negative
splice_*	Positive	Negative	Complex case	Complex case
inframe*	Positive	Negative	Complex case	Complex case
missense	Positive	Negative	Undetermined	Undetermined
no_stop	Positive	Negative	Undetermined	Undetermined
frameshift_ 5'	Positive	Negative	Predicted positive	Predicted positive
frameshift_ 3'	Positive	Negative	Undetermined	Undetermined
nonsense_5'	Positive	Negative	Predicted positive	Predicted positive
nonsense_3'	Positive	Negative	Undetermined	Undetermined
no variant detected for BRCA 1/2	NA			

Table 11. Nomenclature and conventions.

TERM	DESCRIPTION
AA_position	Amino acid position of the variant along the BRCA1_refTranscript or BRCA2_refTranscript reference.
BRCA1_refTranscript	NM_007294.3
BRCA2_refTranscript	NM_000059.3
AA_threshold_BRCA1	AA_threshold_BRCA1 = most 3' AA_position of pathogenic variants as per the BRCAexchange catalog (version in production). Given that the most 3' pathogenic variant for BRCA1 according to BRCA_Exchange is p.(Ala1823_*1864del), this places AA_threshold_BRCA1 value that is aminoacid 1863, which corresponds to the full length of the protein.
AA_threshold_BRCA2	AA_cutoff = 3326 (AA coordinates), as per Mazoyer S et al., Nature Genetics 1996, 14:253-254. This is equivalent to genomic position hg19:13:32972627
codingConsequence	As per codingConsequence column of the Full Variant Table file produced by the annotation system.
BRCA_pathogenicity flags	As per BRCA_pathogenicity column of the Full Variant Table file produced by the annotation system. Pathogenicity assertions provided per variant, as retrieved from BRCA exchange after label recasting and error checking exposed in the annotation sections.
splice_*	any codingConsequence matching with the label "splice"
inframe*	any codingConsequence matching with the label "inframe"
frameshift_5'	BRCA1 : codingConsequence is "frameshift" and AA_position <= AA_threshold_BRCA1
	BRCA2 : codingConsequence IS "frameshift" AND AA_position <= AA_threshold_BRCA2
frameshift_3'	BRCA1 : codingConsequence IS "frameshift" AND AA_position > AA_threshold_BRCA1
	BRCA2 : codingConsequence IS "frameshift" AND AA_position > AA_threshold_BRCA2
nonsense_5'	BRCA1 : codingConsequence IS "nonsense" AND AA_position <= AA_threshold_BRCA1
	BRCA2 : codingConsequence IS "nonsense" AND AA_position <= AA_threshold_BRCA2
nonsense_3'	BRCA1 : codingConsequence IS "nonsense" AND AA_position > AA_threshold_BRCA1
	BRCA2 : codingConsequence IS "nonsense" AND AA_position > AA_threshold_BRCA2

The next step calls the “Proposed BRCA status”, reports the set of supporting variants and emits user warnings. The rule set is detailed in *Table 12*. For that, the bioinformatics pipeline takes into consideration:

a. The variant BRCA score (established in step 1), and ranks for all BRCA variants found in a sample according to their clinical relevance: “Positive” > “Predicted positive” > “Complex case” > “Undetermined” > “Predicted Negative” > “Negative” > “NA”.

b. The uncertainty in variant detection, considering separately high- and low-confidence variant calls.

c. The presence or absence of False Negative risk (see Quality indicator “BRCA_cov_percentile_100”).

Variants gathered from high-confidence calls are used to establish the proposed BRCA status. The sample is called as either BRCA:

- Positive: score of the most relevant high-confidence variant is “Positive”.
- Predicted positive: score of the most relevant high-confidence variant is “Predicted positive”.
- Complex case: score of the most relevant high-confidence variant is “Complex case”.
- Predicted negative: score of the most relevant high-confidence variant is “Predicted negative” and there is no FN risk.
- Negative: score of all variants is “Negative” (or no variants are detected) and there is no FN risk.
- Inconclusive: score of the most relevant high-confidence variant is “Predicted negative” or “Negative” and there is a FN risk.
- Undetermined: none of the previous cases. Is a result of insufficient clinical knowledge regarding the reported BRCA1/2 variants (BRCA_Pathogenicity is “unclear”).

The warnings signal three possible situations to the user:

a. “Review low-confidence variants with relevant BRCA score”: One or more low-confidence variants with a relevant BRCA score have been detected.

b. “Review clinical interpretation”: the most relevant evidence found is a “Complex case” or “Undetermined” high-confidence variant.

c. “False negative risk”: no relevant evidence is found, but a False-Negative risk cannot be excluded for the sample.

The obtained “proposed BRCA status”, the list of supporting evidence and the warnings are then used to initiate the user interface.

The following set of rules are applied to aggregate *variant BRCA scores* into a sample-level *proposed BRCA status*. The *variant BRCA scores* of the obtained variants are combined into a sample-level *proposed BRCA status* according to rules that apply either to a) samples for risk of False- Negatives has not been identified (i.e. FN_risk is PASS) or b) samples with False-negatives risk (i.e. FN_risk is FAIL). The table is formatted to expose rule inputs as rows (*BRCA score* of most clinically relevant variant in the high confidence calls) and columns (*BRCA score* of most clinically relevant variant in low confidence calls). Values in the table represent sample-level proposed BRCA status. Finally, the rule system emits a series of user warnings, listed at the bottom of *Table 12*.

Table 12. Proposed BRCA status aggregation rules

BRCA score of the most relevant variant called with high confidence	BRCA score of the most relevant BRCA variant called with low confidence						
	Positive	Predicted Positive	Complex case	Undetermined	Predicted Negative	Negative	NA
a) Samples for risk of False-Negatives has not been identified (i.e. FN_risk is PASS)							
Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Predicted positive	Predicted positive	Predicted positive	Predicted positive	Predicted positive	Predicted positive	Predicted positive	Predicted positive
Complex case	Complex case[1,2,3]	Complex case[1,2,3]	Complex case[2,3]	Complex case[2,3]	Complex case[2,3]	Complex case[2,3]	Complex case[2,3]
Undetermined	Undetermined [1,2,3]	Undetermined [1,2,3]	Undetermined [1,2,3]	Undetermined [2,3]	Undetermined [2,3]	Undetermined [2,3]	Undetermined [2,3]
Predicted negative	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]
Negative	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]
NA	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]	Inconclusive [1,3]
b) Samples with False-negatives risk (i.e. FN_risk is FAIL)							
Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Predicted positive	Predicted positive	Predicted positive	Predicted positive	Predicted positive	Predicted positive	Predicted positive	Predicted positive
Complex case	Complex case [1,2]	Complex case [1,2]	Complex case [2]	Complex case [2]	Complex case [2]	Complex case [2]	Complex case [2]
Undetermined	Undetermined[1,2]	Undetermined[1,2]	Undetermined[1,2]	Undetermined[2]	Undetermined[2]	Undetermined[2]	Undetermined[2]
Predicted negative	Predicted negative[1]	Predicted negative[1]	Predicted negative[1]	Predicted negative[1]	Predicted negative	Predicted negative	Predicted negative
Negative	Negative[1]	Negative[1]	Negative[1]	Negative[1]	Negative	Negative	Negative
NA	Negative[1]	Negative[1]	Negative[1]	Negative[1]	Negative	Negative	Negative

User warnings: [1]Review low-confidence variants with relevant *BRCA score*, [2]Review clinical interpretation, [3]False negative risk

5.9 Proposed Genomic Integrity Status

The proposed GI status is computed by SOPHiA DDM™ Dx mode. Detailed explanations regarding the GI status calculation are provided in the SOPHiA DDM™ Dx HRD Solution IFU.

6 DESCRIPTION OF PIPELINE DELIVERABLES

6.1 Location Of Results

Output files from SOPHiA DDM™ Desktop App can be found at the run level or sample level.

At the run level, a group of files can be downloaded: all files (including fastq), all vcf, all aligned bam files, aggregated full variant table, aggregated exon coverage and final variant reports.

The summary pipeline QA report can be downloaded here, as well as other summary reports (e.g., CNV summary report).

At the sample level, sample-specific files can be downloaded: fastq, aligned bam, target region coverage statistics, flagged regions, full variant table, sample-specific pipeline QA report and run-level summary reports (QA report, CNV summary report).

Examples are shown in *Figure 13* and in *Figure 14*:

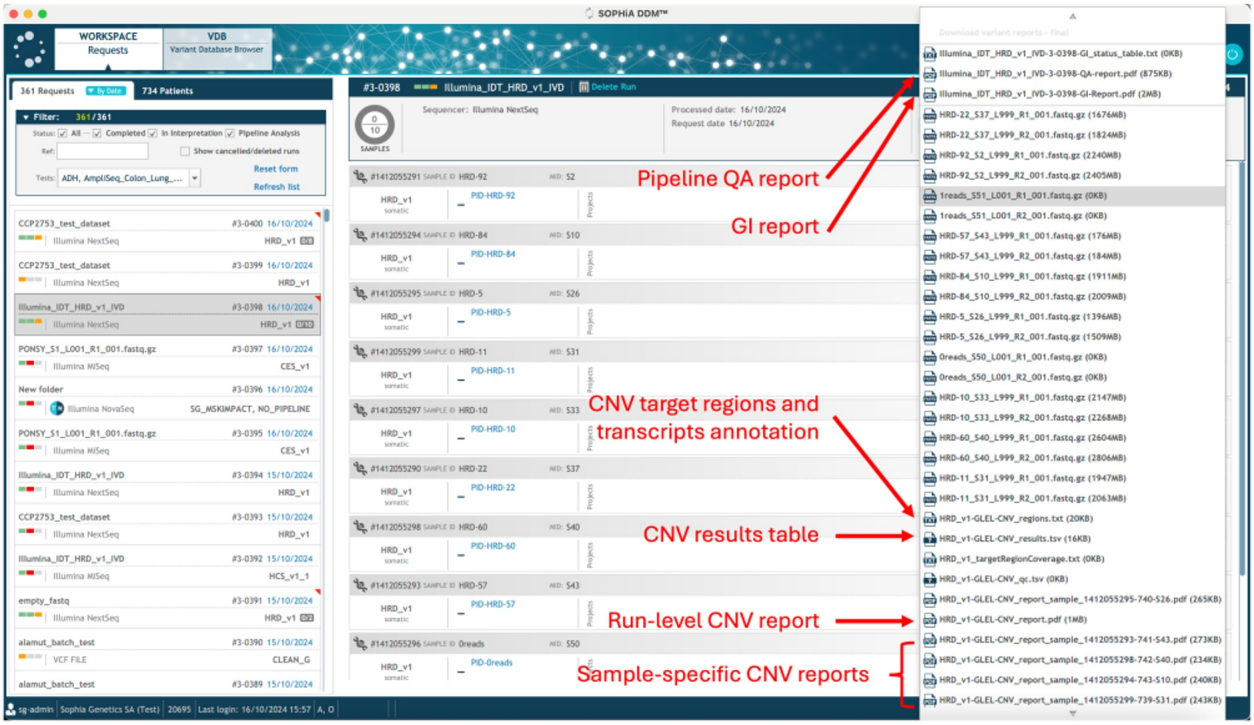


Figure 13. Downloadable run-level output files available on SOPHiA DDM™ Desktop App.

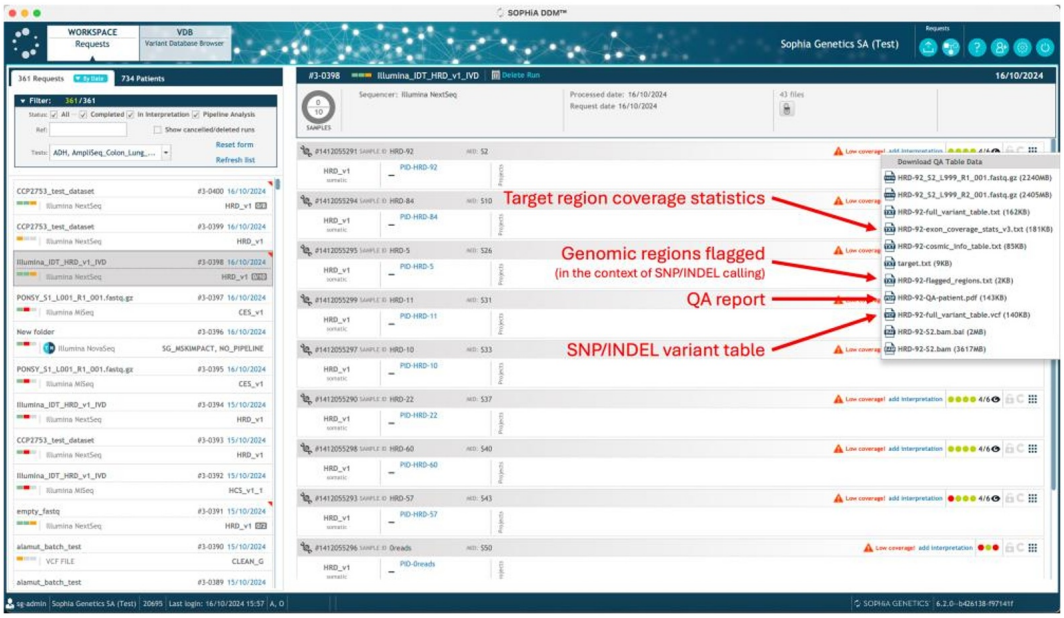


Figure 14. Downloadable sample-level output files available on SOPHiA DDM™ Desktop App.

6.2 File Composition

- Fastq.gz files: The input fastq files zipped.
- Bam and Bai files: The alignment file per sample and its index.
- Full_variant_table.txt/vcf: The detected variants in text and vcf format.
- Cosmic_info_table.txt: A text file containing information from the cosmic database.
- Exon_coverage_stats_v3.txt: A text file containing the coverage at the exon level.
- QA-report: The pipeline QA report in pdf format at the sample and run level.
- GI-report.pdf: The report for the genome integrity analysis in pdf format.
- GI_status_table.txt: A text file summarizing the GI results.
- HRD_v1-GLEL-CNV_report.pdf: CNV report including results for all samples in the run.
- HRD_v1-GLEL-CNV_sample_<SAMPLE_ID>.pdf: CNV reports including results for individual samples.
- HRD_v1-GLEL-CNV_results.tsv: Table with CNV results for all samples in the run.
- HRD_v1-GLEL-CNV_qc.tsv: Table with CNV QA results for all samples in the run.
- HRD_v1-GLEL-CNV_regions.txt: Table listing genomic regions in scope of CNV analysis with associated transcript annotation.

6.3 Results Visualization

For information related to access to analysis results (Variant display, QA report), please refer to the SOPHiA DDM™ Desktop App Operation Manual. Note that as certain modules are only active for selected pipelines, sections of the platform will be greyed out or bolded.

For example, the “SNVs and INDELs” tab is activated, while the “Fusions” and “CNV” tabs are inactive in this pipeline.

Note: CNV results are only made available via the downloadable files.

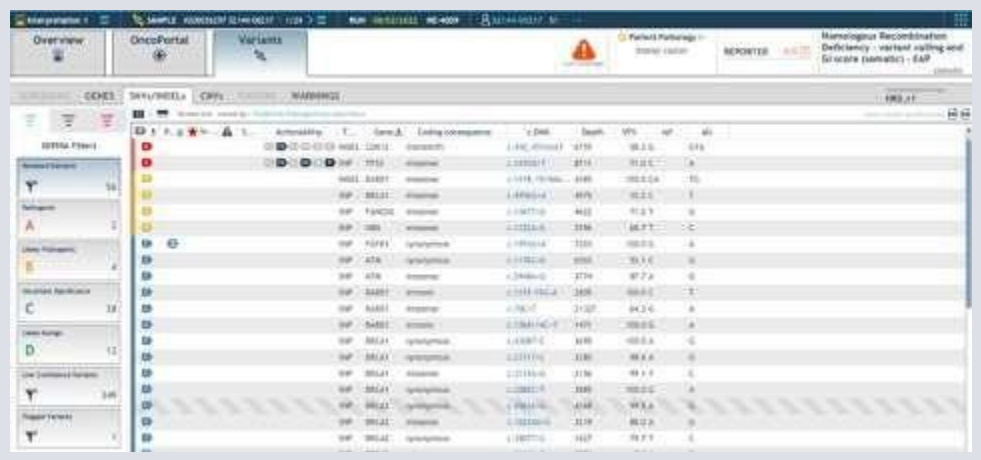


Figure 15. The Results Visualization panel on SOPHiA DDM™ Desktop App.

Quality Indicators: For information on how to interpret the color codes of the quality indicator dots, please refer the SOPHiA DDM™ Desktop App Operation Manual.

7 WARNINGS, LIMITATIONS AND PRECAUTIONS

7.1 Warnings

- For detailed instructions on the IVD component of this product, refer to the Instructions for Use (IFU) for SOPHiA DDM Dx HRD and/or the SOPHiA DDM™ Dx mode User Manual.
- The product components outlined in this document are for research use only and not for use in diagnostic procedures.
- The research use only functions outlined in this document have not been fully validated within the scope of the IVD product. Using the research use only functions of this product is out of the product scope of SOPHiA DDM Dx HRD Solution.
- All reference to HRD status in this document is solely for Research Use Only purposes.

7.2 Limitations and precautions

- The product is designed to process the volume of data produced by a single Illumina® NextSeq® 500/550 run (MidOutput and HighOutput flowcells). The maximal request size cannot exceed 200 Gb. The maximal file size per sample cannot exceed 50Gb. The pipeline performs random read subsampling to all samples exceeding 5 Gb of compressed fastq files.
- Even if sample multiplexing recommendations are followed, the total number of reads may be insufficient to provide conclusive results for various reasons, including poor sample quality, poor NGS data quality, significant uneven read allocation between WGS and captured libraries, significant uneven read allocation between samples multiplexed in the same run.
- The product does not detect nor report sample cross contamination events.

7.3 SNPs / INDELs

- SNVs and INDELs reported may include somatic (not inherited) or germline (inherited) variants; however, the algorithm does not distinguish between germline and somatic variants.
- SNVs and INDELs with VAF<4% (assay cutoff) are filtered and considered as low confidence.
- SNVs/INDELs in homopolymers of length 10 or higher cannot be called confidently as their detection is confounded by high background noise for homopolymers of this length. When detected, they are reported as low confidence.
- For a reliable variant calling performance, a coverage of at least 100x unique molecules is required. Low coverage regions will increase the risk of False Negatives significantly and are reported with warnings in the SOPHiA DDM™ Desktop App.
- The variant calling module was developed and verified to call SNVs and INDELs up to 50bp in length. INDELs >50bp can be detected, however the performance of the module depends on multiple factors, including the nature of the variant, the genomic context and the quality of the sequencing data.

- Genotypes resulting from duplications, insertions or complex patterns of INDELs (e.g., multiple insertions and deletions in the same regions) that are not fully covered by complete reads (including the reference sequence that is duplicated) might be reported inaccurately or result in false negatives.
- Insertions longer than read length have a risk of overestimated variant allele frequency.
- Variant detection has been optimized only within genomic regions defined as “target regions”. In nearby off-target regions any additional variant detected by the module will be reported as low confidence. Variants more than 500 bp away from target regions are not reported. Deletions or insertions with any breakpoint outside of the target region, may not be detected.
- In complex genomic regions, read alignment versus possible genotypes may result in split calls, where two or more equivalent representations of the same variant are reported as distinct variants, diluting the variant allele frequency between them. This could result in variant fraction underestimations or in false negatives.
- Variant patterns leading to alleles which are very different from the reference genome (e.g., multiple SNVs or multiple-nucleotide variants (MNVs) or INDELs) may lower the DNA capture probe affinity for the concerned DNA regions. Such DNA fragments may not be efficiently captured, possibly resulting in false negatives or variant allele frequency underestimation.
- Genomic regions of interest with low-complexity nucleotide sequences, nucleotide bias, repeats of any length (e.g. mono-, di- or trinucleotide repeats, transposable elements, Alu repeats, etc.) are at higher risk of variant calling artefacts including False Positive and False Negative variant calls.
- Regions with high sequence homology can cause uncertainty of mapping and risk of missing or calling wrong variants.
- Complex Delins may be reported as multiple variants in case it is represented in the alignment as multiple smaller variants that are separated by more than 2 nucleotides.

7.4 Copy Number Variations (CNVs)

- The CNV module has been tested exclusively on data from Ovarian Cancer FFPE DNA samples.
- The copy number level reported by the CNV module for a genomic region of interest reflects the number of DNA copies in the sample relative to the average number of copies in other regions targeted by the panel. Thus, the reported copy number level reflects the copy number of tumor DNA in the sample, but it is affected by both sample tumor content and tumor ploidy.
- The copy number levels reported by the CNV module are normalized so that the average copy number across the panel is equal to 2. Therefore, a copy number of 2 corresponds to the ploidy of the sample. However, this normalization approach may not accurately reflect the true copy number in highly aneuploid samples.
- The ability to detect CNVs depends on the sample tumor content and tumor ploidy. CNVs may be missed in samples with low tumor content and/or low tumor ploidy.
- The ability to detect CNVs depends on the magnitude of the event. For example, the ability to detect a copy number change from 2 to 3 (gain of an extra copy) is lower compared to detecting a change from 2 to 1 (heterozygous deletion).
- The ability to detect an intragenic CNV within a gene of interest depends on:
    i. The size of the CNV (i.e., the number of genomic regions affected by the CNV)

ii. The size of the gene (i.e., the total number of genomic regions considered by the CNV module for the gene of interest). Small intragenic CNVs occurring within small genes may be missed or may cause the gene of interest to be excluded from the analysis.

- The CNV module performs coverage signal normalization across the samples being analyzed. When a significant portion of samples share the same CNV event in a genomic region of interest, the signal measured in that genomic region may be biased during normalization, potentially causing false positives and/or false negatives.
- The CNV module is only applied to requests including at least 8 samples. If the total number of non-rejected samples in the batch is below 4, the whole request is rejected from the CNV analysis.
- The CNV module only considers genomic regions targeted by the HRD_v1 panel, with some genomic regions excluded (see Appendix III).

7.5 Proposed Genomic Integrity status

- Please refer to the Instructions for Use (IFU) for SOPHiA DDM™ Dx HRD Solution

7.5.1 Proposed BRCA status

- The proposed BRCA status is computed based on the SNVs and INDELs reported by the pipeline with high confidence. SNVs and INDELs reported by the pipeline with low confidence, as well as other types of genomic aberrations, are not considered for proposed BRCA status calculation. A negative proposed BRCA status does not exclude the presence of the following types of events in the sample:
    - Copy number gains or losses affecting one or multiple exons of BRCA1 and BRCA2
    - Mobile element insertions
    - Promoter methylations
    - Other structural variations
    - SNVs and INDELs under the reporting threshold of 4% variant allele frequency
    - SNVs and INDELs reported with low confidence
- The proposed BRCA status relies on data provided by the BRCA Exchange database, which will be updated asynchronously to ensure appropriate quality control of data importation. As a result, the BRCA Exchange annotations in SOPHiA DDM™ may differ from those seen in the web portal of this database.
- Inability to cover at least 99% of the targeted BRCA1 and BRCA2 regions may result in an inconclusive proposed BRCA status.
- Intronic, synonymous and UTR variants not listed in the BRCA Exchange database are assumed to be benign (predicted negative) and are therefore not considered sufficient to emit a positive, predicted positive, complex case or undetermined proposed BRCA status.

7.5.2 Proposed Research Use Only SOPHiA DDM™ HRD status

- The proposed SOPHiA DDM™ HRD status is computed by combining the proposed BRCA status and the GI status. All limitations applying to proposed BRCA status and GI status also apply to the SOPHiA DDM™ HRD status.
- The proposed SOPHiA DDM™ HRD status and GI status only apply to Ovarian Cancer samples.

8 SUPPORT

In case of difficulty using SOPHiA DDM™ please contact our support line by telephone at +41 21 694 10 60 or e-mail support@sophiagenetics.com. Please visit www.sophiagenetics.com for further details. Support may also be reached via web request from the Dashboard screen in the Support section of SOPHiA DDM™.

Any serious incident occurring in relation to the device should be promptly reported to SOPHiA GENETICS and the competent authorities of the member state, where the user and/ or the patient is established.

9 SYMBOLS

Symbol	Title
	Consult instructions for use
	Catalog number
	Batch code (Lot Number)
	Caution
	Manufacturer
	Temperature Limit
	Use-by date
	RESEARCH USE ONLY
	Contains sufficient for <n> tests
	Refer to - Warnings and Precautions.
	Refer to - Warnings and Precautions.
	Refer to - Warnings and Precautions.
	Refer to - Warnings and Precautions.
	Refer to - Warnings and Precautions.
	Box 1
	Box 2

10 APPENDIX I. SNP/INDEL "TARGET REGIONS" (SUMMARY BY GENE)

GENE	BASES COVERED BY HRD_V1	TOTAL BASES ON CODING REGION	% OF GENE COVERED BY HRD_V1
AKT1	387	4329	8.94
ATM	9171	9171	100
BARD1	7311	7311	100
BRCA1	21078	21078	100
BRCA2	10257	10257	100
BRIP1	3750	3750	100
CCNE1	4605	4605	100
CDK12	8919	8919	100
CHEK1	8250	8250	100
CHEK2	5907	5907	100
ESR1	856	11664	7.34
FANCA	9537	9537	100
FANCD2	13128	13128	100
FANCL	2271	2271	100
FGFR1	5523	21459	25.7
FGFR2	4909	26337	18.6
FGFR3	1531	6933	22.1
MRE11	6294	6294	100
NBN	4284	4284	100
PALB2	3561	3561	100
PIK3CA	1147	3207	35.8
PPP2R2 A	2718	2718	100
PTEN	3564	3564	100
RAD51B	12525	12525	100
RAD51C	1539	1539	100
RAD51D	2685	2685	100
RAD54L	4488	4488	100
TP53	13338	13338	100

11 APPENDIX II. SNP/INDEL “TARGET REGIONS” (GENOMIC COORDINATES)

Chromosome	Start	End
1	46714052	46714105
1	46714158	46714295
1	46715646	46715816
1	46724332	46724443
1	46725610	46725796
1	46726188	46726308
1	46726373	46726712
1	46726907	46727082
1	46733105	46733306
1	46736305	46736482
1	46738112	46738237
1	46738318	46738499
1	46739001	46739162
1	46739270	46739444
1	46739784	46739913
1	46740184	46740414
1	46743463	46743677
1	46743718	46743979
2	58386874	58386960
2	58387217	58387339
2	58388631	58388798
2	58389975	58390107
2	58390138	58390234
2	58390543	58390677
2	58392833	58393034
2	58425688	58425822
2	58431239	58431386
2	58449051	58449202

Chromosome	Start	End
2	58453837	58453944
2	58456923	58457034
2	58459163	58459272
2	58468327	58468473
2	215593374	215593757
2	215595109	215595257
2	215609765	215609908
2	215610420	215610603
2	215617145	215617304
2	215632180	215632403
2	215633930	215634061
2	215645258	215646258
2	215656995	215657194
2	215661759	215661866
2	215674110	215674318
3	10070337	10070410
3	10074511	10074661
3	10076148	10076225
3	10076374	10076487
3	10076852	10076922
3	10077966	10078028
3	10080958	10081046
3	10081400	10081534
3	10083302	10083399
3	10084238	10084352
3	10084729	10084839
3	10085163	10085281
3	10085508	10085553
3	10088259	10088412
3	10089596	10089740
3	10091053	10091194
3	10094066	10094186

Chromosome	Start	End
3	10101973	10102092
3	10103830	10103900
3	10105471	10105600
3	10106035	10106118
3	10106408	10106564
3	10107073	10107183
3	10107543	10107668
3	10108888	10109006
3	10114550	10114670
3	10114932	10115051
3	10116209	10116362
3	10119760	10119886
3	10122779	10122917
3	10123025	10123153
3	10127491	10127611
3	10128813	10128953
3	10130128	10130231
3	10130507	10130639
3	10131971	10132074
3	10133860	10133941
3	10134964	10135012
3	10135968	10136052
3	10136879	10136963
3	10138005	10138161
3	10140399	10140639
3	10142867	10142951
3	178916528	178916975
3	178921322	178921587
3	178927964	178928136
3	178935988	178936132
3	178951872	178952162
4	1803552	1803762

Chromosome	Start	End
4	1806048	1806257
4	1807847	1807910
4	1808263	1808420
6	152332822	152332880
6	152415525	152415555
6	152419900	152419945
8	26149310	26149367
8	26150737	26150824
8	26151156	26151281
8	26196380	26196528
8	26211958	26212174
8	26217659	26217822
8	26218464	26218692
8	26220174	26220389
8	26221211	26221431
8	26223805	26223947
8	26227624	26227954
8	38272287	38272429
8	38274814	38274944
8	38277041	38277263
8	38287190	38287476
8	90947784	90947865
8	90949228	90949328
8	90955455	90955619
8	90958342	90958548
8	90960026	90960145
8	90965446	90965944
8	90967485	90967808
8	90970927	90971107
8	90976612	90976760
8	90982566	90982810
8	90983375	90983543

Chromosome	Start	End
8	90990422	90990576
8	90992936	90993146
8	90993577	90993776
8	90994924	90995108
8	90996727	90996814
10	89623702	89624310
10	89653777	89653871
10	89685265	89685319
10	89690798	89690851
10	89692765	89693013
10	89711870	89712021
10	89717605	89717781
10	89720646	89720880
10	89725039	89725234
10	123247495	123247637
10	123257999	123258129
10	123279483	123279693
11	94153265	94153372
11	94163051	94163177
11	94168972	94169090
11	94170317	94170426
11	94178950	94179084
11	94180359	94180629
11	94189416	94189529
11	94192548	94192772
11	94194076	94194227
11	94197253	94197430
11	94200953	94201084
11	94203611	94203833
11	94204714	94204950
11	94209429	94209594
11	94211875	94212067

Chromosome	Start	End
11	94212814	94212952
11	94219064	94219275
11	94223973	94224156
11	94225922	94225992
11	108098347	108098428
11	108098498	108098620
11	108099900	108100055
11	108106392	108106566
11	108114675	108114850
11	108115510	108115758
11	108117686	108117859
11	108119655	108119834
11	108121423	108121804
11	108122559	108122763
11	108123539	108123644
11	108124536	108124771
11	108126937	108127072
11	108128203	108128338
11	108129708	108129807
11	108137893	108138074
11	108139132	108139341
11	108141786	108141878
11	108141973	108142138
11	108143254	108143339
11	108143444	108143584
11	108150213	108150340
11	108151717	108151900
11	108153432	108153611
11	108154949	108155205
11	108158322	108158447
11	108159699	108159835
11	108160324	108160533

Chromosome	Start	End
11	108163341	108163525
11	108164035	108164209
11	108165649	108165791
11	108168009	108168114
11	108170436	108170617
11	108172370	108172521
11	108173575	108173761
11	108175397	108175584
11	108178619	108178716
11	108180882	108181047
11	108183133	108183230
11	108186545	108186643
11	108186733	108186845
11	108188095	108188253
11	108190676	108190790
11	108192023	108192152
11	108196032	108196276
11	108196780	108196957
11	108198367	108198490
11	108199743	108199970
11	108200936	108201153
11	108202166	108202289
11	108202601	108202769
11	108203484	108203632
11	108204608	108204700
11	108205691	108205841
11	108206567	108206693
11	108213944	108214103
11	108216465	108216640
11	108218001	108218097
11	108224488	108224612
11	108225533	108225606

Chromosome	Start	End
11	108235804	108235950
11	108236047	108236240
11	125495630	125495932
11	125496618	125496753
11	125497476	125497750
11	125499101	125499216
11	125499260	125499380
11	125503032	125503271
11	125505298	125505453
11	125507318	125507464
11	125513661	125513820
11	125513960	125514188
11	125514381	125514563
11	125523615	125523767
11	125525094	125525240
13	32890572	32890689
13	32893188	32893487
13	32899187	32899346
13	32900212	32900312
13	32900353	32900444
13	32900610	32900775
13	32903554	32903654
13	32905030	32905192
13	32906383	32907549
13	32910376	32915358
13	32918669	32918815
13	32920938	32921058
13	32928972	32929450
13	32930539	32930771
13	32931853	32932091
13	32936634	32936855
13	32937290	32937695

Chromosome	Start	End
13	32944513	32944719
13	32945067	32945262
13	32950781	32950953
13	32953428	32953677
13	32953861	32954075
13	32954118	32954307
13	32968800	32969095
13	32971009	32971206
13	32972273	32972932
14	68290235	68290369
14	68292155	68292319
14	68301771	68301938
14	68331694	68331881
14	68352560	68352730
14	68353712	68353946
14	68758575	68758722
14	68878115	68878269
14	68934863	68934992
14	68937214	68937275
14	68944339	68944406
14	68963815	68963882
14	69006891	69006961
14	69061176	69061345
14	69069354	69069412
14	69077697	69077989
14	69149628	69149686
14	105246415	105246563
16	23614754	23615015
16	23619159	23619358
16	23625299	23625437
16	23632657	23632824
16	23634264	23634476

Chromosome	Start	End
16	23635304	23635440
16	23637531	23637743
16	23640499	23640621
16	23640935	23641815
16	23646157	23647680
16	23649145	23649298
16	23649365	23649475
16	23652405	23652503
16	89805004	89805121
16	89805285	89805387
16	89805532	89805702
16	89805881	89805966
16	89806397	89806512
16	89807207	89807279
16	89809203	89809351
16	89811362	89811484
16	89812987	89813101
16	89813234	89813303
16	89815062	89815180
16	89816133	89816315
16	89818541	89818635
16	89824980	89825118
16	89828352	89828435
16	89831293	89831479
16	89833544	89833650
16	89836240	89836437
16	89836569	89836672
16	89836967	89837047
16	89838081	89838227
16	89839674	89839797
16	89842145	89842228
16	89845204	89845263

Chromosome	Start	End
16	89845346	89845416
16	89846272	89846370
16	89849262	89849331
16	89849410	89849515
16	89851257	89851377
16	89857806	89857949
16	89858330	89858481
16	89858874	89858960
16	89862309	89862431
16	89865482	89865492
16	89865569	89865645
16	89866008	89866051
16	89869662	89869754
16	89871683	89871805
16	89874697	89874780
16	89877110	89877215
16	89877332	89877484
16	89880923	89881026
16	89882280	89882399
16	89882940	89883028
17	7572901	7573033
17	7573894	7574058
17	7576511	7576682
17	7576827	7577180
17	7577449	7577660
17	7578114	7578579
17	7579264	7579615
17	7579664	7579746
17	7579813	7579937
17	33427946	33428080
17	33428194	33428409
17	33430247	33430368

Chromosome	Start	End
17	33430447	33430588
17	33433379	33433525
17	33433981	33434166
17	33434359	33434491
17	33443852	33444081
17	33445494	33445663
17	33446104	33446216
17	33446525	33446657
17	37618299	37619395
17	37627106	37628041
17	37646784	37647011
17	37648978	37649168
17	37650751	37650972
17	37657477	37657717
17	37665932	37666039
17	37667756	37667908
17	37671958	37672086
17	37673667	37673834
17	37676183	37676365
17	37680901	37681163
17	37682091	37682594
17	37686831	37687594
17	41197585	41197592
17	41197669	41197844
17	41199634	41199745
17	41201112	41201236
17	41203054	41203159
17	41209043	41209177
17	41215324	41215415
17	41215865	41215993
17	41219599	41219737
17	41222919	41223280

Chromosome	Start	End
17	41226322	41226563
17	41228479	41228656
17	41231325	41231441
17	41234395	41234617
17	41242935	41243074
17	41243426	41246902
17	41247837	41247964
17	41249235	41249331
17	41251766	41251922
17	41256113	41256303
17	41256859	41256998
17	41258447	41258575
17	41267717	41267821
17	41276008	41276138
17	56769979	56770174
17	56772266	56772579
17	56774028	56774245
17	56780531	56780715
17	56787194	56787376
17	56798081	56798198
17	56801375	56801486
17	56809819	56809930
17	56811453	56811608
17	59760631	59761526
17	59763171	59763551
17	59770765	59770898
17	59793286	59793449
17	59820348	59820520
17	59821767	59821977
17	59853736	59853948
17	59857596	59857787
17	59858175	59858391

Chromosome	Start	End
17	59861605	59861810
17	59870932	59871115
17	59876435	59876685
17	59878588	59878860
17	59885802	59886143
17	59924436	59924606
17	59926464	59926642
17	59934393	59934617
17	59937131	59937293
17	59938782	59938925
19	30303458	30303490
19	30303591	30303688
19	30303871	30303949
19	30308039	30308194
19	30308308	30308453
19	30311604	30311760
19	30312624	30312729
19	30312898	30313042
19	30313142	30313263
19	30313348	30313515
19	30314557	30314689
22	29083859	29083999
22	29085097	29085228
22	29089994	29090130
22	29091089	29091255
22	29091672	29091886
22	29092863	29093000
22	29095800	29095950
22	29099467	29099579
22	29105968	29106072
22	29107871	29108030
22	29115357	29115498

Chromosome	Start	End
22	29120939	29121137
22	29121205	29121380
22	29126382	29126561
22	29130365	29130734

12 APPENDIX III. GENOMIC COORDINATES OF THE CNV “TARGET REGIONS”

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
RAD54L	ex1-2	1	46713968	46714381	NM_003579	3	ex1-2	TRUE	TRUE
RAD54L	ex3	1	46715575	46715994	NM_003579	3	ex3	TRUE	TRUE
RAD54L	ex4	1	46724248	46724529	NM_003579	3	ex4	TRUE	TRUE
RAD54L	ex5	1	46725526	46725881	NM_003579	3	ex5	TRUE	TRUE
RAD54L	ex6-8	1	46726104	46727167	NM_003579	3	ex6-8	TRUE	TRUE
RAD54L	ex9	1	46733021	46733392	NM_003579	3	ex9	TRUE	TRUE
RAD54L	ex10	1	46736227	46736568	NM_003579	3	ex10	TRUE	TRUE
RAD54L	ex11-12	1	46738027	46738586	NM_003579	3	ex11-12	TRUE	TRUE
RAD54L	ex13-14	1	46738916	46739530	NM_003579	3	ex13-14	TRUE	TRUE
RAD54L	ex15	1	46739700	46739999	NM_003579	3	ex15	TRUE	TRUE
RAD54L	ex16	1	46740099	46740500	NM_003579	3	ex16	TRUE	TRUE
RAD54L	ex17-18	1	46743377	46744066	NM_003579	3	ex17-18	TRUE	TRUE
FANCL	ex14	2	58386790	58387045	NM_018062	3	ex14	TRUE	TRUE
FANCL	ex13	2	58387133	58387415	NM_018062	3	ex13	TRUE	TRUE
FANCL	ex12	2	58388547	58388869	NM_018062	3	ex12	TRUE	TRUE
FANCL	ex10-11	2	58389891	58390319	NM_018062	3	ex10-11	TRUE	TRUE
FANCL	ex9	2	58390459	58390762	NM_018062	3	ex9	TRUE	TRUE
FANCL	ex8	2	58392749	58393120	NM_018062	3	ex8	TRUE	TRUE
FANCL	ex7	2	58425615	58425907	NM_018062	3	ex7	TRUE	TRUE
FANCL	ex6	2	58431155	58431472	NM_018062	3	ex6	TRUE	TRUE
FANCL	ex5	2	58448967	58449288	NM_018062	3	ex5	TRUE	TRUE
FANCL	ex4	2	58453753	58454030	NM_018062	3	ex4	TRUE	TRUE
FANCL	ex3	2	58456839	58457120	NM_018062	3	ex3	TRUE	TRUE
FANCL	ex2	2	58459079	58459358	NM_018062	3	ex2	TRUE	TRUE
FANCL	ex1	2	58468243	58468607	NM_018062	3	ex1	FALSE	FALSE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
BARD1	ex11	2	215593107	215593845	NM_000465	3	ex11	TRUE	TRUE
BARD1	ex10	2	215595004	215595363	NM_000465	3	ex10	TRUE	TRUE
BARD1	ex9	2	215609635	215609994	NM_000465	3	ex9	TRUE	TRUE
BARD1	ex8	2	215610332	215610691	NM_000465	3	ex8	TRUE	TRUE
BARD1	ex7	2	215617055	215617414	NM_000465	3	ex7	TRUE	TRUE
BARD1	ex6	2	215632022	215632501	NM_000465	3	ex6	TRUE	TRUE
BARD1	ex5	2	215633787	215634146	NM_000465	3	ex5	TRUE	TRUE
BARD1	ex4	2	215645154	215646353	NM_000465	3	ex4	TRUE	TRUE
BARD1	ex3	2	215656871	215657350	NM_000465	3	ex3	TRUE	TRUE
BARD1	ex2	2	215661683	215662052	NM_000465	3	ex2	TRUE	TRUE
BARD1	ex1	2	215673956	215674562	NM_000465	3	ex1	FALSE	FALSE
FANCD2	ex2	3	10070284	10070488	NM_001018115	2	ex2	TRUE	TRUE
FANCD2	ex3	3	10074466	10074705	NM_001018115	2	ex3	TRUE	TRUE
FANCD2	ex4	3	10076067	10076306	NM_001018115	2	ex4	TRUE	TRUE
FANCD2	ex5	3	10076354	10076507	NM_001018115	2	ex5	TRUE	TRUE
FANCD2	ex6	3	10076721	10076972	NM_001018115	2	ex6	TRUE	TRUE
FANCD2	ex7	3	10077878	10078117	NM_001018115	2	ex7	TRUE	TRUE
FANCD2	ex8	3	10080883	10081122	NM_001018115	2	ex8	TRUE	TRUE
FANCD2	ex9	3	10081347	10081586	NM_001018115	2	ex9	TRUE	TRUE
FANCD2	ex10	3	10083281	10083420	NM_001018115	2	ex10	TRUE	TRUE
FANCD2	ex11	3	10084218	10084372	NM_001018115	2	ex11	TRUE	TRUE
FANCD2	ex12	3	10084709	10084859	NM_001018115	2	ex12	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
FANCD2	ex13	3	10085143	10085301	NM_001018115	2	ex13	TRUE	TRUE
FANCD2	ex14	3	10085411	10085650	NM_001018115	2	ex14	FALSE	FALSE
FANCD2	ex15	3	10088152	10088432	NM_001018115	2	ex15	FALSE	FALSE
FANCD2	ex16	3	10089549	10089788	NM_001018115	2	ex16	FALSE	FALSE
FANCD2	ex17	3	10091004	10091243	NM_001018115	2	ex17	FALSE	FALSE
FANCD2	ex18	3	10094046	10094206	NM_001018115	2	ex18	FALSE	FALSE
FANCD2	ex19	3	10101953	10102112	NM_001018115	2	ex19	FALSE	FALSE
FANCD2	ex20	3	10103805	10103953	NM_001018115	2	ex20	FALSE	FALSE
FANCD2	ex21	3	10105416	10105655	NM_001018115	2	ex21	FALSE	FALSE
FANCD2	ex22	3	10105957	10106196	NM_001018115	2	ex22	FALSE	FALSE
FANCD2	ex23	3	10106367	10106606	NM_001018115	2	ex23	FALSE	FALSE
FANCD2	ex24	3	10107053	10107203	NM_001018115	2	ex24	TRUE	TRUE
FANCD2	ex25	3	10107523	10107688	NM_001018115	2	ex25	TRUE	TRUE
FANCD2	ex26	3	10108868	10109026	NM_001018115	2	ex26	TRUE	TRUE
FANCD2	ex27	3	10114530	10114690	NM_001018115	2	ex27	TRUE	TRUE
FANCD2	ex28	3	10114912	10115071	NM_001018115	2	ex28	TRUE	TRUE
FANCD2	ex29	3	10116166	10116405	NM_001018115	2	ex29	TRUE	TRUE
FANCD2	ex30	3	10119740	10119906	NM_001018115	2	ex30	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
FANCD2	ex31	3	10122728	10122967	NM_001018115	2	ex31	TRUE	TRUE
FANCD2	ex32	3	10123005	10123173	NM_001018115	2	ex32	TRUE	TRUE
FANCD2	ex33	3	10127467	10127636	NM_001018115	2	ex33	TRUE	TRUE
FANCD2	ex34	3	10128764	10129003	NM_001018115	2	ex34	TRUE	TRUE
FANCD2	ex35	3	10130108	10130251	NM_001018115	2	ex35	TRUE	TRUE
FANCD2	ex36	3	10130454	10130693	NM_001018115	2	ex36	TRUE	TRUE
FANCD2	ex37	3	10131938	10132107	NM_001018115	2	ex37	TRUE	TRUE
FANCD2	ex38	3	10133781	10134020	NM_001018115	2	ex38	TRUE	TRUE
FANCD2	ex39	3	10134869	10135108	NM_001018115	2	ex39	TRUE	TRUE
FANCD2	ex40	3	10135891	10136130	NM_001018115	2	ex40	TRUE	TRUE
FANCD2	ex41	3	10136802	10137041	NM_001018115	2	ex41	TRUE	TRUE
FANCD2	ex42	3	10137964	10138203	NM_001018115	2	ex42	TRUE	TRUE
FANCD2	ex43	3	10140333	10140932	NM_001018115	2	ex43	TRUE	TRUE
FANCD2	ex44	3	10142812	10143061	NM_001018115	2	ex44	TRUE	TRUE
PIK3CA	ex2	3	178916490	178917086	NM_006218	3	ex2	TRUE	FALSE
PIK3CA	ex5	3	178921215	178921694	NM_006218	3	ex5	TRUE	FALSE
PIK3CA	ex8-9	3	178927774	178928253	NM_006218	3	ex8-9	TRUE	FALSE
PIK3CA	ex10	3	178935910	178936209	NM_006218	3	ex10	TRUE	FALSE
PIK3CA	ex21	3	178951812	178952231	NM_006218	3	ex21	TRUE	FALSE
FGFR3	ex7	4	1803517	1803816	NM_000142	4	ex7	TRUE	FALSE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
FGFR3	ex9	4	1805973	1806332	NM_000142	4	ex9	TRUE	FALSE
FGFR3	ex14	4	1807789	1807968	NM_000142	4	ex14	TRUE	FALSE
FGFR3	ex16	4	1808192	1808491	NM_000142	4	ex16	TRUE	FALSE
ESR1	ex5	6	152332761	152332942	NM_000125	3	ex5	FALSE	FALSE
ESR1	ex7	6	152415436	152415645	NM_000125	3	ex7	FALSE	FALSE
ESR1	ex8	6	152419826	152420020	NM_000125	3	ex8	FALSE	FALSE
PPP2R2A	ex1	8	26149226	26149452	NM_002717	3	ex1	FALSE	FALSE
PPP2R2A	in1	8	26150653	26150910	NM_002717	3	in1	TRUE	TRUE
PPP2R2A	ex2	8	26151072	26151367	NM_002717	3	ex2	TRUE	TRUE
PPP2R2A	ex3	8	26196296	26196613	NM_002717	3	ex3	TRUE	TRUE
PPP2R2A	ex4	8	26211874	26212260	NM_002717	3	ex4	TRUE	TRUE
PPP2R2A	ex5	8	26217575	26217908	NM_002717	3	ex5	TRUE	TRUE
PPP2R2A	ex6	8	26218380	26218778	NM_002717	3	ex6	TRUE	TRUE
PPP2R2A	ex7	8	26220089	26220475	NM_002717	3	ex7	TRUE	TRUE
PPP2R2A	ex8	8	26221080	26221517	NM_002717	3	ex8	TRUE	TRUE
PPP2R2A	ex9	8	26223721	26224069	NM_002717	3	ex9	TRUE	TRUE
PPP2R2A	ex10	8	26227540	26228039	NM_002717	3	ex10	TRUE	TRUE
FGFR1	ex14	8	38272205	38272504	NM_023110	2	ex14	TRUE	FALSE
FGFR1	ex12	8	38274760	38274999	NM_023110	2	ex12	TRUE	FALSE
FGFR1	ex9	8	38276983	38277342	NM_023110	2	ex9	TRUE	FALSE
FGFR1	ex3	8	38287132	38287491	NM_023110	2	ex3	TRUE	FALSE
NBN	ex16	8	90947616	90947975	NM_002485	4	ex16	TRUE	TRUE
NBN	ex15	8	90949069	90949428	NM_002485	4	ex15	TRUE	TRUE
NBN	ex14	8	90955358	90955717	NM_002485	4	ex14	TRUE	TRUE
NBN	ex13	8	90958183	90958662	NM_002485	4	ex13	TRUE	TRUE
NBN	ex12	8	90959884	90960243	NM_002485	4	ex12	TRUE	TRUE
NBN	ex11	8	90965336	90966089	NM_002485	4	ex11	TRUE	TRUE
NBN	ex10	8	90967317	90967916	NM_002485	4	ex10	TRUE	TRUE
NBN	ex9	8	90970789	90971268	NM_002485	4	ex9	TRUE	TRUE
NBN	ex8	8	90976484	90976903	NM_002485	4	ex8	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
NBN	ex7	8	90982470	90982949	NM_002485	4	ex7	TRUE	TRUE
NBN	ex6	8	90983280	90983639	NM_002485	4	ex6	TRUE	TRUE
NBN	ex5	8	90990320	90990679	NM_002485	4	ex5	TRUE	TRUE
NBN	ex4	8	90992772	90993251	NM_002485	4	ex4	TRUE	TRUE
NBN	ex3	8	90993407	90993886	NM_002485	4	ex3	TRUE	TRUE
NBN	ex2	8	90994837	90995196	NM_002485	4	ex2	TRUE	TRUE
NBN	ex1	8	90996561	90996920	NM_002485	4	ex1	FALSE	FALSE
PTEN	ex1	10	89623702	89624325	NM_000314	6	ex1	FALSE	FALSE
PTEN	ex2	10	89653644	89654003	NM_000314	6	ex2	TRUE	TRUE
PTEN	ex3	10	89685197	89685386	NM_000314	6	ex3	TRUE	TRUE
PTEN	ex4	10	89690730	89690919	NM_000314	6	ex4	TRUE	TRUE
PTEN	ex5	10	89692730	89693069	NM_000314	6	ex5	TRUE	TRUE
PTEN	ex6	10	89711786	89712065	NM_000314	6	ex6	TRUE	TRUE
PTEN	ex7	10	89717534	89717813	NM_000314	6	ex7	TRUE	TRUE
PTEN	ex8	10	89720637	89720923	NM_000314	6	ex8	TRUE	TRUE
PTEN	ex9	10	89724977	89725296	NM_000314	6	ex9	TRUE	TRUE
FGFR2	ex11	10	123247436	123247735	NM_000141	4	ex14	TRUE	FALSE
FGFR2	ex9	10	123257947	123258185	NM_000141	4	ex12	TRUE	FALSE
FGFR2	ex4	10	123279416	123279775	NM_000141	4	ex7	TRUE	FALSE
MRE11	ex20	11	94153109	94153468	NM_005591	3	ex20	TRUE	TRUE
MRE11	ex19	11	94162967	94163273	NM_005591	3	ex19	TRUE	TRUE
MRE11	ex18	11	94168822	94169181	NM_005591	3	ex18	TRUE	TRUE
MRE11	ex17	11	94170233	94170550	NM_005591	3	ex17	TRUE	TRUE
MRE11	ex16	11	94178838	94179197	NM_005591	3	ex16	TRUE	TRUE
MRE11	ex15	11	94180261	94180740	NM_005591	3	ex15	TRUE	TRUE
MRE11	ex14	11	94189264	94189623	NM_005591	3	ex14	TRUE	TRUE
MRE11	ex13	11	94192491	94192860	NM_005591	3	ex13	TRUE	TRUE
MRE11	ex12	11	94193972	94194331	NM_005591	3	ex12	TRUE	TRUE
MRE11	ex11	11	94197162	94197521	NM_005591	3	ex11	TRUE	TRUE
MRE11	ex10	11	94200839	94201198	NM_005591	3	ex10	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
MRE11	ex9	11	94203453	94203932	NM_005591	3	ex9	TRUE	TRUE
MRE11	ex8	11	94204563	94205042	NM_005591	3	ex8	TRUE	TRUE
MRE11	ex7	11	94209344	94209703	NM_005591	3	ex7	TRUE	TRUE
MRE11	ex6	11	94211702	94212181	NM_005591	3	ex6	TRUE	TRUE
MRE11	ex5	11	94212704	94213063	NM_005591	3	ex5	TRUE	TRUE
MRE11	ex4	11	94218900	94219379	NM_005591	3	ex4	TRUE	TRUE
MRE11	ex3	11	94223885	94224244	NM_005591	3	ex3	TRUE	TRUE
MRE11	ex2	11	94225748	94226107	NM_005591	3	ex2	TRUE	TRUE
ATM	ex2-3	11	108098298	108098618	NM_000051	3	ex2-3	TRUE	TRUE
ATM	ex4	11	108099900	108100100	NM_000051	3	ex4	TRUE	TRUE
ATM	ex5	11	108106229	108106613	NM_000051	3	ex5	TRUE	TRUE
ATM	ex6	11	108114675	108114850	NM_000051	3	ex6	TRUE	TRUE
ATM	ex7	11	108115510	108115759	NM_000051	3	ex7	TRUE	TRUE
ATM	ex8	11	108117686	108117929	NM_000051	3	ex8	TRUE	TRUE
ATM	ex9	11	108119637	108119856	NM_000051	3	ex9	TRUE	TRUE
ATM	ex10	11	108121285	108121805	NM_000051	3	ex10	TRUE	TRUE
ATM	ex11	11	108122559	108122871	NM_000051	3	ex11	TRUE	TRUE
ATM	ex12	11	108123472	108123711	NM_000051	3	ex12	TRUE	TRUE
ATM	ex13	11	108124536	108124771	NM_000051	3	ex13	TRUE	TRUE
ATM	ex14	11	108126935	108127074	NM_000051	3	ex14	TRUE	TRUE
ATM	ex15	11	108128201	108128401	NM_000051	3	ex15	TRUE	TRUE
ATM	ex16	11	108129638	108129877	NM_000051	3	ex16	TRUE	TRUE
ATM	ex17	11	108137893	108138074	NM_000051	3	ex17	TRUE	TRUE
ATM	ex18	11	108139117	108139356	NM_000051	3	ex18	TRUE	TRUE
ATM	ex19-20	11	108141712	108142138	NM_000051	3	ex19-20	TRUE	TRUE
ATM	ex21-22	11	108143177	108143584	NM_000051	3	ex21-22	TRUE	TRUE
ATM	ex23	11	108150054	108150395	NM_000051	3	ex23	TRUE	TRUE
ATM	ex24	11	108151576	108151900	NM_000051	3	ex24	TRUE	TRUE
ATM	ex25	11	108153432	108153611	NM_000051	3	ex25	TRUE	TRUE
ATM	ex26	11	108154949	108155206	NM_000051	3	ex26	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
ATM	ex27	11	108158265	108158504	NM_000051	3	ex27	TRUE	TRUE
ATM	ex28	11	108159683	108159837	NM_000051	3	ex28	TRUE	TRUE
ATM	ex29	11	108160324	108160533	NM_000051	3	ex29	TRUE	TRUE
ATM	ex30	11	108163296	108163535	NM_000051	3	ex30	TRUE	TRUE
ATM	ex31	11	108163994	108164233	NM_000051	3	ex31	TRUE	TRUE
ATM	ex32	11	108165581	108165855	NM_000051	3	ex32	TRUE	TRUE
ATM	ex33	11	108167941	108168189	NM_000051	3	ex33	TRUE	TRUE
ATM	ex34	11	108170436	108170677	NM_000051	3	ex34	TRUE	TRUE
ATM	ex35	11	108172370	108172527	NM_000051	3	ex35	TRUE	TRUE
ATM	ex36	11	108173575	108173761	NM_000051	3	ex36	TRUE	TRUE
ATM	ex37	11	108175397	108175584	NM_000051	3	ex37	TRUE	TRUE
ATM	ex38	11	108178577	108178780	NM_000051	3	ex38	TRUE	TRUE
ATM	ex39	11	108180882	108181047	NM_000051	3	ex39	TRUE	TRUE
ATM	ex40	11	108183062	108183301	NM_000051	3	ex40	TRUE	TRUE
ATM	ex41-42	11	108186474	108186908	NM_000051	3	ex41-42	TRUE	TRUE
ATM	ex43	11	108188045	108188264	NM_000051	3	ex43	TRUE	TRUE
ATM	ex44	11	108190615	108190854	NM_000051	3	ex44	TRUE	TRUE
ATM	ex45	11	108191968	108192207	NM_000051	3	ex45	TRUE	TRUE
ATM	ex46	11	108195788	108196277	NM_000051	3	ex46	TRUE	TRUE
ATM	ex47	11	108196730	108196957	NM_000051	3	ex47	TRUE	TRUE
ATM	ex48	11	108198338	108198511	NM_000051	3	ex48	TRUE	TRUE
ATM	ex49	11	108199743	108199970	NM_000051	3	ex49	TRUE	TRUE
ATM	ex50	11	108200936	108201153	NM_000051	3	ex50	TRUE	TRUE
ATM	ex51	11	108202108	108202347	NM_000051	3	ex51	TRUE	TRUE
ATM	ex52	11	108202601	108202769	NM_000051	3	ex52	TRUE	TRUE
ATM	ex53	11	108203484	108203632	NM_000051	3	ex53	TRUE	TRUE
ATM	ex54	11	108204564	108204713	NM_000051	3	ex54	TRUE	TRUE
ATM	ex55	11	108205691	108205841	NM_000051	3	ex55	TRUE	TRUE
ATM	ex56	11	108206510	108206749	NM_000051	3	ex56	TRUE	TRUE
ATM	ex57	11	108213874	108214135	NM_000051	3	ex57	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
ATM	ex58	11	108216394	108216640	NM_000051	3	ex58	TRUE	TRUE
ATM	ex59	11	108217929	108218168	NM_000051	3	ex59	TRUE	TRUE
ATM	ex60	11	108224430	108224669	NM_000051	3	ex60	TRUE	TRUE
ATM	ex61	11	108225450	108225689	NM_000051	3	ex61	TRUE	TRUE
ATM	ex62	11	108235753	108235950	NM_000051	3	ex62	TRUE	TRUE
ATM	ex63	11	108236047	108236240	NM_000051	3	ex63	TRUE	TRUE
CHEK1	ex1	11	125495564	125496019	NM_001114121	2	5utr	FALSE	FALSE
CHEK1	ex2	11	125496554	125496839	NM_001114121	2	ex2	TRUE	TRUE
CHEK1	ex3	11	125497392	125497835	NM_001114121	2	ex3	TRUE	TRUE
CHEK1	ex4-5	11	125499017	125499466	NM_001114121	2	ex4-5	TRUE	TRUE
CHEK1	ex6	11	125502948	125503356	NM_001114121	2	ex6	TRUE	TRUE
CHEK1	ex7	11	125505214	125505628	NM_001114121	2	ex7	TRUE	TRUE
CHEK1	ex8	11	125507234	125507549	NM_001114121	2	ex8	TRUE	TRUE
CHEK1	ex9-11	11	125513576	125514648	NM_001114121	2	ex9-11	TRUE	TRUE
CHEK1	ex12	11	125523543	125523853	NM_001114121	2	ex12	TRUE	TRUE
CHEK1	ex13	11	125525010	125525325	NM_001114121	2	ex13	TRUE	TRUE
BRCA2	ex1	13	32889507	32889914	NM_000059	3	5utr	FALSE	FALSE
BRCA2	ex2	13	32890488	32890775	NM_000059	3	ex2	TRUE	TRUE
BRCA2	ex3	13	32893104	32893551	NM_000059	3	ex3	TRUE	TRUE
BRCA2	ex4	13	32899103	32899432	NM_000059	3	ex4	TRUE	TRUE
BRCA2	ex5-7	13	32900126	32900863	NM_000059	3	ex5-7	TRUE	TRUE
BRCA2	ex8	13	32903470	32903739	NM_000059	3	ex8	TRUE	TRUE
BRCA2	ex9	13	32904970	32905259	NM_000059	3	ex9	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
BRCA2	ex10	13	32906297	32907740	NM_000059	3	ex10	TRUE	TRUE
BRCA2	ex11	13	32910292	32915534	NM_000059	3	ex11	TRUE	TRUE
BRCA2	ex12	13	32918585	32918876	NM_000059	3	ex12	TRUE	TRUE
BRCA2	ex13	13	32920854	32921143	NM_000059	3	ex13	TRUE	TRUE
BRCA2	ex14	13	32928887	32929536	NM_000059	3	ex14	TRUE	TRUE
BRCA2	ex15	13	32930482	32930856	NM_000059	3	ex15	TRUE	TRUE
BRCA2	ex16	13	32931769	32932176	NM_000059	3	ex16	TRUE	TRUE
BRCA2	ex17	13	32936549	32936941	NM_000059	3	ex17	TRUE	TRUE
BRCA2	ex18	13	32937206	32937781	NM_000059	3	ex18	TRUE	TRUE
BRCA2	ex19	13	32944429	32944777	NM_000059	3	ex19	TRUE	TRUE
BRCA2	ex20	13	32945000	32945347	NM_000059	3	ex20	TRUE	TRUE
BRCA2	ex21	13	32950697	32951038	NM_000059	3	ex21	TRUE	TRUE
BRCA2	ex22-24	13	32953344	32954409	NM_000059	3	ex22-24	TRUE	TRUE
BRCA2	ex25	13	32968716	32969180	NM_000059	3	ex25	TRUE	TRUE
BRCA2	ex26	13	32970924	32971283	NM_000059	3	ex26	TRUE	TRUE
BRCA2	ex27	13	32972187	32973020	NM_000059	3	ex27	TRUE	TRUE
RAD51B	ex2	14	68290151	68290454	NM_001321809	1	ex2	TRUE	TRUE
RAD51B	ex3	14	68292071	68292404	NM_001321809	1	ex3	TRUE	TRUE
RAD51B	ex4	14	68301687	68302024	NM_001321809	1	ex4	TRUE	TRUE
RAD51B	ex5	14	68331552	68331966	NM_001321809	1	ex5	TRUE	TRUE
RAD51B	ex6	14	68352476	68352897	NM_001321809	1	ex6	TRUE	TRUE
RAD51B	ex7	14	68353554	68354098	NM_001321809	1	ex7	TRUE	TRUE
RAD51B	ex8	14	68758422	68758807	NM_001321809	1	ex8	TRUE	TRUE
RAD51B	ex9	14	68878031	68878354	NM_001321809	1	ex9	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
RAD51B	ex10	14	68934779	68935078	NM_001321809	1	ex10	TRUE	TRUE
RAD51B	in10_1	14	68937129	68937371	NM_001321809	1	in10_1	TRUE	TRUE
RAD51B	in10_2	14	68944194	68944498	NM_001321809	1	in10_2	TRUE	TRUE
RAD51B	in10_3	14	68963731	68963967	NM_001321809	1	in10_3	TRUE	TRUE
RAD51B	in10_4	14	69006750	69007042	NM_001321809	1	in10_4	TRUE	TRUE
RAD51B	in10_5	14	69061061	69061514	NM_001321809	1	in10_5	TRUE	TRUE
RAD51B	in10_6	14	69069266	69069519	NM_001321809	1	ex11	TRUE	TRUE
RAD51B	in10_7	14	69077610	69078093	NM_001321809	1	3utr	TRUE	TRUE
RAD51B	ex11	14	69149504	69149783	NM_001321809	1	dn	TRUE	TRUE
AKT1	ex3	14	105246339	105246638	NM_001014431	1	ex3	FALSE	FALSE
PALB2	ex13	16	23614646	23615190	NM_024675	3	ex13	TRUE	TRUE
PALB2	ex12	16	23618989	23619468	NM_024675	3	ex12	TRUE	TRUE
PALB2	ex11	16	23625189	23625548	NM_024675	3	ex11	TRUE	TRUE
PALB2	ex10	16	23632573	23633026	NM_024675	3	ex10	TRUE	TRUE
PALB2	ex9	16	23634065	23634549	NM_024675	3	ex9	TRUE	TRUE
PALB2	ex8	16	23635193	23635552	NM_024675	3	ex8	TRUE	TRUE
PALB2	ex7	16	23637423	23637902	NM_024675	3	ex7	TRUE	TRUE
PALB2	ex6	16	23640351	23640710	NM_024675	3	ex6	TRUE	TRUE
PALB2	ex5	16	23640836	23641915	NM_024675	3	ex5	TRUE	TRUE
PALB2	ex4	16	23646063	23647862	NM_024675	3	ex4	TRUE	TRUE
PALB2	ex2-3	16	23649043	23649642	NM_024675	3	ex2-3	TRUE	TRUE
PALB2	ex1	16	23652245	23652604	NM_024675	3	ex1	FALSE	FALSE
FANCA	ex42-43	16	89804904	89805436	NM_000135	2	ex42-43	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
FANCA	ex41	16	89805498	89805737	NM_000135	2	ex41	TRUE	TRUE
FANCA	ex40	16	89805804	89806043	NM_000135	2	ex40	TRUE	TRUE
FANCA	ex39	16	89806148	89806532	NM_000135	2	ex39	TRUE	TRUE
FANCA	ex38	16	89807123	89807362	NM_000135	2	ex38	TRUE	TRUE
FANCA	ex37	16	89809157	89809396	NM_000135	2	ex37	TRUE	TRUE
FANCA	ex36	16	89811342	89811504	NM_000135	2	ex36	TRUE	TRUE
FANCA	ex34-35	16	89812967	89813388	NM_000135	2	ex34-35	TRUE	TRUE
FANCA	ex33	16	89815042	89815200	NM_000135	2	ex33	TRUE	TRUE
FANCA	ex32	16	89816105	89816344	NM_000135	2	ex32	TRUE	TRUE
FANCA	ex31	16	89818519	89818658	NM_000135	2	ex31	TRUE	TRUE
FANCA	ex30	16	89824945	89825183	NM_000135	2	ex30	TRUE	TRUE
FANCA	ex29	16	89828314	89828513	NM_000135	2	ex29	TRUE	TRUE
FANCA	ex28	16	89831267	89831617	NM_000135	2	ex28	TRUE	TRUE
FANCA	ex27	16	89833524	89833670	NM_000135	2	ex27	TRUE	TRUE
FANCA	ex26	16	89836219	89836458	NM_000135	2	ex26	TRUE	TRUE
FANCA	ex25	16	89836549	89836692	NM_000135	2	ex25	TRUE	TRUE
FANCA	ex24	16	89836887	89837126	NM_000135	2	ex24	TRUE	TRUE
FANCA	ex23	16	89838035	89838274	NM_000135	2	ex23	TRUE	TRUE
FANCA	ex22	16	89839654	89839817	NM_000135	2	ex22	TRUE	TRUE
FANCA	ex21	16	89842067	89842306	NM_000135	2	ex21	TRUE	TRUE
FANCA	ex19-20	16	89845174	89845441	NM_000135	2	ex19-20	TRUE	TRUE
FANCA	ex18	16	89846252	89846391	NM_000135	2	ex18	TRUE	TRUE
FANCA	ex16-17	16	89849237	89849535	NM_000135	2	ex16-17	TRUE	TRUE
FANCA	ex15	16	89851237	89851397	NM_000135	2	ex15	TRUE	TRUE
FANCA	ex14	16	89857758	89857997	NM_000135	2	ex14	TRUE	TRUE
FANCA	ex13	16	89858286	89858525	NM_000135	2	ex13	TRUE	TRUE
FANCA	ex12	16	89858797	89859036	NM_000135	2	ex12	TRUE	TRUE
FANCA	ex11	16	89862289	89862451	NM_000135	2	ex11	TRUE	TRUE
FANCA	ex10	16	89865330	89865666	NM_000135	2	ex10	TRUE	TRUE
FANCA	ex9	16	89865910	89866149	NM_000135	2	ex9	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
FANCA	ex8	16	89869639	89869778	NM_000135	2	ex8	TRUE	TRUE
FANCA	ex7	16	89871660	89871829	NM_000135	2	ex7	TRUE	TRUE
FANCA	ex6	16	89874653	89874798	NM_000135	2	ex6	TRUE	TRUE
FANCA	ex5	16	89877090	89877235	NM_000135	2	ex5	TRUE	TRUE
FANCA	ex4	16	89877288	89877527	NM_000135	2	ex4	TRUE	TRUE
FANCA	ex3	16	89880903	89881046	NM_000135	2	ex3	TRUE	TRUE
FANCA	ex2	16	89882260	89882419	NM_000135	2	ex2	TRUE	TRUE
FANCA	ex1	16	89882920	89883090	NM_000135	2	ex1	FALSE	FALSE
TP53	ex10	17	7572807	7573118	NM_000546	5	ex11	TRUE	TRUE
TP53	ex9	17	7573817	7574153	NM_000546	5	ex10	TRUE	TRUE
TP53	ex7-8	17	7576427	7577274	NM_000546	5	ex8-9	TRUE	TRUE
TP53	ex6	17	7577369	7577718	NM_000546	5	ex7	TRUE	TRUE
TP53	ex4-5	17	7577995	7578684	NM_000546	5	ex5-6	TRUE	TRUE
TP53	ex2-3	17	7579192	7580032	NM_000546	5	ex2-4	TRUE	TRUE
RAD51D	ex9-10	17	33427847	33428482	NM_001142571	1	ex9-10	TRUE	TRUE
RAD51D	ex7-8	17	33430088	33430687	NM_001142571	1	ex7-8	TRUE	TRUE
RAD51D	ex6	17	33433272	33433627	NM_001142571	1	ex6	TRUE	TRUE
RAD51D	ex4-5	17	33433895	33434605	NM_001142571	1	ex4-5	TRUE	TRUE
RAD51D	in3	17	33443801	33444166	NM_001142571	1	ex3	TRUE	TRUE
RAD51D	ex3	17	33445331	33445780	NM_001142571	1	in2	TRUE	TRUE
RAD51D	ex2	17	33446038	33446278	NM_001142571	1	ex2	TRUE	TRUE
RAD51D	ex1	17	33446412	33446771	NM_001142571	1	ex1	FALSE	FALSE
CDK12	ex1	17	37618106	37619504	NM_016507	3	ex1	FALSE	FALSE
CDK12	ex2	17	37627020	37628129	NM_016507	3	ex2	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
CDK12	ex3	17	37646699	37647097	NM_016507	3	ex3	TRUE	TRUE
CDK12	ex4	17	37648932	37649253	NM_016507	3	ex4	TRUE	TRUE
CDK12	ex5	17	37650667	37651003	NM_016507	3	ex5	TRUE	TRUE
CDK12	ex6	17	37657340	37657803	NM_016507	3	ex6	TRUE	TRUE
CDK12	ex7	17	37665848	37666101	NM_016507	3	ex7	TRUE	TRUE
CDK12	ex8	17	37667672	37667993	NM_016507	3	ex8	TRUE	TRUE
CDK12	ex9	17	37671874	37672171	NM_016507	3	ex9	TRUE	TRUE
CDK12	ex10	17	37673583	37673920	NM_016507	3	ex10	TRUE	TRUE
CDK12	ex11	17	37676102	37676451	NM_016507	3	ex11	TRUE	TRUE
CDK12	ex12	17	37680817	37681248	NM_016507	3	ex12	TRUE	TRUE
CDK12	ex13	17	37682006	37682680	NM_016507	3	ex13	TRUE	TRUE
CDK12	ex14	17	37686744	37687682	NM_016507	3	ex14	TRUE	TRUE
BRCA1	ex24	17	41197555	41197930	NM_007294	3	ex23	TRUE	TRUE
BRCA1	ex23	17	41199560	41199805	NM_007294	3	ex22	TRUE	TRUE
BRCA1	ex22	17	41201028	41201321	NM_007294	3	ex21	TRUE	TRUE
BRCA1	ex21	17	41202970	41203245	NM_007294	3	ex20	TRUE	TRUE
BRCA1	ex20	17	41208959	41209262	NM_007294	3	ex19	TRUE	TRUE
BRCA1	ex19	17	41215240	41215501	NM_007294	3	ex18	TRUE	TRUE
BRCA1	ex18	17	41215781	41216078	NM_007294	3	ex17	TRUE	TRUE
BRCA1	ex17	17	41219541	41219830	NM_007294	3	ex16	TRUE	TRUE
BRCA1	ex16	17	41222835	41223366	NM_007294	3	ex15	TRUE	TRUE
BRCA1	ex15	17	41226238	41226648	NM_007294	3	ex14	TRUE	TRUE
BRCA1	ex14	17	41228395	41228742	NM_007294	3	ex13	TRUE	TRUE
BRCA1	ex13	17	41231205	41231564	NM_007294	3	in12	TRUE	TRUE
BRCA1	ex12	17	41234311	41234703	NM_007294	3	ex12	TRUE	TRUE
BRCA1	ex11	17	41242789	41243159	NM_007294	3	ex11	TRUE	TRUE
BRCA1	ex10	17	41243335	41246994	NM_007294	3	ex10	TRUE	TRUE
BRCA1	ex9	17	41247753	41248050	NM_007294	3	ex9	TRUE	TRUE
BRCA1	ex8	17	41249151	41249484	NM_007294	3	ex8	TRUE	TRUE
BRCA1	ex7	17	41251682	41252007	NM_007294	3	ex7	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
BRCA1	ex6	17	41256104	41256429	NM_007294	3	ex6	TRUE	TRUE
BRCA1	ex5	17	41256775	41257084	NM_007294	3	ex5	TRUE	TRUE
BRCA1	ex4	17	41258351	41258660	NM_007294	3	ex4	TRUE	TRUE
BRCA1	ex3	17	41267633	41267906	NM_007294	3	ex3	TRUE	TRUE
BRCA1	ex2	17	41275924	41276223	NM_007294	3	ex2	TRUE	TRUE
BRCA1	ex1	17	41277088	41277611	NM_007294	3	5utr	FALSE	FALSE
RAD51C	ex1	17	56769856	56770260	NM_058216	2	ex1	FALSE	FALSE
RAD51C	ex2	17	56772182	56772732	NM_058216	2	ex2	TRUE	TRUE
RAD51C	ex3	17	56773944	56774330	NM_058216	2	ex3	TRUE	TRUE
RAD51C	ex4	17	56780447	56780825	NM_058216	2	ex4	TRUE	TRUE
RAD51C	ex5	17	56787106	56787461	NM_058216	2	ex5	TRUE	TRUE
RAD51C	ex6	17	56798023	56798282	NM_058216	2	ex6	TRUE	TRUE
RAD51C	ex7	17	56801291	56801572	NM_058216	2	ex7	TRUE	TRUE
RAD51C	ex8	17	56809701	56810016	NM_058216	2	ex8	TRUE	TRUE
RAD51C	ex9	17	56811369	56811694	NM_058216	2	ex9	TRUE	TRUE
BRIP1	ex20	17	59760543	59761622	NM_032043	2	ex20	TRUE	TRUE
BRIP1	ex19	17	59763044	59763643	NM_032043	2	ex19	TRUE	TRUE
BRIP1	ex18	17	59770713	59771082	NM_032043	2	ex18	TRUE	TRUE
BRIP1	ex17	17	59793188	59793547	NM_032043	2	ex17	TRUE	TRUE
BRIP1	ex16	17	59820280	59820649	NM_032043	2	ex16	TRUE	TRUE
BRIP1	ex15	17	59821570	59822054	NM_032043	2	ex15	TRUE	TRUE
BRIP1	ex14	17	59853573	59854052	NM_032043	2	ex14	TRUE	TRUE
BRIP1	ex13	17	59857470	59857834	NM_032043	2	ex13	TRUE	TRUE
BRIP1	ex12	17	59858098	59858571	NM_032043	2	ex12	TRUE	TRUE
BRIP1	ex11	17	59861446	59861925	NM_032043	2	ex11	TRUE	TRUE
BRIP1	ex10	17	59870844	59871203	NM_032043	2	ex10	TRUE	TRUE
BRIP1	ex9	17	59876321	59876800	NM_032043	2	ex9	TRUE	TRUE
BRIP1	ex8	17	59878485	59878964	NM_032043	2	ex8	TRUE	TRUE
BRIP1	ex7	17	59885644	59886243	NM_032043	2	ex7	TRUE	TRUE
BRIP1	ex6	17	59924330	59924809	NM_032043	2	ex6	TRUE	TRUE

Gene	Region	Chr.	Start	End	Transcript ID	Transcript version	Transcript region	Covered by gene-level analysis	Covered by exon-level analysis
BRIP1	ex5	17	59926374	59926733	NM_032043	2	ex5	TRUE	TRUE
BRIP1	ex4	17	59934236	59934715	NM_032043	2	ex4	TRUE	TRUE
BRIP1	ex3	17	59937007	59937486	NM_032043	2	ex3	TRUE	TRUE
BRIP1	ex2	17	59938674	59939033	NM_032043	2	ex2	TRUE	TRUE
CCNE1	ex2	19	30303384	30303712	NM_001238	3	ex2-3	TRUE	FALSE
CCNE1	ex3	19	30303790	30304029	NM_001238	3	ex4	TRUE	FALSE
CCNE1	ex4-5	19	30307997	30308500	NM_001238	3	ex5-6	TRUE	FALSE
CCNE1	ex6	19	30311546	30311842	NM_001238	3	ex7	TRUE	FALSE
CCNE1	ex7	19	30312582	30312771	NM_001238	3	ex8	TRUE	FALSE
CCNE1	ex8	19	30312811	30313090	NM_001238	3	ex9	TRUE	FALSE
CCNE1	ex9-10	19	30313123	30313521	NM_001238	3	ex10-11	TRUE	FALSE
CCNE1	ex11	19	30314464	30314743	NM_001238	3	ex12	TRUE	FALSE
CHEK2	ex16	22	29083668	29084109	NM_007194	3	ex15	TRUE	TRUE
CHEK2	ex15	22	29084983	29085342	NM_007194	3	ex14	TRUE	TRUE
CHEK2	ex14	22	29089903	29090262	NM_007194	3	ex13	TRUE	TRUE
CHEK2	ex13	22	29090951	29091382	NM_007194	3	ex12	TRUE	TRUE
CHEK2	ex12	22	29091606	29091975	NM_007194	3	ex11	TRUE	TRUE
CHEK2	ex11	22	29092753	29093112	NM_007194	3	ex10	TRUE	TRUE
CHEK2	ex10	22	29095696	29096055	NM_007194	3	ex9	TRUE	TRUE
CHEK2	ex9	22	29099314	29099673	NM_007194	3	ex8	TRUE	TRUE
CHEK2	ex8	22	29105884	29106211	NM_007194	3	ex7	TRUE	TRUE
CHEK2	ex7	22	29107771	29108130	NM_007194	3	ex6	TRUE	TRUE
CHEK2	ex6	22	29115244	29115603	NM_007194	3	ex5	TRUE	TRUE
CHEK2	ex4-5	22	29120805	29121552	NM_007194	3	ex3-4	TRUE	TRUE
CHEK2	ex3	22	29126384	29126579	NM_007194	3	in2	TRUE	TRUE
CHEK2	ex2	22	29130302	29130911	NM_007194	3	ex2	TRUE	TRUE
CHEK2	ex1	22	29137610	29137969	NM_007194	3	5utr	FALSE	FALSE

13 APPENDIX IV. DESCRIPTION OF THE FULL VARIANT TABLE CONTENT

FIELD	DESCRIPTION	EXAMPLE
id	variant run ID, internal to FVT	1
annotation_id	variant ID in annotation database	60245
gene	HGNC gene symbol	BRCA2
overlapKnown	rsid of pathogenic clinvar entries	rs1555760738
type	variant type	SNP / INDEL
codingConsequence	consequence on protein	5'UTR
refGenome	reference genome	GRCh37/hg19
chromosome	chromosome	13
genome_position	genomic position (from variant caller)	32890572
depth	sequencing depth	12224
var_percent	variant fraction (relative depth of alternative allele)	49.32%
exon_rank	exon identifier	2
c.DNA	HGVS cDNA	c.-26G>A
protein	HGVS protein	
ref	ref in reference genome	G
alt	alternative allele	A
refNum	depth reference allele	6178
altNum	depth alternative allele	6029
refSeq	ref codon	
altSeq	alt codon	
refAA	ref amino-acid	
altAA	alt amino-acid	
tx_id	transcript ID in annotation database	35315
tx_name	transcript symbol in annotation database	NM_000059
refSeqId	transcript symbol in RefSeq	NM_000059
tx_version	transcript version in annotation database	3
refSeqIdVersion	transcript version in RefSeq	3
gene_boundaries	Exome / Intergenic qualifier	within

FIELD	DESCRIPTION	EXAMPLE
exon_id	exon legacy identifier	2
pos_in_exon	position in exon (strand specific)	14
dist2exon	position in intron (distance to closest exon)	0
filter	whether any quality filter should apply	.
dbSNP	dbSNP's rsid	rs1799943
g1000	Allele frequency	0.2093
esp5400	Allele frequency	0.2078
ExAC	Allele frequency	0.243
GnomAD	Allele frequency	0.2427
LJB_PhyloP	dbNSFP's precomputed PhyloP score	
LJB_SIFT	dbNSFP's precomputed SIFT score	
LJB_PolyPhen2	dbNSFP's precomputed PolyPhen2 score	
LJB_PolyPhen2_ HumDiv	dbNSFP's precomputed PolyPhen2_HumDiv score	
LJB_LRT	dbNSFP's precomputed LRT score	
LJB_MutationTaster	dbNSFP's precomputed MutationTaster score	
LJB_GERP	dbNSFP's precomputed GERP score	
id_cosmic_coding	COSMIC ID coding variants	COSN20442808
id_cosmic_non_ coding	COSMIC ID non-coding variants	
id_clinvar	Clinvar's rsid	rs1799943
CLNSIG	Clinvar's pathogenicity assertion	Benign
CLNREVSTAT	Clinvar's metadata	reviewed_by_expert_panel
gene_strand	strand	+
ref1	normalized ref (3' alnmt, in direction of strand)	G
alt1	normalized alternative allele (3' alnmt, in direction of strand)	A
first1	normalized genome_position (3' alnmt, in direction of strand)	32890572
last1	normalized genome_position(3' alnmt, in direction of strand)	32890572
multiTranscriptId		1
flagged_region_id		
depth_uniq	Number of unique molecular fragments at the position of a variant taking base Phred scores into account	400

FIELD	DESCRIPTION	EXAMPLE
refNum_uniq	Number of unique molecular fragments supporting the reference allele taking base quality (Phred Score) into account	203
altNum_uniq	Number of unique molecular fragments supporting the alternative allele taking base quality (Phred Score) into account	197
matchStatus		exact
OMIM	mim2gene identifier	600185
hg38_chrom	Chromosome in hg38	1
hg38_pos	Genome position in hg38	46259775
hg38_ref	Reference allele in hg38	C
hg38_alt	Alternative allele in hg38	T
lift_diagnostic		PICARD
hg38_refGenome	Reference for hg38	GRCh38/hg38
sgid		00010001c698114b5b53cf60b6cdb5d02a62beba
Hg38_sgid		00010101651f8aaff0d56960c3121277b4d53606
BRCA_pathogenicity	“BRCA_pathogenicity”; as obtained by aggregating BRCA exchange’s “Pathogenicity_expert” and “Pathogenicity_all” fields, following aggregation rules detailed in *Table 7*	ex:pathogenic

Document Approvals

Approved Date: 28 Jan 2026

Approval Verdict: Approve	Coleman Spence, (cspence@sophiagenetics.com) Regulatory Approval 28-Jan-2026 01:17:08 GMT+0000

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