



Operation Manual

v6.7



The SOPHiA DDM™ Platform is a Research Use Only product, intended for research only and **not for diagnostic, prognosis, therapeutic, or treatment purposes.**

The Operation Manual comprises the following documents:

- Operation Manual
- General Information about SOPHiA DDM™ usage (downloadable through the “General information” link on the Dashboard)

Please note, the Instructions for Use for our CE-IVD marked products:

- SOPHiA DDM™ Dx Hereditary Cancer Solution (HCS)
- SOPHiA DDM™ Dx Solid Tumor Solution (STS)
- SOPHiA DDM™ Dx Myeloid Solution (MYS)
- SOPHiA DDM™ Dx Homologous Recombination Deficiency Solution (HRD)
- SOPHiA DDM™ Dx RNAtarget Oncology Solutions (ROS)

as well as the Operation Manual for the SOPHiA DDM™ web app can be downloaded from www.sophiagenetics.com/docs/ .

Symbols:



See Instruction For Use



Manufacturer

Disclaimer

* The following terms are only applicable in the context of CE-IVD products:

Term	CE-IVD	RUO
Patient	Patient	Genomic profile
Performance	Performance	Analytical Performance
Interpretation Project / Interpretation	Interpretation Project / Interpretation	Project
Diagnosis	Diagnosis	OncoPortal™ insights
Prognosis	Prognosis	OncoPortal™ insights
Actionability	Actionability	OncoPortal™ insights
Disease	Disease	Disorder
Clinicians	Clinicians	Users
Clinical association	Clinical association	Association
Clinical results	Clinical results	Results
Hospital	Hospital	Institution
Clinical Trials	Clinical Trials	Research Study

The content of the recorded information is the sole responsibility of the user. In order to guarantee adequate protection of individual's rights, the user shall limit the recording of personally identifying information to the dedicated fields.

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Revision History (1)

Date YYYY-MM-DD	SOPHiA DDM™ Version	Manual Version	Change
2023-06-14	v5.10.37	v6.7	<ul style="list-style-type: none"> • Minor branding modifications • Update chapter 2.3 BDS numbers • Update chapter 14.1.1 Dual DNA/RNA Analysis • Update chapter 14.3 Fusion tab • Update chapter 14.4 Fusion flagging • Addition of chapter 14.5 Fusion display in IGV
2023-03-01	v5.10.31	v6.6	<ul style="list-style-type: none"> • Addition of chapter 6.8 Cascading Filters - HPO Rank match filter • Addition of chapter 4.11 HPO based prioritization • Update of chapter 6.3 Cascading Filters - Available filters (3) • Addition of chapter 3.12.6 Interpretation Projects* - Add phenotypes • Update of chapter 16.2 Familial Variant Analysis - Create a New FVA Request (1)
2022-11-23	v5.10.28	v6.5	<ul style="list-style-type: none"> • Removed 7.1.1 Global View (CNV analysis) • Removed 7.3.1 Global View (Somatic CNV analysis) • Section 7.1 Targeted Panels replaced by Germline and liquid tumor applications • Section 7.2 Large Panels replaced by Solid tumor applications
2022-06-29	v5.10.21	v6.4	<ul style="list-style-type: none"> • Information related to CE-IVD products: page 2, 54, 87 • Update of chapter 1 User Account • Addition of chapter 1.1.1 Login using token card • Addition of chapter 1.1.2 Login using multi-factor authentication • Update of chapter 6.7 OMIM disease* browser • Update of chapter 12 SIS client • Update of chapter 13.2.3 SIS Sequencing Partner - Manual Sample Upload • Addition of chapter 13.2.4 SIS Sequencing Partner - Semi-Automatic Sample Upload
2022-03-23	v5.10.16	v6.3	<ul style="list-style-type: none"> • Update chapter 5.1 VFB overview - examples • Update chapter 6.7 OMIM disease* browser - limitation • Update chapter 7.3.2 Per Sample View (CNV, somatic) - limitation • Addition chapter 10.4 Variant Database Browser - Export variants

Revision History (2)

Date <i>YYYY-MM-DD</i>	SOPHiA DDM™ Version	Manual Version	Change
2021-11-24	v5.10.10	v6.2	<ul style="list-style-type: none"> • Update chapter 1.1 Login • Update chapter 2.11 Main Window Components • Update chapter 3.12.3 Add a disease • Addition chapter 3.12.4 Add a disease* - Germline analyses • Addition chapter 3.12.5 Add a disease* - Somatic analyses • Update chapter 4.6 Predictions • Update chapter 4.9.9 Flagging Tab • Update chapter 4.9.13 Filters • Update chapter 4.10 hg38 annotation • Update chapter 6.1 Cascading Filters - Overview • Update chapter 6.2 Cascading Filters - Create a new cascade • Update chapter 6.3 Cascading Filters - Available filters • Update chapter 6.5 Cascading Filters - Save and load template • Update chapter 10 Variant Database Browser • Removal CE-IVD logos from screenshots (chapter 4, 7, 8, 9)
2021-06-03	v5.10.0	v6.1	<ul style="list-style-type: none"> • Update chapter 4.4.2 Project Settings • Addition chapter 4.9.16 OMIM • Update chapter 6.3 Cascading Filters - Available filters • Addition chapter 6.7 OMIM disease* browser • Update chapter numbers 6.4 to 6.8
2021-05-17	v5.9.4	v6.0	<ul style="list-style-type: none"> • Update chapter 1.1 Login • Update chapter 1.3 Expert Roles • Update chapter 2.11 Main Windows Components • Update chapter 3.8 Analysis Card Details • Addition chapter 3.10.4 Quality indicators - TSO500 application • Update chapter 4.4 Analysis Overview • Update chapter 4.6 Predictions • Update chapter 4.7.1 Screening

Revision History (3)

Date YYYY-MM-DD	SOPHiA DDM™ Version	Manual Version	Change
			<ul style="list-style-type: none"> • Update chapter 4.9.1 Overview • Update chapter 4.9.2 Flagging - Overview • Update chapter 4.9.6 Links to external sources • Addition chapter 4.10 SNVs/Indels - hg38 annotation • Update chapter 6.3 Available Filters • Update chapter 6.4 Save and load template • Update chapter 7.1.1 Targeted Panels - Global View • Update chapter 7.1.2 Targeted Panels - Per Sample View • Update chapter 7.2.1 Large Panels - Per Sample View • Update chapter 7.3.1 Somatic Applications - Global View • Update chapter 7.3.2 Somatic Applications - Per Sample View • Addition chapter 7.3.3 Somatic Applications - CNV flagging • Update chapter 9.3.1 OncoPortal™ - Overview • Update chapter 9.3.2 OncoPortal™ - Disease* Category • Update chapter 9.3.4 OncoPortal™ - Categories T1 to T4, D and P • Update chapter 9.3.5 OncoPortal™ - Clinical Trials* • Update chapter 9.3.6 OncoPortal™ - User Clinical Associations* • Update chapter 9.4.3 Somatic Report - Variant Summary • Update chapter 9.4.5 Somatic Report - Clinical Results* • Update chapter 9.4.6 Somatic Report - Variant Description • Update chapter 9.4.8 Somatic Report - Annexes • Addition chapter 9.5 - Guide to Molecular Profile terms • Update chapter 10.1 Variant Database Browser - Overview • Update chapter 14. Gene Fusion Analysis • Update chapter 14.1.1 Dual DNA/RNA Analysis • Update chapter 14.3 Fusion Tab • Addition chapter 14.4 Fusion Flagging • Update chapter 15 MSI Status Analysis • Update chapter 16.4 Familial Variant Analysis - SNV/Indels View • Update chapter 17.2 SARS-CoV-2 application - Workspace
2020-12-09	v5.8	v5.0	<ul style="list-style-type: none"> • Update chapter 1.1 Login • Update chapter 1.3 Expert Roles • Update chapter 2.2 Create a New Request • Update chapter 2.3 BDS Numbers • Update chapter 2.6 Disease* Database • Update chapter 2.7 to chapter 2.9 • Addition of chapter 2.10 Manage Report Settings • Update chapter 2.11 Main Window Components • Update chapter 3.1 to chapter 3.4 • Update chapter 3.7 to chapter 3.8 • Addition chapter 3.9 Control Samples • Update chapter 3.10 Quality Indicators

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Revision History (4)

Date YYYY-MM-DD	SOPHiA DDM™ Version	Manual Version	Change
			<ul style="list-style-type: none"> • Addition chapter 3.10.3 SARS-CoV-2 Application • Update chapter 3.12 Interpretation Projects* • Update chapter 4.1 to 4.2 • Update chapter 4.4 • Addition chapter 4.4.2 Project Settings • Addition of chapter 4.5 Report Approval Workflow • Update chapter 4.6 Predictions • Update chapter 4.8 Genes • Update chapter 4.9 SNV/Indels • Addition of chapter 4.9.6 Links to external sources • Addition of chapter 4.9.8 Variant Description Tab • Update chapter 5.1 • Addition chapter 6 Cascading Filters • Update chapter 9.1 to chapter 9.4 • Integration of chapter 9. Somatic Report (OncoPortal) in chapter 9.4 • Addition chapter 9.4.3 Variant Summary • Addition chapter 9.4.4 Interpretation* • Addition chapter 9.4.5 Clinical Results* • Addition chapter 9.4.6 Variant Description • Update chapter 9.4.7 to 9.4.8 • Update chapter 11.12 Replicate Analysis SNV/Indels • Update chapter 14 Gene Fusion Analysis • Addition chapter 14.1 Naming convention sample upload • Update chapter 14.2 to 14.3 • Update chapter 16.4 FVA SNV/Indels View • Update chapter 16.5 FVA Variant Unification Algorithm • Addition of chapter 17 SARS-CoV-2 application
2020-10-23	v5.7.8	v4.6	<ul style="list-style-type: none"> • Addition of Disclaimer
2019-10-08	v5.4.0	v4.5	<ul style="list-style-type: none"> • Addition of chapter 1.2 SAML authentication • Update chapter 2.5 Manage Settings • Addition of chapter 2.8 Manage Contacts • Addition of chapter 2.9 Manage Test Info • Update chapter 3.8 Analysis Card Details • Update chapter 3.11.3 Add a Disease* • Update chapter 4.3 Analysis Header • Update chapter 4.4.1 Project Tab • Update chapter 4.4.2 Patient* Tab • Addition of chapter 4.4.3 Specimen Tab • Addition of chapter 4.4.4 Test Information Tab • Update chapter 4.4.5 Documents Tab • Update chapter 4.9.9 ACMG Tab (5)

Revision History (5)

Date YYYY-MM-DD	SOPHiA DDM™ Version	Manual Version	Change
2019-06-03	v5.3	v4.4	<ul style="list-style-type: none"> • Update chapter 1.2 Expert Roles • Update chapter 2.2 Create a New Request • Update chapter 2.7 Manage Virtual Panels • Update chapter 2.8 Manage Contacts • Update chapter 2.9 Manage Test Info • Update chapter 3.3. Patient* Management • Update chapter 3.11 Interpretation Projects* • Update chapter 4.2 Analysis Management • Update chapter 4.4. Analysis Overview • Update chapter 4.4.1 Patient* Tab • Update chapter 4.4.2 Specimen Tab • Update chapter 4.4.3 Project Tab • Update chapter 4.4.5 Documents Tab • Update chapter 5.1 Variant Filter Builder Overview • Update chapter 14 Gene Fusion Analysis
2019-03-04	v5.2.3	v4.3	<ul style="list-style-type: none"> • Update of chapter 2.2 Create a New Request • Update of chapter 2.7 Manage Virtual Panels • Addition of chapter 3.11.3 Add a disease* • Update chapter 8.2 OncoPortal™ Disease* Selection
2018-12-18	v5.2	v4.2	<ul style="list-style-type: none"> • Update of chapter 2.2 Create a New Request • Update of chapter 3.2 Request Management • Update of chapter 3.4 Run Upload Cancellation • Update of chapter 4.8.3 Virtual Panels - Create • Addition of chapter 4.9.13 Variant Copy Function
2018-10-04	v5.1	v4.1	<ul style="list-style-type: none"> • Update of chapter 2.2 Create a New Request • Addition of chapter 2.3 BDS Numbers • Addition of chapter 3.4 Run Upload Cancellation • Update chapter 3.9 Quality Indicators • Addition of chapter 3.10 Expression Analysis Report • Addition of chapter 4.9.12 Compact Variant Table • Addition of chapter 14.1 Dual DNA/RNA Analysis • Update chapter numbers

Revision History (6)

Date YYYY-MM-DD	SOPHiA DDM™ Version	Manual Version	Change
2018-06-29	v5.0	v4.0	<ul style="list-style-type: none"> • Addition of chapter 16 Familial Variant Analysis • Update of chapter 4.9 SNVs/Indels Tab (ACMG Tab) • Update of chapter 10 Variant Database Browser
2018-05-07	v4.9	v3.7	<ul style="list-style-type: none"> • Addition of chapter 4.8.6 Coverage Calculator • Update of chapter 13.1 IDS Sequencing Partner • Addition of chapter 15 MSI Status Analysis
2018-02-27	v4.8	v3.6.5	<ul style="list-style-type: none"> • Update of chapter 2.4 Manage Settings • Update of chapter 9 OncoPortal™ • Update of chapter 14 Fusion Gene Analysis
2017-11-09	v4.7	v3.6.1	<ul style="list-style-type: none"> • Update of chapter 6 CNV Analysis • Update of chapter 11.8 Variant Unification Algorithm • Update of chapter 14 Fusion Gene Analysis
2017-10-11	v4.6	v3.6	<ul style="list-style-type: none"> • Update of chapter 4.4 Analysis overview • Update of chapter 4.7.1 Screening • Update of chapter 13.2.3 IDS Sequencing Partner • Addition of chapter 14 Fusion Genes
2017-07-17	v4.5	v3.5	<ul style="list-style-type: none"> • Addition of chapter 2.5 Disease* Database • Update of chapter 2.6 Manage Virtual Panels • Update of chapter 5 Variant Filter Builder • Addition of chapter 10 Variant Database Browser • Addition of chapter 11 Replicate Analysis • Change of chapter numbers 10 & 11 Integrated Diagnostic Solutions to chapters 12 & 13
2017-11-05	v4.4	v3.0	<ul style="list-style-type: none"> • Addition of chapter 1.2 Expert Roles • Addition of chapter 1.3 Restrictions • Update of chapter 2.2 Create a New Request • Update of chapter 2.5 Manage Virtual Panels • Update of chapter 3.6-3.7 Analysis Card Overview • Addition of chapter 3.8 Interpretation Projects* • Update of chapter 4.4 Analysis Overview • Update of chapter 4.8 Genes • Addition of chapter 9 OncoPortal™ • Addition of chapter 10 & 11 Integrated Diagnostic Solutions • Update of chapter 12 Appendix

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1. User Account

1.1 Download

- Download the SOPHiA DDM™ Platform from here:
<https://www.sophiagenetics.com/downloads/>
- Install the application
- Ensure to meet the minimum system, internet connection and proxy configuration requirements
- Login to the SOPHiA DDM™ Platform using:
 1. Token card and password (see [chapter 1.2.1](#))
 2. Multi-factor authentication (see [chapter 1.2.2](#))

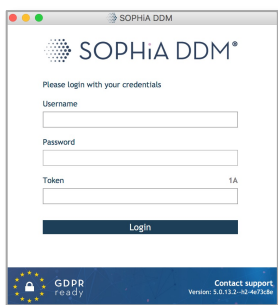
NOTE: Users receive a confirmation email when their user has been created. Only Users and/or Accounts that have been migrated to use the multi-factor authentication have access to this option. Accounts or individual users are informed by email when migrated.

1. User Account

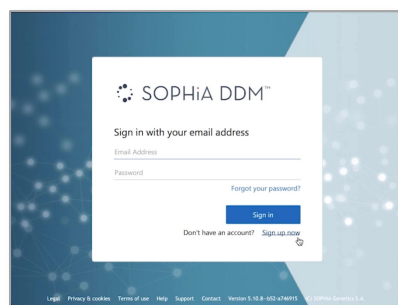
1.2 Login



Application start
Open the SOPHiA DDM™
Platform application.



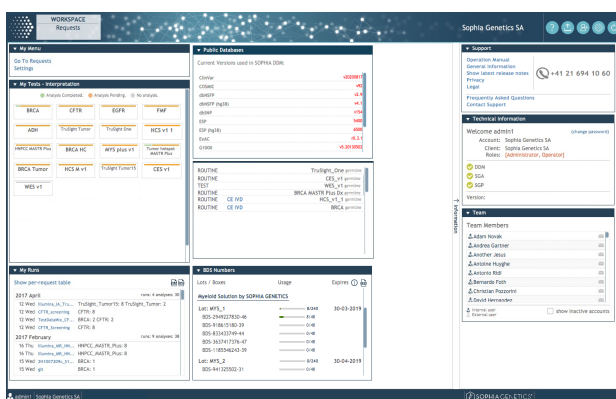
Login using Password & Token card
see [chapter 1.2.1](#)



Login using multi-factor authentication
see [chapter 1.2.2](#)



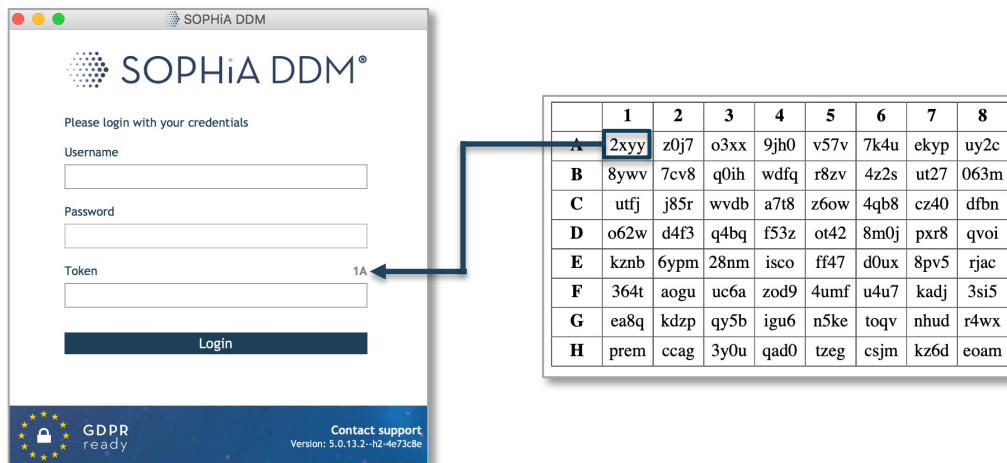
Application dashboard
Main application screen



NOTE: Users receive a confirmation email when their user has been created. Only Users and/or Accounts that have been migrated to use the multi-factor authentication login, have access to this option. Accounts or individual users are informed by email about the migration date.

1. User Account

1.2.1 Login using token card

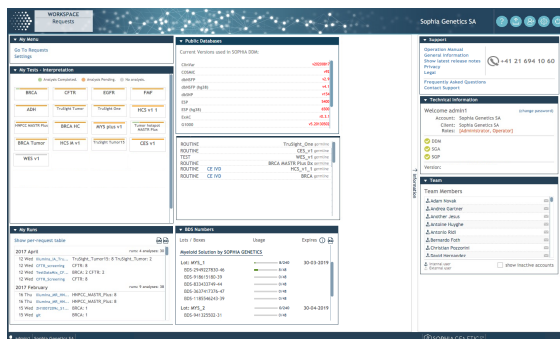


Application login

Enter your username and password. From the token card enter the token from the requested position. Click “Login” to open the application. SOPHiA DDM™ will automatically check for the latest updates.



Application dashboard Main application screen



NOTE: Users with access to several accounts have to select the account they wish to connect to after clicking «Login». To reset the password and or token card, please contact support@sophiagenetics.com.

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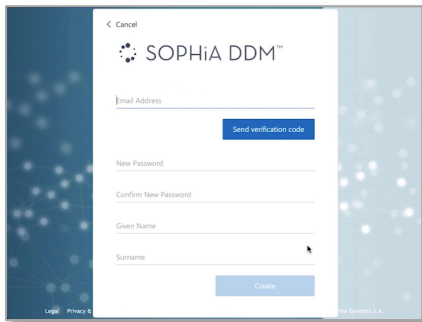
1. User Account

1.2.2 Login using multi-factor authentication



Update authentication method

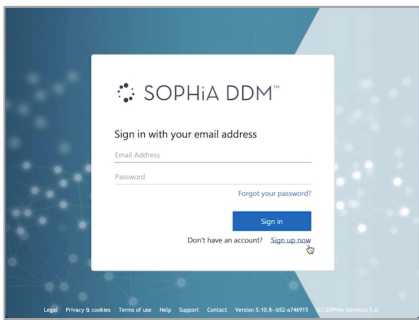
If the user/account was already migrated, click «Update now» to sign up to multi-factor authentication.



Sign-up (first time only)

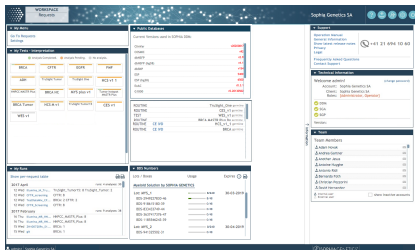
Follow these steps for sign-up:

- 1) Enter email address.
- 2) Input the verification code that was sent to the entered email address.
- 3) Create and confirm a new password and enter name and surname.
- 4) Click “Create”. Then enter again the signed-up email and new verification code.



Login

Login with the registered email and newly created password.



Application dashboard
Main application screen

NOTE: Further information and video instructions available here:
<https://www.sophiagenetics.com/auth-update/>

1. User Account

1.3 Expert Roles (1)

Account

- A SOPHiA DDM™ account with a defined set of activated applications
- One account is shared by several users
- Users can be “admin users”, “restricted users” or both
- Account and user information can be retrieved from the “technical information” and the “team” box on the dashboard (see [chapter 2 - Dashboard](#))

Admin user

- A user who manages the “general scope” of an account (see [chapter 1.3 - Restrictions](#)) and can create Virtual Panels at an account level
- Admin user(s) can change the “general scope” and the “consent restriction” of an analysis after sample upload (see [chapter 3 - Workspace](#))

Restricted user - Operator

- Operators can upload run data
- Operators cannot change the “general scope” of an account
- Operators can add a “consent restriction” before data upload or when accessing an analysis for the first time

Restricted user - Non-Flagger

- Users who have the same rights as “operators” but cannot flag variants (“pathogenicity flag”, “false positive” flag, “in report” flag, “ACMG” flag)

Contact customer service to change user roles:
support@sophiagenetics.com

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1. User Account

1.2 Expert Roles (2)

Feature	Admin	Operator	Non-Flagger	Custom Filter Read-Only	Read-Only
Create run request / upload data	✓	✓	✓	✓	X
Create Interpretation Projects*	✓	✓	✓	✓	X
Open Interpretation Projects*	✓	✓	✓	✓	✓
Edit Virtual Panels in “Application Settings”	✓	X	X	X	X
Add Pathogenicity flag	✓	✓	X	✓	X
Add “In Report” flag	✓	✓	X	✓	X
Add “False Positive” flag	✓	✓	X	✓	X
Create final report	✓	✓	✓	✓	X
Create Virtual Panel in analysis view / Genes tab	✓	✓	✓	✓	X
Add sample consent (first time)	✓	✓	✓	✓	X
Change sample consent	✓	X	X	✓	X
Re-open a completed Interpretation Project*	✓	X	X	X	X
Create, edit, copy, delete custom filters	✓	✓	✓	X	X

✓ Activated

X Blocked

NOTE: User rights are accumulative. For example, a user who has admin rights and needs to upload data, must be assigned “Admin” user rights and “Operator” rights. However, the “Read-Only” role is mutually exclusive, i.e. users can have this or any other role.

1. User Account

1.3 Restrictions

Root panel

- All genes covered by a certain application

General scope

- Restriction specified at the application level for all users of an account
- Can be specified and changed only by an admin user
- Can have the same scope as the ROOT PANEL or could be a subset of genes of the ROOT PANEL

Consent restriction

- Restriction at sample level (to reflect patient's* consent)
- Restriction defined before data upload or before opening an analysis to avoid incidental findings
- Can be specified by “admin users” and “restricted users” (See [chapter 2.2 - New Batch Request](#))
- Can be changed by admin users only

Virtual Panel

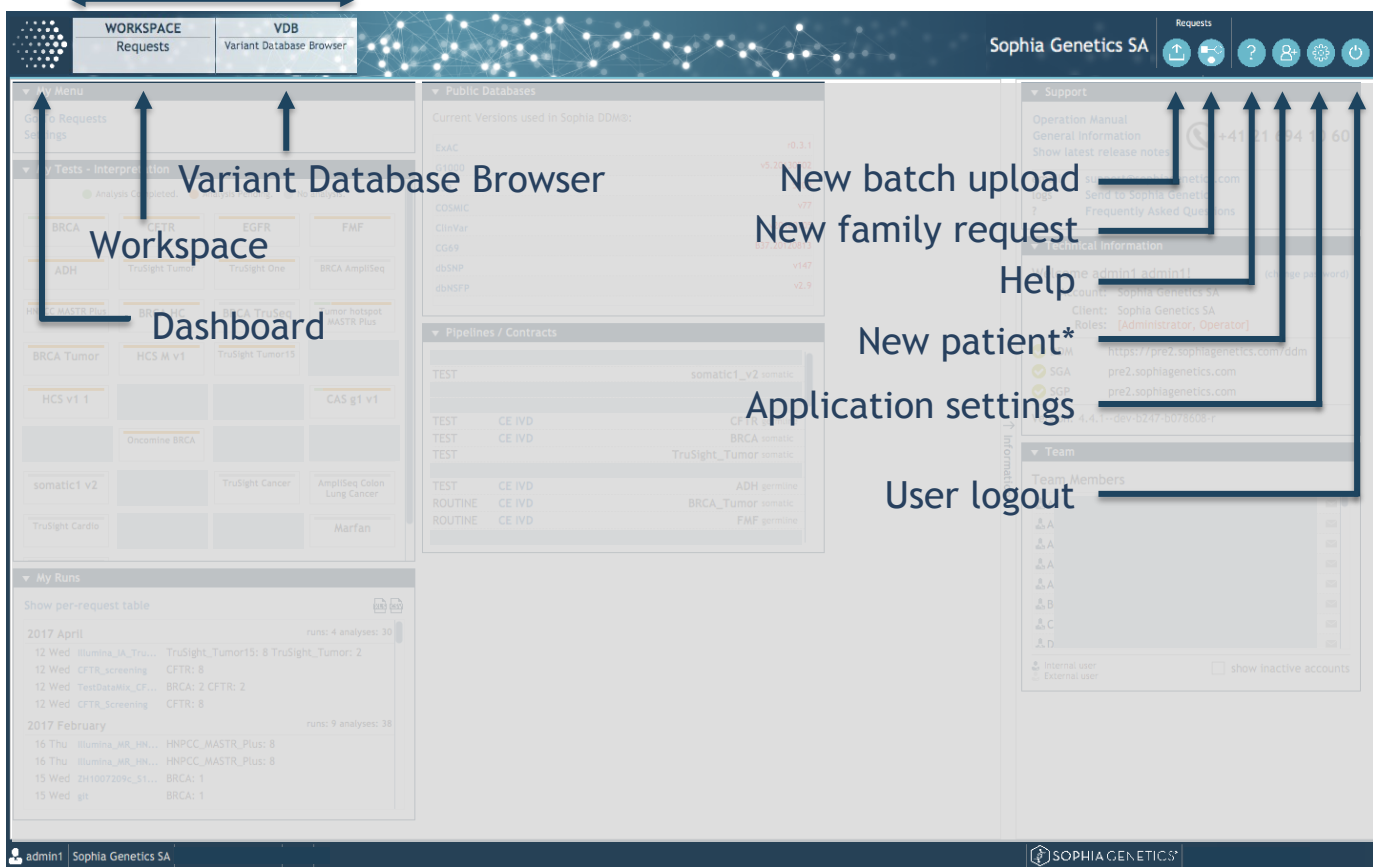
- Restriction at Interpretation Project* level (See [chapter 3.12 - Interpretation Projects*](#) and [chapter 4.8.2 - Virtual Panels - Overview](#))

2. Dashboard

2.1 Main Applications

Application Header

Navigation Bar



User Information:

- Username
- Client
- Starting date of the session

SOPHiA DDM™
release version

Application Footer

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2. Dashboard

2.2 Create a New Request (1)

“Create new batch request”

Creates a new run request for one or multiple sequencing files.

The screenshot displays the Sophia Genetics SA dashboard. A modal window titled "New Run Creation" is open, showing the "Run Parameters" section. The "Reference" field is empty, "Sequencer" is set to "Illumina MiSeq", and "Request Date" is "06-12-2018". The "Sample File(s)" section shows "0 sample(s)" and a "Choose Sequence File" button. The "File Type" is set to "Batch". A "Next" button is visible at the bottom right of the modal. The background dashboard shows various menu items and a table of runs.

Choose a reference name for your request

- Select sequencer
- Choose files to upload
- Click “Yes” to upload all files in a directory or “No” to upload a single file
- Number of samples will be detected automatically
- Click “Next”

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2. Dashboard

2.2 Create a New Request (2)

“Enable primers detection”
De-select checkbox to block automatic primer detection script.

Primer detection status
Primer detection progress bar with the size of the currently uploaded sample and total size of all uploaded samples.

Primer detection script

The primer detection script attempts to automatically identify the application used for library preparation. If primer detection takes too long, the user can press “cancel” and de-select the “enable primers detection” checkbox. In this case, the application has to be chosen manually in the second page of the “create request form” ([see p.22](#)).

NOTE: In case of Illumina NextSeq® or NovaSeq™ sequencers, conversion of the output files (bcl files) to fastq files is required prior to upload to SOPHiA DDM™. Conversion can be done using Illumina’s BaseSpace® application or locally on a Linux system. Please contact Illumina’s tech support for help with this matter.

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2. Dashboard

2.2 Create a New Request (3)

MID (multiplex identifier) & Sample ID
Index used for sample identification & sample name from sample sheet

“Group ID”
If available; see [ch. 14 Gene Fusion Analysis](#)

“Patient*”
By default, the same as sample ID

“Kit”
Library prep kit detected

Patient* consent restriction
[see p.72](#)

Sample Sheet 2/3

5 patient(s), 7 sample(s) group analysis

Sample ID MID	Group ID	Patient	Sample Type	Experiment Type	Library Type	KIT	BDS Number	Control
1 sample5-D S3		sample5	Blood	somatic	DNA	Myeloid Plus Solutio	No BDS Number	🔒 C
2 sample3-D S8		sample3	Blood	somatic	DNA	Myeloid Plus Solutio	No BDS Number	🔒 C
3 sample2-D S9	sample2	sample2	Blood	somatic	DNA	Myeloid Plus Solutio	No BDS Number	🔒 C
4 sample1-D S10	sample1	sample1	Blood	somatic	DNA	Myeloid Plus Solutio	No BDS Number	🔒 C
5 sample1-R S25	sample1	sample1	Blood	somatic	RNA	Myeloid Plus Solutio	N/A	🔒 C
6 sample2-R S27	sample2	sample2	Blood	somatic	RNA	Myeloid Plus Solutio	N/A	🔒 C
7 sample4-R S38		sample4	Blood	somatic	RNA	Myeloid Plus Solutio	N/A	🔒 C

- You must have the same amount of DNA and RNA samples

Back Next

Mouse-over
Uploaded sequencing files per sample.

“Sample type”
Sample material used (default “blood” for germline and hematological, FFPE for “somatic” and “other” for virus applications).

“Experiment type”
Recognized automatically (except if both somatic and germline algorithms are available for one test).

“BDS number”
Sample tracking ID; see [ch. 2.3 BDS numbers](#)

“Control”
Control sample status; see [ch. 3.9 Control Samples](#)

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2. Dashboard

2.2 Create a New Request (4)

The library preparation kit is recognized automatically. To change the detected “KIT”, right-click in field “KIT” and select another application available. To change for several or all samples, press CTRL (⌘ CMD) while selecting. If a “somatic” and a “germline” version of an application are available in one account, the user has to make sure to select the correct sample type to infer the right application.

Sample Sheet 2/3

5 patient(s), 7 sample(s) group analysis

Sample ID MID	Group ID	Patient	Sample Type	Experiment Type	Library Type	KIT	BDS Number
1 sample1-R 525	sample1	sample1	Blood	somatic	RNA	Myeloid Plus Solution by SOPHIA	N/A
2 sample2-R 527	sample2	sample2	Blood	somatic	RNA	Myeloid Plus Solution by SOPHIA	N/A
3 sample4-R 538		sample4	Blood	somatic	RNA	Myeloid Plus Solution by SOPHIA	N/A
4 sample1-D 510	sample1	sample1	Blood	somatic	DNA	Myeloid Plus Solution by SOPHIA	
5 sample3-D 58		sample3	Blood	somatic	DNA	Myeloid Plus Solution by SOPHIA	
6 sample2-D 59	sample2	sample2	Blood	somatic	DNA	Myeloid Plus Solution by SOPHIA	
7 sample5 53		sample5	Blood	somatic	DNA	Myeloid Solution by Sophia	N/A

Automatic kit detection for lar

patient2
patient3
patient4
patient5
patient6
patient7

ected

Back Next

Column “patient*” is editable

To edit patient* ID, click in the cell “Patient*” and start typing. The list of existing patient* IDs shows up in a drop-down menu. Select an existing patient* ID or enter a new patient* ID.

Red: Patient* ID doesn’t exist in account database

Green: Patient* ID already exists in account database

NOTE: Please make sure to always verify the application identified by the primer detection script in the “KIT” column to ensure that the correct pipeline is run for all samples of the batch request.

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2. Dashboard


2.2 Create a New Request (5)

The screenshot shows the SOPHiA DDM interface with a 'New Run Creation' dialog box. The dialog contains a 'Sample Sheet' table with 8 patients and 8 samples. A 'Restriction for Sample' modal is open, showing options for 'Unrestricted' and 'Restricted'. The 'Restricted' option is selected, and a text box contains 'AML'. Below the text box is a checkbox labeled 'I confirm I wish to change the restriction'. A dropdown menu is open, showing a list of predefined Virtual Panels: 'MYS_v1_1 [root] v2 [root] 30', 'AML' (5), and 'MPN' (3). A red message at the bottom of the dialog states: 'You have at least one sample with no bds number selected'.

Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number
1 P03 S3	P03	Blood			
2 P08 S8	P08	Blood			
3 P09 S9	P09	Blood			
4 P10 S10	P10	Blood			
5 P12 S13	P12	Blood			
6 P14 S15	P14	Blood			
7 P15 S16	P15	Blood			
8 P21 S22	P21	Blood	somatic	Myeloid Solution	

Consent restriction

Per-sample-restriction to a subset of genes according to the patient's* consent:

- Click lock symbol to open menu, select “restricted” and chose from a predefined list of Virtual Panels by clicking 
- Click checkbox to confirm restriction

NOTE: Only admin users can create predefined Virtual Panels at an account level (Settings). Consent restrictions can only be changed by admin users after sample upload.

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2. Dashboard

2.2 Create a New Request (6)

Confirmation 3/3

Reference Sequencer: MYS_v1
Request date: 20/09/2018

Sequence File(s): 16 files (2335mb)
Patient(s): 8
Samples(s): 8

	Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number	
1	P03 S3	P03	Blood	somatic	Myetoid Solution by Sophia	BDS-2949227830-46	<input type="checkbox"/>
2	P08 S8	P08	Blood	somatic	Myetoid Solution by Sophia	BDS-2949227830-46	<input type="checkbox"/>
3	P09 S9	P09	Blood	somatic	Myetoid Solution by Sophia	BDS-2949227830-46	<input type="checkbox"/>
4	P10 S10	P10	Blood	somatic	Myetoid Solution by Sophia	BDS-2949227830-46	<input type="checkbox"/>
5	P12 S13	P12	Blood	somatic	Myetoid Solution by Sophia	BDS-2949227830-46	<input type="checkbox"/>
6	P14 S15	P14	Blood	somatic	Myetoid Solution by Sophia	BDS-2949227830-46	<input type="checkbox"/>
7	P15 S16	P15	Blood	somatic	Myetoid Solution by Sophia	BDS-2949227830-46	<input type="checkbox"/>
8	P21 S22	P21	Blood	somatic	Myetoid Solution by Sophia	BDS-2949227830-46	<input type="checkbox"/>

Patient consent is not required for somatic samples.

Back Finish

Summary

- Check all entries (sample & patient* ID, sample type, experiment type, KIT, BDS number, restriction)
- Click checkbox to confirm patient* consent (only for germline samples and tests)
- Click FINISH to start sample upload

NOTE: Selection of BDS numbers is explained in [chapter 2.3](#). If SOPHiA DDM™ is closed before sample upload is completed, upload is paused and resumed after re-login.

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2. Dashboard

2.3 BDS Numbers

2.3.1 Overview

With SOPHiA DDM™ version 5.1, a new feature has been introduced that permits users to track the usage of bundle solution kits. To make this possible, a unique tracking ID (“BDS Number”) is printed on each bundle solution kit - box 1. This number has to be entered in the “create request form” when uploading samples.

BDS numbers are only available for catalog and custom SOPHiA DDM™ bundle solutions. BDS implementation does not concern applications using:

- Swift Biosciences kits
- Devyser kits
- Illumina Inc. kits
- Archer Dx FusionPlex® kits
- Agilent Technologies Inc. MASTR™ kits
- Paragon Genomics, Inc kits
- Twist Bioscience kits

NOTE: Please note, BDS numbers will be phased out and replaced in the next months. Further communications will follow.









2. Dashboard

2.3 BDS Numbers

2.3.2 Selection of BDS Numbers (1)

Step 1 - Locate the BDS number



Box 1 of 2	 -25° to -15° C
REF B1.01.0107.C-48	 03/2019
LOT 1706-2-A	 48  
 BDS-2949227830-46	
 SOPHiA GENETICS Saint-Sulpice Switzerland	  ID-80107

The BDS number can be found:

- On the side sticker of box 1 of the SOPHiA GENETICS bundle solution kit (-15 °C to -25 °C storage temperature)
- In the annex of the delivery note

NOTE: Each BDS number is related to one lot number and bundle solution kit box. If different members of your team conduct library preparation and sample upload, please make sure that they are all informed about this implementation.

2. Dashboard

2.3 BDS Numbers

2.3.2 Selection of BDS Numbers (2)

Step 2 - Upload your data

The screenshot displays the SOPHiA DDM dashboard with a 'New Run Creation' dialog box open. The dialog box has a title bar 'New Run Creation' and a close button. It is divided into two main sections: 'Parameters' and 'Sample File(s)'. In the 'Parameters' section, there are three input fields: 'Reference' (empty), 'Sequencer' (set to 'Illumina MiSeq'), and 'Request Date' (set to '06-12-2018'). In the 'Sample File(s)' section, there is a checkbox for 'Enable Primers Detection' (checked), a 'Sequence File(s)' field with a 'Choose Sequence File' button, and a 'File Type' dropdown set to 'Batch'. The 'Sample File(s)' section also displays '0 sample(s)'. A red box highlights the 'Choose Sequence File' button, and a red arrow points to it from below. The background shows the dashboard interface with a top navigation bar, a sidebar with 'My Menu' and 'My Tests' sections, and a main content area with various data tables and a 'Support' section on the right.

New batch request

Click the “create new batch request” button and upload your data as usual. For more details, please see [chapter 2.2 - Create a new Request](#).

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2. Dashboard

2.3 BDS Numbers

2.3.2 Selection of BDS Numbers (3)

Step 3 - Enter the BDS number in the “create request form”

BDS number column

In the second page of the “create request form”, a new column “BDS number” is available. A grey field indicates that no BDS number was entered, yet.

The screenshot shows the 'New Run Creation' window with a 'Sample Sheet' table. The table has the following columns: Sample ID MID, Patient, Sample Type, Experiment Type, KIT, and BDS Number. The BDS Number column contains greyed-out cells, indicating no BDS number was entered for any of the 8 samples.

Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number
1 P03 S3	P03	Blood	somatic	Myeloid Solution by Sophia	
2 P08 S8	P08	Blood	somatic	Myeloid Solution by Sophia	
3 P09 S9	P09	Blood	somatic	Myeloid Solution by Sophia	
4 P10 S10	P10	Blood	somatic	Myeloid Solution by Sophia	
5 P12 S13	P12	Blood	somatic	Myeloid Solution by Sophia	
6 P14 S15	P14	Blood	somatic	Myeloid Solution by Sophia	
7 P15 S16	P15	Blood	somatic	Myeloid Solution by Sophia	
8 P21 S22	P21	Blood	somatic	Myeloid Solution by Sophia	

You have at least one sample with no BDS number selected

NOTE: Entry of BDS numbers is mandatory to proceed. Kits ordered before the installation of release v5.1 do not carry a BDS number. “No BDS number” will be defaulted until the delivery of the first kit with a BDS number. See the following pages to know more about how to select BDS numbers or the “No BDS number” option.

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2. Dashboard

2.3 BDS Numbers

2.3.2 Selection of BDS Numbers (4)

Step 3 - Enter the BDS number in the “create request form”

OPTION 1 - SPECIFY THE BDS NUMBER OF ONE SAMPLE

1 Select sample
Click to select one sample.

2 BDS number column
Right- or left-click an empty BDS number field. A combo box appears.

Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number
1 P03 S3	P03	Blood	somatic	Myeloid Solution by Sophia	
2 P08 S8	P08	Blood	somatic	Myeloid Solution by Sophia	
3 P09 S9	P09	Blood	somatic	Myeloid Solution by Sophia	
4 P10 S10	P10	Blood	somatic	Myeloid Solution by Sophia	
5 P12 S13	P12	Blood	somatic	Myeloid Solution by Sophia	
6 P14 S15	P14	Blood	somatic	Myeloid Solution by Sophia	
7 P15 S16	P15	Blood	somatic	Myeloid Solution by Sophia	
8 P21 S22	P21	Blood	somatic	Myeloid Solution by Sophia	

You have at least one sample with no BDS number selected

Apply to all samples with this kit

Select BDS Number for 1 sample(s)

Change kit for 1 sample(s)

BDS-1185546243-39 Lot: MYS_1 Expiration: 30-03-2019

BDS-1327254568-43 Lot: MYS_2 Expiration: 30-04-2019

BDS-2829345071-41 Lot: MYS_2 Expiration: 30-04-2019

BDS-283365598-49 Lot: MYS_2 Expiration: 30-04-2019

BDS-2949227830-46 Lot: MYS_1 Expiration: 30-03-2019

3 Dropdown menu selection
Click the dropdown menu and select the right BDS number for the selected sample. Only BDS numbers for the selected kit are shown. Usage of the respective BDS numbers is shown below the number.

NOTE: If kits are ordered through a distributor, the selection of BDS numbers from the dropdown menu is not available. In this case, please manually type in the BDS number from Box 1 in the format “BDS-1234567890-XX” in the dropdown menu field and press enter to confirm. Alternatively, select “No BDS number” from the list.

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2. Dashboard

2.3 BDS Numbers

2.3.2 Selection of BDS Numbers (5)

Step 3 - Enter the BDS number in the “create request form”

OPTION 2 - SPECIFY THE BDS NUMBER FOR SEVERAL SAMPLES

1 Multi-select samples

Click one sample, press CTRL key (⌘/CMD) to multi-select samples. Alternatively, click one sample, press shift, select another sample to multi-select all samples between the two.

2 BDS number column
Right- or left-click into empty BDS number field. A combo box appears.

Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number
1 P03 S3	P03	Blood	somatic	Myeloid Solution by Sophia	
2 P08 S8	P08	Blood	somatic	Myeloid Solution by Sophia	
3 P09 S9	P09	Blood	somatic	Myeloid Solution by Sophia	
4 P10 S10	P10	Blood	somatic	Myeloid Solution by Sophia	
5 P12 S13	P12	Blood	somatic	Myeloid Solution by Sophia	
6 P14 S15	P14	Blood	somatic	Myeloid Solution by Sophia	
7 P15 S16	P15	Blood	somatic	Myeloid Solution by Sophia	
8 P21	P21	Blood	somatic	Myeloid Solution by Sophia	

You have at least one sample with no BDS number selected

Apply to all samples with this kit

BDS-1185546243-39 Lot: MYS_1 Expiration: 30-03-2019
0/48

Myeloid Solution by SOPHIA GENETICS

BDS-1327254568-43 Lot: MYS_2 Expiration: 30-04-2019
0/48

Myeloid Solution by SOPHIA GENETICS

BDS-2829345071-41 Lot: MYS_2 Expiration: 30-04-2019
0/48

Myeloid Solution by SOPHIA GENETICS

BDS-283365598-49 Lot: MYS_2 Expiration: 30-04-2019
0/48

Myeloid Solution by SOPHIA GENETICS

BDS-2949227830-46 Lot: MYS_1 Expiration: 30-03-2019
0/48

Myeloid Solution by SOPHIA GENETICS

3 Dropdown menu selection

Click the dropdown menu and select the right BDS number for the selected sample. Only BDS numbers for the selected kit are shown. Usage of the respective BDS numbers is shown below the number.

NOTE: If kits are ordered through a distributor, the selection of BDS numbers from the dropdown menu is not available. In this case, please multi-select samples then manually type in the BDS number from box 1 in the format “BDS-1234567890-XX” in the dropdown menu field and press enter to confirm. Alternatively, select “No BDS number” from the list.

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2. Dashboard

2.3 BDS Numbers

2.3.2 Selection of BDS Numbers (6)

Step 3 - Enter the BDS number in the “create request form”

OPTION 3 - SPECIFY THE BDS NUMBER FOR ALL SAMPLES WITH THE SAME KIT

1 BDS number column

Right- or left-click into empty BDS number field. A combo box appears.

2 Apply to all samples checkbox

Select the checkbox.

Sample Sheet

8 patient(s), 8 sample(s)

Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number
1 P03 S3	P03	Blood	somatic	Myeloid Solution by Sophia	
2 P08 S8	P08	Blood	somatic	Myeloid Solution by Sophia	
3 P09 S9	P09	Blood	somatic	Myeloid Solution by Sophia	
4 P10 S10	P10	Blood	somatic	Myeloid Solution by Sophia	
5 P12 S13	P12	Blood	somatic	Myeloid Solution by Sophia	
6 P14 S15	P14	Blood	somatic	Myeloid Solution by Sophia	
7 P15 S16	P15	Blood	somatic	Myeloid Solution by Sophia	
8 P21 S22	P21	Blood	somatic	Myeloid Solution by Sophia	

You have at least one sample with no BDS number selected

Select BDS Number for 8 sample(s)

Change kit for 1 sample(s)

Apply to all samples with this kit

BDS-1185546243-39 Lot: MYS_1 Expiration: 30-03-2019

BDS-1327254568-43 Lot: MYS_2 Expiration: 30-04-2019

BDS-2829345071-41 Lot: MYS_2 Expiration: 30-04-2019

BDS-283365598-49 Lot: MYS_2 Expiration: 30-04-2019

BDS-2949227830-46 Lot: MYS_1 Expiration: 30-03-2019

3 Dropdown menu selection

Click the dropdown menu and select the right BDS number for the selected sample. Only BDS numbers for the selected kit are shown. Usage of the respective BDS numbers is shown below the number.

NOTE: If kits are ordered through a distributor, the selection of BDS numbers from the dropdown menu is not available. In this case, please select the checkbox “Apply to all samples with this kit”, manually type in the BDS number from box 1 in the format “BDS-1234567890-XX” in the dropdown menu field type and press enter to confirm. Alternatively, select “No BDS number” from the list.

2. Dashboard

2.3 BDS Numbers

2.3.2 Selection of BDS Numbers (7)

Step 3 - Enter the BDS number in the “create request form”

The screenshot shows the SOPHiA DDM software interface. A 'New Run Creation' dialog box is open, displaying a 'Sample Sheet' for 8 patient(s) and 8 sample(s). The table below shows the details for each sample:

Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number
P03 S3	P03	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
P08 S8	P08	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
P09 S9	P09	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
P10 S10	P10	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
P12 S13	P12	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
P14 S15	P14	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
P15 S16	P15	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
P21 S22	P21	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46

The 'Next' button is highlighted with a red arrow, indicating the next step in the process.

BDS number column

Once BDS numbers are selected for all bundle solution samples, the “next” button becomes active to proceed.

2. Dashboard

2.3 BDS Numbers

2.3.2 Selection of BDS Numbers (8)

Step 4 - Verify all entries and start the upload

The screenshot shows the Sophia Genetics DDM interface. A 'New Run Creation' confirmation dialog is open, displaying a table of 8 samples. The dialog includes a 'Back' button and a 'Finish' button, which is highlighted with a blue arrow. The table lists sample IDs, patient names, sample types, experiment types, kits, and BDS numbers.

Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number
1 P03 S3	P03	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
2 P08 S8	P08	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
3 P09 S9	P09	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
4 P10 S10	P10	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
5 P12 S13	P12	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
6 P14 S15	P14	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
7 P15 S16	P15	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46
8 P21 S22	P21	Blood	somatic	Myeloid Solution by Sophia	BDS-2949227830-46

Reference Sequencer: MYS_v1
 Request date: Illumina MiSeq 20/09/2018
 Sequence File(s): 16 files (2335mb)
 Patient(s): 8
 Samples(s): 8

Patient consent is not required for somatic samples.

Back Finish

Confirm and start upload

In the third page of the “create request form”, BDS numbers are shown for all samples. Verify all entries and click “finish” to start the upload.

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2. Dashboard

2.3 BDS Numbers

2.3.3 Usage Tracking

BDS numbers box

A new box “BDS numbers” is available in the dashboard. Minimize other boxes if needed. BDS numbers are sorted by application, lot number and expiration date. 30 days after expiry, the lot number disappears from the list. The list of kit boxes available for this account can be exported to a CSV.

The screenshot shows the SOPHiA DDM dashboard interface. A callout box highlights the 'BDS Numbers' section, which is a table listing kit boxes. The table is titled 'Myeloid Solution by SOPHiA GENETICS' and contains the following data:

Lots / Boxes	Usage	Expires
Lot: MYS_1		
BDS-918615180-39	0/240	30-03-2019
BDS-833433749-44	0/48	
BDS-3637417376-47	0/48	
BDS-2949227830-46	0/48	
BDS-1185546243-39	0/48	
Lot: MYS_2		
BDS-941325502-31	0/240	30-04-2019
BDS-376003478-27	0/48	

NOTE: If kits are ordered through a distributor, usage tracking is not available.

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2. Dashboard

2.4 Create a New Patient* File

“Patient* detail”
Edit name, date of birth, and other patient* personal details

“Create new patient*”
Add information for a new patient*.

“Medical info”
Edit patient* information and patient’s* parents' details.

“Documents”
Attach files to patient’s* record.

“Medical info”
Edit patient* information and patient’s* parents' details.

This box is not designed to collect direct identifying data such as name or surname. Please restrict the content of this box to medical information.

“Documents”
Attach files to patient’s* record.

2. Dashboard

2.5 Manage Settings

Active tab

“Settings”
Edit application settings and Virtual Panels at account level (general scope).

Disable the checkbox to deactivate background primer loading for large panels.

Click to save changes.

Select checkbox to use the “compact variant table” or the “customizable variant table” (chapter 4.9.14).

OncoPortal™ users (somatic applications only) can select the language for automatically generated conclusion (chapter 9.3.8).

Select date and time format for use in:

- SOPHiA DDM
- Variant Reports

The screenshot shows the 'Settings' window with the 'Configuration' tab active. The 'Load large panels' checkbox is checked. The 'Use new Compact Variant Table' checkbox is also checked. The 'Clinical Results Conclusions Language' is set to 'FR'. The 'Date Format' is 'dd/MM/yyyy' and the 'Time Format' is '24h'. The 'Memory' is set to '4096m'. The 'Save' button is highlighted.

“Memory settings”

A minimum of 2048M RAM memory allocation is recommended. SOPHiA DDM™ checks the RAM of the user’s operating system and recommends up to ½ of the RAM (but no more than 4GB) to the user in a pop-up.

NOTE: If you are experiencing memory issues with SOPHiA DDM™ while uploading large panel data (e.g., WES, CES, TruSight® One), deactivate the “load large panels” checkbox and press the “clear pipelines cache” button. This will improve performance but disable the automatic detection of the application during upload and require manual selection of the application in the “new batch request” form.

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2. Dashboard

2.6 Disease* Database

Active tab

“Settings”

Edit application settings and Virtual Panels at account level (general scope).

The screenshot displays the SOPHiA DDM interface with the 'Settings' dialog box open. The dialog is titled 'DDM Settings' and has several tabs: 'Virtual Panels', 'Diseases', 'Configuration', 'Contacts', 'Test Info', and 'Report'. The 'Diseases' tab is selected, showing a search bar with the text '9089' and a list of diseases. The first disease in the list is 'non-small cell lung carcinoma', which is highlighted. Below the list, there is a note: 'hold cmd to multi-select diseases press Shift B to add selected diseases to bookmarks'. To the right of the list is a 'Metadata' section for the selected disease, showing details such as 'doid: 3908', 'Name: non-small cell lung carcinoma', 'Definition: A lung carcinoma that is characterized as any type of epithelial lung cancer other than small cell lung carcinoma.', 'Link: http://en.wikipedia.org/wiki/Non-small-cell_lung_carcinoma', 'Is a: disease > disease of cellular proliferation > cancer > organ system cancer > respiratory system cancer > lung cancer > lung carcinoma', 'Synonyms: Non-small cell lung cancer, NSCLC', and 'References: MESH:D002289, NCI:C2926, OTHER:0003060, OTHER:C0007131, OTHER:05223'. A 'Close' button is located at the bottom right of the dialog. In the background, the main interface shows 'My Menu', 'My Tests - Interpretation', and 'My Runs' sections.

Type disease* name to search the ontology (list based on disease-ontology.org)

Select one disease* and click the ☆ icon to bookmark it. To bookmark several diseases*, press CTRL (⌘cmd) while selecting.

Metadata of the selected disease* (based on disease-ontology.org)

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2. Dashboard

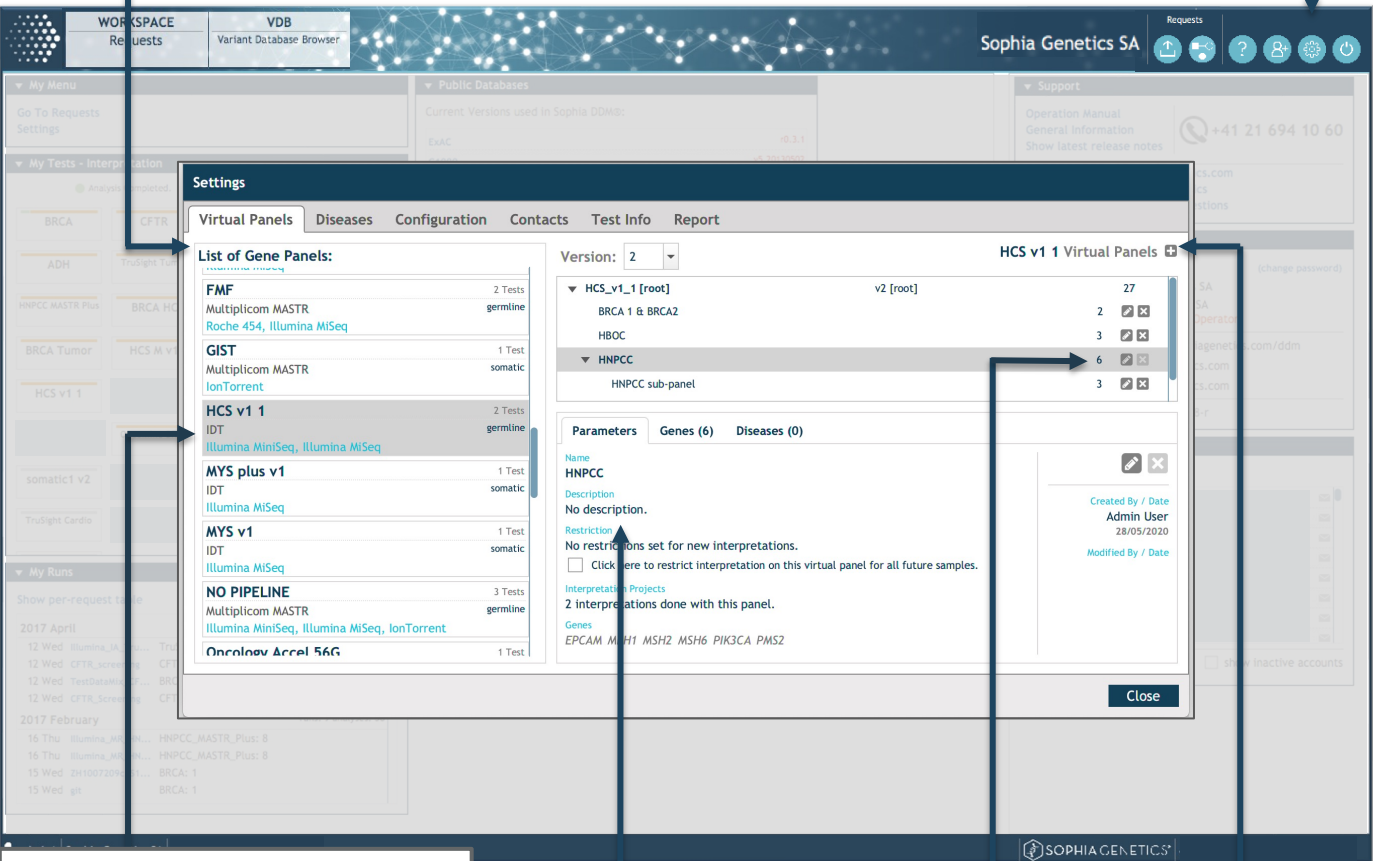
2.7 Manage Virtual Panels (1)

List of Gene Panels

Once clicked on the “Virtual Panel” tab, all applications of an account are listed on the left.

“Settings”

Edit application settings and Virtual Panels at account level (general scope).



“Create / delete / edit” a Virtual Panel

- Select the application of interest
- Access to a detailed view of existing Virtual Panels (at least root panel) on the right

Annotation System version

“Edit/delete”

Click to edit or click X to delete a Virtual Panel.

“Create” a new Virtual Panel

Click to create a new Virtual Panel.

NOTE: Only admin users can change Virtual Panels at an account level. For “restricted users”, this view is read-only.

2. Dashboard

2.7 Manage Virtual Panels (2)

Root Virtual Panel version

“Create Virtual Panel” window
Enter a name and description for the Virtual Panel.

Genes available for Virtual Panel

Add / remove genes
Click > / < to add/remove single genes to/from selection
Click >> / << to add/remove all genes to/from selection

Click “save” to add the Virtual Panel

NOTE: This view is only accessible to admin users. The version of the Root Virtual Panel indicates on which version of the Annotation algorithm it was created. Analyses with gene name changes (according to HGNC nomenclature) run after the Annotation System update (p5.5.0) are automatically assigned to version 2.

2. Dashboard

2.7 Manage Virtual Panels (3)

The screenshot displays the SOPHiA DDM interface with a 'Settings' dialog box open. The dialog is titled 'Settings' and has several tabs: 'Virtual Panels', 'Diseases', 'Configuration', 'Contacts', 'Test Info', and 'Report'. The 'Virtual Panels' tab is selected, showing a 'List of Gene Panels' on the left and a 'Parameters' section on the right. The 'List of Gene Panels' includes entries like 'FMF', 'GIST', 'HCS v1 1', 'MYS plus v1', 'MYS v1', 'NO PIPELINE', and 'Oncology Accel 56G'. The 'Parameters' section for 'HNPCC' shows a checked checkbox under 'Restriction' and a list of genes: 'ERCCAM MLH1 MSH2 MSH6 PIK3CA PMS2'. A blue arrow points from the 'Restriction' section to the 'General scope' text box below.

General scope

- Check box to restrict the general scope of an account (all users) to a sub-panel
- Uncheck box to remove restriction
- Click “Yes” to confirm

**NOTE: Only admin users can change Virtual Panels at account level.
For “restricted users”, this view is read-only.**

2. Dashboard

2.7 Manage Virtual Panels (4)

The screenshot displays the SOPHiA DDM interface with a 'Settings' window open for 'Virtual Panels'. The window has tabs for 'Virtual Panels', 'Diseases', 'Configuration', 'Contacts', 'Test Info', and 'Report'. The 'Virtual Panels' tab is active, showing a 'List of Gene Panels' on the left and a 'HCS v1 1 Virtual Panels' configuration on the right. The 'List of Gene Panels' includes entries like FMF (2 Tests, germline), GIST (1 Test, somatic), HCS v1 1 (2 Tests, germline), MYS plus v1 (1 Test, somatic), MYS v1 (1 Test, somatic), NO PIPELINE (3 Tests, germline), and Oncology Accel 56G (1 Test, somatic). The 'HCS v1 1 Virtual Panels' section shows a tree view with 'HCS_v1_1 [root]' containing 'BRCA 1 & BRCA2', 'HBOC', 'HNPCC', and 'Z Digestive cancer'. Below this, a 'Parameters' section shows 'Genes (27)' and 'Diseases (0)'. A search bar is present, and a list of 27 genes is displayed: ABRAXAS1, APC, ATM, BRAD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, PALB2, PIK3CA, PMS2, MS2CL, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2. Two blue arrows point from the gene list to callout boxes below the screenshot.

Genes selected for the Virtual Panel

Query gene list of the Virtual Panel

2. Dashboard

2.7 Manage Virtual Panels (5)

Add disease* to the Virtual Panel
(See p. [p.76](#) for Disease* Ontology tree)

The screenshot shows the SOPHiA DDM interface with the 'Settings' dialog open for 'HCS v1 1 Virtual Panels'. The 'Diseases' tab is selected, and 'Lynch Syndrome' is chosen from the list. A callout box points to the 'Diseases' tab and the selected disease.

Settings

Virtual Panels | Diseases | Configuration | Contacts | Test Info | Report

List of Gene Panels:

Gene Panel	Tests	Category
FMF	2 Tests	germline
Multiplicom MASTR		
Roche 454, Illumina MiSeq		
GIST	1 Test	somatic
Multiplicom MASTR		
IonTorrent		
HCS v1 1	2 Tests	germline
IDT		
Illumina MiniSeq, Illumina MiSeq		
MYS plus v1	1 Test	somatic
IDT		
Illumina MiSeq		
MYS v1	1 Test	somatic
IDT		
Illumina MiSeq		
NO PIPELINE	3 Tests	germline
Multiplicom MASTR		
Illumina MiniSeq, Illumina MiSeq, IonTorrent		
Oncology Accel 56G	1 Test	somatic
Swift		

Version: 2

HCS v1 1 Virtual Panels

Virtual Panel	Tests	Actions
▼ HCS_v1_1 [root]	27	
BRCA 1 & BRCA2	2	✖
HBOC	3	✖
▼ HNPCC	6	✖
HNPCC sub-panel	3	✖
Z Digestive cancer	7	✖

Parameters | Genes (6) | Diseases (1)

Diseases

Lynch Syndrome

Close

Disease* selection

- Click the link “Select Disease*”
- Start typing disease* name
- Select disease* from list
- Click “OK” and “YES” to confirm

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2. Dashboard

2.8 Manage Contacts (1)

Search a contact

Type within the search field

Add a contact

From left to right: add Facility, Service, Contact Person

Select a contact

Selected contact is highlighted in grey

Modify selected contact details

User can edit or delete a contact (see the buttons in the bottom right corner)

Settings

Virtual Panels Diseases Configuration **Contacts** Test Info Report

Contact list

Search

Jane Smith

Lab

Physician

Name Jane Smith Physician Information Medical Id

Tel Contact Information Fax

Email

Edit Delete

Use this tab to enter the details of any facility, service or contact person that you may need to include in variant reports. Any changes to medical contacts will be retroactively applied to any linked analyses

Close

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2. Dashboard

2.8 Manage Contacts (2)

Add a facility

Click on the corresponding button to open a form on the right-hand side of the panel.

The screenshot displays the 'Settings' application window with the 'Contacts' tab selected. On the left, a 'Contact list' shows several entries, each with a small icon representing its type (person for contact, building for facility). A blue circle with the number '1' highlights the 'Add Facility' button (a building icon) next to the 'Laboratory of Clinical Pathology' entry. On the right, a 'Facility' form is open, containing the following fields:

- Institution:** Institution Type (dropdown), Name (text input), Institution ID (text input), Web (text input).
- Contact Information:** Tel (text input), Fax (text input), Email (text input).
- Address:** Address 1 (text input), Address 2 (text input), Postcode/ZIP (text input), City (text input), State (text input), Country (dropdown menu showing '-- Unknown --').

Buttons for 'Cancel', 'Save', and 'Close' are visible at the bottom of the form. A blue circle with the number '2' points to the 'Facility' form.

Add the details of the facility
Fill in the form.

Follow the same steps to add a Service or Contact Person.

2. Dashboard

2.8 Manage Contacts (3)

The screenshot shows the SOPHiA DDM interface with the 'Settings' window open. The 'Contacts' tab is selected, and the 'Facility' form is displayed. The form contains the following fields:

- Institution Type: Medical Facility
- Name: University Center
- Institution ID: UML
- Web: [empty]
- Contact Information:
 - Tel: +45 456 78 90
 - Fax: [empty]
 - Email: uni.center@mail.com
- Address:
 - Address 1: avenu Leman
 - Address 2: [empty]
 - Postcode/ZIP: 10900
 - City: Boisy
 - State: Vuad
 - Country: Switzerland

Buttons: Cancel, Save, Close

Use this tab to enter the details of any facility, service or contact person that you may need to include in variant reports
Any changes to medical contacts will be retroactively applied to any linked analyses

When the details are added to the form, click Save.

Follow the same steps to add a Service or Contact Person.

2. Dashboard

2.8 Manage Contacts (4)

The screenshot displays the SOPHiA DDM interface with the 'Settings' dialog box open. The 'Contacts' tab is active, showing a 'Contact list' on the left and a 'Facility' details panel on the right. The 'Contact list' contains the following entries:

Name	Facility ID
Jane Smith	1657FR
St James' University Hospital	SJU16785
SJU Pathology	
Pilavullakandi Thekkaparambil Usha	187676
University Center	UML

The 'Facility' details panel for 'University Center UML' shows the following information:

Medical Facility Information	
Name	University Center
Facility ID	UML
Contact Information	
Tel	+45 456 78 90
Email	uni.center@mail.com
Address	
Address 1	avenu Leman
Address 2	Boisy
Postcode/ZIP	10900
State	Vuad
City	Boisy
Country	Switzerland

Below the 'Facility' details panel, there are 'Edit' and 'Delete' buttons. A blue arrow points from the selected facility in the 'Contact list' to the 'Facility' details panel. Another blue arrow points from the 'Edit' and 'Delete' buttons to a text box below.

Created facility appears in the list of contacts. Select the facility to see its details on the right side of the panel.

Facility details
User can edit or delete the details of the facility.

2. Dashboard

2.8 Manage Contacts (5)

Delete

- Select the facility to be deleted
- Click Delete
- Click OK on the warning message to proceed

Deleting a description will result in deletion from all existing Interpretation Projects* where the description is used.

The screenshot shows the SOPHiA DDM interface with the 'Settings' dialog box open. The 'Contacts' tab is selected, displaying a 'Contact list' and a 'Medical Facility' details view. The 'Contact list' shows several facilities, with 'University Center UML' selected. The 'Medical Facility' details view shows the following information:

Medical Facility Information	
Name	University Center
Facility ID	UML
Web	
Contact Information	
Tel	+45 456 78 90
Fax	
Email	uni.center@mail.com
Address	
Address 1	avenu Leman
Address 2	
Postcode / ZIP	10900
City	Botsty
Country	Switzerland
State	Vuad

The 'Delete' button is highlighted with a blue arrow pointing to a callout box.

Add service or person to existing facility

To add a service or a contact person to the selected facility, click on Add Contact or Add Service corresponding icon within the Facility contact card.

Edit

- Select the facility to be edited
- Click Edit

Editing a description will result in the edit being propagated to all existing Interpretation Projects* where the description is used.

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2. Dashboard

2.9 Manage Test Info (1)

Test Performed

Description of the test to be displayed on Variant Report. User can create, edit or delete a test description.

Methodology

Description of the methodology to be displayed on Variant Report. User can create, edit or delete it.

The screenshot displays the 'Settings' window in the SOPHiA DDM™ application, specifically the 'Test Info' tab. The window is divided into two main sections: 'Test Performed' and 'Methodology'. Each section has a 'Create', 'Edit', and 'Delete' button. The 'Test Performed' section shows a table with columns for 'SOPHiA Application' (CES_v1), 'Short Name (not displayed)' (CES Standard), 'Test Performed (as displayed on report)' (Clinical Exome Standard Protocol), and 'Methodology' (Illumina MiSeq germline). The 'Methodology' section shows a table with columns for 'SOPHiA Application' (CES_v1), 'Short Name (not displayed)' (CES Standard), 'Methodology (as displayed on report)' (Clinical Exome standard laboratory methodology, see method number 12345H), and 'Methodology' (Illumina MiSeq germline). A note at the bottom of the window states: 'Any changes to tests performed or methodologies will be retroactively applied to any linked analyses'. The background shows the main dashboard with various navigation options and a sidebar with 'My Tests - Interpretation'.

SOPHiA DDM™ Application

The text entered on Test Performed and Methodology will be available for selection in Interpretation Projects* for analyses on the application selected here.

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2. Dashboard

2.9 Manage Test Info (2)

Create Test Performed or Methodology description

- Click Create button at the top of the appropriate section
- Select the application for which you want to use the description
- Enter the text to be displayed on the report
- Click Save

Delete

- Select the Test Performed, or Methodology to be deleted
- Click Delete
- Click OK on the warning message to proceed

Deleting a description will result in deletion from all existing Interpretation Projects* where the description is used.

Edit

- Select the Test Performed, or Methodology to be edited
- Click Edit

Editing a description will result in the edit being propagated to all existing Interpretation Projects* where the description is used.

2. Dashboard

2.10 Manage Report Settings

Report creation upon Interpretation Project* completion
Select whether the report should be created always, never or upon confirmation.

The screenshot displays the 'Settings' dialog box in the SOPHiA DDM application. The dialog is titled 'Settings' and has several tabs: 'Virtual Panels', 'Diseases', 'Configuration', 'Contacts', 'Test Info', and 'Report'. The 'Report' tab is active, showing two main sections: 'General Settings' and 'Test Specific Settings'.

General Settings:

- Create report upon completion:** Radio buttons for 'Always', 'Always ask' (selected), and 'Never'.
- Save local copy automatically
- Open report automatically after saving
- Variant report download location:** A text field containing '/Users/username/folder' and a 'Change location' button.
- The download location is only for final reports
- All changes are saved automatically

Test Specific Settings:

Test	Report Type
FMF	germline
GIST	somatic
HCS_v1_1	germline
MYS_plus_v1	somatic
MYS_v1	somatic
Oncology_Accel_56G	somatic

HCS_v1_1 germline:

- Show CNVs
- Show Screening
- Show Fusions
- Retained
- Low Confidence
- Low Coverage

A 'Close' button is located at the bottom right of the dialog.

Default download settings

- Select whether a copy of the draft and final reports should be saved locally.
- Specify the download location and whether the report should open automatically.

Default report settings per application

- Select the Test.
- Select all checkboxes for sections that should appear by default in the (Draft and Final) variant report.

NOTE: The default report settings can be adjusted on a per project basis in the «Project Settings» of an analysis (see [ch. 4.4.2 Project Settings](#))

2. Dashboard

2.11 Main Window Components (1)

General account information

“My menu”
 “Go To Requests” navigate to requests and patients*.
 “Application Settings” quickly access the Virtual Panels of existing applications (read-only for non-admin users).

“Public databases”
 Displays current public database versions used in SOPHiA DDM™.

“Pipelines/Contracts”
 Summary of all available applications and status (Test or Routine).

BDS numbers
 Usage of bundle solution kit boxes available in this account (see [chapter 2.3 - BDS Numbers](#)).

“My Tests-Interpretation”
 lists all applications and the current status:
 ● Analysis Completed
 ● Analysis Pending
 ● No Analysis

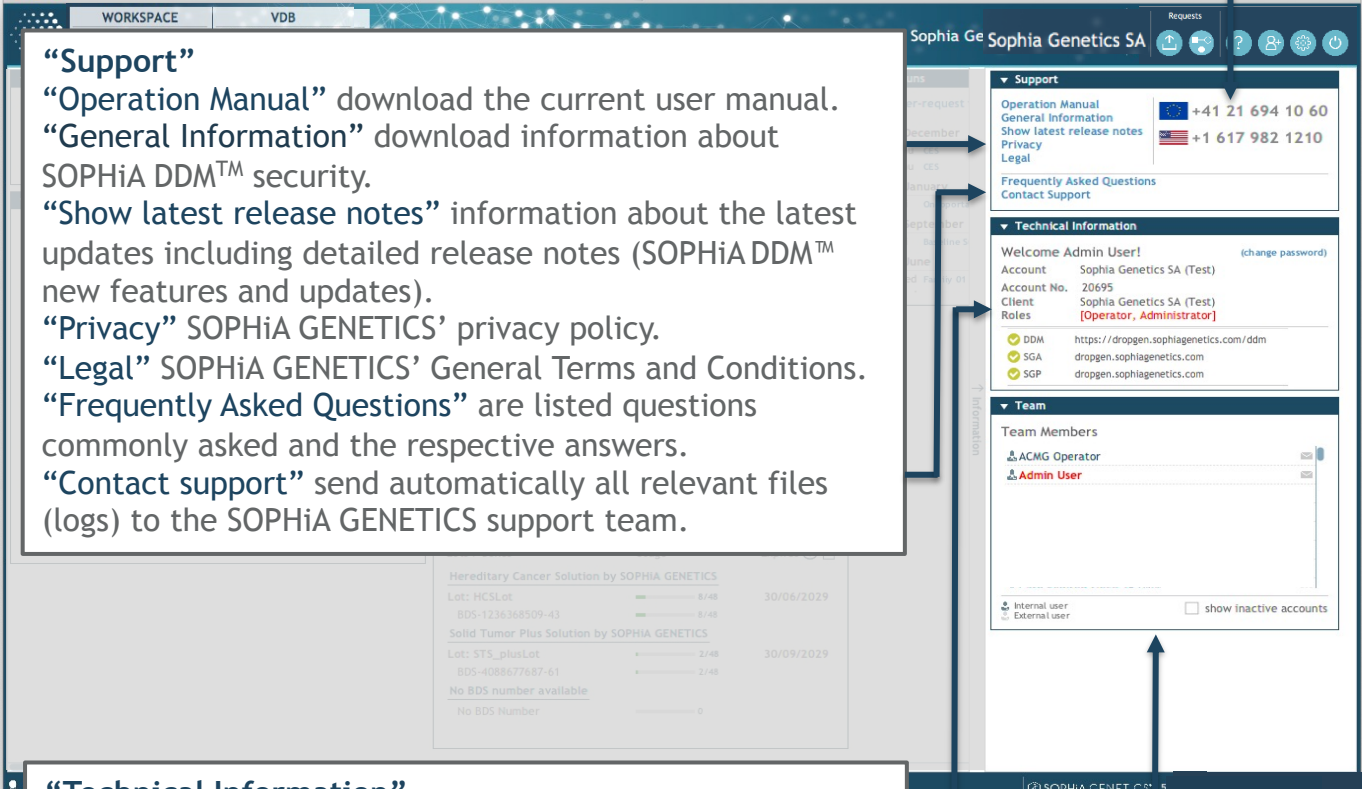
“My Runs”
 Quickly see all runs sorted by date and number of analyses per run per month.

NOTE: To retrieve the Instructions for Use (IFU) for CE-IVD applications, please download them from www.sophiagenetics.com/docs/

2. Dashboard

2.11 Main Window Components (2)

“Support”
 Phone number to get in touch directly with the SOPHiA GENETICS support team.



“Support”
 “Operation Manual” download the current user manual.
 “General Information” download information about SOPHiA DDM™ security.
 “Show latest release notes” information about the latest updates including detailed release notes (SOPHiA DDM™ new features and updates).
 “Privacy” SOPHiA GENETICS’ privacy policy.
 “Legal” SOPHiA GENETICS’ General Terms and Conditions.
 “Frequently Asked Questions” are listed questions commonly asked and the respective answers.
 “Contact support” send automatically all relevant files (logs) to the SOPHiA GENETICS support team.

“Technical Information”
 Indicates the account number, the user role(s) of the logged in user (see also chapter [1.2 Expert Roles](#)) and the option to change the password.

“Team”
 Outlines the role of all users (internal and external) who have access to the SOPHiA DDM™ account.

3. Workspace

3.1 Overview

Requests/Patients*
List of requests

Analyses/Projects
List of analyses and respective projects
within the selected request



Request ID	Request Name	Request Date	Sequencer	Processed Date	Request Date	Files
#3-0154	010620 SOPHiA Hereditary Cancer Solution	01/06/2020	Illumina MiSeq	01/06/2020	01/06/2020	23 files

Analysis ID	Sample ID	MID	Interpretation	Box
#200036282	SG10000003	S3	add interpretation	BDS-1236368509-43
HCS_v1_1	germline		Projects	
			CHVs 0	
#200036283	SG10000004	S4	add interpretation	BDS-1236368509-43
HCS_v1_1	germline		Projects	
			Interpretation 1 [0]	
			CHVs 1	
#200036284	SG10000005	S5	add interpretation	BDS-1236368509-43
HCS_v1_1	germline		Projects	
			Interpretation 1 [0]	
			CHVs 0	
#200036285	SG10000006	S6	add interpretation	BDS-1236368509-43
HCS_v1_1	germline		Projects	
			CHVs 0	
#200036286	SG10000007	S7	add interpretation	BDS-1236368509-43
HCS_v1_1	germline		Projects	
			CHVs 0	
#200036287	SG10000008	S8	add interpretation	BDS-1236368509-43
HCS_v1_1	germline		Projects	
			CHVs 0	
#200036288	SG10000009	S9	add interpretation	BDS-1236368509-43
HCS_v1_1	germline		Projects	
			CHVs 0	

When selecting a request, the box turns grey, and the analyses of the request will be listed on the right-hand side.

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3. Workspace

3.2 Request Management (1)

The screenshot shows the SOPHiA DDM workspace interface. At the top, there are tabs for 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The 'Requests' section is active, showing a list of 139 requests. A filter menu is open, allowing selection of sorting criteria: 'Date' (checked), 'User Ref', 'Ascending', and 'Descending'. The main view displays a list of requests, including '010620 SOPHiA Hereditary Cancer Solution' and 'Hereditary Cancer Solution v1.1 - CNV'. A callout box points to the filter menu with the text: 'Your batch requests will be sorted according to your selection e.g., descending date.'

- Click request tab
- Sort your batch requests (ascending /descending) by
 - Date (of request)
 - User ref

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3. Workspace

3.2 Request Management (2)

Filter by status

Click checkboxes to sort your requests by status “Completed”, “In Interpretation*” (Project* open) or “Pipeline Analysis”.

The screenshot displays the 'Workspace Requests' interface. At the top, there are tabs for 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The main area shows a filter panel on the left and a list of runs on the right. The filter panel includes a 'Filter' dropdown set to '2/139', a 'Status' section with checkboxes for 'All', 'Completed', 'In Interpretation', and 'Pipeline Analysis', a 'Ref:' field containing 'Hereditary Cancer Solu.', a 'Tests:' dropdown set to 'HCS_v1_1', and a 'Show cancelled runs' checkbox. Below the filter panel, there are 'Reset form' and 'Refresh list' buttons. The list of runs shows columns for 'Ref:', 'Tests:', 'Status:', 'Date:', and 'Action:'. The first row is '010620 SG HIA Hereditary Cancer Solution' with a date of '01/06/2020' and a status of 'HCS_v1_1 [1/2]'. The second row is 'Hereditary Cancer Solution v.1 - CNV' with a date of '02/08/2017' and a status of 'HCS_v1_1 [0/3]'. The bottom of the interface shows a user profile for 'sg-admin' and the text 'Sophia Genetics SA (Test)'.

Filter cancelled runs

Select checkbox to include cancelled runs in the run list (see [chapter 3.4 - Run Upload Cancellation](#)).

Reset form & refresh list

Select to reset filters by default and/or refresh the list of runs according to the applied filter.

Filter by run request ref

Sub-string search for run names.

Filter by applications

Check boxes to add run requests of other applications to your selection.

3. Workspace

3.3 Patient* Management

Search for a patient* ID

Click patients* tab and sort patients* (ascending /descending) by:

- Patient* ref
- Last name
- Analysis date

The screenshot displays the 'Workspace' section of the SOPHiA DDM interface. On the left, a 'Patients' tab is active, showing a list of 552 patients. A search box contains 'SG10000004'. The list includes entries for patient #406 SG10000004 (analysis: 3), #434 stsSG10000004 (analysis: 1), and #421 HCS_SG100000004 (analysis: 1). On the right, the 'Patient #406 SG10000004' profile is shown, including personal details and a list of analysis runs. The first run is highlighted in green, showing 'RUN REF 010620 SOPHiA Hereditary Cancer Solution' with 'HCS_v1_1 germline' analysis. Below it, another run is highlighted in grey, and a third in yellow. Each run entry includes a 'Run Ref', 'Sample ID', 'MID', and 'Analysis' details.

Select patient* from the list. The corresponding analysis/analyses will appear on the right-hand side.

Click “Run Ref” link to access corresponding batch request.

3. Workspace

3.4 Run Upload Cancellation

Show cancelled runs

Select to show cancelled runs in the list of batch requests.

“Cancel upload”

Click to cancel selected ongoing batch upload.

The screenshot displays the SOPHiA DDM workspace interface. On the left, a sidebar contains a 'Filter' section with options for 'All', 'Completed', 'In Interpretation', and 'Pipeline Analysis'. A 'Show cancelled runs' checkbox is checked. Below the filter, there are input fields for 'Ref:' and 'Tests:' (set to 'HCS_v1_1'). A 'Refresh list' button is also present. The main area shows a list of batch requests for '020620 HCS by SOPHiA' with request ID '#3-0155' and date '02/06/2020'. A 'Cancel Upload' button is visible. A modal dialog box titled 'Cancel Batch request' is open, displaying the message: 'The batch request #3-0155 With the status: Running download, will be cancelled. Do you want to proceed?' with 'No' and 'Yes' buttons. A 'Cancel' button is also visible on the dialog. The bottom status bar shows 'Uploading: 16 files (#200002769) 50% 5.9 MB/s'.

Cancel batch request

Click “Yes” to confirm abortion of the upload.

NOTE: Only runs in “WD” (Waiting for Download) or “RD” (Running Download) stage can be cancelled. If a run is cancelled shortly before the RD stage is finished, it might be that the cancel button is still visible but the run can no longer be cancelled. Cancelled runs cannot be restarted but a new batch request needs to be created if needed. BDS numbers of samples from cancelled runs will be added back to the list of available box numbers.

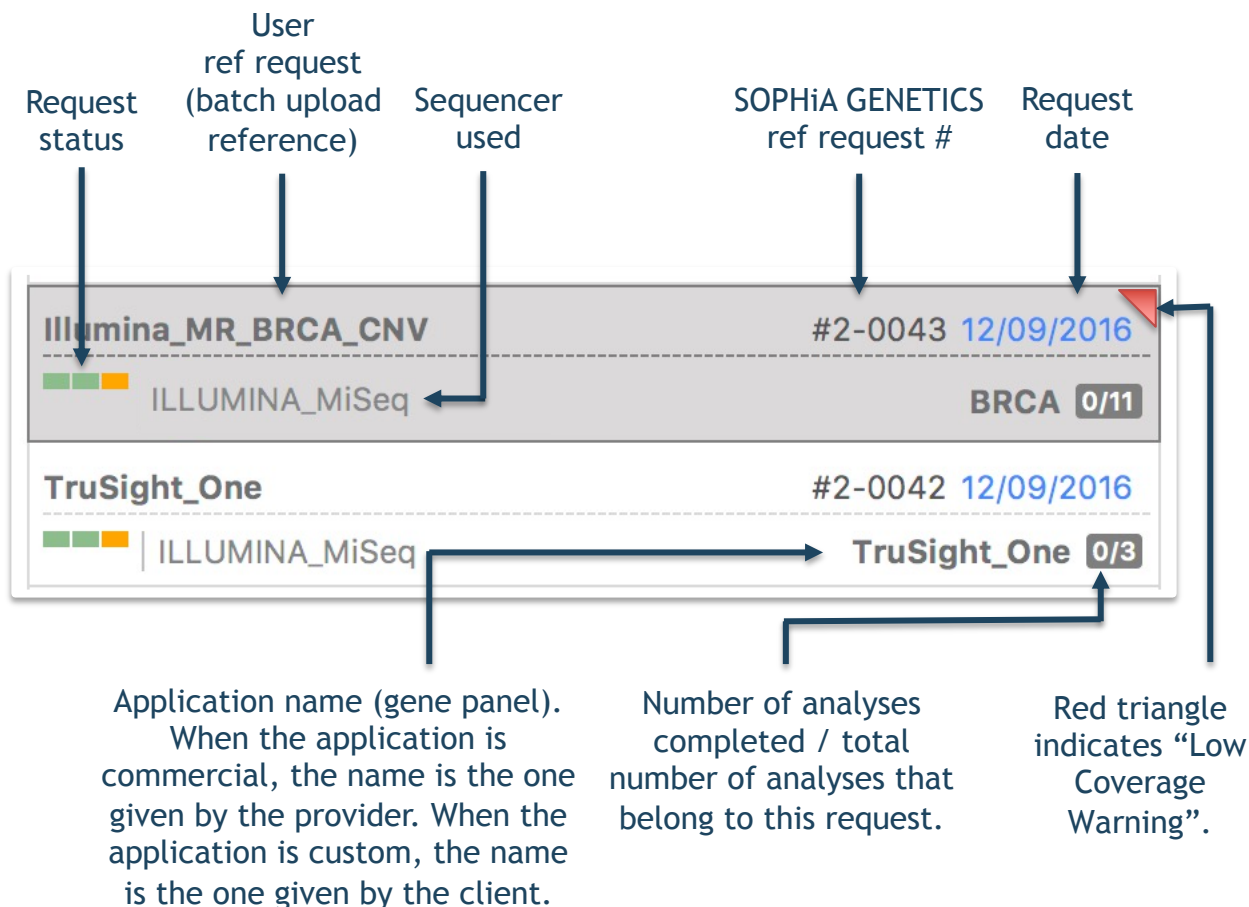
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3. Workspace

3.5 Request Information Summary



3. Workspace

3.6 Request Status

The screenshot displays two project entries in a workspace:

- Project 1:** Illumina, #2-0043, 12/09/2016, BRCA 0/11. Status: Active Storage finished, Analysis Running finished, Analysis Interpretation in progress.
- Project 2:** TruSight_One, #2-0042, 12/09/2016, TruSight_One 0/3. Status: ILLUMINA_MiSeq.

A legend below the screenshot defines the status categories:

- Storage Status**
- Analysis Status**
- Interpretation* Status**

Color Codes

- Not started
- Running
- Error
- Completed

Examples

- Running active storage
- Active storage finished, pipeline analysis running
- Analysis in interpretation* (Project open)
- Active storage finished, pipeline analysis error

3. Workspace

3.7 Analysis Card Overview (1)

Request card summary












SOPHiA DDM™
request ID #

Your ref request
(batch upload request)

Access to all run
level files

CNV
indicator

Request
status

#3-0154	010620 SOPHiA Hereditary Cancer Solution	01/06/2020
 SAMPLES	Sequencer: Illumina MiSeq	Processed date: 01/06/2020 Request date 01/06/2020
		23 files 
		
#200036282	SAMPLE ID SG10000003	MID: S3
HCS_v1_1 germline	SG10000003	Projects
		add interpretation  
		CNVs 0
		Box: BDS-1236368509-43
#200036283	SAMPLE ID SG10000004	MID: S4
HCS_v1_1 germline	SG10000004	Projects
		Interpretation 1 [0] 
		add interpretation  
		Box: BDS-1236368509-43
#200036284	SAMPLE ID SG10000005	MID: S5
HCS_v1_1 germline	SG10000005	Projects
		Interpretation 1 [0] 
		add interpretation  
		CNVs 1
		Box: BDS-1236368509-43

Analyses cards summaries

Indicators



CNV is present BUT has not been seen in a project OR no CNV present



At least one CNV is present AND it has been seen in a project

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3. Workspace

3.7 Analysis Card Overview (2)

Sophia Genetics SA (Test) 01/06/2020

Processed date: 01/06/2020 23 files

Request data

- Download all files
- Download aligned bam files
- Download all vcf files
- Download aggregated full variant table
- Download aggregated exon coverage file
- Download variant reports - final

Sample ref →

Run request ref →

File list:

- SG10000008_S8_L001_R2_001.fastq.gz (123MB)
- SG10000007_S7_L001_R2_001.fastq.gz (90MB)
- SG10000009_S9_L001_R1_001.fastq.gz (76MB)
- SG10000006_S6_L001_R1_001.fastq.gz (71MB)
- SG10000010_S10_L001_R1_001.fastq.gz (72MB)
- SG10000004_S4_L001_R1_001.fastq.gz (72MB)
- SG10000003_S3_L001_R2_001.fastq.gz (78MB)
- SG10000005_S5_L001_R2_001.fastq.gz (80MB)
- SG10000004_S4_L001_R2_001.fastq.gz (88MB)
- SG10000010_S10_L001_R2_001.fastq.gz (87MB)
- SG10000003_S3_L001_R1_001.fastq.gz (64MB)
- SG10000005_S5_L001_R1_001.fastq.gz (69MB)
- SG10000008_S8_L001_R1_001.fastq.gz (102MB)
- SG10000007_S7_L001_R1_001.fastq.gz (72MB)
- SG10000009_S9_L001_R2_001.fastq.gz (92MB)
- SG10000006_S6_L001_R2_001.fastq.gz (87MB)
- 010620 SOPHiA Hereditary Cancer Solution-3-0154-HCS_v1_1-CNV-Report.pdf (1MB)
- 010620 SOPHiA Hereditary Cancer Solution-3-0154-QA-report.pdf (848KB)

Download run-level sample files

- **Aggregated full variant table** contains combined variant lists of all samples in a batch request (only available if no sample in a batch requests is restricted).
- **Aggregated exon coverage file** contains combined exon coverage statistics of all samples in a batch request including mean, max, min coverage values.
- **Download variant reports - final** contains created final pdf reports (if any)

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3. Workspace

3.8 Analysis Card Details (1)

SOPHiA GENETICS

Ref request #

Sample ID

MID (multiplex identifier)

Low Coverage
indicator

Access to all
analysis files

Ref request #	Sample ID	MID (multiplex identifier)	Low Coverage indicator	Access to all analysis files
#200036282	SG1000003	MID: S3	Low coverage!	
HCS_v1_1 germline	SG1000003	Projects	add interpretation	CNVs 0 Box: BDS-1236368509-43
#200036283	SG1000004	MID: S4		
HCS_v1_1 germline	SG1000004 John Smith 02/06/1981	Projects Interpretation 1 [0]	add interpretation	CNVs 1 Box: BDS-1236368509-43

Patient* details

- Patient* ID
- Patient's* gender (unknown - / female ♀ / male ♂)
- Patient's* date of birth

BDS number

BDS number selected during sample upload (see [chapter 2.3 - BDS Numbers](#))

NOTE: To edit patient* details, click the patient* ID. For more information on the “patient* details” view, see [chapter 2.4 - Create a New Patient* File](#).

3. Workspace

3.8 Analysis Card Details (2)

Application name
Experiment type

Click to add new Interpretation Project* (see [ch. 3.12.1](#))

Project with consent restriction

Control sample (see [ch. 3.9](#))

#200036282	SAMPLE ID SG10000003	MID: S3		add interpretation	Control sample
HCS_v1_1 germline	SG10000003	Projects			CNVs 0 Box: BDS-1236368509-43
#200036283	SAMPLE ID SG10000004	MID: S4		add interpretation	Control sample
HCS_v1_1 germline	SG10000004 John Smith 02/06/1981	Projects	Interpretation 1 [0]		CNVs 0 Box: BDS-1236368509-43
#200036284	SAMPLE ID SG10000005	MID: S5		add interpretation	Control sample
HCS_v1_1 germline	SG10000005	Projects	Interpretation 1 [0] Interpretation 2 [1]		CNVs 1 Box: BDS-1236368509-43

Project status



Draft project

Completed project

Project name

Number of reported variants

Analysis status



Analysis not started yet: no Interpretation Projects* created



Analysis finished: all linked projects are completed



Analysis in progress: at least one draft project

If a new project is created on a finished analysis/sample, the analysis/sample will revert back to the in-progress status (yellow).

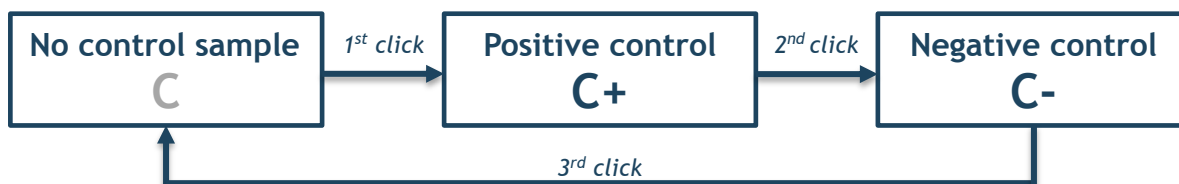
NOTE: A fourth Analysis status “pending approval” is available in accounts with “Report Approval Workflow” activated. Details see [ch. 4.5 Report Approval Workflow](#).

3. Workspace

3.9 Control Samples

Click the C button one or several times to mark a samples as:

- Positive control (C+)
- Negative control (C-)
- No control sample (normal patient* samples)



Before sample upload (Create Request Form):

Sample ID MID	Patient	Sample Type	Experiment Type	KIT	BDS Number	Control
1 SG10000003 S3	SG10000003	Blood	germline	Hereditary Cancer Solution by Sophia		C

After sample upload (Workspace):

#200036285	SAMPLE ID SG10000006	MID: S6	Positive control	C+
HCS_v1_1 germline	SG10000006	Projects	CNVs 1	Box: BDS-1236368509-43
#200036286	SAMPLE ID SG10000007	MID: S7	Negative control	C-
HCS_v1_1 germline	SG10000007	Projects	CNVs 1	Box: BDS-1236368509-43
#200036287	SAMPLE ID SG10000008	MID: S8	Patient* sample, no control	C
HCS_v1_1 germline	SG10000008 01/01/1970	Projects	CNVs 1	Box: BDS-1236368509-43

NOTE: Any sample can be marked as "Positive control" or "Negative control" before or after sample upload. Samples marked as "Control sample" before release v5.7.0 were automatically migrated to status "Positive control" sample. The control sample selection is editable at any time.

Disease* selection is no longer mandatory for somatic analyses, if a sample is marked as "positive" or "negative control" (see section [3.12.3 Add a disease*](#)).

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3. Workspace

3.10 Quality Indicators


3.10.1 Germline BRCA Application



Color codes



In range



Outside range



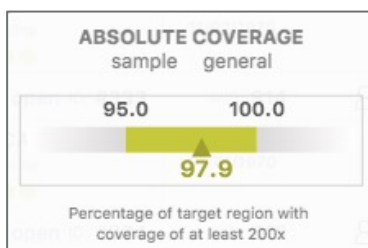
Absolute coverage




Mean read quality



Retained reads




Absolute coverage



< 95%


Percentage of target region covered with at least 200x



95-100%




Mean read quality

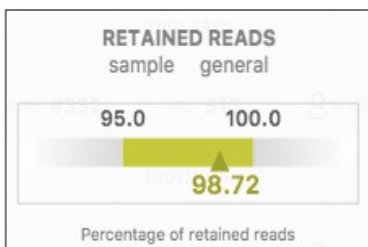


< 80 %


Percentage of reads with mean Phred score >30



80-100%




Retained reads



< 95 %

Percentage of retained reads



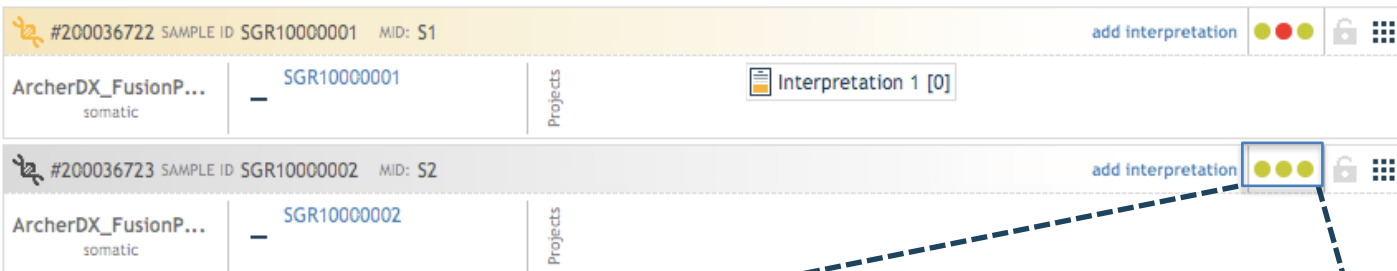
95-100 %

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3. Workspace

3.10 Quality Indicators




3.10.2 Somatic Archer FusionPlex® Application



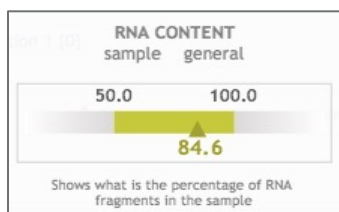
Color codes


In range Outside range


  

RNA content Sequencing depth Library complexity

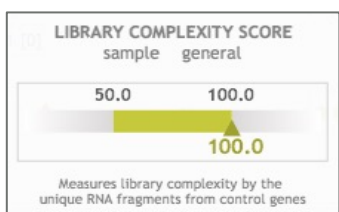


RNA content


 < 50% RNA content


 > 50% RNA content

RNA experiments often have remains of DNA in the sample. This indicator measures the proportion of RNA and DNA molecules. RNA content of < 50% indicates a highly degraded sample.

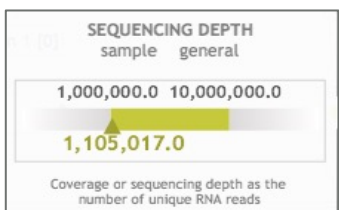


Library complexity score


 ARC < 10 Bad quality


 ARC > 10 - 100 Good quality

Average number of unique RNA (ARC) start sites of 4 control genes is calculated. A lack of unique fragments for these control genes implies a low RNA starting material or a very degraded library in which not enough RNA fragments were converted to sequenced read. ARC is converted to a score between 0-100.



Sequencing depth (RNA reads)

 < 1 M reads

 > 1 M reads

Indicator shows whether enough RNA reads are present in the sample. With too little RNA reads, chances of detecting fusions decrease.


3. Workspace


3.10 Quality Indicators

3.10.3 SARS-CoV-2 Application

#200036231	SAMPLE ID	Sample01	MID: S1	add interpretation	●●●●	🔒	☰
CleanPlex_SARS_h...	♀	Sample01 Anna Smith 19/05/1999	Projects				
#200036232	SAMPLE ID	Sample02	MID: S2	add interpretation	●●●●	🔒	☰
CleanPlex_SARS_h...	♂	Sample02 John Miller 06/04/1980	Projects				

Color codes


 In range

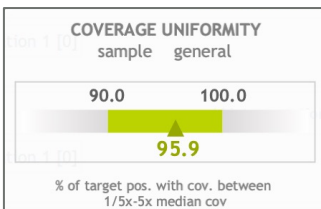

 Outside range

Coverage
uniformity



Effective
reads

Pool 1/2
balance

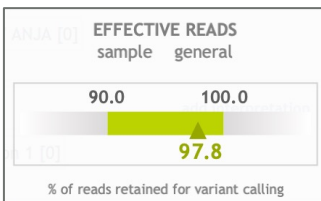
Target
covered





Coverage uniformity

-  < 90% Coverage uniformity
-  > 90% Coverage uniformity

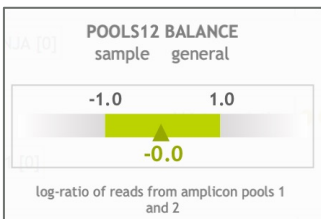
Percentage of target positions with coverage between 1/5x to 5x median coverage.





Effective reads

-  < 90% Effective reads
-  > 90% Effective reads

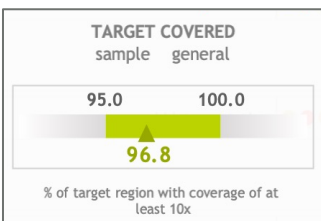
Percentage of reads retained for variant calling.



Pool 1 & 2 balance

-  < -1 and > 1 log ratio
-  > -1 and < 1 log ratio

Log ratio of reads from amplicon pool 1 and 2.



Target covered

-  < 95% target coverage
-  > 95% target coverage

Percentage of target region with coverage of at least 10x.

3. Workspace

3.10 Quality Indicators

3.10.4 TSO500 Application

Eye button for full view
Click to show results for all 5 criteria.

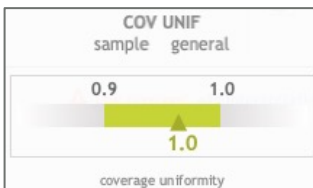
#437523 SAMPLE ID DNA11-D MID: S2 add interpretation ●●●● 4/5 CNVs

TruSight_Oncology... somatic DNA11-D Projects

Color codes

In range Outside range

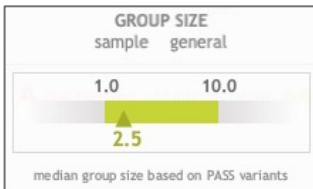
Coverage uniformity Group size On-target bases Deam. score Fragment length



Coverage uniformity

< 90%
 > 90%

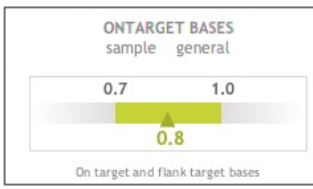
Percentage of target positions with coverage between 1/5x to 5x median coverage.



Group size

> 10
 < 10

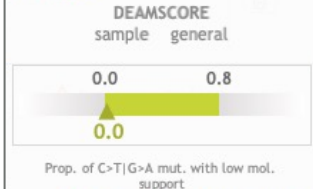
Median group size based on high confidence variants.



On-target bases

< 70%
 > 70%

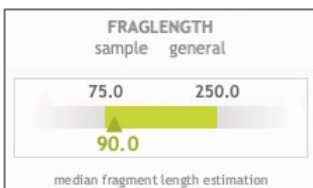
Fraction of bases from the reads that are located on-target or flanking the target.



Deamination score

> 80%
 < 80%

Proportion of low confidence among all C>T or G>A calls within a certain VAF range.



Fragment length

< 75 > 250
 > 75 < 250

Median fragment length estimation (estimated from a subset of reads).

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3. Workspace

3.11 Expression Analysis Report

The screenshot displays the workspace interface for project #3-0283, dated 03/10/2018. The sequencer is identified as Illumina MiSeq. A circular progress indicator shows 0 out of 2 samples. The interface lists two samples: #200036928 (SAMPLE ID HD784, MID: S11) and #200036929 (SAMPLE ID F3071, MID: S12). Both samples are associated with the project 'ArcherDX_FusionP... somatic'. A dropdown menu is open, listing download options for aggregated reports and individual fastq.gz files. The 'Gene-Expression-Report.pdf (189KB)' is highlighted with a blue arrow.

Project	Sample ID	MID
ArcherDX_FusionP... somatic	HD784	S11
ArcherDX_FusionP... somatic	F3071	S12

- Download aggregated full variant table
- Download aggregated exon coverage file
- Download all files to a folder
- Download aligned bam files to a folder
- Download all vcf files to a folder
- fastq-3-0283-QA-report.pdf (280KB)
- Gene-Expression-Report.pdf (189KB)**
- HD784_S11_L001_R1_001.fastq.gz (356KB)
- F3071_S12_L001_R2_001.fastq.gz (1MB)
- F3071_S12_L001_R1_001.fastq.gz (1MB)
- HD784_S11_L001_R2_001.fastq.gz (312KB)

Download gene expression report

The PDF report contains information about limitations, estimations on the library diversity, percentage of DNA and RNA fragments and quantification of relative gene abundance.

NOTE: Gene expression report download is only available for the Archer FusionPlex® CTL application.

3. Workspace

3.12 Interpretation Projects*

3.12.1 Overview

Patient* Birth date
Select the birth date of the patient*

Patient* Gender
Select gender of the patient*

Change restriction
Select Virtual Panel to restrict analysis

Select Disease*
Select patient's* disease*

The screenshot shows the 'New Interpretation Project' dialog box in the SOPHiA DDM workspace. The dialog is titled 'New Interpretation Project' and has a 'Sample Information' section. The 'Sample Details' are listed as follows:

SOPHiA ID	#200036166
Sample ID	SG10001104
Consent	unrestricted
Diseases	None selected
Patient Gender	— Unknown
Birth date	

Below the 'Sample Details' are two buttons: 'change' (with a lock icon) and 'select' (with a magnifying glass icon). A 'Next' button is at the bottom right of the dialog. Arrows from the text boxes above point to the 'Birth date' field, the 'Patient Gender' dropdown, the 'change' button, and the 'select' button.

Interpretation Projects* enable multiple interpretations* of the same sample at either various points in time or with different sets of genes (Virtual Panel) or both. The Project* scope refers to the Virtual Panel selected when creating a Project*.

3. Workspace

3.12 Interpretation Projects*


3.12.2 Restrict to a Virtual Panel (1)

The screenshot shows the SOPHiA DDM workspace interface. A modal window titled "New Interpretation Project" is open, displaying "Sample Information" for a new project. The "Sample Details" section includes:

- SOPHiA ID: #200036166
- Sample ID: SG10001104
- Consent: unrestricted (with a "change" button)
- Diseases: None selected (with a "select" button)
- Patient Gender: — Unknown (dropdown menu)
- Birth date: (calendar icon)

A "Next" button is located at the bottom right of the modal. The background workspace shows a list of requests and a sidebar with filters.

- Click “Add Interpretation” to add a new project for an analysis/sample
- Select “Change” to restrict according to consent restriction

NOTE: Unless there is a global or a consent restriction applied to a sample prior to the sample upload (recognizable by the blue lock symbol in the sample card ) , users can select any Virtual Panel (including the ROOT virtual panel) when creating an Interpretation Project*. Virtual Panels have to be created in the Application Settings (see [chapter 2.7 Manage Virtual Panels](#)). Non-Admin users can add a consent restriction for an analysis only when accessing it for the first time.

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3. Workspace

3.12 Interpretation Projects*

3.12.2 Restrict to a Virtual Panel (2)

Root Virtual Panel version

The screenshot shows the 'New Interpretation Project' dialog box in the SOPHiA DDM workspace. The dialog is titled 'Gene panel restriction' and is for 'Sample #200028339'. It has two radio buttons: 'Unrestricted' and 'Restricted', with 'Restricted' selected. Below the radio buttons, there is a 'Restriction' field with the text 'Breast Cancer - regions:3'. A blue arrow points from the 'Root Virtual Panel version' box to the 'HCS_v1_1 [root] v2 [root] 27' row in the table below.

Virtual Panel	Regions
HCS_v1_1 [root] v2 [root]	27
Breast Cancer	3
HNPCC	6

Consent restriction

To apply a consent restriction:

- Click “restricted” and then
- Select a Virtual Panel from the pre-defined list (defined per application by an admin user at the account level)
- Check the box to confirm the restriction
- Click “OK”

NOTE: Consent restrictions can also be defined prior to run upload ([see p. 24](#)) by admin and non-admin users.

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3. Workspace

3.12 Interpretation Projects*

3.12.2 Restrict to a Virtual Panel (3)

If users choose to perform an interpretation* on a Virtual Panel, this sets the scope of the interpretation to this Virtual Panel. If users want to change the scope of an Interpretation Project*, a new one has to be created for the same sample.

The screenshot displays the 'New Interpretation Project' dialog box in the Sophia Genetics SA interface. The dialog is titled 'Interpretation Project 2/2' and contains the following fields:


- Name:** Interpretation 1
- Virtual Panel Scope:** HBOC - regions: 3
- Start Date:** 10/05/2017
- Owner:** Non-Admin User

A dropdown menu is open for the 'Virtual Panel Scope' field, showing the following options:

- HBOC:** 3
- BRCA1&2:** 1

The background interface shows a workspace with a list of requests and patients. The top navigation bar includes 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The main content area displays a list of requests with columns for 'HCS_v1_1', 'Sample ID', 'Sequencer', 'Sample source', 'Processed date', and 'Request date'. A 'New Interpretation Project' dialog box is overlaid on the workspace, allowing users to create a new project with a specific name and scope.

Project* scope

- The default name for the Project* is “Interpretation 1”
- Type in the field to edit the name
- If user wishes restrict the scope of the Interpretation Project*, click 
- Click “finish” to create and open the overview page of the Project*

NOTE: If a consent restriction is applied (see p. [24](#)), the scope is limited to this Virtual Panel, i.e. only sub-panels can be chosen.

3. Workspace

3.12 Interpretation Projects*

3.12.3 Add a disease* (1)

Selection of a disease* is mandatory for somatic analyses, except for (positive and negative) control samples (see chapter [3.9 Control samples](#)), and optional for germline analyses.

The germline disease tree is based on <https://disease-ontology.org/>, whereas the somatic disease* tree displays a list of most common cancers in addition to a restricted disease* ontology.

The screenshot displays the 'New Interpretation Project' dialog box within the SOPHiA DDM workspace. The dialog box is titled 'New Interpretation Project' and has a 'Sample Information' section. It displays the following details:

- Sample Details:**
 - SOPHiA ID: #200036166
 - Sample ID: SG10001104
 - Consent: unrestricted (with a 'change' button)
 - Diseases: lung cancer (with a 'change' button)
- Form Fields:**
 - Patient Gender: - Unknown (dropdown menu)
 - Birth date: (empty date picker)
- Navigation:** A 'Next' button is located at the bottom right of the dialog box.

The background shows the workspace interface with a list of requests and patients. The top navigation bar includes 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The main header displays 'Sophia Genetics SA' and 'Requests' with various icons. The main content area shows a list of requests with filters and a table of patient data.

Addition of a disease*

- Click “select” or “change” to open Disease* Ontology tree
- Search one or several disease*(s) or select from the bookmarked diseases* (see p. [76](#))
- Click “OK” to confirm

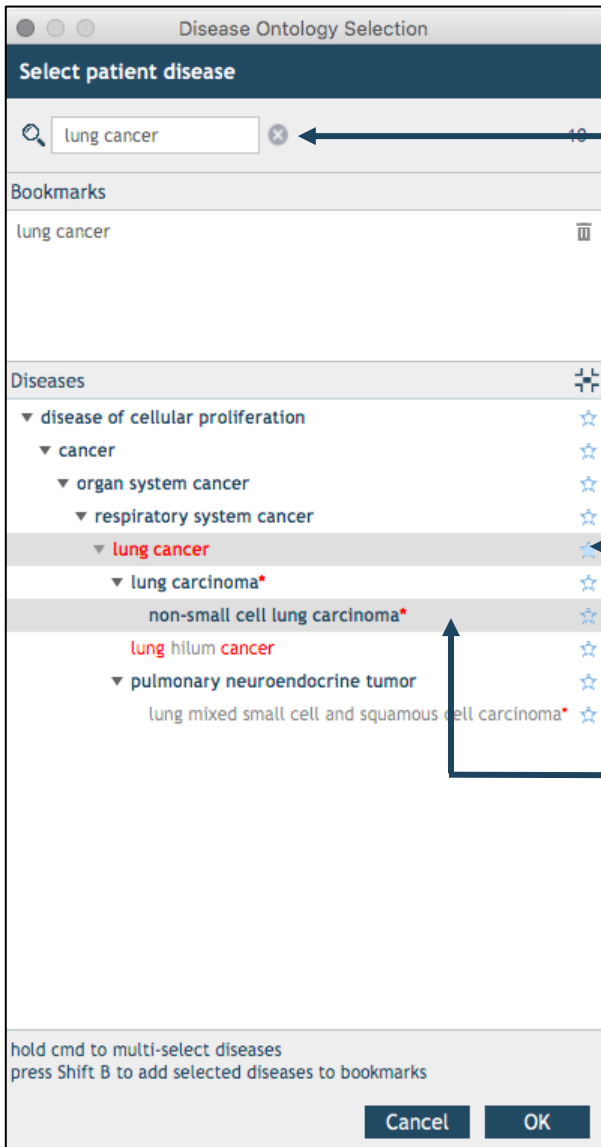
Disease* is now added

3. Workspace

3.12 Interpretation Projects*

3.12.4 Add a disease* - Germline analyses

Disease* tree is based on disease-ontology.org



Search a disease*

Type the suspected disease* name. The list of terms containing the substring is instantly updated and respective disease*s are highlighted. Matching search terms are marked with red text and synonyms are indicated with a red star.

Bookmark a disease*

To bookmark frequently selected diseases*, click the “star” icon next to the disease*. Alternatively, click Shift + B to bookmark a disease*. In both cases, the disease* appears and is then saved in the list of bookmarks above the tree.

Multi-select diseases*

Several diseases* can be selected and added to an Interpretation Project* by clicking CTRL (Mac: ⌘cmd) while selecting several diseases*.

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* Please refer to the Disclaimer (page 3).

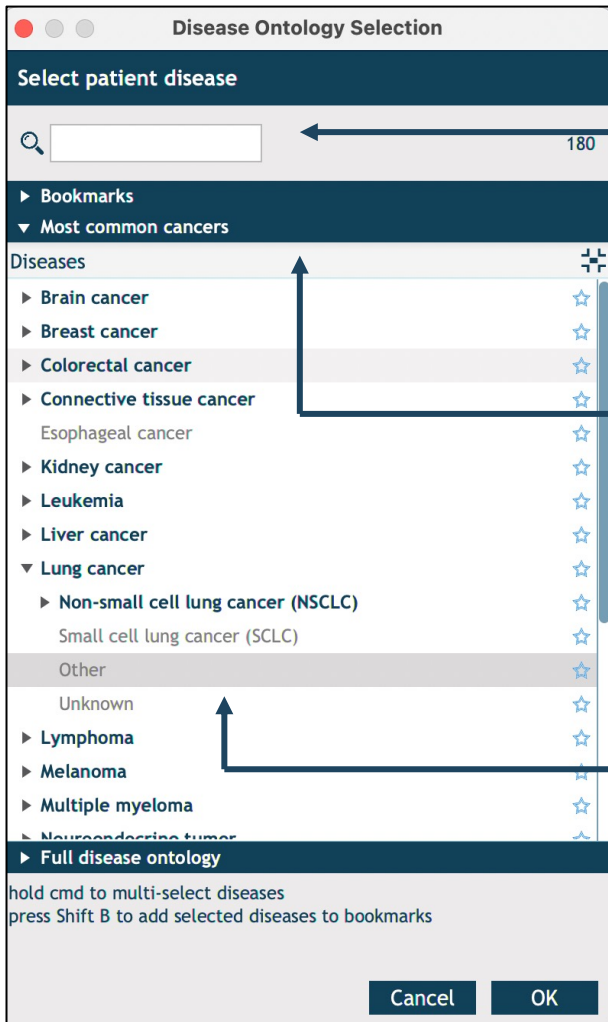
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3. Workspace

3.12 Interpretation Projects*

3.12.5 Add a disease* - Somatic analyses (1)

Somatic disease* tree displays upfront a list of most common cancers.



Search, bookmark and multi-selection of diseases*

The somatic disease* tree offers the same capabilities as the germline disease* tree, meaning that search for a disease*, bookmark a disease* and multi-selection of diseases* is possible.

Most common cancers

22 most common cancers are displayed upfront and selectable by the user, along with children nodes. These diseases* are mapped to DO terms.

Other and unknown diseases*

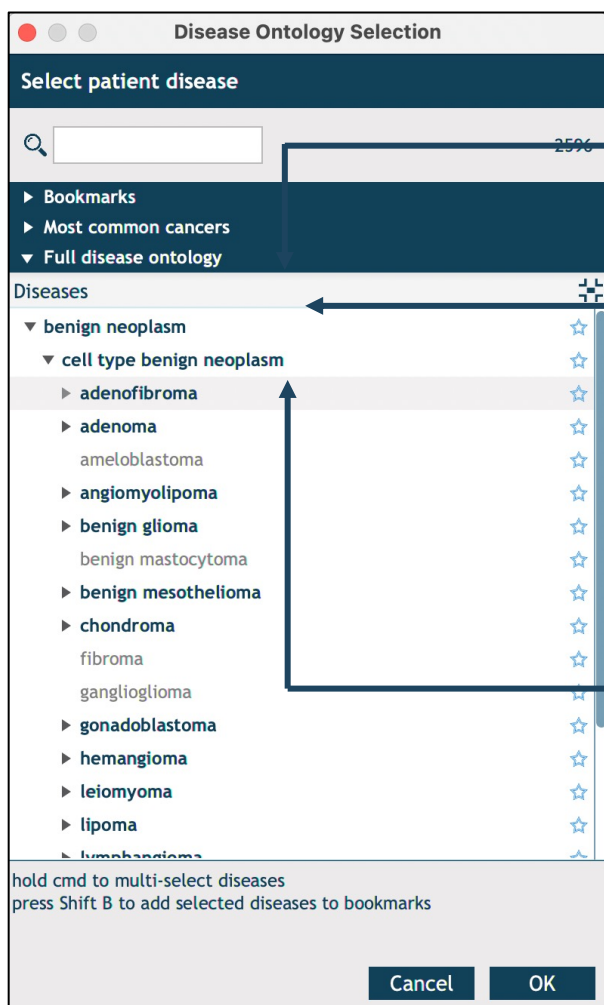
“Unknown” and “Other” disease* terms are introduced for each common cancer term and are mapped to DO terms of their parent disease*.

3. Workspace

3.12 Interpretation Projects*

3.12.5 Add a disease* - Somatic analyses (2)

The somatic disease* tree can be expanded to display the full disease ontology that is based on disease-ontology.org.



Full disease* ontology

Full disease* ontology can be expanded in the somatic disease* tree to allow users to select a disease* from the DO.

Restricted DO

Some high-level nodes from the full disease* ontology are not displayed in the somatic disease* tree.

Restricted levels

High-level nodes of the full disease* ontology are not selectable in the somatic disease* tree. Users can click to expand, view and select a child disease*.

3. Workspace

3.12 Interpretation Projects*

3.12.6 Add phenotypes

Phenotypes can be added to the patient* at the interpretation level. One to multiple HPO terms can be selected 1) when opening a new interpretation project, 2) inside an interpretation project.

The HPO terms are based on <https://hpo.jax.org/>.

Included and excluded phenotypes

You can "include" HPO phenotypes when you select phenotypes associated with the sample, and "exclude" HPO phenotypes when you select phenotypes that are not associated with the sample. This will allow computation of the HPO matching rank in the SNV/INDELS table (see [Chapter 4.11 HPO based prioritization](#)) as:

- **Matching included HPO terms** (corresponding to the number of hits between user-entered included phenotypes and phenotypes associated to the variant)
- **Matching excluded HPO terms** (corresponding to the number of hits between user-entered excluded phenotypes and phenotypes associated to the variant)

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4. Data Analysis

4.1 View Multiple Analyses

A new window opens with the selected project for the patient*.

Open project in a new window
Right click on the project and select “open in new window”.

TEST
27 GENES
331 VARIANTS
55 RETAINED
276 LOW CONFIDENCE
32 DEPTH MIN
1990 DEPTH MAX
18 WARNINGS

Patient
Interpretation 2
Completed

Specimen
Virtual Panel: HCS_v1_1 (27 genes)
Owner: Admin User

Test Information
Date created: 01/06/2020
Sent for approval
Completed: 01/06/2020

Project
Project Settings
Re-Open

Documents
Conclusion

Pathogenicity
Prediction: 0: 329
Pathogenicity Flags: 4

Public Databases
CG69: B37.20120813
ClinVar: v20200312
COSMIC: v87
dbNSFP: v2.9
dbSNP: v151
ESP: 5400
ExAC: r0.3.1
G1000: v5.20130502
GISAID EpicCoV™: v20200512
GnomAD: r2.1

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4. Data Analysis

4.2 Analysis Management

Analysis view
Different tabs for all opened independent projects are shown in the navigation bar.

Click on one analysis tab to access

Root Virtual Panel version

The screenshot displays the SOPHiA DDM software interface. At the top, a navigation bar contains several tabs: 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS SG10000003 #3-0154'. The main content area is divided into several sections. On the left, there is a 'Virtual Panel' section with a circular progress indicator showing 3 genes out of 27. Below this, there are statistics for 'GENES', 'VARIANTS', and 'WARNINGS'. The central part of the interface shows a 'Conclusion' section and a 'Pathogenicity Flags' section with a circular gauge. The right sidebar contains 'Test Information' and 'Public Databases'.

4. Data Analysis

4.3 Analysis Header

General information about the analysis

The screenshot shows the analysis header of the SOPHiA DDM interface. Callouts point to the following elements:

- Dashboard:** Click to go back to requests.
- Workspace:** Click to go back to analyses.
- Active analysis:** Points to the 'ANALYSIS 15C2819' header.
- Sample ID:** Points to the sample ID field.
- Request date:** Points to the date field.
- Project name:** Points to the 'virtual panel1 [0]' dropdown.
- Other projects in the analysis:** Points to the list of virtual panels.
- Project status:** Points to the 'Interpretation 1' status.
- Other patients* in the run:** Points to the list of variant IDs.
- Request ref:** Points to the 'PT001 S1' patient ID.
- MID:** Points to the 'MID' field.
- Patient* ID:** Points to the 'PT001 S1' patient ID.
- Access to the analysis files:** A list of files available for download:
 - Per sample QA report
 - Full variant table (VCF)
 - Full variant table (variant table.txt)
 - Exon coverage stats file
 - BAI, BAM, FASTQ files
 - Run-level QA report

Use to see all projects for the selected sample or to see other samples of the same batch request. To toggle between samples, use < and >.

NOTE: The selection will always jump to the first project for a given sample. If there is no project for a sample, the “new Interpretation Project*” window will open. Samples cannot be opened without creating an Interpretation Project* first.

4. Data Analysis

4.4 Analysis Overview (1)

All tabs are restricted to the interpretation scope

Original application name
Root panel used for this patient*. When “grey”, the interpretation* is restricted.

Interpretation scope
Virtual Panel used for this project (“White” active tab).

Application name
Somatic/germline

“Reported”
Number of selected variants appearing in the report.

“Overview”
Access to the main patient* page analysis (“white” active tab).

“Genes”
General overview of genes and their number of variants and coding consequences. Also offers access to Virtual Panels.

“CNVs”
Indicates all the CNVs or amplifications detected in the analysis.

“Warnings”
Low coverage regions, pseudogenes or other warnings (e.g. noisy regions).

“SNVs/Indels”
Indicates all the variants detected in the analysis. Also offers access to the Variant Filter Builder (see [chapter 5 - Variant Filter Builder](#)), a feature to create your own custom filters.

Pathology number
If the patient* has more than one disease*.

Pathology name
Disease* selected for the patient*.

4. Data Analysis

4.4 Analysis Overview (2)

Reported variants are restricted to the interpretation scope

Access to the reported variants:

Click on the box with the star (can be left open while navigating to the analysis view).

Reported variants
A new window appears with the reported variants and detailed information for each variant is displayed.

Export reported variants
Reported variants can be saved as an .XLS file.

More filters
Click on the “+” and to add different filters.

Reported Variants

Selected Virtual Panel: HBOC (1 out of 1 total reported variants in this panel)

Gene	Coding consequence	VF%	P...	P...	Actionability	T...	c.DNA	Depth	ref	alt
BRCA1	frameshift	59,0	🔴	★	N/A		INDEL c.1175_1214del	1793	TGATT...	T

Close

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4. Data Analysis

4.4 Analysis Overview (3)

Overview tab data is restricted to the interpretation scope

Overview

Active page (white)

The screenshot displays the SOPHiA DDM software interface. The top navigation bar includes 'WORKSPACE', 'VDB', and 'ANALYSIS' sections. Below this is a project information bar with 'PROJECT', 'SAMPLE', 'RUN', and 'HCS' details. The main content area is divided into tabs: 'OVERVIEW', 'SCREENING', 'GENES', 'SNVs/INDELS', 'CNVs', and 'WARNINGS'. The 'OVERVIEW' tab is active and shows a 'Virtual Panel' with a circular progress indicator (3/27) and a list of metrics: GENES (68), VARIANTS (15 RETAINED, 53 LOW CONFIDENCE), and VARIANT DEPTHS (30 DEPTH MIN, 4360 DEPTH MAX). A 'Report' section at the bottom allows filtering by 'Selected', 'Retained', 'Low Confidence', and 'Low Coverage', with a 'Generate Report' button.

“Genes” number of genes in the root panel and number of genes in the interpretation scope of the project

“Variants” total number of variants for this project

“Retained” total number of variants retained for this project (high confidence)

“Low confidence” number of variants not retained

“Variant depths” min and max depth variant coverage

4. Data Analysis

4.4 Analysis Overview (4)

Overview
Active page (white)

The version of the Root Virtual Panel indicates on which version of the annotation algorithm it was created. Analyses with gene name changes (according to HGNC nomenclature) run after the Annotation System update (p5.5.0) are automatically assigned to version 2, while analyses run before the update are linked to version 1.

NOTE: The accuracy of annotations after the Annotation System update (p5.5.0) with HGVS standards has >98%. Accordingly, <2% of annotation cases could deviate from the standards, for which SOPHiA GENETICS shall not bear liability.

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4. Data Analysis

4.4 Analysis Overview (5)

Overview
Active page (white)

Database versions
The displayed database versions are the ones integrated at the time of analysis.

Database	Version	Match Count
ClinVar	v20200817	✓
COSMIC	v92	✓
dbNSFP	v2.9	✓
dbNSFP (hg38)	v4.1	✓
dbSNP	v154	✓
ESP	5400	✓
ESP (hg38)	6500	✓
ExAC	r0.3.1	✓
G1000	v5_20130502	✓
GISAID EpiCoV™	v20210215	✓
GnomAD	r2.1	✓
GnomAD (hg38)	r2.1.1	✓

NOTE: Although versions are displayed for all integrated databases, the matched information might depend on the experiment type (somatic vs. germline) or on the reference genome used for annotation:

- products that use hg19 as the reference genome display and link to the “hg19 version” of the database.
- products that use hg38 are matched with and link to the “hg38 version” of the same database.

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4. Data Analysis

4.4 Analysis Overview (6)

4.4.1 Project Tab

Project Active tab

Project Settings
Per sample report settings (see [p.89](#))

Delete project

Complete project
By clicking this button, the project is completed and becomes green. The final report is created and can be downloaded.

Project
Start date: date of the project creation.
End date: date of completion of the interpretation*.
Status: draft or complete.

Draft report
A draft report can be created before project completion.

Conclusion
A conclusion can be added to the interpretation* for this project.
This box is not designed to collect direct identifying data such as name or surname. Please restrict the content of this box to interpretation.

The report is restricted to the interpretation scope of the project

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4. Data Analysis

4.4 Analysis Overview (6)

4.4.1 Project Tab (2)

Overview
Active page (White)

Project
Active tab

Predictions
The proportion of classes of variants pre-classified by SOPHiA DDM™.

Pathogenicity flags
Done by the user. Showing the different pathogenicity classes found in the retained variants of this project.

Retention criteria: Retained Variant, Low Confidence Variant

Prediction: D: 10

Pathogenicity Flags: 4

Predictions

Use the drop-down menu to select gene of interest & checkbox (retained/low confidence) to see the number of variants categorized according to the pathogenicity prediction level.

4. Data Analysis

4.4 Analysis Overview (6)

4.4.2 Project Settings (1)

Back to Project main tab Project Active tab

Report creation
 Select whether the report should be created upon completion.

Report sections
 Selection of sections included in the Draft or Final report for this specific Interpretation Project*. Available checkboxes depend on the experiment type (germline or somatic). Default report settings per application can be defined in the Application Settings (see [ch. 2.10 Manage Report Settings](#)).

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4. Data Analysis

4.4 Analysis Overview (6)

4.4.2 Project Settings (2)

Annexes available for germline reports

Project settings

Annexes

<input checked="" type="checkbox"/> Show CNVs	<input checked="" type="checkbox"/> Show ACMG Details	<input checked="" type="checkbox"/> Retained (61)	<input type="checkbox"/> Low Confidence (260)
<input checked="" type="checkbox"/> Low Coverage	<input type="checkbox"/> Variant Description	<input checked="" type="checkbox"/> Show filters	

Annexes available for somatic reports

Project settings

Annexes

<input checked="" type="checkbox"/> Association details	<input checked="" type="checkbox"/> Show Screening	<input checked="" type="checkbox"/> Retained (5)	<input checked="" type="checkbox"/> Low Confidence (51)
<input checked="" type="checkbox"/> Low Coverage	<input checked="" type="checkbox"/> Reporting by AMP/ASCO/CAP	<input type="checkbox"/> Summary of variants	<input type="checkbox"/> Variant Description
<input type="checkbox"/> Show filters			

Select checkbox to include respective annex in the variant report:

- **CNVs** - CNV details (see [ch. 7 CNV Analysis](#))
- **ACMG Details** - Information for ACMG criteria (see [chapter 4.9.11 ACMG Tab](#))
- **Retained** - High confidence variants
- **Low Confidence** - Include list of variants classified as low confidence
- **Low Coverage** - Include list of variants with low coverage
- **Variant Description** - Include a description of the variant (see [ch.4.9.8 Variant Description Tab](#))
- **Show filters** - Include information which variant filtering strategy (SOPHiA DDM™ filters, Custom Filters (Variant Filter Builder), Cascading Filters) was applied (see [ch. 6.8](#))
- **Association details** - Include details about reported clinical associations* (see [p. 198](#))
- **Show Screening** - Include screening (hotspot) status (see [ch. 4.7.1](#))
- **Reporting by AMP/ASCO/CAP** - Include variant classification according to AMP/ASCO/CAP tiers (see [ch. 9.3.6](#))
- **Summary of Variants** - Reported variants appear in this optional section (see [ch. 9.4.3](#))
- **Show Fusions** - Only available for somatic applications with fusion calling (see [ch. 14](#))

NOTE: The number of variants that can be included in the report is limited to 2000. Adjust the report settings accordingly or apply a virtual panel.

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4. Data Analysis

4.4 Analysis Overview (6)

4.4.3 Patient* Tab

Personal details

To modify patient* details, click on the patient* ID (blue) to access the patient* detail window (see [chapter 2.4 - Create a New Patient* File](#)).

Diseases*

Users can select a disease* by clicking “Add Disease*”. For somatic analyses, a disease* has to be added when creating an Interpretation Project* (see [Chapter 3.12.3 Add a disease*](#)). For users with access to OncoPortal™ (somatic analyses), SOPHiA DDM™ automatically recalculates the impact of the disease* association with drugs, most recent clinical trials* and the genomic profile of the patient* (see [ch. 9 OncoPortal](#)).

Phenotypes

Users can add one to multiple HPO phenotypes to their Interpretation Project* (see [Chapter 3.12.6 Add phenotypes](#)).

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4. Data Analysis

4.4 Analysis Overview (6)

4.4.3 Specimen Tab (1)

Specimen
Active tab

Specimen
To modify the specimen details, click the Edit button

Laboratory

Contact details of the contact chosen in the “Selected By” field will be displayed here

Variant Report

The Specimen Section will only be displayed in the Variant Report if one or more fields are completed. Blank fields will not be displayed in the report (see an example on the next page Specimen Tab (2)).

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4. Data Analysis

4.4 Analysis Overview (6)

4.4.4 Specimen Tab (2)

Specimen Details

The Specimen Section will only be displayed in the Variant Report with the completed fields. Blank fields will not be displayed.

Specimen Details

Specimen		Laboratory	
Specimen ID	SPEC19999999997655551111	Facility	Laboratory of Clinical Pathology
Date Collected	03/07/2019	Service	NGS
Date Received	25/09/2019	Facility ID	LAB1788676
Selected By	NGS	Name	Medical Id
Specimen Type	Blood	Web	
Preservation Method	EDTA tube	Address 1	
DNA Quantity	25.0 ng	Address 2	
		Post code	City
		State	Country
		Tel	01234 65499
		Email	info@lcp.ucl.co.uk
		Fax	-- Unknown --

Germline Variant Report

Patient	Ordering physician	Specimen	Selected by:
First name:	Name: Pitavullakandi	Specimen ID:	Service: NGS
Last name:	Thekkaparambil Usha	SPEC19999999997655551111	Facility: Laboratory of Clinical Pathology
Patient ID: library01	Medical ID: 187676	Date collected: 03 Jul 2019	Facility ID: LAB1788676
DOB: 1 Jan 1970	Service: SJU Pathology	Date received: 25 Sep 2019	Email: info@lcp.ucl.co.uk
Gender: Unknown	Facility: St James' University Hospital	Specimen type: Blood, EDTA tube	Tel: 01234 65499
Father ethnicity: -- Unknown --	Hospital ID: SJU16785	DNA quantity: 25.0 ng	
Mother ethnicity: -- Unknown --	Central Road		
	NW1 8YT London		
	United Kingdom		
	Email:		
	ptusha@sjupathology.com		
	Tel: 01539 765123		
	Fax: 01786 433663		
	Web: www.sju.com		

Analysis

Analysis ID: 200035992 MID: S1 Run date: 31 May 2017 Run name: DDMAT-69_TestDataMix_CFTR_BRCA Sequencer: Illumina MiSeq

NOTE: Only specimen info relevant to the experiment type can be entered.

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4. Data Analysis

4.4 Analysis Overview (6)

4.4.5 Test Information Tab (1)

Test Information

The Test Information section will only be displayed in the Variant Report with the completed fields. Blank fields will not be displayed in the report (see the example of the Variant Report on [p.92 - Specimen Tab \(2\)](#)).

The screenshot displays the 'Test Information' tab in the SOPHiA DDM software. The interface includes a top navigation bar with 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS library02 #3-0113'. Below this is a project bar with 'PROJECT Interpretation 1', 'SAMPLE #200035993 library02 < 2/4 >', 'RUN 31/05/2017', and 'Operator User'. The main content area is divided into tabs: 'OVERVIEW', 'SCREENING', 'GENES', 'SNVs/INDELS', 'CNVs', 'FUSIONS', and 'WARNINGS'. The 'Test Information' tab is active, showing fields for 'Medical Contact', 'Facility', 'Service', 'Name', 'Web', 'Address 1', 'Address 2', 'Post code', 'City', 'State', 'Country', 'Tel', and 'Email'. A 'Reason for Referral' section is also present. Below these fields is a 'Test Details' section with 'Test Performed' and 'Laboratory Methodology' dropdowns. A link 'Settings | Test Info' is highlighted with a red box and an arrow pointing to a callout box below the screenshot.

Settings | Test Info

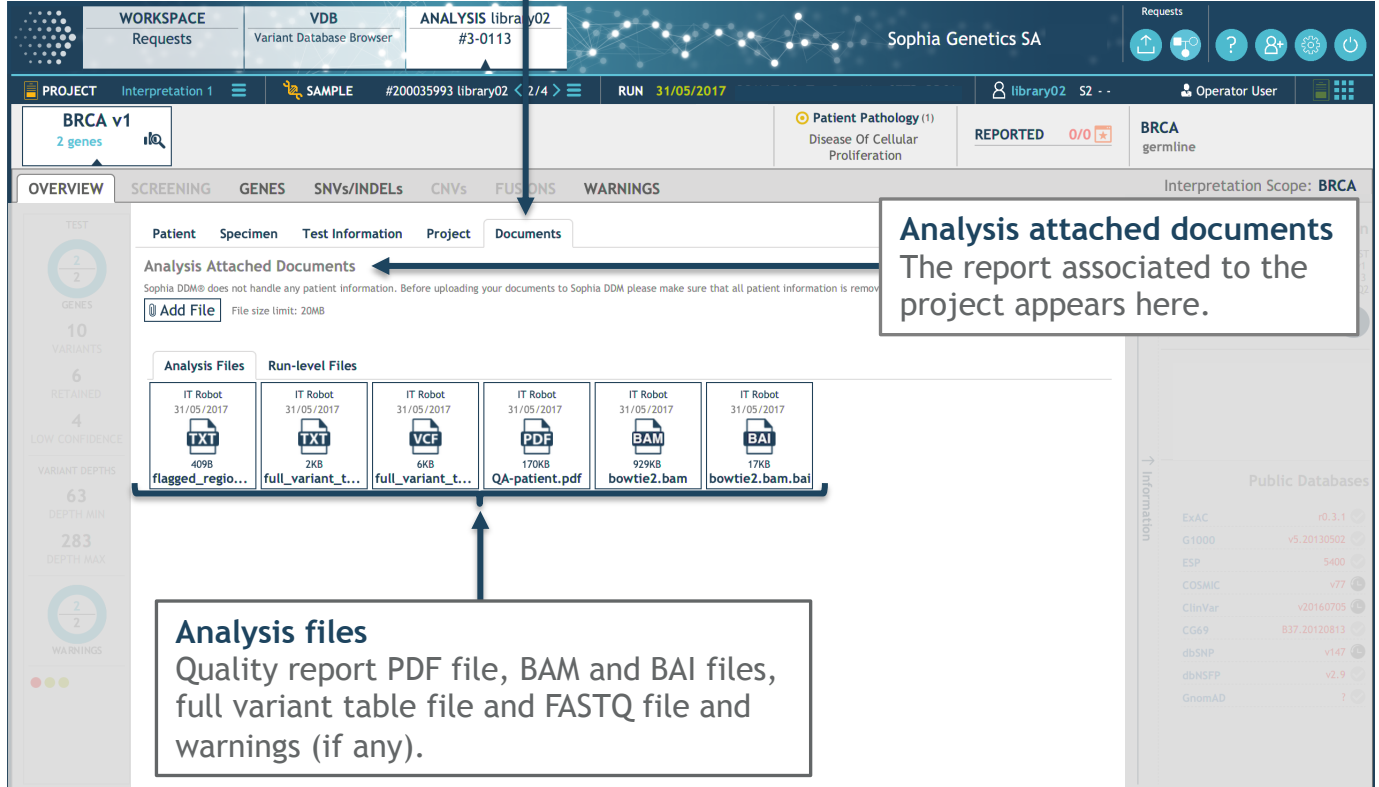
User can open the Settings or Test Info panel by clicking the link.

4. Data Analysis

4.4 Analysis Overview (6)

4.4.6 Documents Tab

Documents
List of attached documents



Analysis files
Quality report PDF file, BAM and BAI files, full variant table file and FASTQ file and warnings (if any).

4. Data Analysis

4.5 Report Approval Workflow (1)

NOTE: This functionality needs to be activated per account. If interested, please contact our support team at support@sophiagenetics.com.

Request approval to finalize project

Per project report settings (see [ch. 4.4.2 Project Settings](#))

Request Project Approval

Do you want to generate a variant report for project interpretation 1?

Use default download location

/Users/username/Desktop

Yes **No** **Cancel**

2

Pending Approval

Interpretation 1 **Pending Approval** **Project Settings**

Virtual Panel HCS_v1_1 (27 genes) Date created 01/06/2020 **Re-work**

Owner Admin User Sent for approval 01/06/2020 **Approve**

Completed

Pending approval

The project changes to “Pending Approval” status. A second user of the account needs to approve the project before it can be completed.

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4. Data Analysis

4.5 Report Approval Workflow (2)

NOTE: Any user of the account (different from the user who requested approval) can approve or ask for re-work of the project.

Interpretation project* with status “Pending Approval”

The screenshot shows the 'WORKSPACE Requests' interface. On the left, there are filters for 139 requests and 552 patients. The main area displays a list of requests, with one selected: '#3-0154 010620 SOPHiA Hereditary Cancer Solution'. The project details show 'Sequencer: Illumina MiSeq', 'Processed date: 01/06/2020', and 'Request date: 01/06/2020'. A table below lists samples with their IDs and MID values. The project status is indicated as 'Pending Approval'.

Open project with status “Pending Approval”

The screenshot shows the 'Interpretation 1' project details page. The status is 'Pending Approval'. The 'Project Settings' section includes 'Re-work' and 'Approve' buttons. Two callout boxes provide details:

- Re-work:** The project changes back to “Draft” status and can be re-worked. The same or another user can then click “Request Approval” again.
- Approve:** The project status changes to “Complete”. The final report can be created and downloaded.

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4. Data Analysis

4.5 Report Approval Workflow (3)

Back to Project main tab

Project Active tab

Report creation
 Select whether the report should be created upon request for approval and/or upon approval.

Report sections
 Selection of sections included in the Draft or Final report for this specific Interpretation Project*. Available checkboxes depend on the experiment type (germline or somatic). Default report settings per application can be defined in the Application Settings (see [ch. 2.10](#))

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4. Data Analysis

4.6 Predictions

4.6.1 Definitions

Predictions for pathogenicity are based on rules defined using machine learning techniques that are part of SOPHiA DDM™. This takes into account the complete set of annotation information and a large number of possible rules, such as:

- Coding consequence = Frameshift
- Is the variant rated pathogenic by ClinVar?
- Polphen2, MutationTaster > 0.9
- etc.

Rules are chosen to minimize cross-over errors (e.g. from B -> D), and to also decrease other classification errors (e.g. A->B).

When compared to clinician's* own ranking they show a marked improvement over the previously used hand-written rules.

A	Pathogenic
B	Likely pathogenic
C	Uncertain significance
D	Likely benign

Germline: Retained variants only = A + B + C + D

Somatic: All variants (retained + low confidence variants) = A + B + C + D with a tag when variants are low confidence

NOTE: Since the pathogenicity predictions found in SOPHiA DDM™ are predictions that use machine learning techniques on data from external data sources, such as ClinVar, these pathogenicity prediction scores can be subject to change if and when information from these data sources is updated. Hence, SOPHiA GENETICS cannot guarantee the accuracy of this information and the predictions provided.

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4. Data Analysis

4.6 Prediction

4.6.2 Pathogenicity Matching

Correspondence between the pathogenicity flagging and the SOPHiA DDM™ prediction.

When flagging a variant with a pathogenicity flag, it is automatically classified as one of A - D category

Pathogenicity Flag		Prediction
	None	A/B/C/D
1	Benign or of no clinical significance	D
2	Likely benign or of little clinical significance	D
3	Uncertain significance	C
4	Likely pathogenic	B
5	Pathogenic	A

4. Data Analysis

4.7 Variants

Screening
Active sub page (white)

Variants
Active page (blue)

The screenshot displays the Sophia Genetics SA interface. At the top, there are tabs for WORKSPACE, VDB, and ANALYSIS. Below this is a navigation bar with buttons for Overview, OncoPortal, and Variants. The main content area is divided into sections: SCREENING, GENES, SNVs/INDELS, CNVs, and WARNINGS. The SNVs/INDELS section is currently active, showing a table of variants. Three callout boxes provide detailed information about the 'Screening', 'Genes', and 'SNVs/Indels' sections.

“SNVs/Indels”
Indicates all the variants detected in the patient*. Also offers access to the “variant filter builder” (see [chapter 5 - Variant Filter Builder](#)), a feature to create your own custom filters.

“Genes”
General overview of genes and their number of variants and coding consequences. Also offers access to Virtual Panels (see [chapter 4.8.2 - Virtual Panels](#)).

“Screening”
Preview major hotspots (codons/indels) present in the patient*.

Sample	Gene	Type	Variant	Frequency	Reference	Accession	IGV
c1	cdna						
c2	cdna						
c3	cdna						
c4	cdna						
c5	cdna						
c6	cdna	KRAS:c.35G>A	undetected	12	KRAS	NM_004985_4529_25398284_25398284	IGV
c7	cdna	KRAS:c.38C>A	undetected	13	KRAS	NM_004985_4529_25398281_25398281	IGV
c8	cdna	KRAS:c.38C>A	undetected	13	KRAS	NM_004985_4529_25398281_25398281	IGV
c9	cdna	KRAS:c.38C>A	undetected	13	KRAS	NM_004985_4529_25398281_25398281	IGV
c10	cdna	KRAS:c.38C>A	undetected	13	KRAS	NM_004985_4529_25398281_25398281	IGV
c11	cdna	KRAS:c.38C>A	undetected	13	KRAS	NM_004985_4529_25398281_25398281	IGV
c12	cdna	KRAS:c.38C>A	undetected	13	KRAS	NM_004985_4529_25398281_25398281	IGV
c13	cdna	KRAS:c.38C>A	undetected	13	KRAS	NM_004985_4529_25398281_25398281	IGV
c14	cdna	KRAS:c.175G>A	undetected	12	KRAS	NM_004985_9990_25380283_25380283	IGV
c21	cdna	EGFR:c.2155G>T	undetected	7	EGFR	NM_005228_12032_55241707_55241707	IGV
c22	cdna	EGFR:c.2155G>A	undetected	7	EGFR	NM_005228_12032_55241707_55241707	IGV
c23	cdna	EGFR:c.2369C>T	undetected	7	EGFR	NM_005228_7187_55249071_55249071	IGV

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4. Data Analysis

4.7 Variants

4.7.1 Screening (1)

“Screening”
Active sub page
(white)

Screening view
Active tab
With all the hotspots listed (white): tabular view.

Graphic view of the hotspots per gene.

The screening contains a list of 52 defined hotspots.

Number of detected hotspots are in **RED**.

Number of undetected hotspots are in **BLACK**.

Number of undetermined hotspots. Algorithms could not check for these hotspot positions.

GENES	SNVs/INDELS	CNVs	WARNINGS
NRAS	PIK3CA	ERBB2	KRAS
BRAF	EGFR		
c1	cdna KRAS:c.181C>G	undetected	12 KRAS NM_004985 9990 25380277 25380277
c2	cdna KRAS:c.181C>A	undetected	12 KRAS NM_004985 9990 25380277 25380277
c3	cdna KRAS:c.179G>A	undetected	12 KRAS NM_004985 9990 25380283 25380283
c4	cdna KRAS:c.176C>G	undetected	12 KRAS NM_004985 9990 25380282 25380282
c5	cdna KRAS:c.351A>C	undetected	12 KRAS NM_004985 15088 25378647 25378647
c6	cdna KRAS:c.351A>T	undetected	12 KRAS NM_004985 15088 25378647 25378647
c7	cdna KRAS:c.436G>A	undetected	12 KRAS NM_004985 11092 25378562 25378562
c8	cdna KRAS:c.437C>T	undetected	12 KRAS NM_004985 11092 25378561 25378561
c9	cdna EGFR:c.2156G>C	undetected	7 EGFR NM_005228 12032 55241708 55241708
c10	cdna EGFR:c.2155G>T	undetected	7 EGFR NM_005228 12032 55241707 55241707
c11	cdna EGFR:c.2155G>A	undetected	7 EGFR NM_005228 12032 55241707 55241707
c12	cdna EGFR:c.2369C>T	undetected	7 EGFR NM_005228 7187 55249071 55249071

Profiling

With the screening view users can quickly visualize the predefined hotspots with their detection level. Click profiling to access the SNVs/Indels view.

4. Data Analysis

4.7 Variants

4.7.1 Screening (2)

Screening
Active sub page
(white)

Screening view
Active tab
With all the hotspots listed (white): tabular view.

The screenshot displays the SOPHiA DDM software interface. At the top, there's a navigation bar with 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS PM16001234 #2-0306'. Below this, a 'PROJECT' and 'SAMPLE' section is visible. The main area is titled 'SCREENING' and contains a table of hotspots. The table has columns for 'Id', 'Type', 'name', 'status', 'chr', 'Gene', 'transcript', 'reads', 'start', 'end', 'Exo...', 'Codon', 'VF%', 'Depth', 'Protein', 'c.DNA', 'alt', 'ref', and 'IGV'. Row c1 shows a 'present' status in red, while rows c2 and c3 show 'undetected' status. A sidebar on the left shows '52 HOTSPOTS', '1 PRESENT', '51 UNDETECTED', and '0 UNDETERMINED'. Callout boxes provide explanations for the 'present' status, the 'undetected' status, and the 'IGV' link.

The presence of a particular mutation in the hotspot region is highlighted in red (high confidence).

“Undetected” hotspots means that there is no genomic alteration at the specific position (high confidence).

Link to IGV for this hotspot position.

The undetermined hotspots means that the algorithms could not determine if the hotspot position is wild-type or altered (low confidence).

4. Data Analysis

4.7 Variants

4.7.1 Screening (3)

Screening
Active sub page (white)

Graphic view
Active tab (white)
with the list of hotspots codons/indels and their positions in the gene.

NCBI RefSeq NM transcript detail.

Position of positive hotspot.

Screening visualization

- Number of hotspot positions listed. **In red, presence of the hotspot position.**
- Number of hotspot range listed (Indels). **In red, presence of the hotspot indel.**

4. Data Analysis

4.7 Variants

4.7.1 Screening (4)

SNVs/Indels tab
Active tab (white)

Screening column
Add the screening column to the variant table to highlight variants present in the screening list.

ID	P...	Actionability	T...	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
A	5			SNP	FBXW7 nonsense	c.1099C>T	18511	20.3	G	A
A	5			SNP	FBXW7 missense	c.1436G>A	21298	20.5	C	T
B	5	✓		SNP	KRAS missense	c.35G>T	16271	22.5	C	A
B				INDEL	FOXL2 missense	c.26_29delinsC...	16395	1.9	TCCT	GCCG
B				SNP	FOXL2 missense	c.20A>C	16545	1.3	T	G
B				INDEL	FOXL2 missense	c.44_47delins...	15005	4.6	AGCA	CGCC
B				SNP	FOXL2 missense	c.58A>C	13273	4.2	T	G
B		✓		SNP	PIK3CA missense	c.1258T>C	14754	22.5	T	C
B				SNP	TP53 missense	c.526T>C	19007	35.4	A	G
C				SNP	EGFR synonymous	c.2361G>A	33347	39.2	G	A
C				SNP	FGFR3 synonymous	c.1953G>A	17555	100.0	G	A
C				SNP	FGFR3 synonymous	c.882T>C	16265	99.5	T	C
C				SNP	FOXL2 synonymous	c.114T>G	18281	2.1	A	C

Hotspot / Screening details

Screening tab
Active tab (white)

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4. Data Analysis

4.8 Genes

4.8.1 Overview

Access a quick-view of genes of interest with the total number of variants for each gene, pathogenicity and prediction levels, variant types and their coding consequences.

Virtual Panels

Genes
Active tab (white)

Calculate coverage of Virtual Panel

Gene list of selected Virtual Panel

Click on the gene name to open IGV at the position of the gene.

Click on the eye to open the gene viewer. It shows where the variants are located in the gene.

Selected Virtual Panel

Virtual Panel search

Chr	Name (IGV)	Prediction	SNV	INDEL	DEL	DUP	INV	Total	FSST	ALSE	INFR	SYN	UTR	SLUR	INGE	INTR	other	CNV
17	BRCA1		29	10	0	0	0	39	1	4			2	1				28
13	BRCA2		20	0	0	0	0	20		2					2	13		
17	TP53		7	3	0	0	0	10		1						1		8

Gene Viewer

Analysis #200036181 - 162829

Gene BRCA1

CHB17
BRCA1
NM_007294

pathogenicity 0%
avg VF: 50%
100%

The displayed transcript structure is based on RefSeq 2012, please be aware that this might not accurately align with the analysis results.

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4. Data Analysis

4.8 Genes

4.8.2 Virtual Panels - Overview

The screenshot displays the SOPHiA DDM software interface. At the top, a navigation bar includes 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS 162829 #3-0130'. The main content area is divided into several sections:

- Root Virtual Panel:** Points to the top-level panel structure.
- Virtual Panel:** Points to a sub-panel in the left sidebar.
- Virtual sub-panel used (number of genes mentioned):** Points to the 'BRCA genes' sub-panel showing '2 genes'.
- Gene search:** Points to the search bar and filters (Case sensitive, Exact match) above the gene list.
- Selection replace:** Points to the 'select / unselect all' button in the gene list.
- List of Virtual Panels:** Points to the sidebar menu showing 'HCS_v1_1 [root]', 'HBOC', 'BRCA genes', and 'HNPC'.
- Virtual Panels:** Points to the '+ »' button for creating a new panel.

The interface also shows a 'Patient's Disease (1) Breast Myoepithelial Neoplasm' and 'Hereditary Cancer Solution v1.1' with a 'REPORTED 0/0' status. The bottom status bar shows 'sg-admin Sophia Genetics SA (Test)' and 'SOPHiA GENETICS'.

NOTE: Virtual Panels can only be deleted and edited in the application settings.

4. Data Analysis

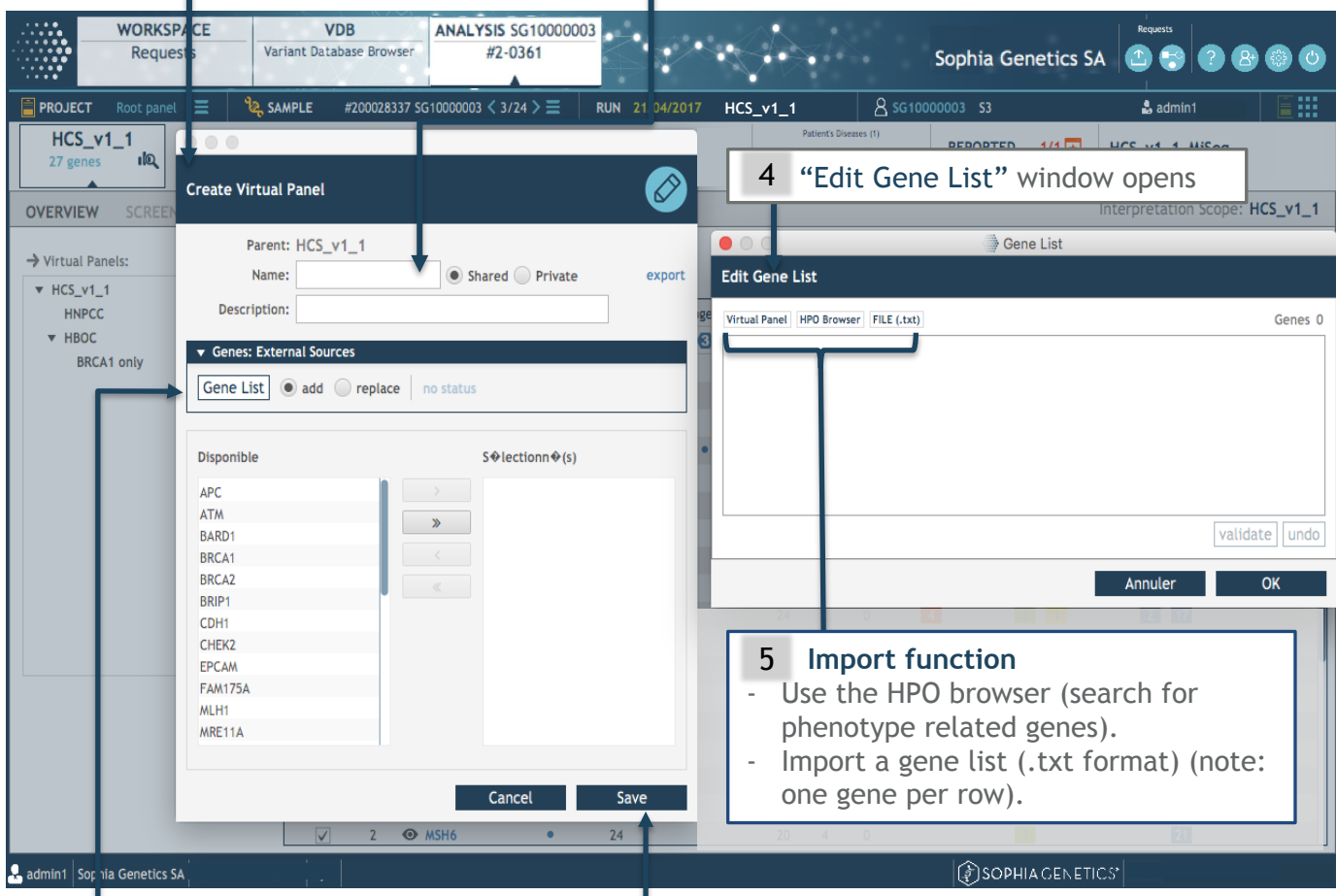
4.8 Genes

4.8.3 Virtual Panels - Create

Create Virtual Panels using local gene lists in text format or by using the HPO (Human Phenotype Ontology) browser (for HPO usage, see [chapter 4.8.4 - Virtual Panels - Create using HPO](#) and [5.4 - HPO Search](#))

1 “Create Virtual Panel”
Window opens after clicking on “+”.

2 Enter a name and description for the Virtual Panel.



4 “Edit Gene List” window opens

5 Import function

- Use the HPO browser (search for phenotype related genes).
- Import a gene list (.txt format) (note: one gene per row).

3 Import function
Click on “gene list” to import a list of genes or use HPO search.

6 Save

4. Data Analysis

4.8 Genes

4.8.4 Virtual Panels - Create using HPO

2 Enter phenotype in search box.

3 Select the phenotype or disease* and click on the arrow (>), the list of genes associated to this phenotype appears.

The screenshot shows the 'Get genes from HPO - Human Phenotype Ontology' window. The search terms are 'breast'. The HPO objects list includes: Abnormality of the breast, Aplasia/Hypoplasia of the breasts, Asymmetry of the breasts, BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBLE (selected), BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBLE, Bilateral breast hypoplasia, Breast aplasia, and Breast carcinoma. The 'Saved Objects' list contains 'Disease BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBLE'. Below, the 'Genes: 19' list includes: BARL1, BRCA1, BRCA2, BRIP1, CHEK2, KLLN, MRE11A, NBN, PALB2, PPM1D, PTEN, RAD50, RAD51, RAD51C, RAD51D, RAD54L, SLC22A18, TP53, and XRCC2. The 'Apply' button is highlighted.

1 "Get genes from HPO" Window opens after clicking on "HPO browser" in the "edit gene list" window.

4 Gene selection
Select genes to be added with CTRL-click (⌘CMD) or click on "apply" to import the full list of genes.

5 Apply

4. Data Analysis

4.8 Genes

4.8.5 Coverage Calculator

WORKSPACE Requests | VDB Variant Database Browser | ANALYSIS 162829 #3-0130 | Sophia Genetics SA (Test) | Requests

Interpretation 1 | SAMPLE #200036181 162829 < 17/19 | RUN 20/09/2019 | 162829 S19 --

HCS_v1_1 v2 27 genes | Patient's Disease (1) Breast Myoepithelial Neoplasm | REPORTED 0/0 | Hereditary Cancer Solution v1.1 germline

OVERVIEW | SCREENING | GENES | SNVs/INDELS | CNVs | FUSIONS | WARNINGS | Interpretation Scope: HCS_v1_1

Virtual Panels: select / unselect all Search: Case sensitive Exact match [Calculate coverage for virtual panel](#)

Search:

Filter	Chr	Name (IGV)	Prediction	Pathogenicity	Molecular Variants										Structural Variants						
					SNV	INDEL	DEL	DUP	INV	Total	FSFT	HLSE	INER	SNK	SUTR	INCE	INTR	other	Deletion	Amplification	
<input checked="" type="checkbox"/>	17	BRCA1	•	•	27	0	0	0	0	0	27										
<input checked="" type="checkbox"/>	13	BRCA2	•	•	20	0	0	0	0	0	20										
<input checked="" type="checkbox"/>	19	STK11	•	•	12	1	0														
<input checked="" type="checkbox"/>	17	BRIP1	•	•	19	4	0														
<input checked="" type="checkbox"/>	16	CDH1	•	•	7	6	0														
<input checked="" type="checkbox"/>	2	EPCAM	•	•	5	0	0														
<input checked="" type="checkbox"/>	22	CHEK2	•	•	11	0	0														
<input checked="" type="checkbox"/>	7	PMS2	•	•	20	3	0	0	0	0	23										
<input checked="" type="checkbox"/>	8	NBN	•	•	3	0	0	0	0	0	3										
<input checked="" type="checkbox"/>	1	MUTYH	•	•	5	0	0	0	0	0	5										
<input checked="" type="checkbox"/>	2	BARD1	•	•	25	2	0	0	0	0	27										
<input checked="" type="checkbox"/>	7	XRCC2	•	•	1	0	0	0	0	0	1										
<input checked="" type="checkbox"/>	3	MLH1	•	•	9	7	0	0	0	0	16										
<input checked="" type="checkbox"/>	16	PALB2	•	•	2	1	0	0	0	0	3										
<input checked="" type="checkbox"/>	2	MSH6	•	•	11	3	0	0	0	0	14										
<input checked="" type="checkbox"/>	17	RAD51D	•	•	1	0	0	0	0	0	1										
<input checked="" type="checkbox"/>	5	RAD50	•	•	3	0	0	0	0	0	3										

sg-admin | Sophia Genetics SA (Test) | 20695 | SOPHiA GENETICS

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4. Data Analysis

4.8 Genes

4.8.5 Coverage Calculator

4.8.5.1 Coverage Statistics Tab (1)

Selected Virtual Panel

Coverage statistics Active tab

Coverage thresholds

% of positions covered with the respective number of reads (exons ±10bp)

Export coverage statistics

Expand to retrieve transcript information

Click transcript for exon coverage visualization (not shown)

Gene	>15	>20	>25	>30	>50	>100	>200	>500	>1000
AAAS	100.0	100.0	100.0	100.0	100.0	100.0	71.6	0.0	0.0
AADAC	100.0	100.0	100.0	100.0	100.0	84.4	32.6	0.0	0.0
AADACL2	100.0	100.0	100.0	100.0	100.0	88.5	17.3	0.0	0.0
AAGAB	100.0	100.0	100.0	100.0	100.0	51.5	0.5	0.0	0.0
AANAT	100.0	100.0	100.0	100.0	100.0	100.0	90.4	21.8	0.0
AARS	100.0	100.0	100.0	100.0	100.0	100.0	78.1	0.0	0.0
AARS2	100.0	100.0	100.0	100.0	100.0	99.9	70.6	0.0	0.0
AASS	99.8	99.6	99.4	99.3	98.8	81.5	32.5	0.0	0.0
ABAT	100.0	100.0	100.0	100.0	100.0	84.7	54.5	0.0	0.0

Coverage statistics tab

The coverage calculator offers an easy-to-use feature to display and export coverage statistics for a Virtual Panel of a given test and analysis. Select your Virtual Panel of choice (or the root panel) from the Virtual Panel list or create a new Virtual Panel. Please refer to [“4.8.3 Virtual Panels - Create”](#) to know how to create Virtual Panels. Click on “calculate coverage for Virtual Panel” link to open the coverage calculator.

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4. Data Analysis

4.8 Genes

4.8.5 Coverage Calculator

4.8.5.1 Coverage Statistics Tab (2)

Coverage Statistics Tab

- Gene Level

For each transcript a weighted sum is calculated. This is done for all transcript exons at a given threshold whilst considering the length of each exon. For each gene, in each threshold column, the global value corresponds to the minimum value (worst case) of all transcripts. The color of each box shows whether a gene is fully (100%) covered at a given threshold (green) or not (red). Coverage information at gene level can be exported to a CSV file by selecting “gene” and clicking “export” at the bottom of the coverage statistics tab.

- Transcript Level

Transcript values are displayed by clicking the triangle next to a gene name to expand the information. Coverage information for the gene and transcripts can be exported to a CSV file by selecting “gene + Tx” and clicking “export” at the bottom of the coverage statistics tab.

- Exon Level

By clicking on one transcript, coverage of each exon of this transcript is visualized in a pop-up window. Coverage information for the gene, transcript and exon can be exported to a CSV file by selecting “gene + Tx + exon” and clicking “export” at the bottom of the coverage statistics tab.

All columns of the coverage statistics table are sortable (ascending, descending, no sorting) by clicking on the header of each column.

The color code of the table header displays coverage information of the Virtual Panel:

- **Green:** all genes (all transcripts, all exons) of the Virtual Panel are covered with 100% at the given threshold.
- **Yellow:** $\geq 90\% < 100\%$ of the regions (genes, transcripts, exons) are covered with the given threshold.
- **Red:** less than 90% of the regions (genes, transcripts, exons) are covered with the given threshold.

4. Data Analysis

4.8 Genes

4.8.5 Coverage Calculator

4.8.5.2 Low Coverage Analysis Tab

The screenshot displays the Sophia Genetics SA interface. The main window is titled 'Coverage calculator - Sample: Ni'. The 'Low Coverage Analysis' tab is active, indicated by a red warning icon and a callout box. The interface includes a 'Threshold' input field, a 'Number of positions in the intron' section with 'Before (0)' and 'After (0)' sliders, and a list of genes with corresponding transcript IDs. A red warning message states: 'The coverage of some genes cannot be calculated using this feature'. The 'Export' and 'Close' buttons are visible at the bottom of the dialog.

Low coverage analysis tab

The low coverage analysis tab allows the user to analyze low coverage regions in detail. For a given Virtual Panel, the user can select a range (exon \pm up to 20 bp of intronic region) and a specific transcript for the analysis and can export this information into CSV files. Two CSV files are created, one showing the analyzed regions and the other one displaying the regions below the selected coverage.

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4. Data Analysis

4.9 SNVs/Indels

4.9.1 Overview

Quick access to the SNVs/Indels table with many filters available (see [chapter 18 - Appendix](#) for more details)

Retained variants
Active page (blue)

SNVs/Indels
Active sub page (white)

Selected variant

Click on the “+” to add more columns and “save column preferences”

The screenshot displays the SOPHiA DDM software interface. At the top, there are tabs for 'WORKSPACE', 'VDB Variant Database Browser', and 'ANALYSIS CGH'. The main header shows 'Sophia Genetics SA (Test)' and 'Interpretation 7'. Below this, there are navigation tabs: 'OVERVIEW', 'SCREENING', 'GENES', 'SNVs/INDELS', 'CNVs', 'FUSIONS', and 'WARNINGS'. The 'SNVs/INDELS' tab is active, showing a table of variants sorted by 'ACMG value'. The table has columns for 'Gene', 'Coding consequence', 'c.DNA', 'Depth', 'VFs', and 'alt'. A row for a variant in the 'ARID1B' gene is highlighted. Below the table, there is a detailed view of the selected variant, showing 'Overview', 'Details', 'Variant Description', 'Flagging', 'Viewer', 'ACMG', 'Similar Patients', 'Warnings', and 'Screening'. The 'Overview' section shows '127 DEPTH' and '42% VARIANT FRACTION'. The 'Flagging' section shows '0' for various flags. The 'Viewer' section shows the variant 'NM_017519.2 c.4986+1G>A' with a 'splice_donor_+1' consequence. The 'Screening' section shows 'MutationTaster 1.0' and 'GnomAD 0.0' scores.

Overview

Information about the currently selected variant: Read depth and variant fraction, Frequencies (within the run, account, community), Flagging (by users in the community, by the client, prediction), Variant details (NM transcript, genomic alteration etc.) and Scores.

NOTE: Chapter 4.9 refers to products based on the hg19 reference genome. For further info, please refer to [4.10 hg38 annotation](#).

4. Data Analysis

4.9 SNVs/Indels

4.9.2 Flagging - Overview

Retained variants
Active filter (blue)

Variant table view
Switch between the “compact variant table” & the “customizable variant table”

Variant copy settings

Click to select variant copy settings and to copy the variant to clipboard. The copied information depends on the reference genome of the selected product (see also [4.10 hg38 annotation](#)).

User pathogenicity flag

Indicator shows:

- Number of community users having flagged the current variant in a particular category
- The account pathogenicity flag

Pathogenicity web plot shows prediction and population database scores (if available). The greater the grey area is, the more likely a variant is pathogenic.

NOTE: Please note, for SIFT db, 1-SIFT scores are displayed. MutationTaster values are only available for SNVs.

4. Data Analysis

4.9 SNVs/Indels

4.9.3 User Flagging

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

The screenshot displays the SOPHiA DDM software interface for variant analysis. The top navigation bar includes 'WORKSPACE', 'VDB', and 'ANALYSIS CGH'. The main content area shows a 'Variant List' table with columns for variant ID, gene, coding consequence, cDNA, depth, VAF, and reference/alternate alleles. A 'SOPHiA Filters' sidebar on the left shows 'Retained' variants (6472) and other categories like 'Highly Pathogenic' (6) and 'Potentially Pathogenic' (143). A 'Flagging' sub-tab is active, showing a detailed view of a variant (NM_017519.2: c.4986+1G>A) with a 'flagging' status of 5. The 'Flagging' section includes a grid for adding flags (e.g., gender, disease*) and a 'Set To False' button. A 'MutationTaster' score plot is also visible on the right.

Flagging tab - History subtab

- It shows details about the flagging status of the selected variant
- It enables editing of the flagging status (addition of gender, disease* and publications/URL) and deletion of the current flagging status of the variant
- It shows the historical flagging of the variant (traceability)

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4. Data Analysis

4.9 SNVs/Indels

4.9.4 Frequencies

Variant frequencies mouseover
Switches between percentage and absolute value.

Diagram illustrating the variant frequencies mouseover feature:

Left gauge: frequencies 3/8, RUN (percentage view)

Right gauge: frequencies 37%, RUN (absolute value view)

Run frequency

The number of times this variant was detected within a batch out of the total number of possible occurrences, considering the experiment type and the application used. If there are several samples from the same subject in the batch, the variant is only counted once.

Account frequency

The number of times this variant was detected across all batches using the same application version in this account out of the total number of possible occurrences. This considers the experiment type (germline or somatic), the application used and the version of the application used. If there are several samples from the same subject in the account, the variant is only counted once.

Community frequency

The number of times this variant was detected across all instances of the gene within SOPHiA GENETICS™ Community routine accounts out of the total number of possible occurrences, considering the experiment type and only retained variants. The Frequency may be biased by the nature of the samples, and the countries contributing to the SOPHiA GENETICS™ Community.

4. Data Analysis

4.9 SNVs/Indels


4.9.5 False Positive Variants


Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

The screenshot displays the SOPHiA DDM software interface. At the top, there are navigation tabs for WORKSPACE, VDB, and ANALYSIS. The main area shows a variant list table with columns: A... (variant type), P... (pathogenicity), S... (status), T... (transcript), Gene, Coding consequence, c.DNA, Depth, VFX, ref, and alt. Below the table, there are several panels: OVERVIEW (reads, depth, variant fraction), DETAILS (frequencies, flagging, predictions), VARIANT DESCRIPTION (transcript, exon rank, cDNA, ref/alt, sequence, amino acid, protein), VIEWER (SNP, splice donor), ACMG (ACMG value), SIMILAR PATIENTS, WARNINGS, and SCREENING (POLYPHEN2, scores). On the right side, there is a sidebar with various databases like GnomAD, ClinVar, COSMIC, IGV, NCBI, ALAMUT, Google, and OMM.

False positive
User can flag false positive variants which will be marked according to the sample status (right).

 False positive flagged in a different sample (not confirmed yet by the user).

 False positive flagged in this sample (confirmed by the user in the same analysis, reported as **"False +" in Red**).

NOTE: A false positive flag can only be removed in the sample where the flag was added.

4. Data Analysis

4.9 SNVs/Indels

4.9.6 Links to external sources

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

Selected variant

Links to Databases & Alamut™ Visual / Visual Plus
Click the link to open the variant in the respective external source. Links are only active if a match with the SOPHiA DDM™ annotation database is available.

Search string:
● ARID1B:c.4986+1G>A
● NM017519:c.4986+1G>A

Would you like to open ALAMUT with or without providing a BAM file?
With Without

Alamut®

Clicking the “Alamut” button allows the user to select the annotation format and whether or not to import the BAM file from SOPHiA DDM™ for visualization in Alamut®. Access to Alamut™ Visual or Alamut™ Visual Plus from SOPHiA DDM™ is possible via API. Visualization of the variant in Alamut™ Visual or Alamut™ Visual Plus requires a separate licence. Check the dedicated webpage to learn more:

<https://www.interactive-biosoftware.com/>

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4. Data Analysis

4.9 SNVs/Indels

4.9.7 Variant Details

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

Variant List - sorted by: ACMG value

A...	D...	P...	S...	T...	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
IV	A	5			SNP ARID1B	splice_donor_+1	c.4986+1G>A	127	42.5	G	A
IV	B	5			SNP COL4A4	splice_donor_+1	c.3397+1G>C	226	50.4	C	G
IV	B				INDEL TYRO3	splice_acceptor_+1	c.1875+1_1876...	346	44.0	TGTGA...	T
IV	C				INDEL SHANK3	frameshift	c.1336_1337del	41	75.0	GCC	G
IV	B	1			INDEL TYRO3	splice_acceptor_+1	c.2145+1_2146...	312	37.0	TGGTG...	T
IV	B	2			INDEL TYRO3	splice_acceptor_+1	c.308+1_309-1del	383	33.0	TCAGG...	T
IV	C				INDEL SHANK3	frameshift	c.1308_1344dup	50	91.0	G	GCCCC...
IV	D				INDEL TYRO3	splice_acceptor_+1	c.1483+1_1484...	410	38.0	TGTGA...	T
III	D				INDEL PEX5	frameshift	c.151del	179	95.0	GA	G
III	D				SNP LRP4	missense	c.3256A>G	103	98.1	T	C
III	D				SNP ZAN	missense	c.5708G>A	247	40.5	G	A
III	D				SNP CUL3	missense	c.1501G>A	75	53.3	C	T
III	B				SNP APOB	missense	c.11477C>T	178	41.6	G	A
III	B				SNP OBSN	missense	c.12052C>T	366	48.1	C	T
III	D				SNP ROR2	missense	c.2455G>A	262	99.6	C	T

DETAILS

OVERVIEW	VARIANT DESCRIPTION	FLAGGING	VIEWER	ACMG	SIMILAR PATIENTS	WARNINGS	SCREENING
Unique Depth	:	Depth	:	127	refAA	:	1-SIFT
Unique refNum	:	VF%	:	42.52	altAA	:	POLYPHEN2
Unique altNum	:	Exon rank	:	18	Transcript	:	LRT
Gene	:	c.DNA	:	c.4986+1G>A	Transcript Version	:	MutationTaster
id	:	Protein	:	p.(?)	RefSeq id	:	GERP
Overlap known	:	ref	:	G	Gene boundaries	:	within
Type	:	alt	:	A	Filter	:	Cosmic Coding
Coding consequence	:	refNum	:	73	dbSNP	:	Cosmic Non Coding
Reference Genome	:	altNum	:	54	G1000	:	Strand
Chromosome	:	RefSeq	:	:	ESPS400	:	alt1
Genome position	:	AltSeq	:	:	PhyloP	:	first1

Details
The details tab presents extensive information about the current variant

4. Data Analysis

4.9 SNVs/Indels

4.9.8 Variant Description Tab

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

The screenshot displays the SOPHiA DDM software interface. At the top, there are navigation tabs for 'WORKSPACE', 'VDB', and 'ANALYSIS CGH'. Below this, a patient information bar shows 'SAMPLE #200036135', 'RUN 02/12/2020', and 'CES_v1_FVA_CNV (8 samples)'. The main interface is divided into several sections. On the left, there is a 'SOPHiA Filters' sidebar with categories like 'Retained' (6472), 'Highly Pathogenic' (6), 'Potentially Pathogenic' (143), 'Unknown Significance' (447), 'Likely Benign' (5875), 'Low Confidence Variants' (25882), and 'Flagged Variants' (8). The main content area is divided into tabs: 'OVERVIEW', 'SCREENING', 'GENES', 'SNVs/INDELS', 'CNVs', 'FUSIONS', and 'WARNINGS'. The 'SNVs/INDELS' tab is active, showing a table of variants with columns for 'Gene', 'Coding consequence', 'c.DNA', 'Depth', 'VF%', 'ref', and 'alt'. A 'Variant description added.' dialog box is open at the bottom, with a 'Save' button. A 'Links' sidebar on the right contains various database links like GnomAD, ClinVar, COSMIC, IGTV, NCBI, ALAMUT, Google, and OMIM.

A...	P...	S...	T...	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
				SNP	ARID1B	splice_donor_+1	c.4986+1G>A	127	42.5	G A
				SNP	COL4A4	splice_donor_+1	c.3397+1G>C	226	50.4	C G
				INDEL	TYRO3	splice_acceptor_-1	c.1875+1_1876...	346	44.0	TG TGA...
				INDEL	SHANK3	frameshift	c.1336_1337del	41	75.0	GCC G
				INDEL	TYRO3	splice_acceptor_-1	c.2145+1_2146...	312	37.0	TGG TG...
				INDEL	TYRO3	splice_acceptor_-1	c.308+1_309-1del	383	33.0	TCAGG...
				INDEL	SHANK3	frameshift	c.1308_1344dup	50	91.0	G GCCC...
				INDEL	TYRO3	splice_acceptor_-1	c.1483+1_1484...	410	38.0	TG TGA...
				INDEL	PEX5	frameshift	c.151del	179	95.0	GA G
				SNP	LRP4	missense	c.3256A>G	103	98.1	T C
				SNP	ZAN	missense	c.5708G>A	247	40.5	G A
				SNP	CUL3	missense	c.1501G>A	75	53.3	C T
				SNP	APOB	missense	c.11477C>T	178	41.6	G A
				SNP	OBSCN	missense	c.12052C>T	366	48.1	C T
				SNP	ROR2	missense	c.2455G>A	262	99.6	C T

Variant Description

A free-text description can be added to the variant. This description is accessible for all samples of the same experiment type (somatic/germline) with the same variant. This description can be selected to report in the Project or Application Settings.

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4. Data Analysis

4.9 SNVs/Indels

4.9.9 Flagging Tab

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

The screenshot displays the SOPHiA DDM interface for a clinical exome solution. The top navigation bar includes 'WORKSPACE Requests', 'VDB Variant Database', and 'ANAL... CGH1040...'. The main header shows 'Sophia Genetics SA (Test)' and 'Clinical Exome Solution by Sophia'. The current analysis is 'CES_v1 v2' with 4890 genes. The 'SNVs/INDELS' tab is active, showing a list of variants. A detailed view of a variant is shown below, including its pathogenicity flag (5), history, and user information.

SOPHiA Pathogenicity	ACMG Pathogenicity	In Report	False+	Warning	Genomic	Sample	Transcript	Scores	Frequen
A	V				SNP chr 6 157525131	G 73 A 54	42.5% ARID1B 127 NM_017519.2	1.0	-
A	I				SNP chr X 66941751	C 104 G 69	39.9% AR 173 NM_000044.3	0.978 0.965 1.0	0.0015 0.0016
A	V				SNP chr 2 227907792	C 112 G 114	50.4% COL4A4 226 NM_000092.4	1.0	-

Flagging tab
The flagging tab shows which user applied a pathogenicity flag, the history of pathogenicity flags as well as the “in report” and ”false +” flags.

NOTE: For better performance, new flags created in the community are not propagated to Interpretation Projects* opened within the preceding 30 minutes.

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4. Data Analysis

4.9 SNVs/Indels

4.9.10 Viewer

Retained variants
Active page (blue)

SNVs/Indels
Active sub page (white)

The screenshot displays the SOPHiA DDM software interface. At the top, there are navigation tabs for 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS CGH #3-0137'. The main header shows 'Sophia Genetics SA (Test)' and 'Interpretation 7'. Below this, there are filters for 'CES_v1 v2' (4890 genes) and 'Patient's Disease (0)'. The main content area is divided into several tabs: 'OVERVIEW', 'SCREENING', 'GENES', 'SNVs/INDELS', 'CNVs', 'FUSIONS', and 'WARNINGS'. The 'SNVs/INDELS' tab is active, showing a table of variants. Below the table, there is a 'VIEWER' window showing a gene structure diagram for NM_017519 (ARID1B) with various variants highlighted. The 'VIEWER' window also displays 'pathogenicity 0%' and 'avg VAF 50%'.

Variant	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
SNP	ARID1B	splice_donor_+1	c.4986+1G>A	127	42.5	G	A
SNP	AR	missense	c.2395C>G	173	39.9	C	G
SNP	EXOSC3	missense	c.395A>C	163	44.2	T	G
SNP	COL4A4	splice_donor_+1	c.3397+1G>C	226	50.4	C	G
INDEL	TYRO3	splice_acceptor_-1	c.308+1_309-1del	383	33.0	TCAGG...	T
INDEL	TYRO3	splice_acceptor_-1	c.2145+1_2146...	312	37.0	TGGTG...	T
SNP		intergenic		121	45.5	T	C
SNP	ABCA4	missense	c.5843C>T	93	45.2	G	A
SNP	ABCC1	missense	c.2012G>T	194	44.3	G	T
SNP	ABCD3	missense	c.122G>A	79	44.3	G	A
SNP	ACACB	missense	c.3113C>T	308	42.9	C	T
SNP	ACSM3	missense	c.725C>T	159	45.9	C	T
SNP	ADAMTSL4	missense	c.2305C>G	229	41.0	C	G
SNP	ADAMTSL4	missense	c.3083G>A	176	47.2	G	A
SNP	ALMS1	missense	c.9911A>G	106	54.7	A	G

Viewer
Displays the current variant position and variant fraction in a gene view window.

4. Data Analysis

4.9 SNVs/Indels

4.9.11 ACMG Tab (1)

The 2015 report from the American College of Medical Genetics and Genomics (ACMG) provides updated recommendations for the reporting and interpretation* of sequence variants for Mendelian disorders in a clinical context ([Richards et al., 2015. *Genet Med* 17:405-424](#)).

The report recommends the use of the well accepted five-tier system: “5-pathogenic”, “4-likely pathogenic”, “3-uncertain significance”, “2-likely benign” and “1-benign” to describe variants identified in genes that cause Mendelian disorders. Most importantly, this recommendation describes a process for pre-classifying variants into these five categories based on 28 criteria using specific types of variant evidence (e.g. population data, computational data, functional data, segregation data).

SOPHiA DDM™ automatically gathers and collates information from various sources to evaluate two sets of criteria: one for classification of pathogenic or likely pathogenic variants and one for classification of benign or likely benign variants. Each pathogenic criterion is weighted as very strong (PVS1), strong (PS1-4), moderate (PM1-6), or supporting (PP1-5), and each benign criterion is weighted as stand-alone (BA1), strong (BS1-4), or supporting (BP1-6). SOPHiA DDM™ then combines the values of these criteria (true or false) according to the scoring rules recommended by the ACMG guidelines and calculates a ACMG pre-classification score (I, II, III, IV, V) corresponding to a level of pathogenicity.

Out of 28 criteria, 13 are automatically evaluated by SOPHiA DDM™ to establish an initial ACMG pre-classification score for all variants of every sample of a run. This initial score is displayed in a column of the variant table next to each variant. The automated evaluation takes into account various data available in SOPHiA DDM™ annotation database acquired from multiple sources. This includes frequencies in the population (GnomAD, ExAC, G1000 and ESP5400), *in silico* scores (SIFT, MutationTaster and PolyPhen-2), disease*-specific data (ClinVar, OMIM), splicing predictors (dbSNV), protein domains (InterPro), loss of function (ExAC pLI) and repetitive regions (RepeatMasker).

If needed, every automated criterion can be overridden. Any non-automated criterion can be manually evaluated and evidence for the state can be recorded. Every time a change is made on one of the criteria, the ACMG score is dynamically recalculated. If a variant has already been flagged and is not in line with the final ACMG pre-classification score, SOPHiA DDM™ informs users and lets them adjust it if needed. Finally, the user can select the assessed variant and add it “In Report“ that has been adapted with an additional section that presents the values of the ACMG criteria and the resulting score.

4. Data Analysis

4.9 SNVs/Indels

4.9.11 ACMG Tab (2)

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

The screenshot displays the SOPHiA DDM interface. At the top, the 'ANALYSIS CGH #3-0132' is visible. The main navigation bar includes 'OVERVIEW', 'SCREENING', 'GENES', 'SNVs/INDELS', 'CNVs', 'FUSIONS', and 'WARNINGS'. The 'SNVs/INDELS' tab is active, showing a list of variants. A variant with Gene: ARID1B, cDNA: c.4986+1G>A, and a splice_donor+1 consequence is selected. Below the variant list, the 'ACMG' tab is open, showing 28 criteria for the selected variant. A 'PVSI' (Creates Null Allele) criterion is highlighted, with a calculated value of 'True' and a 'No decision' user decision. A 'V5' ACMG global score and a user flagging checkbox are also visible.

A...	P...	S...	T...	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
III	A	5		SNP	splice_donor+1	c.4986+1G>A	127	42.5	G	A
III	A			SNP	missense	c.2395C>G	173	39.9	C	G
III	A			SNP	missense	c.395A>C	163	44.2	T	G
III	B	5		SNP	splice_donor+1	c.3397+1G>C	226	50.4	C	G
III	B	2		INDEL	splice_acceptor-1	c.308+1_309-1del	383	33.0	TCAGG...	T
III	B	1		INDEL	splice_acceptor-1	c.2145+1_2146...	312	37.0	TGGTG...	T
III	B			SNP	Intergenic		121	45.5	T	C
III	B			SNP	missense	c.5843C>T	93	45.2	G	A
III	B			SNP	missense	c.2012G>T	194	44.3	G	T
III	B			SNP	missense	c.122G>A	79	44.3	G	A
III	B			SNP	missense	c.3113C>T	308	42.9	C	T
III	B			SNP	missense	c.725C>T	159	45.9	C	T
III	B			SNP	missense	c.2305C>G	229	41.0	C	G
III	B			SNP	missense	c.3083G>A	176	47.2	G	A
III	B			SNP	missense	c.9911A>G	106	54.7	A	G

ACMG tab
Shows the status of the 28 criteria of the selected variant

Checkbox
ACMG global score and user flagging

4. Data Analysis

4.9 SNVs/Indels

4.9.11 ACMG Tab (3)

Change ACMG criteria status and add comment

The value of each criterion (automated or manual) can be changed by selecting it and modifying the status (true/false) from the the drop-down menu. A comment can be added to explain the motivation for the change.

Legend:

- * : Modified and unsaved change of a criterion
- ▼: The blue triangle means that the criterion value has been overridden by the user (True or False value even if the computed value was the same)
- Criterion name: The criterion does not have a calculated value
- Criterion name: The criterion has a calculated value

Variant	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
INDEL	BRC42	frameshift	c.8042_8043del	116	45.5	GAC	G
SNP	ATM	missense	c.7522G>A	47	52.1	G	A
SNP	APC	synonymous	c.4479G>A	178	49.7	G	A
SNP	APC	synonymous	c.1635G>A	121	48.1	G	A
SNP	APC	synonymous	c.5880G>A	135	47.5	G	A
SNP	APC	synonymous	c.5034G>A	48	52.3	G	A
SNP	APC	synonymous	c.5268T>G	141	45.7	T	G
SNP	APC	synonymous	c.5465T>A	181	100.0	T	A
SNP	APC	synonymous	c.5948A>G	90	99.8	A	G
SNP	APC	synonymous	c.4578C>T	154	50.8	C	T
SNP	APC	synonymous	c.1568+14C>T	60	47.5	G	A
SNP	APC	synonymous	c.70C>T	101	42.9	G	A
SNP	APC	synonymous	c.1315-19G>A	300	47.5	C	T
SNP	APC	synonymous	c.1518T>C	85	100.0	A	G
SNP	APC	synonymous	c.1519G>A	101	48.3	C	T
SNP	APC	synonymous	c.1134G>C	166	100.0	C	G

User decision

- No decision
- True
- False
- No decision

Comments

Enter your motivation for the change (1024 chars max)

Cancel OK

NOTE: The length of the comment is limited to 1024 characters. Any sign exceeding the maximum length will be cut.

4. Data Analysis

4.9 SNVs/Indels

4.9.11 ACMG Tab (4)

OVERVIEW DETAILS FLAGGING VIEWER **ACMG** SIMILAR PATIENTS WARNINGS SCREENING

PALB2: c.2851T>C

PVS1 PS1 PS2 PS3 PS4 PM1 PM2 PM3 PM4 PM5 PM6 PP1 PP2 PP3 PP4 PP5 BP7 BP6 BP5 BP4 BP3 BP2 BP1 BS4 BS3 BS2 BS1 BA1

BA1 Allele frequency is >5% in GnomAD, 1000 Genomes Project, Exome Aggregation Consortium or Exome Sequencing Project. The variant is flagged as BA1 if occurring at high frequency af in the general population as. Calculated value: False User decision: No decision

ACMG V 5

Set Patho.

Manual Criteria (light blue)

- PS2
- PS3
- PS4
- PM3
- PM6
- PP1
- PP2
- PP4
- BP5
- BP2
- BP1
- BS4
- BS3
- BS2
- BS1

Automated Criteria (grey)

- PVS1
- PS1
- PM1
- PM2
- PM4
- PM5
- PP3
- PP5
- BP7
- BP6
- BP4
- BP3
- BA1

NOTE: Rule descriptions for all automated criteria are displayed when the respective criterion is selected.

4. Data Analysis

4.9 SNVs/Indels

4.9.11 ACMG Tab (5)

Rules to define ACMG score

V	Pathogenic	<p>1 Very strong (PVS1) AND</p> <p>→ ≥1 Strong (PS1-PS4) OR</p> <p>≥2 Moderate (PM1-PM6) OR</p> <p>1 Moderate (PM1-PM6) and 1 supporting (PP1-PP5) OR</p> <p>≥2 Supporting (PP1-PP5)</p> <p>≥2 Strong (PS1-PS4) OR</p> <p>1 Strong (PS1-PS4) AND</p> <p>≥3 Moderate (PM1-PM6) OR</p> <p>2 Moderate (PM1-PM6) AND ≥2 Supporting (PP1-PP5) OR</p> <p>1 Moderate (PM1-PM6) AND ≥4 Supporting (PP1-PP5)</p>
IV	Likely pathogenic	<p>Very strong (PVS1) AND 1 moderate (PM1-PM6) OR</p> <p>1 Strong (PS1-PS4) AND 1-2 moderate (PM1-PM6) OR</p> <p>1 Strong (PS1-PS4) AND ≥2 supporting (PP1-PP5) OR</p> <p>≥3 Moderate (PM1-PM6) OR</p> <p>2 Moderate (PM1-PM6) AND >-2 Supporting (PP1-PP5) OR</p> <p>1 Moderate (PM1-PM6) AND ≥4 Supporting (PP1-PP5)</p>
I	Benign	<p>1 Stand-alone (BA1) OR</p> <p>≥2 Strong (BS1-BS4)</p>
II	Likely benign	<p>1 Strong (BS1-BS4) and 1 supporting (BP1-BP7) OR</p> <p>≥2 Supporting (BP1-BP7)</p>
III	Uncertain significance	<p>Other criteria shown above are not met OR</p> <p>the criteria for benign and pathogenic are contradictory</p>

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4. Data Analysis

4.9 SNVs/Indels

4.9.12 Similar Patients* (1)

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

The screenshot displays the SOPHiA DDM software interface. At the top, the 'ANALYSIS CGH1' section shows sample information: #3-0132, RUN 02/12/2020, CES_v1_FVA_CNV (8 samples), and CGH1. The main panel shows a list of variants under the 'SNVs/INDELS' tab, sorted by 'Prediction>Pathogenicity class>Gene'. The variants table includes columns for A... (action icons), P... (pathogenicity), S... (status), Gene, Coding consequence, c.DNA, Depth, VFX, ref, and alt. A 'SOPHiA Filters' sidebar on the left shows 'Retained' variants (6472) and other categories like 'Highly Pathogenic' (6), 'Potentially Pathogenic' (143), 'Unknown Significance' (447), 'Likely Benign' (5875), 'Low Confidence Variants' (25882), and 'Flagged Variants' (9). A 'Similar Patients' pop-up window is open, showing a search bar, a 'Case sensitive' checkbox, and a table of similar patients. The table has columns for Patient, Run Name, Date, Analysis Type, Experiment Type, and Conclusions. Two patients are listed: CGH1206-P (trio anja, 04/12/2020, CES_v1, germline) and CGH1206-P (Family 01 - Duo, 27/06/2018, CES_v1, germline). A 'Show for this test only' checkbox is checked. A 'Links' sidebar on the right lists various databases: GnomAD, ClinVar, COSMIC, IGV, NCBI, ALAMUT, Google, and OMIM.

Similar patients*
Shows the list of samples / analyses that have the same currently selected variant

View
Opens the corresponding analysis in a new window

Checkbox
Checkbox to show similar patients* for same application or across application(s)

NOTE: If consent restrictions are applied to a “Similar Patient*”, this patient* is excluded from the list. If a Virtual Panel for Project interpretation* is applied, the Similar Patient* is not excluded from the list (details see [ch. 3.12.2 Restrict to a Virtual Panel](#)).

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4. Data Analysis

4.9 SNVs/Indels

4.9.12 Similar Patients* (2)

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

The screenshot shows the SOPHiA DDM software interface. At the top, there are tabs for WORKSPACE Requests, VDB Variant Database Browser, and ANALYSIS CGH1206-P-father #3-0132. The main panel displays a variant list with columns for A, ID, P, S, T, Gene, Coding consequence, c.DNA, Depth, VF%, ref, and alt. A 'SOPHiA Filters' sidebar on the left shows various filter categories like Retained (6472), Highly Pathogenic (6), etc. A callout box titled 'ANALYSIS: CGH1206-P-father - CONCLUSIONS' is open over the 'Interpretation' dropdown menu, which currently shows 'Interpretation 1'. The 'Similar Patients' table at the bottom lists patient information, run names, dates, and analysis types.

Variant ID	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
SNP ARID1B	splice_donor_+1	c.4986+1G>A	127	42.5	G	A	
SNP AR	missense	c.2395C>G	173	39.9	C	G	
SNP EXOSC3	missense	c.395A>C	163	44.2	T	G	
SNP C							
INDEL T							
SNP							
SNP A							
SNP A							
SNP A							
SNP A							
SNP A							
SNP A							
SNP ADAMTSL4	missense	c.3083G>A	17	47.2	G	A	
SNP ALMS1	missense	c.9911A>G	10	54.7	A	G	

Patient	Run Name	Date	Analysis Type	Experiment Type	Conclusions
CGH1206-P	trio anja	04/12/2020	CES_v1	germline	View
CGH1206-P	Family 01 - Duo	27/06/2018	CES_v1	germline	View

Project*
Select an Interpretation Project* from the dropdown menu to open similar patients* or create a new Project*

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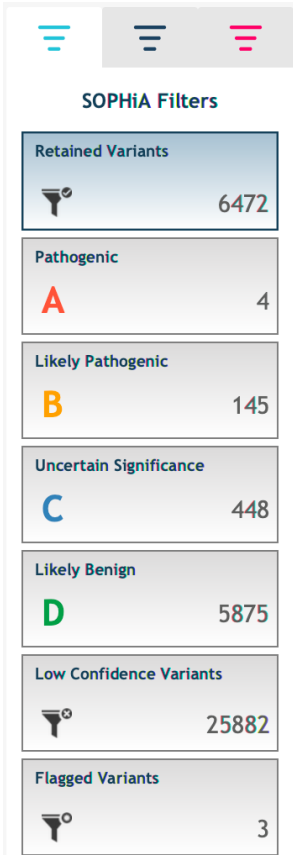
4. Data Analysis

4.9 SNVs/Indels

4.9.13 Filters

Variant filters

- 1) SOPHiA DDM™ predefined filters (light blue tab):
retained and low confidence variants, prediction categories
- 2) The user can also define custom filtering strategies with the Variant Filter Builder (dark blue tab): see [chapter 5 - Variant Filter Builder](#) for more details
- 3) Cascading Filters (pink tab): see [ch. 6 Cascading Filters](#)



The screenshot shows the 'SOPHiA Filters' interface with three filter tabs at the top: Light blue (predefined), Dark blue (custom), and Pink (cascading). The main panel displays a list of filter categories with their respective counts:

Filter Category	Count
Retained Variants	6472
Pathogenic (A)	4
Likely Pathogenic (B)	145
Uncertain Significance (C)	448
Likely Benign (D)	5875
Low Confidence Variants	25882
Flagged Variants	3

Annotations on the right side of the screenshot explain the filter types and categories:

- Light blue filter: predefined filters (SOPHiA DDM™ filters)
- Dark blue filter: custom filters (Variant Filter Builder)
- Pink filter: Cascading filters
- Retained variants are categorized in 4 categories: A, B, C, D: (see [chapter 4.6 - Prediction Definitions](#))
 - A: Pathogenic
 - B: Likely pathogenic
 - C: Uncertain significance
 - D: Likely Benign
- Low confidence variants: Variants identified by the system with a low confidence
- Flagged variants: Variants flagged by the user

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4. Data Analysis

4.9 SNVs/Indels

4.9.14 Compact Variant Table

SNVs/Indels
Active sub page (white)

Compact variant table

SOPHiA	ACMG	Pathogenicity	In Report	False Warning	Genomic	Sample	Transcript	Scores	Frequency	
SOPHiA	ACMG	Pathogenicity	In Report	False Warning	Type Chrom. Position	ref alt refNum altNum	Gene Transcript Strand	refSeq altSeq refAA altAA	CDNA Protein Exon Rank Consequence Exon Position	1-SIFT Polyphen2 Mut. Taster GnomAD G1000 ESP5400
A	V	B			SNP chr 6 157525131	G 73 A 54	42.5% ARID1B 127 NM_017519.2	c.4986+1G>A p.(?) splice_donor_+1	exon 18	1.0
A	III	B			SNP chr X 66941751	C 104 G 69	39.9% AR 173 NM_000044.3	c.2395C>G p.(Gln799Glu) missense	exon 6	0.978 0.965 1.0
A	V	B			SNP chr 2 227907792	C 112 G 114	50.4% COL4A4 226 NM_000092.4	c.3397+1G>C p.(?) splice_donor_+1	exon 36	1.0
A	III	B			SNP chr 9 37783990	T 91 G 72	44.2% EXOSC3 163 NM_001002269.2	c.395A>C p.(Asp132Ala) missense	exon 2	0.999 0.979 1.0
B	III	B			SNP chr 7 21778429	T 66 C 55	45.5% 121	- intergenic	-	1.0 0.98 1.0
B	III	B			SNP chr 1 94473846	G 51 A 42	45.2% ABCA4 93 NM_000350.2	c.5843C>T p.(Pro1948Leu) missense	exon 42	0.921 0.009 1.0
B	III	B			SNP chr 16 16173232	G 108 T 86	44.3% ABCC1 194 NM_004996.3	c.2012G>T p.(Gly671Val) missense	exon 16	1.0 1.0 1.0
B	III	B			SNP chr 1 16173232	G 44 A 35	44.3% ABCD3 79 NM_001122674.1	c.122G>A p.(Gly41Glu) missense	exon 2	0.774 0.998

Variant table switch

- Click to switch between the compact and standard variant table
- Select the checkbox to use the selected variant table format (standard or compact variant table) as default on the next SOPHiA DDM™ launch
- Confirm with OK

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4. Data Analysis

4.9 SNVs/Indels

4.9.15 Variant Copy Function

SNVs/Indels
Active sub page (white)

The screenshot displays the SOPHiA DDM software interface. The top navigation bar includes 'WORKSPACE Requests', 'Variant Database Browser', and '#3-0132'. The main header shows 'Interpretation 7', 'SAMPLE', 'RUN 02/12/2020 CES_v1_FVA_CNV (8 samples)', and 'Clinical Exome Solution by Sophia'. The 'SNVs/Indels' tab is active, showing a table of variants sorted by ACMG value. A 'Variant Copy Settings' dialog box is open, allowing users to select attributes to be copied to the clipboard. The dialog includes options for 'rs Number', 'chr', 'position', 'ref/alt', 'gene', 'transcript', 'cDNA', 'protein', and 'exon'. A preview shows the copied text for a specific variant: 'rs Number:rs1057518984 chr:6 position:157525131 ref/alt:G/A gene:ARID1B transcript:NM_017519/2 cDNA:c.4986+1G>A protein:p.(?) exon:18'. The background table lists variants with columns for ID, Type, Gene, Coding consequence, c-DNA, Depth, VFI, ref, and alt.

ID	Type	Gene	Coding consequence	c-DNA	Depth	VFI	ref	alt
SNP	ARID1B	splice_donor_+1	c.4986+1G>A	127	42.5	G	A	
SNP	COL4A4	splice_donor_+1	c.3397+1G>C	226	50.4	C	G	
INDEL	TYRO3	splice_acceptor_+1	c.1875+1_1876...	346	44.0	TGTA...	T	
INDEL	SHANK3	frameshift	c.1336_1337del	41	75.0	GCC	G	
INDEL	TYRO3	splice_acceptor_+1	c.2145+1_2146...	312	37.0	TGGTG...	T	
INDEL	SHANK3	frameshift	c.108+1_109del	183	33.0	TGAGG...	T	
INDEL	TYRO3	splice_acceptor_+1	c.1875+1_1876...	346	44.0	TGTA...	T	
INDEL	TYRO3	splice_acceptor_+1	c.1875+1_1876...	346	44.0	TGTA...	T	
INDEL	PEX5	frameshift	c.108+1_109del	183	33.0	TGAGG...	T	
SNP	LRP4	missense	c.108+1_109del	183	33.0	TGAGG...	T	
SNP	ZAN	missense	c.108+1_109del	183	33.0	TGAGG...	T	
SNP	CUL3	missense	c.108+1_109del	183	33.0	TGAGG...	T	
SNP	APOB	missense	c.108+1_109del	183	33.0	TGAGG...	T	
SNP	OBSN	missense	c.108+1_109del	183	33.0	TGAGG...	T	
SNP	ROR2	missense	c.108+1_109del	183	33.0	TGAGG...	T	

Copy variant information

- Select variant
- Press CTRL+C (Mac ⌘+C)
- Variant information is copied to clipboard in text format

Copy variant settings

- Click the settings button
- Menu opens to select attributes that are copied to clipboard
- Click "OK" to copy variant to clipboard

NOTE: Click "save as default" to save selected variant copy settings. Otherwise, settings are kept only for the current session.

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4. Data Analysis

4.9 SNVs/Indels

4.9.16 OMIM (1)

OMIM® (Online Mendelian Inheritance in Man®) is a comprehensive, authoritative compendium of human genes and genetic phenotypes that references information on all known mendelian disorders and over 16,000 genes.

SOPHiA DDM™ automatically gathers and displays the inheritance mode and related disease* information from OMIM® database for each detected variant (where available) to facilitate the interpretation process.

The user can select to display these variables in the variant table of the SNV/Indels tab (both compact and standard view) and access detailed OMIM® database entries through a link-out.

In addition, the user can select these variables to filter out the variant list through the Cascade Filters (see chapter [6. Cascading Filters](#)) and the Variant Filter Builder (see chapter [5. Variant Filter Builder](#)) for a faster and easier variant filtration and prioritization.

The following inheritance modes are displayed:

- AD - Autosomal dominant
- AR - Autosomal recessive
- PD - Pseudoautosomal dominant
- PR - Pseudoautosomal recessive
- DD - Digenic dominant
- DR - Digenic recessive
- IC - Isolated cases
- ICB - Inherited chromosomal imbalance
- Mi - Mitochondrial
- Mu - Multifactorial
- SMO - Somatic mosaicism
- SMu - Somatic mutation
- Unknown - Familial aggregation without simple mendelian pattern
- XL - X-linked
- XLD - X-linked dominant
- XLR - X-linked recessive
- YL - Y-linked

4. Data Analysis

4.9 SNVs/Indels

4.9.16 OMIM (2)

OMIM information

MIM number(s), OMIM inheritance mode(s), and related disease(s)* columns can be added to the variant table.

The screenshot displays the SOPHiA DDM software interface. The main window shows a variant table with columns for 'OMIM MIM number', 'OMIM disease', and 'OMIM inheritance modes'. Three callout boxes provide detailed information about these columns:

- OMIM MIM number:** Pipe-separated MIM numbers. By clicking on the MIM IDs, the user can access the detailed OMIM disease* entry.
- OMIM disease label:** Pipe-separated OMIM disease list. By clicking on the disease* name block, the user can access the OMIM Clinical Synopsis Table.
- OMIM inheritance mode:** Inheritance mode(s) associated to the variant from the 17 existing ones.

Variant ID	Gene	Coding co...	c.DNA	Depth	VAF	ref	alt	OMIM	OMIM MIM number	OMIM disease	OMIM inheritance modes
INDEL PRP1	PRP1	frameshift	c.301_302del	54	46.3	ACT	A	601538			
SNP IL11RA	IL11RA	missense	c.886C>T	40	60.0	C	T	600939	614188	CRANIOSYNOSTOSIS AND DENTAL ANOMALIES; CRSDA	AR
INDEL KIF1A	KIF1A	Inframe_6	c.2748_2753del	36	58.3	ATC...	A	601255	610357 614213 614255	SPASTIC PARAPLEGIA 30, AUTOSOMAL DOMINANT; SPG30 NEU... AD, ARI ARIAD	
SNP OR13F1	OR13F1	missense	c.290G>A	22	54.5	G	A				
SNP TME260	TME260	missense	c.140C>T	41	43.9	C	T	617449	617478	STRUCTURAL HEART DEFECTS AND RENAL ANOMALIES SYNDRO...	AR
SNP SGSH	SGSH	missense	c.1159G>A	58	53.4	C	T	605270	252900	MUCOPOLYSACCHARIDOSIS, TYPE IIIA; MPS3A	AR
SNP FLT7	FLT7	missense	c.505G>A	65	36.9	C	T	602030			
INDEL ZNF705E	ZNF705E	nonsense	c.545_546del...	37	45.9	CG	TA				
SNP MAP6	MAP6	missense	c.1055A>G	33	48.5	T	C	601783			
SNP ST8DIA1	ST8DIA1	missense	c.770G>A	71	56.3	C	T	601123			

NOTE: Only for samples uploaded after the installation of release v5.10.0 the additional OMIM® information (MIM number, disease(s)*, inheritance mode(s)) can be displayed. The previously existing “OMIM” column displaying the OMIM® identifier, that is used for the OMIM® link-out button, remains unchanged.

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4. Data Analysis

4.10 hg38 annotation (1)

hg38 annotation information

From release v5.9.4 - p5.5.41 onwards, hg38 annotation information is available for:

1) Products that use the hg19 reference genome (samples uploaded before the release):

- The full variant table *.txt file was created before the release, i.e., hg38 coordinate information is not available in these files.
- In the SOPHiA DDM™ Platform, 5 new columns can be added to the variant table in the SNV/Indels tab: hg38 Reference Genome, hg38 Chromosome, hg38 Genome position, hg38 ref and hg38 alt.
- The hg38 coordinate information in these columns is filled if a variant that was called based on the hg19 reference genome, can be matched with the SOPHiA DDM™ hg38 variant database.

2) Products that use the hg19 reference genome (samples uploaded after the release):

- The full variant table *.txt file is created after the release, hg38 coordinate information is available in 8 new columns:
 - hg38_chrom: chromosome number based on GRCh38 genome assembly
 - hg38_pos: variant coordinate in the hg38 reference genome
 - hg38_ref: genomic reference allele based on the hg38 reference genome
 - hg38_alt: genomic alternative allele based on the hg38 reference genome
 - lift_diagnostic: Lift-over information; e.g. if PICARD tool was used
 - hg38_refGenome: version of the genome used
 - sgid & hg38_sgid: SOPHiA GENETICS internal IDs
- These columns are filled by a lift-over (PICARD) of the hg19 variants during the annotation step (where possible). If not possible, those fields in the hg38 columns are left empty.
- In the SOPHiA DDM™ Platform, this information can be viewed by adding the respective columns to the variant table in the SNV/Indels tab or in the Details sub-tab.

4. Data Analysis

4.10 hg38 annotation (2)

3) Products that use the hg38 reference genome (samples uploaded after the release):

- In products that are based on the hg38 reference genome, variants are called and annotated in hg38.
- If possible, variants are lifted over to hg19. If such a lift-over is not possible, the hg38 annotation information is added to the full variant table *.txt file in these columns.
- In the SOPHiA DDM™ Platform, coordinate information of the called variants can be viewed by adding the hg38 alt, hg38 Chromosome, hg38 ref and hg38 Reference Genome columns to the variant table in the SNV/Indels tab or in the Details sub-tab. The “hg38 ref” and the “hg38 alt” columns will be displayed by default for such products.
- The hg19 coordinate information of variants lifted over from hg38 (PICARD) during the annotation step, are displayed in the “ref”, “alt”, “genome position” etc. columns of the variant table.

NOTE: Only for “hg38 products” variants are called and aligned with the hg38 reference genome. For “hg19 products”, variants are called against the hg19 reference genome, and the position is lifted over during the annotation step. Therefore, variants that could be called in hg38 but not in hg19 are not displayed in the variant table or full variant table *.txt for hg19 products. The same applies for the opposite case when variants are called in “hg38 products”. Those are lifted over to but not called in hg19.

4. Data Analysis

4.10 hg38 annotation (3)

Product based on the hg19 reference genome
e.g., SOPHiA DDM™ Hereditary Cancer Solution

Customize variant table
hg38 coordinate information
columns can be added to the
variant table.

The screenshot displays the SOPHiA DDM software interface. At the top, there are navigation tabs for WORKSPACE, VDB, and ANALYSIS. The main area shows a variant table with columns for Variant ID, Gene, Coding consequence, c.DNA, Depth, VF%, ref, alt, hg38, hg38 Genome position, and hg38 alt. A dropdown menu is open on the right side of the table, showing options to add columns to the variant table. The options include:

- GERP
- ClinVar
- hg38 alt
- hg38 Chromosome
- hg38 Genome position
- hg38 ref
- hg38 Reference Genome
- ID ClinVar
- In report
- last1
- LRT
- MutationTaster
- OMIM
- Overlap known
- Pathogenicity class
- Pathogenicity class other
- PhylLoP
- POLYPHEN2

hg38 annotation information

- hg38 alt: genomic alternative allele based on the hg38 reference genome.
- hg38 chromosome: chromosome number based on hg38 reference genome.
- hg38 genome position: Variant coordinate in the hg38 reference genome.
- hg38 ref: genomic reference allele based on the hg38 reference genome.
- hg38 Reference Genome: version of the genome used.

NOTE: The content of these columns is filled from different sources. Please refer to the previous page for details.

4. Data Analysis

4.10 hg38 annotation (4)

Cascading Filters

Select whether to filter for genomic region based on the hg19 or hg38 reference genome (see [ch. 6.3 Available filters \(2\)](#))

The screenshot displays the SOPHiA DDM software interface. At the top, there are navigation tabs for 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS SG10000004 #3-0139'. Below this, a header bar shows 'HCS_v1_1 v2 27 genes' and 'Patient's Disease (0) REPORTED 0/0 Hereditary Cancer Solution by Sophia...'. The main area is a table of variants with columns for 'Variant List - sorted by: Prediction', 'Gene', 'Coding consequence', 'c.DNA', 'Depth', 'VF%', 'ref', 'alt', 'hg38 ...', 'hg38 Geno...', 'hg38 ref', 'hg38 alt', and 'hg38 Referen...'. A 'SOPHiA Filters' sidebar on the left shows various filter categories like 'Retained Variants', 'Highly Pathogenic', etc. A 'DETAILS' sub-tab is active, showing variant information for 'last1' and 'extld'. A 'Relative Frequency' popup window is open, displaying details for 'hg38 Chromosome : 5', 'hg38 Genome position : 112840073', 'hg38 ref : G', 'hg38 alt : A', and 'hg38 Reference Gen... : GRCh38/hg38'. A 'GnomAD' link is visible in the bottom right corner of the details view.

hg38 annotation information in Details sub-tab

Variant copy details and link-out to GnomAD are based on the selected product (i.e., based on hg19 or hg38 reference genome).

NOTE: The content of these columns is filled from different sources. Please refer to the previous pages for details.

4. Data Analysis

4.11 HPO based prioritization

HPO columns

Add the HPO rank columns (matching included and matching excluded HPO terms) and the list of associated phenotypes based on the phenotypes you entered at the interpretation level (see [ch3.12.6 Add phenotypes](#)).

Sort by matching included or matching excluded HPO terms

P	...	P...	★	▲	T...	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt	Phenotypes list	matching incl...	matching excl...	
C						SNP	TRIO	synonymous	c.5100A>C	287	46.3	A	C	Show	3	0
C						SNP	FOXFED1	5'UTR	c.-2T>C	100	50.0	T	C	Show	3	0
C						SNP	TRAPPC9	synonymous	c.2292C>T	184	34.8	G	A	Show	3	1
C						SNP	SMC3	synonymous	c.3039A>G	97	100.0	A	G	Show	3	0
C						INDEL	NDUFA10	intronic	c.1000-5delC	131	56.5	TGGGGG	TGGGGG	Show	3	0
C						SNP	GPC4	missense	c.1325C>T	140	46.4	G	A	Show	3	0
C						SNP	CDON	synonymous	c.3294G>A	63	49.2	C	T	Show	3	0
C						SNP	SPTBN1	synonymous	c.3480C>T	202	52.5	C	T	Show	3	1
C						SNP	CDON	synonymous	c.330T>C	163	38.0	A	G	Show	3	0
C						SNP	SMARCA4	synonymous	c.4887T>C	177	61.6	T	C	Show	3	0
C						SNP	SOX10	synonymous	c.927T>C	408	55.9	A	G	Show	3	0
C						SNP	SETBP1	synonymous	c.3618T>C	239	54.8	T	C	Show	3	1
C						SNP	GLB1	synonymous	c.34T>C	104	100.0	A	G	Show	3	0
C						SNP	EDNRB	synonymous	c.831A>G	132	43.9	T	C	Show	3	0
C						SNP	EHMT1	synonymous	c.1089T>C	277	40.8	T	C	Show	3	1
C						SNP	SCO2	synonymous	c.633A>C	300	54.7	T	G	Show	3	0
C						SNP	EDNRB	synonymous	c.552T>C	174	100.0	A	G	Show	3	0
C						SNP	XYLT1	synonymous	c.1284C>G	122	52.5	G	C	Show	3	0
C						SNP	AFF3	synonymous	c.2124C>G	212	51.4	G	C	Show	3	0
D						SNP	AFF3	missense	c.1556A>G	129	52.7	T	C	Show	3	0

Click "Show" to display the list of matching included and matching excluded HPO terms

NOTE: These columns are also available in the compact view of the table.

5. Variant Filter Builder

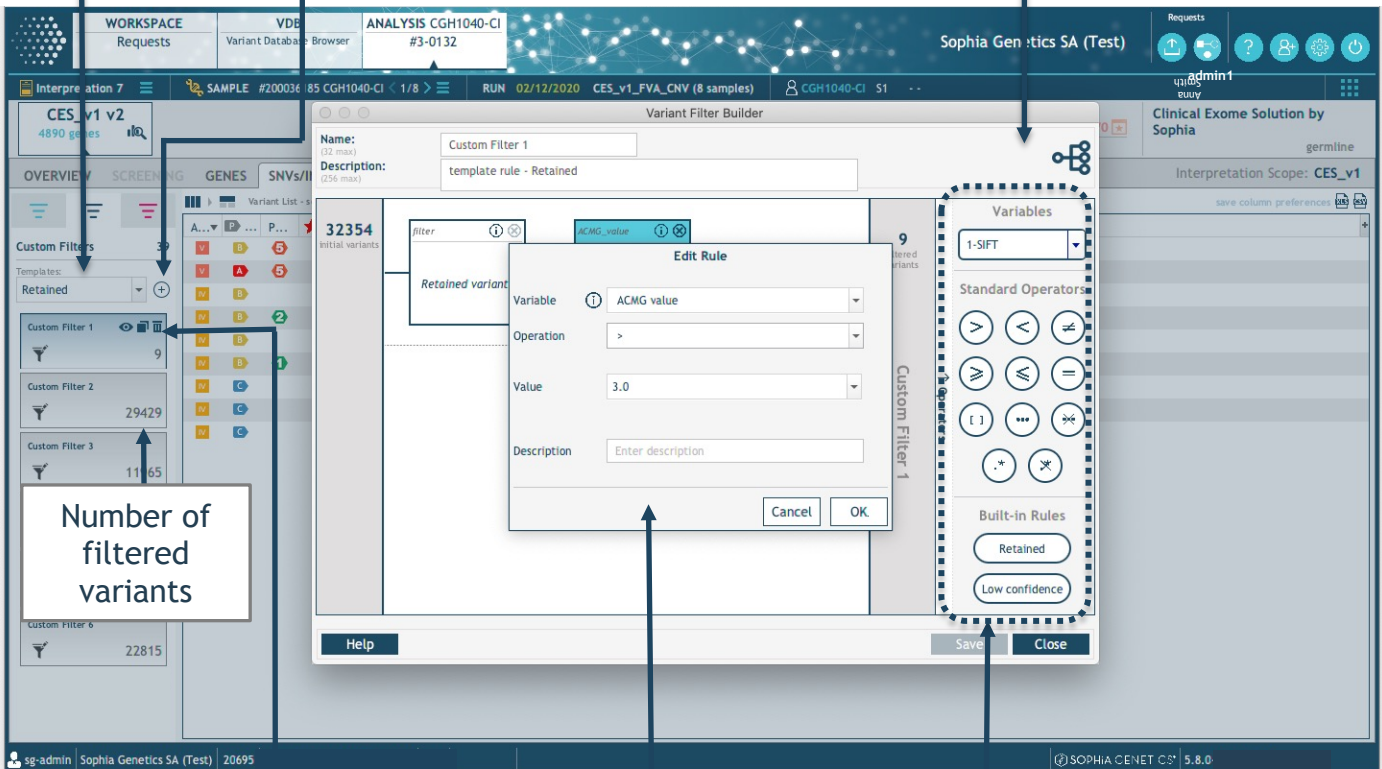
5.1 Overview (1)

Create custom filters using the Variant Filter Builder (VFB)




- Click ⊕
- Select a template: “Retained”, “LowConfidence” or “ExonAndSplices” (see [chapter 5.5 - Templates](#))

The VFB opens

List of custom filters



Number of filtered variants

View and edit existing filters 
 Copy/duplicate filters 
 Delete filter 
 Not available for “Read-only custom filter” user role.

Edit rules
 Rule-editing-box is shown after operators or variables are dragged to far left box or when clicking the I button.

Operators/Variables/Built-in Rules
 Drag and drop variables, operators or built-in rule boxes to the far-left panel or onto an existing filter

NOTE: Variants with no database entries (empty fields) are treated as 0 in case of ESP5400, G1000 and ExAC and as 1 in case of MutationTaster, PolyPhen-2 and SIFT. Thus, those variants are present in the variant table when applying filters on one of those variables.

5. Variant Filter Builder (VFB)

5.1 Overview (2)

Branching
“Or” function can be used to combine filters (see [chapter 5.3 - Branching](#))

“Variables”

- Select variable first (drop-down menu)
- Drag and drop variable box
- Select operator

Initial number of variants

Name of custom filter

Number of filtered variants

Built-in rules
Default filters for “low confidence” and “retained” classified variants

Filter Rules

- Filters in the same row are additive as “AND”
- Filters in different rows are applied as either “OR”

Drag & Drop standard operators

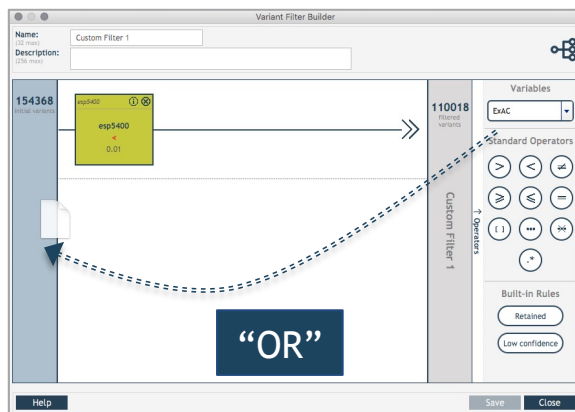
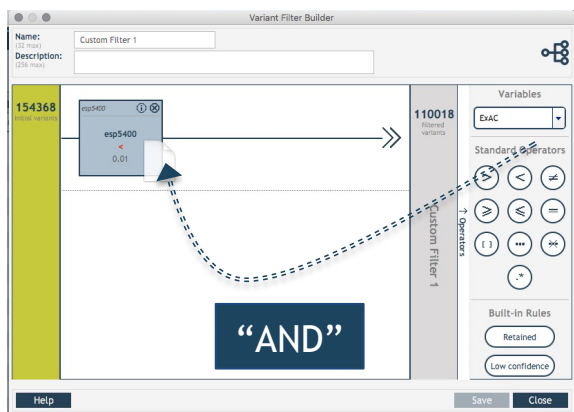
> Greater than	≥ Greater than or equal to	●●● In
< Less than	≤ Less than or equal to	●●● Not in
≠ Not equal	[] Between (value 1 & 2)	.* Matches with
		✘ Does not match with

- If the IN operator is used, the exact naming of a variant attribute (e.g., gene name) needs to be specified e.g., *variable: gene + operator: IN + value: BRCA1*.
- If the MATCHES WITH or DOES NOT MATCH operators are used, an asterisk can be added to simulate “starts with”, “ends with”, “contains”, “does not contain” operators, e.g.:
 - filter for variants in *BRCA1* and *BRCA2*: *variable: gene + operator: .* + value: BRCA**
 - filter for variants in genes with a MIM number: *variable: OMIM MIM number + operator: .* + value: **
 - filter for variants in genes with no MIM number: *variable: OMIM MIM number + operator: ✘.* + value: **

5. Variant Filter Builder

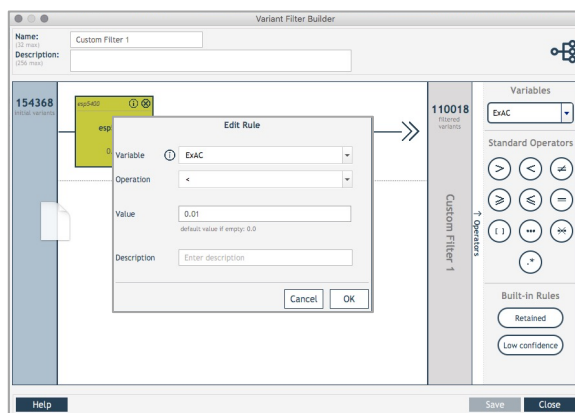
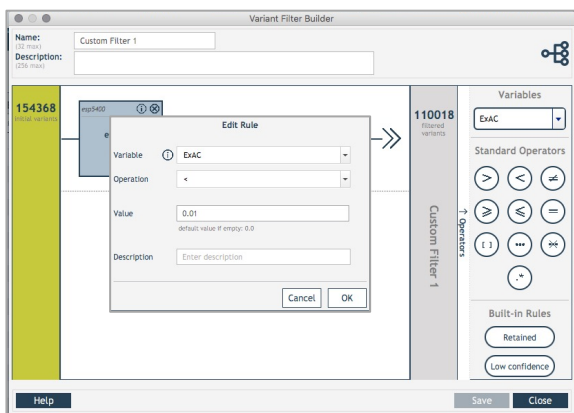
5.2 “AND” and ”OR” Functions

Drag and drop an operator or variable to the corresponding box (box will turn blue).



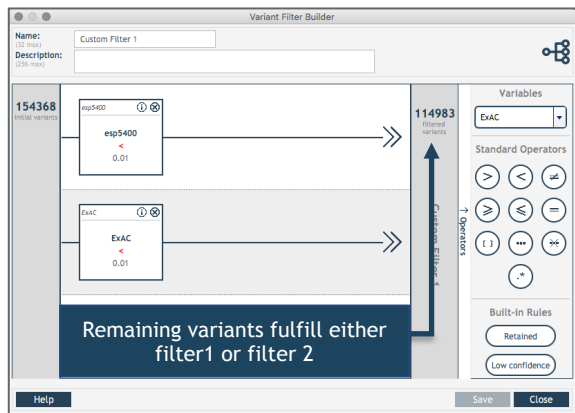
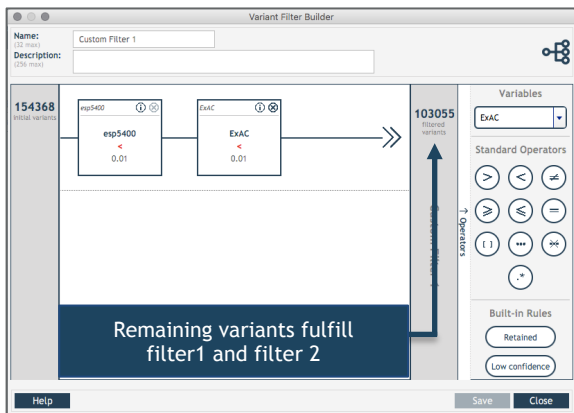
1

“Edit rule” window enables modification of variables, operators and values.



2

Filter boxes placed in same (AND) or separate row (OR). Click close to save custom filter.

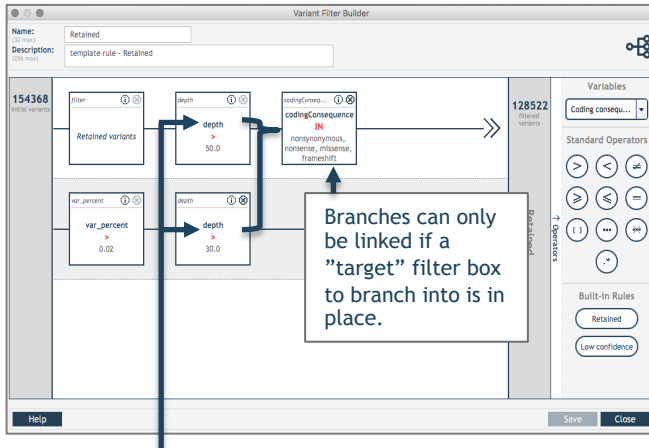


3

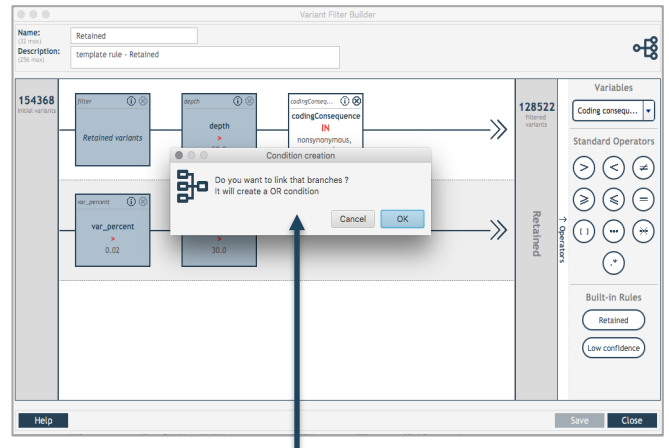
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5. Variant Filter Builder

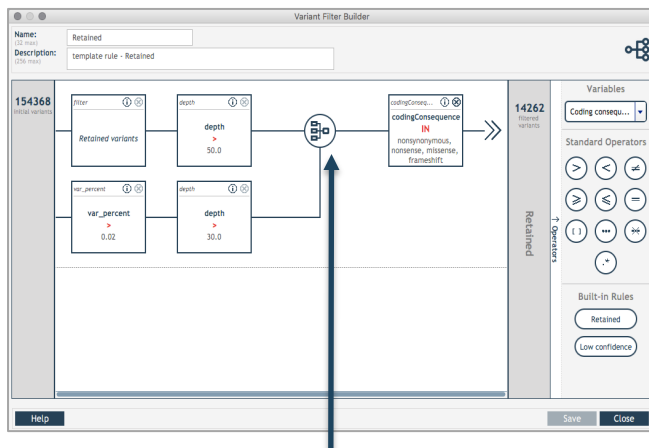
5.3 “Branching” of Filters



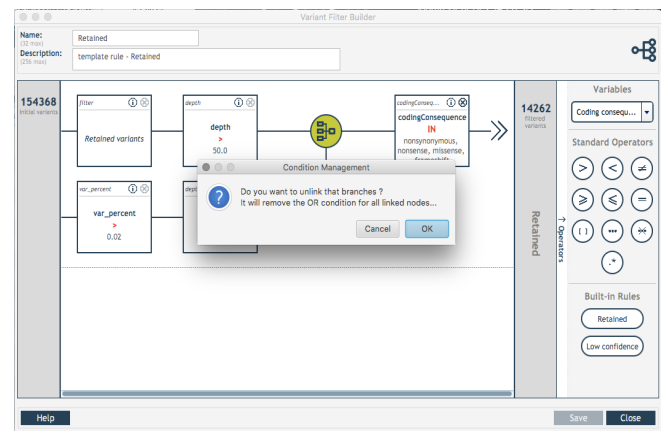
1 Connect the first branch with the second branch by selecting the boxes to connect and holding the “CTRL” key (boxes will turn blue).



2 A pop-up window appears to confirm the action.



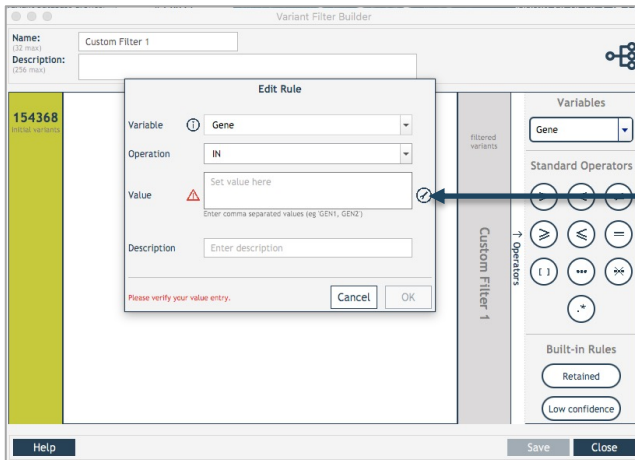
3 Both branches are now linked. Here the first two filters of row 1 and 2 are additive (“AND”). After linking the branches, the “codingConsequences” filter will be applied to both rows.



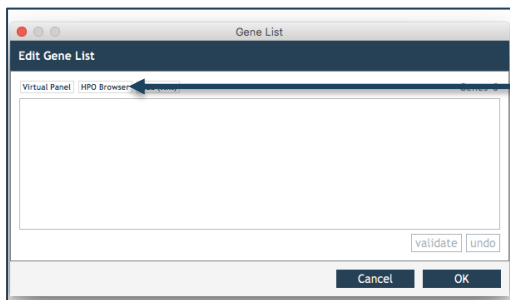
4 To unlink both branches again, click the branching tree button and click OK.

5. Variant Filter Builder

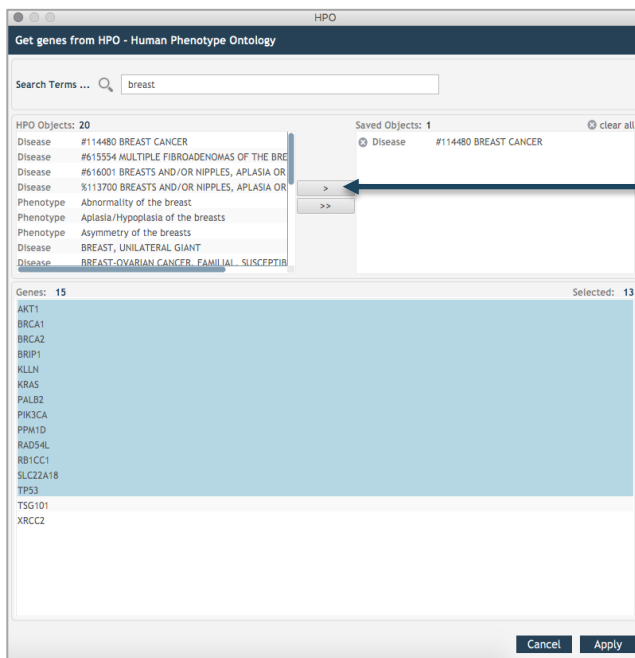
5.4 HPO Search



1 To filter by genes associated to a disease* according to the Human Phenotype Ontology (HPO) database, select operator “IN” with variable “gene” and click toolbox icon.



2 Select HPO browser in the pop-up window. Alternatively, genes can be imported from a txt-file or from selecting an existing Virtual Panel.

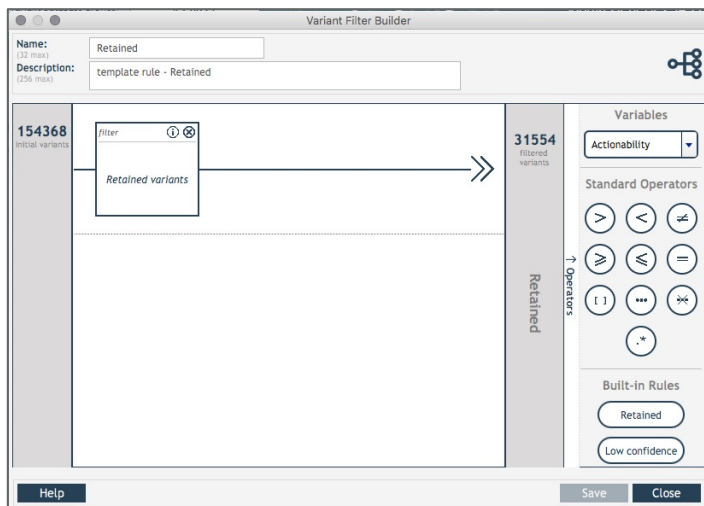


3 Type in the disease* name. Select the disease* from list and click. Several diseases* can be selected by holding shift.

4 Either apply the filter with all genes or select genes by holding “Shift”. Click “apply” to add the genes to the gene list.

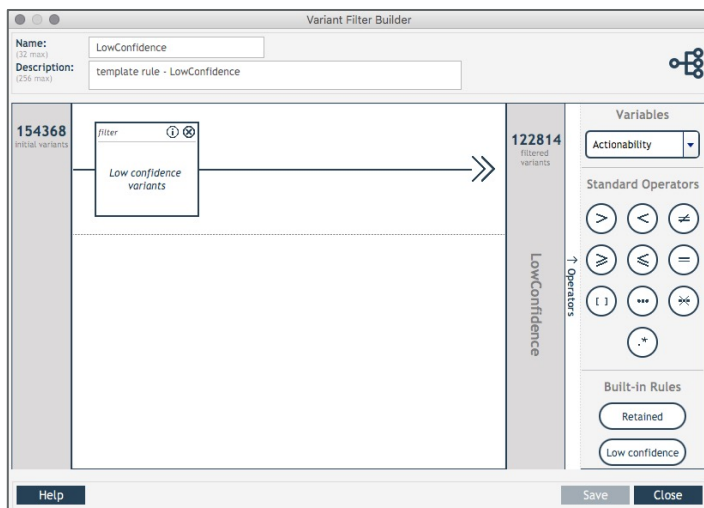
5. Variant Filter Builder (VFB)

5.5 Templates (1)



Template “Retained”

- Build your custom filter starting with the variants classified as “retained”
- To remove the “retained” filter box, click X



Template “LowConfidence”

- Build your custom filter starting with the variants classified as “low confidence”
- To remove the “LowConfidence” filter box, click X

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5. Variant Filter Builder (VFB)

5.5 Templates (2)

Template “ExonAndSplices”

Build your custom filter search for variants in exons and in a defined range of intronic regions up- and downstream of the exon.

“Except intergenic”
This filter box is built using the “NOT IN” operator together with “coding consequence” = intergenic (variable). This filter box removes intergenic variants not excluded by the previous filters.

dist2exon filter
The input of this filter is a positive integer. It checks the absolute value of the distance (number of nucleotides) to the closest exon boundary. If the filter is set to = 0, it filters for variants within the exon.

c.DNA matches with “+” and “-”

The dist2exon value is absolute, so the “+” and “-” are used to distinguish distances to the left and to the right of the boundaries of the exon. “+” searches for variants present beyond the rightmost boundary; “-” searches for variants beyond the leftmost boundary.

NOTE: By default, the “ExonAndSplices” template searches for exonic variants as well as variants 25 bp beyond the right and 50 bp beyond the left boundary of the exon. You can adapt the range by clicking the “i” button of the “dist2exon” filter boxes.

6. Cascading Filters

The Cascading Filters is an easy-to-use variant filtering feature created to support and streamline interpretation* of your datasets (especially for large panels) and comfortably create re-usable filtering strategies.

It allows you to:

- Quickly create and edit combination of filters tailored to your needs
- Save and re-use cascades of filters throughout your account
- Track and report your filtering strategies

An explanation of this functionality can be found here:



<https://www.youtube.com/watch?v=wKqmx4zz-tk&feature=youtu.be>

6. Cascading Filters

6.1 Overview

Cascading Filters tab

SNVs/Indels

Active sub page (white)

Load Template
Load existing, previously created cascade templates

Create new Cascade
Select from 13 predefined filter options

Clear all
Remove all added filters or loaded templates

NOTE: Cascades are saved within the interpretation*. If you create a cascade and leave an interpretation project*, the cascade will be auto-saved and can be retrieved when you come back in the interpretation*.

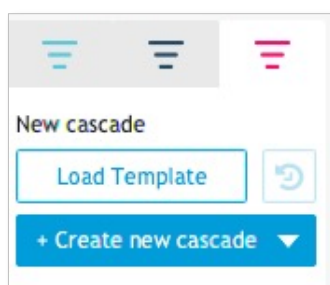
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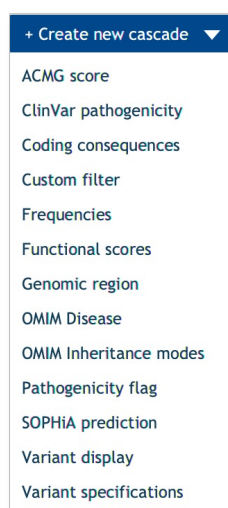
6. Cascading Filters

6.2 Create a new Cascade

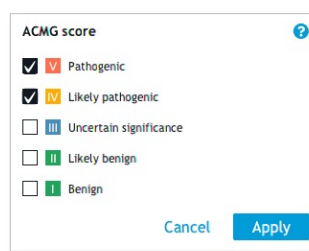
1 Click “Create new cascade” button



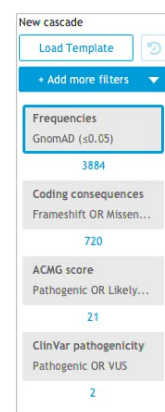
2 Select filter from the list



3 Adjust and apply filter settings



4 Add further filters



NOTE: Within a cascade, an AND rule is applied between all filters. Within a filter, an OR rule is applied. Two filters of the same category (e.g., ACMG score) with different settings (e.g., Pathogenic and Likely pathogenic) within one Cascade will be exclusive and result in no variant in the table.

Also, the list of selectable filter options depends on the experiment type, since “ACMG score”, “OMIM Disease” and “OMIM Inheritance modes” are not applicable for somatic analyses.

6. Cascading Filters

6.3 Available filters (1)

- **ACMG score** - Filter for one or several ACMG score values (I, II; II, IV, V). Multiple filtering values can be selected. The filter will display variants matching any one of those values.
- **ClinVar pathogenicity** - Filter for one or several ClinVar pathogenicity values: Pathogenic is regrouping the Pathogenic and likely pathogenic classification from ClinVar; Benign is regrouping the Benign and Likely benign classification from ClinVar. Multiple filtering values can be selected. The filter will display variants matching any one of those values.
- **Coding consequences** - Filter for one or several coding consequences (for exonic variants) or location (for non exonic variants). UTR regroups variants located in 5'UTR and 3'UTR. Splice site regroups all variants affecting splice site sequences. Multiple filtering values can be selected. The filter will display variants matching any one of the selected values.
- **Custom filters** - Filter using a Custom filter. You can load an existing one using the dropdown menu or create a new one using the Variant Filter Builder.
- **Frequencies** - Filter for one or several frequency criteria (population or community frequencies). To apply a \leq or \geq rule leave the left or right text field empty. Multiple filtering values can be selected. The filter will display variants matching any one of the selected values.

6. Cascading Filters

6.3 Available filters (2)

- **Functional scores** - Filter for SIFT, Poly-Phen-2 or MutationTaster. Filter according to database score. To apply a \leq or \geq rule leave the left or right text field empty. Multiple filtering values can be selected. The filter will display variants matching any of the selected values.
- **Genomic region** - Filter for a list of genes or genomic coordinates (based on the hg19 or hg38 reference genome) and/or chromosome number. To filter for mitochondrial variants, select the Chromosome filter option and choose “MT” from the dropdown menu. To apply a search on the Chromosome value only, select the Gene or Genomic coordinates option but leave the fields empty, then select the Chromosome checkbox and corresponding chromosome number(s). Gene(s) can be entered manually (comma-separated), or loaded from a *.txt file, a Virtual Panel, or HPO.

NOTE: Make sure to select the correct reference genome when filtering for genomic coordinates. A pink frame around the filter box indicates that a product is based on the hg19 reference genome, but the selected coordinates refer to hg38 and vice versa (see also chapter [4.10 hg38 annotation](#)).

- **OMIM disease*** - Filter for variants related to one or several OMIM diseases*. Select OMIM disease(s)* using the OMIM disease* browser (see [6.6 OMIM disease* browser](#)). In case of multiple filtering values selected, the operator “OR” is automatically applied between the selected values.
- **OMIM inheritance modes** - Filter for variants related to one or several OMIM inheritance modes. Multiple filtering values can be selected; in this case the operator “OR” is applied between the selected inheritance modes.

6. Cascading Filters

6.3 Available filters (3)

- **Pathogenicity flag** - Filter for one or several Pathogenicity flag values (1, 2, 3, 4, 5). Multiple filtering values can be selected. The filter will display variants matching any one of those values.
- **SOPHiA DDM™ prediction** - Filter for one or several SOPHiA DDM™ prediction values (A, B, C, D). Multiple filtering values can be selected. The filter will display variants matching any one of those values.
- **Variant display** - Filter to see all, retained or low confidence variants. Only one selection is possible. Additionally, you can also choose to hide false positives by checking the corresponding checkbox.
- **Variant specification** - Filter for one or several variant type and for associated variant fraction and depth. Selecting a value in all categories is not mandatory (e.g., selecting SNV only will display all SNVs regardless of variant fraction and depth). To apply a \leq or \geq rule to the variant fraction and depth categories leave the left or right text field empty, respectively.
- **HPO Rank match** - Filter for variants matching the user-entered included and/or excluded HPO phenotypes. This allows to retrieve variants related to the patient's phenotypes. A range (min, max) for included and/or excluded number of HPO matches can be defined. The filter will display variants matching any of the two criteria ("included" or "excluded"). To apply a \leq or \geq rule, leave the left or right text field empty, respectively.

6. Cascading Filters

6.4 Edit, disable, and remove filters


To edit an applied filter:

- Click on the filter you want to edit. The filter box is outlined in blue
- Edit the filter settings
- Click apply

To disable/enable an applied filter:

- Hover over the filter you want to disable. The enable/disable checkbox and remove icon are shown
- Uncheck the checkbox to disable the filter
- Check the checkbox to enable the filter


To remove an applied filter:

- Hover over the filter you want to disable. The enable/disable checkbox and remove icon are shown
- Click on the remove icon  to remove the filter

6. Cascading Filters

6.5 Save and load template

To save a cascade as template (e.g., for reuse in other samples or tests):

- Click on the “Save” button 
- In the dialog window, enter a name into the Name field
- Click “Save”

To load a saved template

- Click on the “Load template” button
- In the dialog window select a template
- Click “Load”

NOTE: Some filter options are only available for certain experiment types (e.g., ACMG score or OMIM Inheritance modes filters are only relevant for germline analyses). If such filter options are applied in a template, they are only available if used in a sample with the respective experiment type. Otherwise, these boxes are disabled in the template.

To edit a saved cascade



- Load a previously saved cascade
- Edit the cascade
- Save the edited cascade

NOTE: When editing a template, you can always go back to the previously saved version by clicking on the “Reload” button.

6. Cascading Filters

6.6 History button

SOPHiA DDM™ allows you to retrieve the cascades used to report variants. When reporting a variant, the displayed cascade is automatically saved and can be retrieved through the “Load cascade history” button.

- Click on the “cascade history” button 
- The dialog window displays the reported variants, the date and author of the reported flag
- The information button  provides details about the cascade used to report the selected variant
- Select a specific variant and click on “Load” to load the cascade used to report this specific variant

6. Cascading Filters

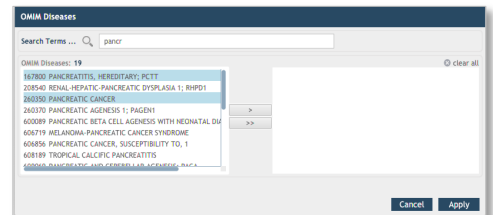
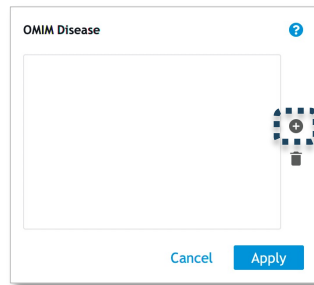
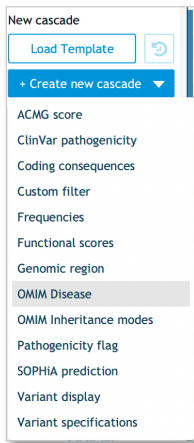
6.7 OMIM disease* browser

The user can use the OMIM disease* browser to select a disease* in order to filter variants by OMIM disease*.

1 Click “Create new cascade” button and select “OMIM disease*” from the list.

2 Click on (+) to select disease(s)* using the OMIM disease* browser.

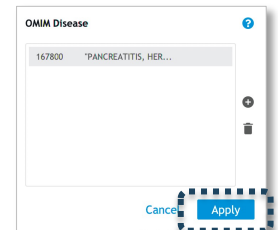
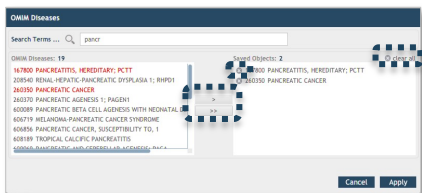
3 Start typing the disease* name in the search field and/or select the corresponding disease* from the list.



4 Click > to add disease(s)*, or >> to add all diseases to your selection. A maximum of 100 disease* entries can be manually added. Click x to remove individual disease(s)* or “clear all” to remove all items from the list.

5 Click “Apply” to add the disease(s)* to the filter.

6 Click “Apply” to add the filter to cascade.



6. Cascading Filters

6.8 HPO Rank match filter

The user can use the HPO Rank match filter in order to select variants matching the user-entered HPO phenotypes.

1 Click “Create new cascade” button and select “HPO Rank match” from the list.

New cascade

Load Template

+ Create new cascade

- ACMG score
- AMP /ASCO/CAP tier and evidence level
- ClinVar pathogenicity
- Coding consequences
- Custom filter
- Frequencies
- Functional scores
- Genomic region
- HPO Rank Match**
- OMIM Disease
- OMIM Inheritance modes
- Pathogenicity flag
- SOPHiA prediction
- Variant display
- Variant specifications

2 Enter the range [min, max] of included or excluded HPO terms for your filtering rule.

Note: An "OR" logic is applied between the two conditions of "Included HPO phenotype" and "Excluded HPO phenotype". If you want to apply an "AND" logic, you can superimpose cascade filters.

HPO Rank Match

Included HPO Phenotype

2 To 10 Reset

Excluded HPO Phenotype

To 0 Reset

Cancel Apply

3 To apply a \leq or \geq rule, leave the left or right text field empty.

By default the number of matching excluded phenotypes is zero.

4 Click “Apply” to add the filter to cascade.

HPO Rank Match

Included HPO Phenotype

1 To Reset

Excluded HPO Phenotype

To 0 Reset

Cancel Apply

New cascade

Load Template

+ Add more filters

Variant display

Retained

6452

HPO Rank Match

HPO included rank (≥ 1)

1939

HPO Rank Match

HPO excluded rank (≤ 0)

1810

Clear all

Filtered variants

1810 / 25736

6. Cascading Filters

6.9 Add to report

Each time you report a variant, SOPHiA DDM™ will save the filtering strategy that was used to find the variant (SOPHiA DDM™ filters, Custom filters (Variant Filter Builder) or Cascading Filters). Filtering strategy can be reported together with the selected variants.

- From anywhere in SOPHiA DDM™, go to Application Settings > [Report Settings](#)
- In the Analysis View go to Overview > [Project Settings](#)
- Check the “Show filters” checkbox

In the report, the filtering strategy is displayed within the annexes:

RESULTS

SNVs/INDELS (selected in report)

Gene Transcript	Exon	Coding DNA alteration Protein alteration	Variant Fraction Coverage (ref / alt)	Coding consequence	Pathogenicity	ClinVar
ARID1B NM_017519	18	c.4986 + 1G>A p.(?)	42.52 % (73 / 54)	splice_donor_ + 1	Prediction A Highly Pathogenic	Likely pathogenic rs1057518984

ANNEXES

Filtering strategy (for reported variant)

Gene Variant	Filter type	Description
ARID1B p.(?)	Cascade	[Frequencies: GnomAD (≤0.01)] AND [Coding consequences: Missense OR Nonsense OR No-start OR No-stop OR Splice site] AND [ACMG score: Pathogenic OR Likely pathogenic] AND [ClinVar pathogenicity: Pathogenic]

Template version 2.2
Draft - - Sample 1 - Sample 01_CL - 15/10/2020 10:30
1 / 31

7. CNV Analysis

7.1 Germline and liquid tumor applications

7.1.1 CNV table (1)

Restriction
Scope of the project

CNV tab
Active tab (white)

CNV information
By region/amplicon

Noise level
Noise level medium/low (detected) or high (undetected)

IGV browser
Click link to visualize the gene in IGV viewer

Filter view (according to scope of Project* or applied Virtual Panel)

Detected: genes with CNVs

Undetermined: genes with regions where CNV could not be determined (high noise level)

Undetected: genes with normal copy numbers

All: status of all genes of the panel where CNV detection is available

NOTE: Please consult the CNV-report.pdf or the CNV region file for more details on the covered target region of the CNV module for each application. The CNV region file can be retrieved from support@sophiagenetics.com.

NOTE: To enhance loading time of CNV display for large panels, restrict the scope of the Project* to a subset of genes.

7. CNV Analysis

7.1 Germline and liquid tumor applications

7.1.1 CNV table (2): liquid tumor applications

Variant Overview

Select a CNV to open the variant overview panel.
Not available for germline analyses.

The screenshot displays the SOPHiA DDM software interface. At the top, there's a navigation bar with 'WORKSPACE', 'VDB', and 'A...' sections. Below that, a 'Variants' tab is active, showing a table of CNVs. The table has columns for Pathogenicity, Actionability, AMP/ASCO/CAP, Report, Type, Gene, and Chromosome. Two rows are visible: one for SRSF2 (Amplification, Chromosome 17) and one for TP53 (Loss, Chromosome 17). The TP53 row is highlighted with a red star and a '5' in a red circle. Below the table, a detailed 'OVERVIEW' panel for the TP53 variant is shown, including fields for Gene (TP53), Type (Loss), Chromosomes (17), Start (7,572,788), End (7,580,031), and Transcript (NM_000546). The panel also features a 'Pathogenicity' and 'Actionability' scale (0-5) and an 'In Report' indicator (2). On the right side of the interface, there are 'Links' buttons for dbVar, IGV, and OMIM, with an upward-pointing arrow indicating they are linked to the variant overview panel.

Overview

Information for the selected CNV:

- Gene, transcript, chromosome, positions
- Copy number
- Pathogenicity
- Actionability
- In Report Indicator
- False + indicator

Interactive features: (see also [ch. 7.3 Somatic applications](#))

- Add or adjust Pathogenicity (1-5)
- Add or remove False + flag
- Add to/remove from report

Links

Additional variant information in external sources

7. CNV Analysis

7.1 Germline and liquid tumor applications

7.1.1 CNV table (3): liquid tumor applications

Region names
 Hover over a region box to see the region name

The screenshot shows the SOPHiA DDM software interface. At the top, there's a navigation bar with 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'A... #3-0141'. Below this is a 'Variants' tab with a 'CNVs' sub-tab. A table displays CNV results for genes SUZ12, NF1, and KDM6A. A scatter plot below the table shows CNV copy numbers across various regions (KDM6A_ex1-2 to KDM6A_ex29). A callout box points to a region box in the table, stating 'Region: KDM6A_ex1-2 - plex 1'.

Pathogenicity	Actionability	AMP/ASCO/CAP tier	In Report	Type	Gene	Regions (copy number)
III				Amplification	SUZ12	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100
III				Amplification	NF1	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100
III				Loss	KDM6A	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

NOTE:

- Analyses prior to pipeline version 5.5.68 or CE-IVD analyses: CNV target regions are labelled the same as in CNV report and may not correspond to the transcript used for variant annotation.
- Analyses on pipeline v5.5.68 or later: CNV target regions are labelled with gene symbol and exon, intron, 5'UTR, 3'UTR, (or upstream or downstream region) based on the transcript used for annotation. To view the region names used for your application, you can access the region_map.tsv file in the workspace.

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7. CNV Analysis

7.1 Germline and liquid tumor applications

7.1.2 Gene viewer

Restriction
Scope of the project

CNV tab
Active tab (white)

Access to CNV viewer per amplicon / region

1 Exon view of the current gene (gene in bold)

2 Amplicons / regions of the application

3 Confidence level per region (high, medium or undetermined)

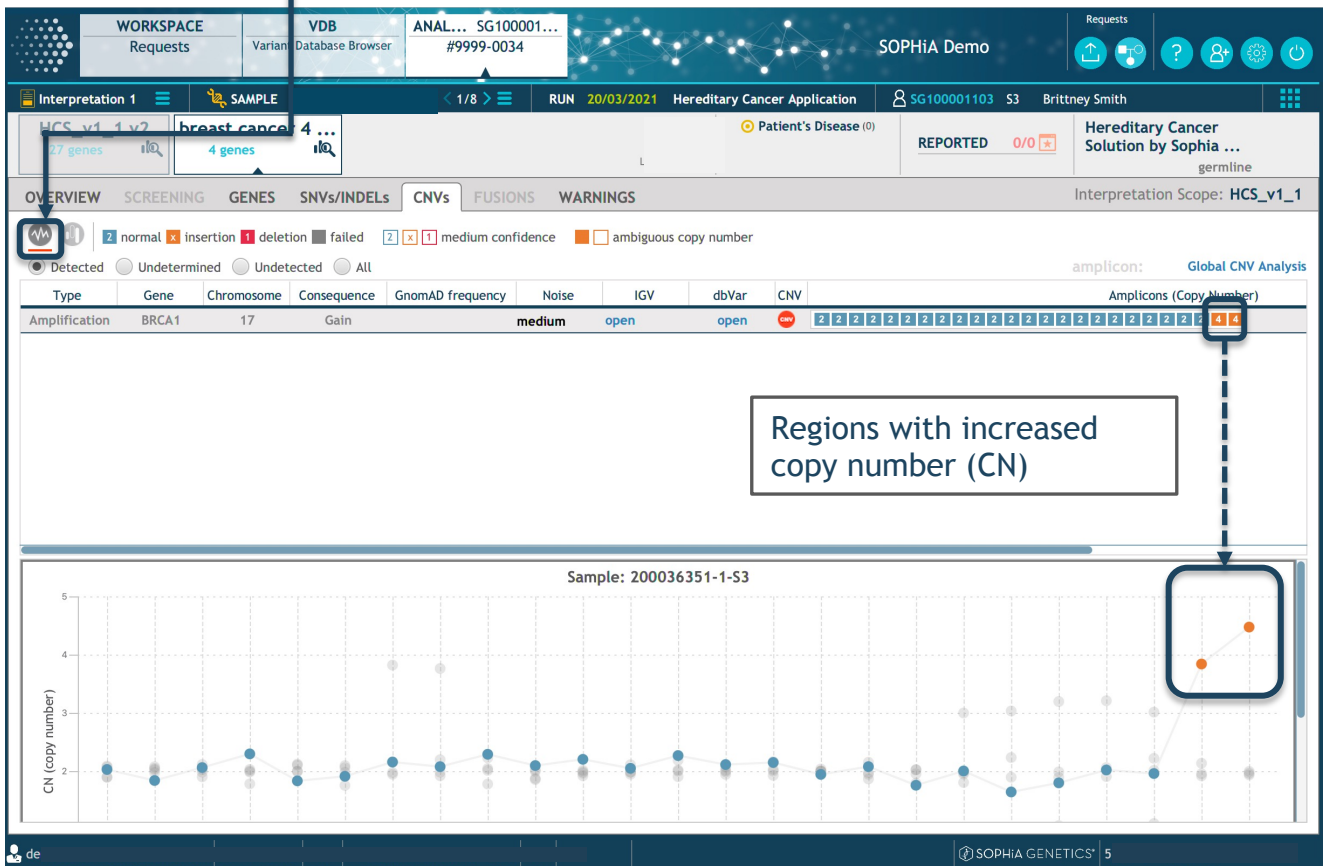
7. CNV Analysis

7.1 Germline and liquid tumor applications

7.1.3 Sample graph

Each dot corresponds to the coverage level per region/amplicon

CNV amplicon-based graphic view
(active view is underlined)



Regions with increased copy number (CN)











-  Rejected due to high noise levels
-  Increased copy number
-  Normal copy number
-  Decreased copy number
-  Other samples in the same batch analysis

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7. CNV Analysis

7.1 Germline and liquid tumor applications

7.1.4 Legend for regions graph

-  Insertion called with high confidence (the number indicates the copy number)
-  Insertion called with high confidence (copy number was not determined)
-  Insertion called with medium confidence
-  Normal copy number with high confidence
-  Normal copy number with medium confidence
-  Deletion called with high confidence
-  Deletion called with medium confidence
-  Rejected region (high level noise)

7. CNV Analysis

7.2 Solid tumor applications

7.2.1 CNV table (1)

CNV tab
Active sub-tab (white)

The screenshot shows the SOPHiA DDM interface with the 'CNVs' sub-tab selected. The table below displays the results for various genes, including their pathogenicity, actionability, and amplification status.

Pathogenicity	Actionability	AMP/ASCO/CAP tier	In Report	Type	Gene	Chromosome	Gene Amplification	Inner Start	Inner End	Consequence	GnomAD frequency	Noise
3		III		Amplification	EGFR	7	detected	55241466	55259699	Gain		low
N/A					NRAS	1	not detected					low
N/A					PIK3CA	3	not detected					low
		III	★	Amplification	TERT	5	detected	1258663	1295428	Gain		low
N/A					CDK4	12	not detected					low
N/A					MYOD1	11	not detected					low
N/A					KIT	4	not detected					low
N/A					ERBB2	17	not detected					low
N/A					KRAS	12	not detected					low
N/A					RAF1	3	not detected					low
N/A					SF3B1	2	not detected					low
N/A					FGFR3	4	not detected					low
N/A					ROS1	6	not detected					low
N/A					MET	7	not detected					low
N/A					HRAS	11	not detected					low
N/A					TP53	17	not detected					low
N/A					FGFR2	10	not detected					low
N/A					FGFR1	8	not detected					low

NOTE: The minimal resolution for gene amplification detection of the SOPHiA DDM™ solid tumor solutions is 3.25 copies (6 for high confidence level).

NOTE: Gene symbols displayed in the CNV tab are based on the MANE or RefSeq transcript used for annotation and may not correspond to the target region labels defined in the CNV report.

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7. CNV Analysis

7.2 Solid tumor applications

7.2.1 CNV table (2)

Variant Overview

Select a CNV to open the variant overview panel.

Note that the overview panel is not available for genes with normal copy number.

The screenshot displays the Sophia Genetics SA interface. At the top, there are navigation tabs for WORKSPACE, VDB, and ANA... SG1000010... #3-0151. The main header shows 'Interpretation 1', 'SAMPLE', 'RUN 16/11/2022 STS again', and 'Patient's Disease (1) Lymphoma'. Below this is a table of CNVs with columns for Pathogenicity, Actionability, AMP/ASCO/CAP tier, In Report, Type, Gene, Chromosome, Gene Amplification, Copy Number, Inner Start, Inner End, Consequence, and GnomAD frequency. The table lists several genes, with EGFR and TERT showing 'detected' amplification and copy numbers of 3.7 and 3.4 respectively. Other genes like NRAS, PIK3CA, CDK4, MYOD1, KIT, and ERBB2 are listed as 'not detected' with various copy numbers. Below the table, a detailed 'OVERVIEW' panel for the TERT gene is shown, including its type (Amplification), copy number (3.4), and a pathogenicity/actionability scale (1-5). The 'Add To Report' button is set to 1, and 'Set To False +' is set to 0. On the right side, there are 'Links' buttons for dbVar, IGV, and OMIM.

Pathogenicity	Actionability	AMP/ASCO/CAP tier	In Report	Type	Gene	Chromosome	Gene Amplification	Copy Number	Inner Start	Inner End	Consequence	GnomAD frequency
3		III	★	Amplification	EGFR	7	detected	3.7	55241466	55259699	Gain	
N/A					NRAS	1	not detected	2.1				
N/A					PIK3CA	3	not detected	2.8				
		III		Amplification	TERT	5	detected	3.4	1258663	1295428	Gain	
N/A					CDK4	12	not detected	2.1				
N/A					MYOD1	11	not detected	2.2				
N/A					KIT	4	not detected	2.0				
N/A					ERBB2	17	not detected	1.8				

Overview

Information for the selected CNV:

- Gene, transcript, chromosome, positions
- Copy number
- Pathogenicity
- Actionability
- In Report Indicator
- False + indicator

Interactive features: (see also [ch. 7.3 Somatic applications](#))

- Add or adjust Pathogenicity (1-5)
- Add or remove False + flag
- Add to/remove from report

Links

Additional variant information in external sources

7. CNV Analysis

7.3 Somatic applications

7.3.1 Add pathogenicity flag

The screenshot displays the SOPHiA DDM software interface for a CNV analysis. The top navigation bar includes 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS #3'. The main interface shows a 'Variants' tab with a table of CNVs. The table has columns for Pathogenicity, Actionability, In Report, Type, Gene, Chromosome, Consequence, GnomAD frequency, Noise, IGV, dbVar, CNV, and Amplicons (Copy Number). A row is highlighted for a 'Loss' variant on chromosome X for the gene ZRSR2. Below the table, a detailed view of the variant is shown, including a 'Pathogenicity' and 'Actionability' section. This section contains five boxes representing pathogenicity levels (1-5) and two buttons: 'Add To Report' and 'Set To False +'. A red circle highlights the pathogenicity boxes, and a blue arrow points to the 'Add To Report' button.

Pathogenicity flag distribution (community) and account pathogenicity flag
 The numbers above the boxes indicate the number of community users having flagged the variant for each pathogenicity category. The colored numbers (1-5) indicate the pathogenicity level of the variant in your account.

7. CNV Analysis

7.3 Somatic applications

7.3.2 Add to report (1)

Reported CNV
Complete the sections with relevant information, such as:

- Comment that you would like to add to the report
- References/Publications

7. CNV Analysis

7.3 Somatic applications

7.3.2 Add to report (2)

The screenshot displays the SOPHiA GENETICS SA interface. At the top, the workspace is identified as 'ANALYSIS P03 #3-0144'. The main navigation bar includes 'Overview', 'OncoPortal', and 'Variants'. The 'Variants' tab is active, showing a table of variants. The variant for ZRSR2 is highlighted, and its details are shown in a pop-up panel below. In the 'In Report' section of this panel, a red star is placed above the checkbox, indicating that the CNV has been added to the report. A callout box with the text 'CNV has been added to the report' points to this star.

In Report
 The red star indicates that the CNV has been added to the report.

7. CNV Analysis

7.3 Somatic applications

7.3.3 Mark as false positive

“False positive” button
Click to mark a CNV as a false positive. Add comment, as necessary.

Mark this cnv as False Positive

comment

Cancel OK

Set To False +

Gene	Chromosome	Pathogenicity	Actionability	In Report	Consequence	GnomAD frequency	Copy Number	
FBXW7	4	N/A	low	open	no	1.9		
CDKN2A	9	N/A	low	open	no	1.9		
BRAF	7	N/A	low	open	no	2.0		
Amplification	EGFR	7	N/A	Gain	low	open	yes	3.3
PDGFRA	4	N/A	low	open	no	2.1		

False positive CNV
Hatching indicates that CNV was set “false positive” (see also [4.9.5 False Positive Variants](#))

8. Warnings

Warning
Active page (white)

The screenshot displays the 'Warnings' section of the SOPHiA DDM software. The top navigation bar includes 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS #3-0105'. Below this, the patient information bar shows 'PROJECT BRCA CNV', 'SAMPLE #200028411 BRCA', 'RUN 25/04/2017', and 'BRCA S17'. The main content area features a 'Warnings' table with the following data:

chr	gene	specificity	category	start	end	mean reads	min reads	max reads	transcript	exon rank	exon id	c.DNA	comment
13	BRCA2	sample	low_coverage	32912495	32912625	44	44	44	NM_00059	11	11	c.4003_4133	
13	BRCA2	sample	low_coverage	32914907	32915108	47	47	47	NM_00059	11	11	c.6415_6616	
13	BRCA2	sample	low_coverage	32937290	32937487	37	37	37	NM_00059	18	18	c.7977-26_8148	
17	BRCA1	sample	low_coverage	41245408	41245622	43	43	43	NM_07294	10	11	c.1926_2140	
17	BRCA1	sample	low_coverage	41256134	41256434	46	46	46	NM_07294	6	7	c.302-156_441+5	
17	BRCA1	sample	low_coverage	41267692	41267883	43	43	43	NM_07294	3	3	c.81-87_134+51	
17	BRCA1	sample	potential_allel...	41244431	41244700	142	132	227	NM_07294	10	11	c.2848_3117	

Warnings
Low coverage regions,
pseudogenes, other warnings (e.g.
noisy regions)

Warnings
Export warnings table in XLS or
CSV format

9. OncoPortal™

9.1 Overview

The screenshot shows the OncoPortal interface with several callout boxes:

- OncoPortal: Therapeutic, diagnosis* & prognosis* information**
Access to clinical associations* between variants, a specific pathology and treatments, based on latest clinical databases
- Pathology Disease* selected for the patient***
Non-small Cell Lung Carcinoma
- Actionability* categories**
The proportion of variants found in each category amongst all variants
- Database versions**
Currently integrated OncoPortal™ data source version (Jackson Laboratory's JAX® Clinical Knowledgebase, JAX-CKB™)

The interface also displays a 'Patient Pathology' section with 'Non-small Cell Lung Carcinoma' and 'REPORTED 0/0'. A 'Pathogenicity Flags' section shows 'No Flags'. An 'Actionability' gauge shows 19 DISEASES, 40 DRUGS, and 346 TRIALS. A 'Database Versions' table is visible on the right:

Database	Version
ESP	5400
CCSMIC	v3
ClinVar	v0017029
CG69	837,20120819
dbSNP	v150
dbNSFP	v2.9
GnomAD	v2.6.2
JAX-CKB™	v00191018

Actionability*

Quick overview on the actionable variants with related medical information

NOTE: With SOPHiA DDM™ version v5.5.0, the data source for the OncoPortal™ has been updated. Up-to-date clinical associations* will be available only for samples run after this update.

9. OncoPortal™

9.2 Disease* Selection (1)

Patient*
Active tab

The screenshot displays the OncoPortal interface for a patient. The 'Patient' tab is active, showing personal details and patient identifiers. The 'Diseases' section is highlighted with a dashed box, indicating the selection of 'Non-small Cell Lung Carcinoma'. The interface includes a top navigation bar with 'OncoPortal' and 'Variants' tabs, and a right sidebar with 'Test Information' and 'Public Databases'.

Disease*

Users with access to the OncoPortal™:

- Choose the patient's* disease* in the list by clicking on "Add Disease*"
- Select the disease* from the disease* tree (see p. [77](#))
- Click on "OK"

SOPHiA DDM™ will automatically recalculate the impact of the disease* association with drugs and the genomic profile of the patient*.

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9. OncoPortal™

9.2 Disease* Selection (2)

The screenshot shows the OncoPortal interface. In the 'Diseases' section, 'Non-small Cell Lung Carcinoma' is listed. A modal dialog titled 'Add Disease' is open, asking 'Are you sure you want to add this disease? We will recalculate the actionability for the analysis.' with 'Cancel' and 'OK' buttons. A callout box points to the 'OK' button with the text: 'Click "OK" To confirm the disease*'. The interface also shows patient details, test information, and a sidebar with various databases like EVAC, G1000, ESP, COSMIC, ClinVar, CG69, dbSNP, dbNSFP, GnomAD, and JAX-CKB.



This screenshot shows the 'Diseases' section with 'Carcinoma, Non-Small-Cell Lung' selected. A callout box points to the trash icon next to the disease name with the text: 'Click trash icon To remove the disease*'. Below this, two callout boxes are shown: 'Selected disease*' pointing to the disease name and 'User Who selected the disease*' pointing to the 'User name' field. The sidebar on the right shows the same database list as the previous screenshot.

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.1 Overview (1)

Help section
Expandable section with explanation of the evidence levels and access to disclaimer text.

Disclaimer

SOPHIA GENETICS SA ("SOPHIA GENETICS"), including its subsidiaries, does not provide medical services, nor do any of the employees of SOPHIA GENETICS active as a medical practitioner for or on behalf of SOPHIA GENETICS. Some drugs identified in the OncoPortal™ may not be approved by regulatory bodies (including but not limited to FDA, EMA, or NICE) for a particular use or validated for that use. Therefore, the user is required to independently validate that such drug may be lawfully used in the territory of prescription and that said drug has been deemed safe and efficient for the contemplated use. The content of the OncoPortal™ is compiled from currently available sources. The content is subject to change and may be adapted from time to time as such sources are updated. Despite best efforts, content may contain typographical errors and omissions. The OncoPortal™ is intended for professional medical and scientific users only. The user of the platform remains solely liable for any treatment, therapy, recommendation or decision for any given case.

Clinical Associations displayed in the OncoPortal™ are limited to those related to the following types of alterations: single-nucleotide variants ("SNVs"), insertions/deletions ("Indels"), gene fusions and exon skipping events identified at RNA level ("fusions"), and copy number variants ("CNVs"). Clinical Associations are not currently available for other variant types. Clinical Associations based on a lack of detected variants (i.e. based on a gene being a so-called wild type) are not yet provided. Clinical Associations based on combinations of variants are not provided. Clinical Trials are matched based on Clinical Associations and are currently available for clinical trials in USA and Canada. Without limitation to the foregoing, the system may not necessarily display clinical information or clinical trial availability in certain situations. For more information, contact SOPHIA GENETICS at support@sophiagenetics.com.

For analyses completed before 10/03/2021 Clinical Associations displayed in the OncoPortal™ are limited to those related to single-nucleotide variants ("SNVs") and insertions/deletions ("Indels") only.

Clinical significance and evidence levels published on the SOPHIA DDM® platform in the column entitled "AMP/ASCO/CAP", are based on those provided by the Jackson Laboratory Clinical Knowledgebase (JAX-CKB™) and are available for associations within tier I and tier II only. If the association disease does not match the patient's disease selected on the SOPHIA DDM® platform, the tiers and evidence levels are adjusted according to Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer (PMID:27993330), except for associations related to the disease term "Advanced Solid Tumor" for which tiers and evidence levels provided by JAX-CKB™ are displayed directly. Information displayed from third-party databases is provided by third parties and SOPHIA GENETICS accepts no liability towards its content.

Unless specifically indicated otherwise, the SOPHIA DDM® platform and any application pertaining thereto is FOR RESEARCH USE ONLY and must not be used for diagnostic purposes.

Click to dismiss the disclaimer window for this session. The disclaimer can be found at any time in the Help menu.

NOTE: The user must accept the Disclaimer in order to access the OncoPortal™ (once per active session).

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.1 Overview (2)

OncoPortal™

Choose the genes of interest (e.g. Virtual Panel, per gene)

Actionability* vs Evidence level of the associations (see [ch. 9.3.3 Evidence Level](#))

The screenshot shows the OncoPortal interface with the following components:

- Active tab:** OncoPortal
- Filters:** Pathologies (Advanced Solid Tum...), Regions of interest (MYS_plus_v1 - regio), Variants of interest (Hide Low Confidence, By Pathogenicity Level), Actionability (vs) Evidence Level (grid with values 12, 13, 14, 15, 6, 13, 4, 7), Filter Shortcuts (Actionables, Actionables Other Pathology, Clinical Trials, Research, Diagnosis, Prognosis, All Associations).
- Associations:** 45 of 45 TOTAL
- Variant Details Table:**

Gene	Variant	Type	VF	Annotations	Molecular profiles Diseases	Actionability Actionability & AMP/ASCO/CAP Tier	Flagging	Molecular Mechanism(s)	Summary
ASXL1	p.(Glu1102Asp)	missense	47.9%	ASXL1 mutant	ASXL1 mutant	1D	1D		
DNMT3A	p.(Ile705Aspfs*8)	frameshift	46.7%	DNMT3A mutant	DNMT3A mutant	1D	1D		
NPM1	p.(Trp288Cysfs*)	frameshift	41.5%	NPM1 mutant	NPM1 W288fs	1D	1D		
SETBP1	p.(Pro1130Thr)	missense	49.6%	SETBP1 mutant	SETBP1 mutant	1D	1D		
TET2	p.(Ile1762Val)	missense	49.5%	TET2 mutant	TET2 mutant	1D	1D		
TET2	p.(Gly355Asp)	missense	50.4%	TET2 mutant	TET2 mutant	1D	1D		
TP53	p.(Pro72Arg)	missense	49.1%	TP53 mutant	TP53 mutant	1D	1D		

The patient's* disease* is automatically checked if the disease* is added in the patient* tab. The user gets all associations of the genomic alterations with existing drugs related to the patient's* disease* and with actual clinical trials*. The user can also check for other types of diseases* related to the patient's* genomic profile.

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.2 Disease* Category

Check patient's disease*
Get all associations of the patient's genomic alterations with existing drugs related to the patient's disease*.

Low confidence filter
Select to include low confidence associations.

Impact on the number of clinical associations.*

The screenshot shows the OncoPortal interface for a patient named 'MYS_plus_v1'. The interface includes a top navigation bar with 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS #3'. Below this is a patient information bar showing 'Myeloid Plus Solution by SOPHiA GENETICS' and 'DNA - RNA'. The main content area is divided into several sections: 'Filters', 'Regions of Interest', 'Variants of Interest', 'Actionability (vs) Evidence Level', and 'Filter Shortcuts'. The 'Filters' section has a dropdown menu set to 'Advanced Solid Tum...'. The 'Regions of Interest' section has a radio button selected for 'MYS_plus_v1 - regio'. The 'Variants of Interest' section has a checkbox checked for 'Hide Low Confidence'. The 'Actionability (vs) Evidence Level' section has a grid of buttons for different evidence levels (T1, T2, T3, T4, D, P). The 'Filter Shortcuts' section has buttons for 'Actionables', 'Actionables Other Pathology', 'Clinical Trials', 'Research', 'Diagnosis', 'Diagnosis Other Pathology', 'Prognosis', 'Prognosis Other Pathology', and 'All Associations'. The 'Associations' section shows a total of 45 of 45 associations. The main table displays variant details for ASXL1, DNMT3A, NPM1, SETBP1, and TP53. Callout boxes provide detailed explanations for the 'Filters', 'Low confidence filter', 'Association level filter', and 'Gene filter' options.

Association level filter
Filter associations based on actionability and evidence level.

Gene filter
Filter associations based on the list of genes covered by the application.

Check or uncheck the other diseases*
To get all associations of the patient's genomic alterations with existing drugs related to other diseases*.

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.3 Evidence Level I to III

Evidence Levels:

Level III

The clinical association* is well established and has been approved by at least one regulatory agency (e.g. Food and Drug Administration) or recommended by clinical societies of international standing (e.g. American Society of Clinical Oncology).

The confidence level is high.

Level II

The clinical association* has agreements from different sources but is not approved by any regulatory agency or clinical society of international standing.

The confidence level is intermediate

Level I

The clinical association* has been published in only one paper or source.

The confidence level is low.

The table represents the clinical associations* per category. The Evidence Levels displayed vary according to the filter shortcuts applied.

Click on “All Associations”

To get access to all the clinical associations* related to the genomic profile of the patient*. Please note, by default none are selected.

Actionability (vs) Evidence Level		T1	T2	T3	T4	D	P
III	56	4	-	-	-	-	-
II	-	4	-	90	2	-	-
I	-	-	-	15	4	-	-

Filter Shortcuts		
Actionables	Diagnosis	All Associations
Actionables (other Pathology)	Diagnosis (other Pathology)	
Clinical Trials	Prognosis	
Research	Prognosis (other Pathology)	

Colored boxes indicate the number of clinical associations*.

Click on the blue links

Quick access to the related categories with evidence levels III and II (T1, T2, T3, T4, D and P).

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.4 Categories T1 to T4, D and P (1)

Categories T1 to T4:

T1

- T1: Drug approved by FDA, EMA, NICE or by a clinical society with an international standing in the same tumor entity

T2

- T2: Drug approved by FDA, EMA, NICE or by a clinical society with an international standing in a different tumor entity

T3

- T3: Drugs in clinical trials* phase 1 to phase 4

T4

- T4: Drugs in research only or case studies

D

- Diagnosis* (to establish a pathology if unsure with other biochemical methodologies)

P

- Prognosis* (to establish the outcome of the survival rate when a patient* harbors a specific genomic alteration)

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.4 Categories T1 to T4, D and P (2)

Click on eye button
Access to the genomic alteration information window

Click ▼ for variant of interest:
Information about the diseases* associated with the genomic profile of the patient*

Click ▼ for disease* of interest:
Information about available treatments for this particular disease* and genomic alteration

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.4 Categories T1 to T4, D and P (3)

Click "+" to add the clinical association* to the report

Double-click on treatment
More information about the treatment

Summary
With reference(s)

Summary
Available for this clinical association*

Variant Details
Clinical Association Details

Variant	Treatment	Actionability	Flagging	Molecular Mechanism(s)
TP53 p.(Pro72Arg)		T3		
TP53 p.(Gly266Val)		T2		
TP53 mutant	Acalabrutinib	T2	II, C	BTK inhibitor
TP53 mutant	Decitabine	T2	II, C	DNMT inhibitor (Pan)
TP53 mutant	Duvelisib	T2	II, C	PI3KCD inhibitor

Association Details
TP53 predicted mutant (unknown)

TP53 p.(Gly266Val) acute myeloid leukemia
Decitabine (5-aza-2-deoxycytidine) (sensitive)

VF 23.7% T2

Summary
Dacogen (decitabine) is included in guidelines for adult patients with acute myeloid leukemia harboring a TP53 mutation (NCCN.org).
(Approval status: Guideline)

Variant Description
TP53 mutant indicates an unspecified mutation within the TP53 gene.

Molecular Mechanisms
Decitabine: - DNMT inhibitor (Pan)

Add Clinical Association in Report
Clinical Association: Decitabine
p.(Gly266Val) TP53 acute myeloid leukemia
Decitabine (5-aza-2-deoxycytidine) (sensitive)
Variant will be automatically flagged in report.
No Yes

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.5 Clinical Trials* (1)

Access to clinical trials*:

- 1) Through a chosen clinical association*
- 2) Through the clinical trials* tab

Clinical Trials for acute myeloid leukemia

Phase	Status	NCT Number	Country
Phase II	Recruiting	NCT/03063203	United States
Phase II	Recruiting	NCT/03931291	United States
Phase I	Recruiting	NCT/04214860	United States

Number of clinical trials* for this specific clinical association* (if available)

Double-click on the clinical trial* number to access details

Click on clinical trial* of choice
Open clinical trial*

Clinical Associations 1 Clinical Trials

Filters: Phase 2 Clinical, Recruitment Status Recruiting, Countries France, Spain, US

Public Title	Official Title	Phase	Recruitment Status	Variants	Patients	Start Date	Finish Date	Countries	Inclusions	Exclusions
Phase II Study of Tipifarnib In Squamous Head and Neck Cancer With HRAS Mutations	An Open-Label, Phase II Study of Tipifarnib In Advanced Non-Hematological Malignancies With HRAS Mutations	Phase 2 Clinical	Recruiting	NCT		29/03/2015	29/12/2017	France, Spain, US		

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.5 Clinical Trials* (2)

Access to Clinical Trials*:

- 1) Through chosen clinical association*
- 2) Through the clinical trials* tab

The screenshot shows the OncoPortal interface with the following callouts:

- Click on clinical trials* tab**: Points to the 'Clinical Trials' tab in the 'Clinical Associations' section.
- Filters to get access to the most relevant clinical trials***: Points to the filter dropdowns for 'Phase' (Phase I, Phase Ib/II, Phase II, ...), 'Recruitment Status' (Active, not recruiting, Recruit...), and 'Countries' (France, Germany, Japan, Net...).
- Keyword search**: Points to the search bar with '(0)' results.

Public Title	Official Title	Phase	Recruitment Status	Variants	Patients: Gender (Age Group)	Start Date	Finish Date	Countries	Inclusions	Exclusions
Single Agent Decitabine in TP53 Mutated Relapsed/Refractory Acute Myeloid Leukemia	An Open Label, Multicenter, Phase II Trial Testing Single Agent Decitabine in TP53 Mutated Relapsed/Refractory Acute Myeloid Leukemia	Phase II	Recruiting	TP53 mutant (unknown)	both (adult senior)	14/07/2017	31/07/2025	United States		
APR-246 in Combination With Azacitidine for TP53 Mutated AML (Acute Myeloid Leukemia)	Phase II Trial of APR-246 in Combination With Azacitidine as Maintenance Therapy for TP53 Mutated AML or MDS Following Allogeneic HSCT	Phase II	Recruiting	TP53 mutant (unknown)	both (adult senior)	16/09/2019	30/09/2021	United States		
Testing Nivolumab in Combination With Decitabine and Venetoclax in Patients With Newly Diagnosed TP53 Gene Mutated Acute Myeloid Leukemia	A Pilot Study of Nivolumab in Combination With Decitabine and Venetoclax in TP53-Mutated Acute Myeloid Leukemia	Phase I	Recruiting	TP53 mutant (unknown)	both (adult senior)	06/02/2020	28/02/2022	United States		
APR-246 in Combination With Venetoclax and Azacitidine in TP53-Mutant Myeloid Malignancies	Phase I Study of APR-246 in Combination With Venetoclax and Azacitidine in TP53-Mutant Myeloid Malignancies	Phase I	Recruiting	TP53 mutant (unknown)	both (adult senior)	13/12/2019	15/12/2021	United States		
Phase 1b/2 Safety and Efficacy of APR-246 w/Azacitidine for tx of TP53 Mutant Myeloid Neoplasms	A Phase 1b/2 Study to Evaluate the Safety and Efficacy of APR-246 in Combination With Azacitidine for the Treatment of TP53 Mutant Myeloid Neoplasms	Phase Ib/II	Active, not recruiting	TP53 mutant (unknown)	both (adult senior)	05/05/2017	01/05/2021	United States		
Study to Determine and Evaluate a Safe and Tolerated Dose of HDN201 in Patients With Selected Advanced Tumors That Are TP53wt	A Phase I, Open Label, Multicenter, Dose-escalation Study of HDN201 in Adult Patients With Advanced Solid and Hematological Tumors Characterized by Wild-type TP53	Phase I	Active, not recruiting		both (adult senior)	07/07/2014	21/07/2020	France, Germany, Japan, Netherlands, Singapore, Spain, Taiwan, United States		
APR-246 & Azacitidine for the Treatment of TP53 Mutant Myelodysplastic Syndromes (MDS)	A Phase III Multicenter, Randomized, Open Label Study of APR-246 in Combination With Azacitidine Versus Azacitidine Alone for the Treatment of TP53-Mutated MDS	Phase III	Recruiting	TP53 mutant (unknown)	both (adult senior)	11/01/2019	01/12/2020	France, United States		

- Details for each clinical trial*:**
- Public and official titles of the clinical trial*
 - Phase and recruitment status
 - Genomic alteration status
 - Available countries
 - Inclusion/exclusion
 - End dates
 - NCT number if available

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.6 User Clinical Associations*

The clinical associations* database is updated on a regular basis. However, it may happen that a specific clinical association* is not yet present in the database. In this case, users can create clinical associations* themselves and add them to the report.

Actionability* column for clinical association* prediction (T1 to T4, D and P):

- **Blue:** Clinical associations* available for this particular actionability* type
- **Grey:** No clinical associations* for this particular actionability* type
- **Empty:** No clinical associations* available for any actionability* type

The screenshot displays the OncoPortal interface for a patient sample. The main table lists variants with columns for Gene, Protein, c.DNA, ref, alt, Coding consequence, V%F, Depth, Cosm..., and ClinVar rating. The 'Actionability' column is highlighted with a dashed box, showing various letters (T1, T2, T3, T4, D, P) and their corresponding icons. Below the table, the 'Add To Report' button is visible, and a detailed view of a variant (p.(Glu12Lys) in ERBB2) is shown at the bottom, including its pathogenicity and actionability predictions.

Actionability* tab:

- Actionability* prediction (T1 to T4, D and P)
- Clinical associations* (AT for approved therapies, CT for clinical trials*, D for Diagnosis* and P for Prognosis*) added by the user

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.6 User Clinical Associations*

9.3.6.1 Creation of a Clinical Association* (1)

The screenshot displays the OncoPortal interface for a patient sample (#200). The main table lists variants with columns for Gene, Protein, c.DNA, ref, alt, Coding consequence, VF%, Depth, and ClinVar rating. The 'Actionability' column is highlighted with a dashed box, and a callout box explains that the number in the cell (e.g., 4) represents the number of clinical associations added by the user for that variant.

Gene	Protein	c.DNA	ref	alt	Coding consequence	VF%	Depth	ClinVar rating
CDKN2A	p.(Arg22Pro)	c.65G>C	C	G	missense	5.0	28707	COSM1...
CTNNB1	p.(Ser71Pro)	c.211T>C	T	C	missense	5.3	27573	
DDR2	p.(Leu405Ser)	c.1214T>C	T	C	missense	0.3	43192	
ERBB2	p.(Glu812Lys)	c.2434G>A	G	A	missense	7.4	26352	
ERBB2	p.(Asp880Glu)	c.2640_2643de...	TGGG	AGGA	missense	2.0	18855	
FGFR3	p.(Leu398Arg)	c.1193T>G	T	G	missense	10.0	10193	
IDH2	p.(Arg149Trp)	c.445C>T	G	A	missense	7.1	7542	COSM6...
KIT	p.(Ala659Thr)	c.1975G>A	G	A	missense	5.6	12557	
KRAS	p.(Glu107Asp)	c.321A>T	T	A	missense	7.7	8734	
PIK3CA	p.(Gln75Pro)	c.224A>C	A	C	missense	7.1	6923	COSM6...
PIK3CA	p.(Glu525Gly)	c.1574A>G	A	G	missense	14.3	3843	
EGFR	p.(Gln787=)	c.2361G>A	G	A	synonymous	80.0	4473	COSM1... Benign/Likely benign
FGFR3	p.(Thr651=)	c.1953G>A	G	A	synonymous	100.0	18524	
AKT1	p.(Thr1500=)	c.175+18C>T	G	A	intronic	44.4	7223	
ALK	p.(Thr1500=)	c.4500C>A	G	T	synonymous	0.6	41432	

The callout box states: "The number reflects the clinical associations* added by the user related to the variant".

Click on the category of choice in order to provide information

NOTE: Association flags are shared between Interpretation Projects* of the same sample.

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.6 User Clinical Associations*

9.3.6.1 Creation of a Clinical Association* (2)

Complete the sections, as necessary:

- Select source(s) of approval (required)
- Use patient's* disease* or choose other disease* (click the selected disease* to access the Disease Ontology Selection menu)
- Comment (summary of the clinical association*)
- Treatment(s) (required)
- Effect of the treatment(s)
- References/Publications supporting the association*

AMP/ASCO/CAP category:

The tier depends on whether the approved therapy is in the patient's* disease* (tier I) or other disease* (tier II).

NOTE: Information provided will be displayed in the OncoPortal™ tab and will be available to add to the report. Providing accurate information is therefore important.

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.6 User Clinical Associations*

9.3.6.1 Creation of a Clinical Association* (3)

Add "Approved Therapy" Flag

Select Sources: FDA EMA NICE Other

AMP/ASCO/CAP category: Tier I

Use Patient's Disease Choose other disease

Selected Disease: Lung Carcinoma

Comments (max. 1000 characters)

Details of Tyrosine Kinase Inhibitors approved for use in lung carcinoma and approval status.

Treatments: Tyrosine Kinase Inhibitors Effect: Sensitive

References/Publications (1)

Thyroid dysfunction in non-small cell lung cancer patients treated with epidermal gro...
Conclusions: NSCLC patients may need to be monitored for occurrence of thyroid dysfunction during treatment with E...

Cancel OK

Reference(s) added

Click "OK"

G 4687 47.6% RET CTG L

DESCRIPTION FLAGG

Pathogenicity Action

AT

Flag: Approved Therapy

AT

User: NN Operator User

Date: 2020/12/07

Disease: Lung Carcinoma

Treatment: Tyrosine Kinase Inhibitors

Effect: Sensitive

Close

Number of AT flags for this variant on this account

Click on the clinical association* of your choice to get more details

Details of the clinical association* added

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.6 User Clinical Associations*

9.3.6.2 Traceability of a Clinical Association* Created by a User

The screenshot displays the OncoPortal interface. At the top, there are navigation tabs for WORKSPACE, VDB, and ANA... #3. The main header shows 'Sophia Genetics SA' and 'Patient Pathology (1) Cancer'. Below this, there are tabs for Overview, OncoPortal, and Variants. The main content area shows a list of variants with columns for Actionability, Gene, Protein, c.DNA, ref, alt, Coding consequence, VF%, Depth, Cosm..., and CtinVar rating. The 'Actionability' column is highlighted in yellow for several variants. Below the list, there is a detailed view of a clinical association in the 'FLAGGING' tab. This view shows the user 'Operator User' who added the association on '20/02/2018' for the disease 'Non-small-cell Lung Carcinoma'. The association is for the variant 'NM_001904.3' and is categorized as 'Approved Therapy'. The treatment is '1st and 2nd generation EGFR inhibitors, 3rd generation EGFR inhibitors' and the effect is 'Less Sensitive'. The comment is 'summary to be added here'.

Actionability	Gene	Protein	c.DNA	ref	alt	Coding consequence	VF%	Depth	Cosm...	CtinVar rating
B	CDKN2A	p.(Arg22Pro)	c.65G>C	C	G	missense	5.0	28707	COSM1...	
B	CTNNB1	p.(Ser71Pro)	c.211T>C	T	C	missense	5.3	27573		
B	DDR2	p.(Leu405Ser)	c.1214T>C	T	C	missense	0.3	43192		
B	ERBB2	p.(Glu812Lys)	c.2434G>A	G	A	missense	7.4	26352		
B	ERBB2	p.(Asp880Glu)	c.2640_2643de...	TGGG	AGGA	missense	2.0	18855		
B	FGFR3	p.(Leu398Arg)	c.1193T>G	T	G	missense	10.0	10193		
B	IDH2	p.(Arg149Trp)	c.445C>T	G	A	missense	7.1	7542	COSM6...	
B	KIT	p.(Ala659Thr)	c.1975G>A	G	A	missense	5.6	12557		
B	KRAS	p.(Glu107Asp)	c.321A>T	T	A	missense	7.7	8734		
B	PIK3CA	p.(Gln79Pro)	c.224A>C	A	C	missense	7.1	6923	COSM6...	
B	PIK3CA	p.(Glu525Gly)	c.1574A>G	A	G	missense	14.3	3843		
C	EGFR	p.(Gln787=)	c.2361G>A	G	A	synonymous	80.0	4473	COSM1...	Benign/Likely benign
C	FGFR3	p.(Thr651=)	c.1953G>A	G	A	synonymous	100.0	18524		
C	AKT1		c.175=18C>T	G	A	intronic	44.4	7223		
C	ALK	p.(Thr1500=)	c.4500C>A	G	T	synonymous	0.6	41432		

In the flagging tab, in order to track the clinical associations* added by a user, the following information is added:

- The user who added the clinical association*
- The time when the clinical association* was added

NOTE: Clinical associations* can be edited if necessary or suppressed if not reported in a patient's* report before.

9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.6 User Clinical Associations*

9.3.6.3 Display of a Clinical Association* in OncoPortal™ Tab

The AMP/ASCO/CAP tier is populated based on the selections made when creating a user-entered association.

The screenshot displays the OncoPortal interface for a clinical association. The top navigation bar shows 'Genetics SA' and 'Solid Tumor Solution by Sophia'. The main content area is divided into several sections:

- Filters:** Includes 'Pathologies' (Patient's diseases), 'Regions of interest' (STS_v1 - regions: 45, ERBB2, HIST1H3B), 'Variants of Interest' (Hide Low Confidence, By Pathogenicity Level), and 'Actionability (vs) Evidence Level' (T4, T3, D, II, 1, 2, 3, 4, 5).
- Clinical Associations:** Shows 10 Clinical Trials. A table lists two actionable variants in two clinical associations:

Variant Details	Molecular profiles Diseases	Actionability Actionability & AMP/ASCO/CAP Tier	Flagging	Molecular Mechanism(s)
HIST1H3B p.(Lys38=) synonymous VF 42.9%	HIST1H3B synonymous	T4	AT	
HIST1H3B c.*10C>T 3'UTR VF 50.0%	HIST1H3B 3'UTR	D	D	

The table includes icons for 'Expand Table' and 'Collapse Table' in the top right corner. The 'Flagging' column contains flags (AT, D) indicating user-entered associations.

Callout 1: The AMP/ASCO/CAP tier is populated based on the selections made when creating a user-entered association.

Callout 2: The AT, CT, D or P flags are an easy way to find user-entered clinical associations*. Variants with a user-entered association have an indicator in the flagging column. Data entered by the user in the actionability* flag is displayed in the table.

Callout 3: Expand Table: Show all clinical associations* included in the selected filter. Collapse Table: Quick overview of the number and type of variants associated with clinical associations*.

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.6 User Clinical Associations*

9.3.6.4 Addition of a User Clinical Association* to Report

The screenshot shows the OncoPortal interface with a list of clinical associations for a TP53 p.(Gly266Val) variant. A modal window titled "Association Details" is open, displaying information for "TP53 predicted mutant (unknown)". The modal includes a "Summary" section with a reference to NCCN.org, a "Variant Description" section, and a "Molecular Mechanisms" section. A red "+" icon is visible in the top right corner of the modal, indicating that the association has been added to the report.

Double-click on the user clinical association* of interest:
All of the information previously provided is displayed. This information are also displayed in the report.

Click on "+" to add the user clinical association* to the report
The grey "+" becomes red "+" once added.

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.7 Clinical Results*

Overview tab
Active

Clinical results*
Active

Number of clinical associations* or variants reported in each category

Click on the clinical results* tab to access clinical associations* and variants reported by the user that will appear in the report:

- Genomic alterations associated to approved therapies in the patient's* disease* (T1, user AT in the patient's* pathology)
- Other potentially actionable genomic alterations (T2, T4, user AT in another pathology, CT, variants flagged 4 and 5)
- Other genomic alterations (variants flagged 3, undefined actionability* (UA))
- Diagnosis* - Prognosis* (D and P)

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.8 Automatically Generated Conclusions (1)

Overview tab
Active

Project tab
Active

The screenshot shows the OncoPortal interface with the 'Project' tab active. The top navigation bar includes 'Overview', 'OncoPortal', and 'Variants'. The main content area is divided into several sections:

- TEST OVERVIEW:** Shows 42 genes, 159 variants, 17 retained, and 142 low confidence variants.
- Patient Information:** Includes 'Interpretation 1' (Draft), 'Virtual Panel: STS_plus_v1 (42 genes)', 'Owner: Admin User', and 'Date created: 06/12/2020'.
- Conclusion:** A large empty text area for the conclusion, with a 'Clinical Results' button at the bottom left.
- Prediction and Pathogenicity:** A circular chart showing 'Prediction' with segments for D: 4, C: 149, B: 4, and A: 2. Below it, 'Pathogenicity Flags' shows 5 flags.
- Actionability:** A circular chart showing 'ACTIONABILITY' with segments for D: 2, P: 2, T4: 6, T3: 1, and T2: 9. Above it, statistics show 15 diseases, 39 drugs, and 123 trials.
- Public Databases:** A list of databases with checkmarks, including ClinVar, COSMIC, dbNSFP, dbSNP, ESP, ExAC, G1000, GSAID EpiCoV, GnomAD, and JAX-CKB.

Click on the clinical results* button in order to generate the automatically generated conclusion.

- All the information previously provided is displayed
- In the next window, click on “Add” to add/replace the automatically generated conclusion
- Information will be added to the report

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9. OncoPortal™

9.3 Actionability* - Diagnosis* - Prognosis*

9.3.8 Automatically Generated Conclusions (2)

Overview tab
Active

Project tab
Active

The screenshot displays the OncoPortal interface with the 'Project' tab selected. The top navigation bar shows 'WORKSPACE', 'VDB', and 'ANALYSIS Sample3 #3-0140'. The main content area is divided into several sections:

- TEST:** Summary statistics including 42 GENES, 159 VARIANTS, 17 RETAINED, 142 LOW CONFIDENCE, 46 VARIANT DEPTHS, 11011 DEPTH MAX, and 1 FUSION.
- Conclusion:** A text area containing three numbered points:
 - Genomic alterations associated to approved therapies in patient's disease: None Reported!
 - Other potentially actionable genomic alterations: > EGFR p.(Thr790Met) exon 20 - this mutation has been associated with sensitive to EGFR Inhibitor (Pan), EGFR Inhibitor 2nd gen, HER Inhibitor (Pan), HER3 Inhibitor in lung non-small cell carcinoma.
 - Other Genomic Alterations: > EGFR p.(Glu746_Ala750del) exon 19 - this mutation has no known effects.
- Pathogenicity Flags:** A circular chart showing 5 flags.
- Actionability:** A circular chart showing 15 DISEASES, 39 DRUGS, and 123 TRIALS.

A 'Save' button is highlighted at the bottom of the conclusion section. The interface also includes a 'Project Settings' panel with 'Delete' and 'Complete' buttons, and a 'Public Databases' panel on the right.

Edit the conclusions and save

Additional information provided by the user will be displayed in the interpretation section of the report.

9. OncoPortal™

9.4 Somatic Report

9.4.1 Creation

The screenshot displays the OncoPortal interface for a project named 'Sample3 #3-0140'. The 'Project Settings' dialog box is open, showing options to 'Delete' or 'Complete' the project. A callout box points to the 'Draft Report' button at the bottom of the interface, stating: 'Click "Draft Report" to create a draft report or "Complete" to a create final report.' Another callout box points to the 'Project Settings' dialog, stating: 'Change selection of included report sections in "Project Settings" (see ch. 4.4.2)'. The interface also shows a 'Conclusion' section with genomic alterations and a 'Clinical Results' section.

NOTE: the language of the conclusion (English or French) can be changed in the application settings. See [chapter 2.5 - Manage Settings](#).

9. OncoPortal™

9.4 Somatic Report

9.4.2 Header

The header contains information about the institute, patient* and analysis information:

- Institute contact information and logo (on request)
- First name, last name, patient* ID, date of birth, gender, pathology
- Analysis ID, MID, request run date, request run name, sequencer

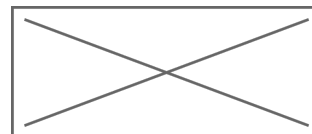
Contact details of the institute

Address, phone number, fax number and any other relevant information. Request to be sent to support@sophiagenetics.com

Institute logo

Request to be sent with a high resolution logo to support@sophiagenetics.com

SOPHiA GENETICS SA
Rue du Centre, 172
1025 Saint-Sulpice, Switzerland



Somatic Variant Report

Patient

First name: Jane
Last name: Jones
Patient ID: SG100001017
DOB: 1971/11/03
Gender: Female
Pathology: Lung Adenocarcinoma

Ordering physician

Name: John
Medical ID: 29938aa
Facility: St John's University Hospital
Facility ID: Medical Facility 1

Specimen

Specimen ID: SP12345688
Date collected: 2020/11/10
Date received: 2020/11/16
Specimen type: FFPE
Tumor cell: 57.0%
Disease status: Initial

Analysis

Analysis ID: 388248
MID: S17
Run date: 2020/09/16
Run name: upload
Sequencer: Illumina MiniSeq

Medical history

49 year old female with new diagnosis of lung adenocarcinoma

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9. OncoPortal™

9.4 Somatic Report

9.4.3 Variant Summary

The Summary of Alterations section contains a list of all reported variants. AMP/ASCO/CAP tier and evidence level are displayed when "Reporting by AMP/ASCO/CAP" setting is selected (see [ch. 4.4.2](#))

SUMMARY OF ALTERATIONS

Gene(s)	Alteration	Supporting values	AMP/ASCO/CAP
<i>BRAF-KDM7A</i>	Gene-fusion	Supporting Unique Molecules 5.95 %	Tier I Therapeutic
<i>EGFR</i>	p.(Leu702.Thr706del) c.2105_2119del	Variant fraction 33.5 %	Tier II, C Therapeutic
<i>EGFR</i>	p.(Thr745Met) c.2234C>T	Variant fraction 36.8 %	Tier II, C Therapeutic
<i>CCND1</i>	Amplification	Copy number 3.4	Tier II, C Therapeutic
<i>COL4A3BP-BRAF</i>	Gene-fusion	Supporting Unique Molecules 24.17 %	No actionability information

9. OncoPortal™

9.4 Somatic Report

9.4.4 Interpretation*

The interpretation section contains the automatically generated conclusion that you can edit before generating the report, as well as two signature fields.

INTERPRETATION

1. Genomic alterations associated to approved therapies in patient's disease:
None Reported!

2. Other potentially actionable genomic alterations:

> EGFR EGFR L858R has long been recognized as a functionally significant mutation in cancer, and is one of the most prevalent single mutations in lung cancer. Best described in non-small cell lung cancer (NSCLC), the mutation seems to confer sensitivity to first and second generation TKI's like gefitinib and neratinib. NSCLC patients with this mutation treated with TKI's show increased overall and progression-free survival, as compared to chemotherapy alone. Third generation TKI's are currently in clinical trials that specifically focus on mutant forms of EGFR, a few of which have shown efficacy in treating patients that failed to respond to earlier generation TKI therapies. - p.(Leu858Arg) EXON 21, this mutation has been associated with Sensitivity to 1st generation EGFR Tyrosine Kinase Inhibitor in Non-small Cell Lung Carcinoma.

> EGFR Deletions within exon 19 of EGFR are most common in lung cancer. These deletions, in non-small cell lung cancer, have been shown to be sensitive to the EGFR tyrosine kinase inhibitors gefitinib, afatinib, and erlotinib. There is also data to suggest that this event is a good prognostic marker in lung adenocarcinoma. - p.(Glu746_Ala750del), this mutation has been associated with Sensitivity to 1st generation EGFR Tyrosine Kinase Inhibitor in Non-small Cell Lung Carcinoma.

> KRAS While the KRAS G12 region is a widely studied recurrent region in cancer, its impact on clinical action is still actively debated. Often associated with tumors that are wild-type for other drivers (EGFR and ALK specifically), the prognosis for patients with this mutation seems to be worse than the KRAS wild-type cohort in patients with colorectal and pancreatic cancer, however this hypothesis is in need of further validation. This mutation, along with the mutations affecting the neighboring G13 position, may result in a less responsive tumor when treated with first-generation TKI's like gefitinib. The NCCN guidelines for colorectal cancer contain recommendations that the targeted therapies cetuximab and panitumumab should only be used in the context of wild type KRAS. However, cetuximab treatment was shown to extend survival in a single cohort of colorectal patients with G12D mutations. Overall, the interpretation for KRAS mutations in most clinical scenarios is still undecided. - p.(Gly12Asp) EXON 2, this mutation has been associated with Resistance or Non-Response to Chemotherapy in Multiple Myeloma.

3. Other Genomic Alterations:

> MET - p.(Leu238Tyrfs*25) EXON 2, this mutation has no known effects.

> TP53 - EXON 6, this mutation has no known effects.

4. Diagnosis - Prognosis:

> IDH1 Coding-synonymous mutation - p.(Gly105=) EXON 4, this mutation has been associated with Likely pathogenic in Leukemia, Myeloid, Acute.

Validated by:

Date:

Signature:

Analysed by: Operator User

Date: 13-02-2018 | 16:17:13

Signature:

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9. OncoPortal™

9.4 Somatic Report

9.4.5 Clinical Results*

The results section contains all the information related to the different clinical associations* and variants reported in the clinical results* tab in SOPHiA DDM™. The most relevant information is included, such as: Gene, NM transcript, variant, protein alteration, depth coverage, variant fraction, available treatment and its effect on the pathology.

CLINICAL RESULTS

Genomic alterations associated to approved therapies in patient's disease

Gene(s) Transcript(s) Exon(s)	Chromosome Positions	Alteration details	Supporting Values	Clinvar	Actionability
<i>MET</i> NM_001127500 14	7 116412045	c.3082+3del	Variant fraction 49.4 % Depth 10733		Treatment Crizotinib (ROS1 Inhibitor , MET Inhibitor , ALK Inhibitor , RON Inhibitor) Effect sensitive Pathology lung non-small cell carcinoma

Other potentially actionable genomic alterations

Gene(s) Transcript(s) Exon(s)	Chromosome Positions	Alteration details	Supporting Values	Clinvar	Actionability or Pathogenicity
<i>IDH1</i> NM_005896 4	2 209113112	c.395G>A p.(Arg132His)	Variant fraction 32.6 % Depth 8369	Pathogenic rs121913500	Treatment Ivosidenib (IDH1 Inhibitor) Effect sensitive Pathology acute myeloid leukemia

Other genomic alterations

Gene(s) Transcript(s) Exon(s)	Chromosome Positions	Alteration details	Supporting Values	Clinvar	Pathogenicity
<i>IDH2</i> NM_002168 4	15 90631837	c.516G>T p.(Arg172Ser)	Variant fraction 49.2 % Depth 11148		Flagged Pathogenicity 3: Uncertain

Diagnosis - Prognosis

Gene(s) Transcript(s) Exon(s)	Chromosome Positions	Alteration details	Supporting Values	Clinvar	Actionability
<i>KRAS</i> NM_004985 3	12 25380278	c.178_180delinsCGC p.(Gly60Arg)	Variant fraction 25.0 % Depth 11005	Pathogenic rs104894359	Type Prognosis Effect not available Pathology lung non-small cell carcinoma

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9. OncoPortal™

9.4 Somatic Report

9.4.6 Variant Description

The section displays the entered variant descriptions for reported variants. Variant descriptions can be entered in the Variant tab as shown in [ch. 4.9.8 Variant Description Tab](#)

VARIANT DESCRIPTION		
Gene(s) Transcript(s) Exon(s)	Alteration details	Description
COL4A3BP - BRAF NM_001130105 - NM_004333 4 - 9	Gene-fusion In-Frame	description of variant

9. OncoPortal™

9.4 Somatic Report

9.4.7 Methodology

The methodology section contains the information related to the application performed, the reference genome used for the analysis, the SOPHiA DDM™ version, the OncoPortal™ version, the specimen type used in the analysis and the version of the algorithm.

METHODOLOGY

SOPHiA application: STS_v2_1 **Reference genome:** GRCh37/hg19 **SOPHiA DDM:** 5.7.11--b260-92bcd0d

JAX-CKB™ version: v20200529

Sample type: FFPE **Pipeline ID / Revision number / Splitting ID:** ILL1XG1S4_FFPE_miniseq / v5.5.26 / GEN1GN1FSQ2

The gene list of the panel of the Virtual Panel is mentioned at the end of the report.

Gene Panel (44)

Version:v1

AKT1 , ALK , BRAF , CDK4 , CDKN2A , CTNNB1 , DDR2 , DICER1 , EGFR , ERBB2 , ERBB4 , ESR1 , EZH2 , FBXW7 , FGFR1 , FGFR2 , FGFR3 , FOXL2 , GNA11 , GNAQ , GNAS , H3F3A , H3F3B , HIST1H3B , HRAS , IDH1 , IDH2 , KIT , KRAS , MAP2K1 , MET , MYOD1 , NRAS , PDGFRA , PIK3CA , PTPN11 , RAC1 , RAF1 , RET , ROS1 , SF3B1 , SMAD4 , TERT , TP53

9. OncoPortal™

9.4 Somatic Report

9.4.8 Annexes (1)

The annexes section contains the options mentioned in [chapter 9.4.1 Creation](#)

ANNEXES

ASSOCIATION DETAILS

Gene(s) Transcript(s) Exon(s)	Alteration details	Summary
<i>MET</i> NM_001127500 14	c.3082+3del	Xalkori (crizotinib) is included in guidelines for non-small cell lung cancer patients with MET exon 14 skipping mutations (NCCN.org). (Approval status: Guideline)
<i>EGFR</i> NM_005228 19	c.2239_2256del p.(Leu747.Ser752del)	In a Phase III trial (RELAY) that supported FDA approval, Cyramza (ramucirumab) in combination with Tarceva (erlotinib) demonstrated improved progression-free survival compared to Tarceva (erlotinib) plus placebo (19.4 vs 12.4 months, HR=0.59, p<0.0001) in patients with advanced non-small cell lung cancer harboring EGFR exon 19 deletion mutations or L858R (PMID: 31591063; NCT02411448). (Approval status: FDA approved)
<i>KRAS</i> NM_004985 3	c.178_180delinsCGC p.(Gly60Arg)	KRAS mutations are associated with shorter survival in patients with non-small cell lung carcinoma (NCCN.org). (Approval status: Guideline)

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9. OncoPortal™

9.4 Somatic Report

9.4.8 Annexes (2)

The annexes section contain the options mentioned in [chapter 9.4.1 Creation](#)

ANNEXES

Somatic screening

RET - NM_020975			
Exon	Codons	Mutation	Depth
Exon 16	Codon 918 , 919	No mutation	127
	Codon NA	No mutation	129
Exon 11	Codon 630 , 632-633 , 666 , 634	No mutation	16692

Low coverage (Threshold: 1000)

Chromosome	Gene	Transcript	Exon	c.DNA	Start	end	Main Coverage
1	NRAS	NM_002524.4	4	c.291-10_450+10	115252180	115252359	213
1	NRAS	NM_002524.4	3	c.112-10_290+10	115256411	115256609	126
1	NRAS	NM_002524.4	2	c.-10_111+10	115258661	115258791	350
1	DDR2	NM_006182.2	17	c.2284-10_2433+10	162748360	162748529	195

SNVs/INDELS (retained)

Gene Transcript	Exon	c.DNA Protein alteration	Variant Fraction Coverage (ref / alt)	Coding consequence	Pathogenicity	ClinVar
ALK NM_004304_4	21	c.3375C>A p.(Gly1125=)	8.8 % (4835 / 466)	synonymous	Prediction C Unknown Significance	
BRAF NM_004333_4	15	c.1799T>A p.(Val600Glu)	10.3 % (5299 / 605)	missense	Prediction A Highly Pathogenic	Pathogenic rs113488022

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9. OncoPortal™

9.5 Guide to Molecular Profile terms (1)

This guide details the matches made between detected alterations in a sample and the category and non-specific variant terms referred to in clinical association* data sources.

Category variants

Category variants are descriptive classes for variants that are similar by either position or function. They can be considered a parent variant to a group of other variants and are used when a type or group of variants is indicated in published research or guidelines, but the specific variant is not.

- **act mut:** variant results in a gain of function in the protein. Applied to:
 - SNVs/INDELs with gain of function (GOF) annotation in an oncogene (based on JAX-CKB™ annotations)
 - gene amplification in an oncogene
 - GOF gene fusions and exon skipping variants
- **del exonX:** deletion of the entirety of the specified exon e.g., *MET* del exon14. Applied to predicted splice site variants.
- **exonX:** unspecified mutation in the exon e.g., *KRAS* exon2. This term is applied to missense, indel, nonsense, or frameshift variants of clinical interest. Clinical interest is ascertained using variant gain of function (GOF) or loss of function (LOF) annotation (in JAX-CKB™), oncogene or tumor suppressor status of the impacted gene (JAX-CKB™ annotation), and protein consequence.
- **exon X del/ins:** unspecified deletion or insertion within the exon e.g., *EGFR* exon 19 del
- **fusion:** a fusion of the gene, but the fusion partner is not specified.
- **inact mut:** variant results in a loss of function of the protein
- **mutant:** unspecified mutation in the gene, including missense, indel, nonsense, frameshift, gene fusion or CNV of clinical interest. Clinical interest is ascertained using variant gain of function (GOF) or loss of function (LOF) annotation (in JAX-CKB™), the role of the gene in oncogenesis (tumor suppressor or oncogene; JAX-xv annotation), and SOPHiA DDM™ prediction.
- **rearrange:** any CNV, fusion, or exon skipping event showing clinical importance based on impact annotations (loss of function inactivating mutations or gain of function activating mutations).

9. OncoPortal™

9.5 Guide to Molecular Profile terms (2)

Non-specific variants

Non-specific variants are variants that are not attributed to a specific genetic change and are not considered categories.

- **amp:** refers to increased number of copies of the gene and is used when a gene is located in a CNV with increased copy number
- **del:** refers to deletion of the gene and is used when a gene is located in a deleted region (CNV with copy number = 0)
- **loss:** refers to loss of the gene, mRNA, and protein and is used when a gene is located in a deleted region (CNV with copy number = 0)
- **over exp:** refers to overexpression of the mRNA and/or protein and is used when a gene is located in a CNV showing increased copy number. At least 80% of the gene must be in the CNV region in order for the term to be match to be made.

Predicted Molecular Profile matches

Predicted Molecular Profiles are matched using predictions generated by either SOPHiA DDM™ or an external data source. Molecular Profiles that are not predicted are based on empirical evidence, as determined by external data sources.

When applied to gene amplification or deletion, “predicted” means that only part of the gene (>80%) is within the borders of the detected CNV event, due to coverage limitations.

9. OncoPortal™

9.5 Guide to Molecular Profile terms (3)

“Molecular profiles”
The column displaying the molecular profiles and linked diseases

The screenshot shows the OncoPortal interface with a table of variant details. The table has the following columns: Clinical Association, Molecular profiles Diseases, Actionability & AMP/ASCO/CAP Tier, Flagging, and Molecular Mechanism(s). The 'Clinical Association' column contains variant details like 'EGFR 1790M' and 'RBB2 p.(Pro1140A) missense'. The 'Molecular profiles Diseases' column lists diseases such as 'lung non-small cell carcinoma'. The 'Actionability' column shows tiers like 'I, A' and 'II, C'. The 'Molecular Mechanism(s)' column lists mechanisms like 'EGFR Inhibitor 3rd gen'.

Clinical Association
Light box of the variant indicates that matching is done by prediction

Clinical Association
Dark blue box of the variant indicates that the matching is supported by published evidence

10. Variant Database Browser

10.1 Overview

Variant Database Browser

Search tab
Query the whole database of account variants (retained and low confidence) of germline and somatic applications.

Export tab
Export account variants based on pre-defined queries.

Warning:
Only the first 500 variants are displayed.
Please use the filters at your disposal to refine your search.

SOPHiA GENETICS | 5.10.16-

10. Variant Database Browser

10.2 Variant Search (1)

The screenshot shows the SOPHiA Variant Database Browser interface. The top navigation bar includes 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The main search area has fields for 'Chromosome', 'Position', 'Gene', 'Transcript', 'cDNA', and 'Protein', along with checkboxes for 'Flagged' and 'Reported'. A 'Search' button is on the left, and 'Clear filters' and 'Load all' buttons are on the right. The results table displays columns for 'Chromosome', 'Position', 'Gene', 'Transcript', 'cDNA', 'Protein', 'Pathogenicity', and 'Frequency'. A warning message at the bottom states: 'Warning: Only the first 500 variants are displayed. Please use the filters at your disposal to refine your search.' A 'Refresh' button is located in the bottom right corner.

Search tab

Click to “Load all” variants

Filter variants for chromosome number & genomic position

Search for transcript, specific positions in cDNA or protein annotations e.g. “4327” for variant c.4327C>T

Search for variants with pathogenicity or “in-report” flags

Click to remove filters applied

Sub-string search for gene name (case-insensitive) e.g. “brca” for BRCA1

The first 500 variants are displayed after a filter has been applied.

Use mouse to scroll the list and load more variants

- Apply one or several filters to search your account’s variant database:
 - by chromosome number, genomic position, gene name, cDNA or protein annotation
 - Select checkbox to restrict to “reported” or “flagged” variants
- Press Enter or click “Search”
- A notification informs the user once variants are loaded
- Click “Clear filters” to remove all filters

Use mouse to scroll the list and load more variants

10. Variant Database Browser

10.2 Variant Search (2)

Drag and drop the columns of the variant table to change the order

Detailed information for the variant:

- Transcript versions (RefSeq) with cDNA & protein annotation
- Coding consequence
- Pathogenicity flag of the account (if flagged)
- Pathogenicity flagging distribution of the community

The screenshot shows the Variant Database Browser interface. At the top, there are tabs for 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The main area contains a search bar and a table of variants. A dashed box highlights a row for a BRCA2 variant, with arrows pointing to callouts that describe the detailed information available for that variant. Another callout points to the table headers, indicating that columns can be dragged and dropped to change their order. A third callout points to a single row in the table, stating 'One row per variant'. At the bottom left, a warning message states: 'Warning: Only the first 500 variants are displayed. Please use the filters at your disposal to refine your search.'

Chr	Position	REF ALT	Type	Pathogenicity		Gene	Transcript	CDNA	Protein	Exon	Consequence	Frequency	
				Germ.	Soma.							Germ.	Soma.
17	41209018	A G	SNP			BRCA1	NM_007294	c.5277+51T>C		19	intronic	N/A	N/A
13	32936646	T C	SNP	4	1	BRCA2	NM_000059	c.7806-14T>C		17	intronic	N/A	N/A
13	32915410	CAATT C	INDEL			BRCA2	NM_000059	c.6841+80_6841+8		11	intronic	N/A	N/A
7	117176568	AGATT A	INDEL			CFTR	NM_000492	c.744-9_744-6delC		7	intronic	N/A	N/A
17	41251931	G A	SNP			BRCA1	NM_007294	c.442-34C>T		7	intronic	N/A	N/A
13	32953388	T C	SNP			BRCA2	NM_000059	c.8755-66T>C		22	intronic	N/A	N/A
13	32929387	T C	SNP			BRCA2	NM_000059	c.7397T>C	p.Val2466Ala	14	missense	N/A	N/A
7	117175189	G T	SNP			CFTR	NM_000492	c.580-113G>T		6	intronic	N/A	N/A
13	32906729	A C	SNP			BRCA2	NM_000059	c.1114A>C	p.Asn372His	10	missense	N/A	N/A
13	32928936	A G	SNP			BRCA2	NM_000059	c.7008-62A>G		14	intronic	N/A	N/A
17	41242938	GCA G	INDEL			BRCA1	NM_007294	c.4185+21_4185+2		11	intronic	N/A	N/A

Access to analyses (of this account) in which the variant has been found

NOTE: Display of variants annotated in or lifted-over to the hg38 reference genome are not in scope of the Variant Database Browser search.

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10. Variant Database Browser

10.3 Open Variant / Analysis

Click the  button to access the analysis/es in which a variant was found in this account.

Analysis	Patient	Transcript	cDNA	Consequence	V Fraction	Depth
200035999	399	NM_000492	c.1521_1523delCTT	Inframe_3	33.59 %	2950
200029436	398	NM_000492	c.1521_1523delCTT	Inframe_3	50.38 %	395
200035998	397	NM_000492	c.1521_1523del...	Inframe_3	50.85 %	1294
200036003	396	NM_000492	c.1521_1523delCTT	Inframe_3	40.28 %	3121
200035997	295	NM_000492	c.1521_1523delCTT	Inframe_3	50.38 %	395
200029434	293	NM_000492	c.1521_1523delCTT	Inframe_3	52.14 %	3228
200029442	291	NM_000492	c.1521_1523delCTT	Inframe_3	40.28 %	3121
200035996	290	NM_000492	c.1521_1523delCTT	Inframe_3	52.92 %	359
200035995	289	NM_000492	c.1521_1523delCTT	Inframe_3	52.83 %	318
200029440	288	NM_000492	c.1521_1523delCTT	Inframe_3	52.83 %	318
200036033	287	NM_000492	c.1521_1523delCTT	Inframe_3	52.83 %	318

List of analyses in which the selected variant was found. To open a certain analysis, click the eye button next to the analysis number.

Read depth and variant fraction of the selected variant.

Database pathogenicity information (see [chapter 4.9 - SNVs/Indels](#)).

10. Variant Database Browser

10.4 Export variants

10.4.1 Overview (1)

Variant export types

The Variant Database Export functionality allows the user to export account variants (SNVs and Indels) with 3 pre-defined query options:

1. All account variants linked to analyses that were run within the timeframe of 1 year. The export includes a list of most important attributes for each variant but no user annotations (flags or comments).
2. All account variants with a pathogenicity flag (incl. user comments).
3. All account variants with an in-report flag (incl. user comments).

The export of Variant Database Browser “search” results, as well as any alteration or combination of above listed query options, is not in scope of the functionality. For out-of-scope export requests, a chargeable custom export can be offered. Please contact support@sophiagenetics.com or your local sales representative.

Export file format

Once an export query has finished, results are available for download in compressed, tab-separated values format (*.tsv.gz) for all internal users of an account.

Depending on the operating system and user settings, decompression of the output files might happen automatically after download (e.g., Archive Utility tool on MacOS). Alternatively, publicly available software tools to decompress the files can be used.

Decompressed *.tsv files may be imported to spreadsheet tools for tabular format display or opened with a text editor.

NOTE: The output files of all 3 queries contain dates information. Date formats are auto-formatted by some spreadsheet tools. To bypass auto-formatting and view full date/time information, use a text editor to open the file.

10. Variant Database Browser

10.4 Export variants

10.4.1 Overview (2)

The screenshot shows the 'Export' tab in the Variant Database Browser. The interface includes a search bar, a 'Refresh' button, and a 'New export request' button. A table titled 'History of export requests' displays the following data:

Request ID	Time of request	User	Variant export type	Status	Download
1	18/03/2022 13:18	NonFlagger User	All	Finished	
2	18/03/2022 13:19	NonFlagger User	Pathogenicity flag	Finished	
3	18/03/2022 13:20	NonFlagger User	In-report flag	Finished	
4	18/03/2022 15:49	Admin User	All	Finished	
5	18/03/2022 15:53	Admin User	All	Finished	
6	18/03/2022 15:55	Admin User	Pathogenicity flag	Finished	
7	18/03/2022 15:55	Admin User	In-report flag	Finished	
8	18/03/2022 15:56	Admin User	In-report flag	Finished	
9	18/03/2022 15:57	Admin User	All	Finished	
10	18/03/2022 15:58	Admin User	All	Finished	
11	18/03/2022 15:58	Admin User	In-report flag	Finished	

Below the table, there is an 'Important notice' section with the following text:

The VDB Export tool allows the export of account-variants with the following conditions:

- Any internal account user can initiate an export request and can select between the following options:
 - all account-variants (without flagging information or comments)
 - variants for which a pathogenicity flag has been added (including user comments)
 - variants for which an in-report flag has been added (including user comments)
- The timeframe for an export of "all account-variants" is limited to 1 year and/or 1000 analyses, whichever criteria is met first. If a query would exceed 1000 analyses, the selected timeframe of the query will need to be shortened by the user.
- The number of export requests that can be initiated per account is not limited.
- Export requests are queued and addressed by the order of reception so that similar requests can take different amount of time depending on the current server load.
- Once an export query has finished, results are available for download in *.tsv format for all users of an account.

For export requests not covered by the scope of this functionality, a charged custom export can be offered. Please contact support@sophiagenetics.com or your local sales representative.

- View export requests created in the account, including:
 - Request ID
 - Date and time of the request
 - Name of the user who created the request
 - Type of the request (all variants, variants with pathogenicity or in-report flag)
 - Status of the request (submitted, finished, failed)
- Download finished export request output files in compressed *.tsv format

NOTE: The creation of export requests and the download of output files is restricted to internal users. For external account users, the "History of export requests" table is read-only. In case of failed export requests, please contact support and provide the dg.log file.

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10. Variant Database Browser

10.4 Export variants

10.4.1 Create request - all variants (1)

The screenshot shows the SOPHiA DDM Variant Database Browser interface. The top navigation bar includes 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The main content area has 'Search' and 'Export' tabs. A 'History of export requests' table is visible. A 'New request' dialog box is open, prompting the user to select variants to export and a timeframe. The dialog includes radio buttons for 'All account variants (no user flags and comments)', 'Variants with a pathogenicity flag', and 'Variants with an in-report flag'. It also has date pickers for 'Start date' (18/03/2021) and 'End date' (18/03/2022 (Today)). A callout box highlights the text 'Variants linked to 28 analyses included in your request.' Below the dialog, an 'Important notice' section provides details about the export tool's conditions.

Export query launch menu

Initiate new export request

New request

Please select which variants to export

- All account variants (no user flags and comments)
- Variants with a pathogenicity flag
- Variants with an in-report flag

Please select the timeframe

Start date: 18/03/2021 End date: 18/03/2022 (Today)

Variants linked to 28 analyses included in your request.

Cancel Submit

Important notice

The VDB Export tool allows the export of account variants with the following conditions:

- Any internal account user can initiate an export request and can select between the following options:
 - all account variants (without flagging information or comments)
 - variants for which a pathogenicity flag has been added (including user comments)
 - variants for which an in-report flag has been added (including user comments)
- The timeframe for an export of "all account variants" is limited to 1 year and/or 1000 analyses, whichever criteria is met first. If a query would exceed 1000 analyses, the selected timeframe of the query will need to be shortened by the user.
- The number of export requests that can be initiated per account is not limited.
- Export requests are queued and addressed by the order of reception so that similar requests can take different amount of time depending on the current server load.
- Once an export query has finished, results are available for download in *.tsv format for all users of an account.

For export requests not covered by the scope of this functionality, a charged custom export can be offered. Please contact support@sophiagenetics.com or your local sales representative.

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Number of analyses linked to the variants included in the "all account variants" export query based on the timeframe selection.

NOTE: The export of "all account variants" does not include user annotations (flags or comments) and is restricted to 1 year and / or 1000 analyses. If exceeded, the timeframe selection must be reduced before the query can be submitted. Several requests with different timeframe selections can be submitted.

10. Variant Database Browser

10.4 Export variants

10.4.1 Create request - all variants (2)

Export query launch menu

The screenshot shows the SOPHiA DDM Variant Database Browser interface. The top navigation bar includes 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The user is logged in as 'Sophia Genetics SA (Test)'. The 'Export' menu is active, and a 'New request' dialog box is open. The dialog box prompts the user to 'Please select which variants to export' and 'Please select the timeframe'. The 'All account variants (no user flags and comments)' option is selected. The timeframe is set from '18/03/2022 (Today)' to '18/03/2022 (Today)'. A red error message states: 'Your current request includes no variants and analyses. To proceed, please change the timeframe selection.' The dialog box has 'Cancel' and 'Submit' buttons. Below the dialog box, an 'Important notice' section provides details about the VDB Export tool's conditions.

Important notice

The VDB Export tool allows the export of account variants with the following conditions:

- Any internal account user can initiate an export request and can select between the following options:
 - all account variants (without flagging information or comments)
 - variants for which a pathogenicity flag has been added (including user comments)
 - variants for which an in-report flag has been added (including user comments)
- The timeframe for an export of "all account variants" is limited to 1 year and/or 1000 analyses, whichever criteria is met first. If a query would exceed 1000 analyses, the selected timeframe of the query will need to be shortened by the user.
- The number of export requests that can be initiated per account is not limited.
- Export requests are queued and addressed by the order of reception so that similar requests can take different amount of time depending on the current server load.
- Once an export query has finished, results are available for download in *.tsv format for all users of an account.

For export requests not covered by the scope of this functionality, a charged custom export can be offered. Please contact support@sophiagenetics.com or your local sales representative.

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If 0 or >1000 analyses would be included in an export request, the timeframe selection needs to be adapted to proceed with the submission of the query.

NOTE: The analysis date corresponds to the date when the bioinformatic pipeline for a specific sample started. The maximum selectable timeframe corresponds to a start/end analysis date and the same day one year later/earlier, but not 365 days.

10. Variant Database Browser

10.4 Export variants

10.4.1 Create request - all variants (3)

Click ⓘ button to see selected start and end dates of “all account variants” export queries.

Click to see the updated status of a request.

History of export requests

Request ID	Time of request	User		Status	Download
1	18/03/2022 13:18	NonFlagger User	All ⓘ	Submitted	

Selected start date: 18/03/2021
Selected end date: 18/03/2022

Refresh New export request

Important notice

The VDB Export tool allows the export of account variants with the following conditions:

- Any internal account user can initiate an export request and can select between the following options:
 - all account variants (without flagging information or comments)
 - variants for which a pathogenicity flag has been added (including user comments)
 - variants for which an in-report flag has been added (including user comments)
- The timeframe for an export of “all account variants” is limited to 1 year and/or 1000 analyses, whichever criteria is met first. If a query would exceed 1000 analyses, the selected timeframe of the query will need to be shortened by the user.
- The number of export requests that can be initiated per account is not limited.
- Export requests are queued and addressed by the order of reception so that similar requests can take different amount of time depending on the current server load.
- Once an export query has finished, results are available for download in *.tsv format for all users of an account.

For export requests not covered by the scope of this functionality, a charged custom export can be offered. Please contact support@sophiagenetics.com or your local sales representative.

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Submitted requests appear in the “History of export requests” table. The compressed *.tsv output file becomes available for download once the query has finished.

NOTE: Use the “refresh” button to see status updates of submitted requests or requests submitted by other internal account users in the meantime. The table is auto-refreshed by the system if the user leaves and returns to the Export tab.

10. Variant Database Browser

10.4 Export variants

10.4.2 Create request - pathogenicity flagged variants

The screenshot shows the SOPHiA DDM Variant Database Browser interface. At the top, there are tabs for 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The user is logged in as 'Sophia Genetics SA (Test)'. A 'New export request' button is visible in the top right. A 'New request' dialog box is open in the center, with the following options:

- All account variants (no user flags and comments)
- Variants with a pathogenicity flag
- Variants with an in-report flag

The 'Submit' button is highlighted with a red arrow. Below the dialog box, there is an 'Important notice' section with the following text:

The VDB Export tool allows the export of account variants with the following conditions:

- Any internal account user can initiate an export request and can select between the following options:
 - all account variants (without flagging information or comments)
 - variants for which a pathogenicity flag has been added (including user comments)
 - variants for which an in-report flag has been added (including user comments)
- The timeframe for an export of "all account variants" is limited to 1 year and/or 1000 analyses, whichever criteria is met first. If a query would exceed 1000 analyses, the selected timeframe of the query will need to be shortened by the user.
- The number of export requests that can be initiated per account is not limited.
- Export requests are queued and addressed by the order of reception so that similar requests can take different amount of time depending on the current server load.
- Once an export query has finished, results are available for download in *.tsv format for all users of an account.

For export requests not covered by the scope of this functionality, a charged custom export can be offered. Please contact support@sophiagenetics.com or your local sales representative.

All variants with a pathogenicity annotation (flag and comment) are included in the export without any timeframe or analyses number restriction.

NOTE: The output file is provided in compressed, tab-separated values format. The use of tab separations in comments for pathogenicity flags can impact the display in tabular format if the *.tsv file is imported to a spreadsheet tool.

10. Variant Database Browser

10.4 Export variants

10.4.3 Create request - in-report flagged variants

The screenshot shows the SOPHiA DDM Variant Database Browser interface. At the top, there are tabs for 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The user is logged in as 'Sophia Genetics SA (Test)'. There are navigation icons for 'Requests', a search icon, a help icon, a user profile icon, and a power icon. Below the navigation bar, there are 'Search' and 'Export' buttons. A 'History of export requests' table is visible on the left, with columns for 'Request ID', 'Time of request', 'Status', and 'Download'. A 'New request' dialog box is open in the center, with the following options:

- All account variants (no user flags and comments)
- Variants with a pathogenicity flag
- Variants with an in-report flag

The 'Submit' button in the dialog box is highlighted with a dashed box. Arrows point from text boxes above to the 'Export query launch menu' and 'Initiate new export request' buttons. Below the dialog box, there is an 'Important notice' section with the following text:

The VDB Export tool allows the export of account variants with the following conditions:

- Any internal account user can initiate an export request and can select between the following options:
 - all account variants (without flagging information or comments)
 - variants for which a pathogenicity flag has been added (including user comments)
 - variants for which an in-report flag has been added (including user comments)
- The timeframe for an export of "all account variants" is limited to 1 year and/or 1000 analyses, whichever criteria is met first. If a query would exceed 1000 analyses, the selected timeframe of the query will need to be shortened by the user.
- The number of export requests that can be initiated per account is not limited.
- Export requests are queued and addressed by the order of reception so that similar requests can take different amount of time depending on the current server load.
- Once an export query has finished, results are available for download in *.tsv format for all users of an account.

For export requests not covered by the scope of this functionality, a charged custom export can be offered. Please contact support@sophiagenetics.com or your local sales representative.

The footer of the interface shows 'SOPHiA GENETICS | 5.10.16-'.

All variants with an in-report flag (including the user comment) are included in the export query without any timeframe or analyses number limitation.

NOTE: The output file is provided in compressed, tab-separated values format. The use of tab separations in comments for in-report flags can impact the display in tabular format if the *.tsv file is imported to a spreadsheet tool.

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10. Variant Database Browser

10.4 Export variants

10.4.4 Export queries (1)

1) “All account variants” export query output

Column header	Description	Example
SampleID	User sample reference	Sample4
AnalysisID	Unique analysis ID	200036217
PatientID	SOPHiA DDM™ patient ID*	200021212
GenePanelName	Name of the gene panel in which the variant was called	CMYS_v3
AnalysisDateTime	Date and time when the pipeline started (yyyy-mm-dd hh:mm:ss)	2021-07-13 15:00:00
ExperimentType	Experiment type in which the variant was called	somatic
VariantID	Unique variant identifier that can be used to join output files from different variant export types	6446
VariantType	SNP or INDEL (variant type as defined in the full variant table)	SNP
ReferenceGenome	Reference genome used by the pipeline version at the time the variant was called	GRCh37/hg19
Depth	Variant depth	343
VariantFraction	Percent variant fraction	100
Chromosome	Chromosome number	10
GenomePosition	Genomic position of the variant	27389197
ref	Reference sequence	T
alt	Alteration sequence	C
Gene	Gene name	ANKRD26
TranscriptName	Transcript name	NM_014915
TranscriptVersion	Transcript version (it can be empty for older analyses)	2
cDNA	cDNA annotation of the variant	c.59A>G
Protein	Protein annotation of the variant	p.(Gln20Arg)
CodingConsequence	Coding consequence (exonic variants) or location (non-exonic variants)	missense
PredictionCategory	A/B/C/D pre-classification	D
Filter	Retained (.) or low confidence variant (explanation)	.
dbSnplD	ID of the variant in dbSNP	rs7897309
ClinVarID	ClinVar variation ID (for older analyses dbSNP ID)	260472

The export file

- Includes low confidence and retained variants (SNVs / Indels) detected in the account within the specified time range (of max. 1 year and in a maximum of 1000 analyses), one line per sample and variant
- Is sorted by SOPHiA DDM™ patient ID*, then Analysis ID

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10. Variant Database Browser

10.4 Export variants

10.4.4 Export queries (2)

2) “Pathogenicity flagged variants” export query output

Column header	Description	Example
VariantID	Unique variant identifier that can be used to join output files from different variant export types	6446
ReferenceGenome	Reference genome used by the pipeline version at the time the variant was called	GRCh37/hg19
Gene	Gene name	BRCA2
Chromosome	Chromosome number	13
GenomePosition	Genomic position of the variant	32936646
VariantType	SNP or INDEL (values as defined in the full variant table)	SNP
ref	Reference sequence	T
alt	Alteration sequence	C
TranscriptName	Transcript name	NM_000059
TranscriptVersion	Transcript version (it can be empty for older analyses)	3
cDNA	cDNA annotation of the variant	c.7806-14T>C
Protein	Protein annotation of the variant	
CodingConsequence	Coding consequence (exonic variants) or location	intronic
ExperimentType	Experiment type in which the variant was called	somatic
PathoFlagLevel	Most recent pathogenicity flag level (1-5)	1
PathoComment	Pathogenicity flag comment	
FlagDateTime	Date and time when the variant was flagged or updated (yyyy-mm-dd hh:mm:ss)	2021-07-13 15:00:00
FlagUserID	User ID who added the pathogenicity flag	65093

The export file

- includes low confidence and retained variants (SNVs / Indels) with a germline or somatic pathogenicity flag or both
- lists the annotation information (transcript, gene name, protein, coding consequence etc.) of the most recent analysis
- lists the latest pathogenicity flag information (level, user, date, comment) but not the history (e.g., flag level/comment change, removed flags)
- displays one row per sample and experiment type
- is sorted by Variant ID, then Gene

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10. Variant Database Browser

10.4 Export variants

10.4.4 Export queries (3)

3) “In-report flagged variants” export query output

Column header	Description	Example
VariantID	Unique variant identifier that can be used to join output files from different variant export types	364
AnalysisID	Unique analysis ID	200036183
SampleID	User sample reference	Sample4
PatientID*	SOPHiA DDM™ patient ID*	200054321
AnalysisDateTime	Date and time when the pipeline started (yyyy-mm-dd hh:mm:ss)	2021-07-13 15:00:00
GenePanelID	Gene panel ID	400002085
GenePanelName	Name of the gene panel in which the variant was flagged	HCS_v1_1
InterpretationName	Interpretation project name in which this variant was added to report	Interpretation1
Gene	Gene name	ABRAXAS1
AccountID	ID of the account	20695
ReferenceGenome	Reference genome used by the pipeline version at the time the variant was called	GRCh37/hg19
Chromosome	Chromosome number	4
GenomePosition	Genomic position of the variant	84383810
VariantType	SNP or INDEL (values as defined in the full variant table)	SNP
ref	Reference sequence	C
alt	Alteration sequence	T
TranscriptName	Transcript name	NM_139076
TranscriptVersion	Transcript version (it can be empty for older analyses)	2
cDNA	cDNA annotation of the variant	c.1042G>A
Protein	Protein annotation of the variant	p.(Ala348Thr)
CodingConsequence	Coding consequence (exonic variants) or location	missense
ExperimentType	Experiment type in which the variant was called	germline
FlagDateTime	Date and time when the variant was flagged or updated (yyyy-mm-dd hh:mm:ss)	2021-07-13 15:00:00
ReportingComment	Comment added when a variant is flagged to report; per sample and interpretation project for a specific variant	comment1
FlagUserID	User ID who added the in-report flag	66238

The export file

- includes low confidence and retained variants (SNVs / Indels) with an in-report flag
- displays one row per variant, sample and interpretation project
- is sorted by variant ID, then sample ID, then interpretation project name

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11. Replicate Analysis

This section will guide the user through the use of replicates in ctDNA samples. It will only show the steps that are unique to the replicate analysis. Please check the full single analysis guide for details on the entire workflow.

11. Replicate Analysis

11.1 Create a New Request (1)

“Create New Batch Request”

Creates a new run request for one or multiple sequencing files

- Choose a reference name for your request
- Select sequencer
- Choose files to upload
- Click “Yes” to upload all files of a directory or “No” to upload single files
- Number of samples will be detected automatically
- Click “Next”

Note: Replicates are only recognized automatically when using a sequential numbering tag after the sample name (-n) and is only available for certain workflows. The sample name needs to be the same in all replicates (e.g. Q5-2ng-1_S47_L001_R1_001.fastq, Q5-2ng-2_S47_L001_R1_001.fastq...).

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11. Replicate Analysis

11.1 Create a New Request (2)

“MID” and “Sample ID”
Index used for sample identification & sample ref defined in sample sheet

“Group ID”
Replicates are marked by the same name

“Patient*”
By default, the same as the replicate ID

“Group analysis”
Uncheck if single sample analysis is needed

The screenshot shows the 'Sample Sheet' dialog box with the following table:

Sample ID MID	Group ID	Patient	Sample Type	Experiment Type	KIT
1 Q5-2ng-1 S47	Q5-2ng	Q5-2ng	ctDNA	somatic	Accel-Amplicon 56G Oncology Panel ctDNA
2 Q5-2ng-2 S48	Q5-2ng	Q5-2ng	ctDNA	somatic	Accel-Amplicon 56G Oncology Panel ctDNA
3 Q5-5ng S49	Q5-5ng	Q5-5ng	ctDNA	somatic	Accel-Amplicon 56G Oncology Panel ctDNA

“Sample type”
Sample material used

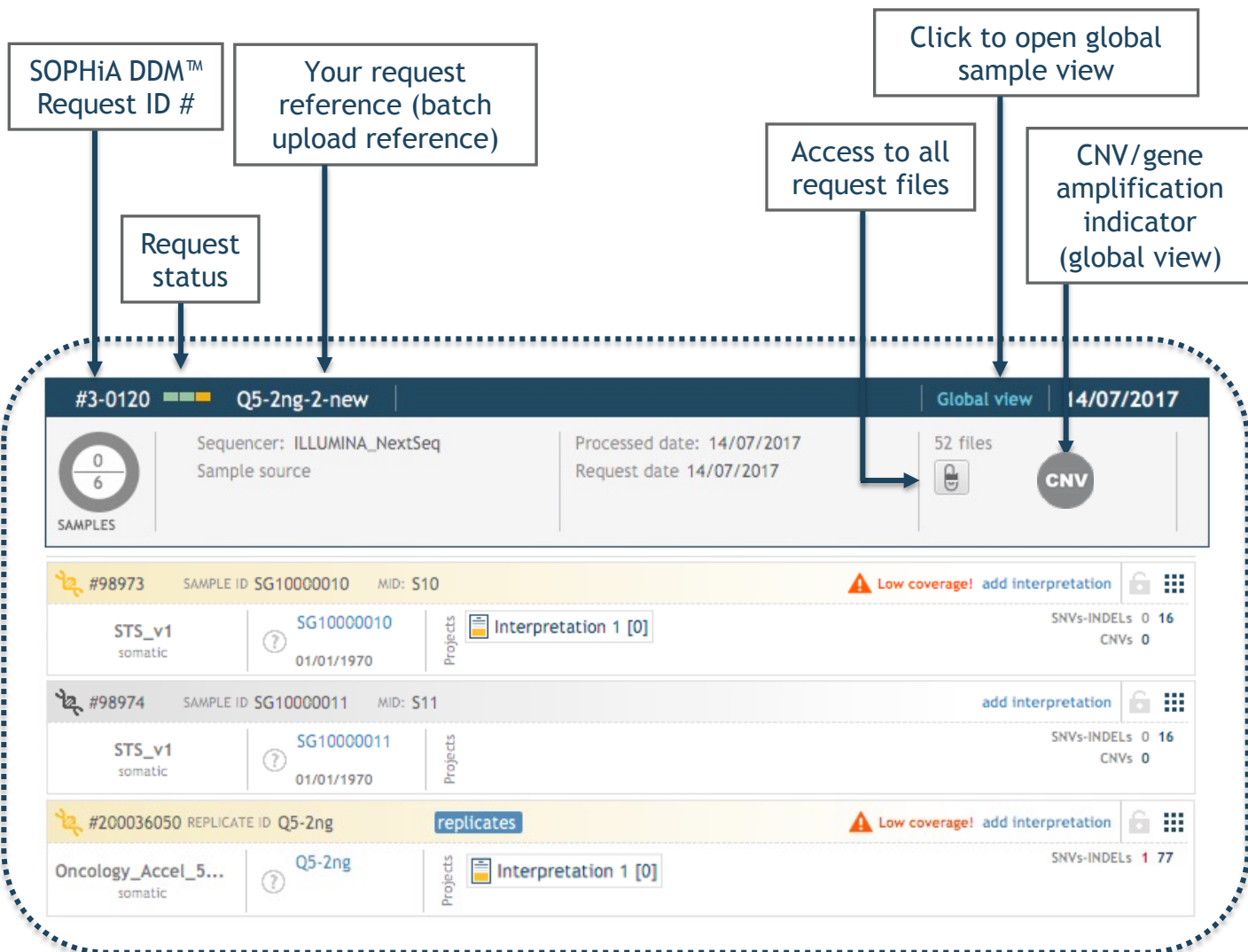
“Experiment type”
Recognized automatically

Note: To proceed with a replicate analysis kit, experiment type and sample type need to be identical for replicate group.

11. Replicate Analysis

11.2 Analysis Card Overview

Request card summary



#3-0120	Q5-2ng-2-new	Global view	14/07/2017
0/6 SAMPLES	Sequencer: ILLUMINA_NextSeq Sample source	Processed date: 14/07/2017 Request date 14/07/2017	52 files CNV
#98973	SAMPLE ID SG10000010 MID: S10	Low coverage! add interpretation	SNVs-INDELS 0 16 CNVs 0
STS_v1 somatic	SG10000010 01/01/1970	Projects Interpretation 1 [0]	
#98974	SAMPLE ID SG10000011 MID: S11	add interpretation	SNVs-INDELS 0 16 CNVs 0
STS_v1 somatic	SG10000011 01/01/1970	Projects	
#200036050	REPLICATE ID Q5-2ng	replicates	Low coverage! add interpretation
Oncology_Accel_5... somatic	Q5-2ng	Projects Interpretation 1 [0]	SNVs-INDELS 1 77

Indicators



CNV is present BUT has not been seen in a project OR no CNV is present



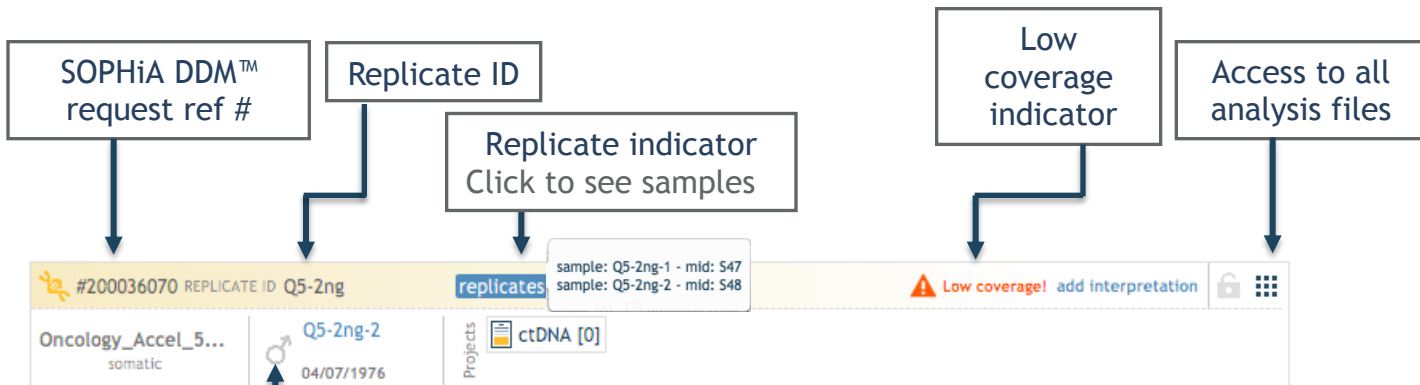
At least one CNV is present AND it has been seen in a project



Replicates have been detected for this analysis

11. Replicate Analysis

11.3 Analysis Card Details



Patient* Details

- Patient* ID
- patient's* gender (unknown - / female ♀ / male ♂)
- patient's* date of birth

Note: To edit patient* details, click the patient* ID. For more information on the “patient* details” view, see [chapter 2.4 - Create a New Patient* File](#).

11. Replicate Analysis

11.4 Global Sample View Hotspots

The global view lets the user quickly screen hotspots and variants for all samples in a run. Variants are represented in a “unified” view which also gives details on very low variant fractions. The global view can be accessed from the analysis card (see [p. 214](#))

“Hotspots”
Active tab

“Filters”
Allows users to filter for coverage, samples, genes and coding consequences

“Filter indicators”
Shows the outcome of applied filters

“Download files”
Text files for hotspots, variants and coverage can be downloaded

Note: If “NA” (Not Available) is shown across samples in a row, no variant was detected in any of the samples.

Indicates that a variant in the replicate group is **present** or **undetermined**

<ul style="list-style-type: none"> ● Variant is <i>present</i> in at least one of the samples ● Variant is <i>undetermined</i> in at least one of the samples ● Variant is <i>absent</i> (wild type) in at least one of the samples 	<p>Coverage Indicators (variable)</p> <p><500 </p> <p><1000 </p> <p><2500 </p> <p>>2500 </p>
---	---

11. Replicate Analysis

11.5 Global Sample View Variants

▶ “Hotspot link”
Variant present in hotspot screen

“Variants”
Active tab

WORKSPACE Requests VDB Variant Database Browser GLOBAL #3-0120 samples:6 Sophia Genetics SA

Filters - 35-2n -2-new, Request: 3-0120, 14/07/2017 No active filters

Hotspots	Variants	Coverage	Coverage plot	Chromosome Genome pos.	Gene Transcript [Exon rank]	Ref Alt	c.DNA Protein	Coding consequence	ClinVar rating	Cosmic Coding	n-392		n-467		Q
											1	2	1	2	
	chr 12 25398285			chr 12 25398285	KRAS NM_004985 [2]	ref C alt G	c.34G>C p.Gly12Arg	missense	Pathogenic	COSM518	0.09%	0.0%	0.0%	0.0%	1.75%
	chr 12 25398284			chr 12 25398284	KRAS NM_004985 [2]	ref C alt A	c.35G>T p.Gly12Val	missense	Pathogenic	COSM520	0.0%	0.06%	0.07%	0.0%	1.54%
	chr 12 25398284			chr 12 25398284	KRAS NM_004985 [2]	ref C alt G	c.35G>C p.Gly12Ala	missense	Pathogenic	COSM522	0.09%	0.0%	0.0%	0.0%	3.65%
	chr 12 25398281			chr 12 25398281	KRAS NM_004985	ref C alt T	c.38G>A p.Gly13Asp	missense	Pathogenic	COSM532	0.17%	0.0%	0.0%	0.15%	25.53%
	Hotspots				KRAS_p.Gln61Leu_c.182A>T		c.182A>T p.Gln61Leu	missense	Pathogenic, Likely patho...	COSM553	0.06%	0.05%	0.12%	0.0%	0.98%
	chr 11 108236137			chr 11 108236137	ATM NM_000051 [63]	ref G alt T	c.9073G>T p.Val3025Leu	missense			0.0%	0.03%	0.0%	0.83%	0.02%
	chr 11 108236083			chr 11 108236083	ATM NM_000051 [63]	ref G alt T	c.9019G>T p.Glu3007*	nonsense	Pathogenic, Likely patho...		0.0%	0.03%	0.0%	1.1%	0.07%
	chr 11 108138045			chr 11 108138045	ATM NM_000051 [17]	ref C alt T	c.2614C>T p.Pro872Ser	missense	Benign	COSM5020323	0.0%	0.0%	0.0%	0.0%	4.68%
	chr 11 534302			chr 11 534302	HRAS NM_001130442 [2]	ref C alt A	c.21G>T p.= (p.Val7Val)	synonymous			0.0%	0.02%	0.41%	0.0%	0.0%
	chr 11 534242			chr 11 534242	HRAS NM_001130442 [2]	ref A alt G	c.81T>C p.= (p.His27His)	synonymous	Benign	COSM249860	49.02%	48.45%	0.52%	0.24%	81.66%
	chr 10 123279677			chr 10 123279677	FGFR2 NM_000141 [7]	ref G alt C	c.755C>G p.Ser252Trp	missense	Pathogenic	COSM36903	0.0%	0.0%	0.0%	0.0%	2.1%
	chr 10			chr 10	PTEN	ref C	c.837C>A	missense			0.0%	0.0%	0.0%	0.0%	0.0%

Hotspot link Variant Fraction: 0 - 0.5% 0.5 - 2% 2 - 5% 5 - 100% Coverage: <500 <1000 <2500 >2500

GREY depicts variant fractions between 0-0.5 %
 RED depicts variant fractions between 0.5-2 %
 YELLOW depicts variant fractions between 2-5 %
 BLUE depicts variant fractions between 5-100 %

Indicates that a variant in the replicate group is present or undetermined

Coverage Indicators (variable)

<500 <1000 <2500 >2500

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11. Replicate Analysis

11.6 Global Sample View Coverage (1)

“Coverage”
Active tab

Workspace: Requests | VDB: Variant Database Browser | GLOBAL #3-0120 samples:6

Filters - Q5-2ng-2-new, Request 3-0120, 14/07/2017

Sophia Genetics SA

Hotspots Variants Coverage Coverage plot

Chromosome Start End	Gene Transcript [Exon rank]	c.DNA Protein	n-392		n-467		Q5-2ng	
			1	2	1	2	1	2
chr 1 43814952 43815064	MPL NM_005373 [10]	c.1487_1565+34 p.Thr496_Arg522	1900	2796	1122	628	2335	2470
chr 1 115252139 115252232	NRAS NM_002524 [4]	c.408_450+51 p.Ser136_Gln150	4582	6298	2857	1119	2043	2434
chr 1 115256481 115256576	NRAS NM_002524 [3]	c.135_230 p.Val45_Gly77	970	1505	937	446	749	954
chr 1 115258699 115258783	NRAS NM_002524 [2]	c.-2_83 p.Met1_Phe28	3913	4922	2065	831	1363	1375
chr 1 162748352 162748419	DDR2 NM_001014796 [18]	c.2284-18_2333 p.Gly762_Trp778	1191	1196	631	349	410	505
chr 2 25457175 25457249	DNMT3A NM_022552 [23]	c.2638_2712 p.Met880_Pro904	2307	2305	932	495	470	549
chr 2 29432652 29432713	ALK NM_004304 [25]	c.3775_3836 p.Cys1259_Arg1279	7196	5415	1798	1042	926	1173
chr 2 29443608 29443702	ALK NM_004304 [23]	c.3516-1_3609 p.Ser1172_Asp1203	2337	3090	1432	622	876	1075
chr 2 48030560 48030652	MSH6 NM_000179 [5]	c.3174_3266 p.Asp1058_Leu1089	5628	7752	3618	1559	2166	2720
chr 2 48030630 48030732	MSH6 NM_000179 [5]	c.3244_3346 p.Pro1082_Gly1116	2013	2759	1654	718	1107	1441
chr 2 48030728	MSH6 NM_000179	c.3342_3416 p.Leu1114_Gly1139	594	778	563	307	413	670

Coverage: <500 <1000 <2500 >2500

Coverage Indicators (variable)

Coverage is < 500 Coverage is < 2500

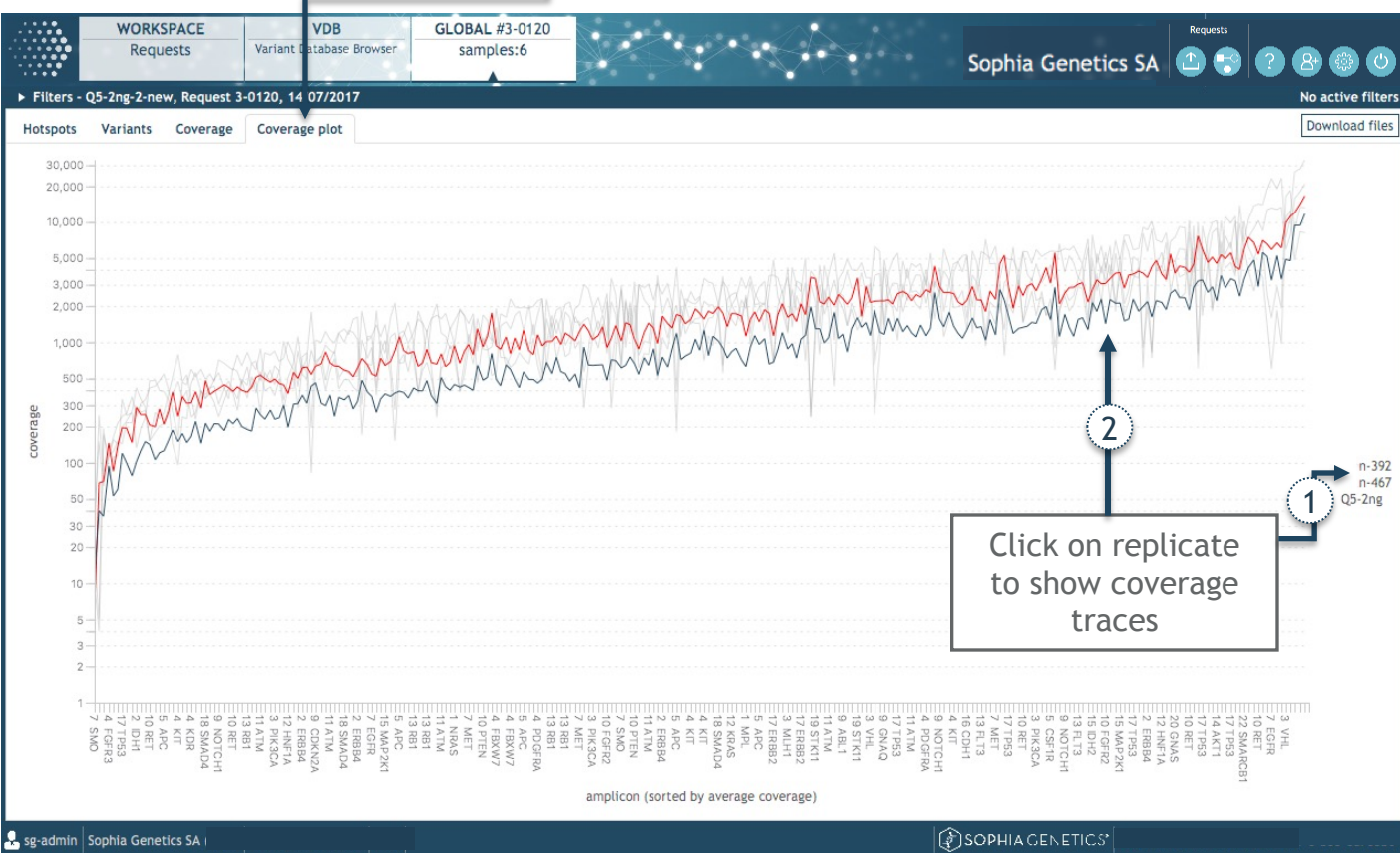
Coverage is < 1000 Coverage is > 2500

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11. Replicate Analysis

11.6 Global Sample View Coverage (2)

“Coverage plot”
Active tab




11. Replicate Analysis

11.7 Analysis Header

The screenshot displays the SOPHiA DDM software interface, specifically the Analysis Header section. The interface is annotated with callouts explaining various elements:

- “Dashboard”**: Click to go back to requests
- “Workspace”**: Click to go back to analyses
- “Active analysis”**: Selected analysis
- Replicate ID**: Points to the replicate information in the header.
- Request date**: Points to the date of the request.
- Project name**: Points to the project name in the header.
- Other projects in the analysis**: Points to the list of other projects.
- Project status**: Points to the status of the project.
- Other patients* in the run**: Points to the list of other patients.
- Patient* ID**: Points to the patient ID in the header.
- Request ref**: Points to the request reference in the header.
- Report completion as**: - A draft report, - A final report
- Access to the analysis files :**
 - Full variant table (VCF)
 - TEXT (variant table.txt)
 - BAI
 - BAM
 - Warnings
- MIDs**: Points to the MID information in the header.
- Project owner**: Points to the project owner information in the header.

Use  to see all projects for the selected sample or to see other samples of the same batch request. To toggle between samples, use < and >.

NOTE: The selection will always jump to the first project for a given sample. If there is no project for a sample, the “new Project*” window will open. Samples cannot be opened without creating an Interpretation Project* first.

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11. Replicate Analysis

11.8 Variant Unification Algorithm

SOPHiA DDM™ variant unification (VU) allows the visualization of very low variant fractions. The algorithm compares variants among all samples in a run for a given genomic position, with variants that have been filtered out during the variant calling process. If high confidence variants have been called for a given position, filtered variants are recovered and visualized in SOPHiA DDM™.

For example, in table 1a, a common variant in sample 2 and 3 has been filtered due to a low variant fraction percentage. At the same genomic position, high confidence variants are called in sample 1,4 and 5. Here the VU algorithm has recovered variants with low variant fractions in samples 2 and 3 (table 1b) which are then reported in SOPHiA DDM™. For the genomic position B no high confidence variants are called in any sample and hence no VF% is reported in SOPHiA DDM™.

	Variant Fraction (%)				
Sample Name	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
VF % (Genomic Position A)	1%	Filter Flag: low VF	Filter Flag: low VF	2%	0.50%
VF% (Genomic Position B)	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF

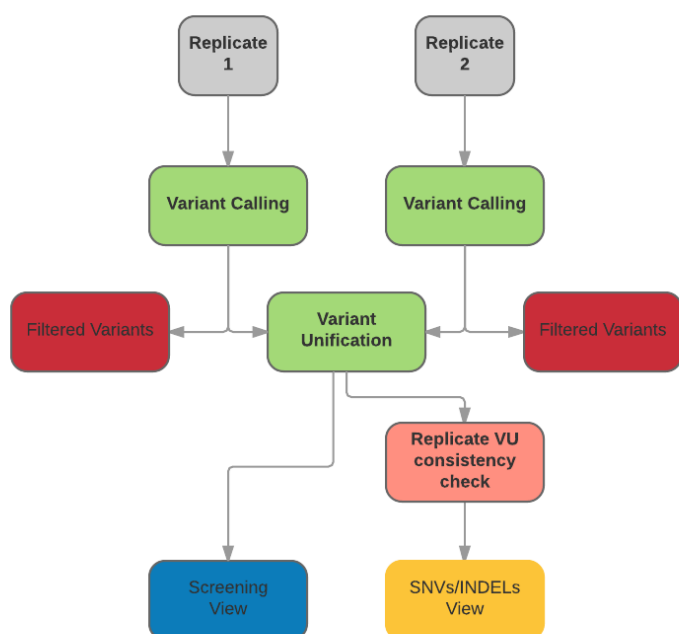
Table 1a: Variant table before Variant Unification. VF = Variant Fraction

	Variant Fraction (%)				
Sample Name	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
VF % (Genomic Position A)	1%	0.20% *	0.10% *	2%	0.50%
VF% (Genomic Position B)	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF

Table 1b: Variant table after variant unification. VF = Variant fraction * Unified variants

11. Replicate Analysis

11.9 Variant Calling Replicate Analysis



Variant calling:

SOPHiA DDM™ variant calling technology PEPPER™ is taking into account many factors such as positional information (e.g. positional background noise), coverage and read quality to calculate the probability that a variant is a true positive. This will result in a variable variant fraction percentage cut-off value which for ctDNA samples is in the range of 0.3%-0.7% for high confidence variants. Low confidence variants (variants in problematic or homopolymer regions) are filtered out. To proceed to the next step all variants are retained (except low confidence variants) even variants that are called from low variant fractions.

Variant unification:

During variant unification (VU), variants are unified and variants that have been below the variant fraction cut-off will be flagged “VU”. Variants are only flagged VU if the same variant has been called with high confidence in at least one other sample in the same run.

Screening view:

VU is important for the screening view as this feature allows users to check for all variants including those that would have otherwise been filtered out.

SNVs/Indels view:

Before the variants are displayed in the SNVs/Indels view, a replicate VU consistency check is carried out. In essence, replicates that contain a VU flagged sample and a high confidence sample will be marked as inconsistent so that the user is aware that one of the replicates is not a high confidence variant.

11. Replicate Analysis

11.10 Screening (1)

“Screening”
Active sub page

Graphic view of the hotspots per gene

The screening contains a list of 426 defined hotspots

Number of detected hotspots are shown in **RED**

Number of undetected hotspots are shown in **BLUE**

Number of undetermined hotspots are shown in **GREY**

Out of 426 variants 379 were consistent among replicates

Among replicates 45 showed consistently the status “undetermined”

The status “inconsistent” was detected in 2 replicate groups

Variant	Position	Gene	Status	Replicate 1	Replicate 2	Replicate 3	Replicate 4
h85	IGV KRAS_p.Gly12Arg_c.34G>C	chr12	present	present	present	present	present
h89	IGV KRAS_G12R	chr12	present	present	present	present	present

Using the screening view for replicates the user can not only quickly visualize pre-defined hotspots but also inspect if replicate samples are consistent.

Consistent: Replicate group shows the same status (present, undetected or undetermined)

Consistent undetermined: All replicates in a group are undetermined

Inconsistent: Replicates in a group show different statuses (e.g. present and undetected)

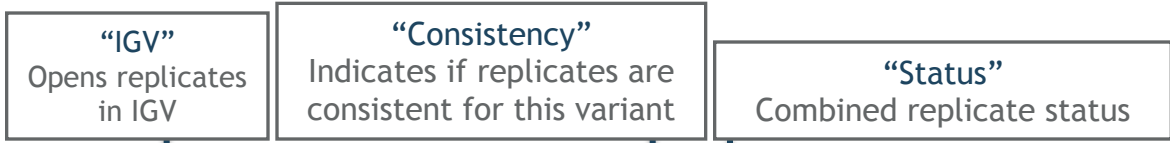
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11. Replicate Analysis

11.10 Screening (2)



SCREENING	GENES	SNVs/INDELS	CNVs	WARNINGS	Interpretation Mode: Replicates	Interpretation Scope: Oncology_Accel_56G_ctDNA						
ID	IGV	Name	Type [exon]	Chr. Start End	Gene Transcript [Codon]	Consistency	Status	HotSpot Status / Coverage		Variants		
								replicates (status/reads)	RefSeq	REF-ALT / cDNA-Protein	replicates (VF% / 1)	
								Q5-2ng-1	Q5-2ng-2	Q5-2ng-1	Q5-2	
h412	IGV	PIK3CA_p.Glu545Lys_c.1 633G>A	cdna [10]	chr3 178936091 178936091	PIK3CA NM_006218 [NA]	✓	present	present 1662	present 2218	1 G A	c.1633G>A p.Glu545Lys	1.81% 1662
h419	IGV	PIK3CA_p.Gly914Arg_c.2 740G>A	cdna [19]	chr3 178947865 178947865	PIK3CA NM_006218 [NA]	✓	present	present 614	present 775	1 G A	c.2740G>A p.Gly914Arg	19.87% 614
h424	IGV	PIK3CA_p.His1047Arg_c. 3140A>G	cdna [21]	chr3 178952085 178952085	PIK3CA NM_006218 [NA]	✓	present	present 1701	present 2023	1 A G	c.3140A>G p.His1047Arg	31.98% 1701
h116	IGV	ALK_p.Phe1174Leu_c.35 22C>A	cdna [23]	chr2 29443695 29443695	ALK NM_004304 [NA]	✗	undetermined	undetected 876	present 1075	1 G T	c.3522C>A p.Phe1174Leu	2
h120	IGV	ALK_F1174L	codon [23]	chr2 29443695 29443697	ALK NM_004304 [1174]	✗	undetermined	undetected 876	present 1075	1 G T	c.3522C>A p.Phe1174Leu	2
h327	IGV	BRAF_K601_W604del	codon [15]	chr7 140453123 140453134	BRAF NM_004333 [601-604]	✓	undetermined	undetected 394	undetetermined 394	0		
h328	IGV	BRAF_V600_R603del	codon [15]	chr7 140453126 140453137	BRAF NM_004333 [600-603]	✓	undetermined	undetetermined 394	undetetermined 394	0		
h23	IGV	KRAS_C118S	codon [4]	chr12 25378644 25378646	KRAS NM_004985 [118]	✓	undetected	undetected 1555	undetected 1845	0		
h330	IGV	BRAF_K601N	codon	chr7	BRAF	✓	undetermined	undetetermined	undetetermined	0		

Status:

present

Variant is present with high confidence in all replicates

undetected

No genomic alteration (wild type) has been detected with high confidence in all replicates

undetermined

SOPHiA DDM™ could not determine with high confidence if the hotspot wild type or altered in one or more replicate samples

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11. Replicate Analysis

11.11 Genes

Access a quick-view of genes of interest with the total number of variants for each gene, pathogenicity and prediction levels, variant types and their coding consequences.

The screenshot displays the SOPHiA DDM software interface. At the top, there are navigation tabs: WORKSPACE Requests, VDB Variant Database Browser, and ANALYSIS circan-467 #3-0118. Below this is a header with 'Sophia Genetics SA' and various icons. The main navigation bar includes Overview, Therapeutic, Diagnosis Prognosis, and Variants. A 'REPORTED 0/0' indicator is visible. The 'GENES' tab is active, showing a list of genes with columns for Filter, CHR, Name (IGV), Prediction, Total Variants, Pathogenicity, Variant Types, and Coding Consequences. A 'Selected Virtual Panel' is shown on the left. A callout box points to the 'Gene list of selected Virtual Panel' table. Another callout points to the 'Click on gene name to open IGV at the position of the gene' instruction. A third callout points to the 'Click on the eye to open the gene viewer. It shows where the variants are located in the gene' instruction. Below the table, a detailed view of the ALK gene is shown, including its structure and variant data.

Virtual Panels

“Genes” Active tab

Calculate coverage Virtual Panel

Selected Virtual Panel

Gene list of selected Virtual Panel

Click on gene name to open IGV at the position of the gene

Click on the eye to open the gene viewer. It shows where the variants are located in the gene

Note gene viewer: In the replicate interpretation mode, VF% is represented as an average of replicates.

11. Replicate Analysis

11.12 SNVs/Indels

“Retained variants”
Active page (blue)

“SNVs/Indels”
Active sub page

Selected variant

Replicate consistent
Replicate inconsistent

Click on the
“+” to add
more filters

Variant ID	Gene	Consequence	c.DNA	Depth	VF%	ref	alt	ID Clin...	Cosm...	Cosm...	O...
A	ALK	missense	c.3522C>A	876.0	0.46%	G	T	rs8632...	COSM2...		
A	CTNNB1	inframe_3	c.133_135delTCT	1947.0	19.05%	CCTT	C	rs5877...	COSM6128		
A	CTNNB1	missense	c.98C>A	1947.0	25.01%	C	A	rs1219...	COSM5673		
A	EGFR	missense	c.2369C>T	13370.0	1.52%	C	T	rs1214...	COSM6...		
A	EGFR	missense	c.2155G>A	3191.0	15.70%	G	A	rs2892...	COSM6252		
A	EGFR	missense	c.2573T>G	1744.0	1.15%	T	G	rs1214...	COSM6224		

Overview

Information about the currently selected variant:

- Read depth and variant fraction for each replicate
- Replicate consistency
- Frequencies (within the run, account, community)
- Flagging (by users in the community, by the client, prediction)
- Variant details (NM transcript, genomic alteration etc.)
- Scores

Links

Possibility to retrieve more external information about the variant by clicking on the corresponding database link.

12. SIS client

12.1 Dashboard

Navigation Bar

SIS Interface

Workspace

SISboard

New Request

Help

New Patient*

Settings

Logout

Public Databases	Current Versions used in SOPHiA DDM:
EXAC	v5.3.1
G1000	v5.20120802
ESP	v400
CGSCAC	v97
ChivVar	v20160705
CGEP	837.20120813
dbSNP	v147
dbNSFP	v2.9

SIS (SOPHiA DDM™ Integrated Solutions) helps institutions that need to outsource their NGS based applications to benefit from the World's Largest Clinical Genomics Community by letting their samples be prepared and sequenced by SOPHiA GENETICS validated partners. SIS offers a full-service solution from biological samples to results ready for interpretation in SOPHiA DDM™. The SIS user interface enables users to create and follow purchase orders (PO) directly in SOPHiA DDM™. This ensures a complete tracking of samples through the whole process and monitoring of the turnaround time between the date of reception of the samples and the upload of the raw data to SOPHiA DDM™.

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12. SIS Client

12.2 Purchase Orders

12.2.1 Purchase Orders - Overview

Purchase order statuses

- Created: Awaiting validation
- Validated: Ready to ship samples
- Shipped: The client has shipped the samples
- In Progress: The sequencing partner has received the samples
- Finished: The run has been uploaded
- Canceled: The purchase order has been canceled by the client

Dates

- PO creation date
- PO validation date
- Samples' shipment date to the sequencing partner lab
- Samples' arrival date at the sequencing partner lab
- Upload run data

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12. SIS Client

12.2 Purchase Orders

12.2.2 Purchase Order Creation (1)

Product/Application
Applications available for the client

Next
Is only enabled
after selecting the
application, sample
type and the
number of samples

Samples
Number of samples to
be sent

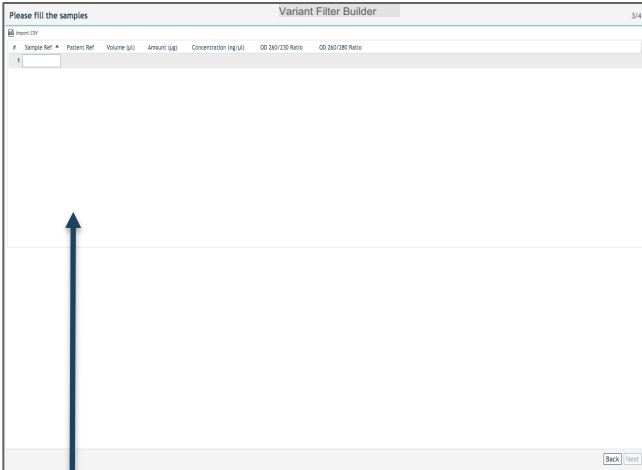
Options
Sample Type: DNA, Blood, Buccal swabs,
FFPE block, FFPE Slice, Bone Marrow
MLPA: Request MLPA Analysis
Interpretation: Request interpretation*
DHL: Shipment with SOPHiA GENETICS DHL
account

Validation check box

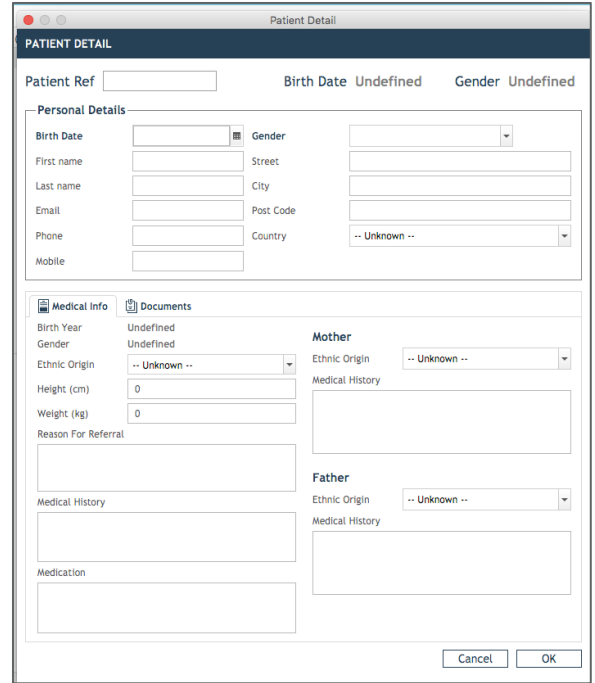
12. SIS Client

12.2 Purchase Orders

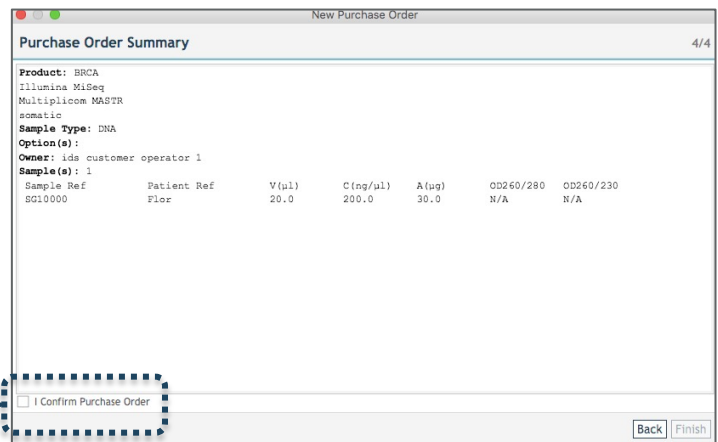
12.2.2 Purchase Order Creation (2)



- 1 Depending on the sample type selected:
Sample ref: Give a ref alphanumeric code
Patient* ref: See box 2
Volume: Sample volume
Amount: Sample amount
Concentration: Sample concentration
OD 260/230 Ratio
OD 269/280 Ratio



- 2 A pop-up window appears to fill in the patient* details (patient* ref, birth date and gender are mandatory)

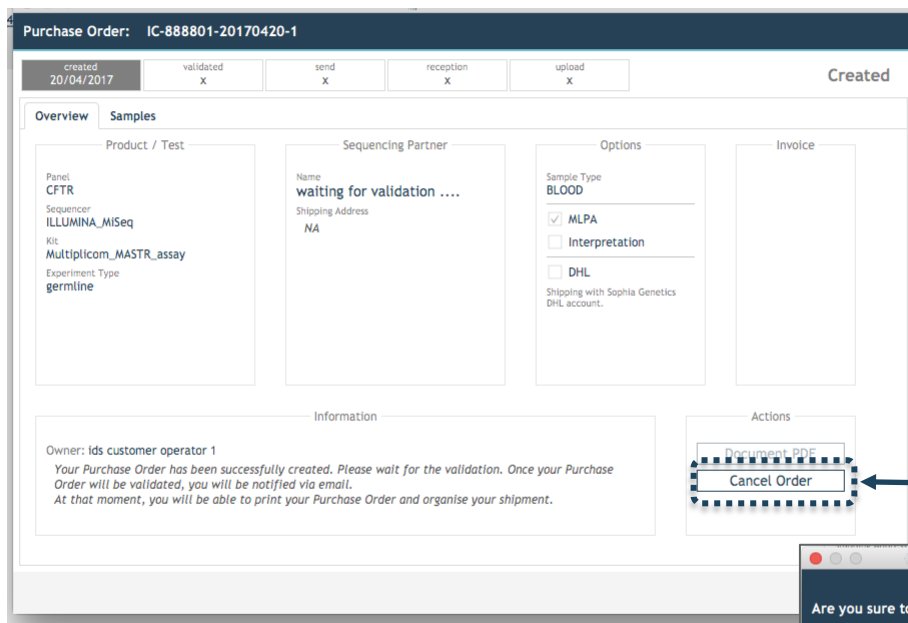


Validation check box

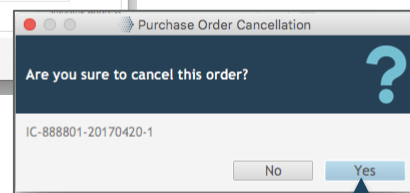
12. SIS Client

12.2 Purchase Orders

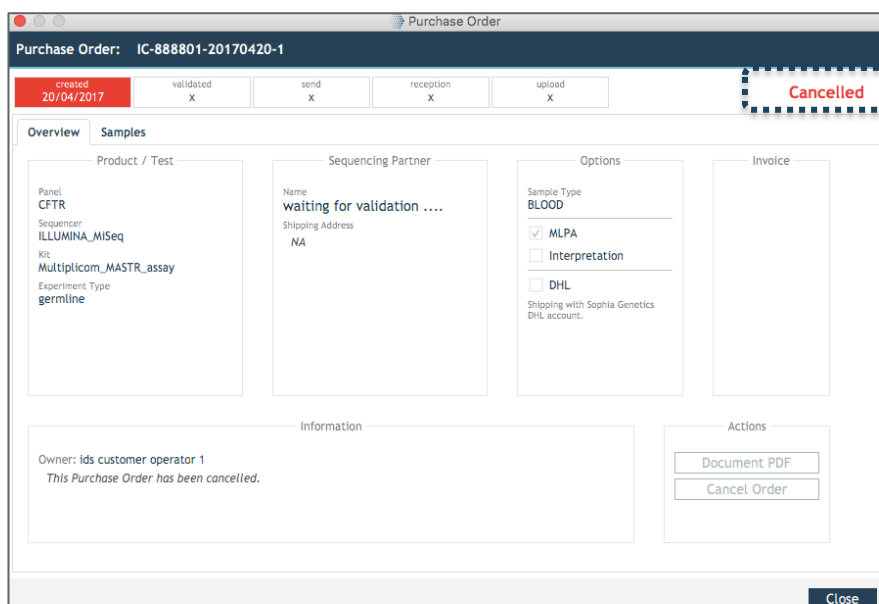
12.2.3 Purchase Order Cancellation



Validation check box



Yes



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12. SIS Client

12.2 Purchase Orders

12.2.4 Validated PO Sample Shipment

The screenshot displays the SIS Client interface for Integrated Diagnostic Solutions. The main window shows a list of purchase orders with columns for IDs, status, invoice numbers, products, sequencing partners, options, and dates. Annotations include:

- Click SIS-number:** A dashed box highlights the 'Validated' status of POs IC-888801-20170424-1, -2, and -3.
- Validated POs Ready to send samples:** A callout box pointing to the validated POs.
- Select shipment date:** A callout box pointing to a date selection calendar for PO IC-888801-20170420-3.
- Print PO Samples must be accompanied by a printed document:** A callout box pointing to the 'Document PDF' button in the shipment details window.

Purchase Order	IDS Number	Status	Invoice	N	Product	Sequencing Partner	Options	Turnaround Time	Created	Validated	Sent	Received	Upload
IC-888801-20170420-3	IC-888801-20170420-3	Validated		1	BRCA Illumina MiSeq Multiplicom MASTR somatic	IDS Sequencing Partner	888800 BLOOD		20/04/2017	20/04/2017	24/04/2017		
IC-888801-20170424-1	IC-888801-20170424-1	Validated		1	BRCA Illumina MiSeq Multiplicom MASTR somatic	IDS Sequencing Partner	888800 BLOOD		24/04/2017	24/04/2017			
IC-888801-20170420-2	IC-888801-20170420-2	Validated		1	CFTR Illumina MiSeq Multiplicom MASTR germline	IDS Sequencing Partner	888800 DNA	✓ ✓ ✓	20/04/2017	20/04/2017			
IC-888801-20170424-2	IC-888801-20170424-2	Validated		1	CFTR Illumina MiSeq Multiplicom MASTR germline	CHU Grenoble	20995 BLOOD	✓	24/04/2017	24/04/2017			
IC-888801-20170424-3	IC-888801-20170424-3	Validated		1	CFTR Illumina MiSeq Multiplicom MASTR germline	CHU Grenoble	20995 BLOOD	✓	24/04/2017	24/04/2017			
IC-888801-20170424-4	IC-888801-20170424-4	Created		1	CFTR Illumina MiSeq Multiplicom MASTR germline		BLOOD	✓	24/04/2017				

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12. SIS Client

12.2 Purchase Orders

12.2.5 Status Overview

WORKSPACE Requests YDB Variant Database Browser SIS Integrated Solutions IDS Customer

Integrated Diagnostic Solutions Search:

Purchase Orders: 6

New Purchase Order

IDS Number	Status	Invoice	N	Product	Sequencing Partner	Options	Turnaround Time	Created	Validated	Sent	Received	Uploa
IC-888801-20170420-3	In Progress		1	BRCA Illumina MiSeq Multiplicom MASTR somatic	IDS Sequencing Partner	888800 BLOOD	0	20/04/2017	20/04/2017	24/04/2017	24/04/2017	
IC-888801-20170424-1	Validated		1	BRCA Illumina MiSeq Multiplicom MASTR somatic	IDS Sequencing Partner	888800 BLOOD		24/04/2017	24/04/2017			
IC-888801-20170420-2	In Progress		1	CFTR Illumina MiSeq Multiplicom MASTR germline	IDS Sequencing Partner	888800 DNA	0	20/04/2017	20/04/2017	21/04/2017	24/04/2017	
IC-888801-20170424-2	Validated		1	CFTR Illumina MiSeq Multiplicom MASTR germline	20995 CHU Grenoble	BLOOD		24/04/2017	24/04/2017			
IC-888801-20170424-3	Shipped		1	CFTR Illumina MiSeq Multiplicom MASTR germline	20995 CHU Grenoble	BLOOD		24/04/2017	24/04/2017	24/04/2017		
IC-888801-20170424-4	Created		1	CFTR Illumina MiSeq Multiplicom MASTR germline		BLOOD		24/04/2017				

Refresh

Range: Last Week

From: 17/04/2017

To: 24/04/2017

Filters

- Created
- Validated
- Shipped
- In Progress
- Finished
- Cancelled

Status "In Progress"
The sequencing partner has received the samples

Idscadmin | IDS Customer

SOPHIA GENETICS

13. SIS - Sequencing Partner

13.1 Dashboard

Navigation Bar

Application Header

SIS interface

Workspace

Dashboard


New request

Help

New patient*

Settings

Logout

- User Information:**
- Username 
 - Client
 - Starting date of the session

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13. SIS - Sequencing Partner

13.2 Assigned Purchase Orders

13.2.1 Assigned POs - Overview

Integrated Diagnostic Solutions

Purchase Orders: 3

IDS Number	Status	N	Product	Client	Type	Options			Turnaround Time	Dates				
						MLPA	Inter.	DHL		Created	Validated	Sent	Received	Uploaded
IC-888801-20170420-3	Shipped	1	BRCA Illumina MiSeq Multiplicom MASTR somatic	888801 IDS Customer	BLOOD		✓			20/04/2017	20/04/2017	24/04/2017		
IC-888801-20170424-1	Validated	1	BRCA Illumina MiSeq Multiplicom MASTR somatic	888801 IDS Customer	BLOOD		✓			24/04/2017	24/04/2017			
IC-888801-20170420-2	Shipped	1	CFTR Illumina MiSeq Multiplicom MASTR germline	888801 IDS Customer	DNA	✓	✓	✓		20/04/2017	20/04/2017	21/04/2017		

Callout Box:
 Purchase orders assigned sequencing partner
 - Validated: The PO is assigned to the sequencing partner
 - Shipped: The shipment has been sent

13. SIS - Sequencing Partner

13.2 Assigned Purchase Orders

13.2.2 Sample Reception

The screenshot shows the 'Integrated Diagnostic Solutions' interface. At the top, there are tabs for 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'SIS Integrated Solutions'. The main area displays a table of 'Purchase Orders' with columns for 'IDS Number', 'Status', 'N', 'Product', 'Client', 'Options', 'Turnaround Time', and 'Dates'. A circular 'POs' gauge is on the left. A callout box points to the 'Shipped' row for 'IC-888801-20170420-2' with the text 'Click SIS-number Sample reception'. Below this, a detailed view of the purchase order is shown. A callout box points to the 'reception' tab with the text 'Select reception date'. Another callout box points to the 'In Progress' status and the 'Document PDF' button with the text 'Status changes to "In Progress" and the document is available as a PDF'. A calendar widget is visible in the background of the detailed view.

IDS Number	Status	N	Product	Client	Options	Turnaround Time	Created	Validated	Sent	Received	Uploaded
IC-888801-20170420-3	Shipped	1	BRCA Illumina MiSeq Multiplicom MASTR somatic	888801 IDS Customer	BLOOD	✓	20/04/2017	20/04/2017	24/04/2017		
IC-888801-20170424-1	Validated	1	BRCA Illumina MiSeq Multiplicom MASTR somatic	888801 IDS Customer	BLOOD	✓	24/04/2017	24/04/2017			
IC-888801-20170420-2	Shipped	1	CFTR Illumina MiSeq Multiplicom MASTR germline	888801 IDS Customer	DNA	✓ ✓ ✓	20/04/2017	20/04/2017	21/04/2017		

13. SIS - Sequencing Partner

13.2 Assigned Purchase Orders

13.2.3 Manual Sample Upload (1)

“Create New Batch Request”

Create a new run request for one or multiple sequencing files

Choose a reference name for your request

- Select sequencer
- Choose files to upload
- Click “Yes” to upload all files of a directory or “No” to upload single files
- Number of samples will be detected automatically
- Click “Next”

This workflow is also valid for SOPHiA DDM™ Dispatch. For more information, please consult the related user manual.

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13. SIS Sequencing Partner

13.2 Assigned Purchase Orders

13.2.3 Manual Sample Upload (2)

“MID”
Index used for sample identification

“Patient*”
By default, the same as the sample ID (see [p. 22](#))

“SIS Number”*
Select from the dropdown menu an available SIS number or “Not SIS”

* Valid for SIS and SOPHiA DDM™ Dispatch

“Kit”
Library prep kit used (see [p. 22](#))

Sample ID	Patient	SIS Number	Sample Type	Experiment Type	KIT	Control
1 library01 S1	library01	Choose one...	Other		NO_PIPELINE	C
2 library02 S2	library02	Choose one...	Other		NO_PIPELINE	C
3 SG10000008 S8	SG10000008	Choose one...	Blood	germline	CFTR MASTR® Dx	C
4 SG10000009 S9	SG10000009	Choose one...	Blood	germline	CFTR MASTR® Dx	C

- At least one sample doesn't have a valid associated kit and will not be analyzed
- Please select different SIS Numbers (or Not SIS) for each sample. Note that the analysis type, kit and experiment type must match.

“Sample Type”
Sample material used (the default is blood for germline applications and FFPE for somatic applications)

“Experiment Type”
Recognized automatically

13. SIS- Sequencing Partner

13.2 Assigned Purchase Orders

13.2.3 Manual Sample Upload (3)

The screenshot displays the SIS Sequencing Partner interface. The top navigation bar includes 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'SIS Integrated Solutions'. The main content area shows a list of requests with filters for '5 Requests' and '6 Patients'. A filter section allows selecting status (All, Completed, In Interpretation, Pipeline Analysis) and tests (BRCA). A sample card for 'TestDataMix_CFTR_BRCA_DDMAT-69' is highlighted, showing a status of 0/4 samples, sequencer 'ILLUMINA_MiSeq', processed date '02/05/2017', and request date '02/05/2017'. A callout box with an arrow points to this sample card, containing the text: 'Sample has been uploaded Sequencing partner can't access the analysis'.

Note: Independently of the selected upload method (manual or semi-automatic), the Sequencing Partner can view the list of uploads without access to results in their account. The Sequencing Client can access the result of the analysis in their account and the FASTQ file(s) and QA report per patient* are accessible for download from the sample card of the respective sample.

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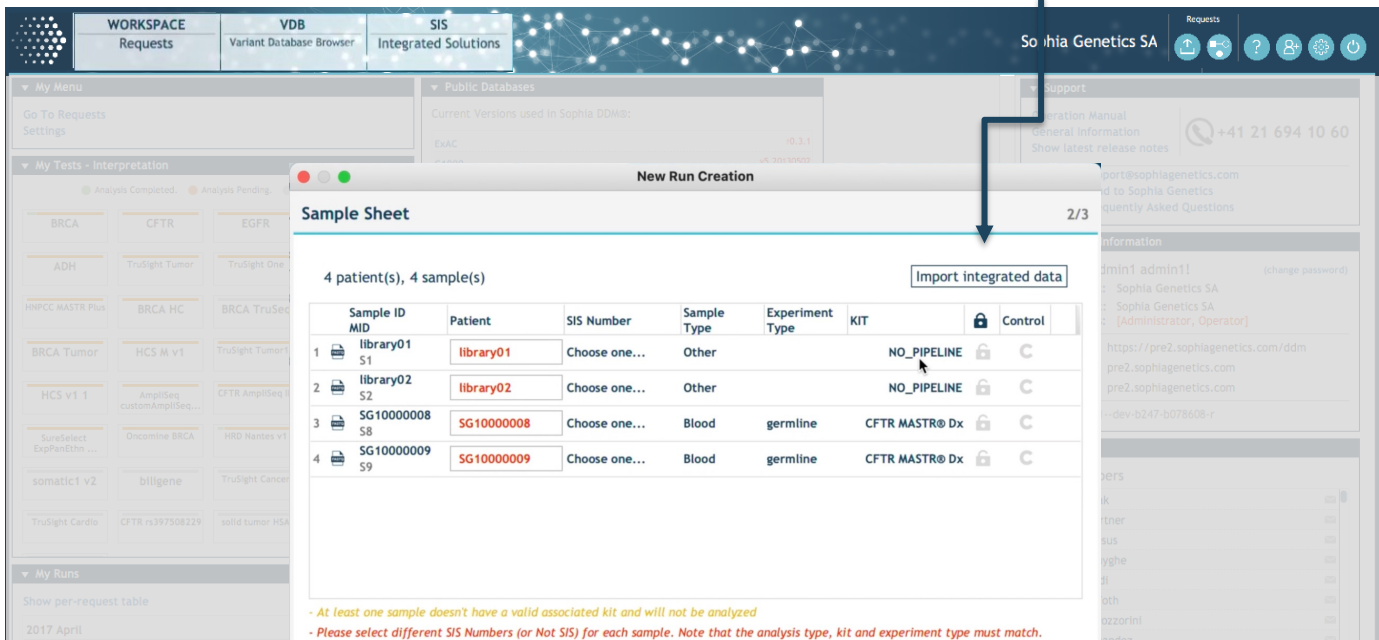
13. SIS Sequencing Partner

13.2 Assigned Purchase Orders

13.2.4 Semi-Automatic Sample Upload (1)

Please Note:
Please perform step 1 of the manual sample upload (see [p. 248](#)) before starting the import of integrated data

“Import Integrated Data”
Import a *.csv file with a link between your sample and the sequencing data



Format of the CSV file

The CSV file shall include the following fields and column names:

- Sample Number: The SIS number of the sample (**mandatory**)
- Sample Reference: The client sample reference (optional)
- Purchase Order: The SOPHiA GENETICS SIS purchase order number (optional)
- Sequencing Field: The sample sequencing ID from the FASTQ file (**mandatory**)
- File: The FASTQ file name (optional)
- Sequencer: Information of the sequencer used in the experiment (optional)
- Example:

SIS ID Sample	Sample Reference	SIS PO ID	Sequencing ID	FASTQ File	Sequencer
sis-1234567890-10	yyyy	IC1-121212-20220608-1	S1	-	-
sis-1234567890-11	-	IC1-121212-20220608-1	S2	-	MiSeq
sis-1234567890-12	4321	IC1-121212-20220608-2	S3	-	MiSeq
sis-1234567890-13	5432	IC1-121212-20220608-2	S4	-	MiSeq

13. SIS Sequencing Partner

13.2 Assigned Purchase Orders

13.2.4 Semi-Automatic Sample Upload (2)

The screenshot shows the SOPHiA DDM software interface. A 'New Run Creation' dialog box is open, titled 'Sample Sheet'. It contains a table for 'Multi-modal data import' with the following data:

Sample Number	Sample Reference	Purchase Order	Sequencing ID	File	Sequencer
1	sts-2650185634-40	sample1	IC1-888801-20220607-2	S1	
2					
3					
4					

The dialog box also has 'Cancel' and 'Apply' buttons at the bottom right. A blue arrow points from the 'Apply' button to a text box below the screenshot.

Apply and confirm to save the patient's data

Please Note:

- Outcome of the manual and semi-automatic upload is the same (see [p. 248](#)): the sequencing client can access the analysis in his account. The FASTQ file and QA report per patient* is accessible for download from the sample card of the respective sample.

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14. Gene Fusion Analysis

Detection of fusion genes and exon skipping events is available for the following applications:

- SOPHiA DDM™ Myeloid Plus Solution (MYS+)
- SOPHiA DDM™ Solid Tumor Solution™ (STS+)
- SOPHiA DDM™ for TruSight™ Tumor 170
- SOPHiA DDM™ for TruSight™ Oncology 500
- Oncomine™ Focus (RNA-only)
- Archer FusionPlex® CTL application

For MYS+ and STS+, SNV/Indel detection is performed on DNA samples and fusion gene detection on RNA samples. This requires a joint upload of DNA and RNA samples (see [chapter 14.1.1 - Dual DNA RNA upload](#)).

For the Archer FusionPlex® CTL application, SNV and fusion gene detection is performed on a single RNA sample only.

14. Gene Fusion Analysis

14.1 Naming convention sample upload

14.1.1 Dual DNA/RNA Analysis (1)

Users can perform paired upload and simultaneous analysis of a DNA (SNVs/Indels) and RNA (Fusions) sample of a patient*. If a naming convention is applied at sample upload, the DNA and RNA samples are matched to one patient* in the Analysis View.

Sample Sheet 2/3

4 patient(s), 6 sample(s) group analysis

	Sample ID MID	Group ID	Patient	Sample Type	Experiment Type	Lib... Type	KIT	BDS Number	
1	sample3-D S8		sample3	Blood	somatic	DNA	Myeloid Plus Solution by Soph	BDS-3546191474-44	
2	sample4-R S38		sample4	Blood	somatic	RNA	Myeloid Plus Solution by Soph	N/A	
3	sample1-D S10	sample1	sample1	Blood	somatic	DNA	Myeloid Plus Solution by Soph	BDS-3546191474-44	
4	sample1-R S25	sample1	sample1	Blood	somatic	RNA	Myeloid Plus Solution by Soph	N/A	
5	sample2-D S9	sample2	sample2	Blood	somatic	DNA	Myeloid Plus Solution by Soph	BDS-3546191474-44	
6	sample2-R S27	sample2	sample2	Blood	somatic	RNA	Myeloid Plus Solution by Soph	N/A	

Back Next

To perform a combined DNA and RNA sample analysis of a single patient*, a naming convention has to be applied to the uploaded FASTQ files before the batch upload:

- A “-D” added after the sample ref will indicate the DNA sample.
- An “-R” added after the sample ref will indicate the RNA sample.
- If the same sample ref is given to the DNA and RNA sample, both samples will be grouped together into one single analysis.

In the above example, for “sample1” both, the DNA and RNA sample, are available. Since the naming convention is applied, the DNA and RNA samples will be grouped together into one analysis. The same is true for “sample2”, whereas “sample3” and “sample4” will be assigned to different patients*. For “sample3” only SNV/Indel calling will be available and for “sample4” only the analysis of gene fusion events.

14. Gene Fusion Analysis

14.1 Naming convention sample upload

14.1.1 Dual DNA/RNA Analysis (2)

The following naming conventions apply to the applications where fusion analysis is available and DNA and / or RNA samples can be uploaded for each patient*.

Application	Naming convention / Example	Impacted Files	Upload restrictions
MYS+ / STS+	<ul style="list-style-type: none"> The RNA files need to have -R in the file name and the DNA files -D <p>Example: sample1-D_S10_L001_R1_001.fastq.gz sample1-D_S10_L001_R2_001.fastq.gz sample1-R_S25_L001_R1_001.fastq.gz sample1-R_S25_L001_R2_001.fastq.gz</p>	*.fastq	<ul style="list-style-type: none"> The number of DNA FASTQ files (-D) should be equal or greater than the number of RNA FASTQ files (-R).
Oncomine™ Focus	<ul style="list-style-type: none"> Naming conventions (-D and -R) have to be applied to the *.bam files` header to differentiate the DNA and RNA samples The bam file is created by the Ion Torrent sequencer and naming convention is applied ideally during run setup on the sequencer <p>Example: IonXpress013- D_R_2018_12_12_08_05_16_user_GSS5-0087-12-181211_KFJ_Oncomine_RNA_DNA_1_Auto_use_r_GSS5-0087-12-181211_KFJ_Oncomine_RNA_DNA_1_154.bam</p>	*.bam	<ul style="list-style-type: none"> No restrictions
TruSight™ Tumor 170 (TST170) & TruSight™ Oncology 500 (TSO500)	<ul style="list-style-type: none"> Naming convention (-D and -R) has to be applied to the DNA and RNA samples, respectively <p>Example: sample01-D_S9_L001_R1_001.fastq.gz sample01-D_S9_L001_R2_001.fastq.gz sample01-R_S11_L001_R1_001.fastq.gz sample01-R_S11_L001_R2_001.fastq.gz</p>	*.fastq	<ul style="list-style-type: none"> The first upload of a batch to an account needs to include at least one DNA sample. Afterwards RNA-only uploads are possible.

14. Gene Fusion Analysis

14.1 Naming convention sample upload

14.1.2 RNA-only Analysis

For the following applications fusion detection and SNV/Indel calling is available on the RNA sample.

Application	Naming convention / Example	Impacted Files	Upload restrictions
Archer Fusion Plex CTL	<ul style="list-style-type: none"> No naming convention has to be applied, all samples are automatically considered RNA SNVs/Indels and Fusions are detected from the RNA sample 	*.fastq	<ul style="list-style-type: none"> No restrictions

14. Gene Fusion Analysis

14.2 Analysis overview

Overview
Overview tab is highlighted

Analysis
Active analysis (highlighted in white)

The screenshot shows the SOPHiA DDM software interface for Gene Fusion Analysis. The top navigation bar includes 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS #20247-0041'. The 'ANALYSIS' tab is highlighted in white. Below the navigation bar, the 'Overview' tab is selected, showing a summary of the analysis. The main content area displays the 'Interpretation Project' details, including the name 'Interpretation 1', start date '30/09/2017', and end date. A 'Prediction' chart shows a score of 39, with a breakdown of 9 (D), 10 (B), and 1 (A). The 'Pathogenicity Flags' section shows 1 flag. The 'Actionability' section shows 0 flags for Diseases, Drugs, and Trials. The 'Report' section includes checkboxes for 'Selected', 'Retained', 'Low Confidence', and 'Low Coverage', and radio buttons for 'DRAFT' and 'FINAL'. The 'Application information column' on the right side of the interface provides additional details, including 'Public Databases' and 'Test Information'.

Application information column

In addition to the SNV/Indel information, the column also indicates how many fusion genes have been called with high confidence (retained) or low confidence

14. Gene Fusion Analysis

14.3 Fusion Tab

Fusion Active tab

Download
Data can be downloaded as CSV or XLS files

The screenshot shows the 'Fusions' tab in the SOPHiA DDM software. The interface includes a top navigation bar with 'Interpretation', 'DNA - RNA', and 'Variants' tabs. Below this is a 'Fusion Filter' sidebar with 'Retained Fusions' (2) and 'Low Confidence Fusions' (13). The main table displays gene fusion results with columns for Pathogenicity, Actionability, In Report, Fused Genes 5'-3', Type, In-Frame, RC % SR, UMC % SUM, Supporting Databases, Unique ID, and Filter. Two gene fusions are visible: SDC4-e2-PPP1R21-e16 and SDC4-e2-ROS1-e32. A 'Download' button is located in the top right corner.

Fusion filter
 “Retained Fusion”: High confidence gene fusions
 “Low Confidence Fusion”: Filtered gene fusions

Columns can be re-arranged by dragging them to the desired position

Note: The number and content of columns available in the fusion table depend on the used application.

14. Gene Fusion Analysis

14.4 Fusion flagging

Fusion Active tab

Click on fusion to see details

Pathogenicity	AMP/ASCO/CA...	In Report	Fused Genes 5'-3'	Type	Junction Annotation	In-Frame	5' Transcript Gene Junction	3' Transcript Gene Junction	RC % SR	UMC % SUM	Supporting Databases	Unique ID
			SLC34A2 - ROS1 e4 - e32	Gene-fusion	Exon-Exon	Yes	NM_001177998 4:25665952	NM_002944 6:117650609	1927 99.69%	471 54.77%	Links Cosmic ChimerDB	SLC34A2(4:25665952)-ROS1(6:117650609)
				fusion	Exon-Exon	Yes	NM_005436 10:61665880	NM_020630 10:43612032	361 89.14%	163 65.46%	Links ChimerPub ChimerKB ChimerSeq	CCDC4(10:61665880)-RET(10:43612032)
				fusion	Exon-Exon	Yes	NM_001177998 4:25665952	NM_002944 6:117645578	284 5.81%	84 3.22%	Links ChimerPub ChimerKB ChimerSeq	SLC34A2(4:25665952)-ROS1(6:117645578)
			SLC34A2 - ROS1 e4 - e33 Out-Frame	Gene-fusion	Exon-Exon	No	NM_001177998 4:25665952	NM_002944 6:117647577	83 2.81%	51 3.05%	Links ChimerPub ChimerKB ChimerSeq	SLC34A2(4:25665952)-ROS1(6:117647577)

Overview DETAILS VARIANT DESCRIPTION FLAGGING

Gene(s) SLC34A2 - ROS1
Chromosomes(s) chr4 - chr6
5' Transcript NM_001177998
3' Transcript NM_002944

Type Gene-fusion
Junction annotation Exon - Exon
Exons e4 - e33
Read supported cDNA sequence 5'-3' GTAGGCGCTTCCAGCTGGTGGAG - AAAGAGCACTTCAAATAATTACA
Consequence Out-Of-Frame
Unique ID SLC34A2(4:25665952)-ROS1(6:117647577)

Pathogenicity Actionability

0 0 0 0 0
1 2 3 4 5

In Report 2
Set To False + 0

IGV
ChimerPub
ChimerKB
ChimerSeq

Overview

Information about the currently selected fusion:
Genes, chromosome, transcript, junction annotation

Flagging

- Pathogenicity flagging distribution (community) & account flags
- False positive flags
- Actionability flags

See also [chapter 4.9.2 Flagging - SNV/INDELS](#) for more details on variant flagging.

Links

Possibility to retrieve more external information about the variant by clicking on the corresponding database link (if available).

14. Gene Fusion Analysis

14.5 Fusion display in IGV

Fusion
Active tab

Click on a fusion in the table or the IGV button to open fusion display in the IGV browser (if available).

Pathogenicity	AMP/ASCO/CA...	In Report	Fused Genes 5'-3'	Type	Junction Annotation	In-Frame	5' Transcript Gene Junction	3' Transcript Gene Junction	RC % SR	UMC % SUM	Supporting Databases	Unique ID
			SLC34A2 e4 - e32 ROS1	Gene-fusion	Exon-Exon	Yes	NM_001177998 4:25665952	NM_002944 6:117650609	1927 99.69%	471 54.77%	Links Cosmic ChimerDB	SLC34A2(4:25665952)-ROS1(6:117650609)
			CCDC6 e1 - e12 RET	Gene-fusion	Exon-Exon	Yes	NM_005436 10:61665880	NM_020630 10:43612032	361 89.14%	163 65.46%	Links ChimerPub ChimerKB ChimerSeq	CCDC6(10:61665880)-RET(10:43612032)
			SLC34A2 e4 - e34 ROS1	Gene-fusion	Exon-Exon	Yes	NM_001177998 4:25665952	NM_002944 6:117650609	1927 99.69%	471 54.77%	Links Cosmic ChimerDB	SLC34A2(4:25665952)-ROS1(6:117650609)
			SLC34A2 e4 - e33 ROS1	Gene-fusion	Exon-Exon	Yes	NM_001177998 4:25665952	NM_002944 6:117650609	1927 99.69%	471 54.77%	Links Cosmic ChimerDB	SLC34A2(4:25665952)-ROS1(6:117647577)

OVERVIEW DETAILS VARIANT DESCRIPTION FLAGGING

Genes: SLC34A2 - ROS1
Type: Gene-fusion
Junction annotation: Exon - Exon

Chromosomes: chr4 - chr6
Exon: e4 - e33
Read aligned cDNA sequence 5-3'
GTAGCGCCTCCAGCTGGTGGAG - AAAGAGCACTCAATAATTACA

5' Transcript: NM_001177998
Consequence: Out-Of-Frame
Gene ID: SLC34A2(4:25665952)-ROS1(6:117647577)

3' Transcript: NM_002944

Pathogenicity: Actionability

In Report: 2
Set To False +

IGV
ChimerPub
ChimerKB
ChimerSeq

IGV browser for fusions

The visualization of fusions in IGV is only available for applications that are aligned against the human reference genome. These applications include:

- Archer FusionPlex® CTL
- Illumina TruSight™ Tumor 170 and TruSight™ Oncology 500
- SOPHiA DDM™ RNAtarget Oncology Solution (ROS)

The fusion display in IGV is not possible for the SOPHiA DDM™ Myeloid Plus and Solid Tumor Plus Solutions, as well as OncoPrint™ Focus. For those applications, the IGV button is disabled.

Note: When visualizing results in IGV, the variant fraction % and the % of supporting reads may differ from what is reported in SOPHiA DDM™. IGV only takes total reads into account and does not read groups that are created when using molecular barcodes during library preparation.

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15. MSI Status Analysis

15.1 Overview

MSI status analysis is available in two formats for the following two applications:

- 1) SOPHiA DDM™ Solid Tumor Solution (STS) - downloadable as a pdf report (see [ch. 15.2](#)).
- 2) SOPHiA DDM™ for TruSight™ Oncology 500 (TSO500) - display in the Overview tab (see [ch. 15.3](#))




15. MSI Status Analysis

15.2 MSI status pdf report (STS)

The MSI algorithm module is based on Next-Generation Sequencing (NGS) data using alignments of six well-characterized SSRs within long homopolymers. The sites are: BAT_25, BAT_26, CAT_25, NR_21, NR_22, NR_27.

For a given sample, the distance scores within the six loci (listed above) are computed based on both the run-specific and global average profiles. These are summed together to evaluate the overall MSI status.

The developed algorithm classifies MS into 3 categories:

-  MSS (MS stable) with a score below 6
-  MSI-HC (MSI with high confidence) with a score > 14
-  MSI-LC (MSI with low confidence) with a score between 6 and 14

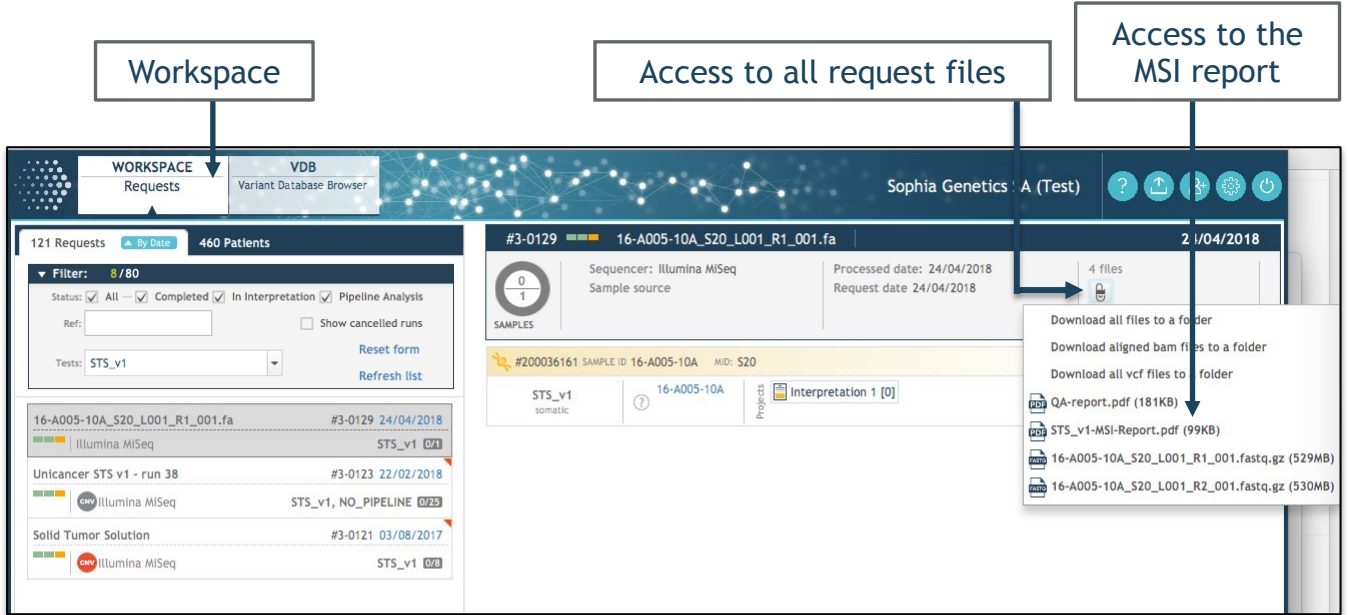
The algorithm displays 2 MSI scores per analysis:

- At the run level
- At the global level, calculated on a dataset of over 400 clinical research FFPE samples (independent dataset)

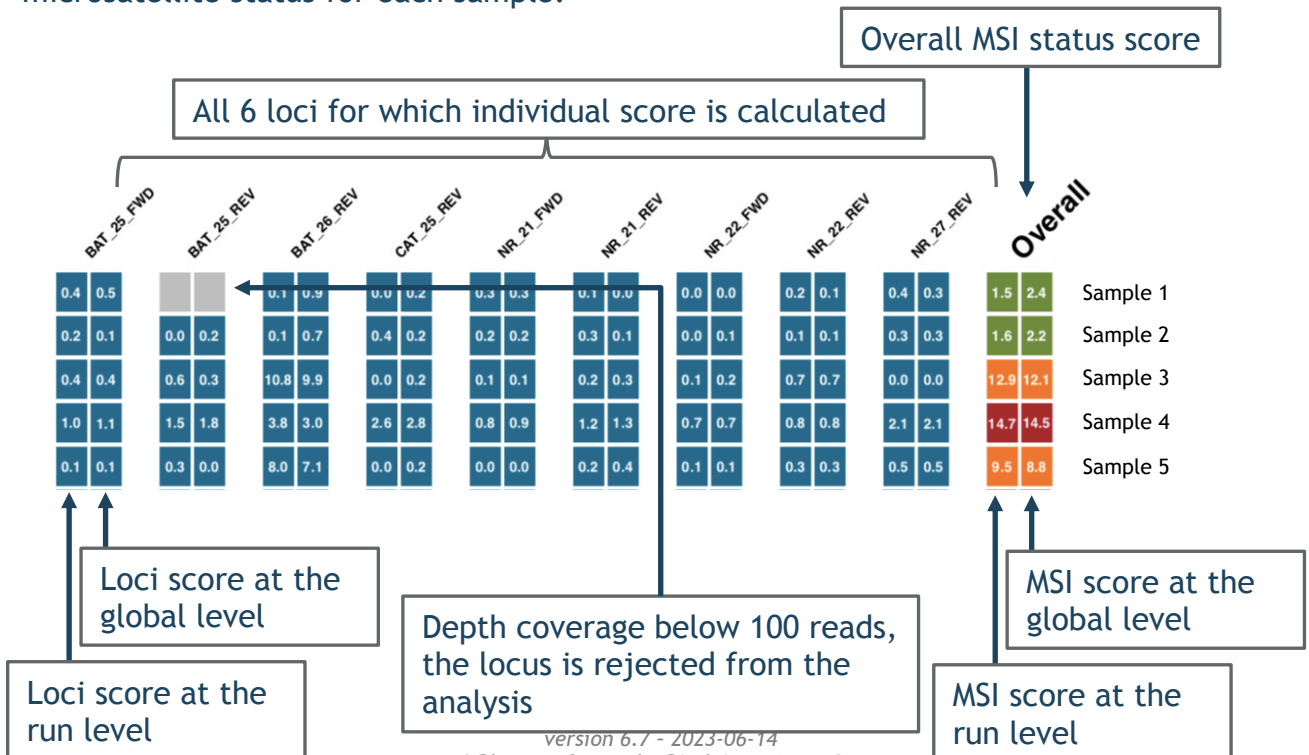
Note: The MSI algorithm requires a minimum depth coverage of as little as 100 reads per locus.

15. MSI Status Analysis

15.2 MSI status pdf report (STS)



The MSI status report can be downloaded in pdf format from the run overview in the workspace of SOPHiA DDM™. This comprehensive report displays a summary table of the microsatellite status for each sample.



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15. MSI Status Analysis

15.3 MSI status display (TSO500)

For the TSO500 application the MSI status is displayed in the Overview tab.

The screenshot displays the SOPHiA DDM™ software interface for the TSO500 application. The main navigation bar includes 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANAL... SG10002... #9999-0037'. The 'Overview' tab is active, showing a 'High' MSI status with a score of 68.3 mut/Mb. The 'Test Information' section on the right shows the test name 'TruSight Oncology 500 (somatic)' and the patient's pathologic diagnosis 'Non-small Cell Lung Carcinoma'. The 'SNVs/Indels Prediction' section shows a circular chart with segments for C (7655), R (2357), and D (125). The 'SNVs/Indels Pathogenicity Flags' section shows 'No Flags'. The 'Actionability' section shows a circular chart with segments for D (22), T1 (28), and T2 (32). The Overview section also displays various statistics such as 10,443 genes, 1418 variants, and 9225 retained variants.

The developed algorithm classifies MS into 4 categories:

- Stable (MS stable) with a score below 6
- High (MSI with high confidence) with a score > 14
- Equivocal (MSI with low confidence) with a score between 6 and 14
- Rejected (Analysis failed at detecting MSI status)

Note: The MSI status display is only available for the TSO500 application (like is the TMB score). For further info, please refer to the SOPHiA DDM™ for TruSight™ Oncology 500 User Guide.

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16. Familial Variant Analysis

16.1 Overview

This section will guide the user through the use of the Familial Variant Analysis (FVA) feature. It will only show the steps that are unique to this interpretation* mode. Please check the batch upload section (see [chapter 2.2 - Create a New Request](#)) for details on the entire workflow.

FVA is used to facilitate variant interpretation* by enabling the identification of the causative variant(s) responsible for the proband's phenotype through the analysis of parental samples. Users can filter the variants based on different modes of inheritance (i.e. de novo, autosomal recessive, including compound heterozygosity, autosomal dominant and X-linked) and thus increase the diagnostic yield of NGS based tests. In this initial version, users can perform both duo and trio family analysis in a simple and straightforward way.



16. Familial Variant Analysis

16.2 Create a New FVA Request (1)

“Create new FVA request”

Create a new family request for a duo (1 parent and proband) or trio (both parents and proband).

- Choose a request reference for your familial batch request
- Select specific test and sequencer (mandatory)
- Enter references for any trio member to filter in the next step (optional)
- Click “Next”

Note: Samples have to be captured with the same application to run FVA.

* Please refer to the Disclaimer (page 3).
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16. Familial Variant Analysis

16.2 Create a New FVA Request (2)

“Mother”
Select maternal sample

Affection status of the mother
Affected/unaffected

“Father”
Select paternal sample

Affection status of the father
Affected/unaffected

“Proband”
Select proband sample

Affection status of the proband
Affected/unaffected

Proband gender
Select if the proband is male (♂), female (♀) or unknown (-)

- Choose the corresponding analyses for the parent(s) and the proband
- Define the affection status (affected = filled / unaffected = empty circle or square) of all family members
- Click “Next” to continue

Note: To proceed with FVA, the application type needs to be identical. Users can either define a duo (mother or father and proband) or a trio (mother, father and proband).

16. Familial Variant Analysis

16.2 Create a New FVA Request (3)

The screenshot displays the 'New Familial Run Creation' window in the SOPHiA DDM software. The window title is 'Familial Variant Analysis Request' and it shows a pedigree chart with three individuals: Mother (CGH150475-M), Father (CGH150474-P), and Proband (Carolina Smith (CGH1040-CI) - Female). Below the chart, there is a checkbox for 'I am aware of the risk of identification of incidental findings...' which is checked. The background shows the 'My Tests - Interpretation' section with various test panels like BRCA, CFTR, EGFR, etc.

- Select checkbox to confirm that the risk of incidental findings is known
- Click “Finish” to create the new FVA request
- When completed, the user receives an email notification

Note: Completion of the FVA request automatically triggers re-annotation of all the variants via a proprietary Variant Unification algorithm that compares the BAM files of the selected individuals. This algorithm enables the establishment of the presence or absence of variants in all individuals of the family with high sensitivity and specificity, as well as their zygosity.

Depending on the server load, analysis times can vary. Usually, a request should be finished within 1-2 hours.

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16. Familial Variant Analysis

16.3 Open a Family Request (1)

The screenshot displays the SOPHiA DDM software interface. On the left, a 'Requests' panel shows a list of 188 requests for 600 patients. The list is filtered to 46/188 requests. The filter criteria include 'Status' (All, Completed, In Interpretation, Pipeline Analysis) and 'Tests' (CES_v1, CES_v2). The list includes entries for 'Family 01' through 'Family 05' and a 'Clinical Home Solution by SOPHiA' entry. Each entry shows the request ID, date, and test type. A pedigree icon is present next to the 'Family 01' entry.

On the right, a detailed view of a family request is shown. The request is identified as '#3-0273 Family 01 (Sales Meeting, please don't change)' with a date of 21/06/2018. The sequencer is 'Illumina MiSeq' and the processed date is 21/06/2018. The request date is 21/06/2018. The list of samples includes 'CES_v1' for the proband (CGH1040-CJ, Carolina Smith), mother (CGH1207-M, Anna Maria Smith), and father (CGH1206-P).

Annotations on the screenshot include:

- List of requests**: A box pointing to the list of requests on the left, with the text 'Select run request or family request'.
- Family request**: A box pointing to the pedigree icon next to the 'Family 01' entry, with the text 'Pedigree icon indicates family request'.

16. Familial Variant Analysis

16.3 Open a Family Request (2)

Request status

Family request creation date

Family files
Download full variant tables of all family members

Family request sample card

Application used

Family members

Interpretation Project*
Create an Interpretation Project* and restrict the analysis to a Virtual Panel if needed

Results of the FVA (duo or trio analysis) appear next to the other runs in the requests tab of the workspace. These results are grouped in a single analysis named “Familial Variant Analysis”. When a user opens/creates an Interpretation Project* of this type, SOPHiA DDM™ automatically triggers a new interpretation mode specific to FVA, focused on the proband. In the variant list, dedicated columns visually display the presence/absence and zygosity status of the variants of the duo or trio next to each other.

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16. Familial Variant Analysis

16.4 SNVs/Indels View

Inheritance mode

Select and test different modes of inheritance. Variants are filtered accordingly.

Family affection status

The color of the box indicates if the family member is affected or not (pink/white).

The screenshot displays the SOPHiA DDM interface for a Familial Variant Analysis. At the top, the workspace is set to 'ANALYSIS CGH' with variant ID '#3-0152'. The main view is titled 'FAMILY' and shows 'Interpretation 4' for a 'trio anja' analysis run on '04/12/2020'. The variant list is sorted by 'ACMG Value > Gene > Transcript > Strand'. The table below shows four variants: ARID1B (SNP, chr 6), COL4A4 (SNP, chr 2), NXNL1 (INDEL, chr 19), and PEX5 (INDEL, chr 12). Each variant row includes columns for Genomic coordinates, Sample (ref/alt), Family (VF(%) and Depth), Gene/Transcript, and Transcript details (refSeq, refAA, altSeq, altAA, CDNA Protein, Exon Rank, Exon Position, and Scores). Family affection status is indicated by colored boxes: pink for affected and white for unaffected. The ARID1B variant is highlighted, showing a family affection status of 41.8% and a transcript of NM_017519.2. The bottom section provides a detailed view of the ARID1B variant, including a variant diagram showing the splice donor site and a mutation taster score plot.

Note: Inheritance mode filters are only available for trio analyses but not for duo analyses.

16. Familial Variant Analysis

16.5 Variant Unification Algorithm

SOPHiA DDM™ Variant Unification (VU) algorithm for FVA improves the variant calling by using information derived from all available samples of all individuals of the same family. SOPHiA DDM™ FVA makes use of BAM and VCF files of all family members integrated in the VU Algorithm. The algorithm compares variants among all samples of a familial request for a given genomic position. In this way, variant calling can be enhanced for all variants including those that could not be detected due to low coverage in individual samples.

Genotype icons for family members



Variant is confidently absent (wildtype)



Variant is confidently heterozygous



Variant is confidently homozygous



Variant is confidently present but genotype (hetero- or homozygous) cannot be defined



Homozygous state can be excluded but genotype (heterozygous or absent) cannot be defined



Noisy region (genotype cannot be determined)

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16. Familial Variant Analysis

16.6 Inheritance Mode Filter

Inheritance mode

Select and test different modes of inheritance. Variants are filtered accordingly.

The screenshot displays the SOPHiA DDM™ interface for a variant analysis. A dropdown menu for 'Inheritance pattern' is open, showing the following options: None selected, Autosomal recessive, Autosomal dominant, De novo (highlighted), and X-linked. The background shows a variant list table with columns for Genomic, Transcript, and Scores.

Genomic	Transcript	Scores
SNP chr 6 157525131	ARID1B NM_017519 c.4986+1G>A exon 18 p.? splice_donor_+1	41.8% 146 1.0
SNP chr 2 111292832	RGPD6 NM_001123363 c.3131C>G exon 21 p.Pro1044Arg missense	42.4% 106 1.0
SNP chr 2 113147391	RGPD8 NM_001164463 c.3131C>G exon 20 p.Pro1044Arg missense	25.3% 146 1.0
SNP chr 15 113147391	ACAN NM_001135 c.3465C>T exon 12 p.= (p.Thr1155Thr) synonymous	33.3% 63 1.0

Select a mode of inheritance from the drop-down list. SOPHiA DDM™ instantly filters the variants accordingly and displays the resulting list. The user may change the inheritance mode at his/her convenience and at any time during the interpretation.

The interpretation can be further facilitated by using all of the other SOPHiA DDM™ features e.g. Virtual Panels, custom filters, determination of the pathogenicity level according to the ACMG standards and guidelines (see [chapter 4.9.11](#)), variant flagging, inclusion of variants in the report and variant report generation. Finally, the variant report has been adapted to display FVA specific information and columns.

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17. SARS-CoV-2 application

SOPHiA DDM™ for SARS-CoV-2
SOPHiA DDM™ supports variant calling for this amplicon-based panel. High-quality variant calling is critical to create full genome FASTA files for any downstream analysis like multiple alignment and phylogenetic trees.

Several features are available for this application:

- **Metadata import:** Upload of patient* and sampling metadata via an “Import” button in the Create Request Form and in the Workspace
- **Quality indicators:** 4 indicators for all samples in the Workspace allow easy assessment of sequencing results` quality ([ch. 3.10 Quality Indicators](#))
- **FASTA files:** Download of high-quality FASTA files for each sample as well as an accumulated FASTA file for all samples of a batch request
- **Virus presence report:** Download of a CSV file from the Workspace (run-level and sample-level) allows easy export of results and import into spreadsheet programs
- **Global viral allele frequencies:** Allele-frequencies retrieved from the GISAID EpiCoV™ database are available in the full variant table

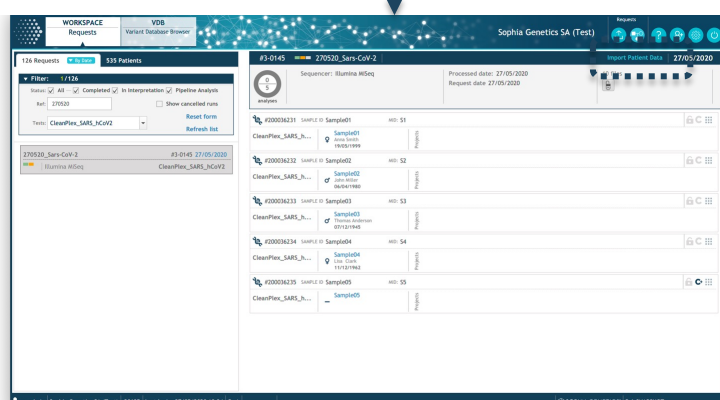
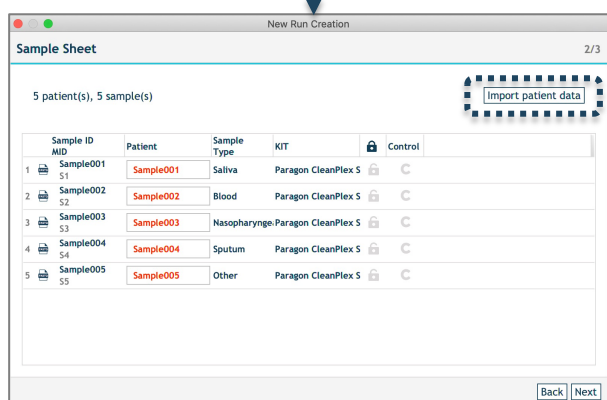
Note: With exception of the quality indicators, described functionalities are specific to this application and are not available for other panels. Viral allele frequencies are not updated dynamically.

17. SARS-CoV-2 application

17.1 Metadata import (1)

Sampling and patient* data can be imported from a csv file:

1. Before sample upload in the Create Request Form
2. After sample upload in the Workspace



Requirements CSV file:

- Data matching is based on the Patient* ID, so «Patient Ref» column cannot be empty
- Columns should be named exactly like in the example (see next page). The order of the columns does not matter
- Ensure correct values (see possible entries on the next page)
- All column headers should be present but not all fields need to be filled
- Make sure to format the date fields in the scheme YYYY.MM.DD
- Select «CSV UTF-8 (comma-delimited) (.csv)» when exporting the csv file to ensure that umlauts or other special characters are correctly parsed

Note: This functionality is only available for the Sars-CoV-2 application. Example CSV files are available from our support team at support@sophiagenetics.com.

17. SARS-CoV-2 application

17.1 Metadata import (2)

	-	Collection data			Patient* data			
Column name	Patient Ref	Date of collection	Location of collection	Sample type	First name	Last name	Date of birth	Gender
Possible entries / Format	Sample ID	YYYY.MM.DD	Free text	Sputum Saliva Nasopharyngeal swab Bronchoalveolar lavage Other*	Free text	Free text	YYYY.MM.DD	Male Female Unknown
Example	Sample001	2020.08.01	Lausanne	Nasopharyngeal swab	Anna	Miller	1947.09.19	Female

	Sample data		Clinical presentation	
Column name	RNA quantity	Ct value	Date of symptom onset	Date of hospital admission
Possible entries	comma value	comma value	YYYY.MM.DD	YYYY.MM.DD
Example	10.8	15.5	2020.07.27	2020.07.29

	Medical history / Diseases*							
Column name	Hypertension	Cardiovascular disease	Diabetes	Chronic respiratory disease	COPD	Asthma	Renal disease	Obesity
Possible entries	yes no	yes no	yes no	yes no	yes no	yes no	yes no	yes no
Example	yes	no	yes	no	no	yes	no	no

	Medical history / Diseases*				PCR test results		
Column name	BMI	Smoking status	Immuno-suppressive treatment	Cancer	PCR test done	Date of PCR test	PCR test result
Possible entries	comma value	current past never	yes no	yes no	yes no	YYYY.MM.DD	positive negative
Example	23.5	past	no	no	yes	2020.07.29	positive

Note: Make sure to use the exact column header naming. Further sample types that are available in the Create Request Form (e.g., Blood, Fresh Tumor, FFPE, Biopsy Cell Line, ctDNA or Buccal Swab), can also be imported. Dates can only be imported if they follow the format YYYY.MM.DD.

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17. SARS-CoV-2 application

17.1 Metadata import (3)

1 Create New Batch Request

The screenshot shows the SOPHiA DDM interface. At the top, there are tabs for 'WORKSPACE Requests' and 'VDB Variant Database Browser'. The user is logged in as 'Sophia Genetics SA (Test)'. A 'Sample Sheet' table is displayed with 5 rows of sample data. A button labeled 'Import patient data' is highlighted with a dashed box. Below the table, a 'Multi-modal data import' dialog box is open, showing a table with columns for 'Collection data', 'Patient data', and 'Sample data'. The table contains 6 rows of data, with the last row (row 6) having a date of birth '01.05.00' which is highlighted in yellow. A 'View Warnings' button is also highlighted with a dashed box.

Sample ID MID	Patient	Sample Type	KIT	Control
1 Sample001 S1	Sample001	Nasopharynge...	Paragon CleanPlex SARS-CoV-2 Panel	C
2 Sample002 S2	Sample002	Sputum	Paragon CleanPlex SARS-CoV-2 Panel	C
3 Sample003 S3	Sample003	Bronchoalveol	Paragon CleanPlex SARS-CoV-2 Panel	C
4 Sample004 S4	Sample004	Saliva	Paragon CleanPlex SARS-CoV-2 Panel	C
5 Sample005 S5	Sample005	Other	Paragon CleanPlex SARS-CoV-2 Panel	C

CSV Row	Patient ref	Collection data			Patient data			Sample data		
		Date of collection	Location of collection	Sample type	First name	Last name	Date of birth	Gender	RNA Quantity	CT Value
#2	Sample001	01/05/2020	London	Saliva	Anna	Smith	19/05/1999	Female	10.6	10.0
#3	Sample002	01/05/2020	Lausanne	Blood	John	Miller	06/04/1980	Male	29.7	15.0
#4	Sample003	01/05/2020	Zurich	Nasopharyng...	Thomas	Anderson	07/12/1945	Male	50.0	22.0
#5	Sample004	02/05/2020	Paris	Sputum	Lisa	Clark	11/12/1962	Female	29.7	22.0
#6	Sample005							Unknown		

2 Import patient* metadata
Click "Import patient data" button. Select and upload csv file with sample data. Matching is done with the help of the Patient* ref.

Multi-modal data import

Import

View Warnings
Some imported patients were not found in the request, they will be ignored.
Some patients from the request were not found in the import.

Cancel Apply

Import Warnings

2 warning(s) found while parsing CSV file

- Unknown column "Additional column"
- Can not parse date "01.05.00" on row 6 for column Date of birth

3 Check warnings (if any)
Click "View Warnings" and verify which fields cannot be parsed correctly. If needed, correct the csv file, close Warnings, then re-upload corrected csv file.

17. SARS-CoV-2 application

17.1 Metadata import (4)

4 Re-upload corrected csv file and apply data

After correcting the errors, re-upload the csv file. The Warnings message is no longer shown. Click "Apply" to import the sample data.

Multi-modal data import

Import

CSV Row	Patient ref	Collection data			Patient data			Sample data		
		Date of collection	Location of collection	Sample type	First name	Last name	Date of birth	Gender	RNA Quantity	C Value
#2	Sample001	01/05/2020	London	Saliva	Anna	Smith	19/05/1999	Female	10.6	14.0
#3	Sample002	01/05/2020	Lausanne	Blood	John	Miller	06/04/1980	Male	29.7	11.0
#4	Sample003	01/05/2020	Zurich	Nasopharyng...	Thomas	Anderson	07/12/1945	Male	50.0	21.0
#5	Sample004	02/05/2020	Paris	Sputum	Lisa	Clark	11/12/1962	Female	29.7	21.0
#6	Sample005			Other			11/12/1988	Male		

Confirmation

Are you sure you want to save these patients' data?

Buttons: Cancel, Apply, OK, Cancel

5 Confirmation

Click OK to confirm data import.

6 Sample upload

If Sample Type data were imported, the column is now filled. Click "Next", then "Finish" to start the batch request.

Sample Sheet

5 patient(s), 5 sample(s)

Sample ID	Patient	Sample Type	KIT	Control
1 Sample001 S1	Sample001	Saliva	Paragon CleanPlex S	C
2 Sample002 S2	Sample002	Blood	Paragon CleanPlex S	C
3 Sample003 S3	Sample003	Nasopharyng...	Paragon CleanPlex S	C
4 Sample004 S4	Sample004	Sputum	Paragon CleanPlex S	C
5 Sample005 S5	Sample005	Other	Paragon CleanPlex S	C

Buttons: Import patient data, Back, Next

Note: If a "Patient* Ref» is already present in the database, existing values (e.g., Birth date or Gender) are not overwritten. Only new entries are added.

17. SARS-CoV-2 application

17.2 Workspace (1)

Batch request
Selected batch request.

Run-level files
Run-level file download

Quality indicators
See [ch. 3.10.3](#)

Imported Patient* data
Gender, birthdate and (first/last) name imported during sample upload.

Import Patient* Data
Upload metadata (see [p. 261](#))

Sample-level files
Sample-level file download.

17. SARS-CoV-2 application

17.2 Workspace (2)

Downloadable files & available links

File / Download / Link	Run-level	Sample-level
Virus presence report	X	X
All FASTA	X	
Aggregated FASTA	X	
Individual FASTA		X
Load in IGV		X
Full variant table (*.vcf and *.txt)	X	X

Note: With exception of the full variant table, only files/download links particular to this application are listed. A description of each file can be found on the following page. Information on general run- and sample-level files not specific to this application, can be found in chapter [3.7 Analysis Card Overview](#).

17. SARS-CoV-2 application

17.2 Workspace (3)

Virus presence report

A csv format report for all/individual samples of the batch request stating status of virus presence (positive, negative, unknown), clade naming based on Nextstrain and Pangolin lineage, number of amplicons covered, imported sampling info (collection date & place, sample type, patient*`s age, co-morbidities, RNA quantity, Ct value, run date and number, run name, Sequencer and read length).

FASTA files

Text-based whole virus genome nucleotide sequence excluding 300 bp at 5` and 3` end. FASTA files are available per individual sample (sample card) and as zip-download of all individual FASTA files (run files). Also, an aggregated file is available containing all individual sequences.

Load IGV

A link to load IGV from the sample card is available, allowing the user to investigate the covered regions and detected variants. The option to load IGV from the detected variant is available from the Analysis view as usual.

Full variant table

Available in txt and vcf format.

17. SARS-CoV-2 application

17.3 Analysis View (1)

Imported Patient* data

Imported Patient* diseases*

The screenshot shows the 'ANALYSIS Sample001 #3-0156' view. The 'Patient' tab is active, displaying 'Personal Details' and 'Diseases'. The 'Personal Details' table includes:

Field	Value
Age	N/A
Gender	Female
First Name	Anna
Last Name	Smith

The 'Diseases' section lists 'Respiratory System Disease' and 'Hypertension', both with an 'Admin User' assigned. A 'Patient's Disease' dropdown menu is open, showing 'Respiratory System Disease, Hypertension'. The 'Specimen' tab is also visible, showing details like 'Specimen ID: 12345' and 'Date Collected: 01/12/2020'.

This screenshot shows the 'Specimen' tab selected. The 'Specimen' table displays the following information:

Field	Value
Specimen ID	12345
Place Collected	London
Date Collected	01/12/2020
Date Received	02/12/2020
Selected By	
Specimen Type	Saliva
Preservation Method	
Ct Value	10.0
DNA Quantity	
RNA Quantity	10.6 ng

The 'Diseases' section is now empty. The 'Patient' tab is also visible, showing 'Personal Details' and 'Diseases'.

Imported Sampling / Specimen data

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17. SARS-CoV-2 application

17.3 Analysis View (2)

Variant list and export

The screenshot displays the SOPHiA DDM analysis interface for a SARS-CoV-2 sample. The top navigation bar includes 'WORKSPACE Requests', 'VDB Variant Database Browser', and 'ANALYSIS Sample001 #3-0156'. The main header shows 'Sophia Genetics SA (Test)' and 'Interpretation 1'. Below this, the 'CleanPlex_SARS...' panel is visible with '12 genes'. The 'OVERVIEW' tab is active, showing a 'Variant List - sorted by: Coding consequence'. A table of variants is displayed, with a dashed box highlighting a specific row. Below the table, a detailed view for the variant 'c.1841A>G' is shown, including 'OVERVIEW' statistics (3741 reads, 99% variant fraction), 'DETAILS' (4/5 frequencies, 57% RUN), 'VARIANT DESCRIPTION' (flagging 0-5), and 'VIEWER' (transcript GU280_sp02, exon rank 1, cDNA c.1841A>G, ref/alt A>G, sequence GAT->GGT, amino acid D->G, protein p.(Asp614Gly)).

ID	P...	S...	Type	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
...	OTHER	5UTR	5UTR	c.1-25C>T	881	100.0	C	T
...	OTHER	N	missense	c.610G>C	26613	99.8	G	C
...	OTHER	ORF1ab	missense	c.14144C>T	2331	98.7	C	T
...	OTHER	S	missense	c.1841A>G	3741	99.8	A	G
...	OTHER	N	missense	c.608G>A	26613	99.7	G	A
...	OTHER	ORF1ab	synonymous	c.48C>T	775	100.0	C	T
...	OTHER	N	synonymous	c.609G>A	26613	99.7	G	A
...	OTHER	ORF1ab	synonymous	c.2772C>T	1258	100.0	C	T

Note: No particular experiment type is existent for viral samples, they are displayed as “germline“. This has no impact on the displayed variant list.

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18. Appendix - Variant Table (1)

Field (Column)	Description
Actionability*	OncoPortal™ actionability*
alt	Genomic alternative allele
altAA	Alternative amino acid
altNum	Number of reads supporting the alternative allele taking Phred scores into account
AltSeq	Alternative codon sequence
c.DNA	Variant coordinates relative to the coding c.DNA according to HGVS nomenclature
Chromosome	The chromosome number
ClinVar rating	Pathology significance in ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/)
Coding consequence	Variants not overlapping the coding sequence of a gene are classified as 3'/5'-UTR or intronic. Exceptions are variants falling within the +1 to +4 splice donor sites or the -2 and -1 splice acceptor sites. These variants are classified as splicing variants, i.e. as variants that might affect the splicing of the transcript. Variants falling within the coding sequence are classified as: synonymous, missense, in-frame, frameshift, no-start, no-stop and nonsense variants
Codon	Triplet of adjacent nucleotides coding for a specific amino acid
Community	Community flagging distribution
Cosmic coding/non-coding	Overlapped variants ID in cosmic database (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/)
dbSNP	Variant annotation in NCBI dbSNP Short Genetic Variations (http://www.ncbi.nlm.nih.gov/projects/SNP/)
Depth	Total coverage at the position of the variant taking Phred score into account
Distance to exon	Number of nucleotides to closest exon border (positive integer)
ESP	Variant frequency in Exome Sequencing Project (http://evs.gs.washington.edu/EVS/)
ExAC	Variant frequency in the Exome Aggregation Consortium (http://exac.broadinstitute.org)

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18. Appendix - Variant Table (2)

Field (Column)	Description
Exon ID	ID of the exon in which the variant is located
Exon rank	The exon rank in the given transcript structure
Filter	Annotation filter
Frequency in Account	The number of times this variant was detected using the same application version in this account. Note: If there are several samples from the same subject in the account, the variant is only counted once.
Frequency in Community	The number of times the variant has been found in all the patients* in routine diagnostic* in the SOPHiA DDM community; only retained variants are considered.
Frequency in Run	The number of times the variant has been found in the samples of the same run (germline or somatic applications)
g1000	1000 genome project variant frequency (http://www.1000genomes.org)
Gene	The HGNC (HUGO Gene Nomenclature Committee) gene symbol
Gene boundaries	Indicator if the variant is within the gene
Genome position	The variant coordinate on the reference genome
GERP	GERP conservation score
gnomAD	Variant frequency in the Genome Aggregation Database (gnomad.broadinstitute.org/)
Id	Unique, sample-specific variant identifier
ID ClinVar	Overlapped variants in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/)
In report	Indicates if a variants has been flagged to be included in the report
LRT	LRT score
MutationTaster	Mutation Taster conservation score (http://www.mutationtaster.org) only available for SNVs
OMIM	OMIM identifier (http://omim.org)
overlapKnown	ID of variant in other databases <small>* Please refer to the Disclaimer (page 3).</small>
PhyloP	PhyloP conservation score

18. Appendix - Variant Table (3)

Field (Column)	Description
PolyPhen2	Polyphen2 conservation score (http://genetics.bwh.harvard.edu/pph2/)
Position in Exon	Position of the variant in the exon
Protein	The variant description in terms of protein coordinates (HGVS nomenclature)
ref	Genomic Reference allele
refAA	Reference amino acid
Reference Genome	The NCBI and UCSC version of the human genome used
refNum	Number of reads supporting the reference allele taking Phred scores into account
RefSeq	Reference codon sequence
refSeqId	RefSeq accession number
Screening ID	Unique, hotspot-specific identifier
SIFT	SIFT conservation score (http://sift.jcvi.org)
Strand	Indicates whether the gene is located on the plus or minus strand of the reference genome
Transcript	The gene transcript structure annotation actually used - either the annotation from Ensembl, when available, or NCBI Reference Sequence
type	Indicates the type of the variant, either Single Nucleotide Polymorphism (SNP) or Insertion/Deletion (Indel)
VF%	Percent variant fraction (proportion of reads supporting the variant count taking Phred score into account)

Support

SUPPORT AND CONTACT DETAILS

In case of difficulty using SOPHiA DDM™, please consult the troubleshooting section of the “General information: SOPHiA DDM™ usage” document, or contact our support line by phone +41 21 694 10 or by email at support@sophiagenetics.com

The SOPHiA DDM™ Platform and services are designed and operated by SOPHiA GENETICS SA:



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Document Approvals

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