SOPHiA DDM™

Operation Manual

v6.7

SOPHiA GENETICS™

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.

Revision History (1)

Date *YYYY-MM-DD*	SOPHiA DDM™ Version	Manual Version	Change
2023-06-14	**v5.10.37**	**v6.7**	• 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**	• 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**	• 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**	• 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**	• 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 *YYYY-MM-DD*	SOPHiA DDM™ Version	Manual Version	Change
2021-11-24	**v5.10.10**	**v6.2**	• 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**	• 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**	• 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
			• 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**	• 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

Revision History (4)

Date *YYYY-MM-DD*	SOPHiA DDM™ Version	Manual Version	Change
			• 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**	• Addition of Disclaimer
2019-10-08	**v5.4.0**	**v4.5**	• 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**	• 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**	• 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**	• 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**	• 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**	• 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**	• 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**	• 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**	• 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**	• 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**	• 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**	• 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

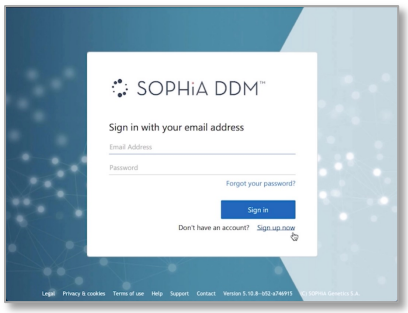
1. User Account
1.1 Download

- 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

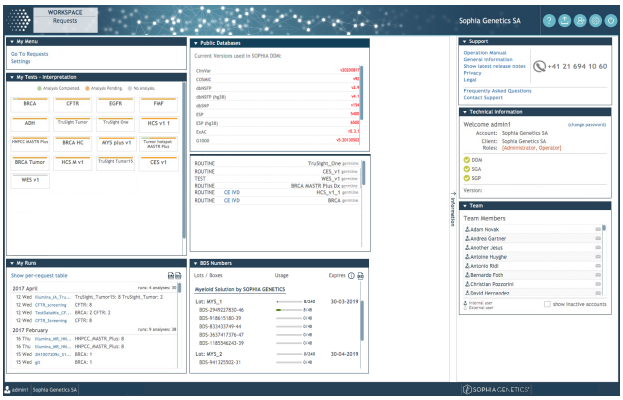
Application start
Open the SOPHiA DDM™ Platform application.



Login using Password & Token card
see chapter 1.2.1

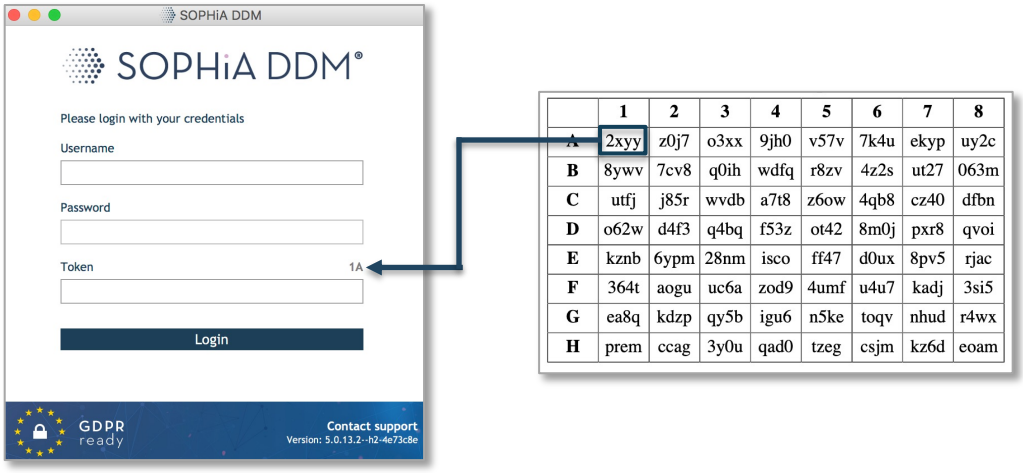
Login using multi-factor authentication
see chapter 1.2.2

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.

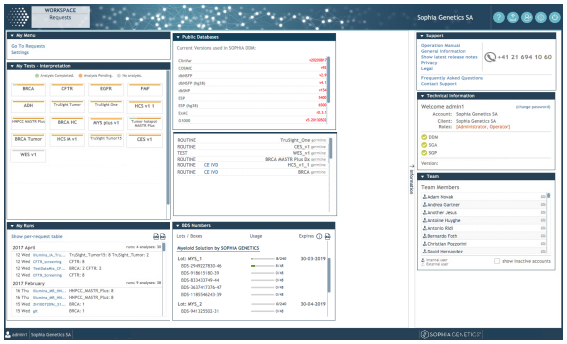
1. User Account
1.2.1 Login using token card



	1	2	3	4	5	6	7	8
A	2xyy	z0j7	o3xx	9jh0	v57v	7k4u	ekyp	uy2c
B	8ywv	7cv8	q0ih	wdfq	r8zv	4z2s	ut27	063m
C	utfj	j85r	wvdb	a7t8	z6ow	4qb8	cz40	dfbn
D	o62w	d4f3	q4bq	f53z	ot42	8m0j	pxr8	qvoi
E	kznb	6ypm	28nm	isco	ff47	d0ux	8pv5	rjac
F	364t	aogu	uc6a	zod9	4umf	u4u7	kadj	3si5
G	ea8q	kdzp	qy5b	igu6	n5ke	toqv	nhud	r4wx
H	prem	ccag	3y0u	qad0	tzeg	csjm	kz6d	eoam

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

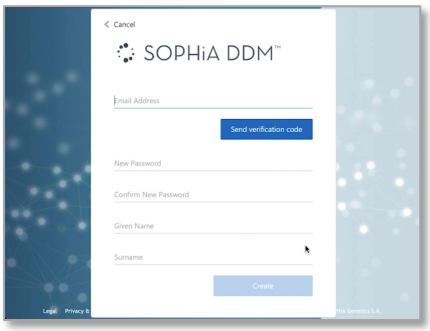


NOTE: Users with access to several accounts have to select the account they wish to connect to after clicking «Login». To reset the password and or token card, please contact support@sophiagenetics.com.

1. User Account
1.2.2 Login using multi-factor authentication

Update authentication method

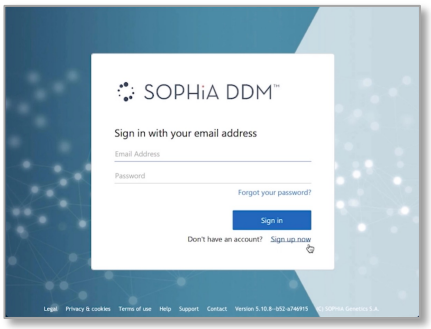
If the user/account was already migrated, click «Update now» to sign up to multi-factor authentication.



Sign-up (first time only)

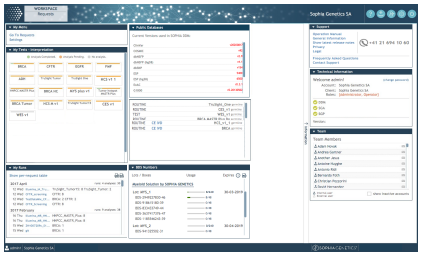
Follow these steps for sign-up:

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

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

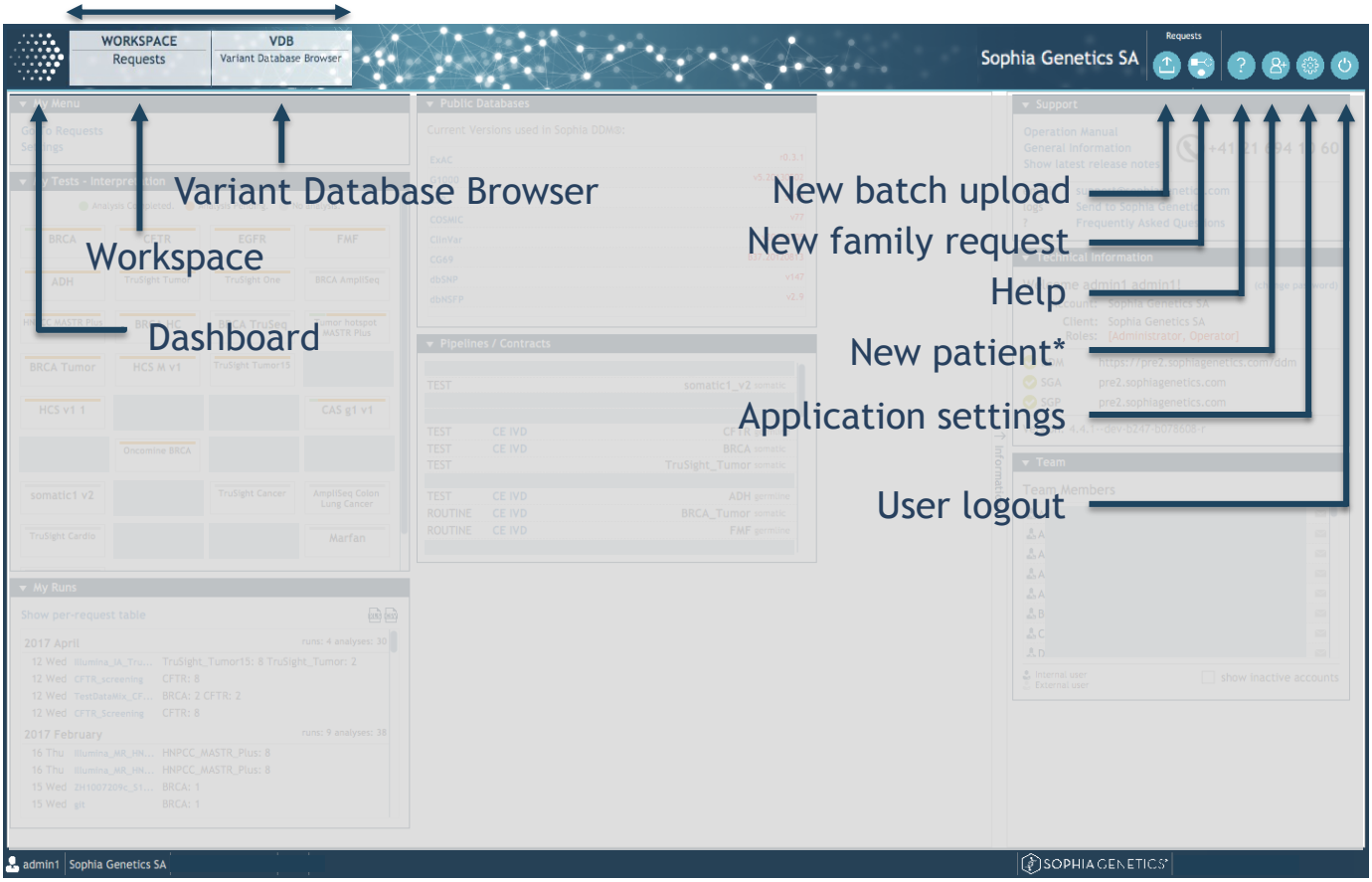
Consent restriction
- Restriction at sample level (to reflect patient's* consent)
- Restriction defined before data upload or before opening an analysis to avoid incidental findings
- Can be specified by "admin users" and "restricted users" (See chapter 2.2 – New Batch Request)
- Can be changed by admin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

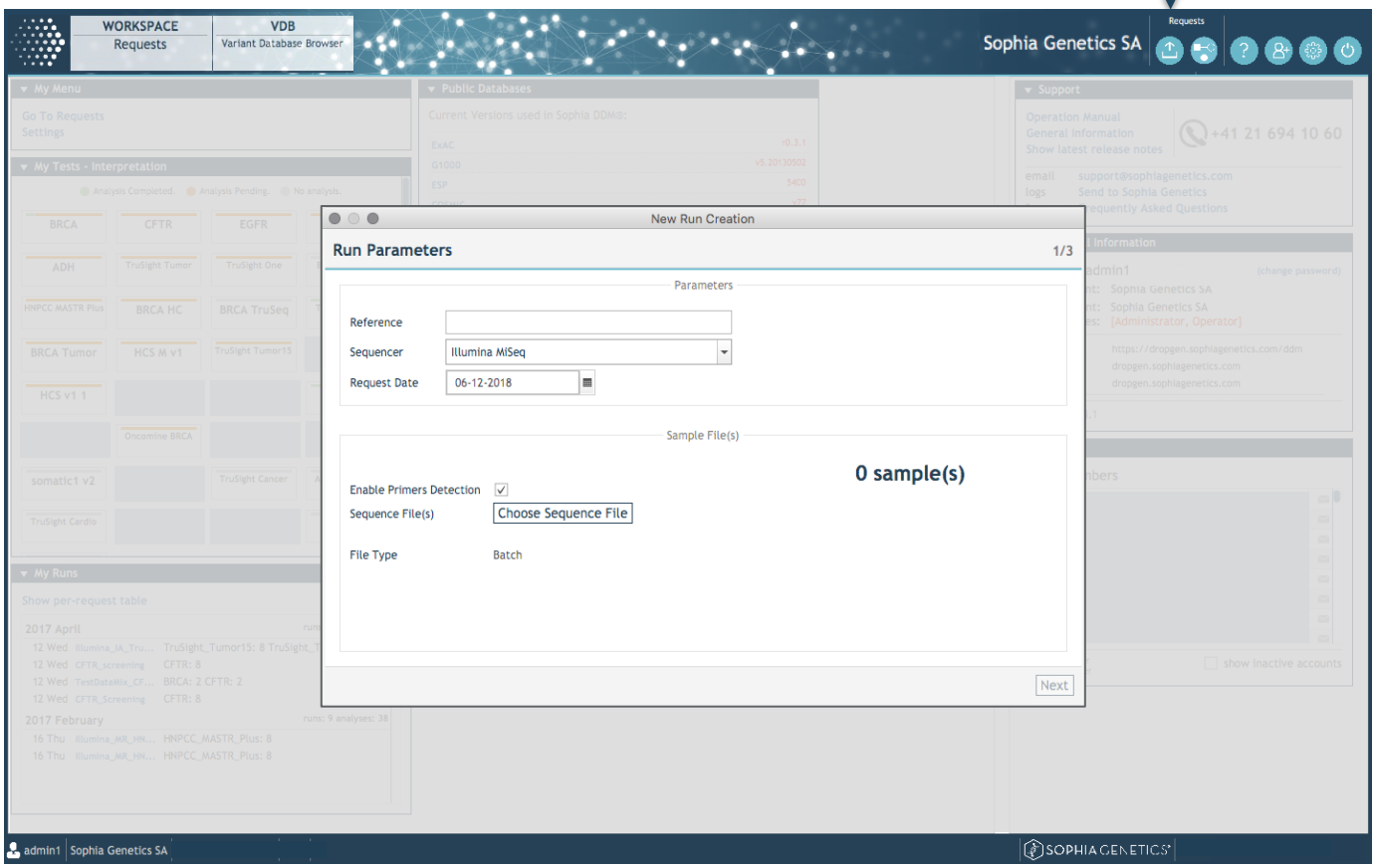
SOPHiA DDM™ release version

Application Footer

version 6.7 - 2023-06-14
** Please refer to the Disclaimer (page 3).*
Research Use Only. Not for use in diagnostic procedures.

2. Dashboard
2.2 Create a New Request (1)

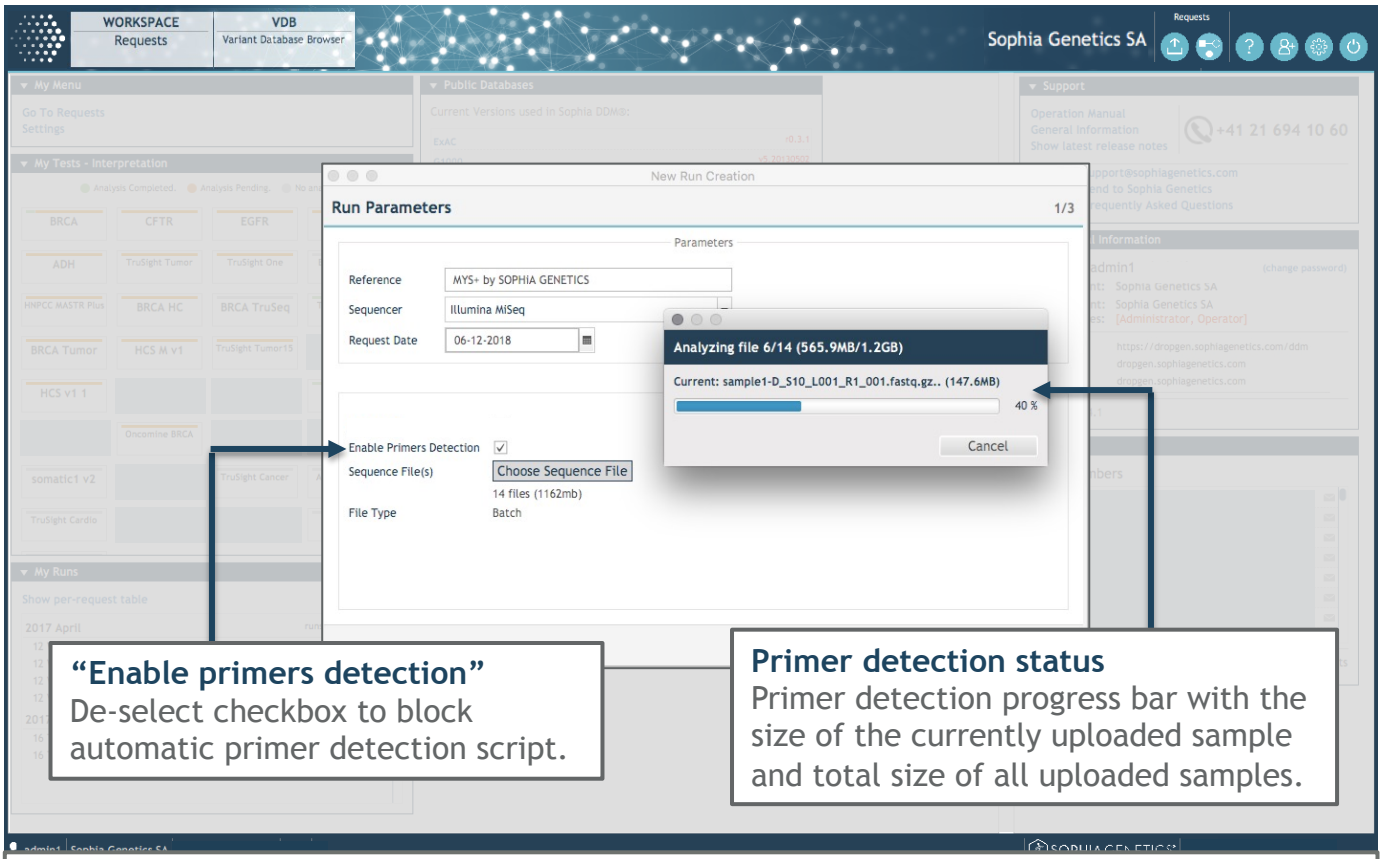
“Create new batch request”
Creates a new run request for one or multiple sequencing files.



Choose a reference name for your request

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

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.

2. Dashboard
2.2 Create a New Request (3)

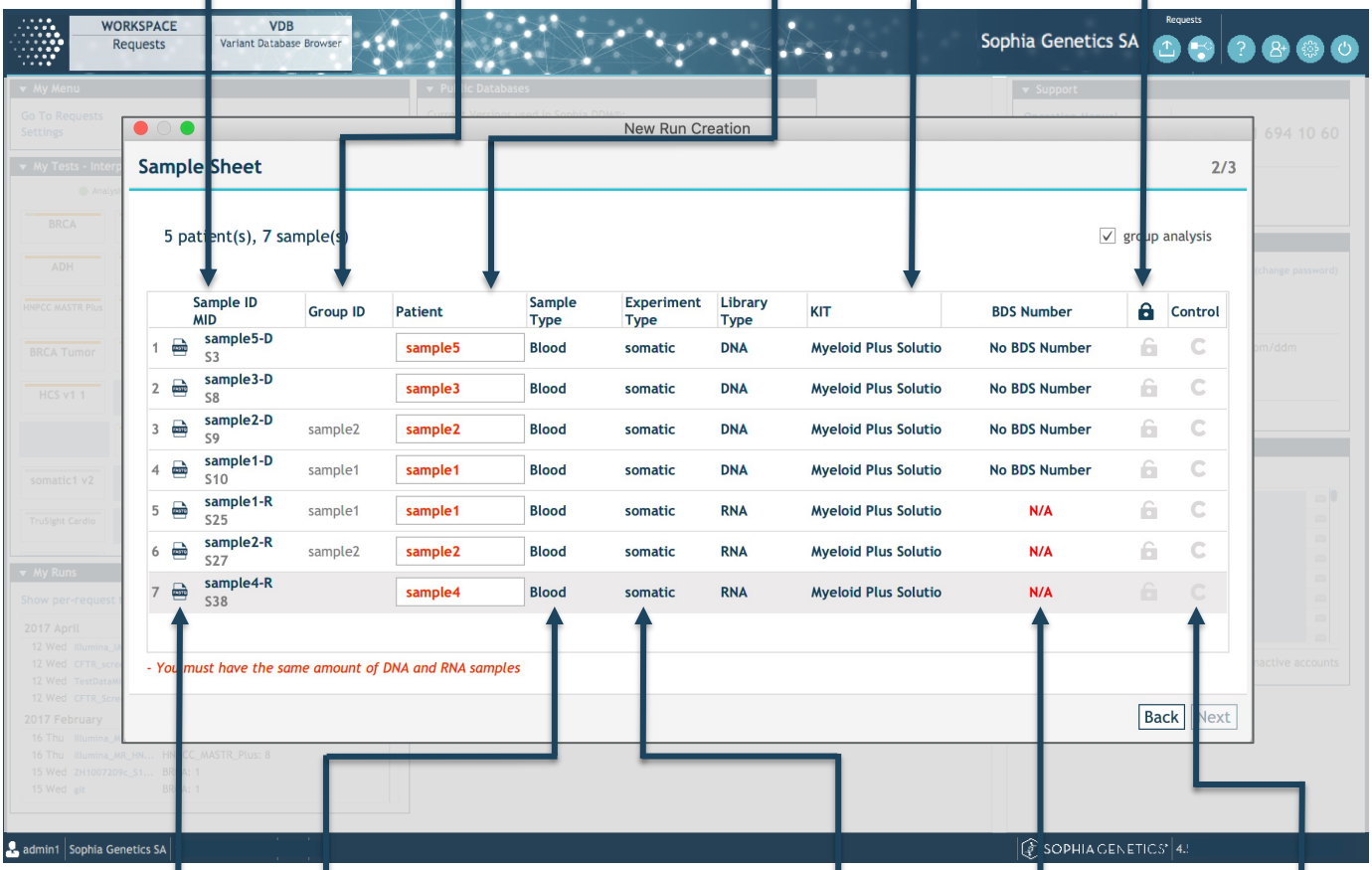
MID (multiplex identifier) & Sample ID
Index used for sample identification & sample name from sample sheet

"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



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).

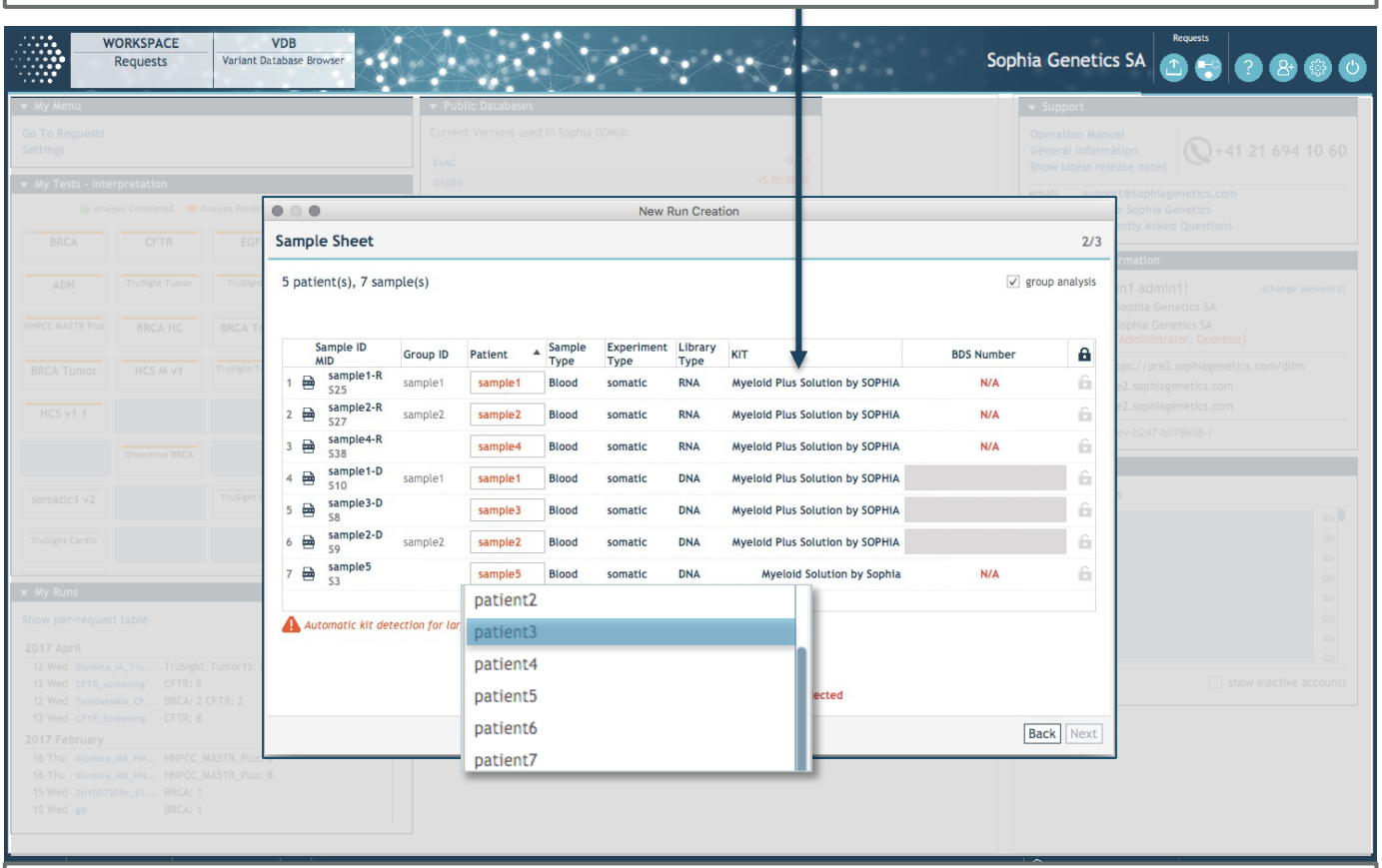
"Experiment type"
Recognized automatically (except if both somatic and germline algorithms are available for one test).

"BDS number"
Sample tracking ID; see ch. 2.3 BDS numbers

"Control"
Control sample status; see ch. 3.9 Control Samples

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.

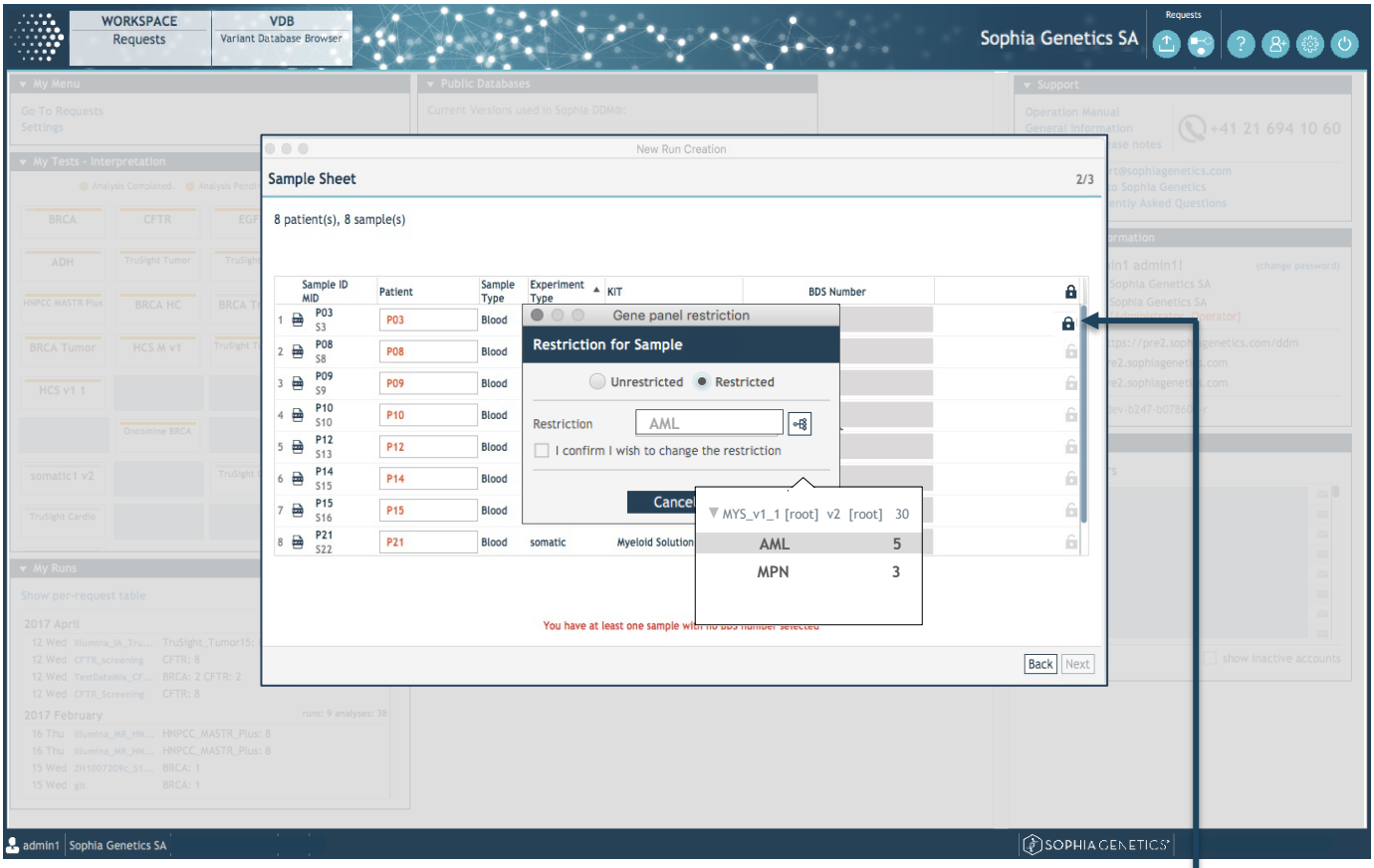


Column "patient*" is editable
To edit patient* ID, click in the cell "Patient*" and start typing. The list of existing patient* IDs shows up in a drop-down menu. Select an existing patient* ID or enter a new patient* ID.

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.

2. Dashboard
2.2 Create a New Request (5)



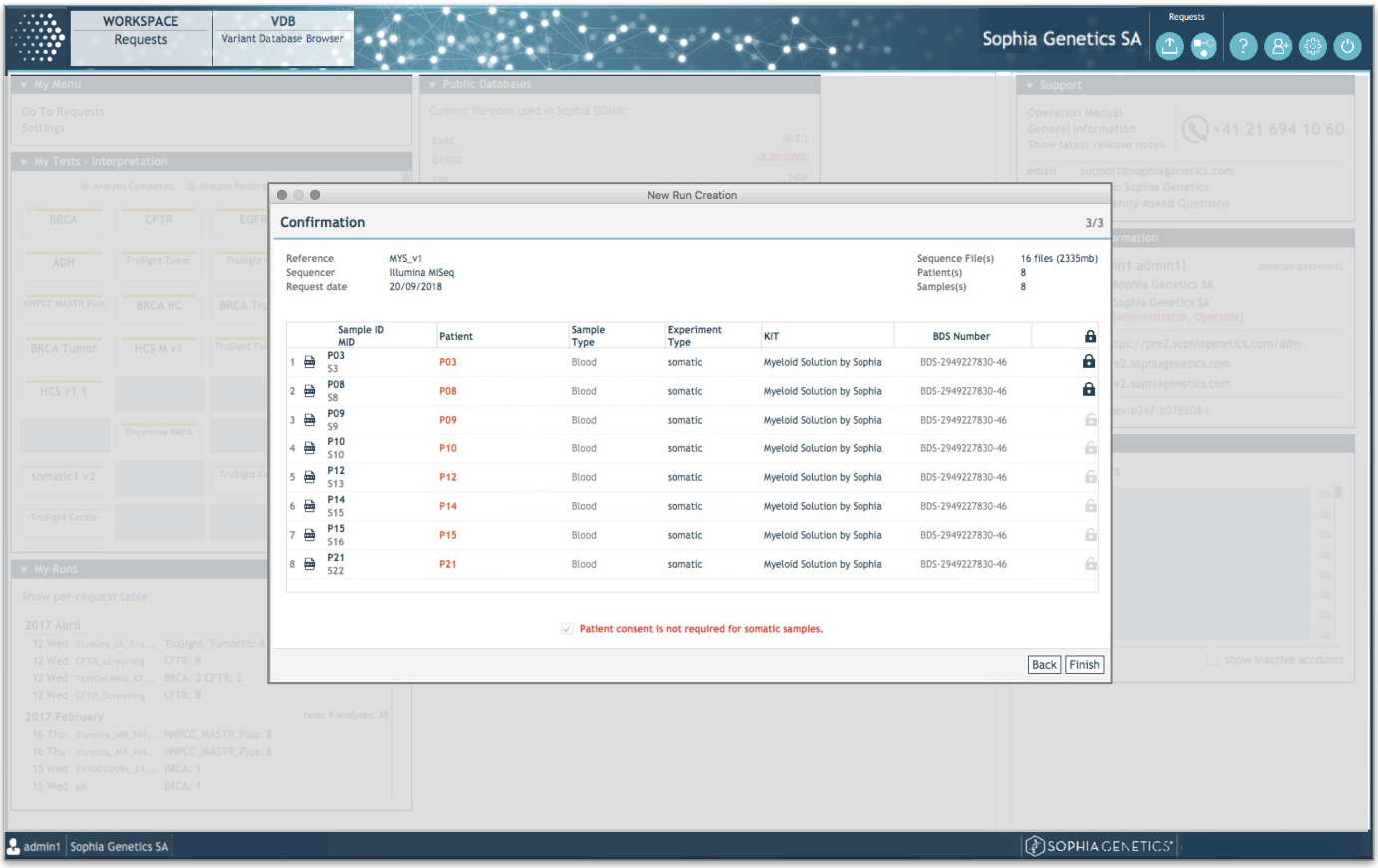
Consent restriction

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.

2. Dashboard
2.2 Create a New Request (6)



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.

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.

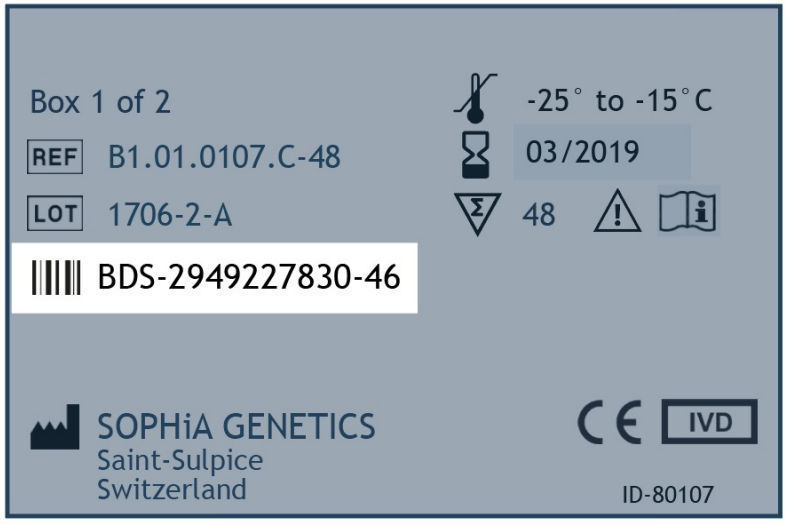
BDS numbers are only available for catalog and custom SOPHiA DDM™ bundle solutions.
BDS implementation does not concern applications using:

- 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

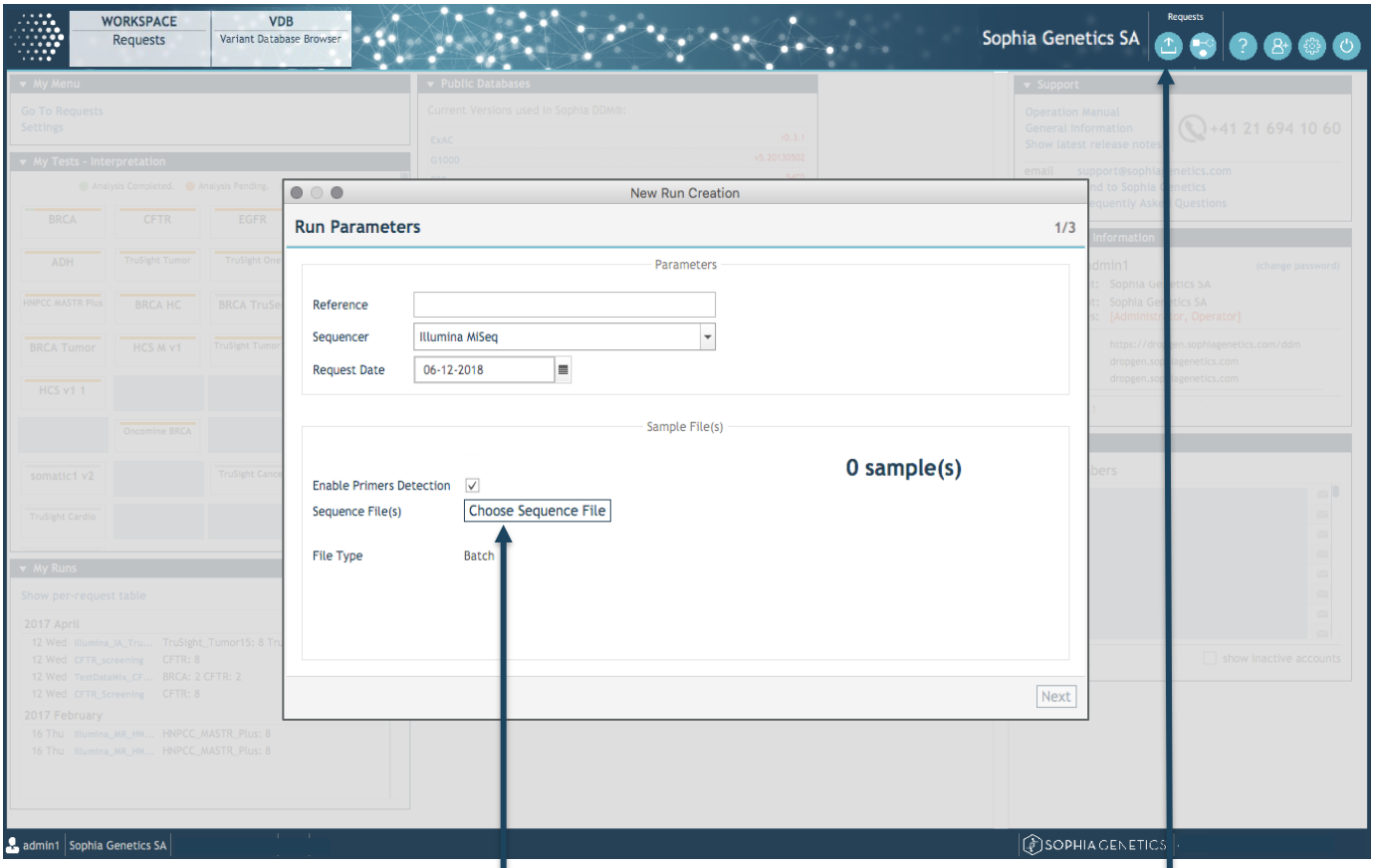


The BDS number can be found:
- On the side sticker of box 1 of the SOPHiA GENETICS bundle solution kit (-15 °C to -25 °C storage temperature)
- In the annex of the delivery note

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)

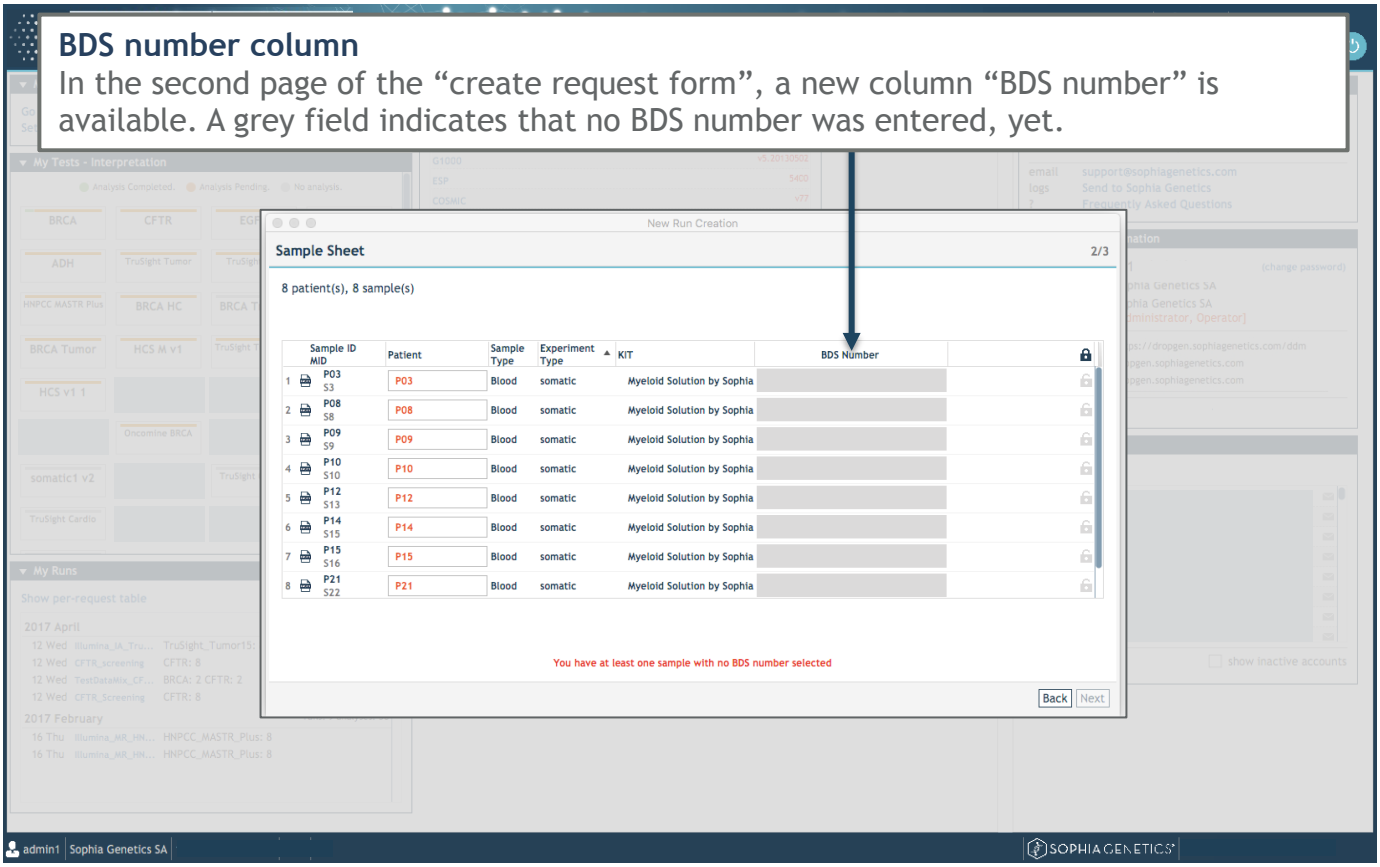
Step 2 - Upload your data



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.

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"



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.

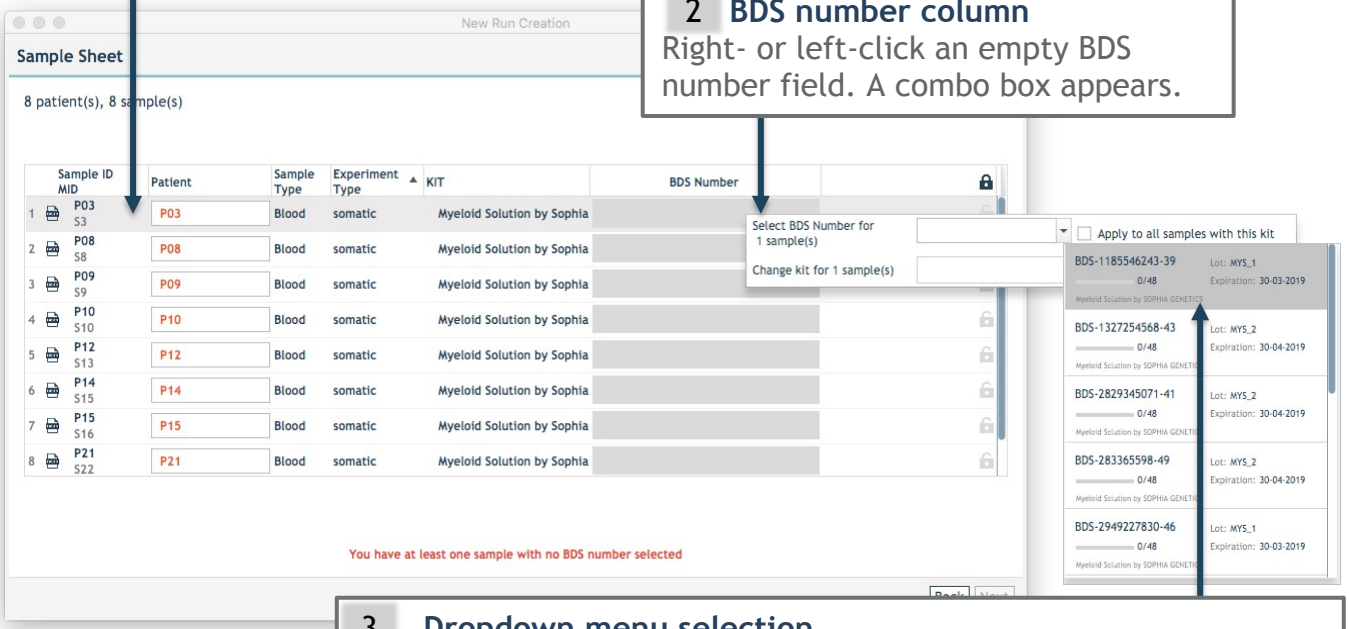
2. Dashboard
2.3 BDS Numbers
2.3.2 Selection of BDS Numbers (4)

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.



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.

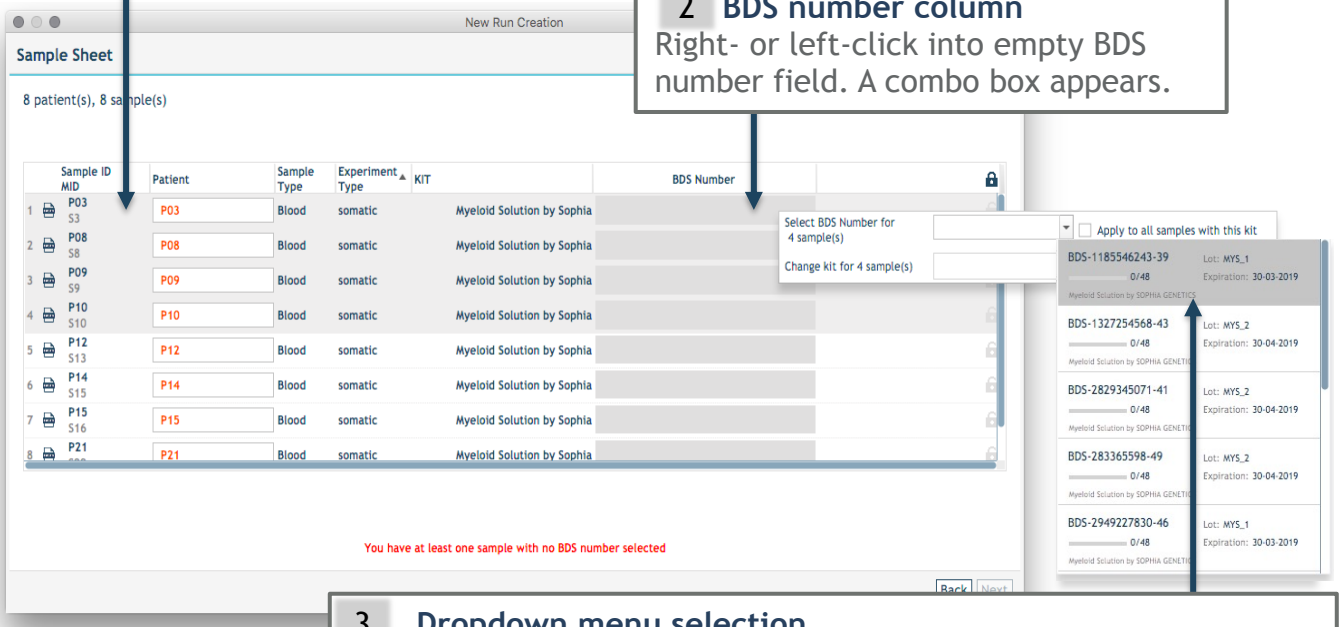
2. Dashboard
2.3 BDS Numbers
2.3.2 Selection of BDS Numbers (5)

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.



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.

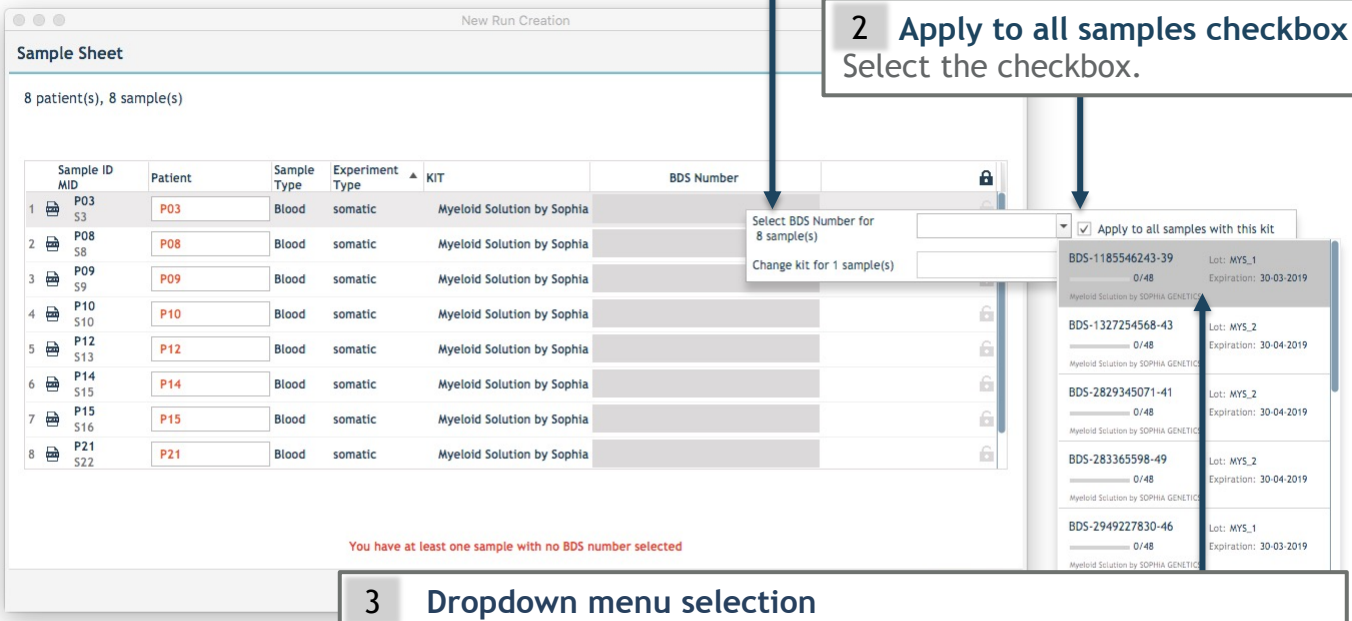
2. Dashboard
2.3 BDS Numbers
2.3.2 Selection of BDS Numbers (6)

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.

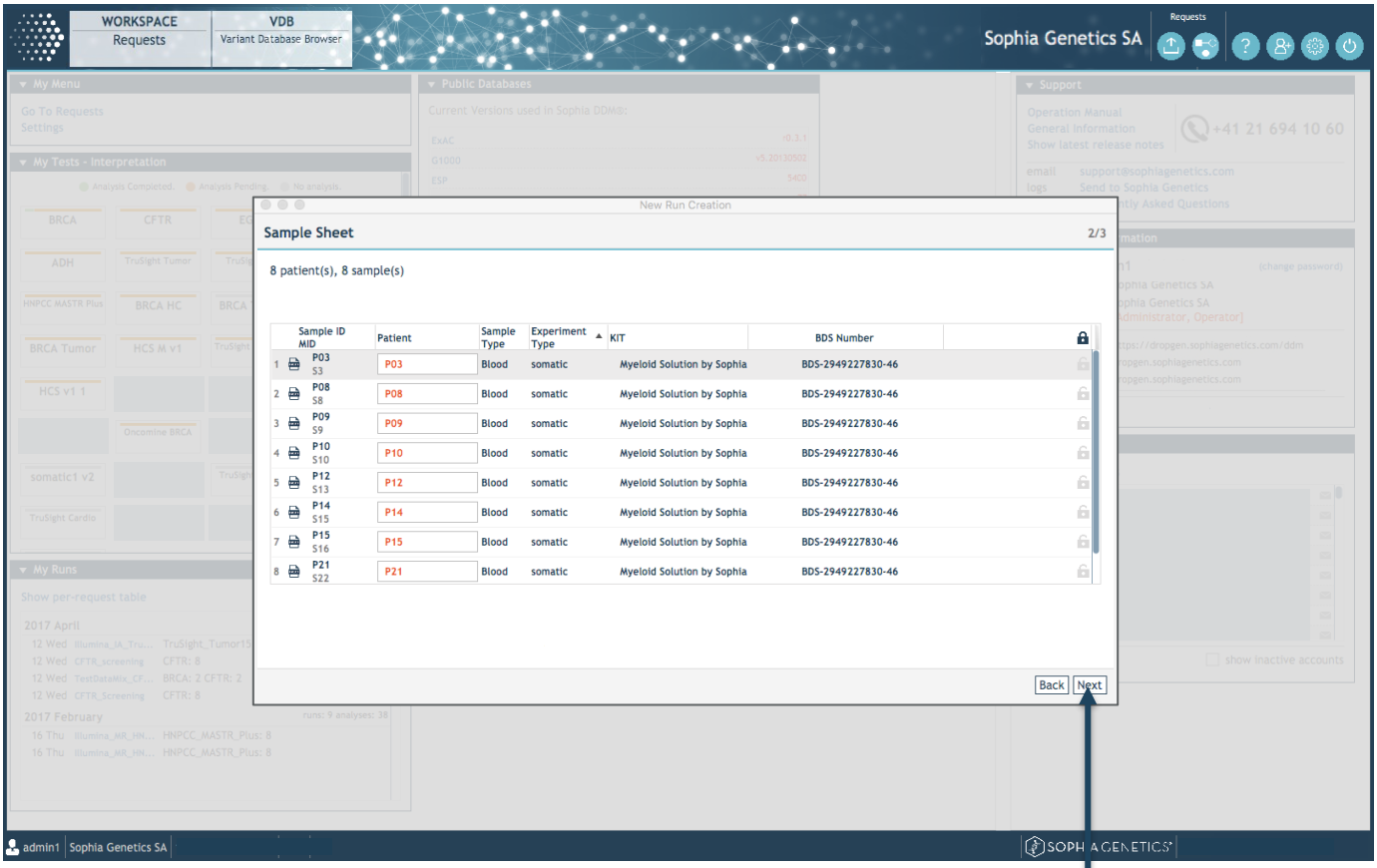


3 Dropdown menu selection
Click the dropdown menu and select the right BDS number for the selected sample. Only BDS numbers for the selected kit are shown. Usage of the respective BDS numbers is shown below the number.

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)

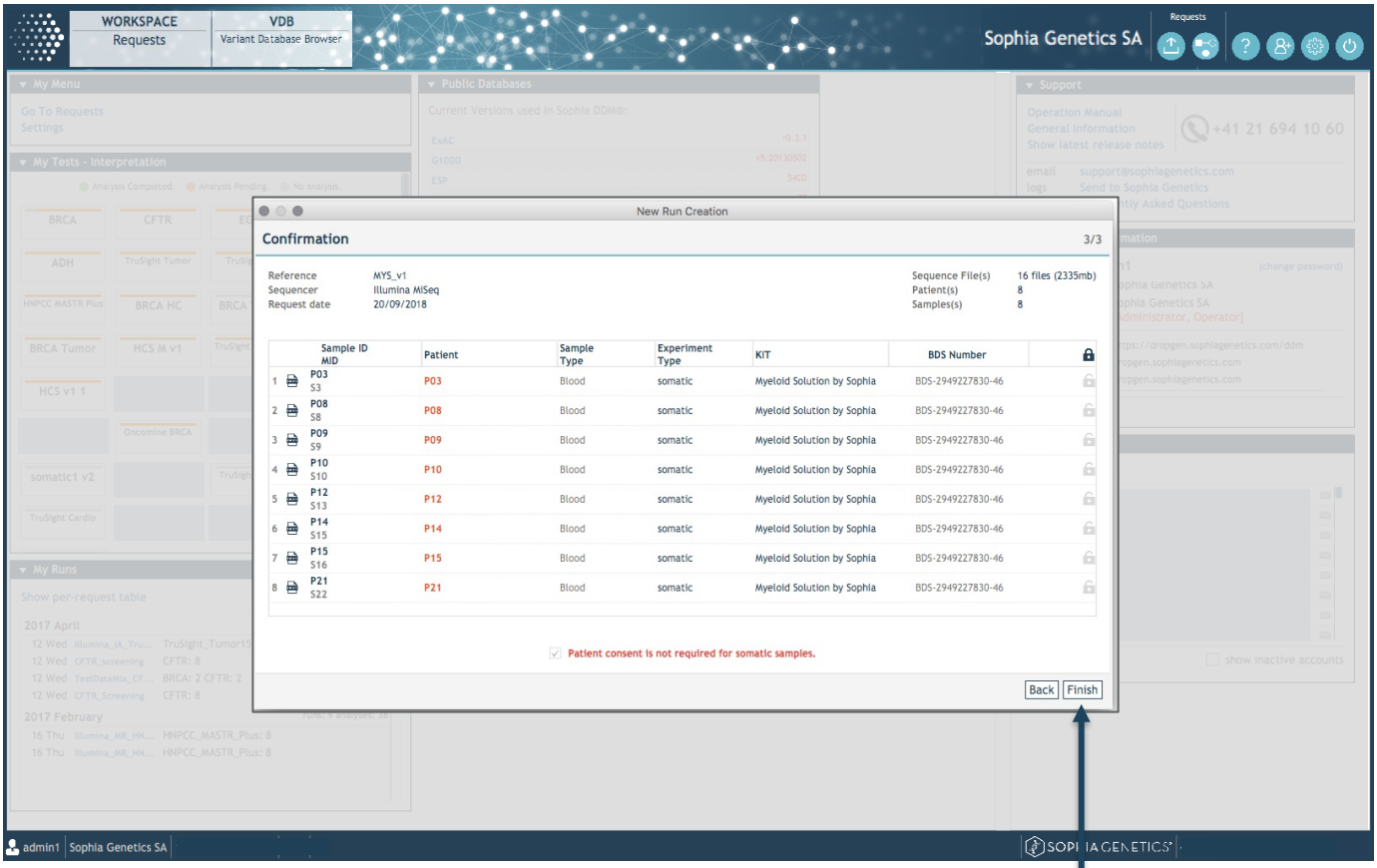
Step 3 - Enter the BDS number in the "create request form"



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)

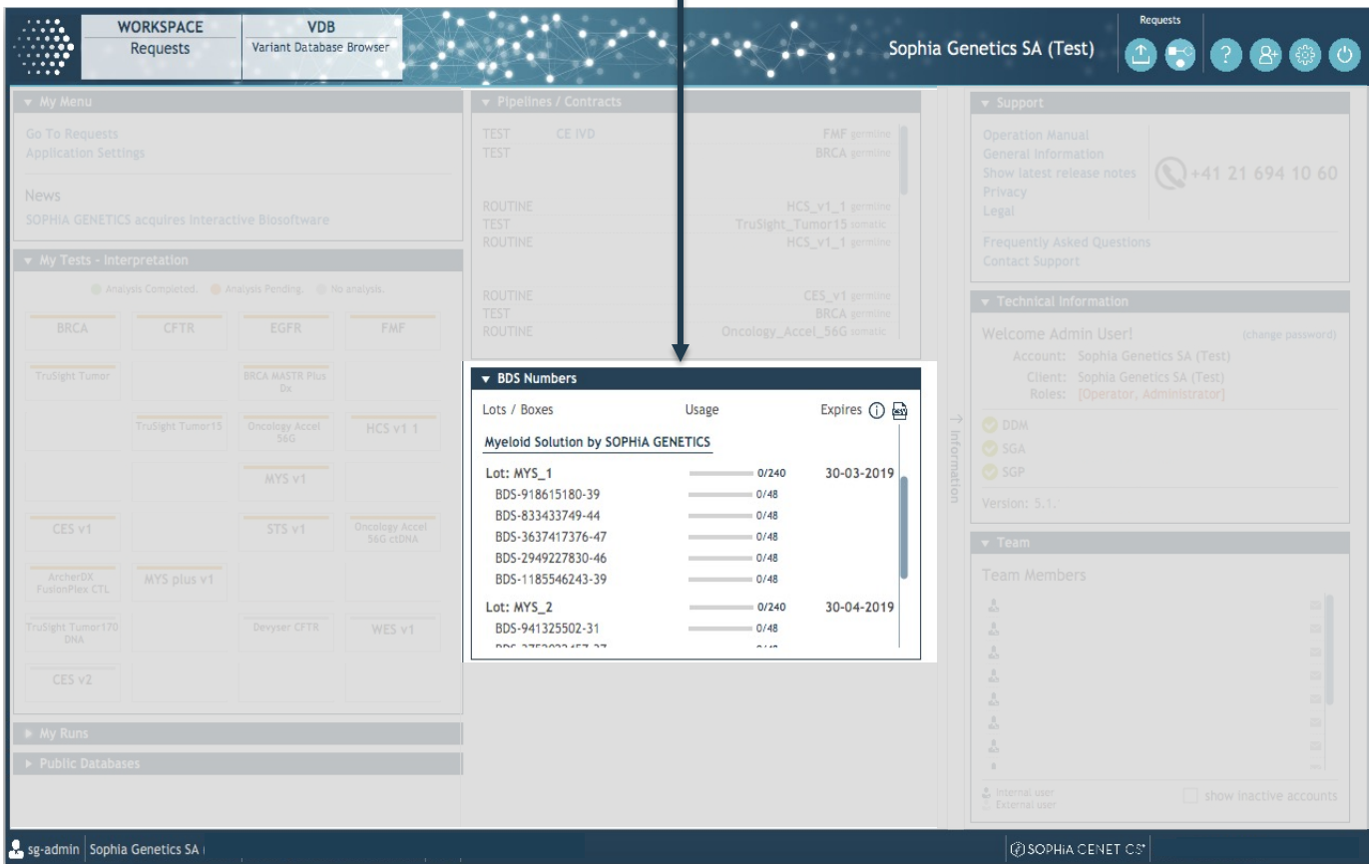
Step 4 - Verify all entries and start the upload



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.

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.



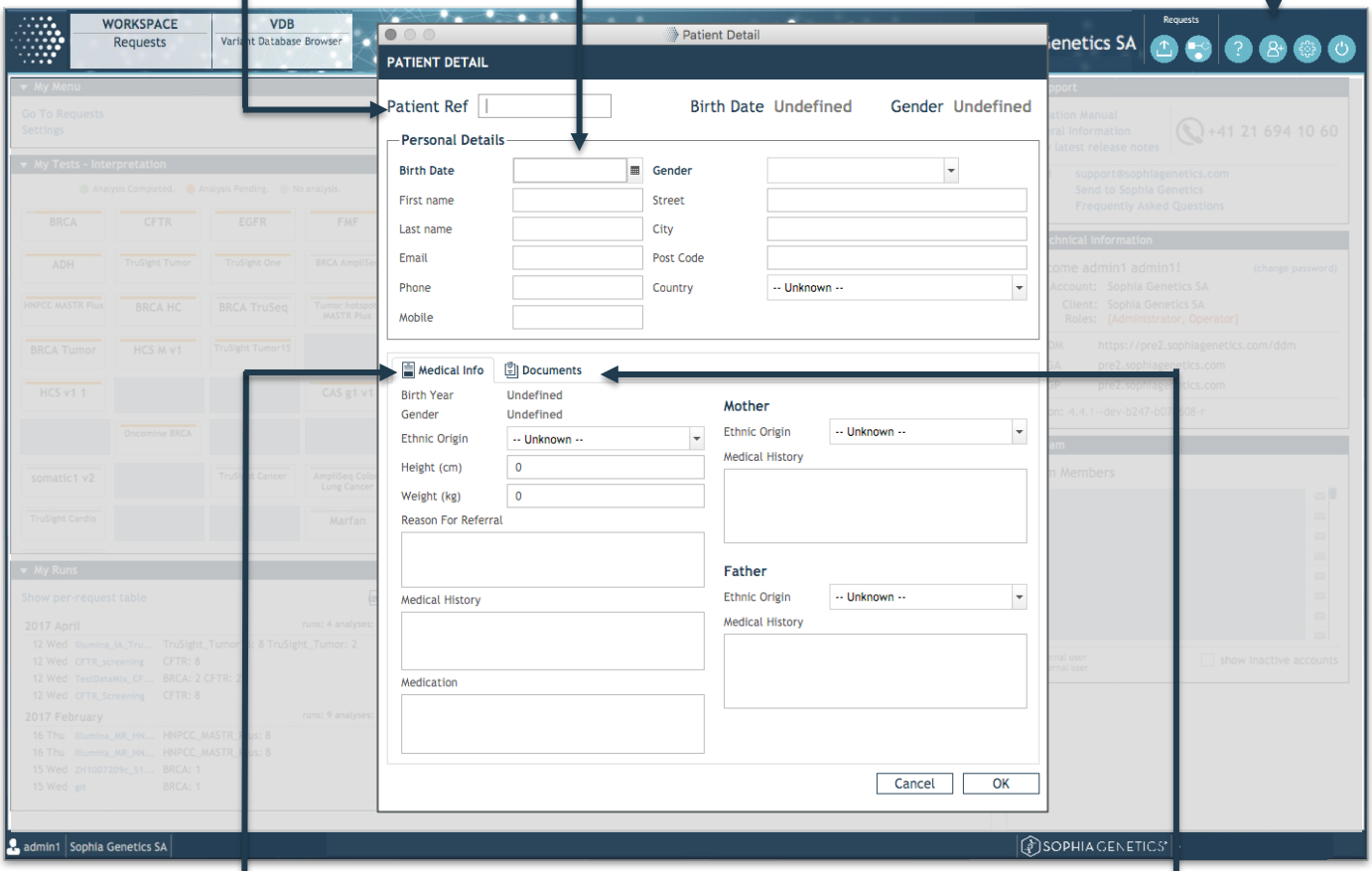
NOTE: If kits are ordered through a distributor, usage tracking is not available.

2. Dashboard
2.4 Create a New Patient* File

Edit patient* ID

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

"Create new patient*"
Add information for a new patient*.

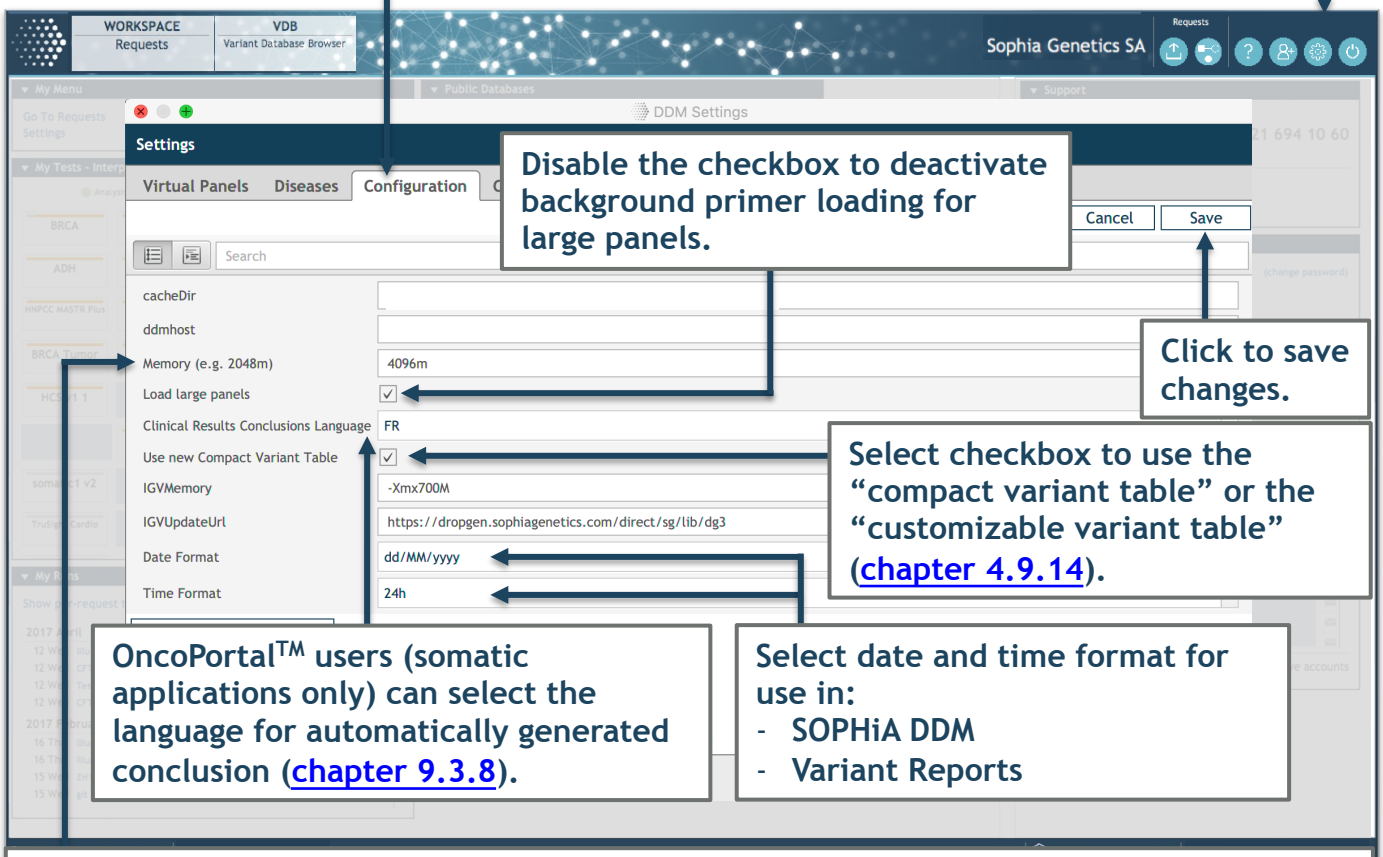


"Medical info"
Edit patient* information and patient's* parents' details.

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



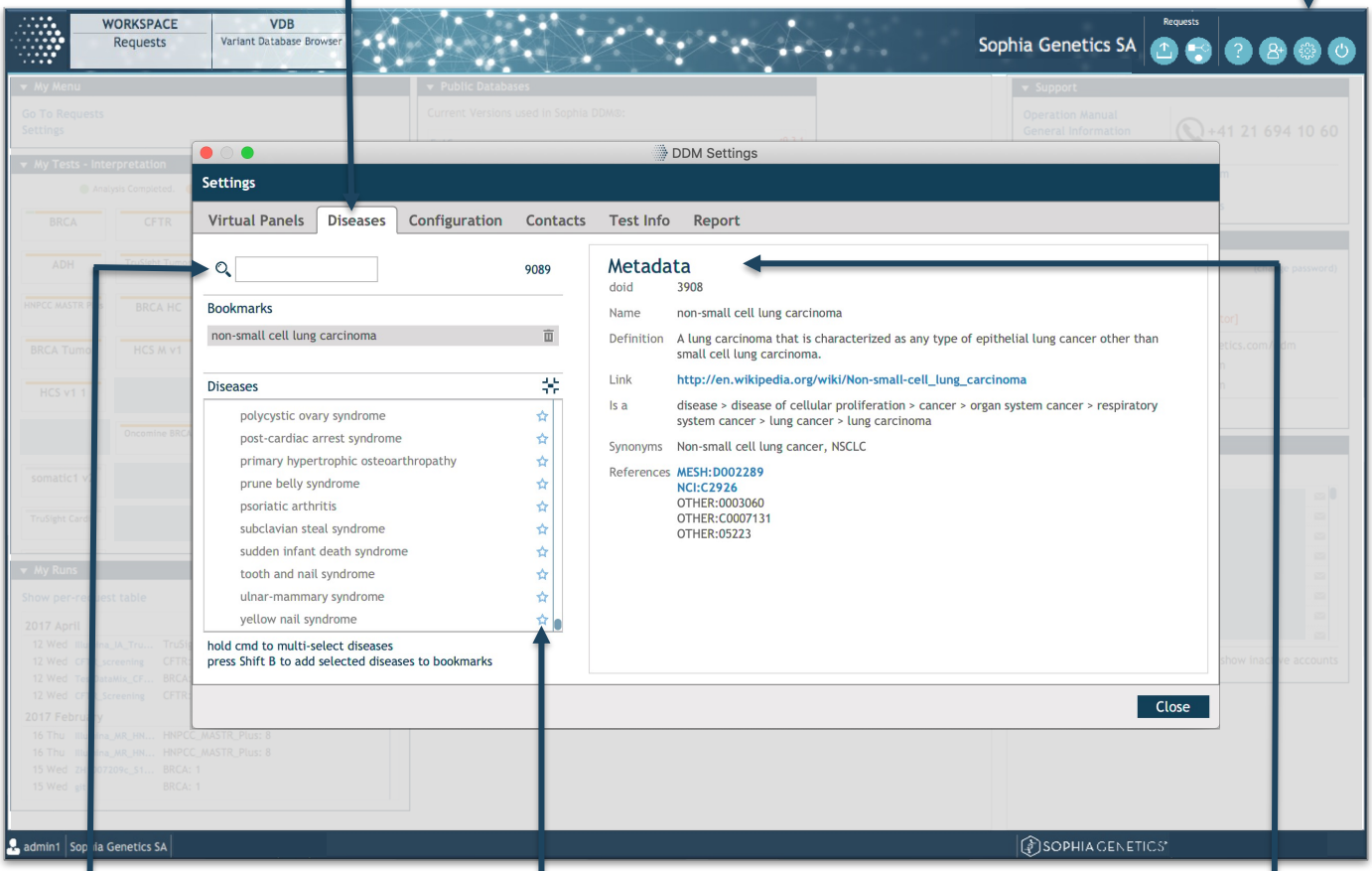
“Memory settings”
A minimum of 2048M RAM memory allocation is recommended. SOPHiA DDM™ checks the RAM of the user’s operating system and recommends up to ½ of the RAM (but no more than 4GB) to the user in a pop-up.

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.

2. Dashboard
2.6 Disease* Database

Active tab

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



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

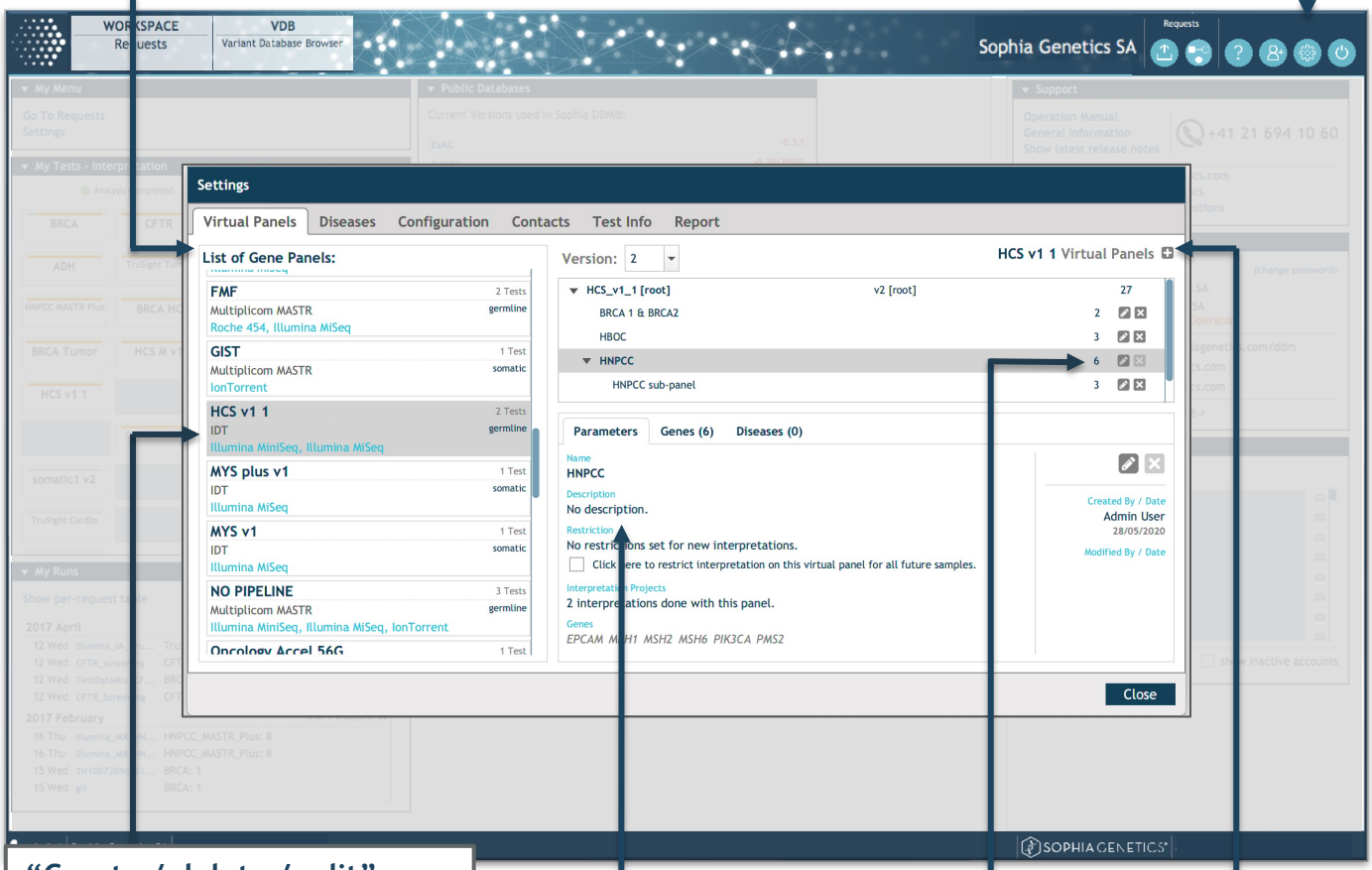
Select one disease* and click the ☆ icon to bookmark it. To bookmark several diseases*, press CTRL (⌘cmd) while selecting.

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

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.

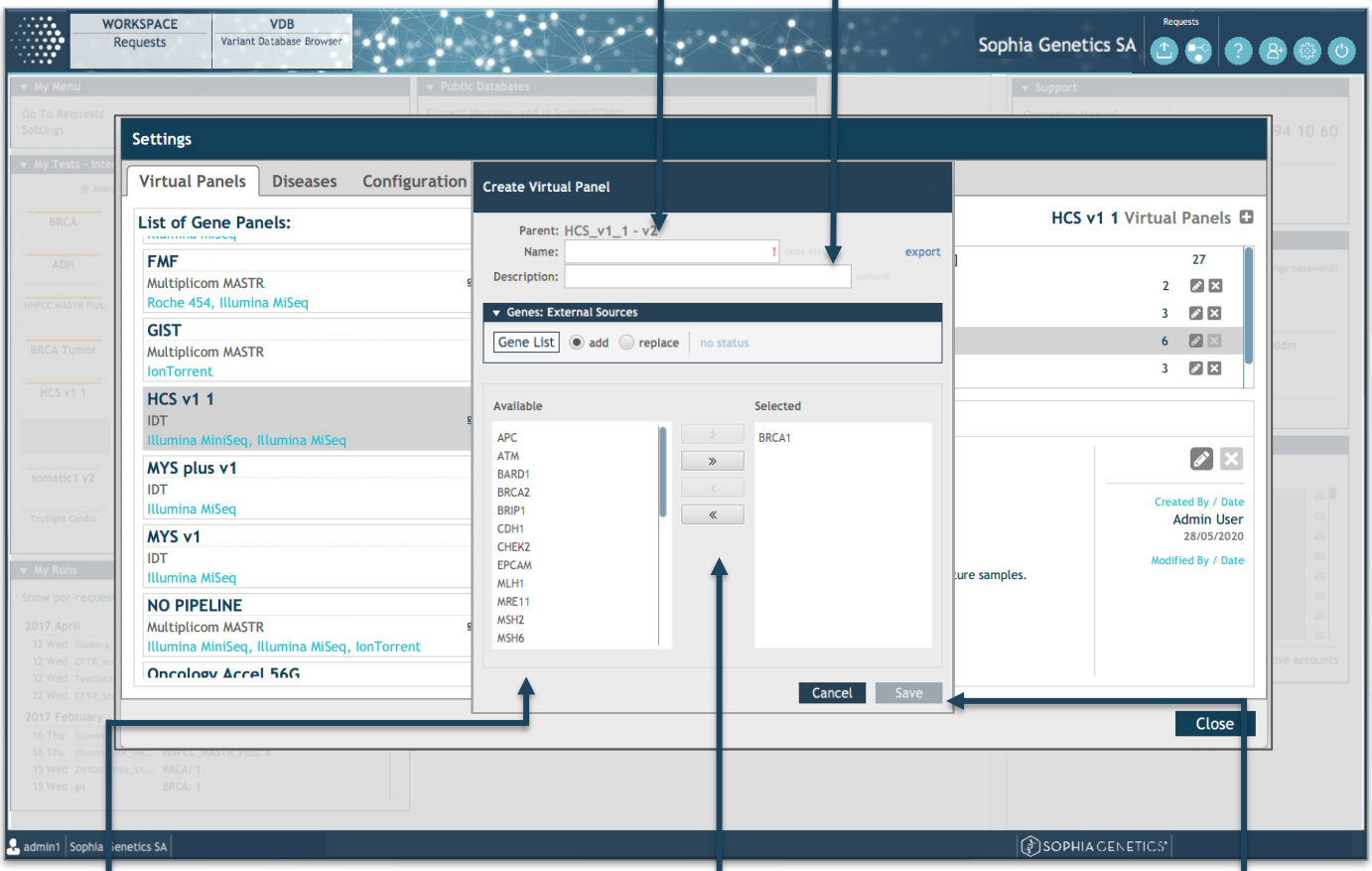
"Create" a new Virtual Panel
Click ✚ to create a new Virtual Panel.

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.



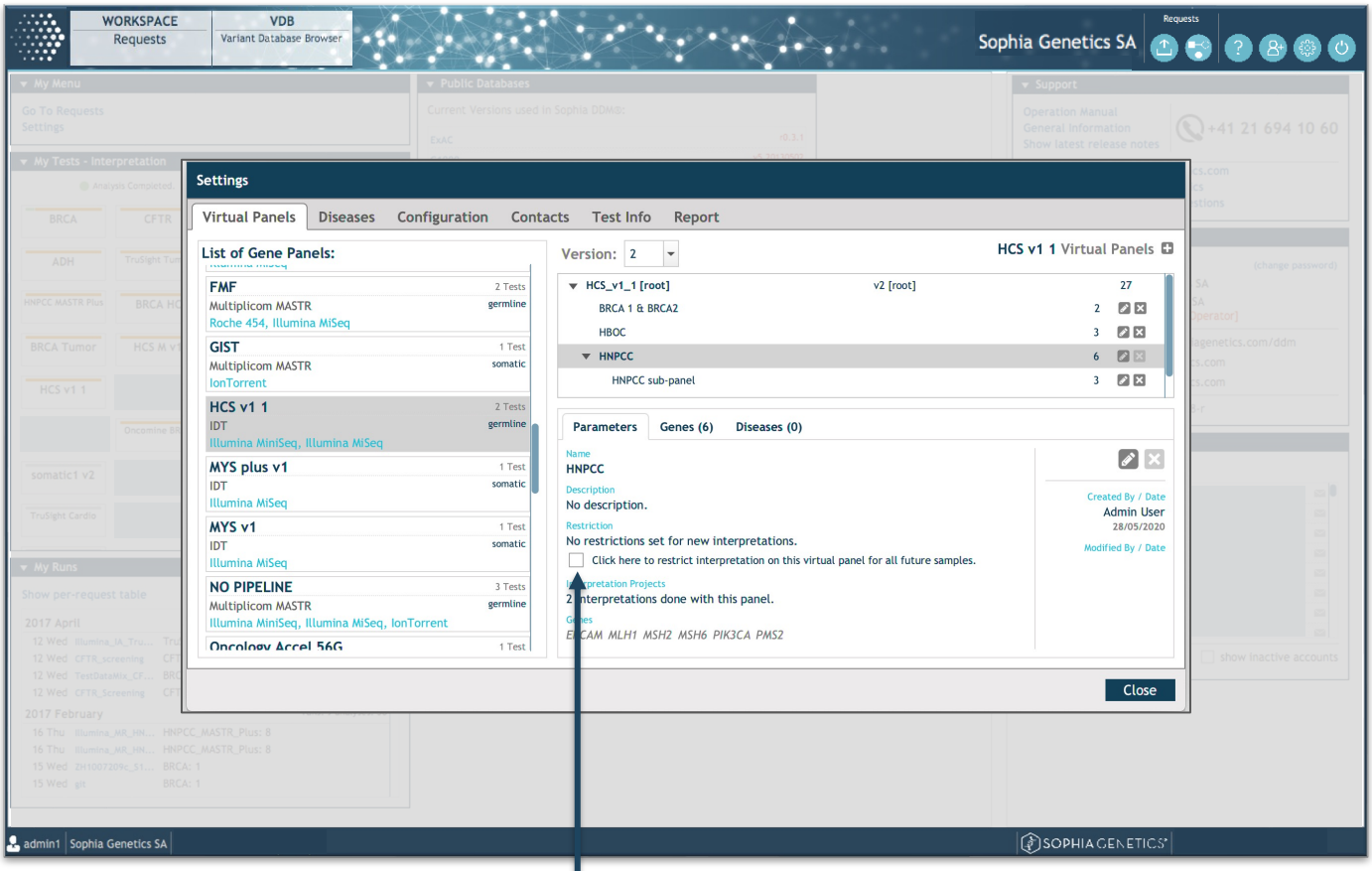
Genes available for Virtual Panel

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)

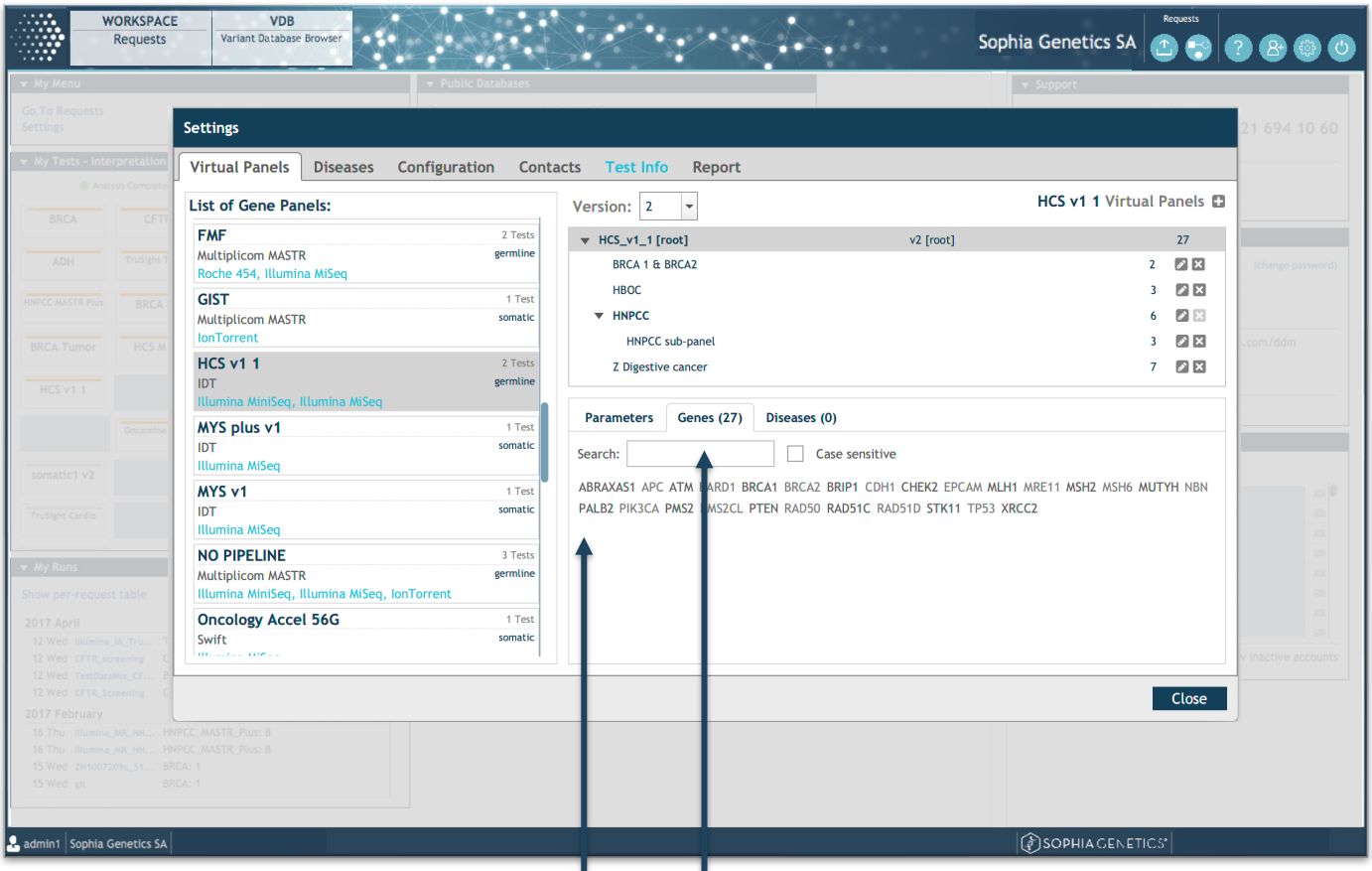


General scope

- 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

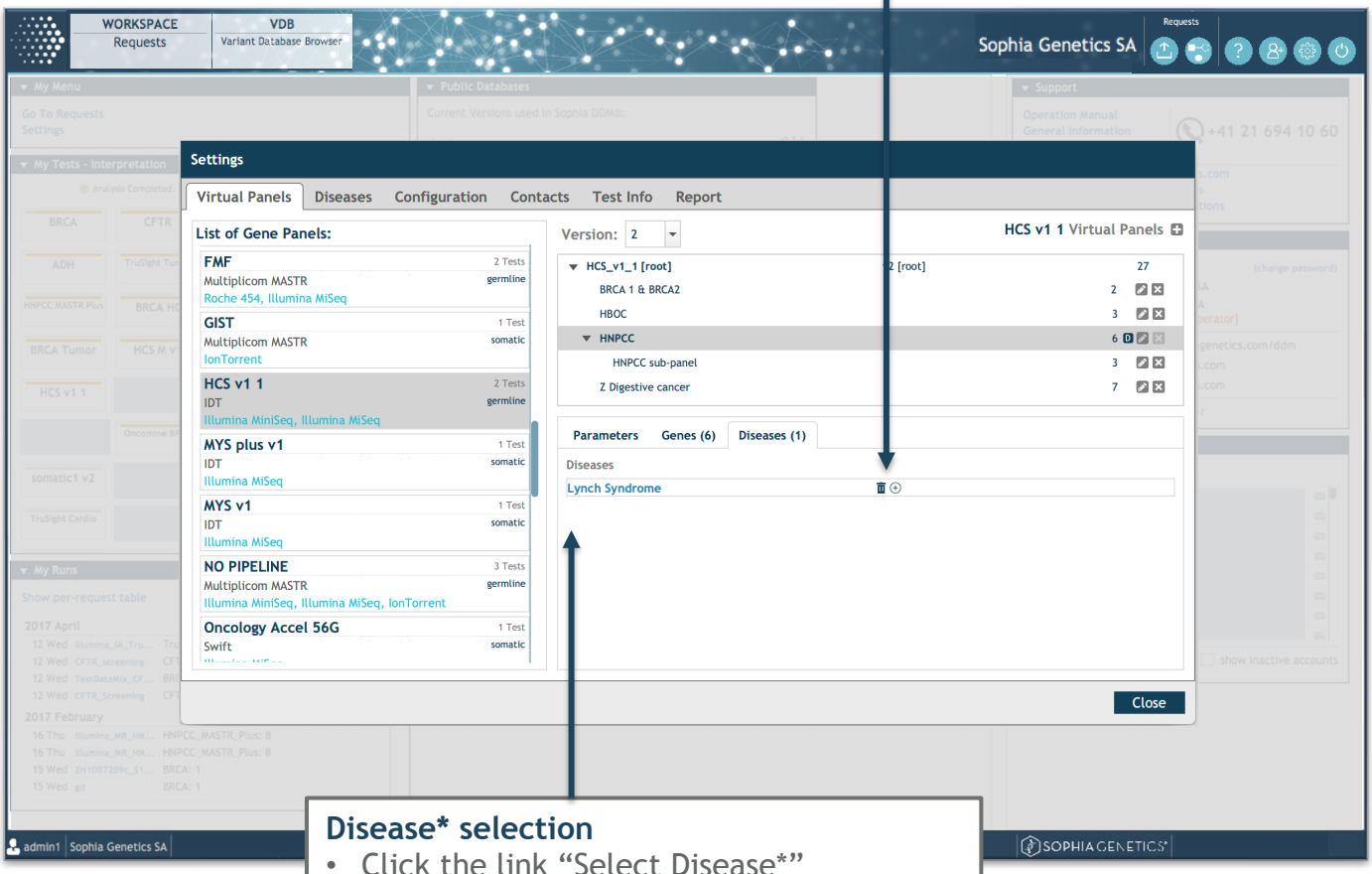
NOTE: Only admin users can change Virtual Panels at account level.
For “restricted users”, this view is read-only.

2. Dashboard
2.7 Manage Virtual Panels (4)



2. Dashboard
2.7 Manage Virtual Panels (5)

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



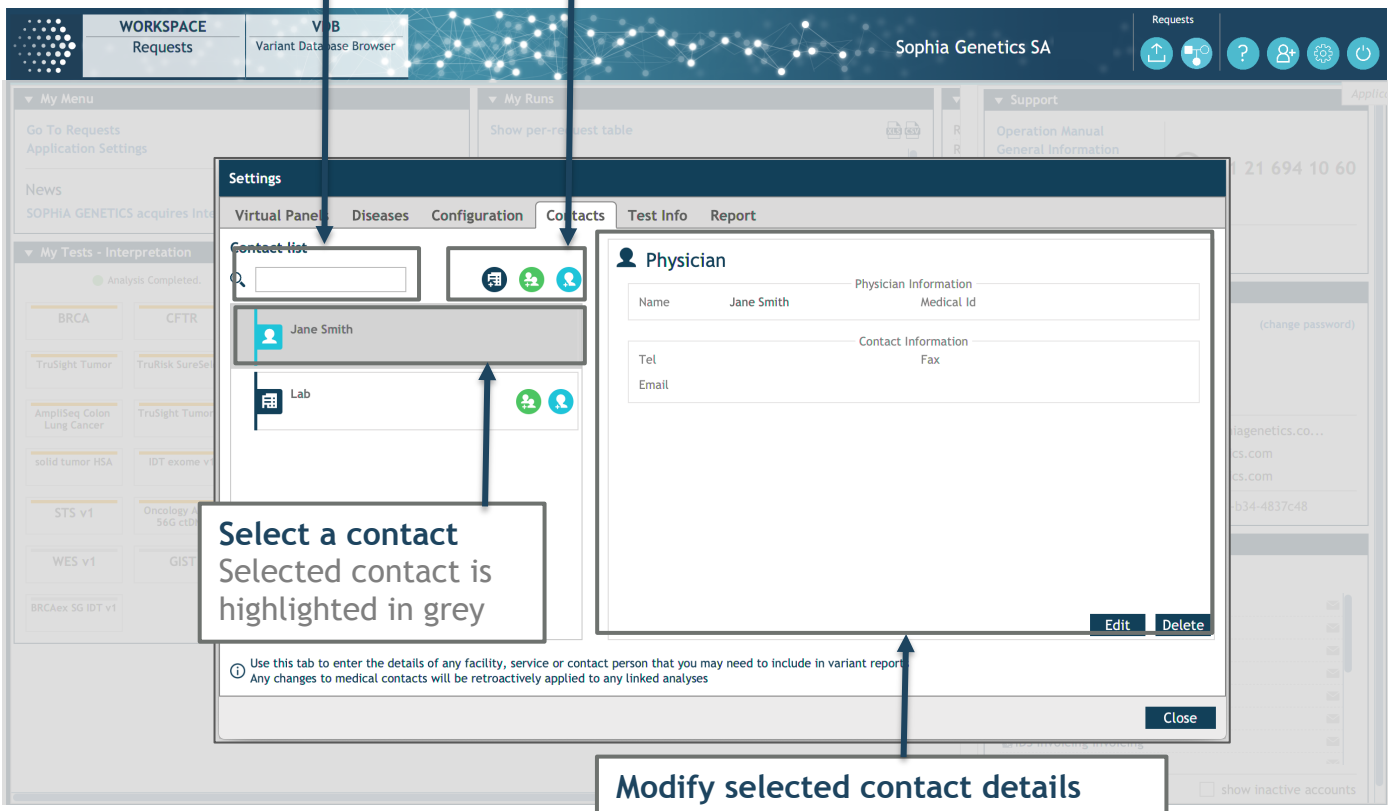
Disease* selection
- Click the link “Select Disease*”
- Start typing disease* name
- Select disease* from list
- Click “OK” and “YES” to confirm

** Please refer to the Disclaimer (page 3).*
Research Use Only. Not for use in diagnostic procedures.

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

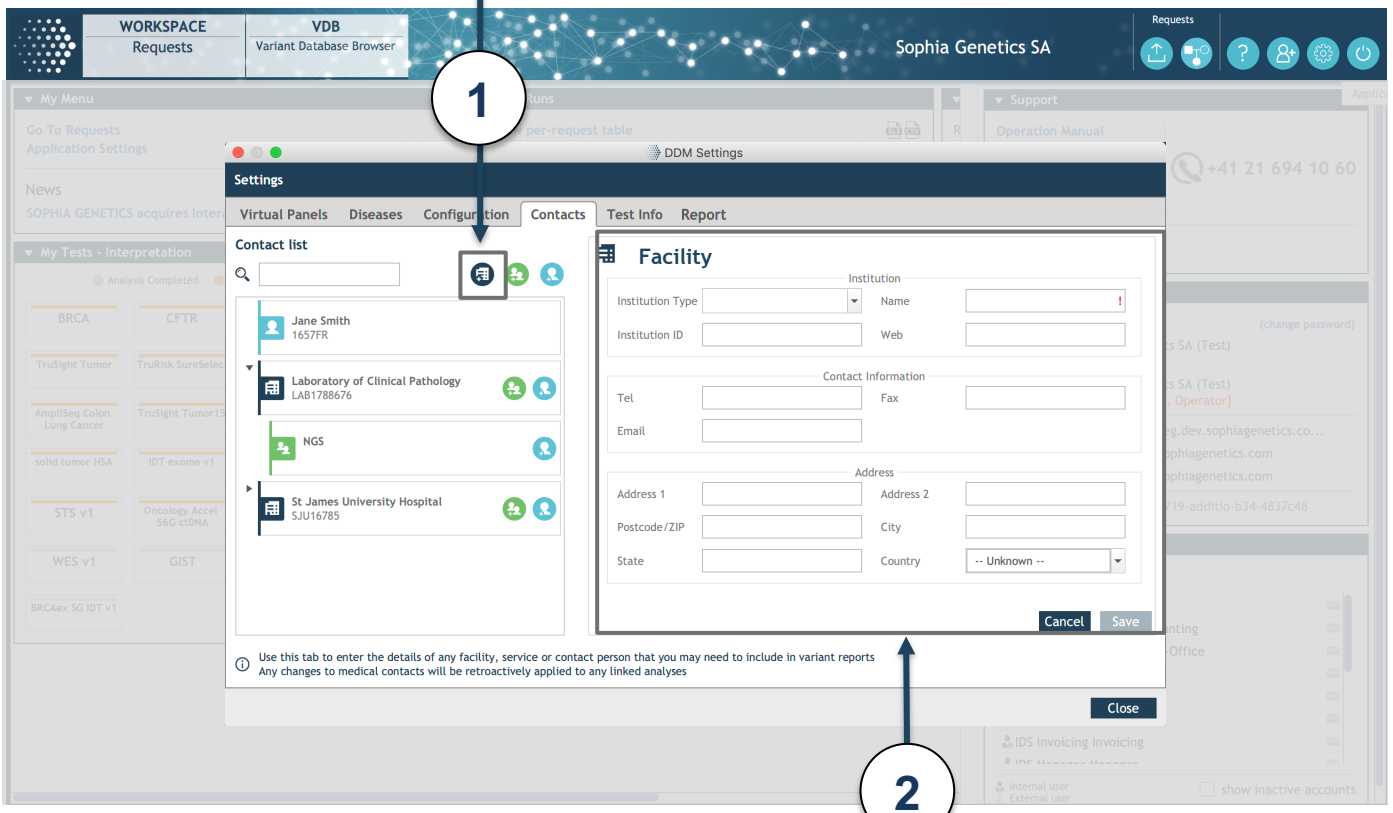


Select a contact
Selected contact is highlighted in grey

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

2. Dashboard
2.8 Manage Contacts (2)

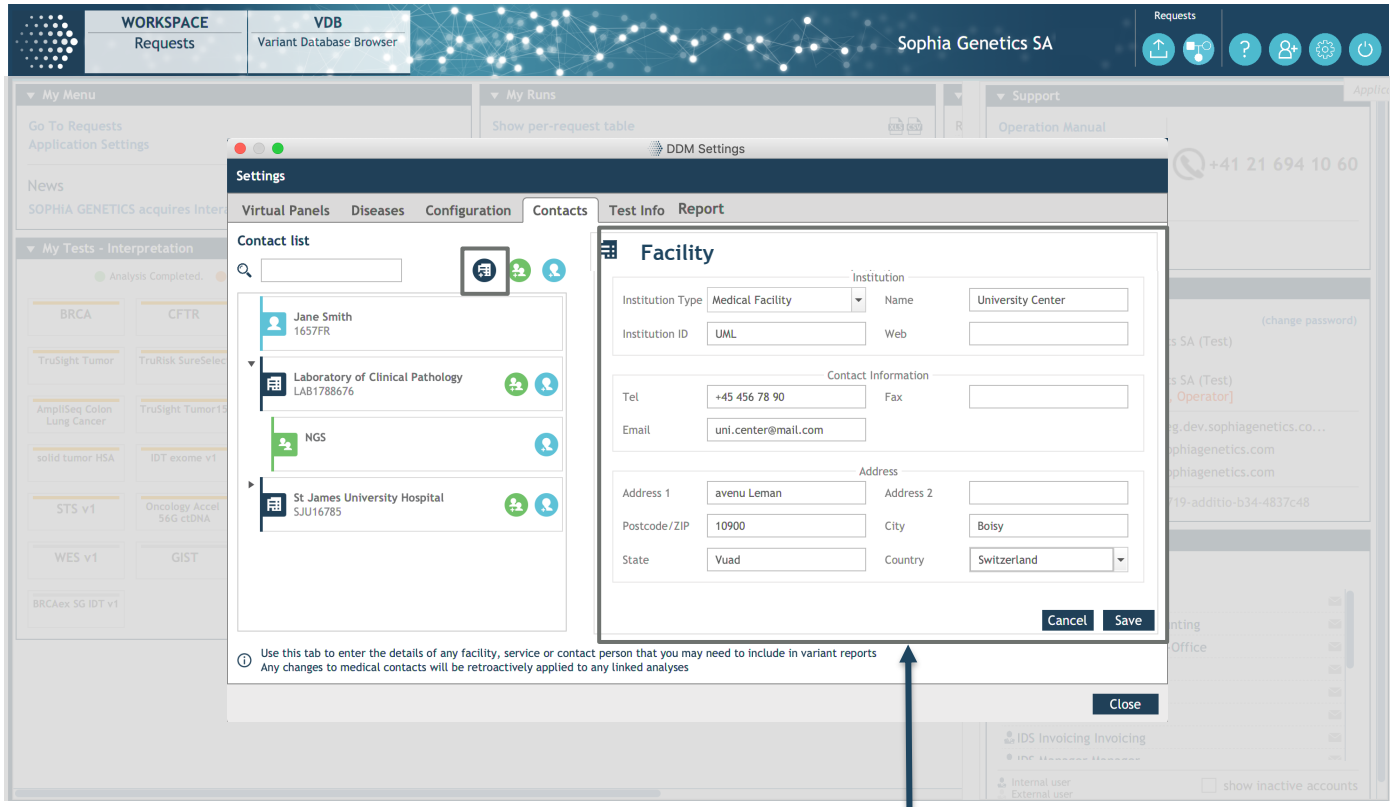
Add a facility
Click on the corresponding button to open a form on the right-hand side of the panel.



Add the details of the facility
Fill in the form.

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

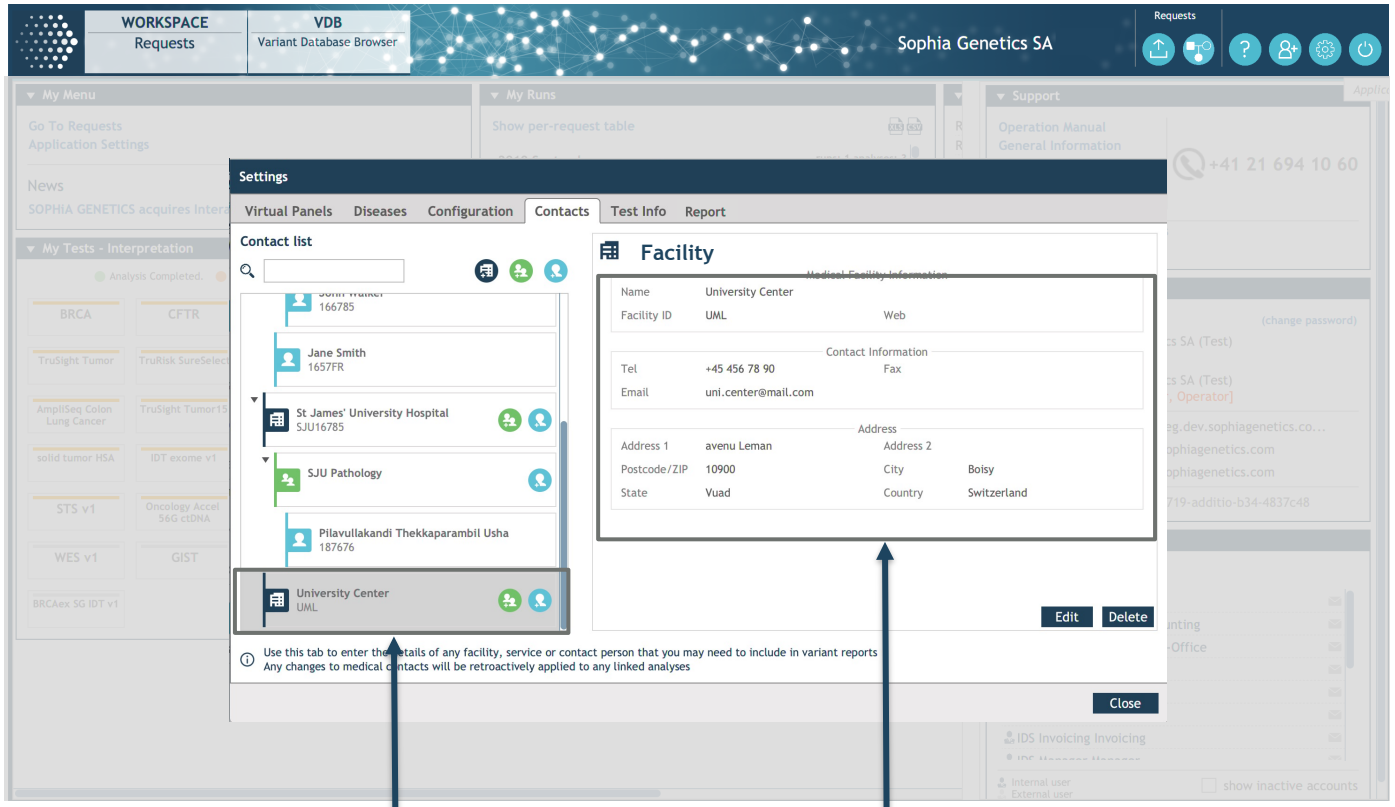
2. Dashboard
2.8 Manage Contacts (3)



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)



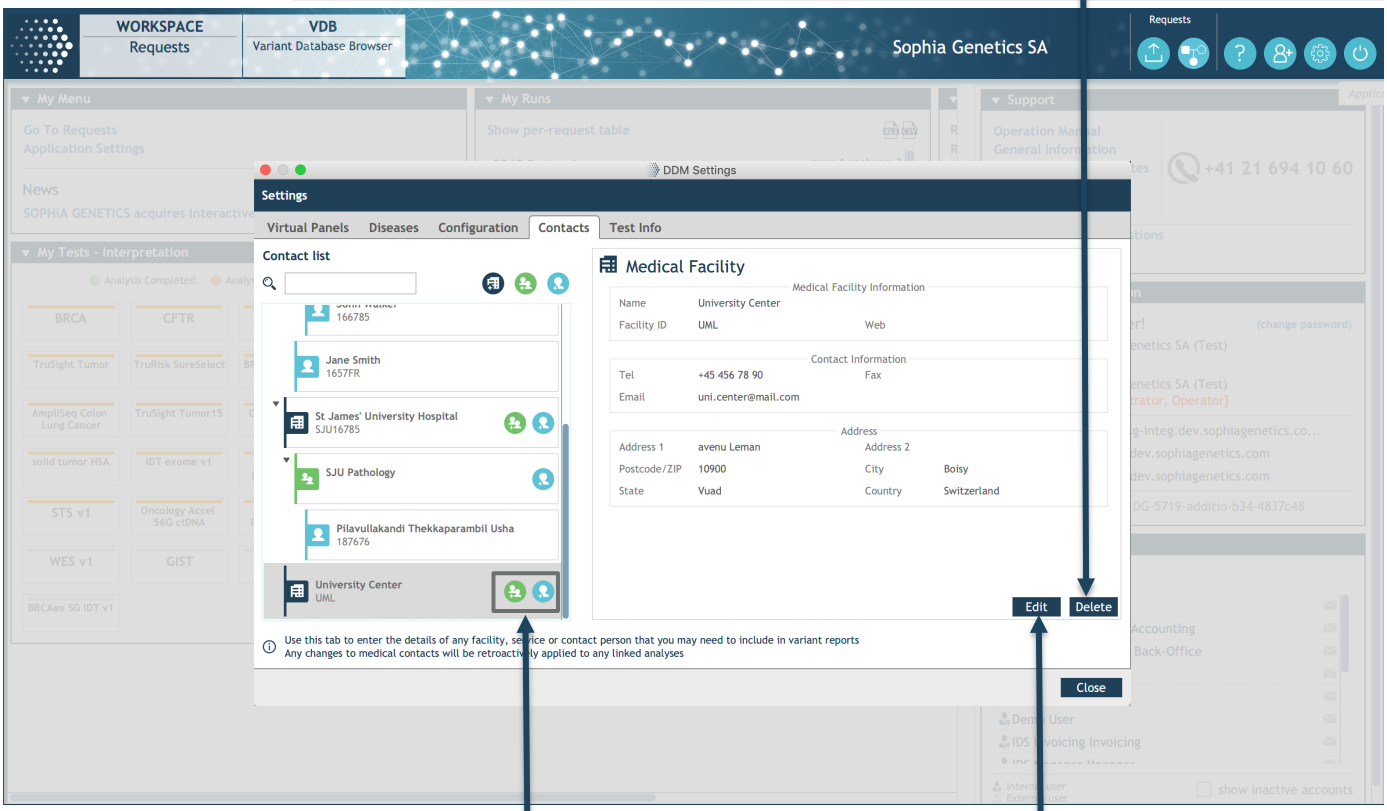
Created facility appears in the list of contacts. Select the facility to see its details on the right side of the panel.

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.



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.

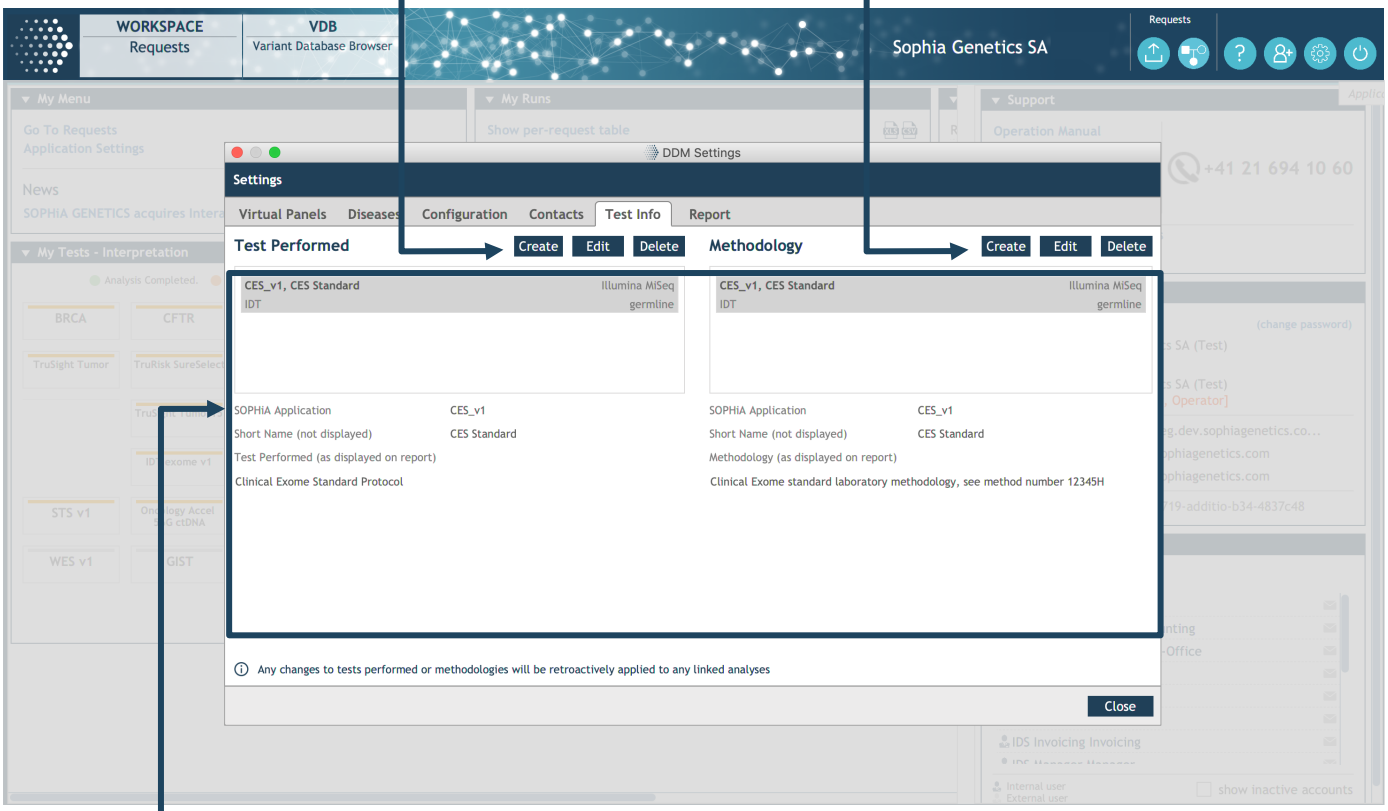
Edit
- Select the facility to be edited
- Click Edit

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

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.

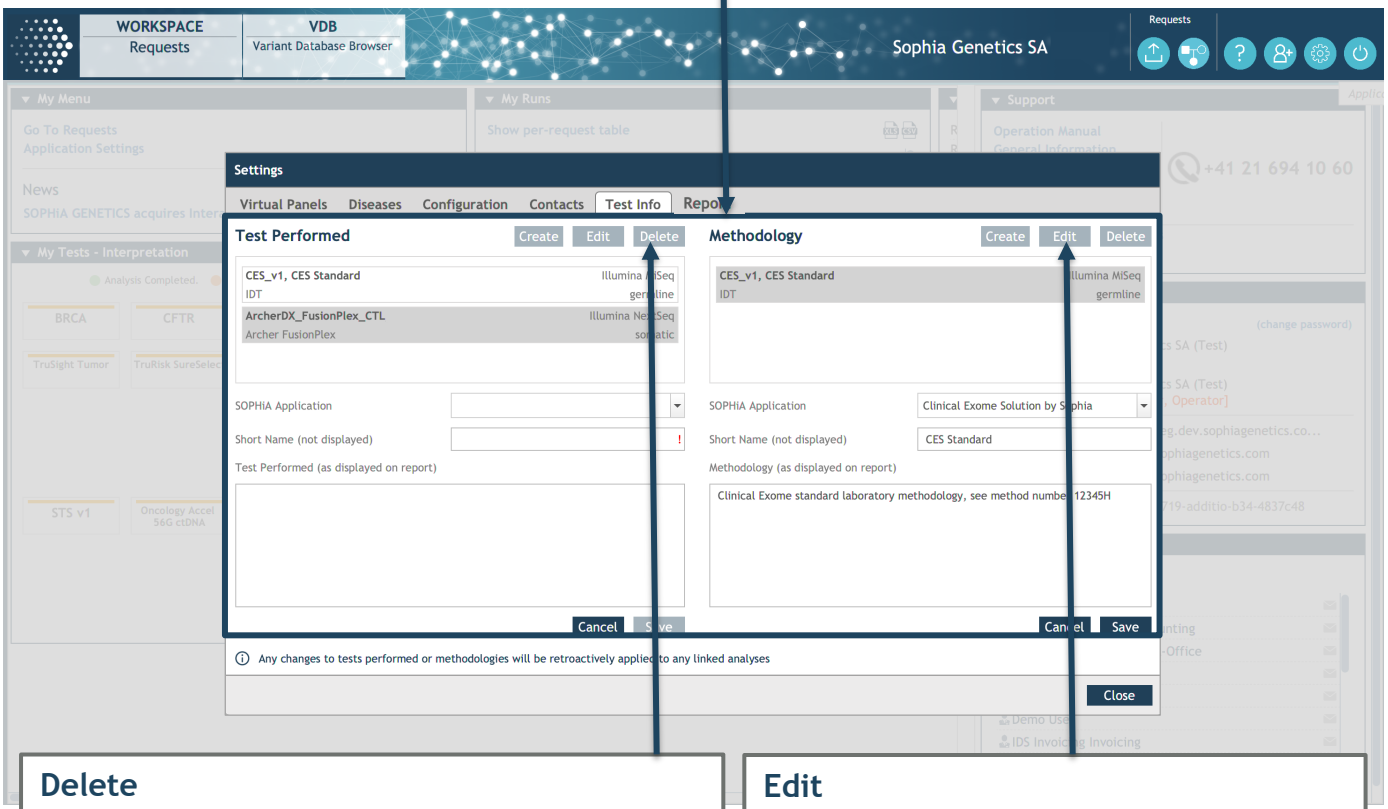
Methodology
Description of the methodology to be displayed on Variant Report. User can create, edit or delete it.



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.

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

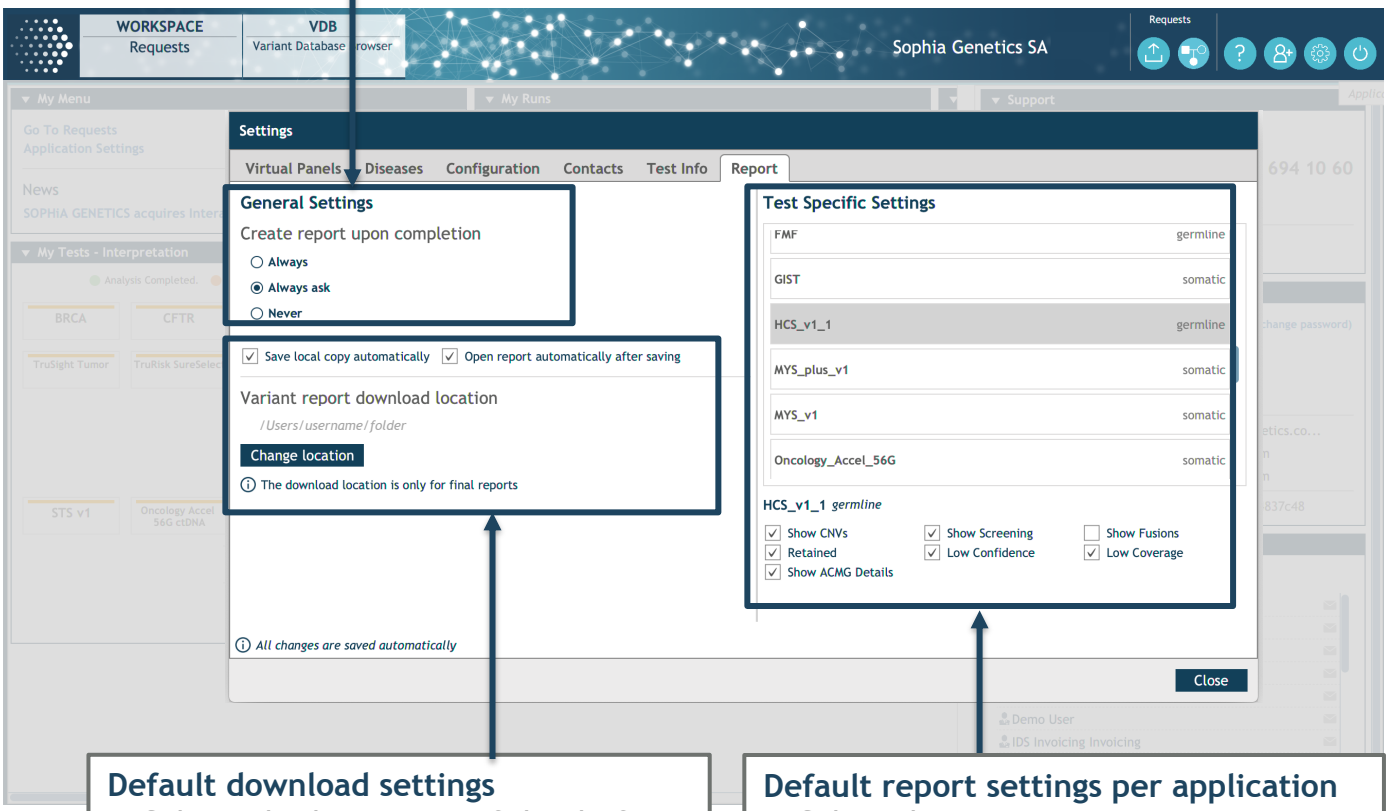
Deleting a description will result in deletion from all existing Interpretation Projects* where the description is used.

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.



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.

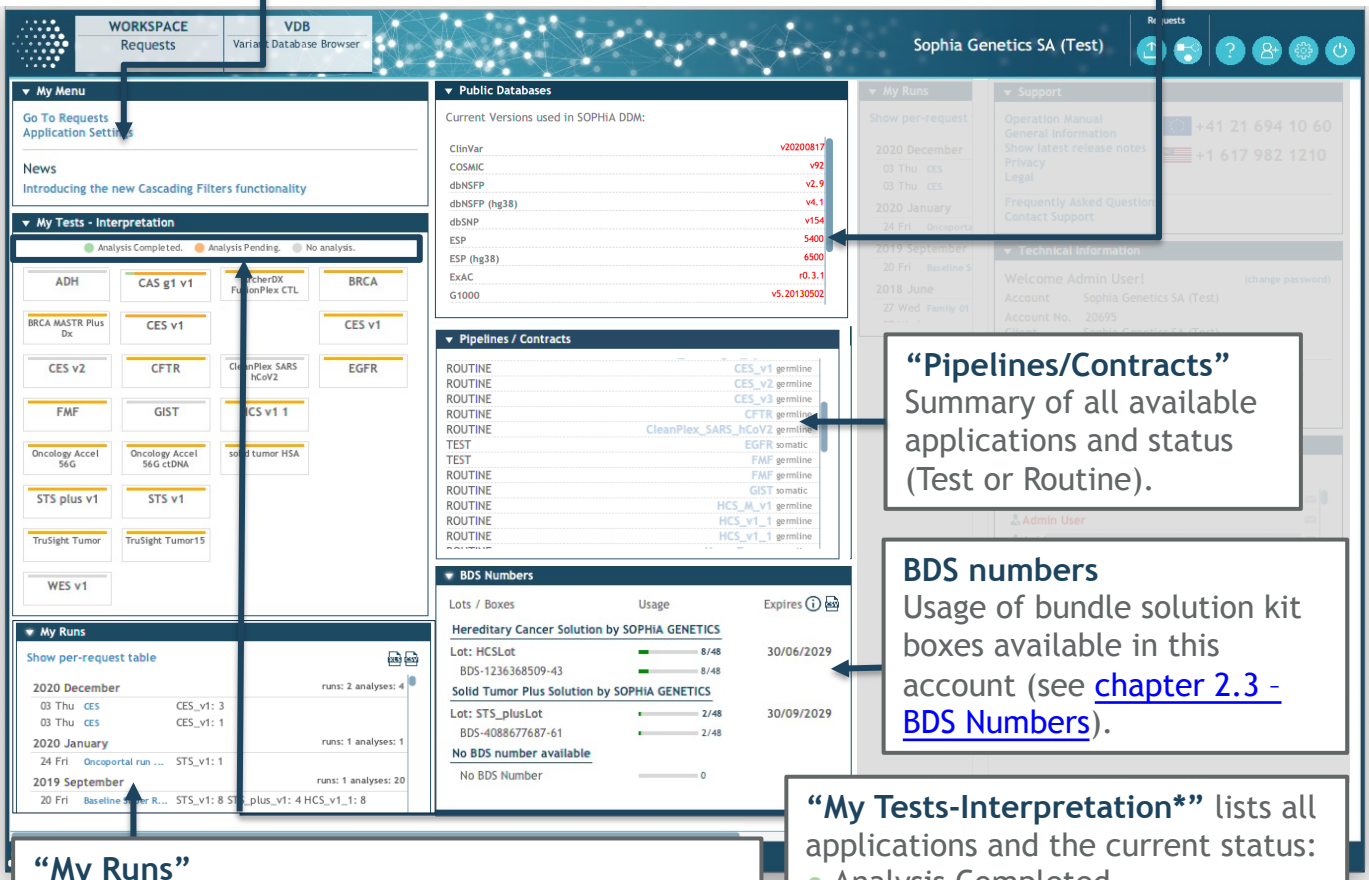
NOTE: The default report settings can be adjusted on a per project basis in the «Project Settings» of an analysis (see ch. 4.4.2 Project Settings)

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).

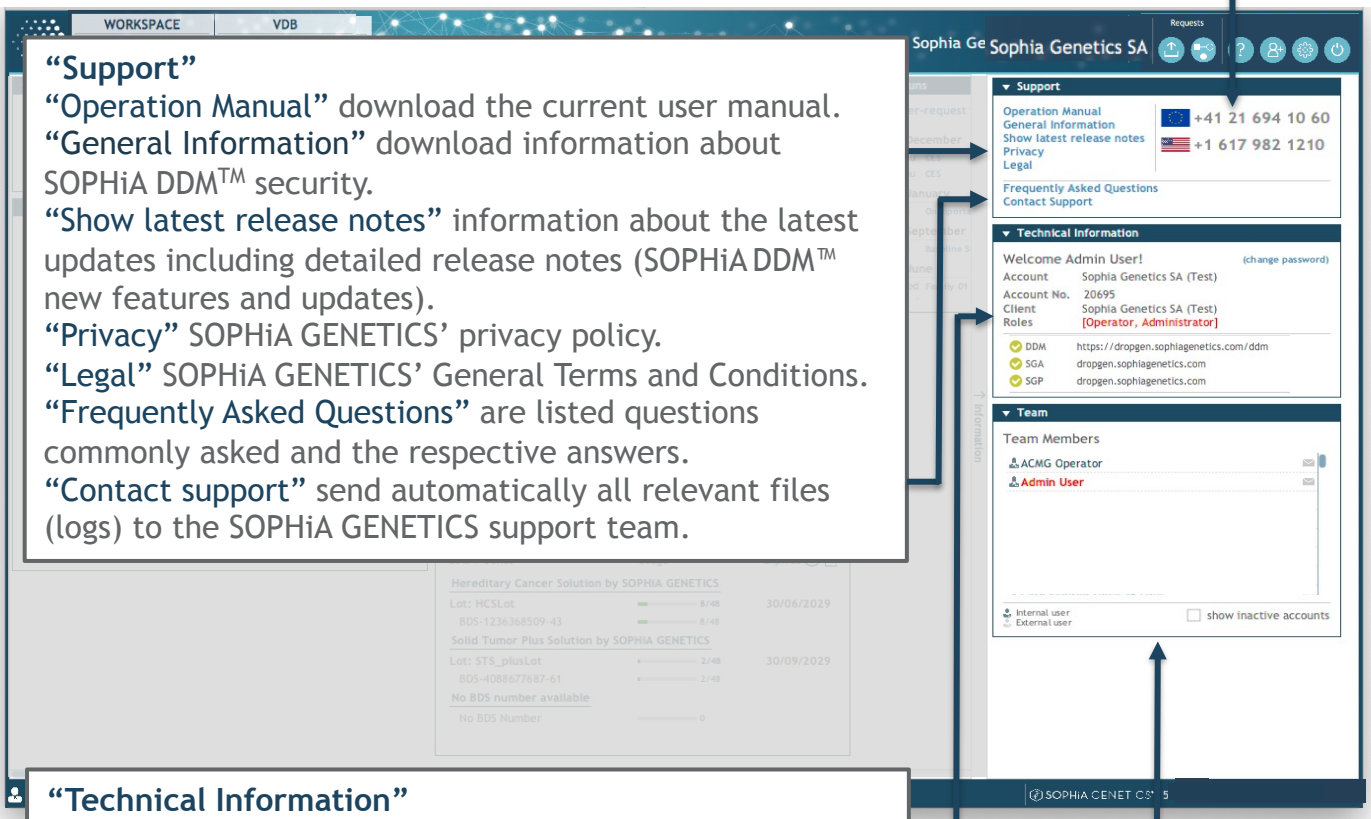
"My Runs"
Quickly see all runs sorted by date and number of analyses per run per month.

"My Tests-Interpretation*" lists all applications and the current status:
- Analysis Completed
- Analysis Pending
- No Analysis

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.

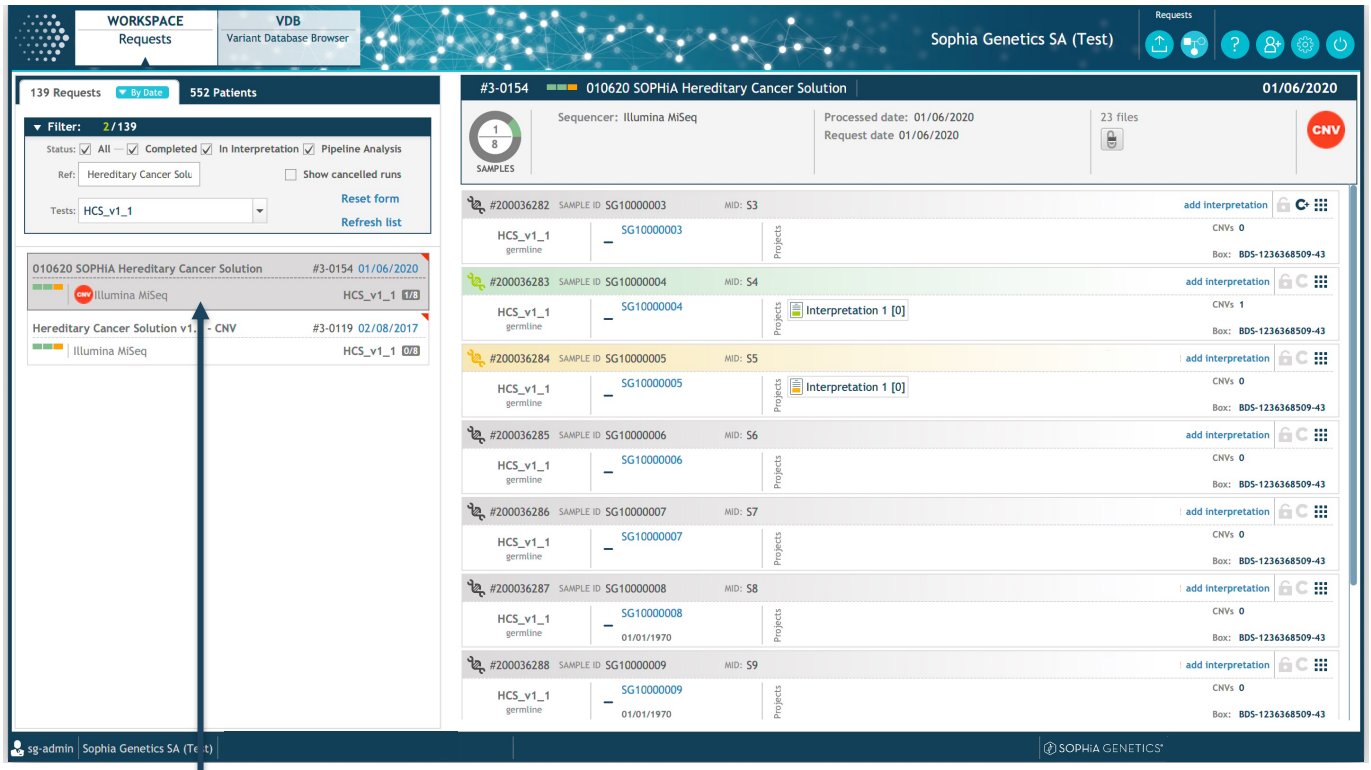
“Technical Information”
Indicates the account number, the user role(s) of the logged in user (see also chapter 1.2 Expert Roles) and the option to change the password.

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

3. Workspace
3.1 Overview

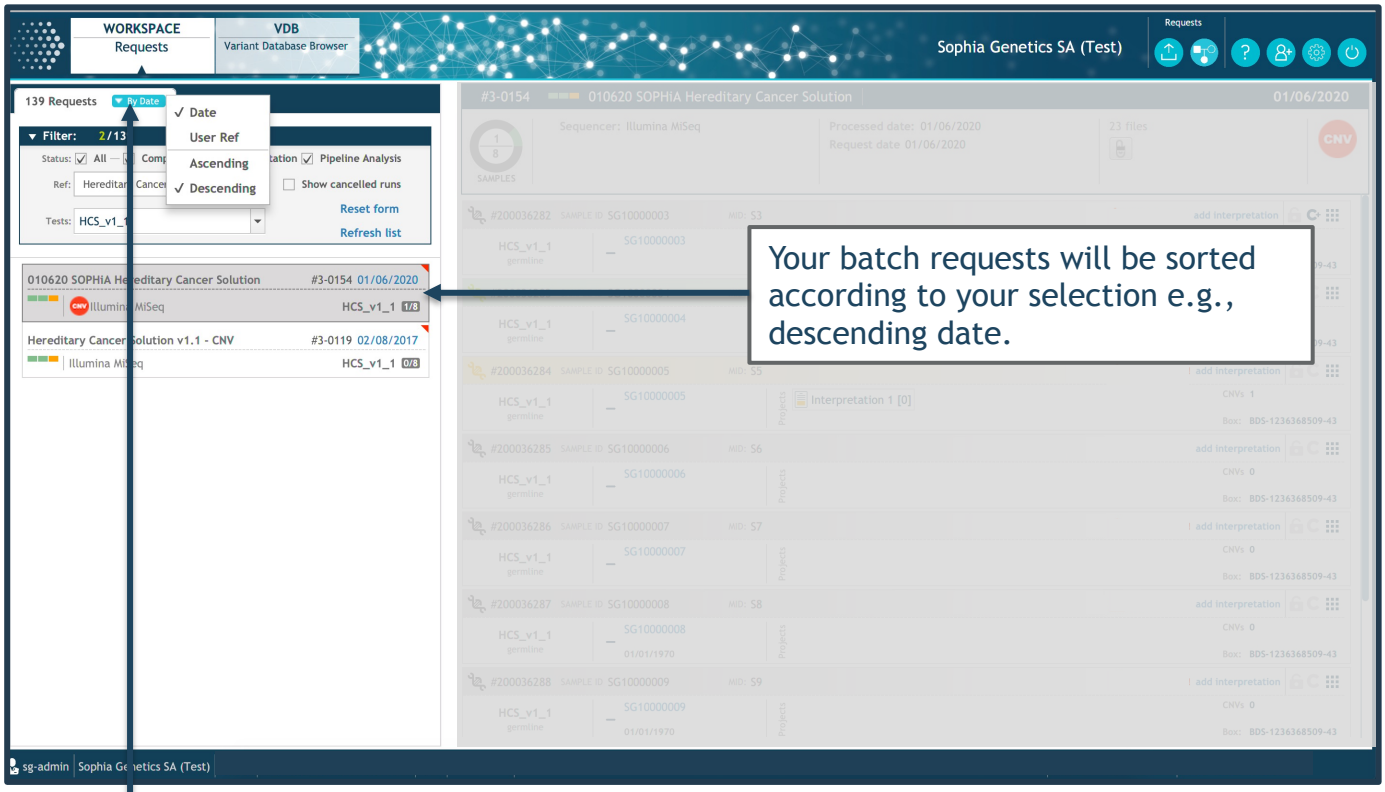
Requests/Patients*
List of requests

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



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

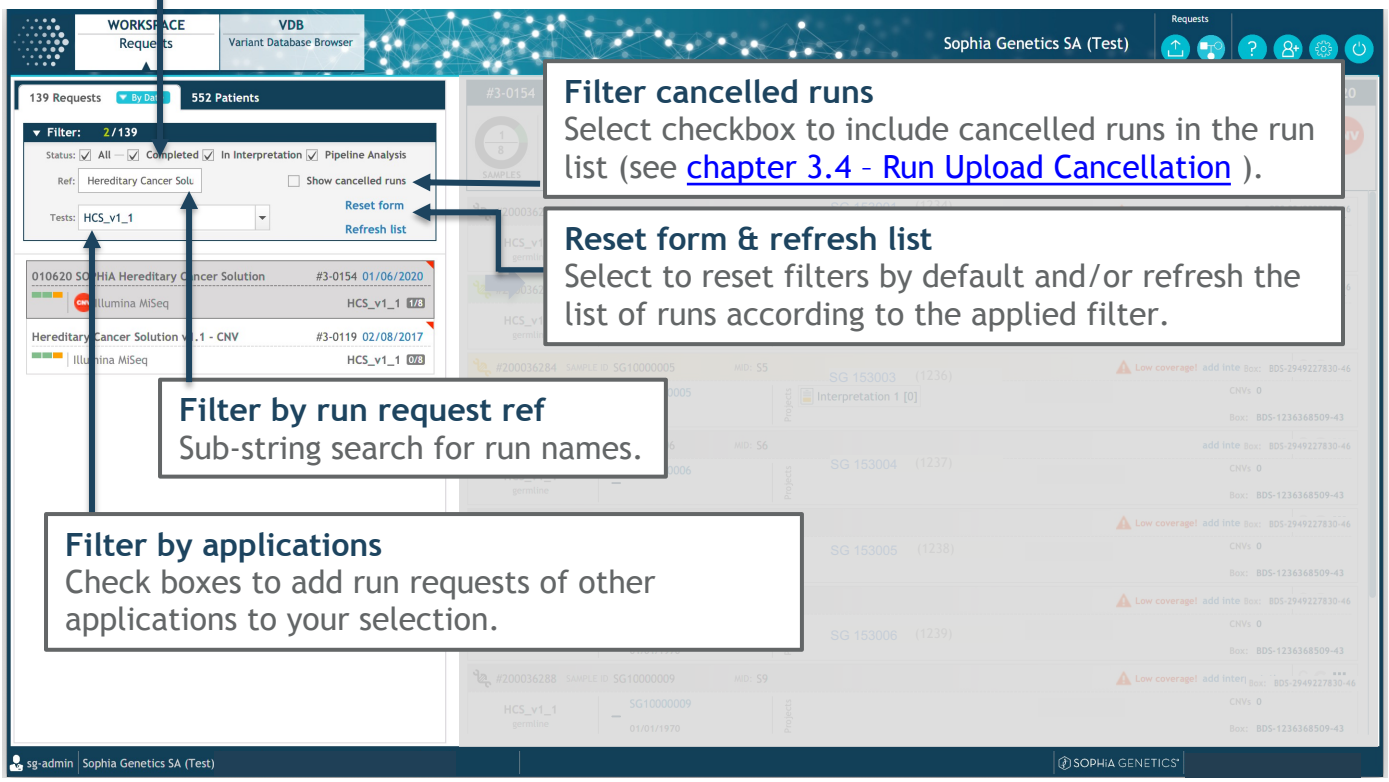
3. Workspace
3.2 Request Management (1)



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

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”.



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.

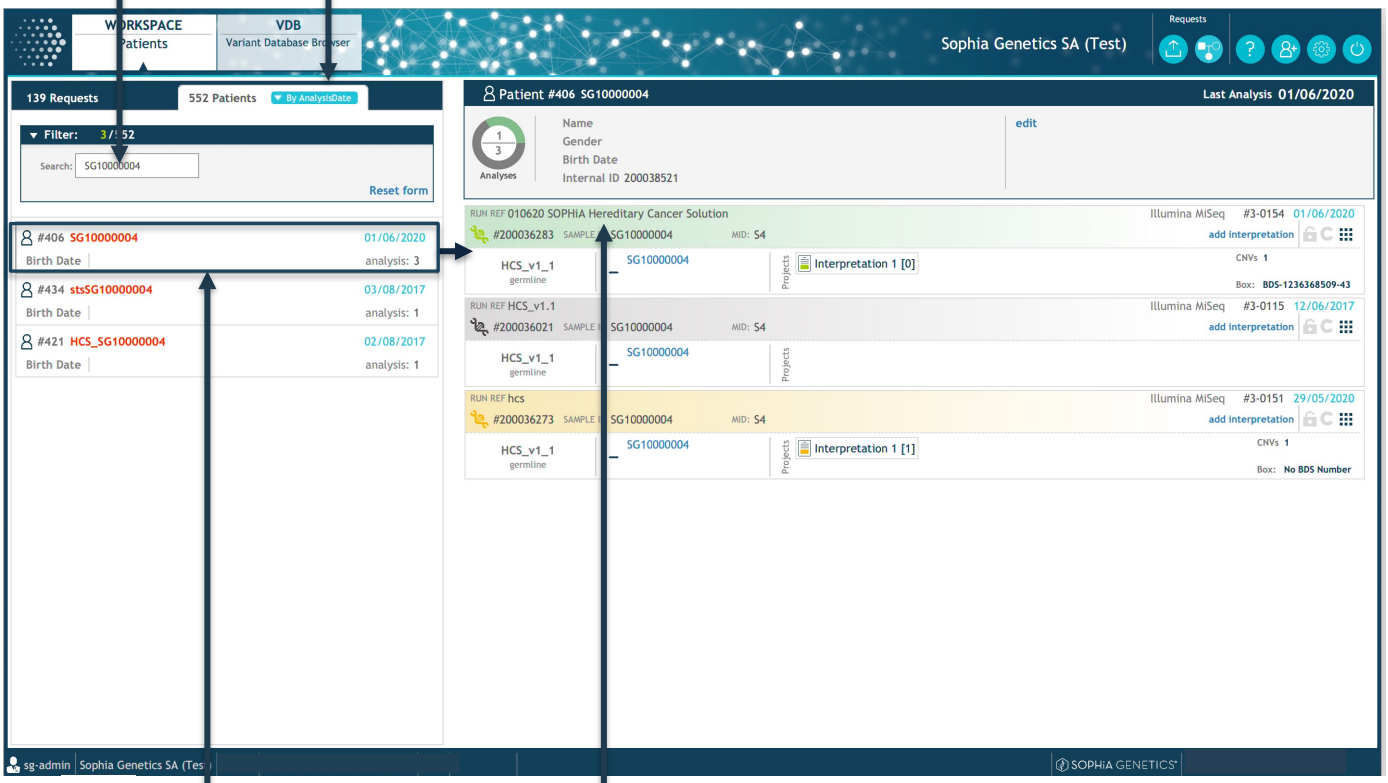
Filter by run request ref
Sub-string search for run names.

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



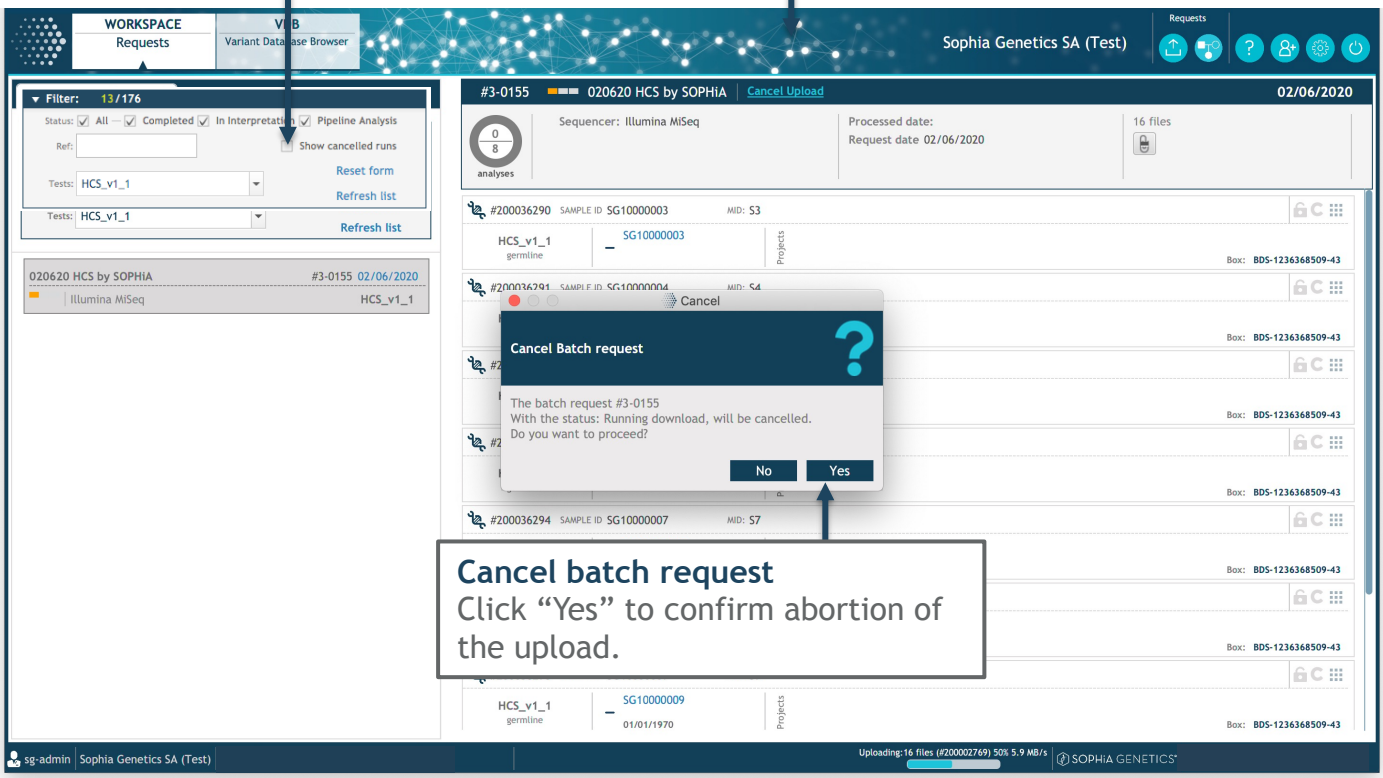
Select patient* from the list. The corresponding analysis/analyses will appear on the right-hand side.

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.

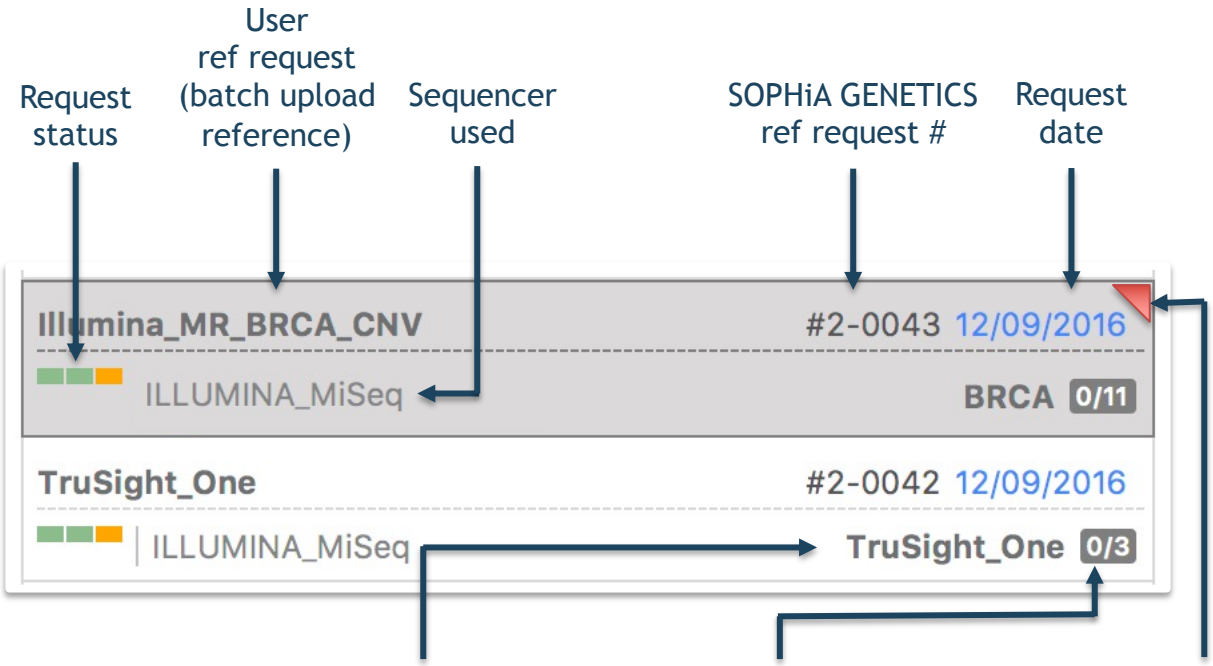
“Cancel upload”
Click to cancel selected ongoing batch upload.



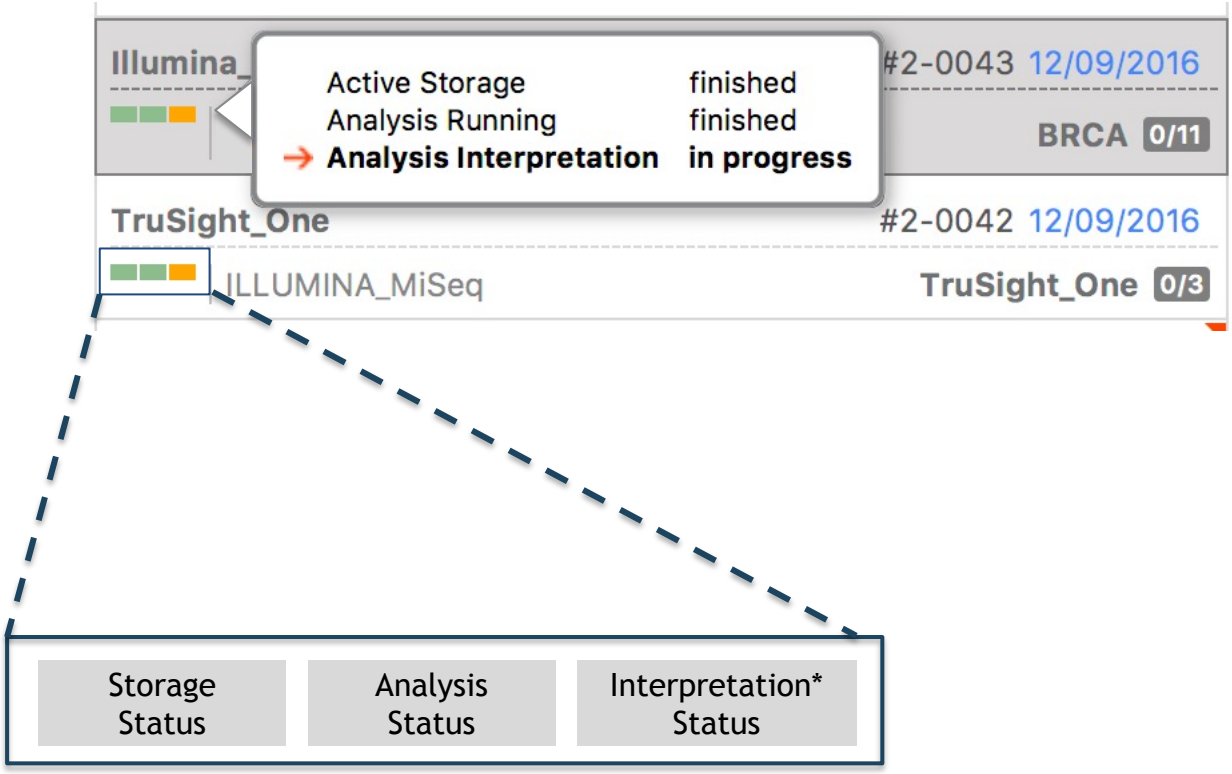
Cancel batch request
Click “Yes” to confirm abortion of the upload.

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.

3. Workspace
3.5 Request Information Summary



3. Workspace
3.6 Request Status



Color Codes

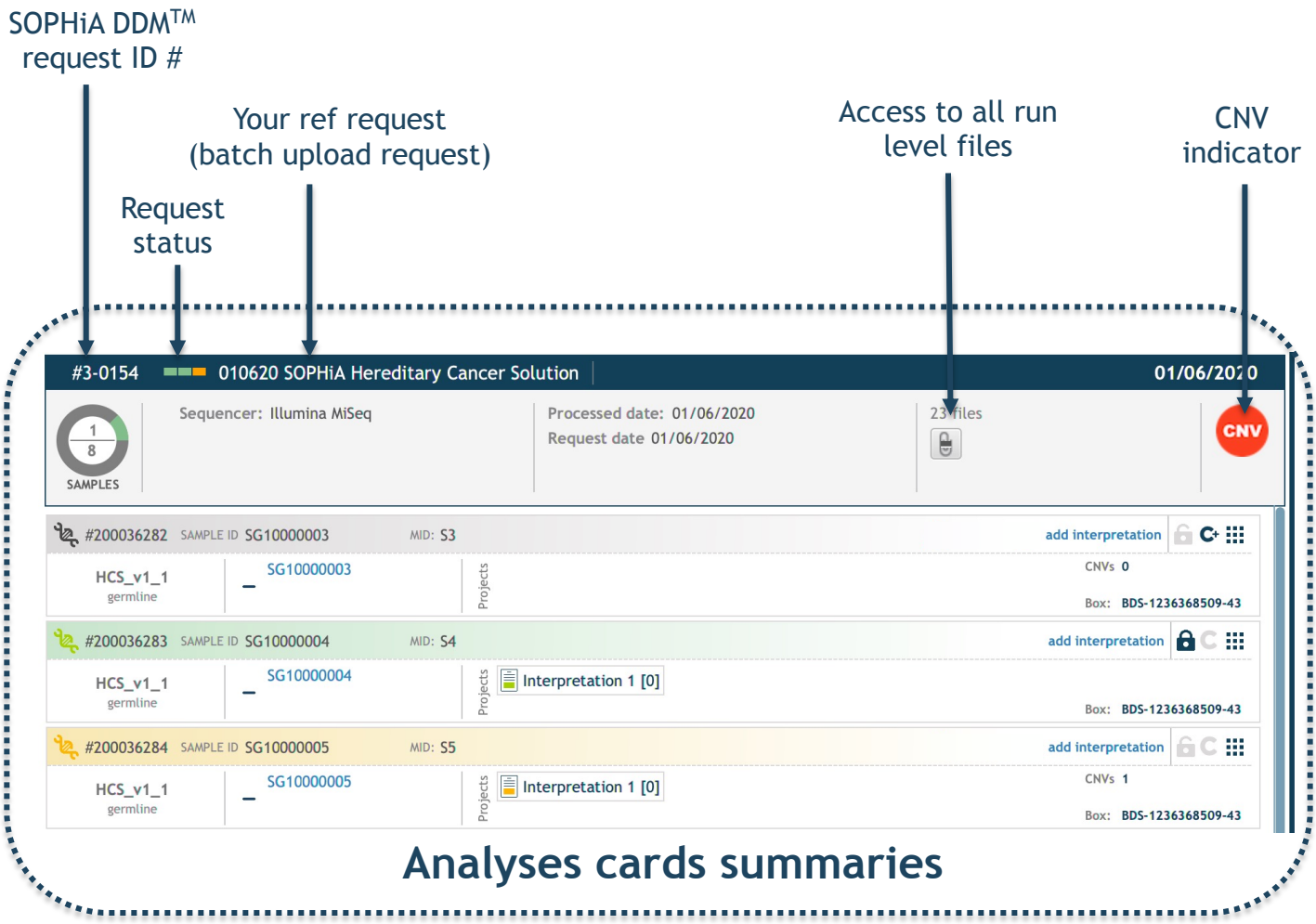
- Not started
- Running
- Error
- Completed

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

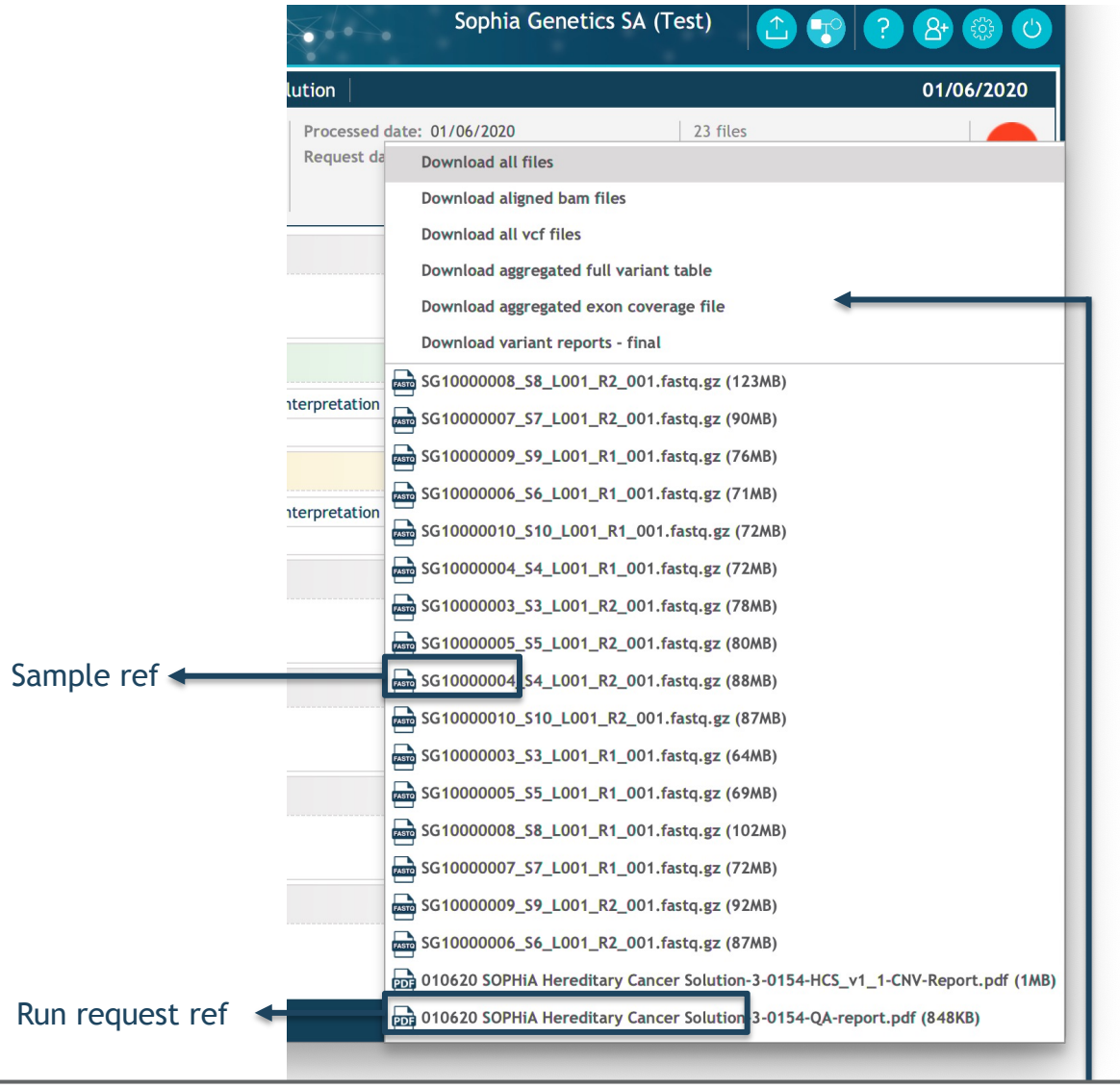


Analyses cards summaries

Indicators

- CNV — CNV is present BUT has not been seen in a project OR no CNV present
- CNV — At least one CNV is present AND it has been seen in a project

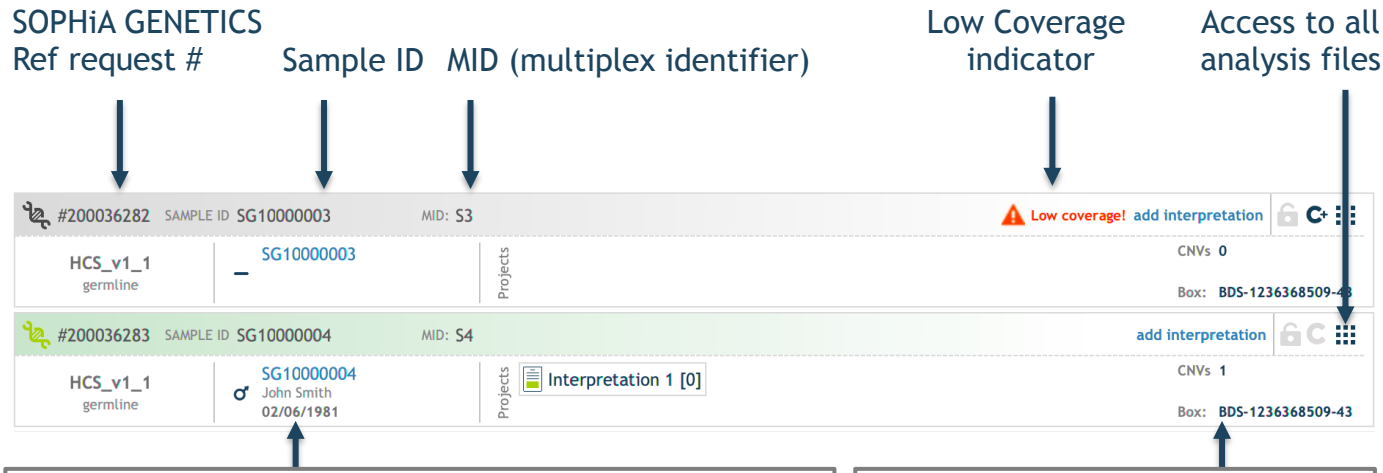
3. Workspace
3.7 Analysis Card Overview (2)



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)

3. Workspace
3.8 Analysis Card Details (1)

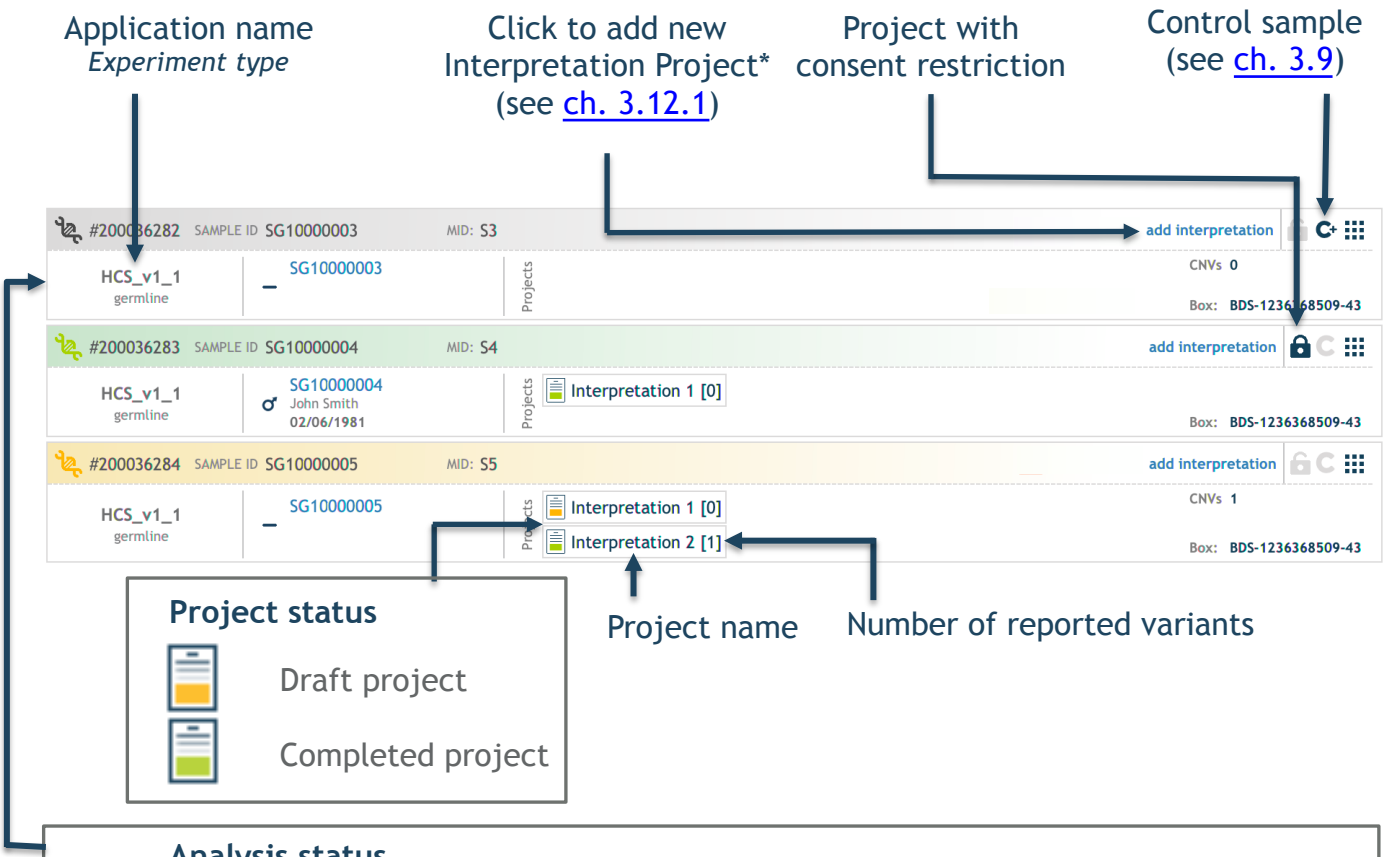


Patient* details
- Patient* ID
- Patient's* gender (unknown - / female ♀ / male ♂)
- Patient's* date of birth

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)



Analysis status

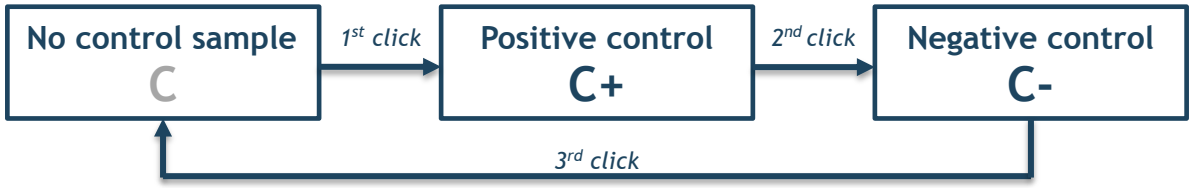
- Analysis not started yet: no Interpretation Projects* created
- Analysis finished: all linked projects are completed
- Analysis in progress: at least one draft project

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

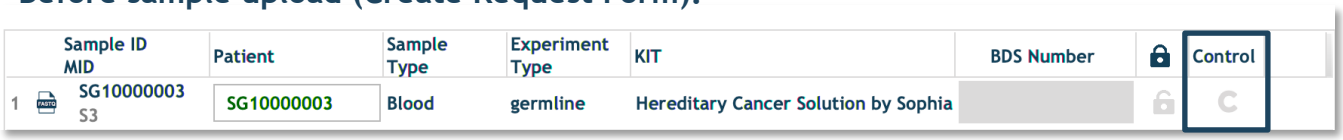
NOTE: A fourth Analysis status "pending approval" is available in accounts with "Report Approval Workflow" activated. Details see ch. 4.5 Report Approval Workflow).

3. Workspace
3.9 Control Samples

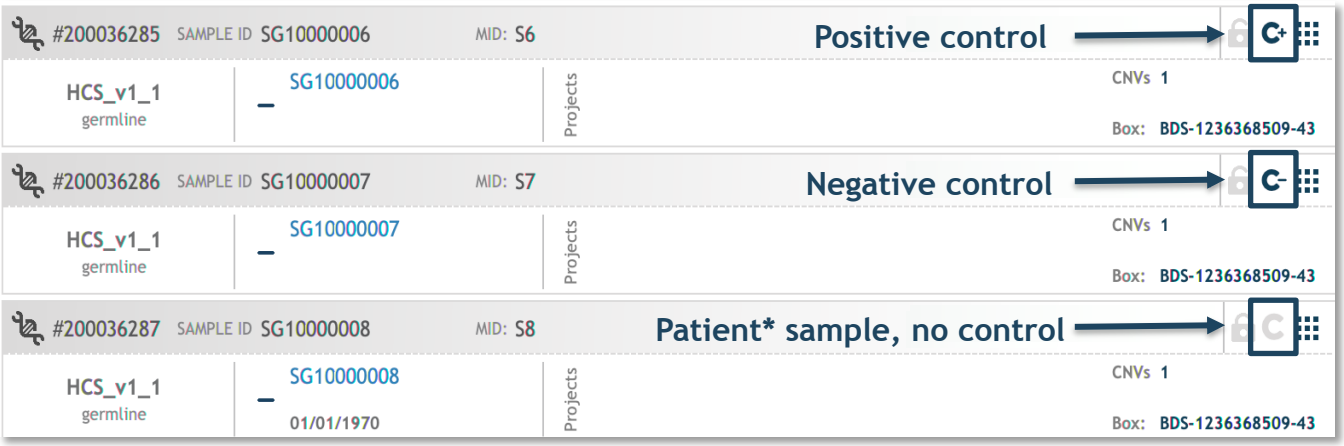
Click the C button one or several times to mark a samples as:
- Positive control (C+)
- Negative control (C-)
- No control sample (normal patient* samples)



Before sample upload (Create Request Form):

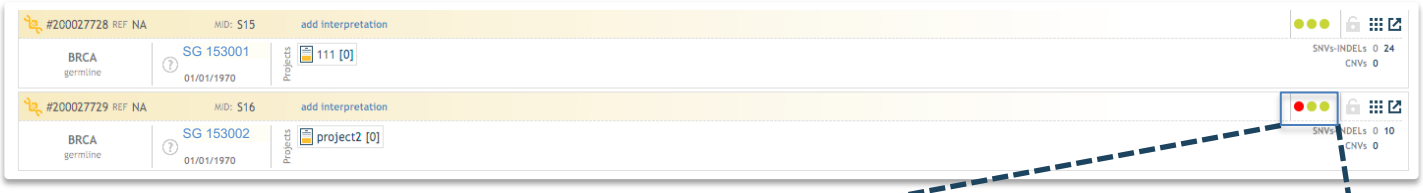


After sample upload (Workspace):



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*).

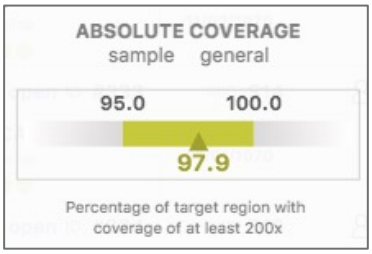
3. Workspace
3.10 Quality Indicators
3.10.1 Germline BRCA Application



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

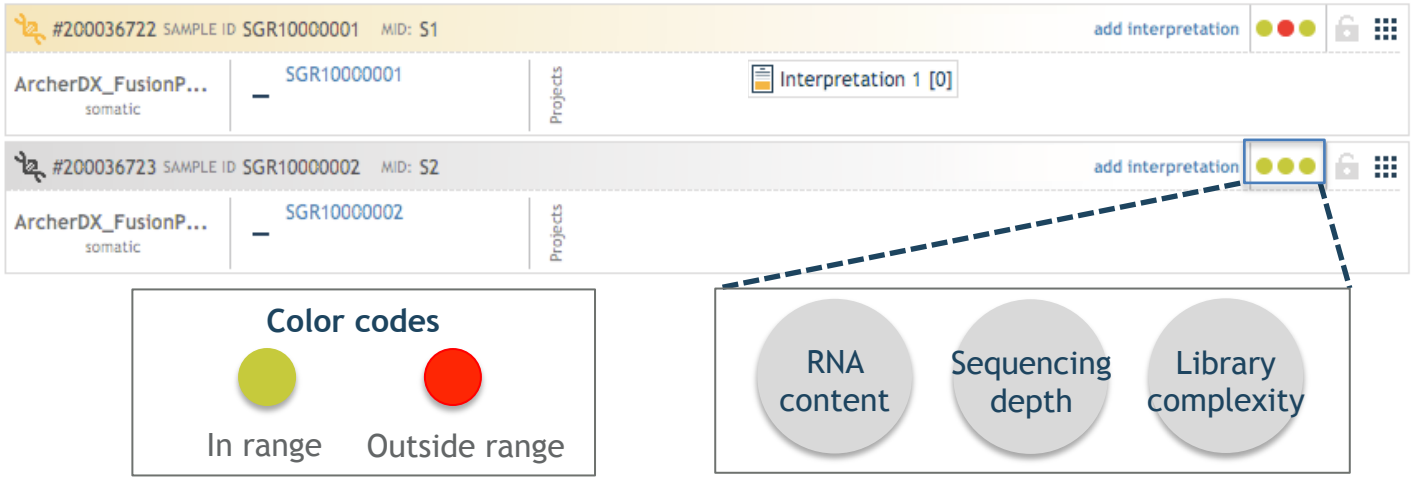
80-100%

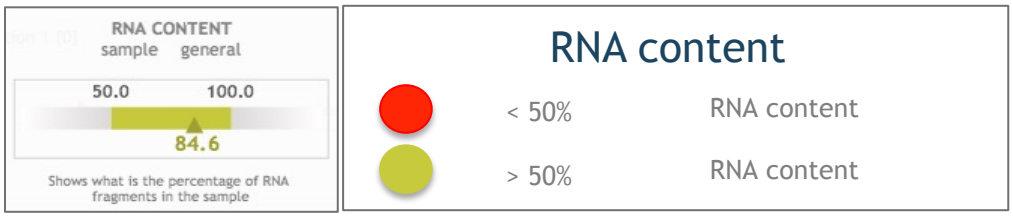
Retained reads

< 95 % Percentage of retained reads

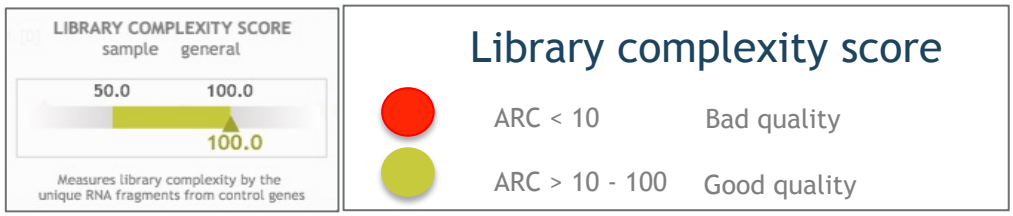
95-100 %

3. Workspace
3.10 Quality Indicators
3.10.2 Somatic Archer FusionPlex® Application

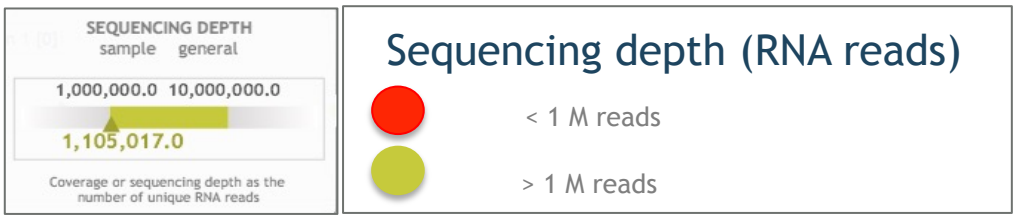




RNA experiments often have remains of DNA in the sample. This indicator measures the proportion of RNA and DNA molecules. RNA content of < 50% indicates a highly degradated sample.

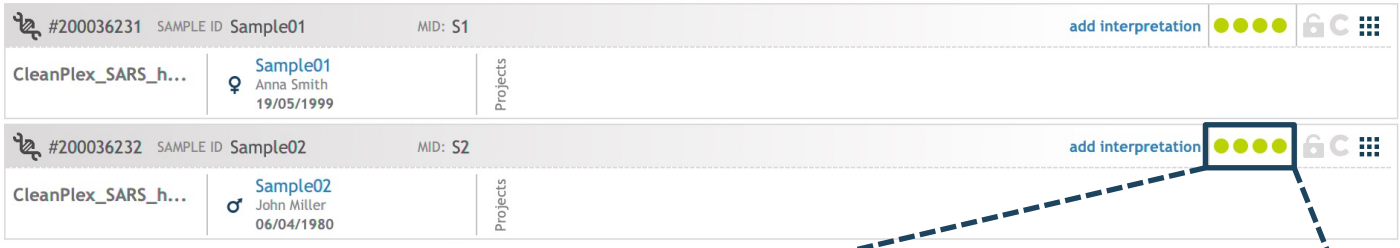


Average number of unique RNA (ARC) start sites of 4 control genes is calculated. A lack of unique fragments for these control genes implies a low RNA starting material or a very degraded library in which not enough RNA fragments were converted to sequenced read. ARC is converted to a score between 0-100.



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

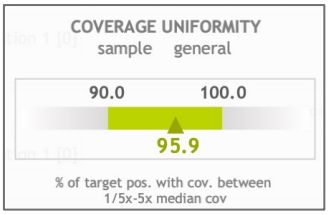
3. Workspace
3.10 Quality Indicators
3.10.3 SARS-CoV-2 Application



Color codes

In range — Outside range

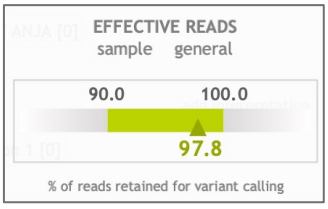
Coverage uniformity | Effective reads | Pool 1/2 balance | Target covered



Coverage uniformity

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

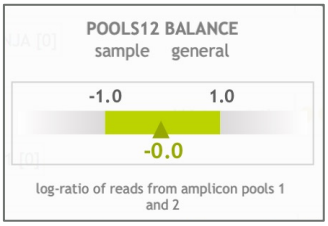
Percentage of target positions with coverage between 1/5x to 5x median coverage.



Effective reads

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

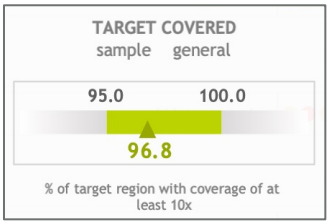
Percentage of reads retained for variant calling.



Pool 1 & 2 balance

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

Log ratio of reads from amplicon pool 1 and 2.

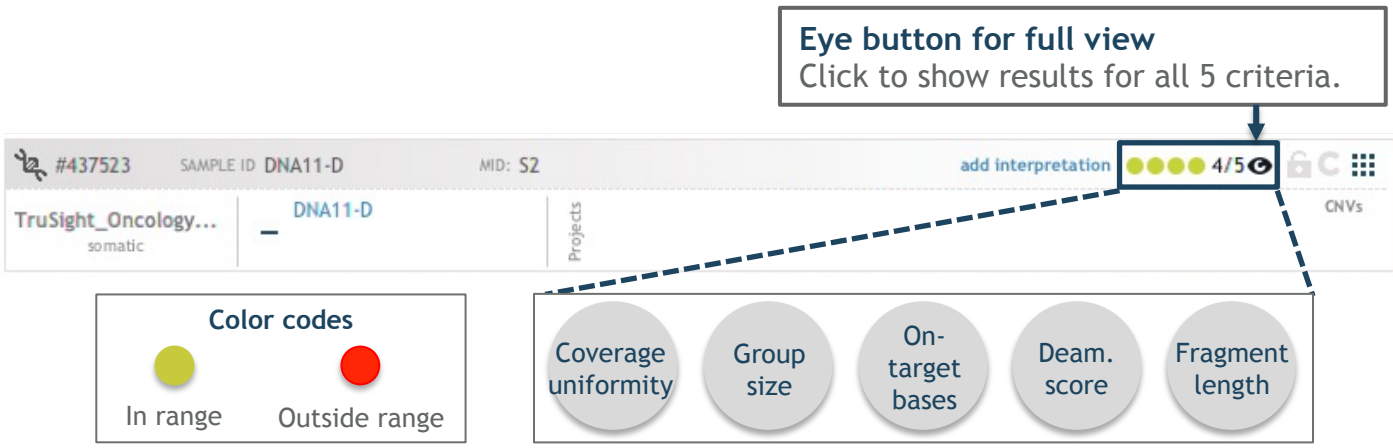


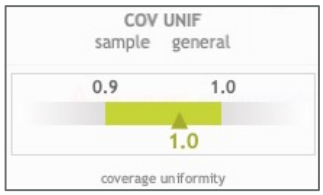
Target covered

- < 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

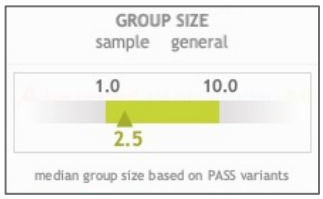




Coverage uniformity

- < 90%
- > 90%

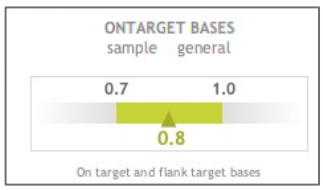
Percentage of target positions with coverage between 1/5x to 5x median coverage.



Group size

- > 10
- < 10

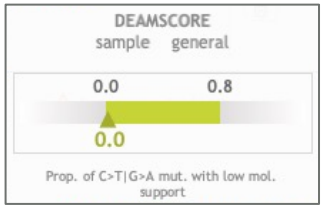
Median group size based on high confidence variants.



On-target bases

- < 70%
- > 70%

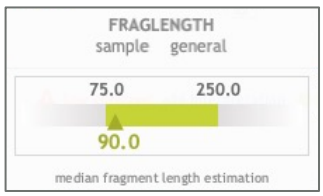
Fraction of bases from the reads that are located on-target or flanking the target.



Deamination score

- > 80%
- < 80%

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

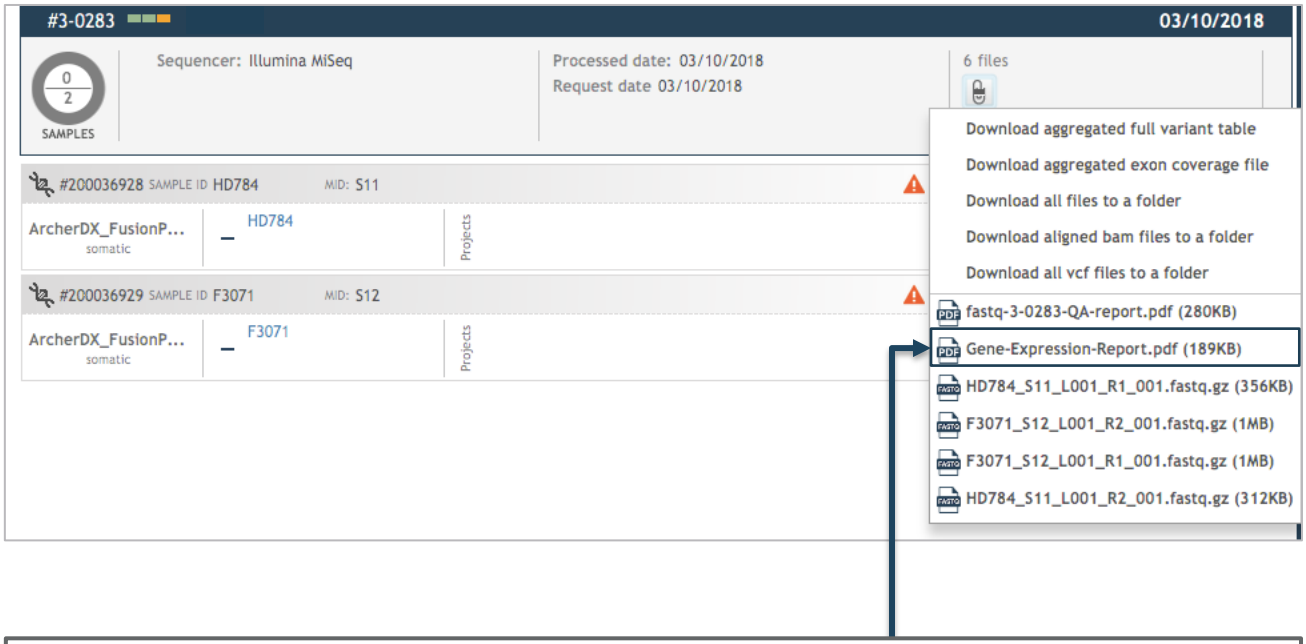


Fragment length

- < 75 > 250
- > 75 < 250

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

3. Workspace
3.11 Expression Analysis Report



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.

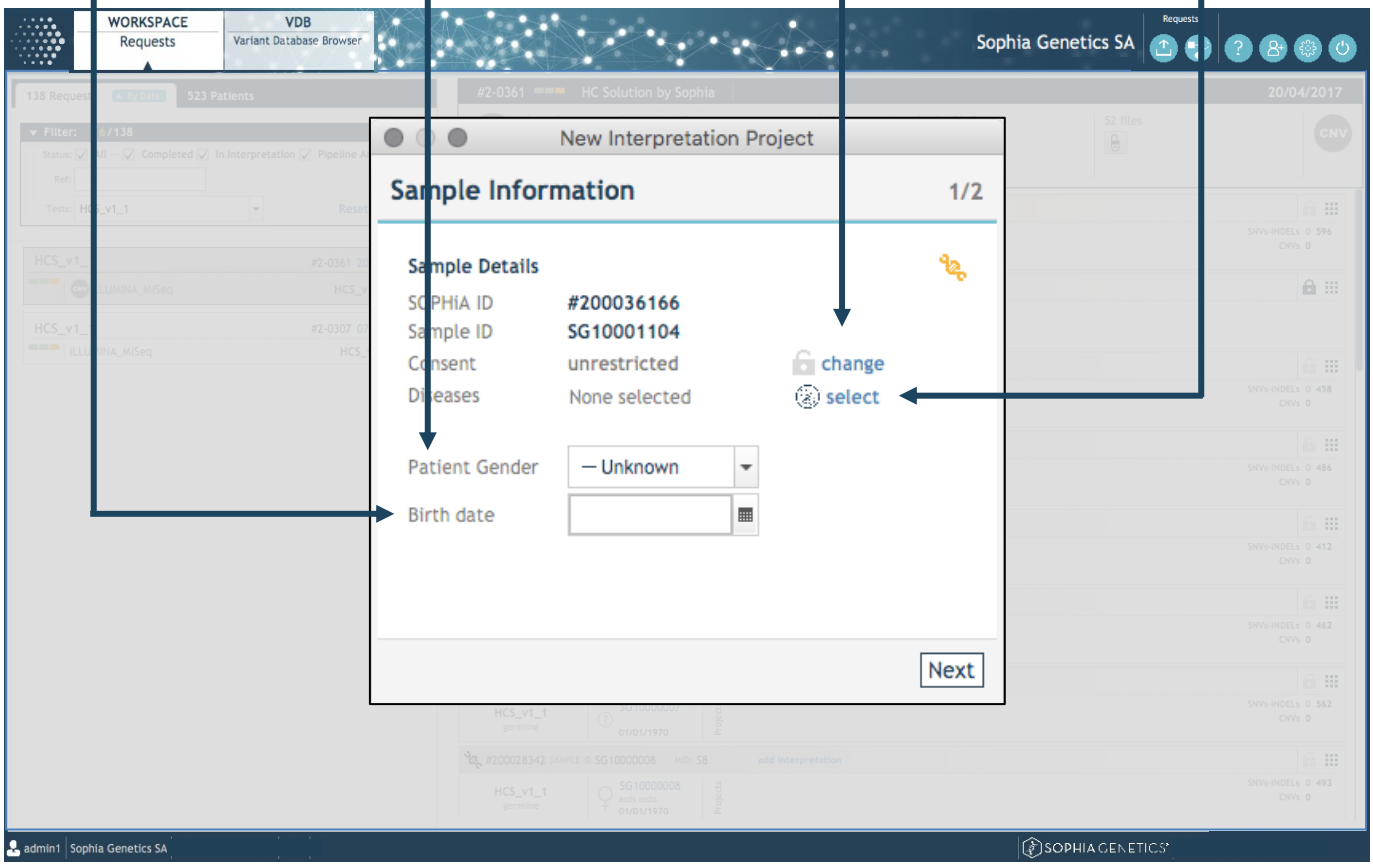
3. Workspace
3.12 Interpretation Projects*
3.12.1 Overview

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

Patient* Gender
Select gender of the patient*

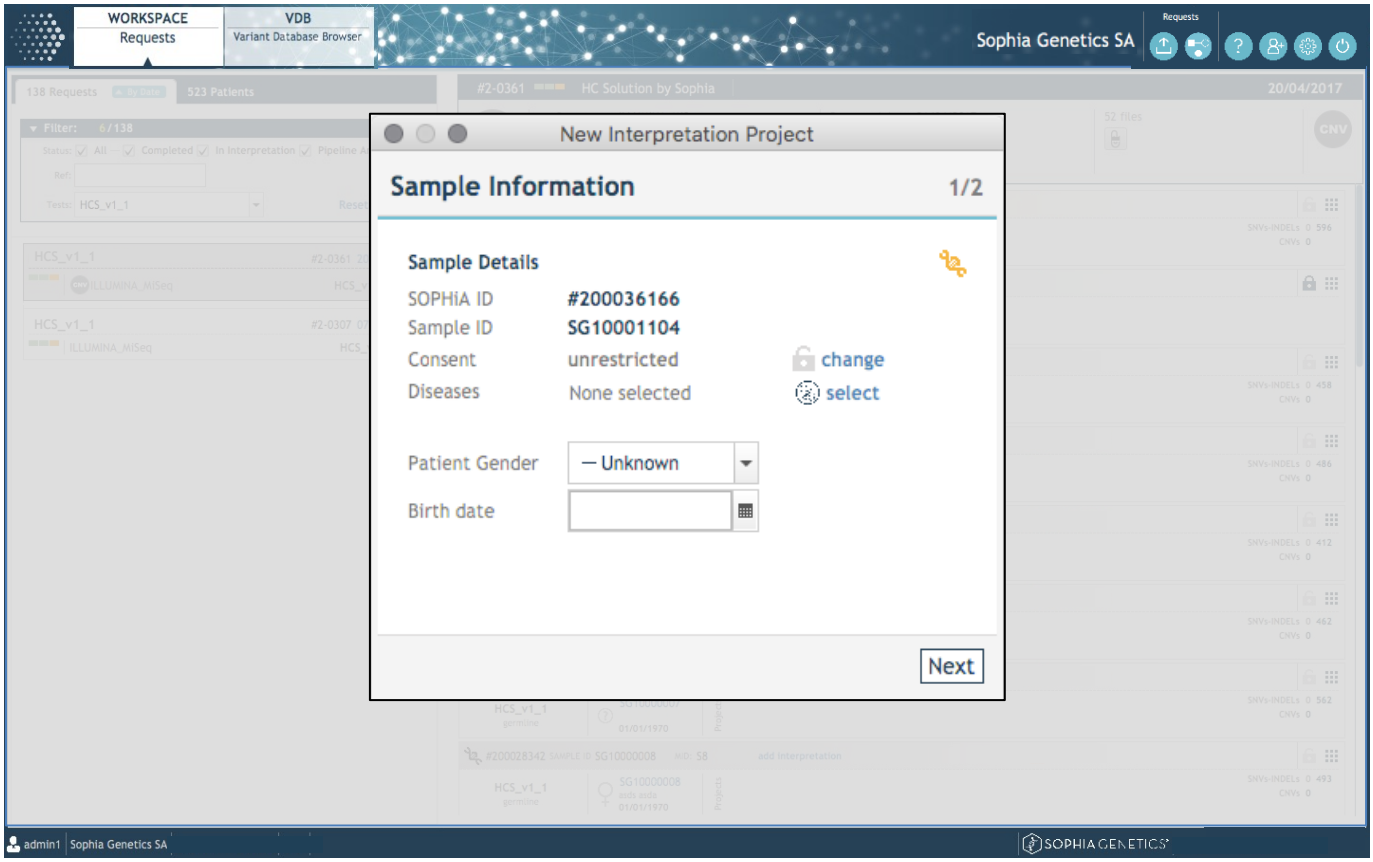
Change restriction
Select Virtual Panel to restrict analysis

Select Disease*
Select patient's* disease*



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*.

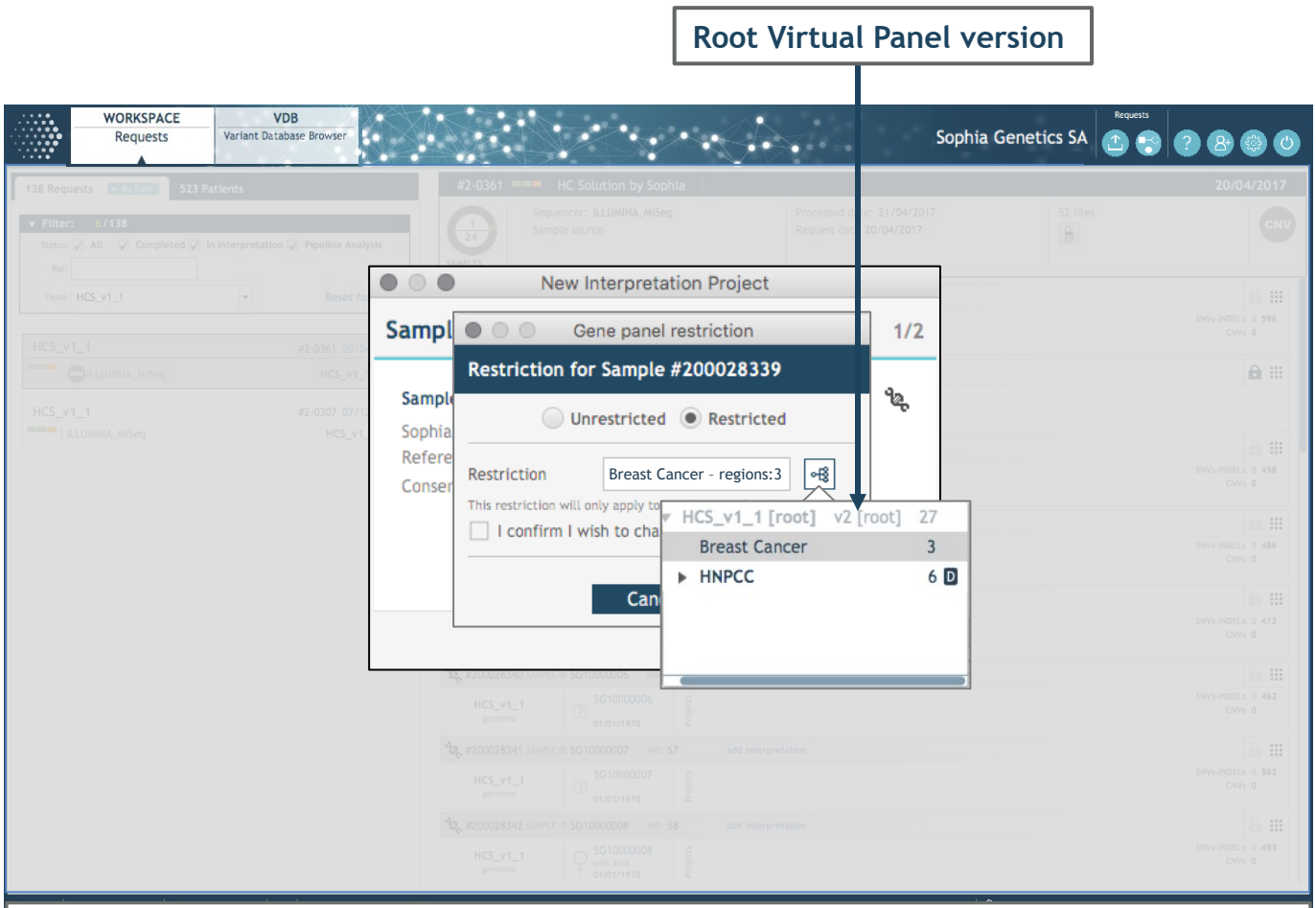
3. Workspace
3.12 Interpretation Projects*
3.12.2 Restrict to a Virtual Panel (1)



- 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.

3. Workspace
3.12 Interpretation Projects*
3.12.2 Restrict to a Virtual Panel (2)

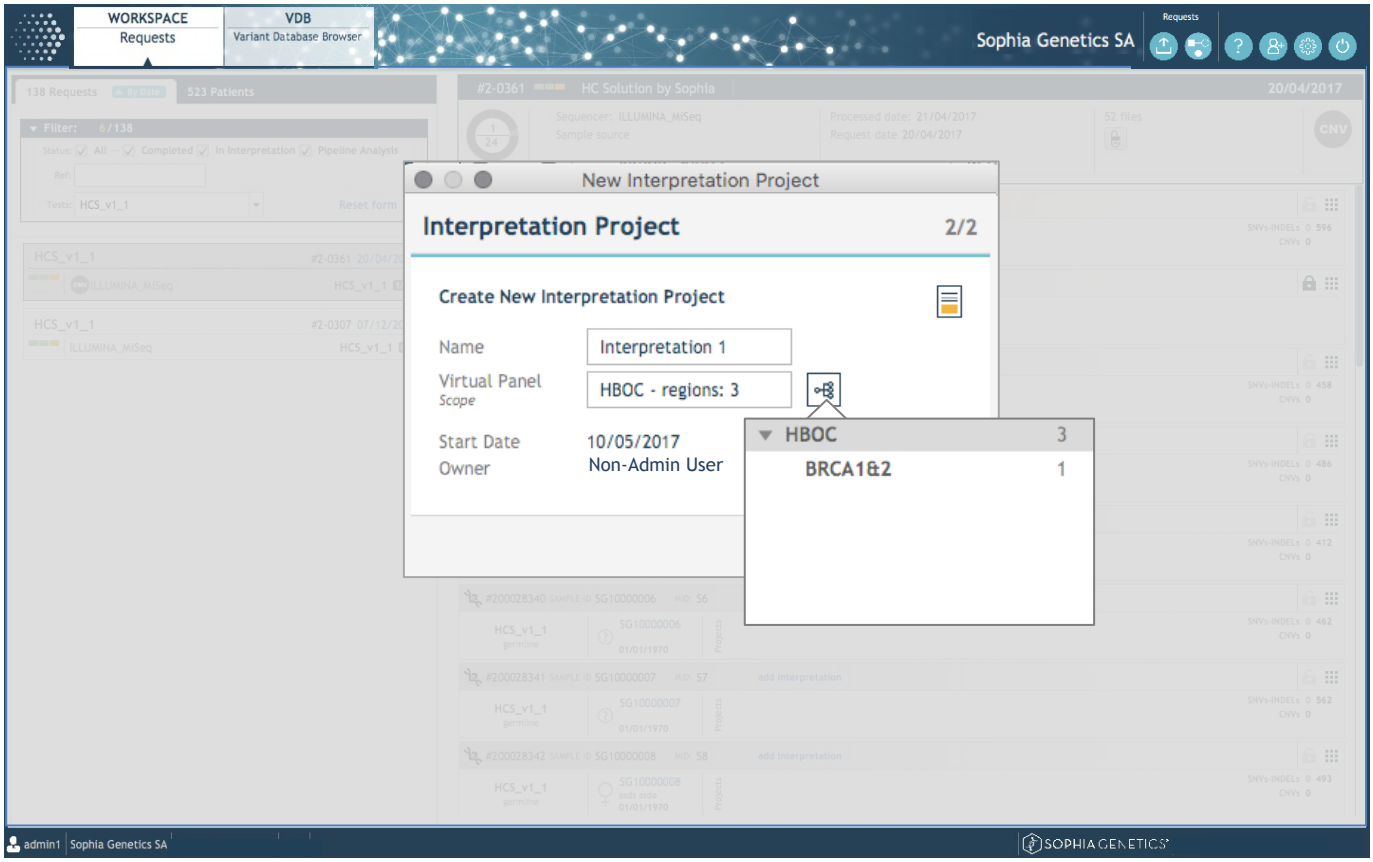


Consent restriction
To apply a consent restriction:
- Click “restricted” and then
- Select a Virtual Panel from the pre-defined list (defined per application by an admin user at the account level)
- Check the box to confirm the restriction
- Click “OK”

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

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.

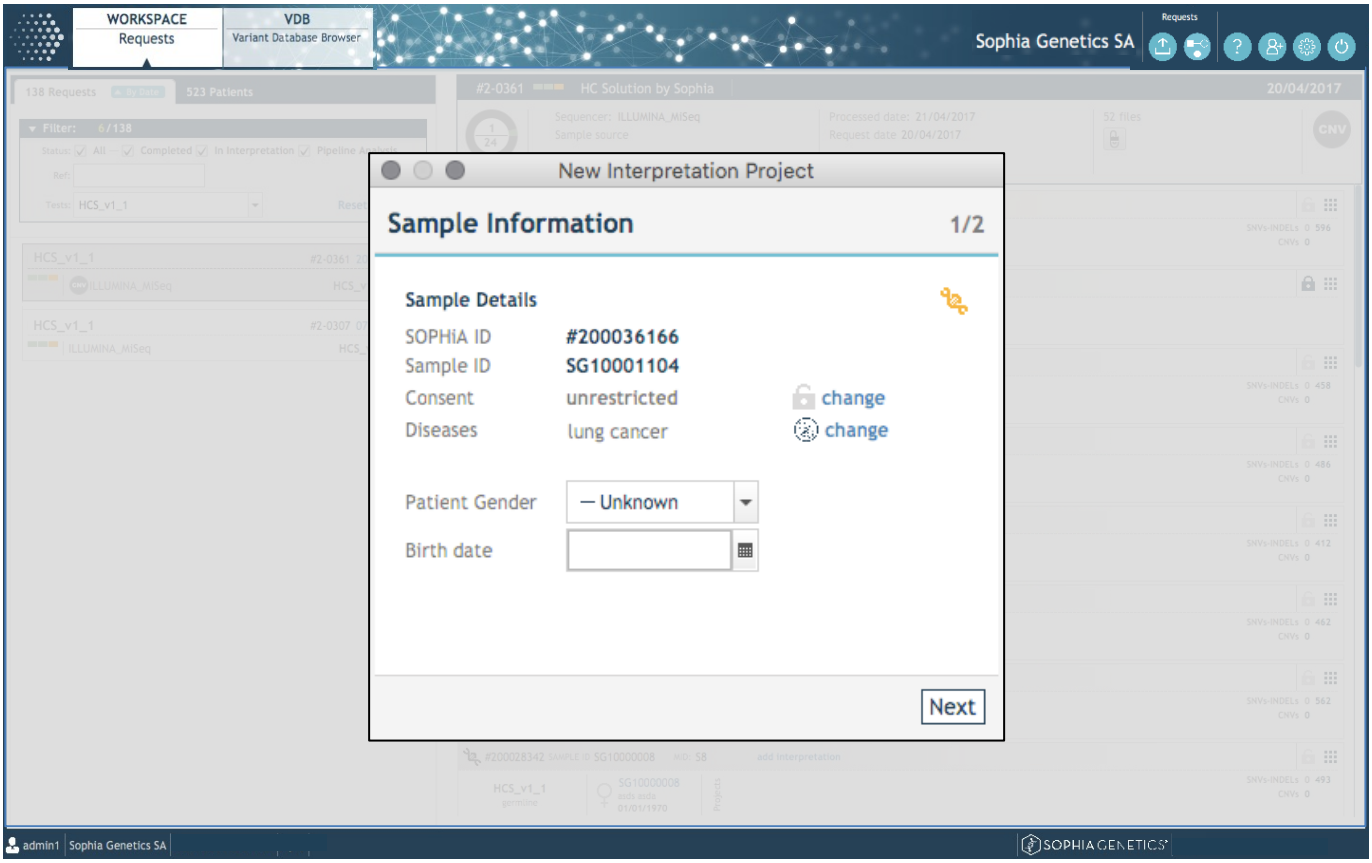


Project* scope
- The default name for the Project* is “Interpretation 1”
- Type in the field to edit the name
- If user wishes restrict the scope of the Interpretation Project*, click
- Click “finish” to create and open the overview page of the Project*

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.

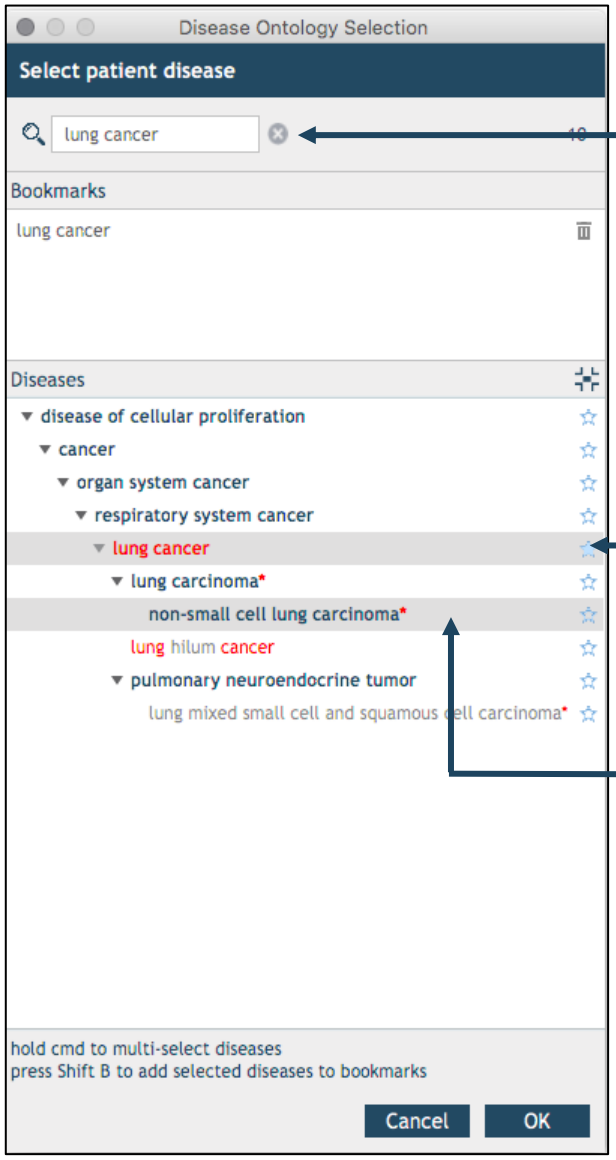


Addition of a disease*
- Click “select” or “change” to open Disease* Ontology tree
- Search one or several disease*(s) or select from the bookmarked diseases* (see p. 76)
- Click “OK” to confirm

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



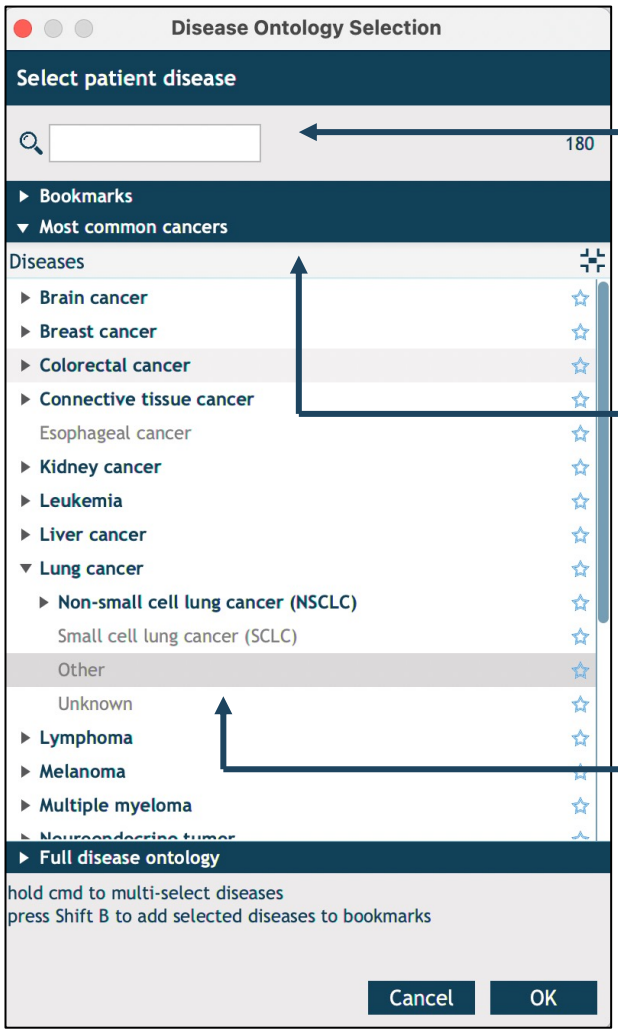
Search a disease*
Type the suspected disease* name. The list of terms containing the substring is instantly updated and respective disease*s are highlighted. Matching search terms are marked with red text and synonyms are indicated with a red star.

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*.

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

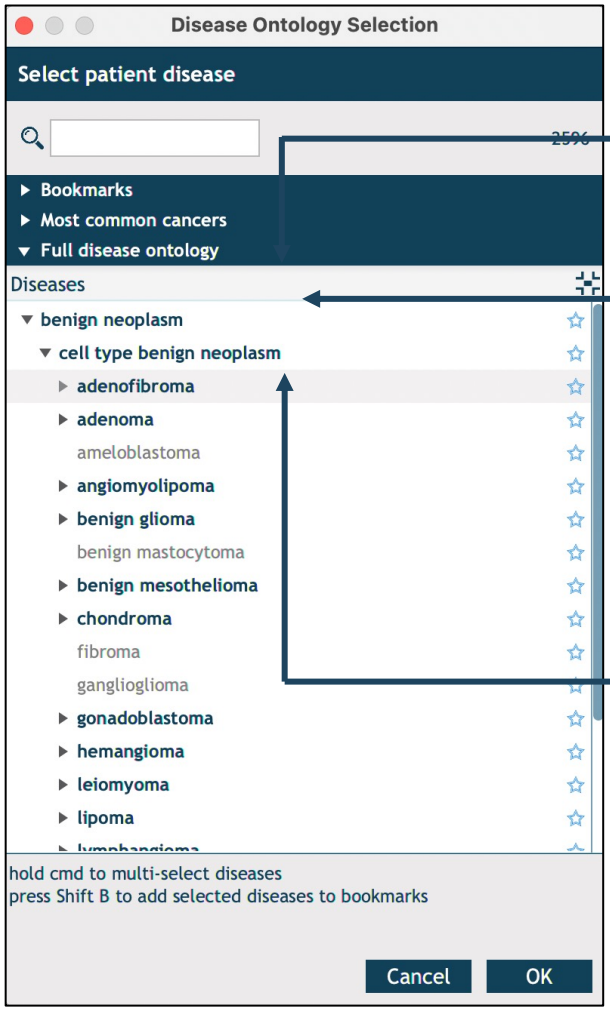
22 most common cancers are displayed upfront and selectable by the user, along with children nodes. These diseases* are mapped to DO terms.

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.

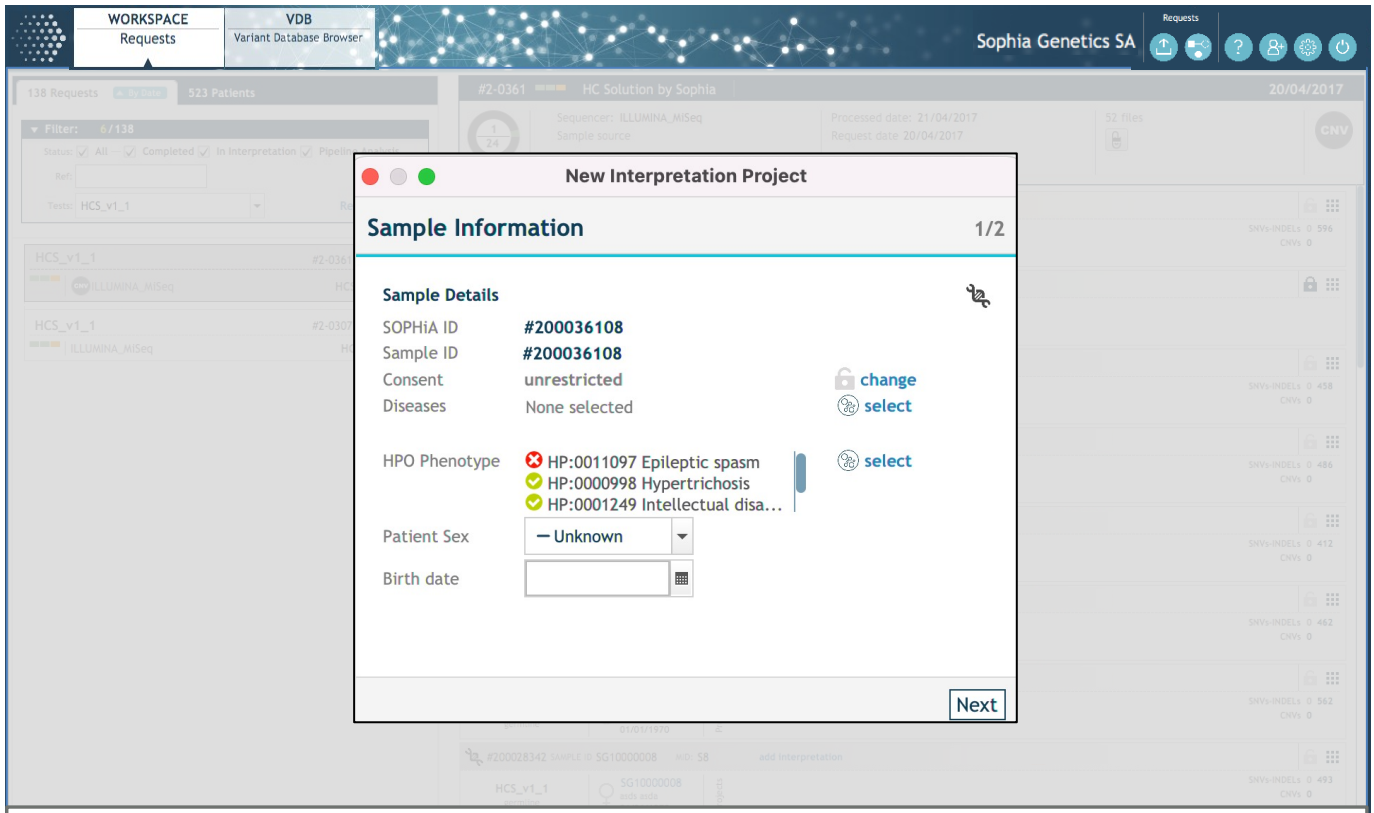
Restricted DO
Some high-level nodes from the full disease* ontology are not displayed in the somatic disease* tree.

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/.

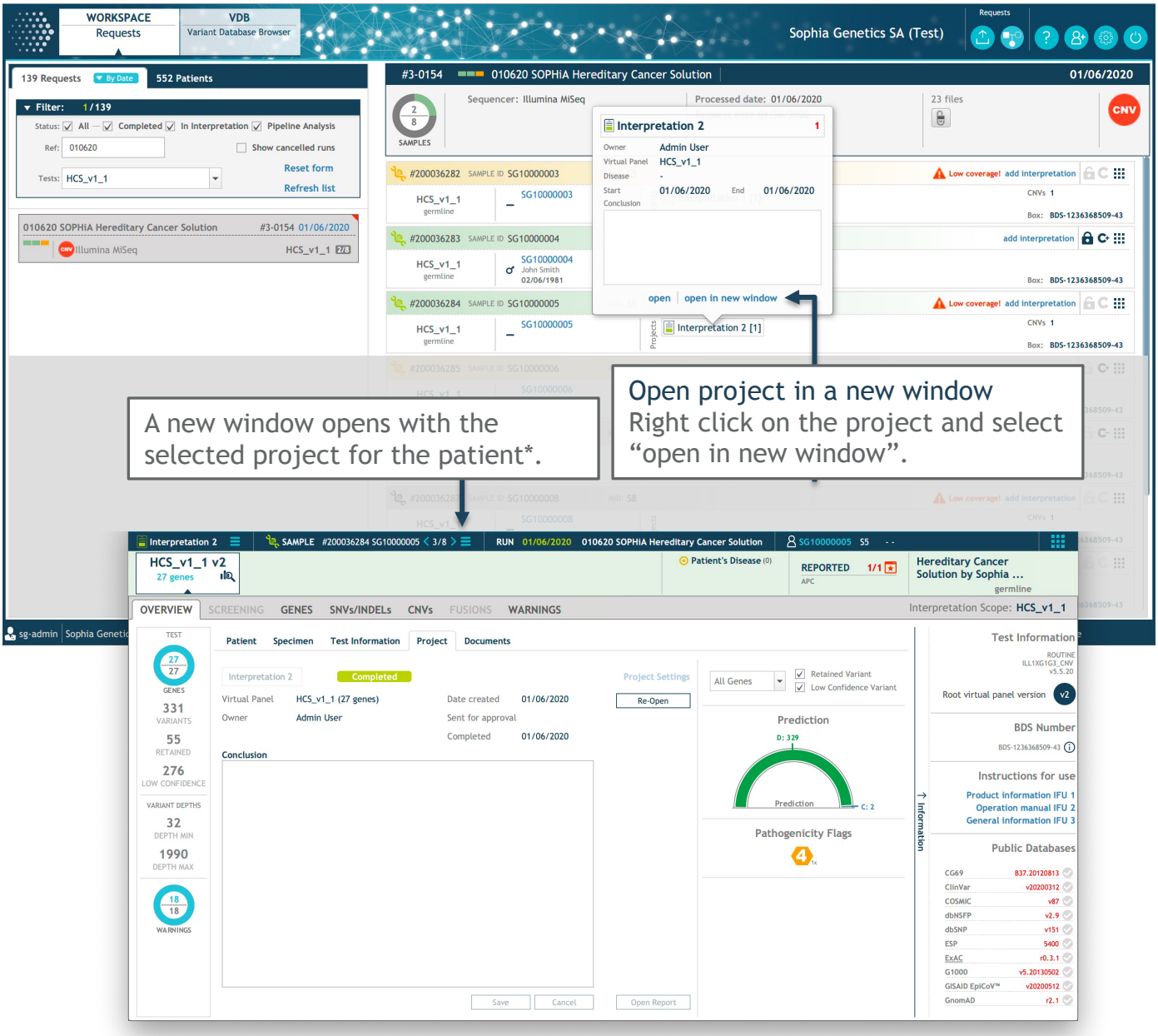


Included and excluded phenotypes

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)

4. Data Analysis
4.1 View Multiple Analyses

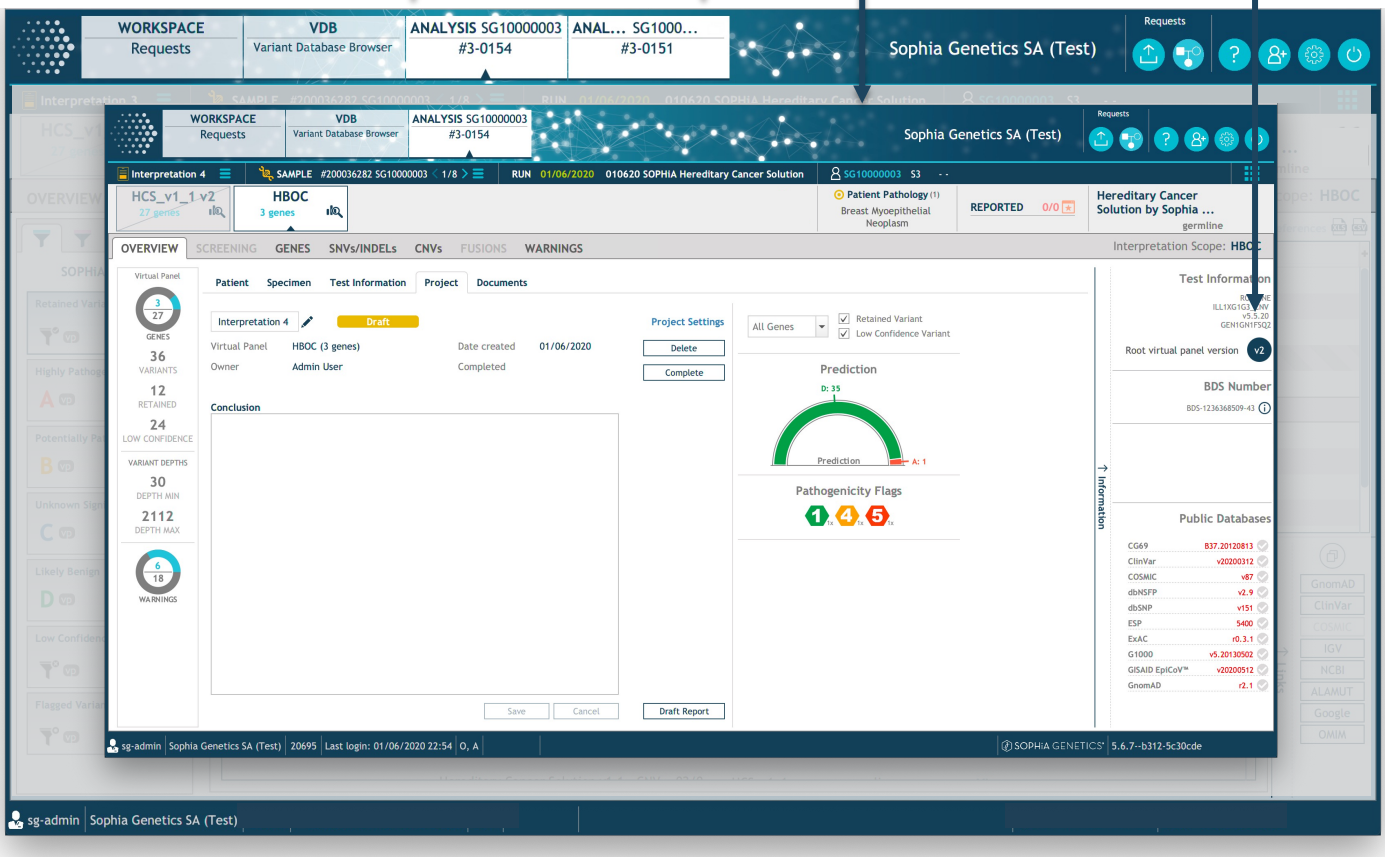


4. Data Analysis
4.2 Analysis Management

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

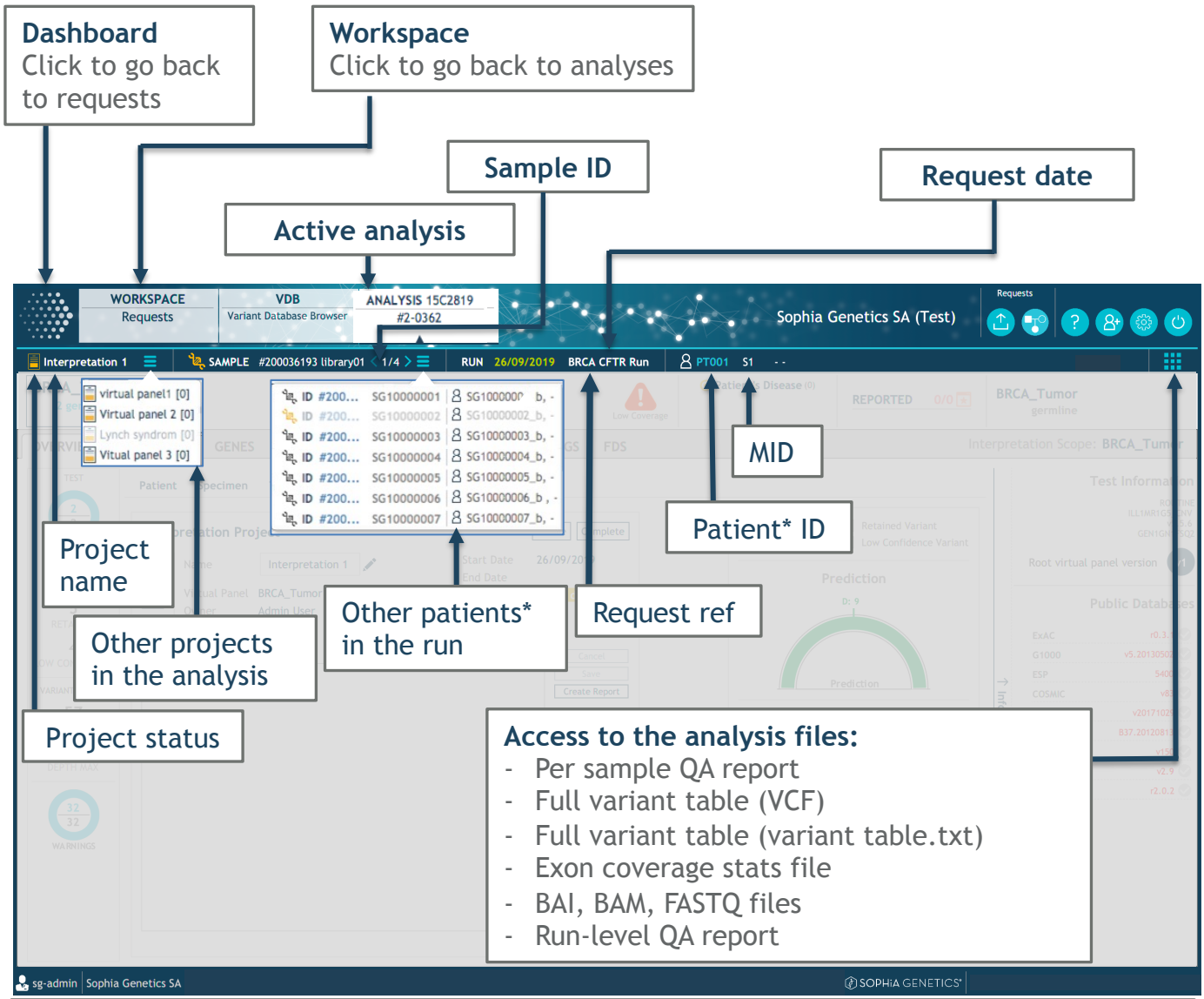
Click on one analysis tab to access

Root Virtual Panel version



4. Data Analysis
4.3 Analysis Header

General information about the analysis



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)

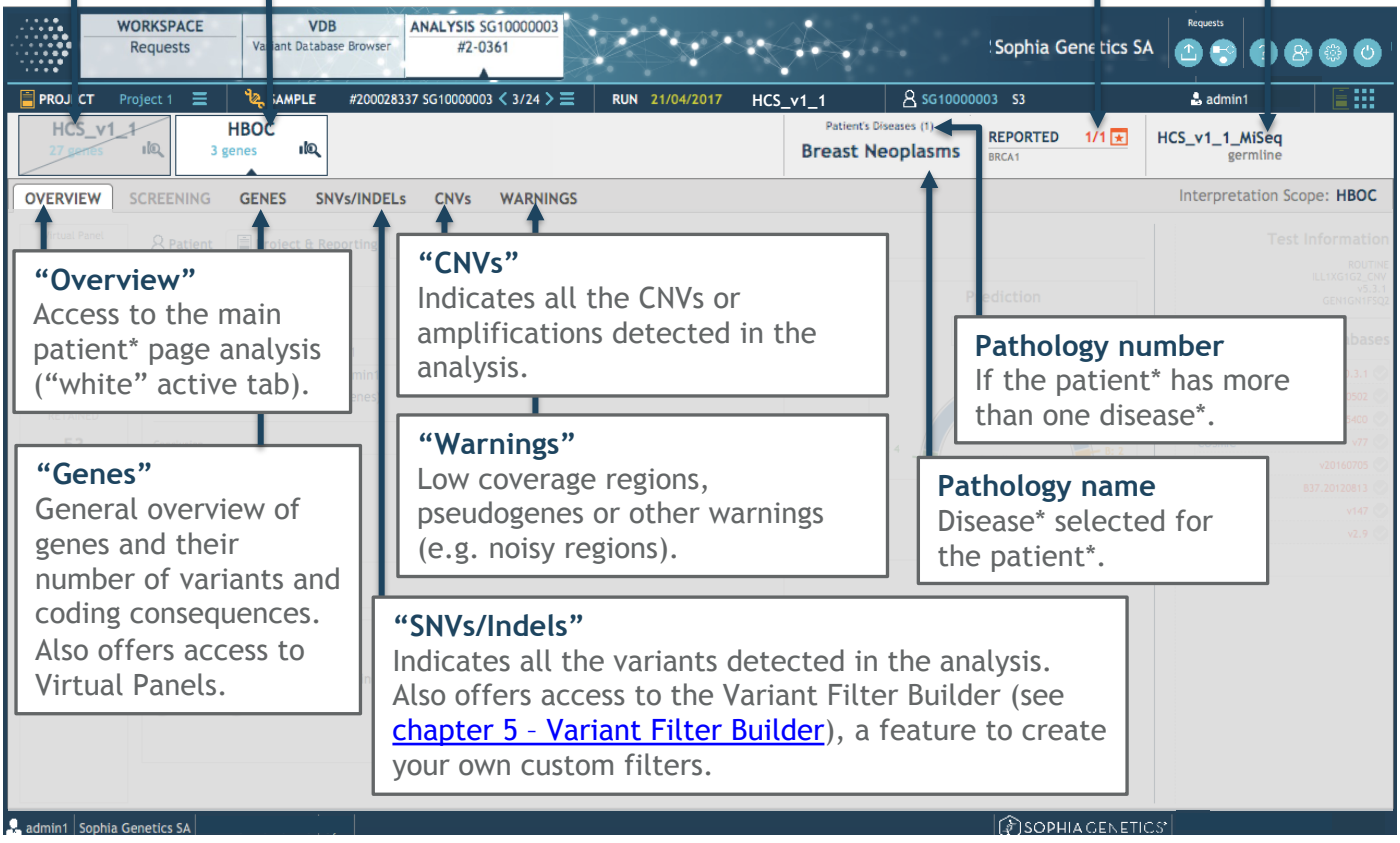
All tabs are restricted to the interpretation scope

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

Application name
Somatic/germline

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

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



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

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

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

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

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

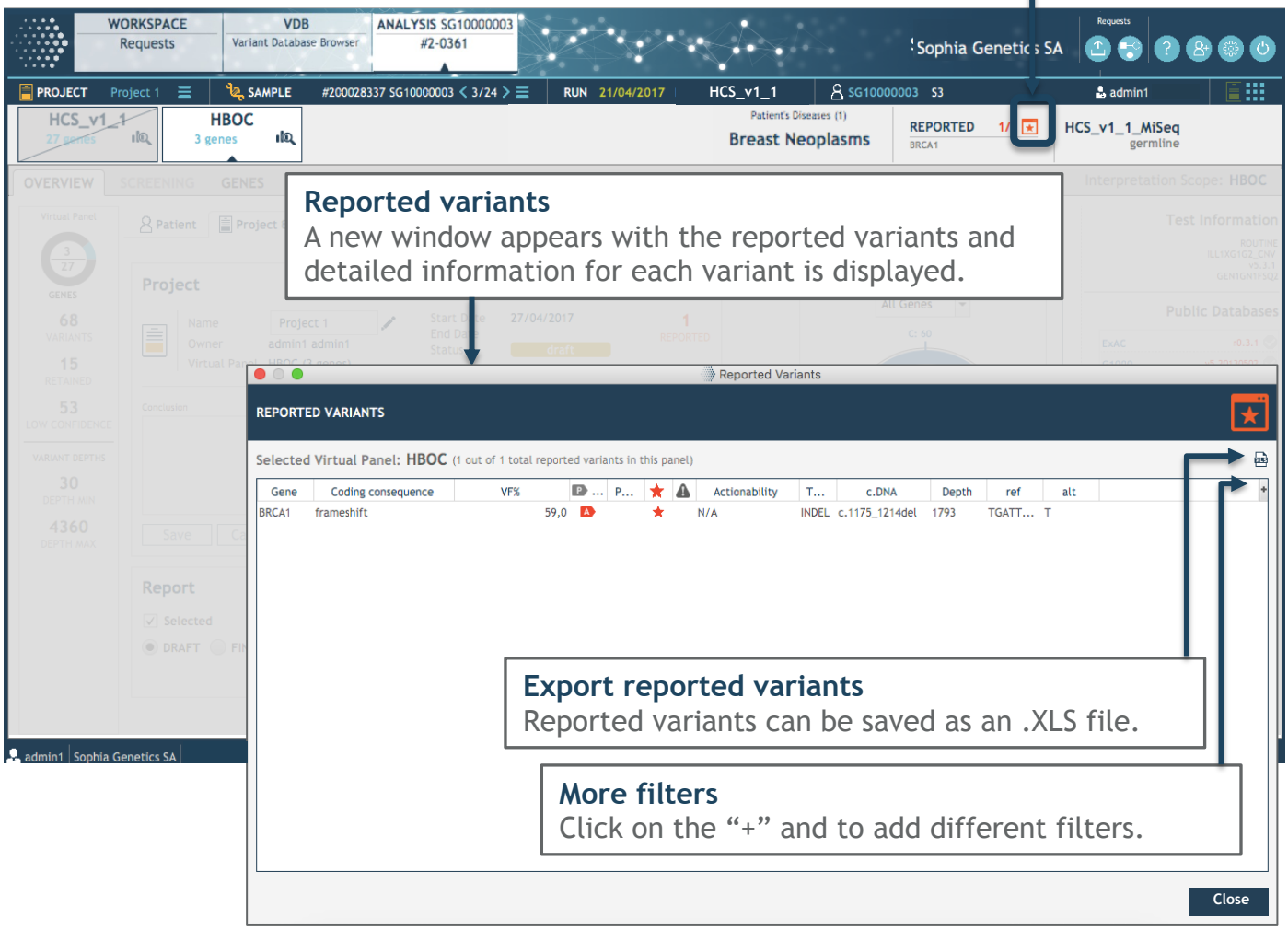
Pathology name
Disease* selected for the patient*.

“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.

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.

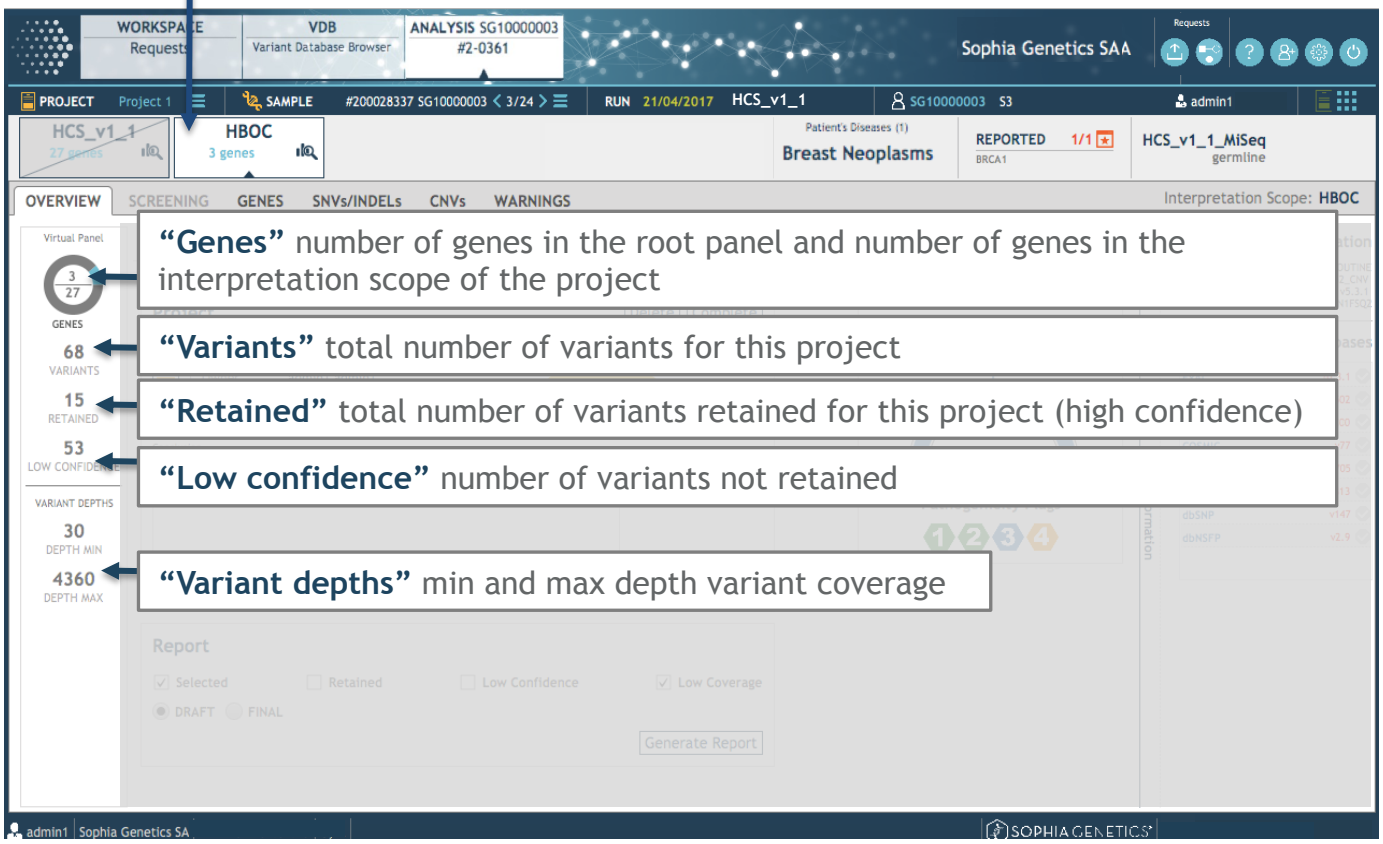
Export reported variants
Reported variants can be saved as an .XLS file.

More filters
Click on the "+" and to add different filters.

4. Data Analysis
4.4 Analysis Overview (3)

Overview tab data is restricted to the interpretation scope

Overview
Active page (white)



"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

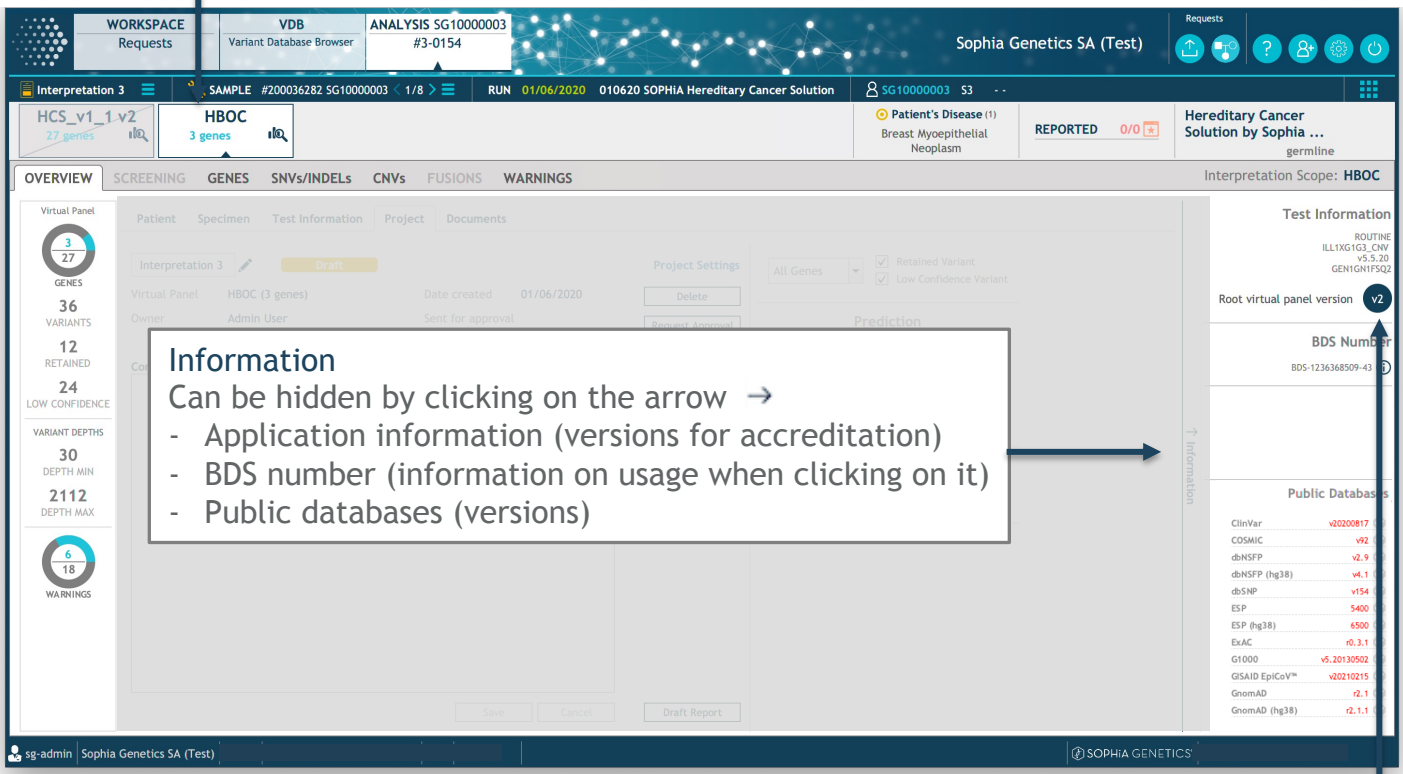
"Retained" total number of variants retained for this project (high confidence)

"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)



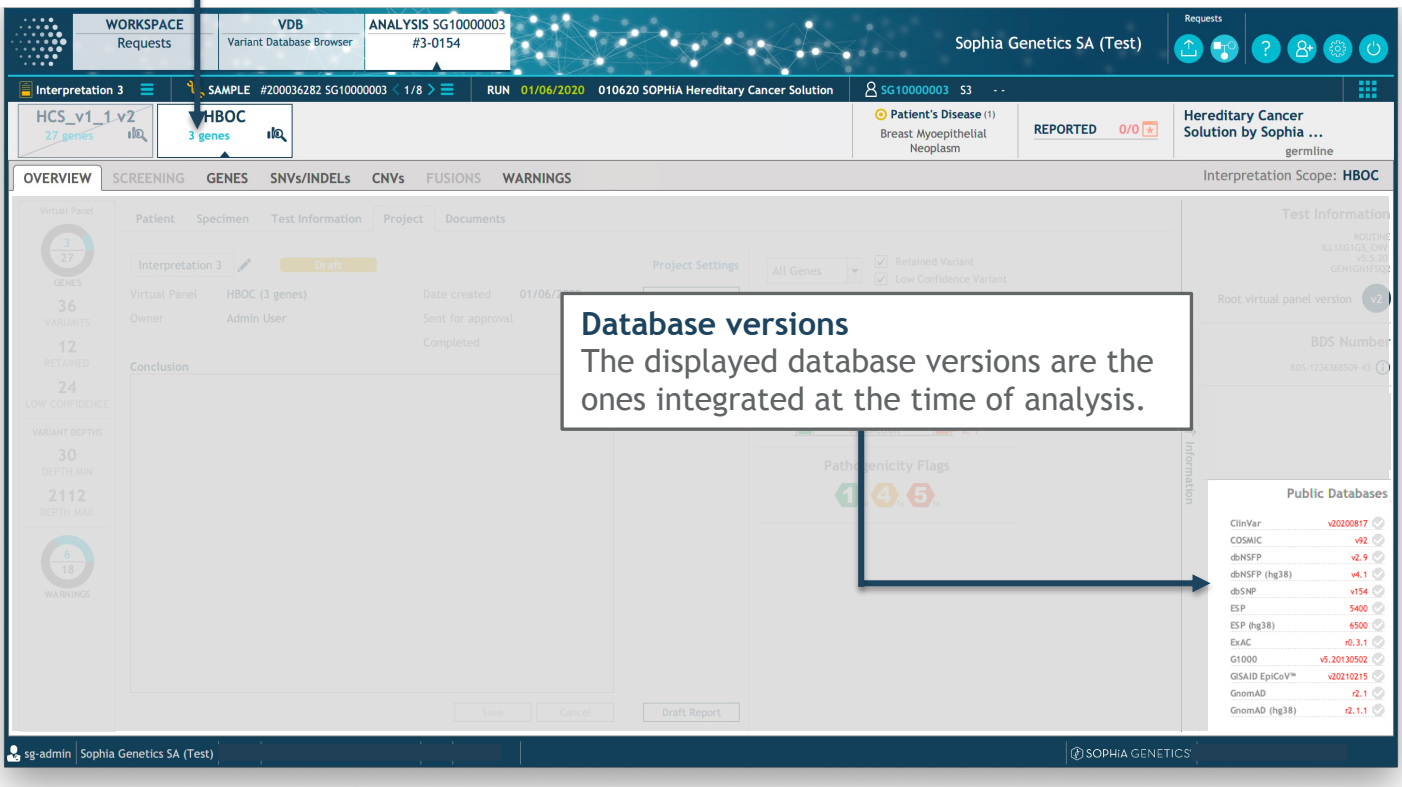
Information
Can be hidden by clicking on the arrow →
- Application information (versions for accreditation)
- BDS number (information on usage when clicking on it)
- Public databases (versions)

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.

4. Data Analysis
4.4 Analysis Overview (5)

Overview
Active page (white)



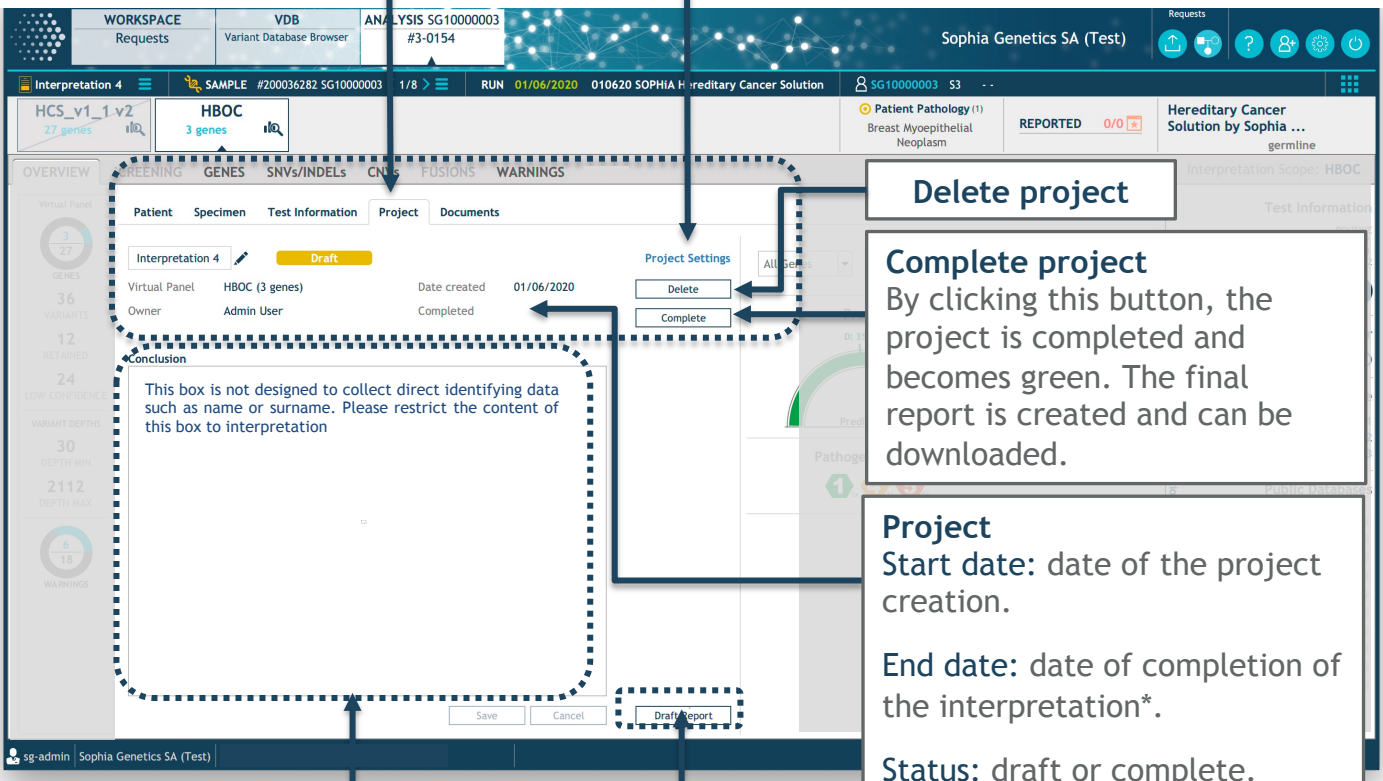
NOTE: Although versions are displayed for all integrated databases, the matched information might depend on the experiment type (somatic vs. germline) or on the reference genome used for annotation:

- **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.**

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.

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.

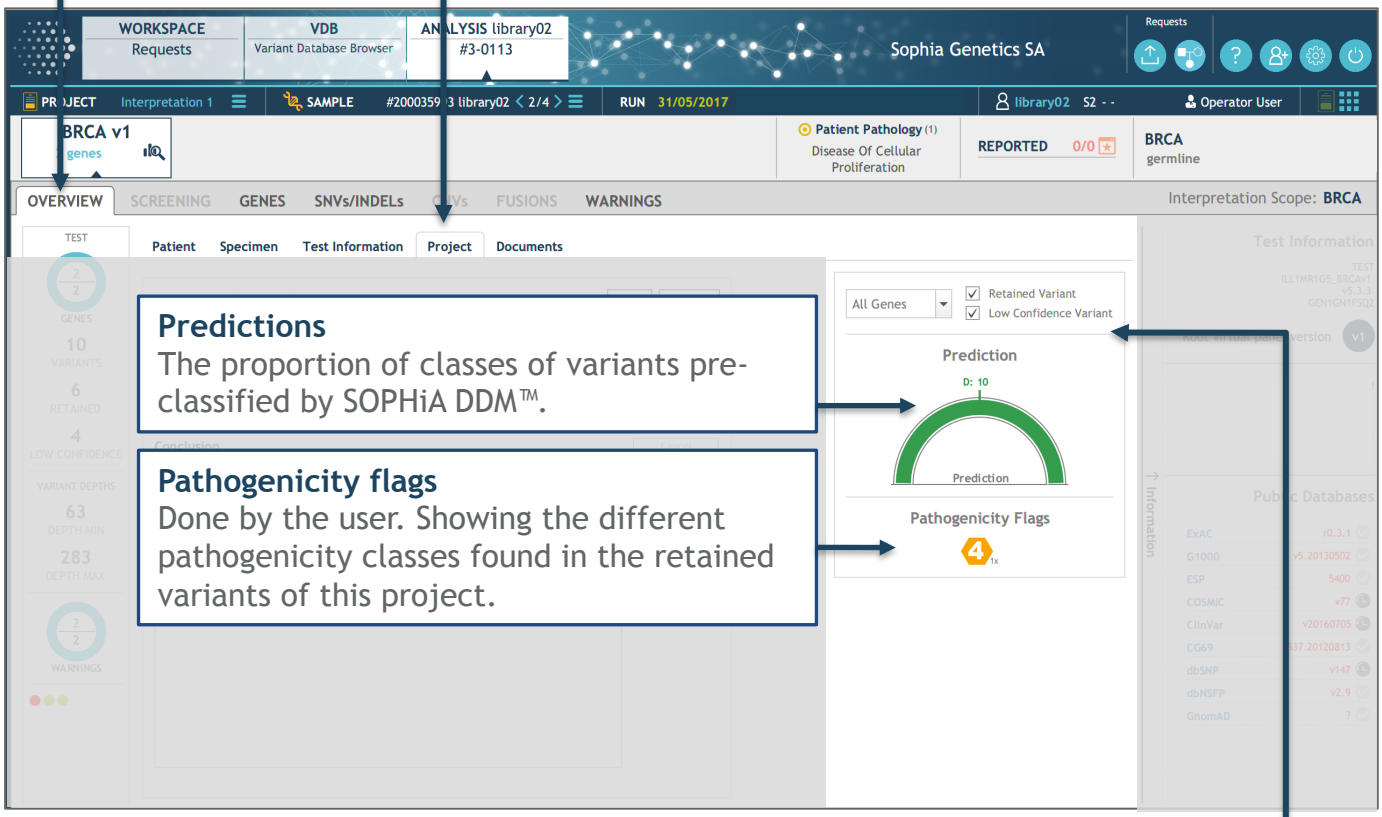
Draft report
A draft report can be created before project completion.

The report is restricted to the interpretation scope of the project

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™.

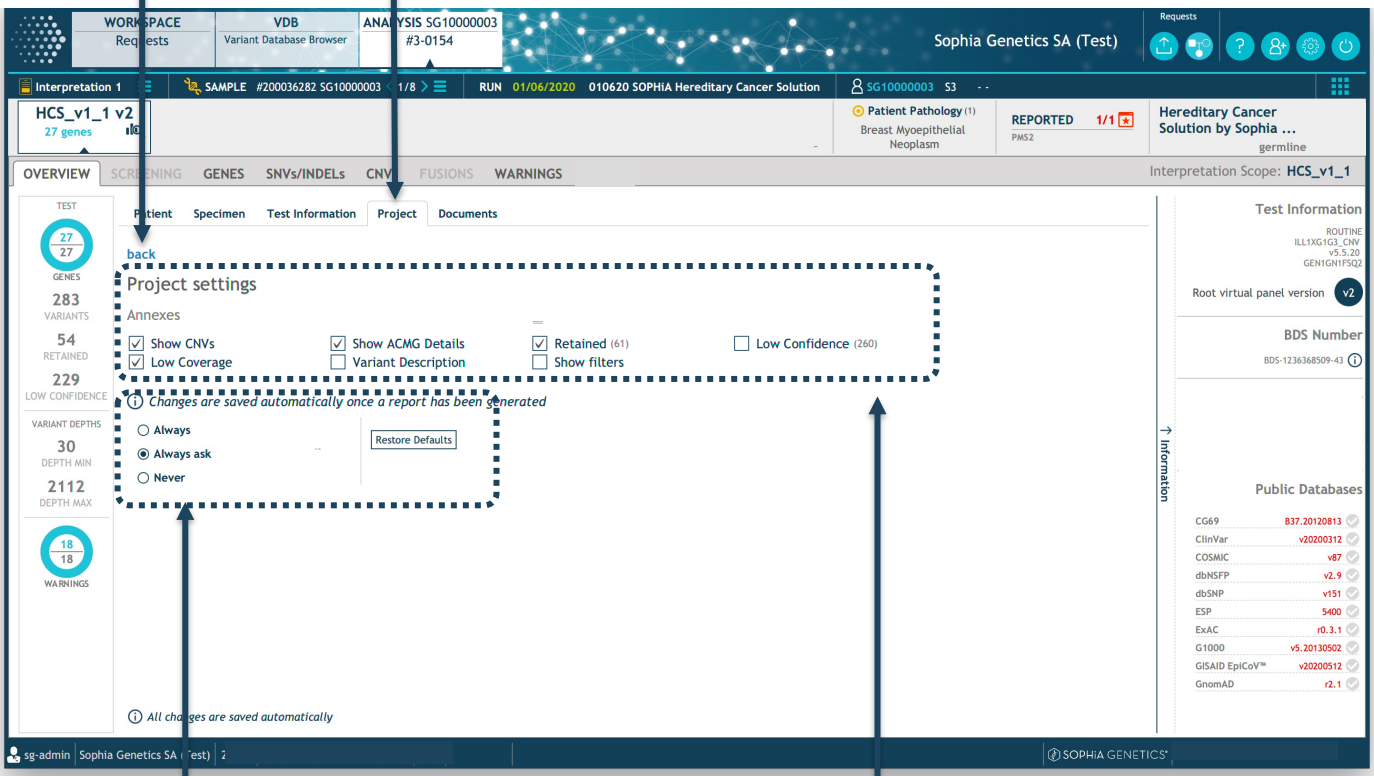
Pathogenicity flags
Done by the user. Showing the different pathogenicity classes found in the retained variants of this project.

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

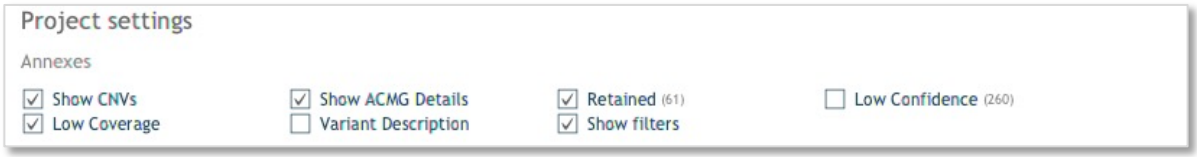


Report creation
Select whether the report should be created upon completion.

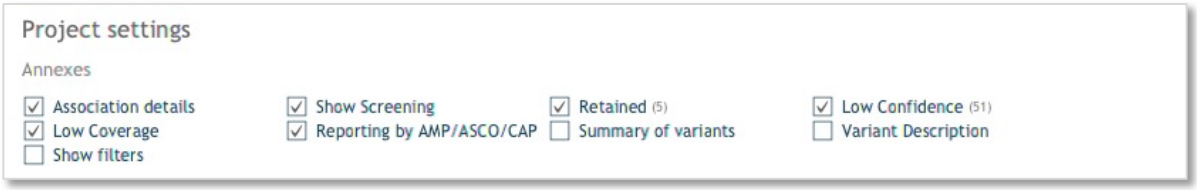
Report sections
Selection of sections included in the Draft or Final report for this specific Interpretation Project*.
Available checkboxes depend on the experiment type (germline or somatic).
Default report settings per application can be defined in the Application Settings
(see ch. 2.10 Manage Report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

4. Data Analysis
4.4 Analysis Overview (6)
4.4.2 Project Settings (2)

Annexes available for germline reports



Annexes available for somatic reports



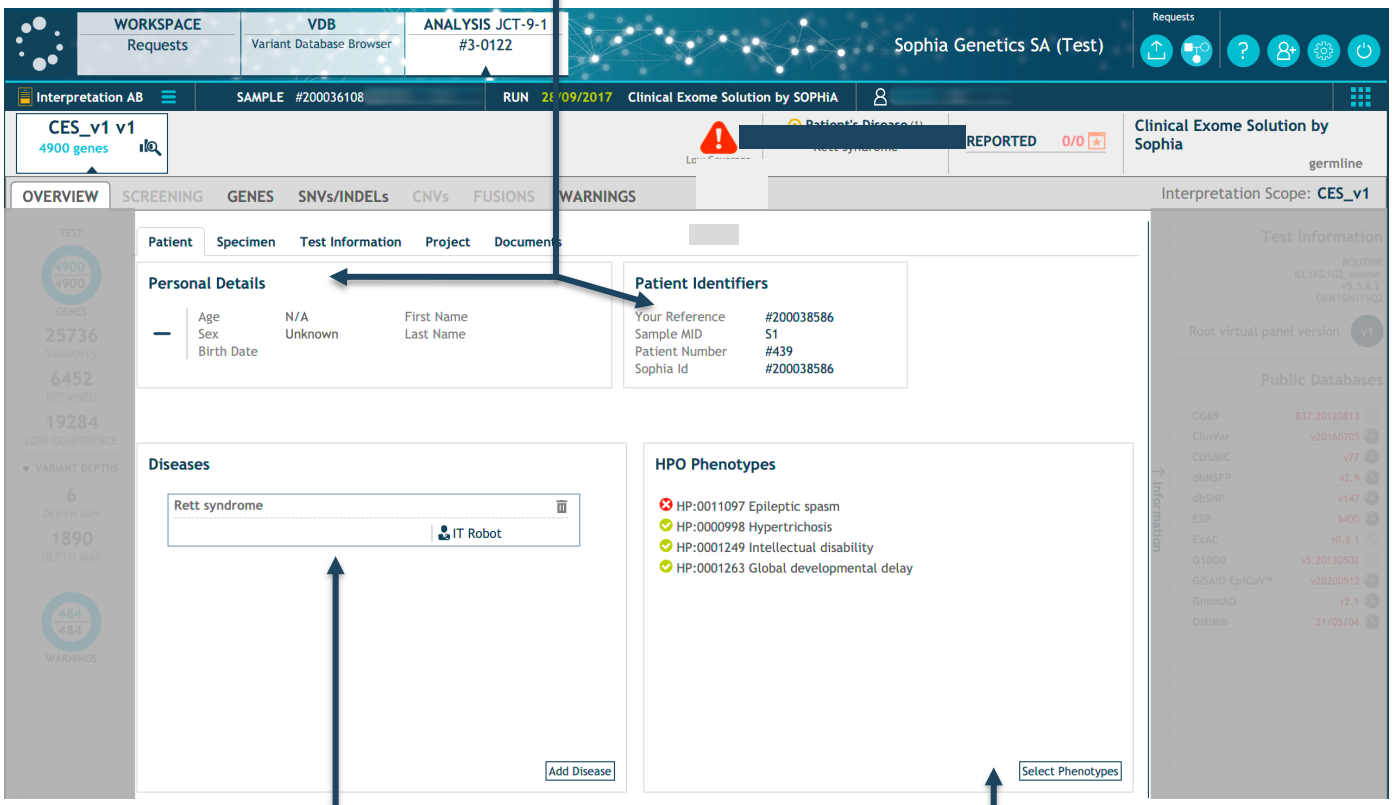
Select checkbox to include respective annex in the variant report:

- **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.

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).



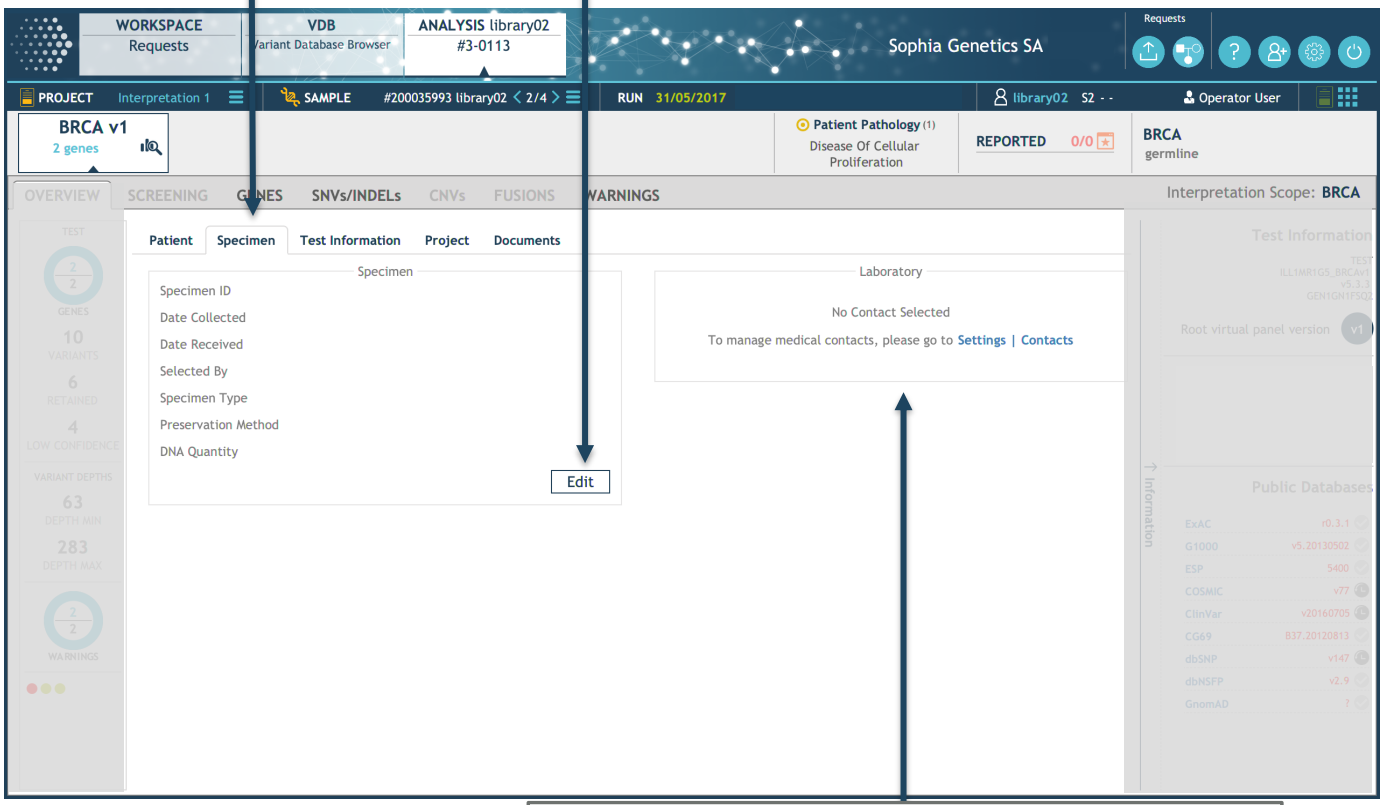
Diseases*
Users can select a disease* by clicking "Add Disease*". For somatic analyses, a disease* has to be added when creating an Interpretation Project* (see Chapter 3.12.3 Add a disease*). For users with access to OncoPortal™ (somatic analyses), SOPHiA DDM™ automatically recalculates the impact of 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).

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

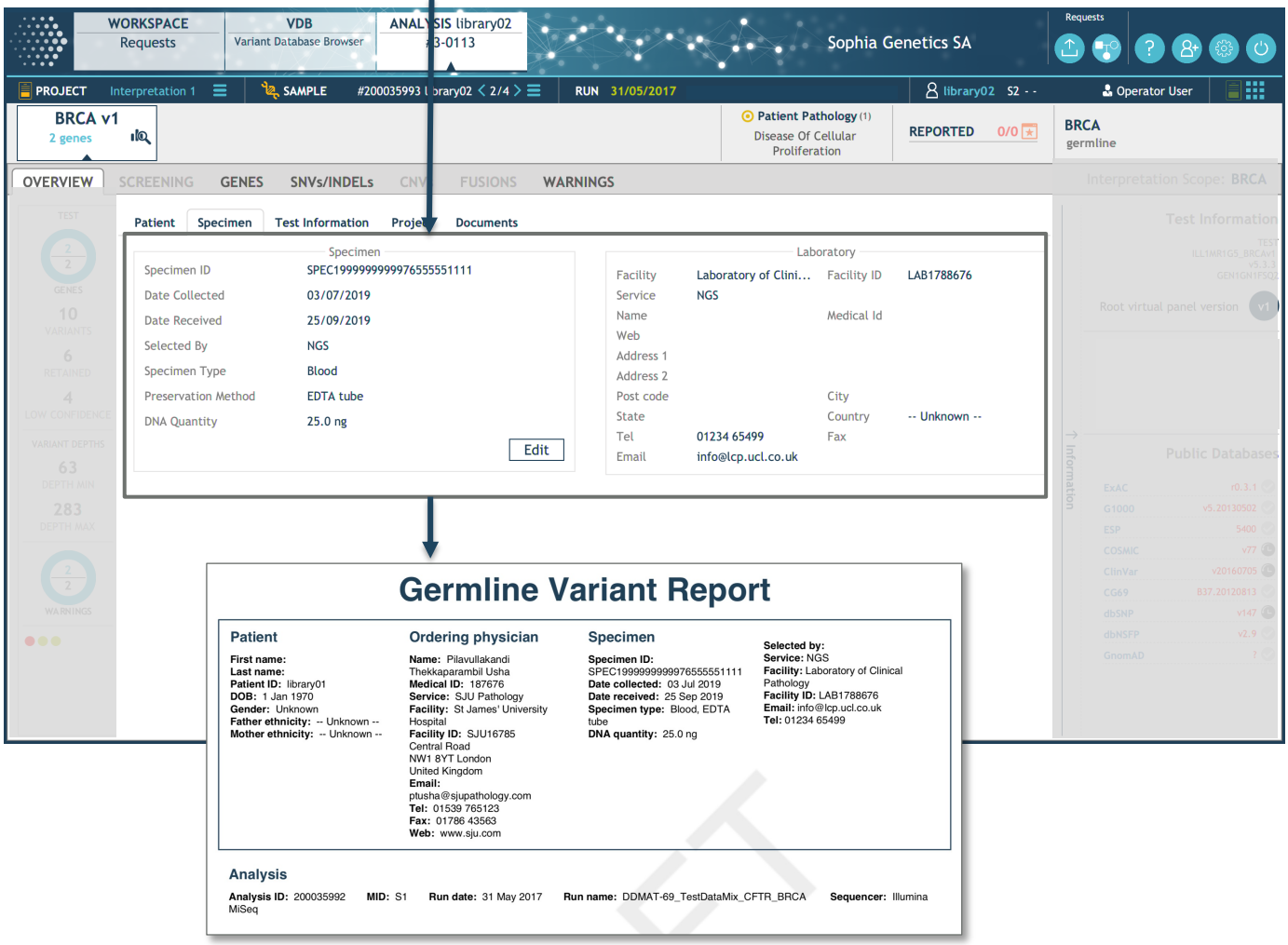


Laboratory
Contact details of the contact chosen in the "Selected By" field will be displayed here

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)).

4. Data Analysis
4.4 Analysis Overview (6)
4.4.4 Specimen Tab (2)

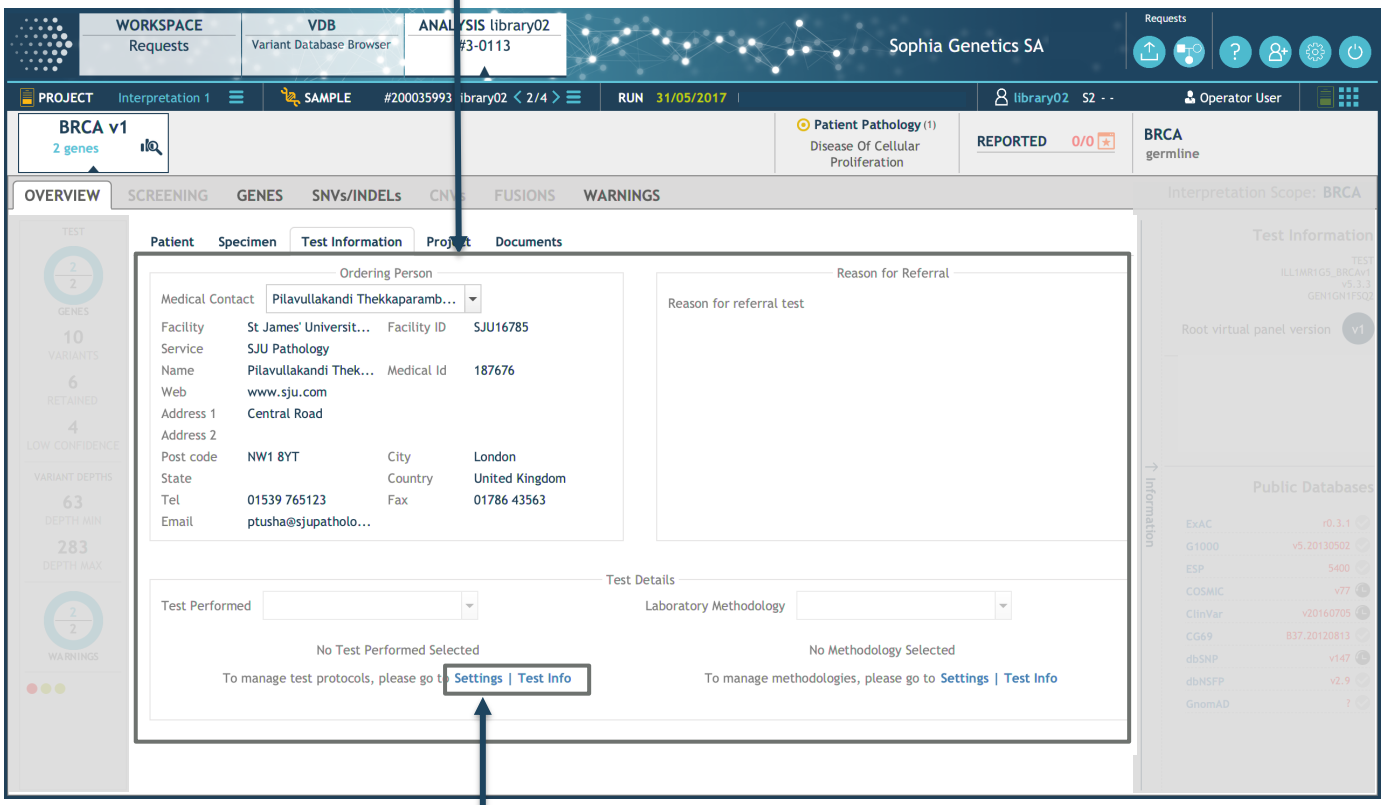
Specimen Details
The Specimen Section will only be displayed in the Variant Report with the completed fields. Blank fields will not be displayed.



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

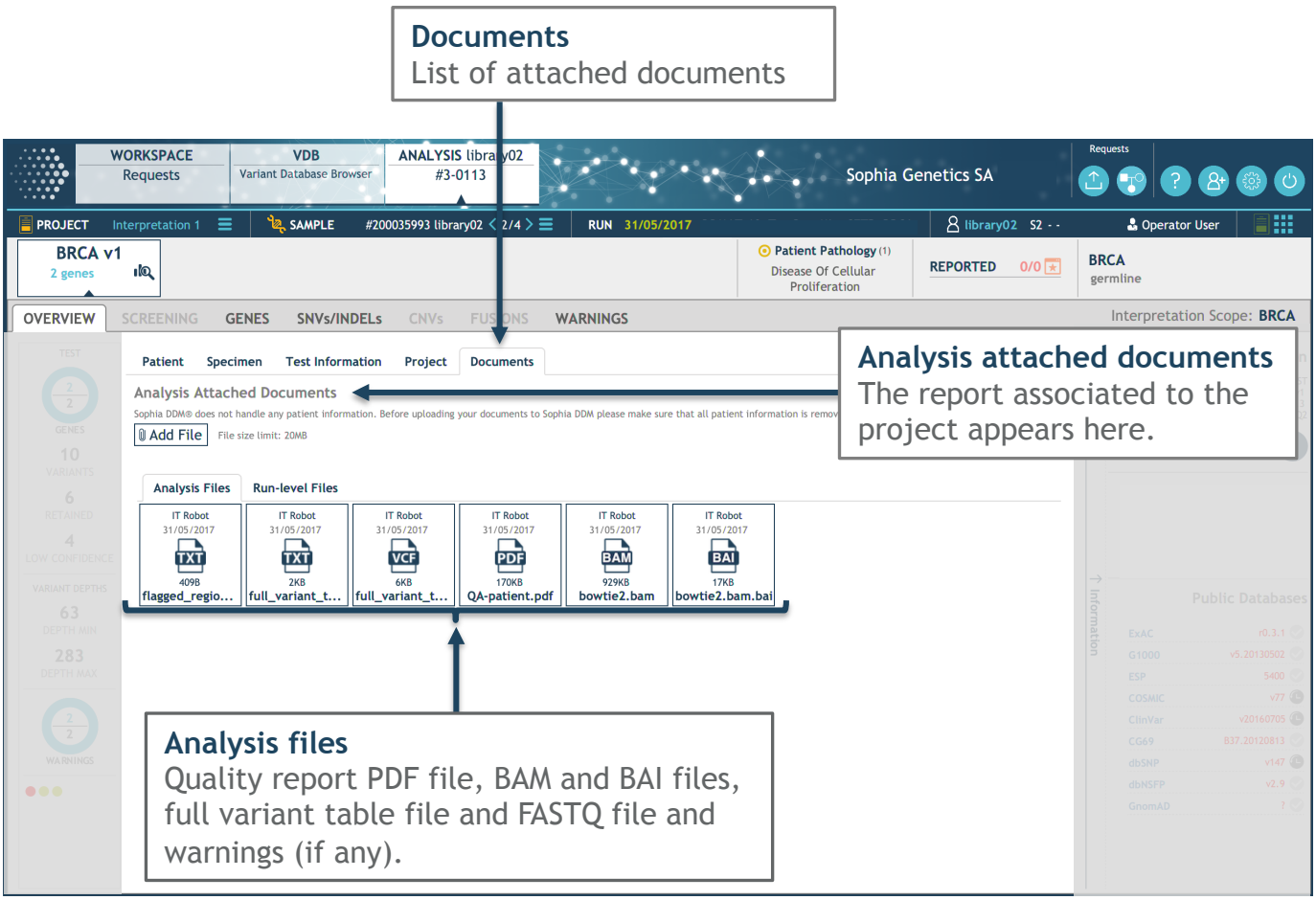
4. Data Analysis
4.4 Analysis Overview (6)
4.4.5 Test Information Tab (1)

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).



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

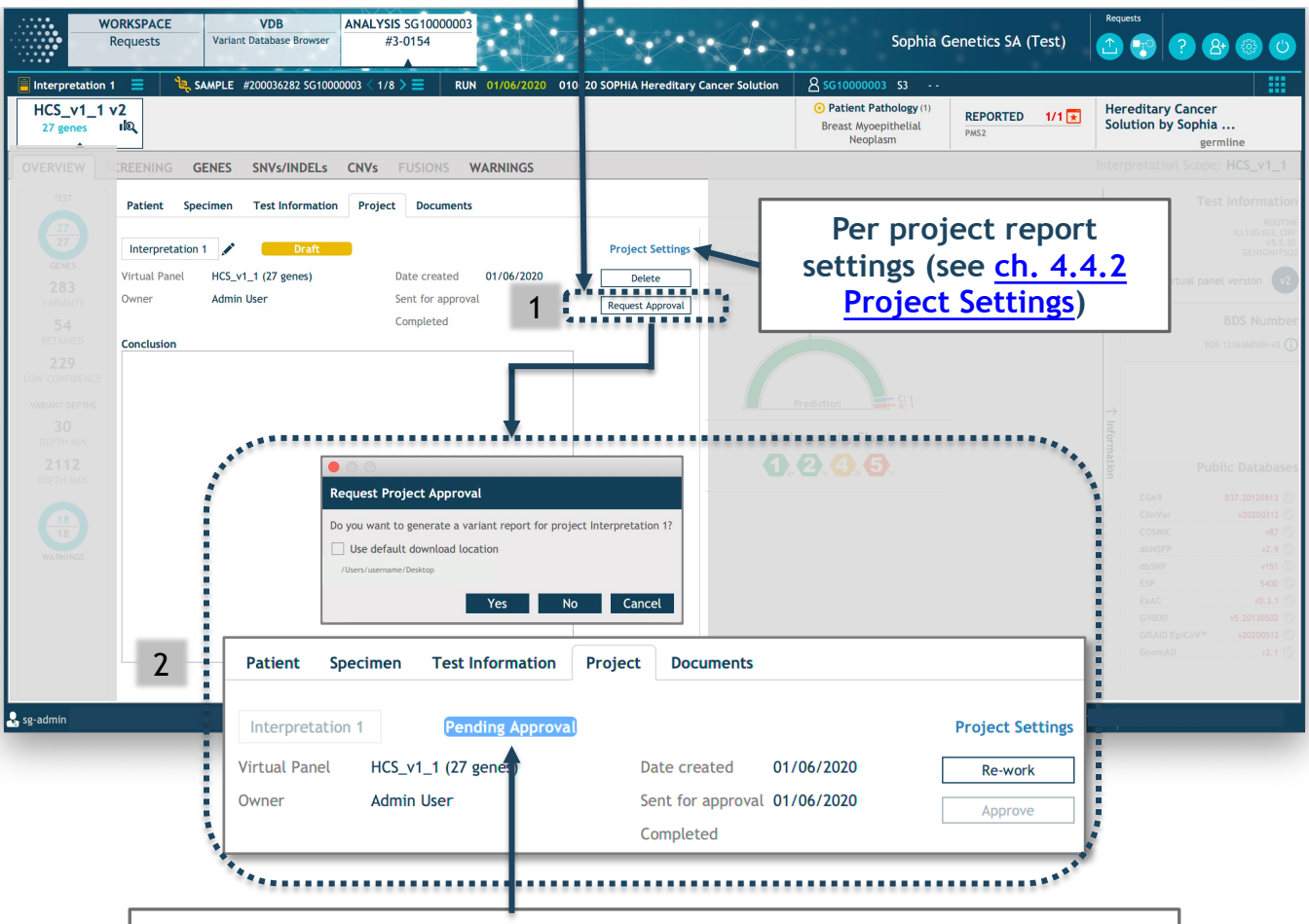
4. Data Analysis
4.4 Analysis Overview (6)
4.4.6 Documents Tab



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

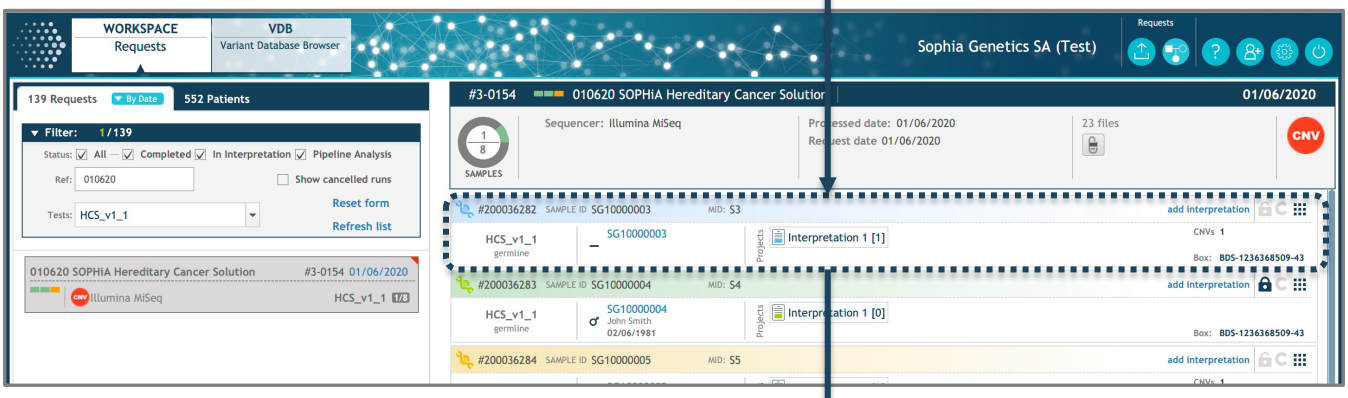


Pending approval
The project changes to “Pending Approval” status. A second user of the account needs to approve the project before it can be completed.

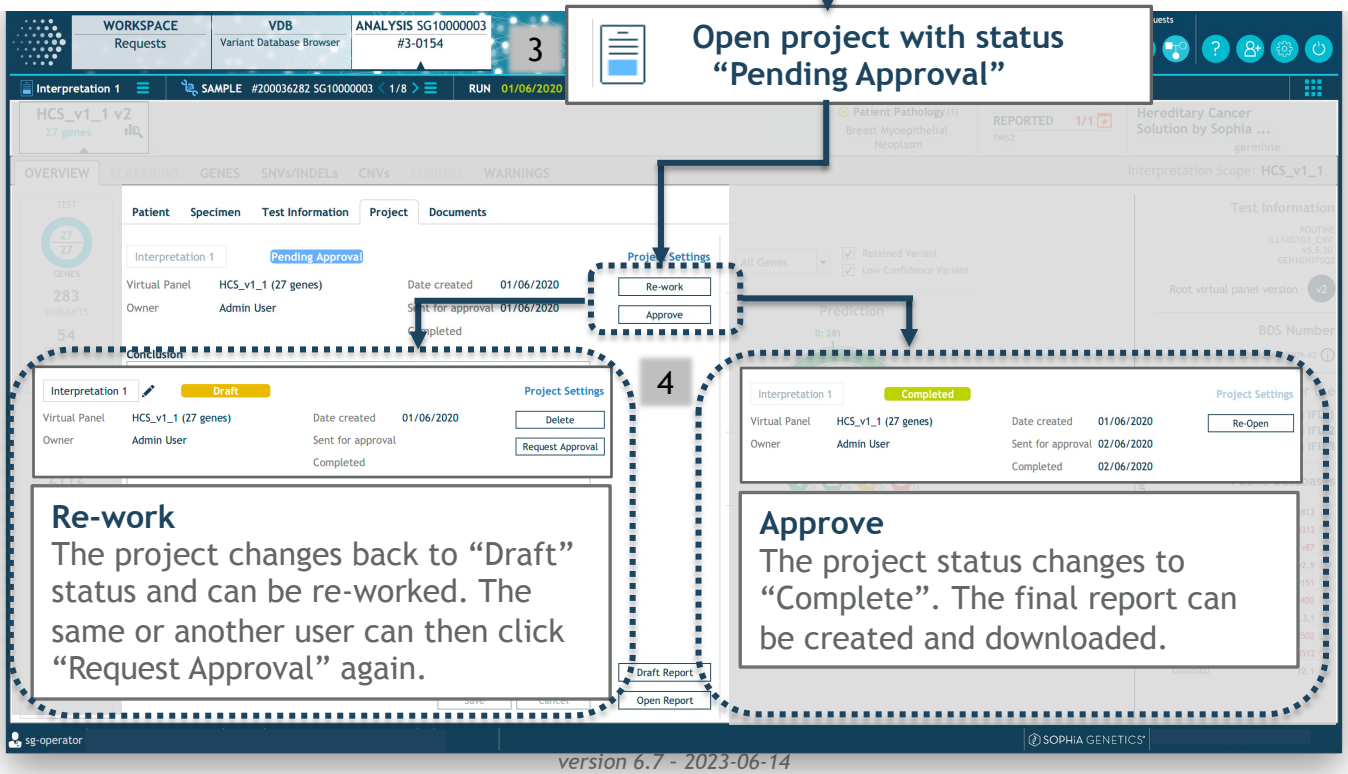
4. Data Analysis
4.5 Report Approval Workflow (2)

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"



Open project with status "Pending Approval"



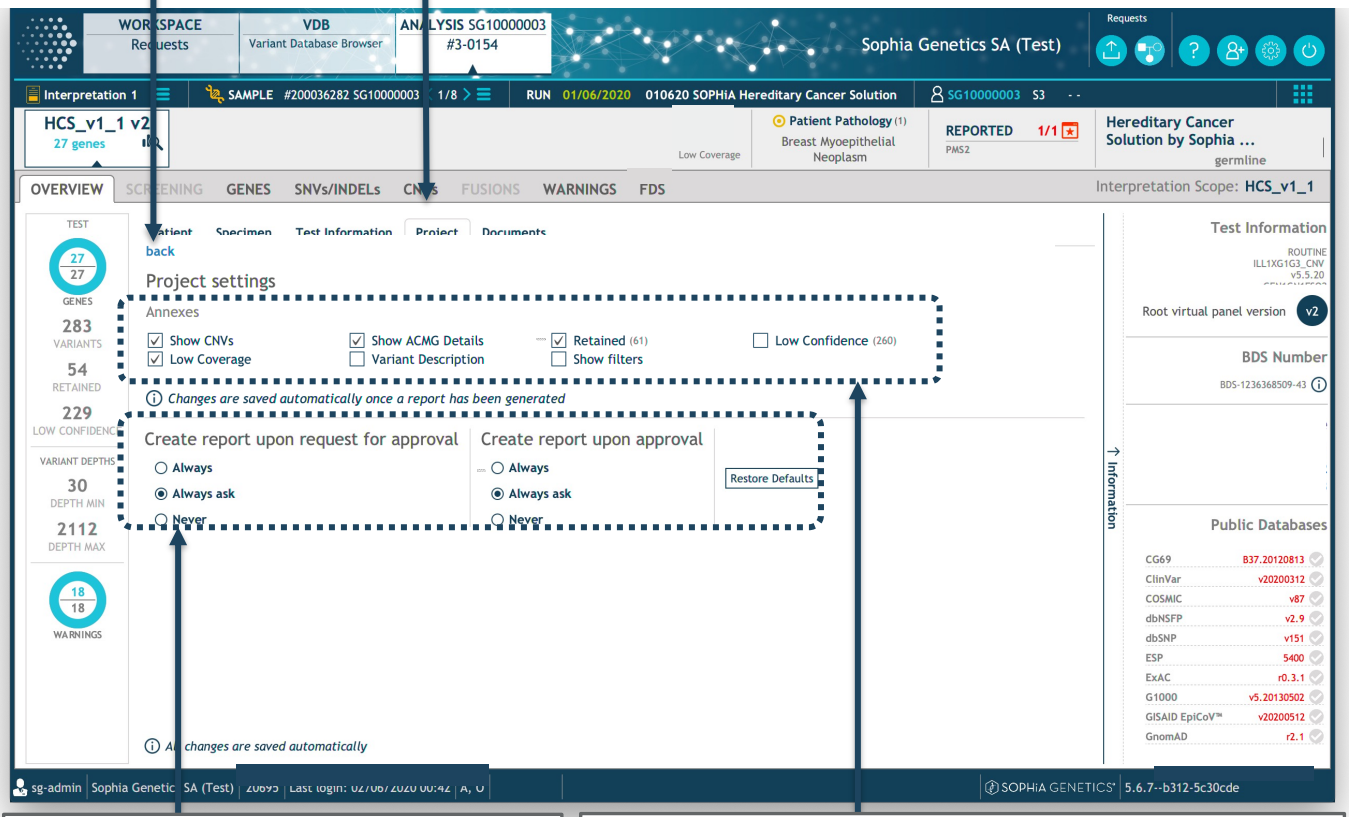
Re-work
The project changes back to "Draft" status and can be re-worked. The same or another user can then click "Request Approval" again.

Approve
The project status changes to "Complete". The final report can be created and downloaded.

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)

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.

4. Data Analysis
4.6 Prediction
4.6.2 Pathogenicity Matching

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

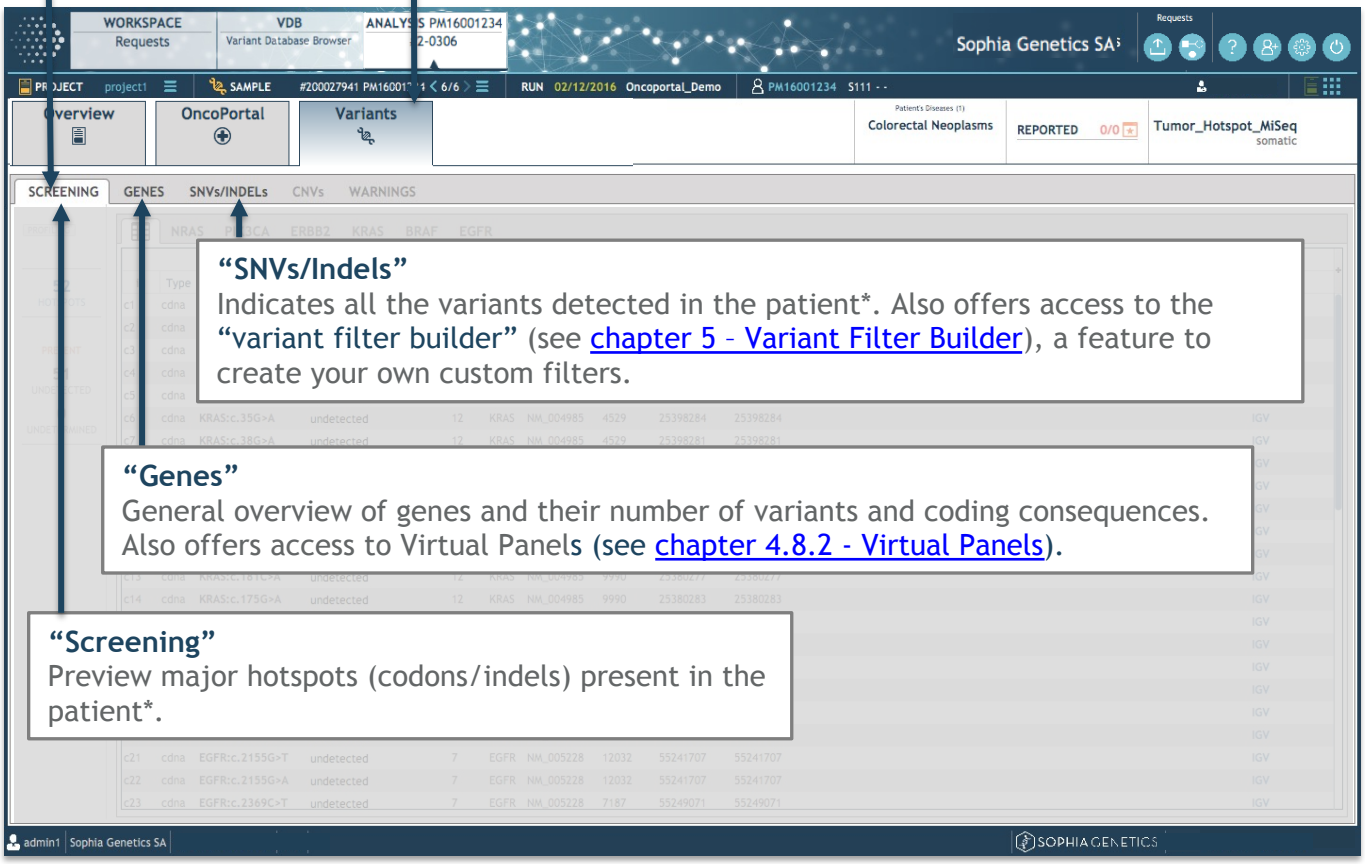
When flagging a variant with a pathogenicity flag, it is automatically classified as one of A – D category

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)



"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.

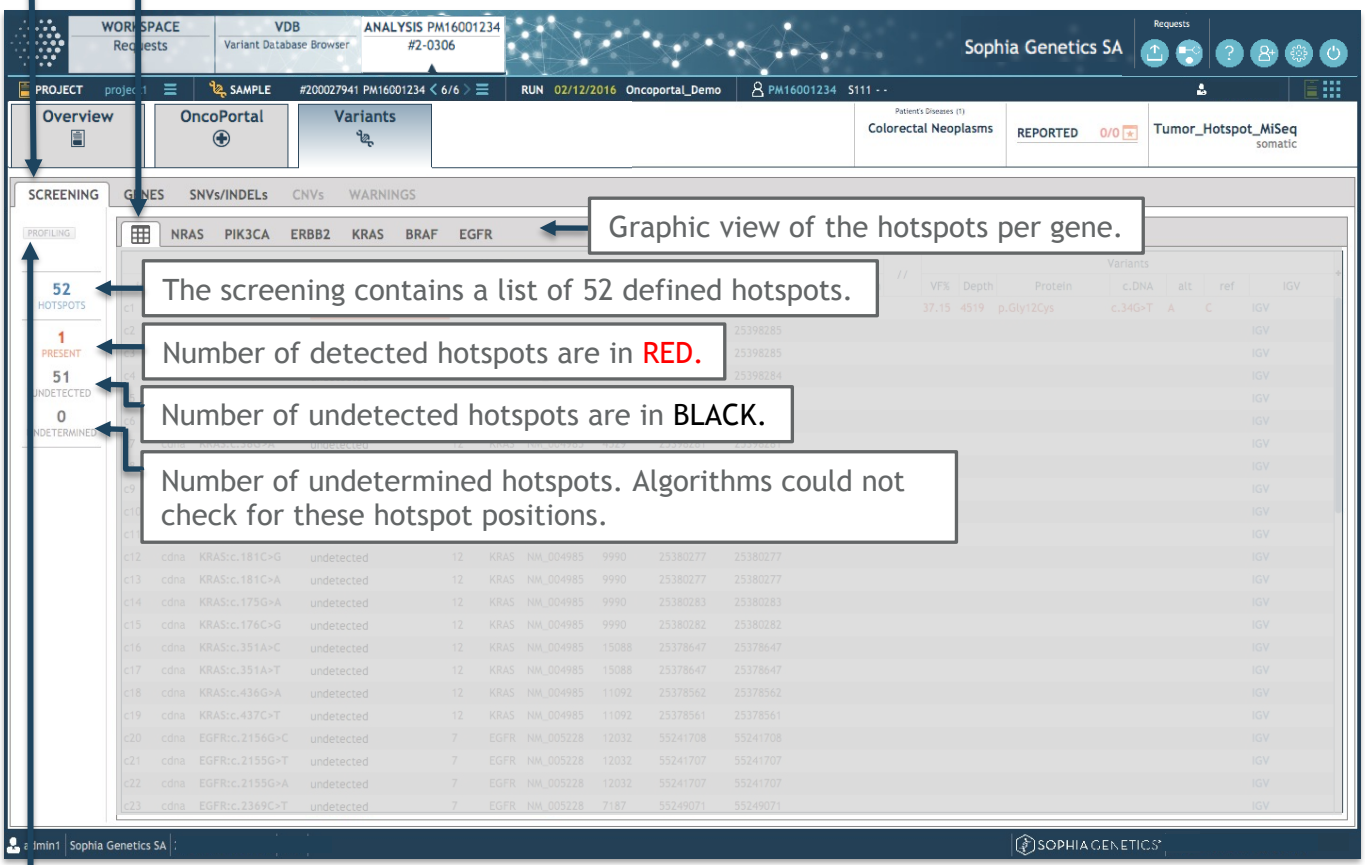
"Genes"
General overview of genes and their number of variants and coding consequences. Also offers access to Virtual Panels (see chapter 4.8.2 - Virtual Panels).

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

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.

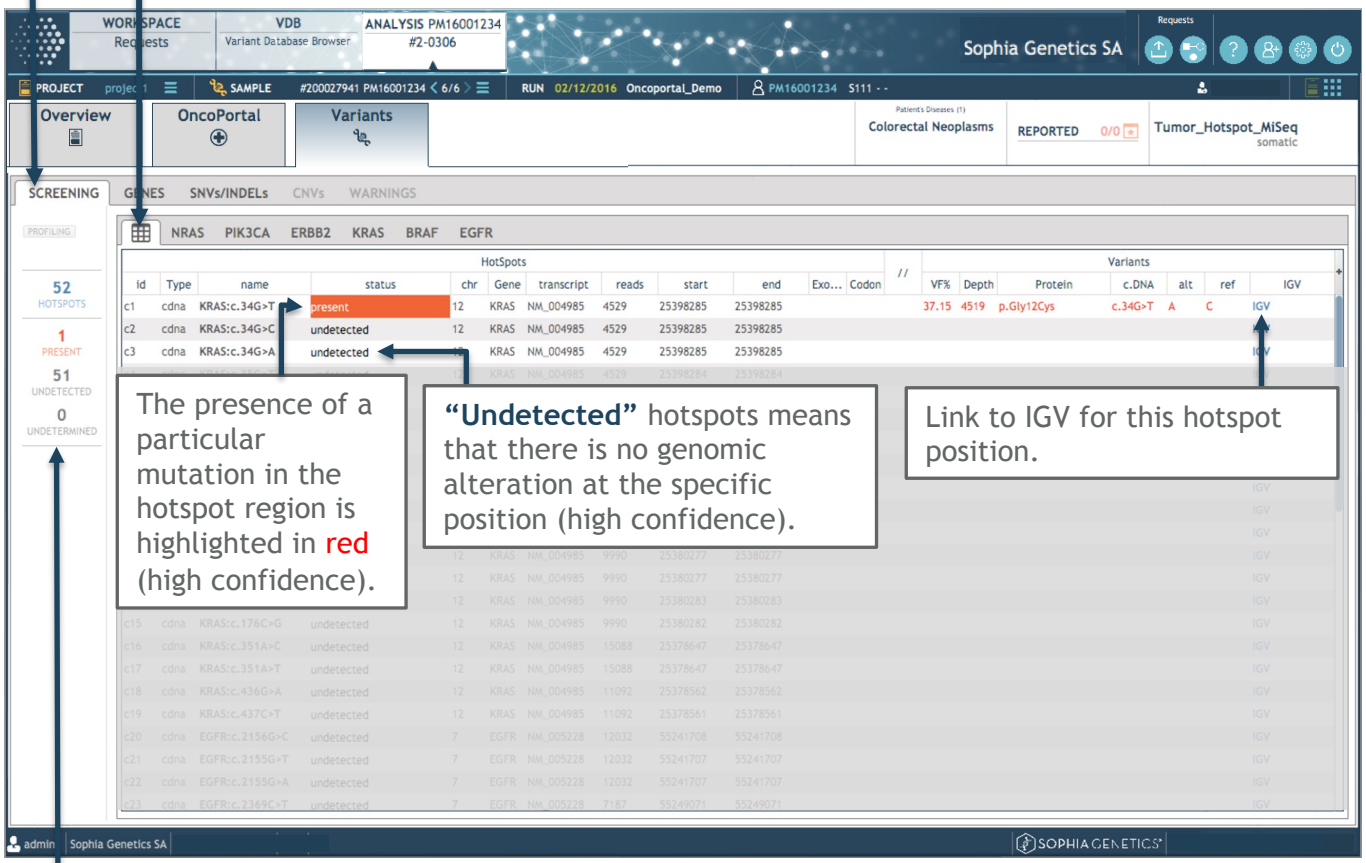
Number of undetermined hotspots. Algorithms could not check for these hotspot positions.

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 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).

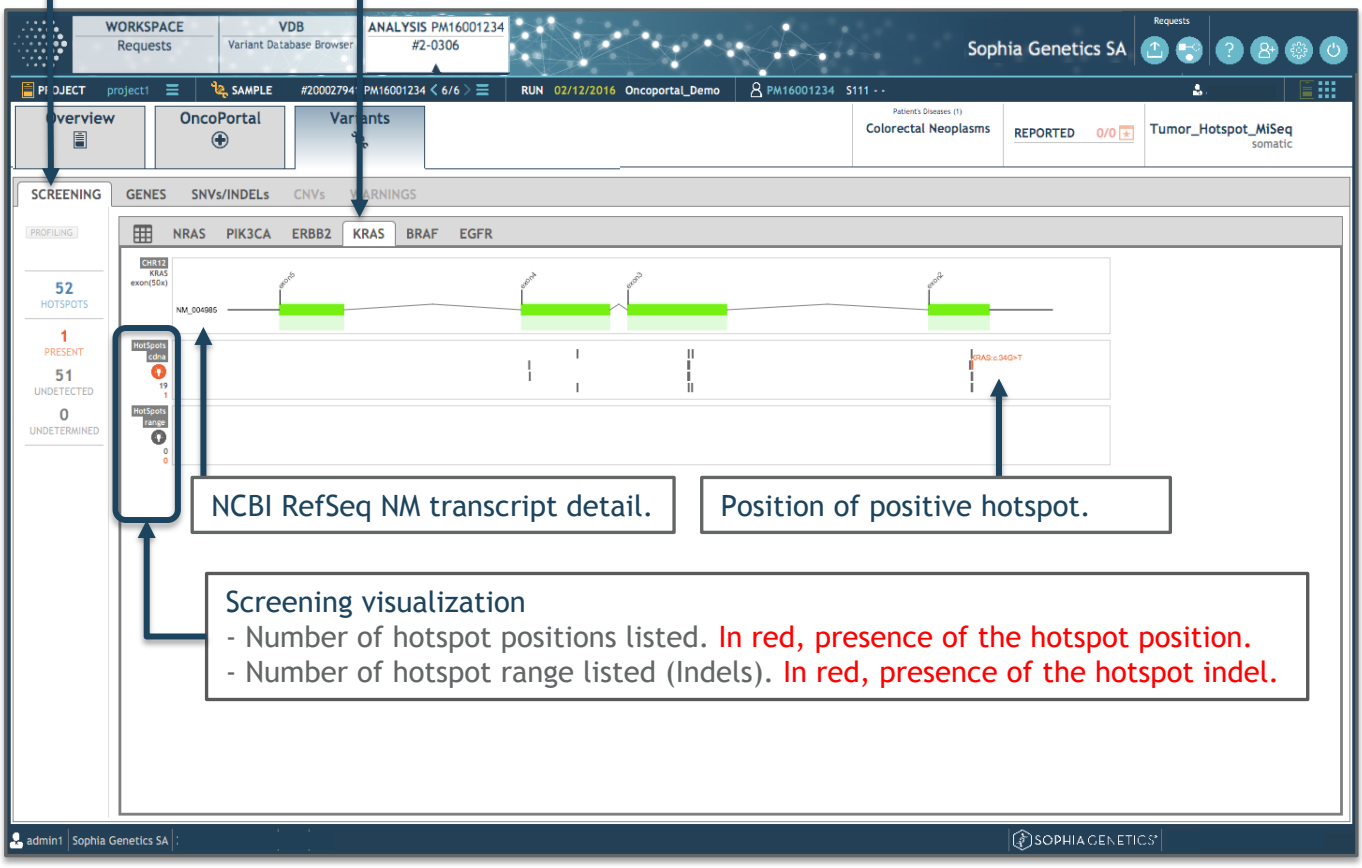
Link to IGV for this hotspot position.

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.

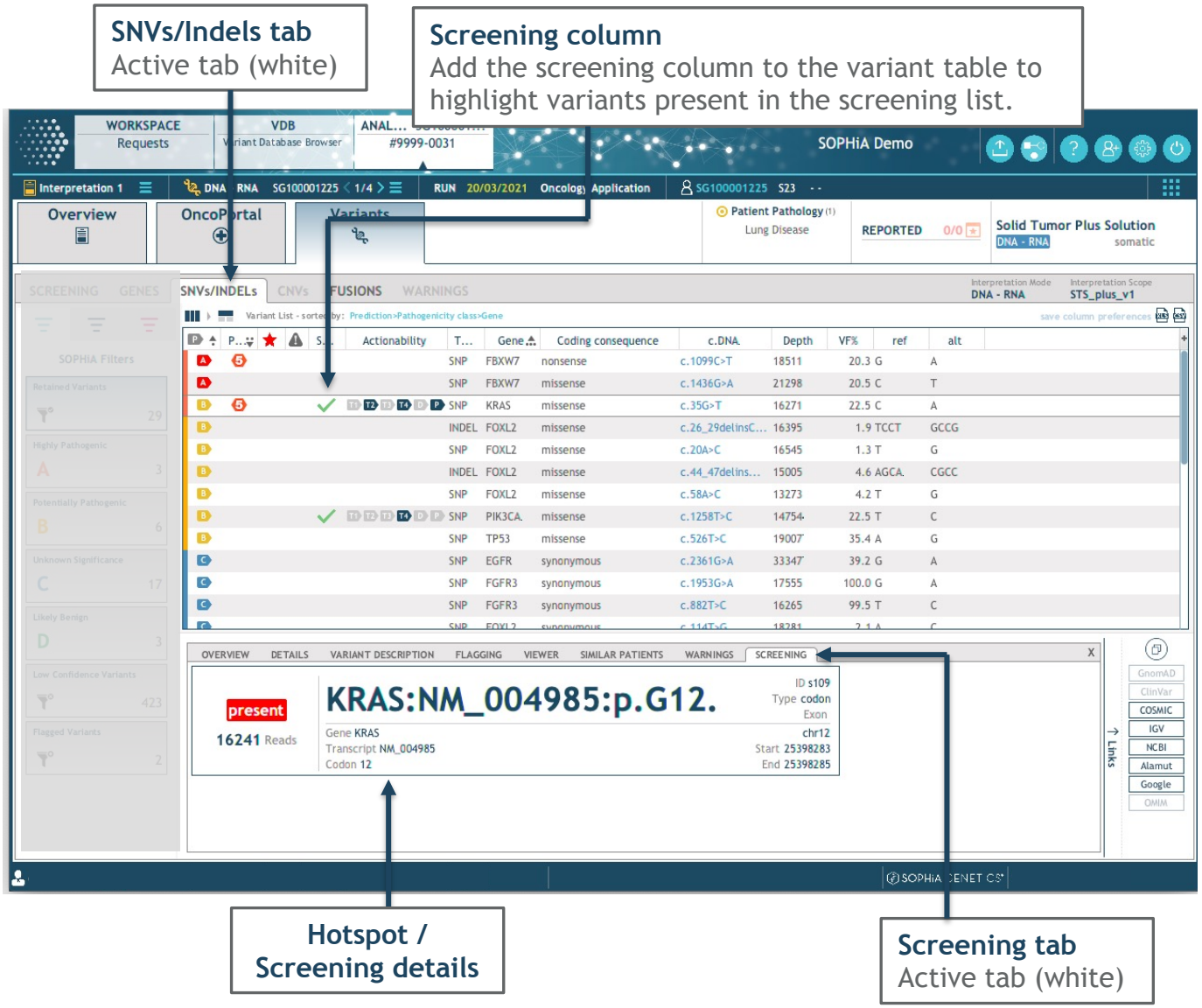


NCBI RefSeq NM transcript detail.

Position of positive hotspot.

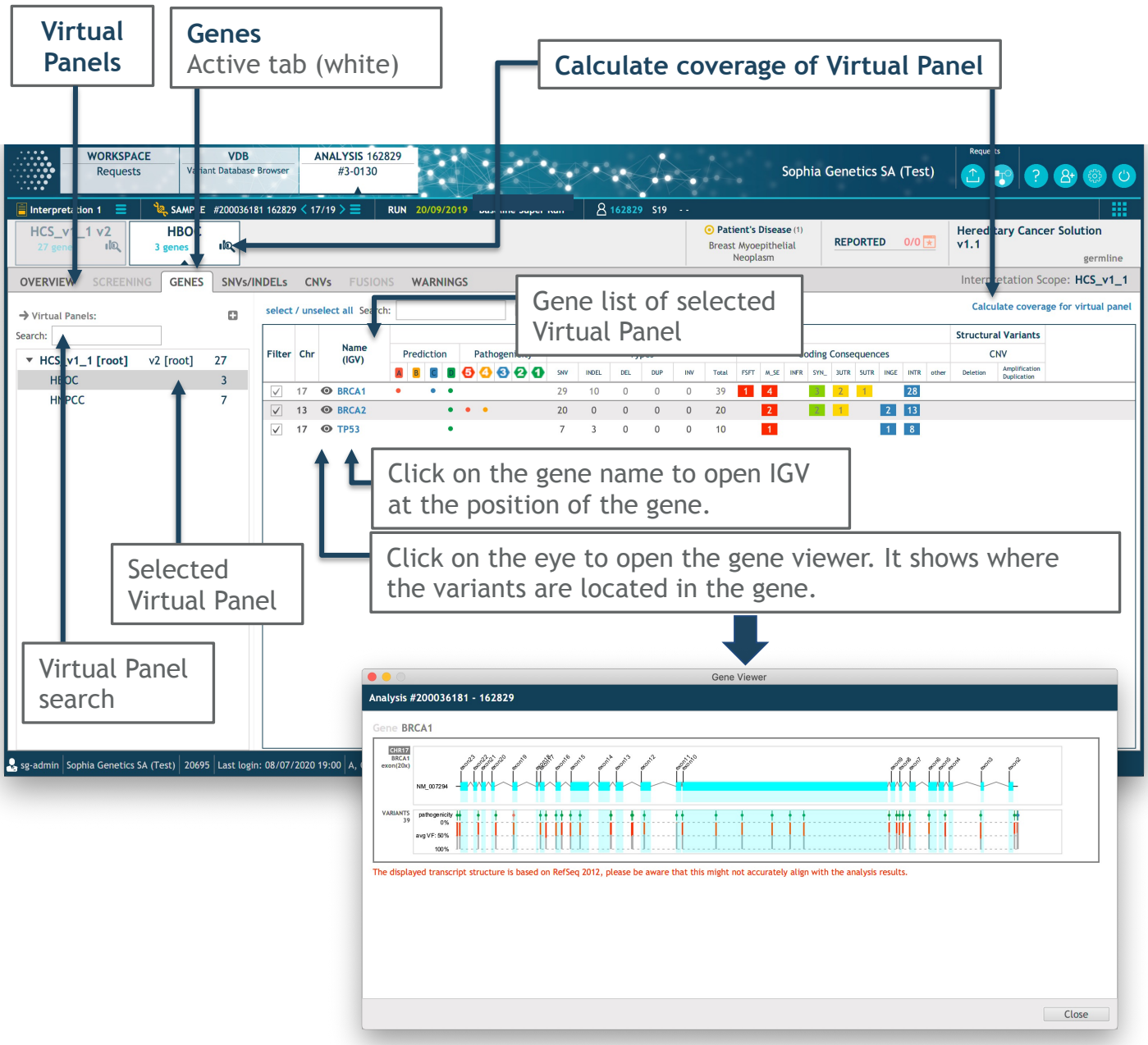
Screening visualization
- Number of hotspot positions listed. In red, presence of the hotspot position.
- Number of hotspot range listed (Indels). In red, presence of the hotspot indel.

4. Data Analysis
4.7 Variants
4.7.1 Screening (4)

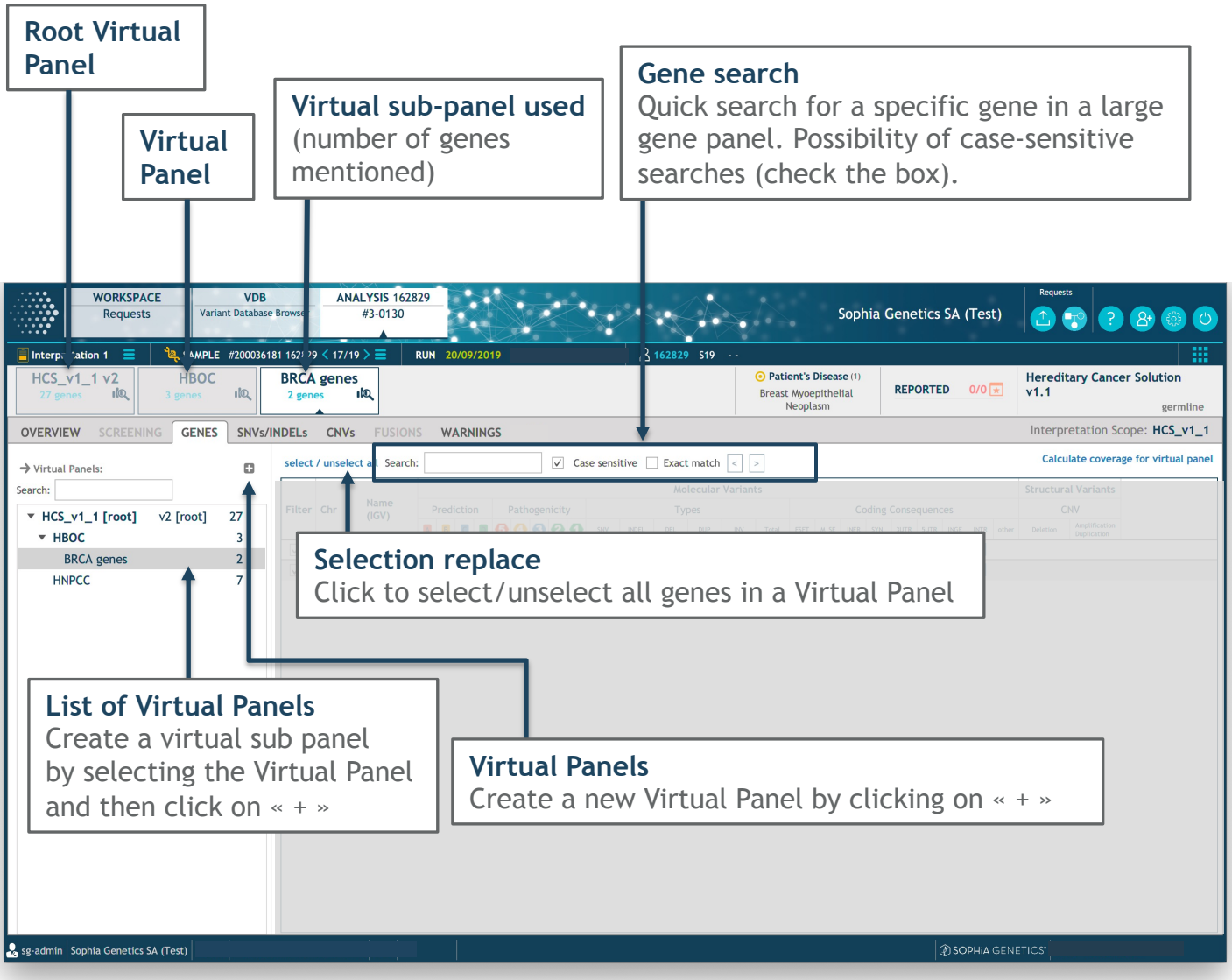


4. Data Analysis
4.8 Genes
4.8.1 Overview

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.



4. Data Analysis
4.8 Genes
4.8.2 Virtual Panels – Overview



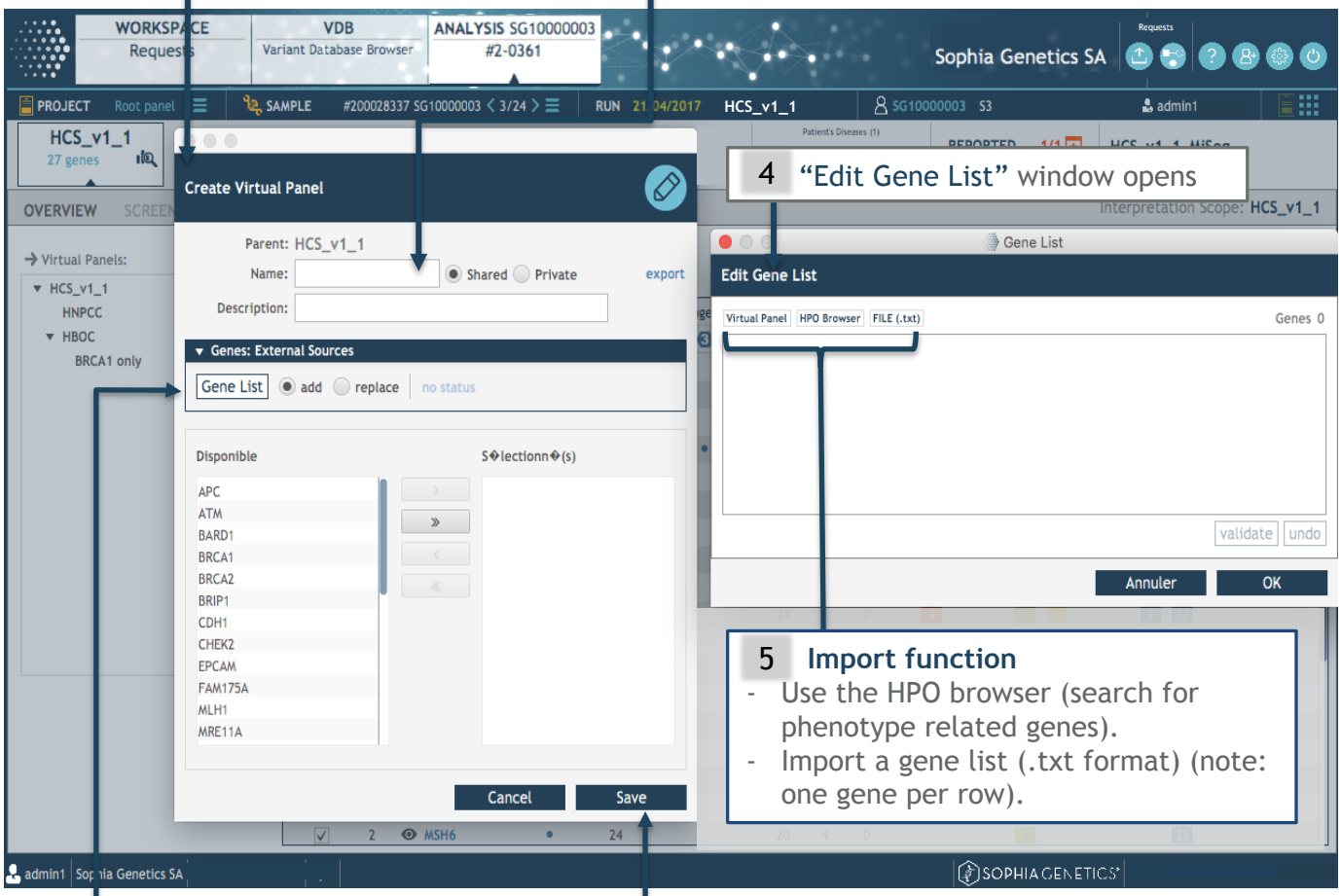
NOTE: Virtual Panels can only be deleted and edited in the application settings.

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.



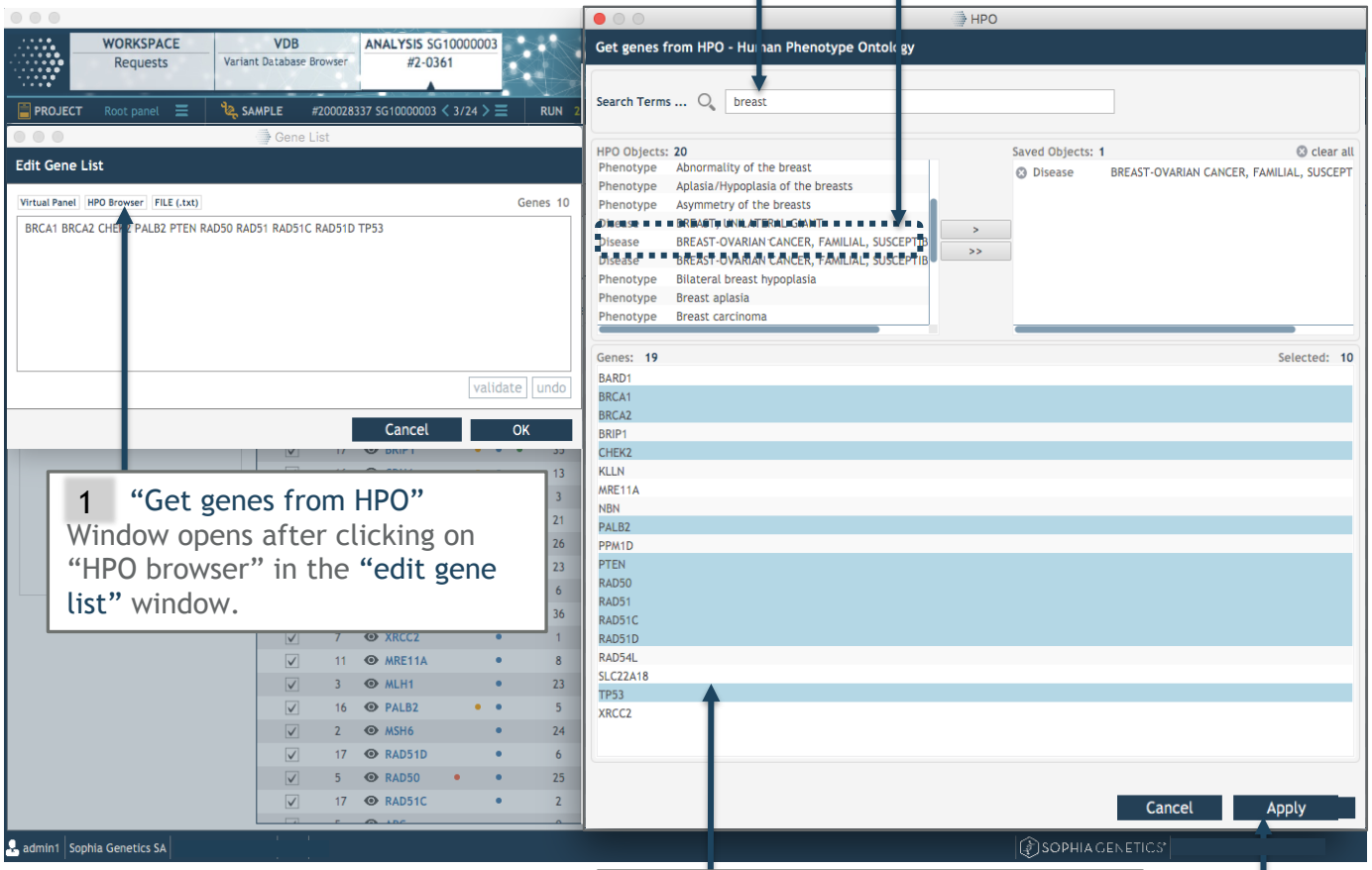
4 "Edit Gene List" window opens

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

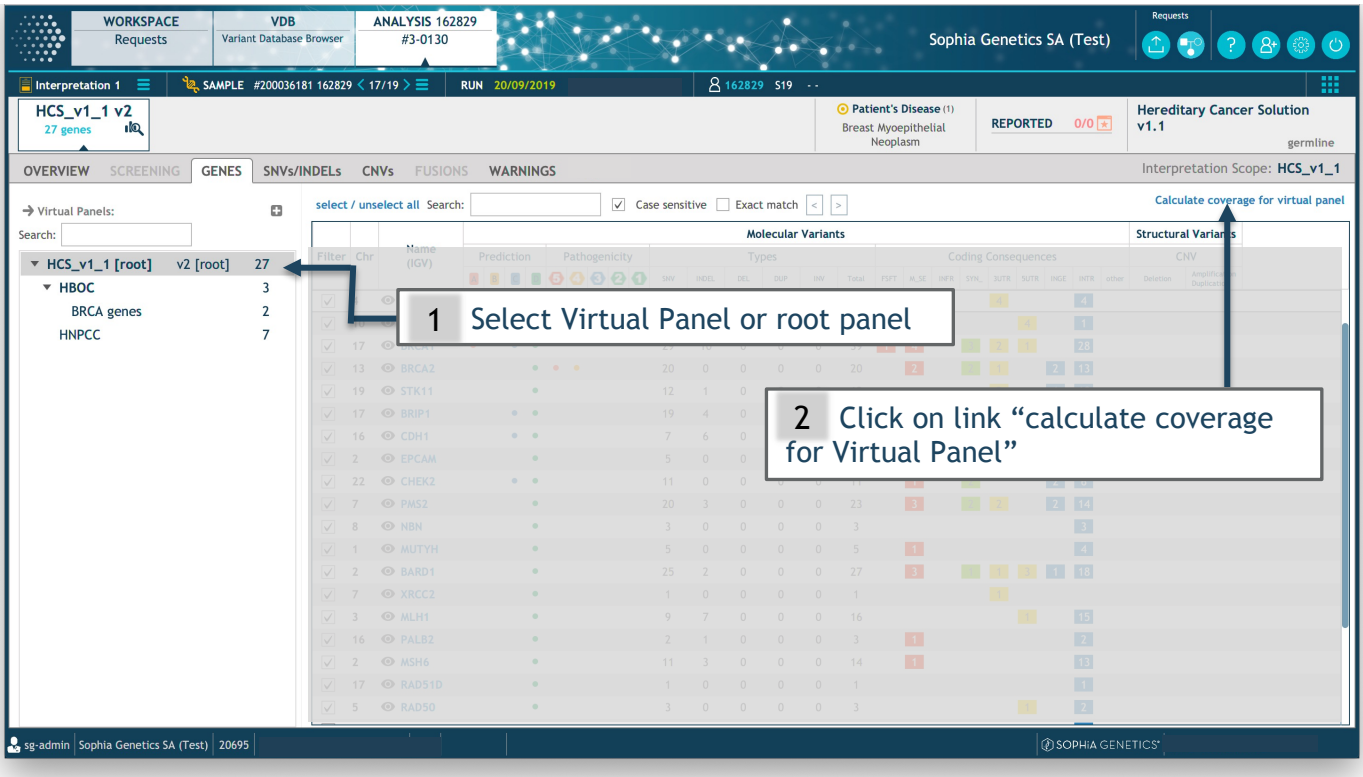
3 **Import function**
Click on "gene list" to import a list of genes or use HPO search.

6 Save

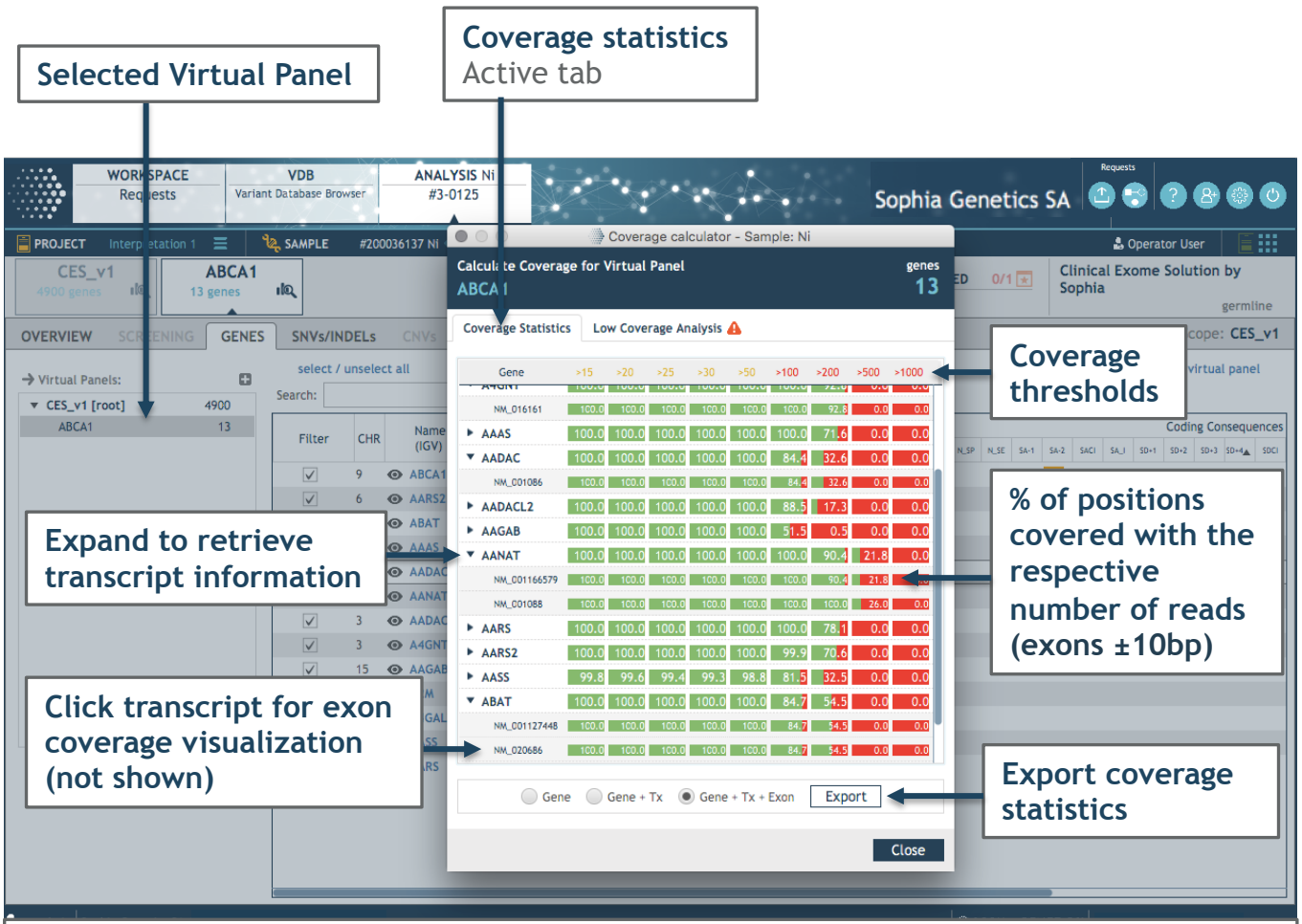
4. Data Analysis
4.8 Genes
4.8.4 Virtual Panels – Create using HPO



4. Data Analysis
4.8 Genes
4.8.5 Coverage Calculator



4. Data Analysis
4.8 Genes
4.8.5 Coverage Calculator
4.8.5.1 Coverage Statistics Tab (1)



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.

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.

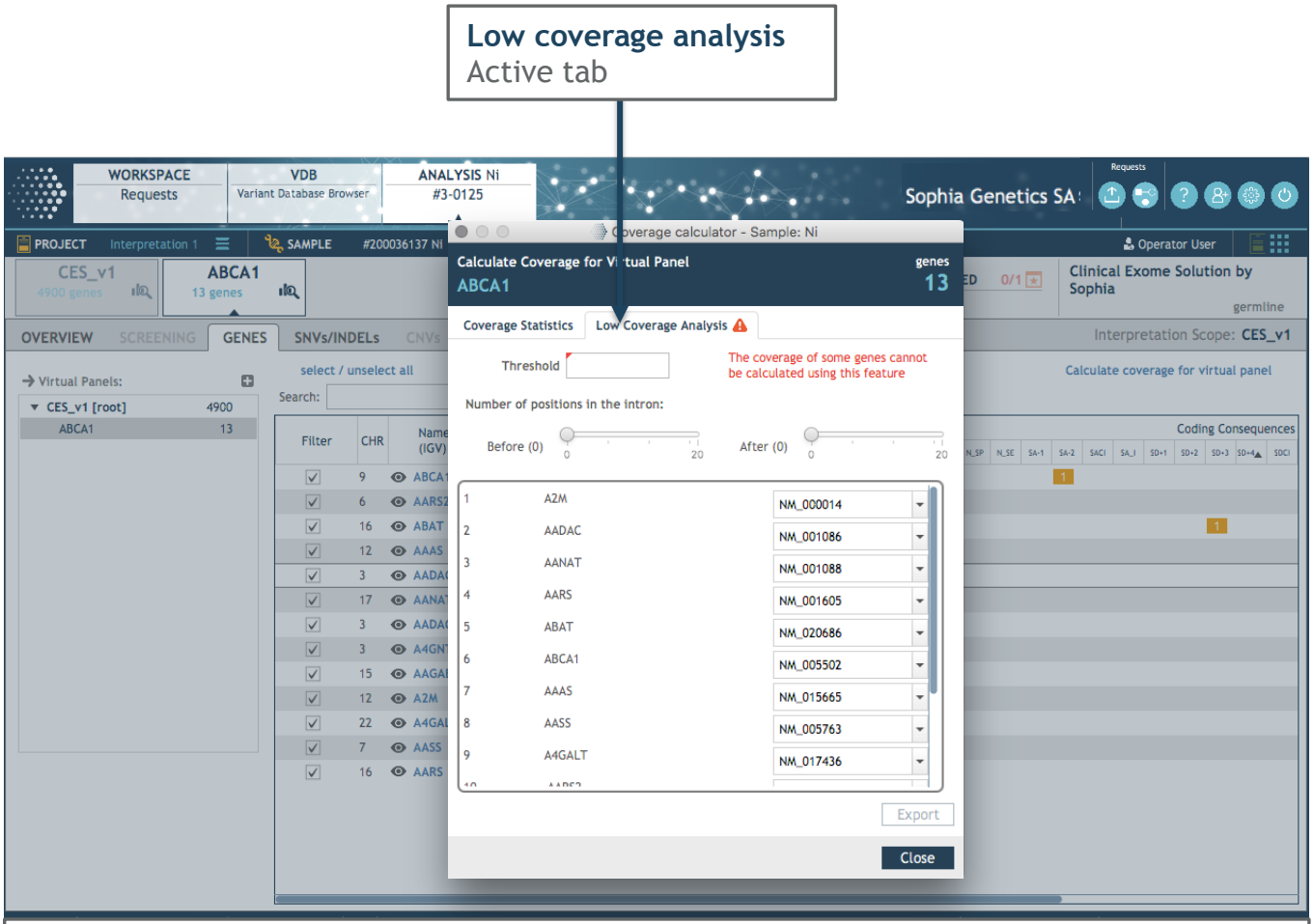
- Exon Level

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: ≥ 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



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 ± 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.

4. Data Analysis
4.9 SNVs/Indels
4.9.1 Overview

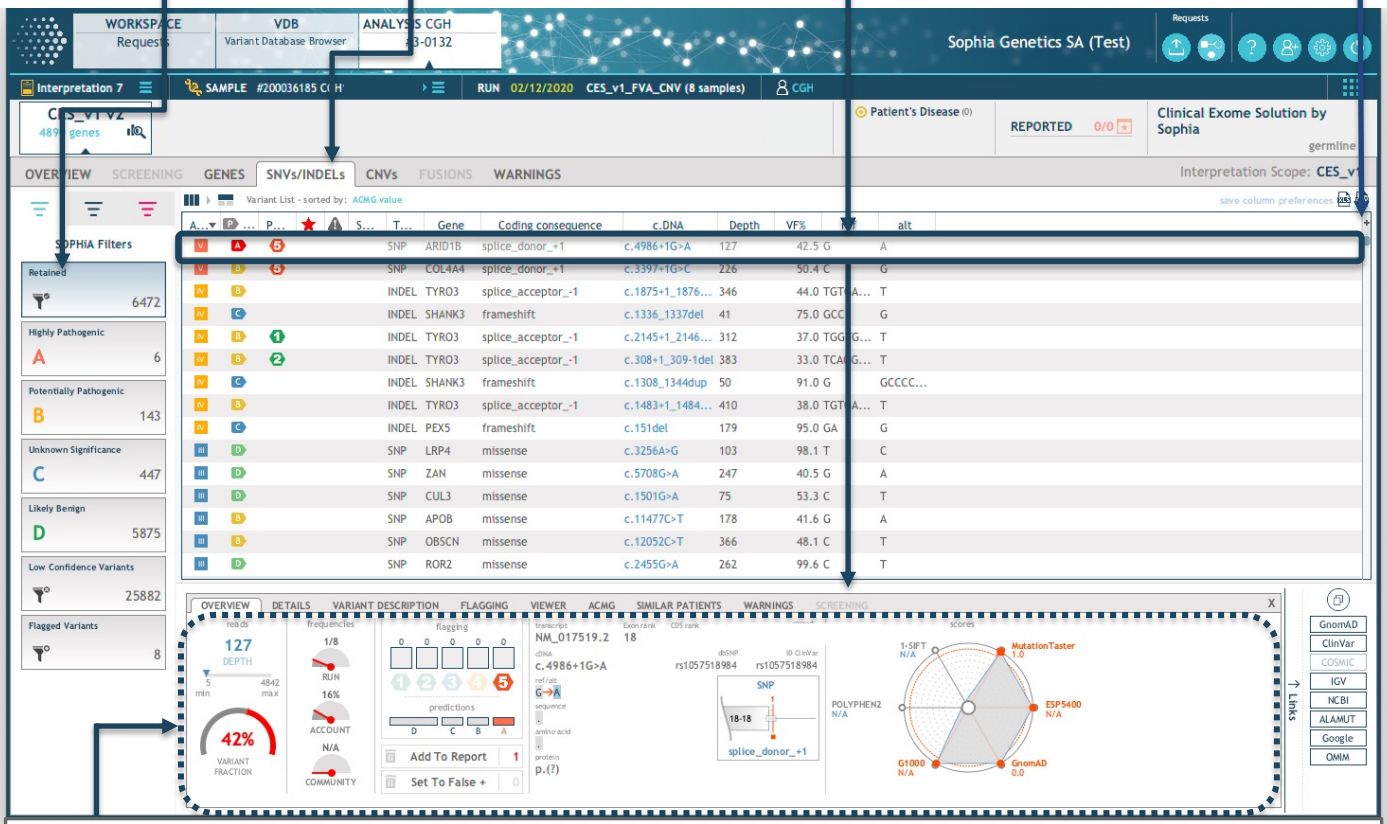
Quick access to the SNVs/Indels table with many filters available (see chapter 18 - Appendix for more details)

Retained variants
Active page (blue)

SNVs/Indels
Active sub page (white)

Selected variant

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



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

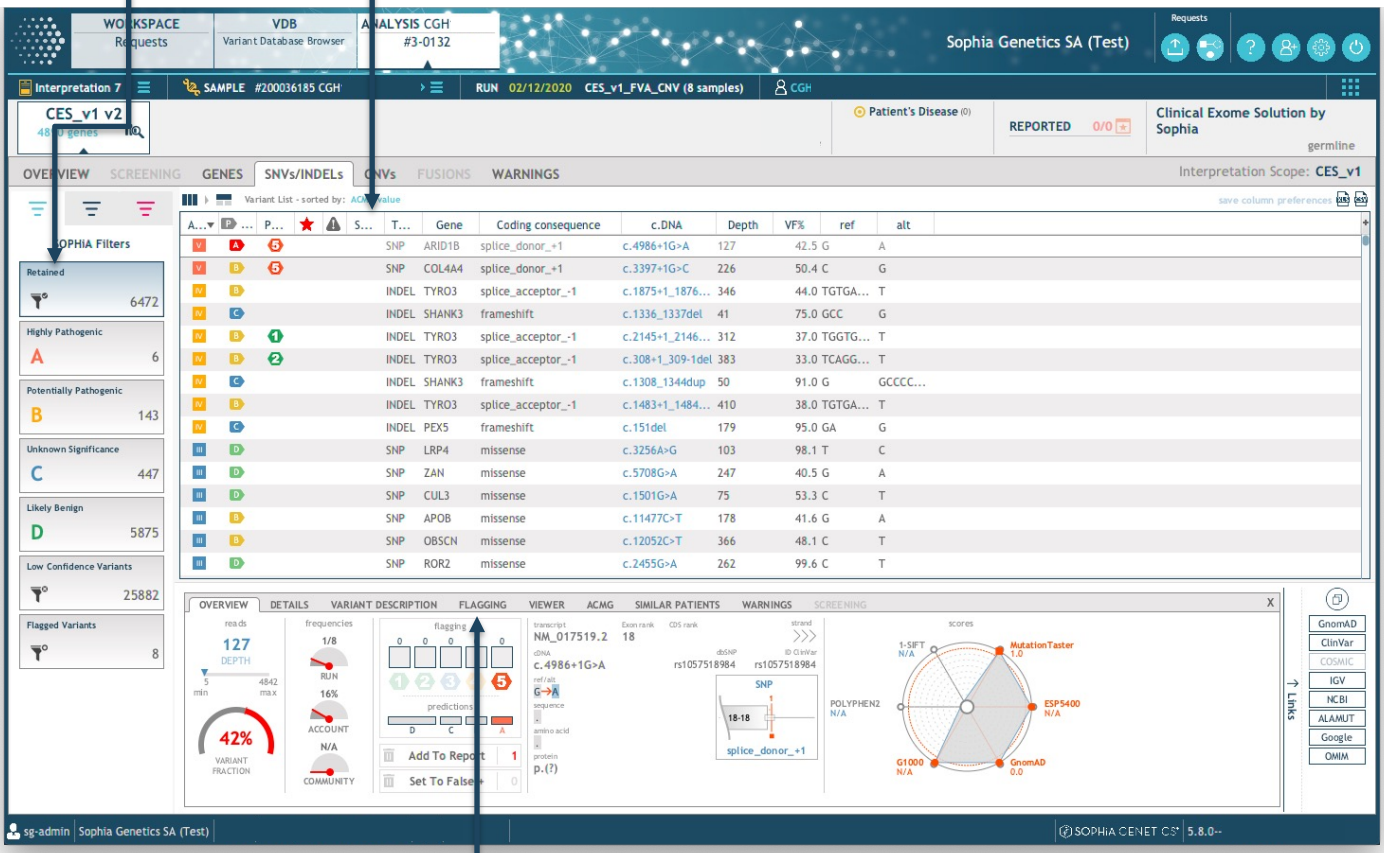
Pathogenicity web plot shows prediction and population database scores (if available). The greater the grey area is, the more likely a variant is pathogenic.

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)

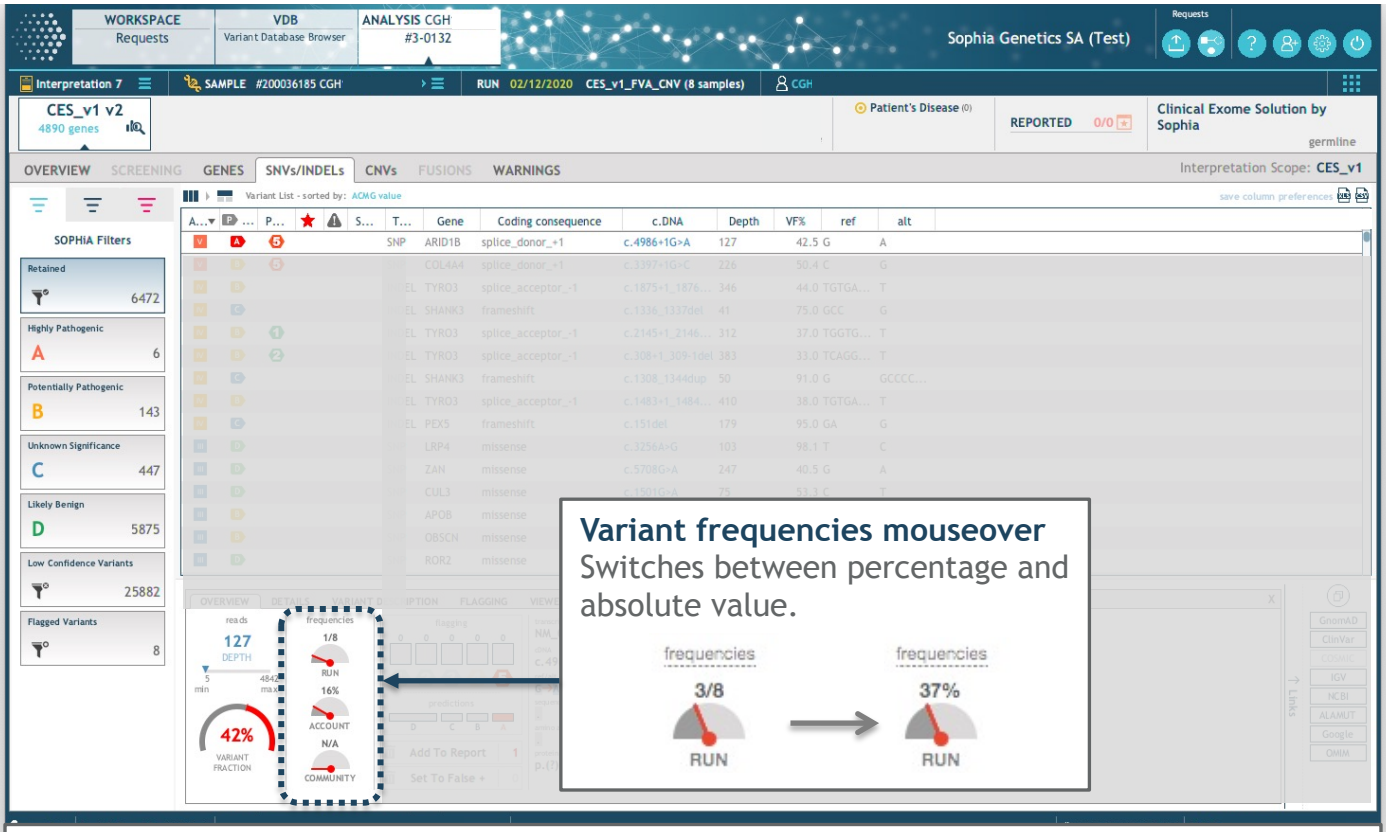
SNVs/Indels
Active sub page (white)



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)

4. Data Analysis
4.9 SNVs/Indels
4.9.4 Frequencies



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.

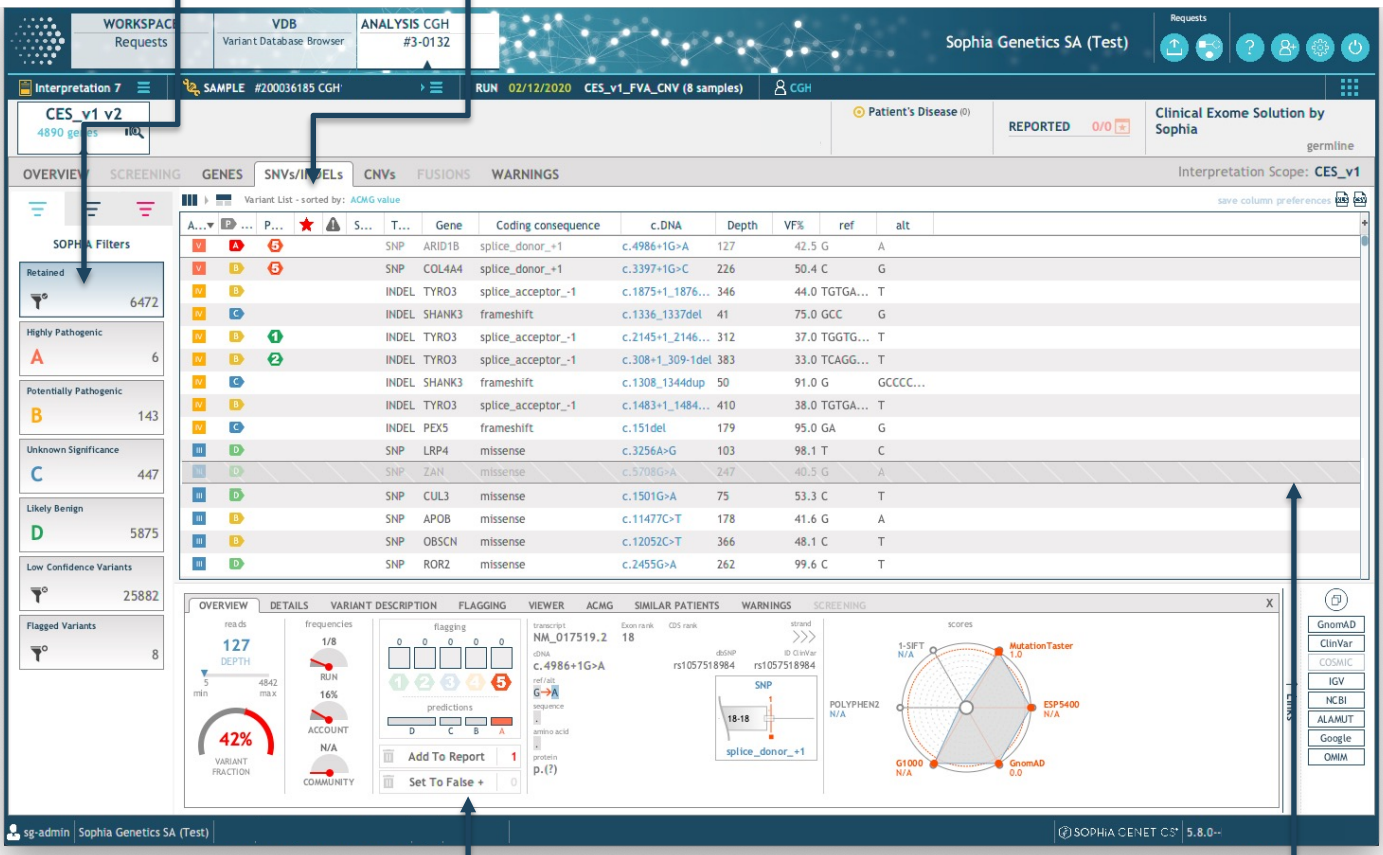
Community frequency
The number of times this variant was detected across all instances of the gene within SOPHiA GENETICS™ Community routine accounts out of the total number of possible occurrences, considering the experiment type and only retained variants. The Frequency may be biased by the nature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

Research Use Only. Not for use in diagnostic procedures.

4. Data Analysis
4.9 SNVs/Indels
4.9.5 False Positive Variants

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)



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).

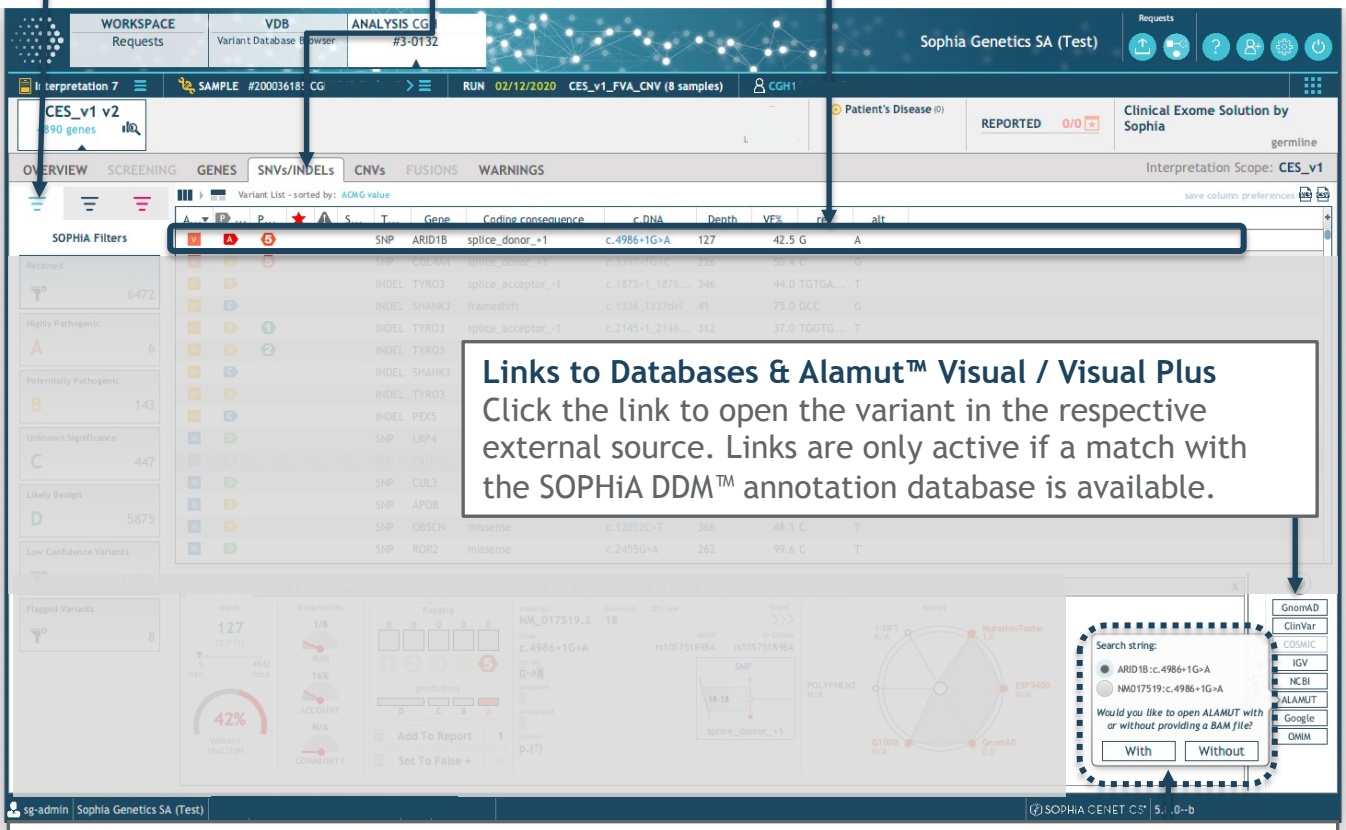
NOTE: A false positive flag can only be removed in the sample where the flag was added.

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

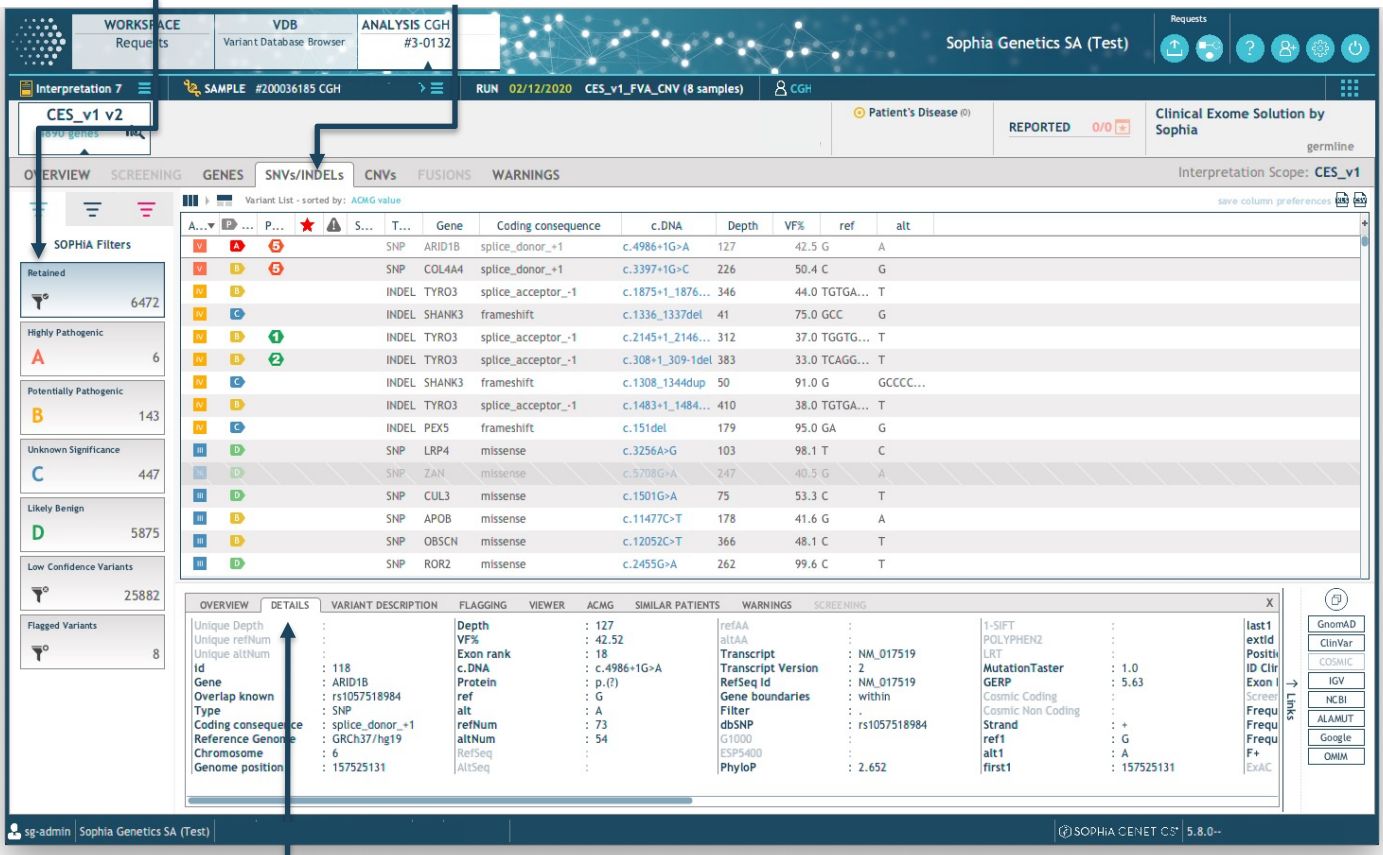


Alamut®
Clicking the “Alamut” button allows the user to select the annotation format and whether or not to import the BAM file from SOPHiA DDM™ for visualization in Alamut®. Access to Alamut™ Visual or Alamut™ Visual Plus from SOPHiA DDM™ is possible via API. Visualization of the variant in Alamut™ Visual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

4. Data Analysis
4.9 SNVs/Indels
4.9.7 Variant Details

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

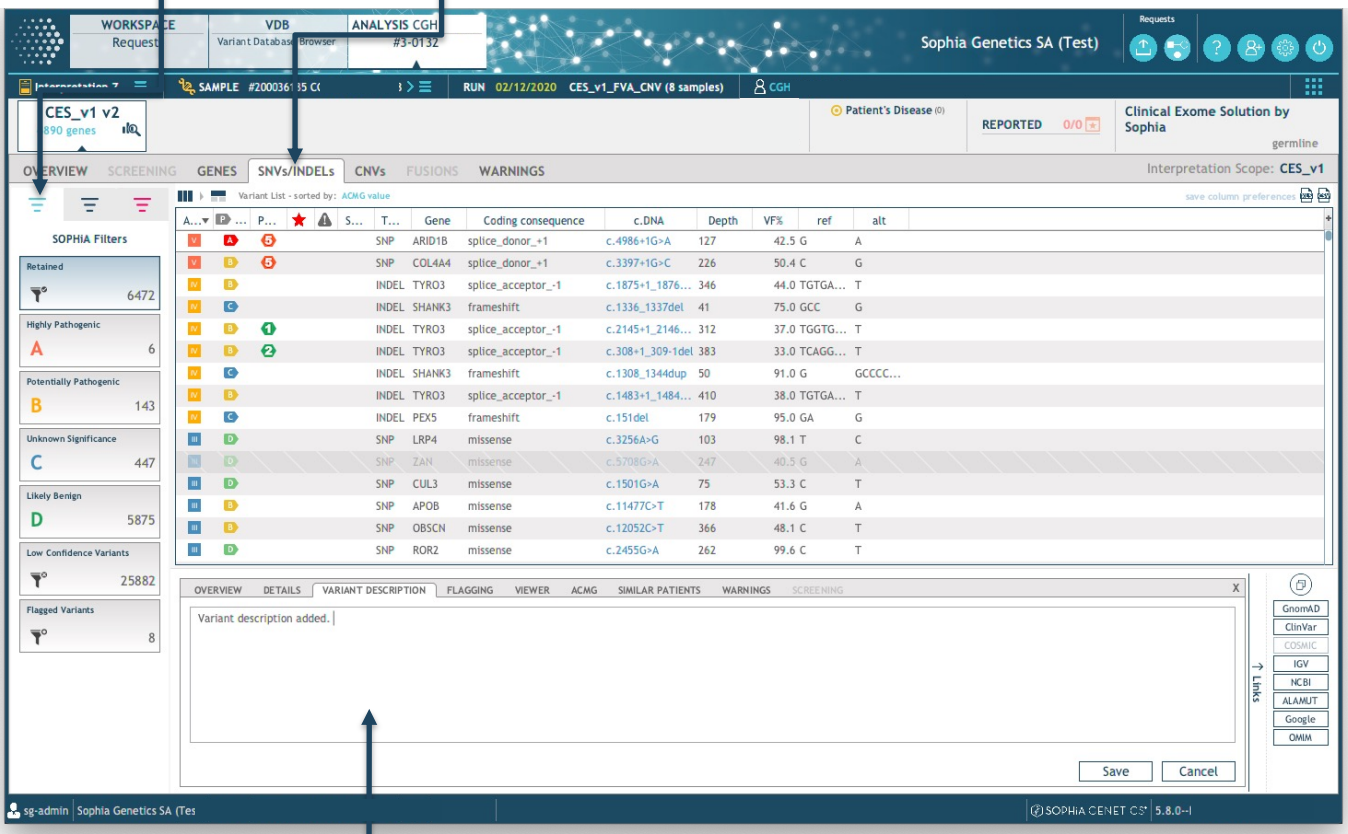


Details
The details tab presents extensive information about the current variant

4. Data Analysis
4.9 SNVs/Indels
4.9.8 Variant Description Tab

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

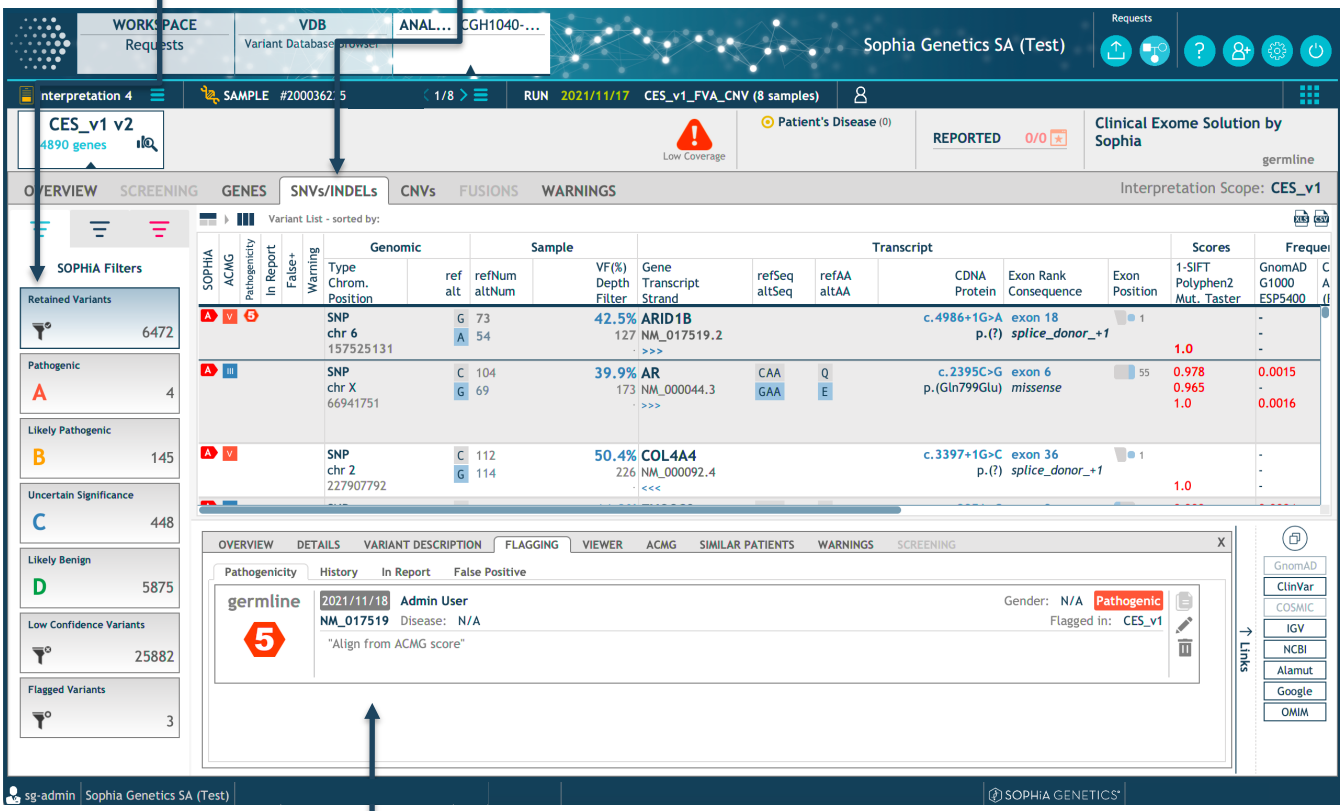


Variant Description
A free-text description can be added to the variant. This description is accessible for all samples of the same experiment type (somatic/germline) with the same variant. This description can be selected to report in the Project or Application Settings.

4. Data Analysis
4.9 SNVs/Indels
4.9.9 Flagging Tab

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)



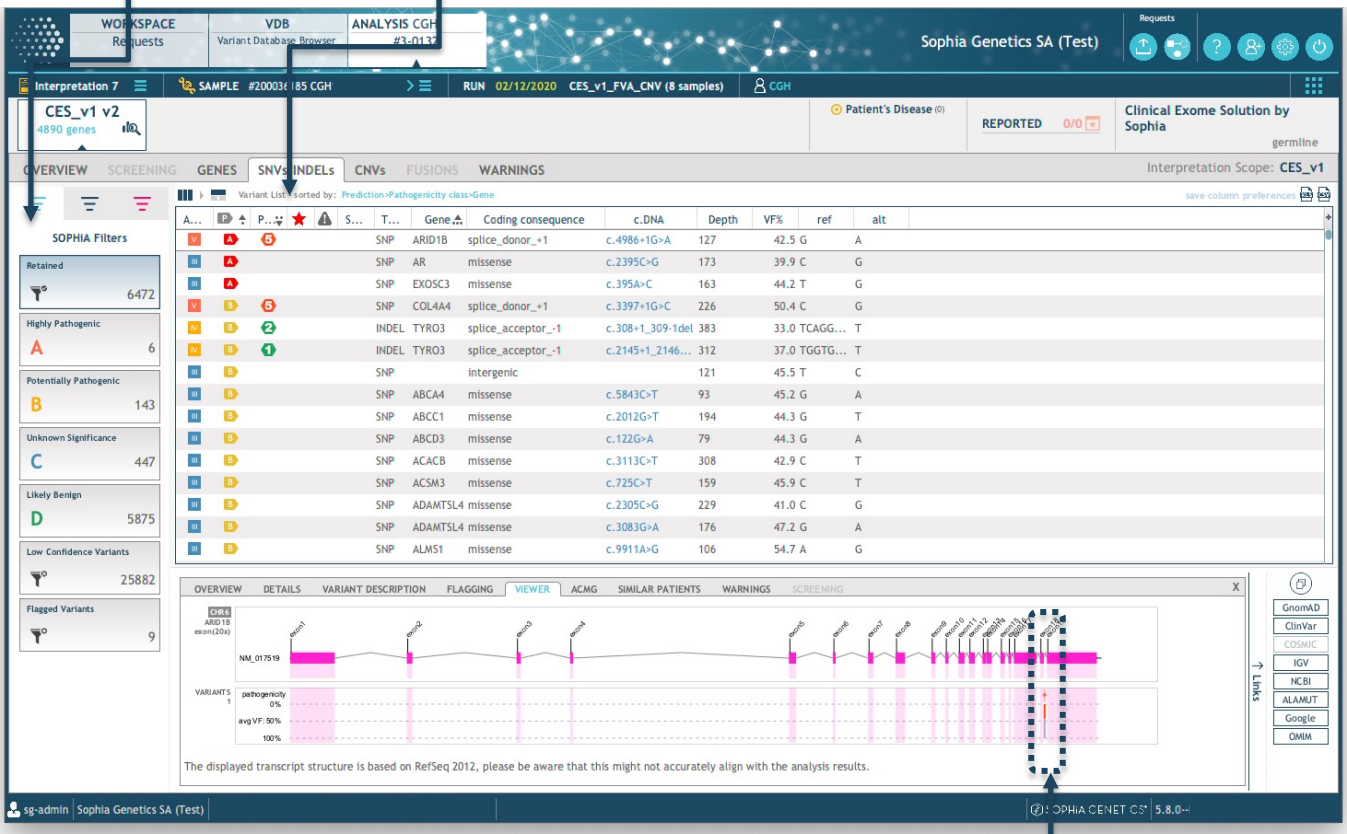
Flagging tab
The flagging tab shows which user applied a pathogenicity flag, the history of pathogenicity flags as well as the “in report” and ”false +” flags.

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

4. Data Analysis
4.9 SNVs/Indels
4.9.10 Viewer

Retained variants
Active page (blue)

SNVs/Indels
Active sub page (white)



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.

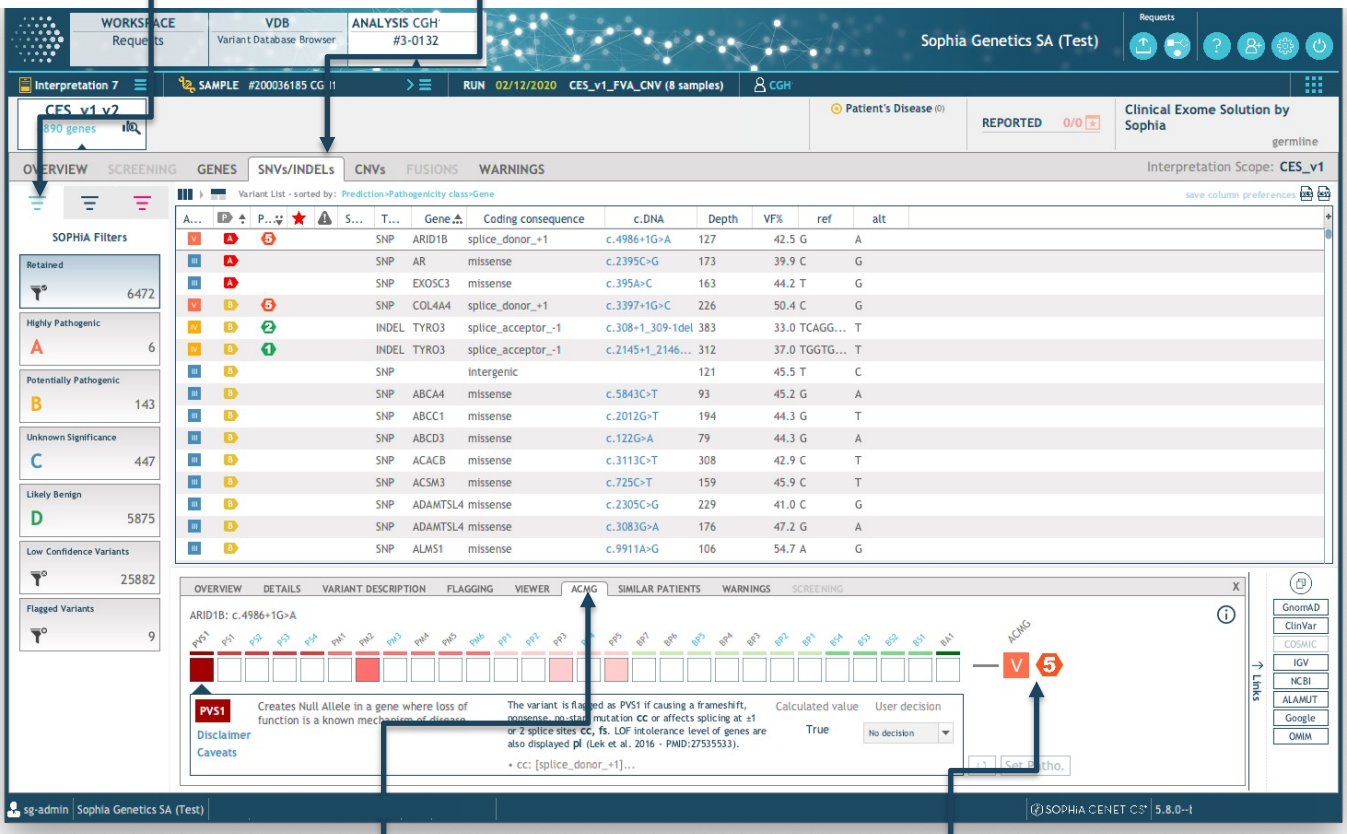
Out of 28 criteria, 13 are automatically evaluated by SOPHiA DDM™ to establish an initial ACMG pre-classification score for all variants of every sample of a run. This initial score is displayed in a column of the variant table next to each variant. The automated evaluation takes into account various 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 (dbscSNV), 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)

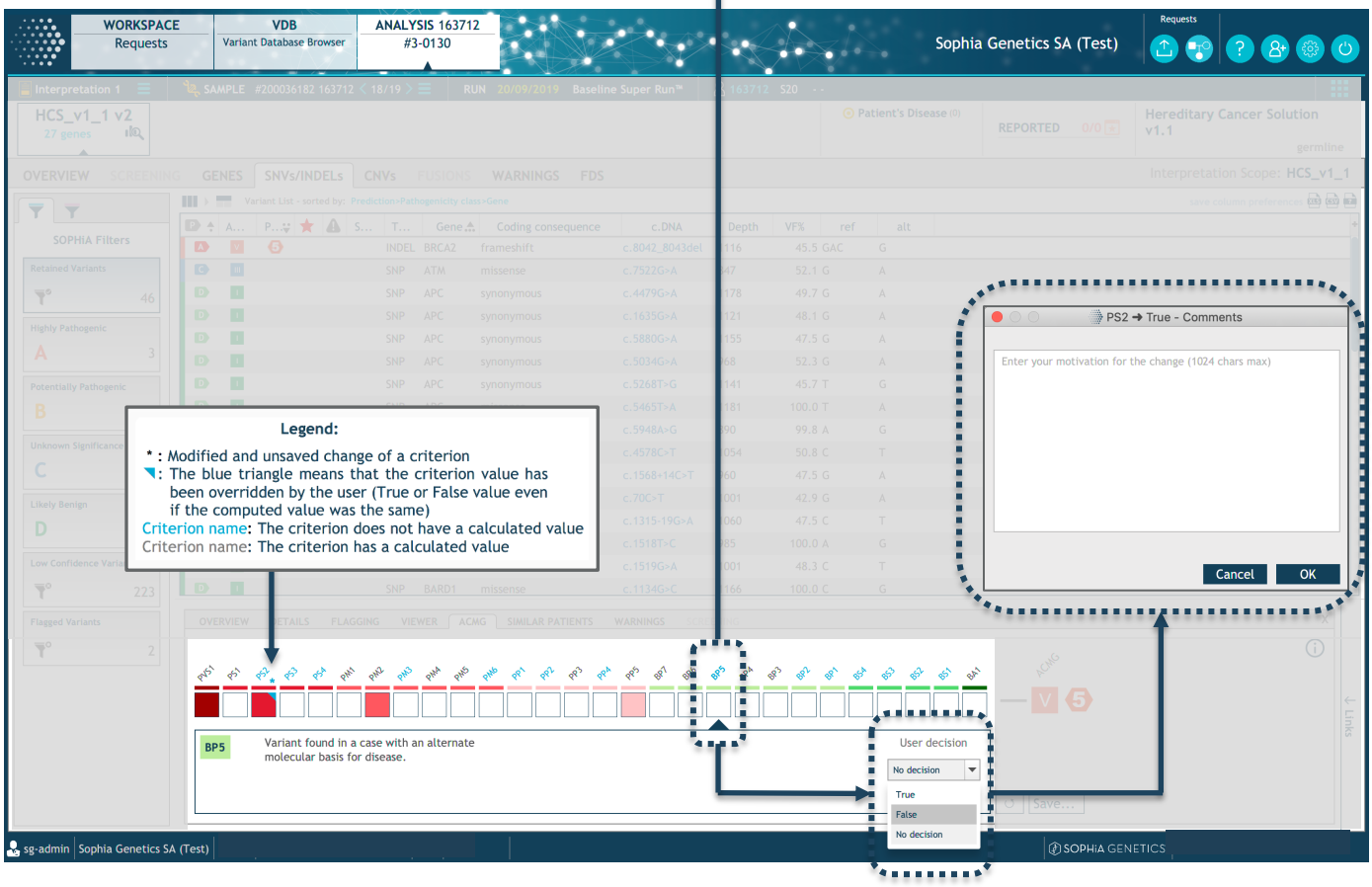


ACMG tab
Shows the status of the 28 criteria of the selected variant

Checkbox
ACMG global score and user flagging

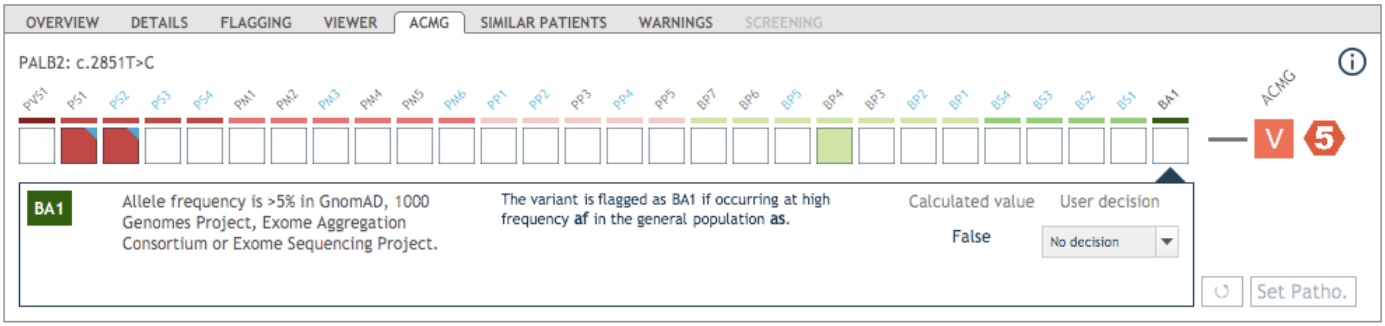
4. Data Analysis
4.9 SNVs/Indels
4.9.11 ACMG Tab (3)

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.



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)



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)

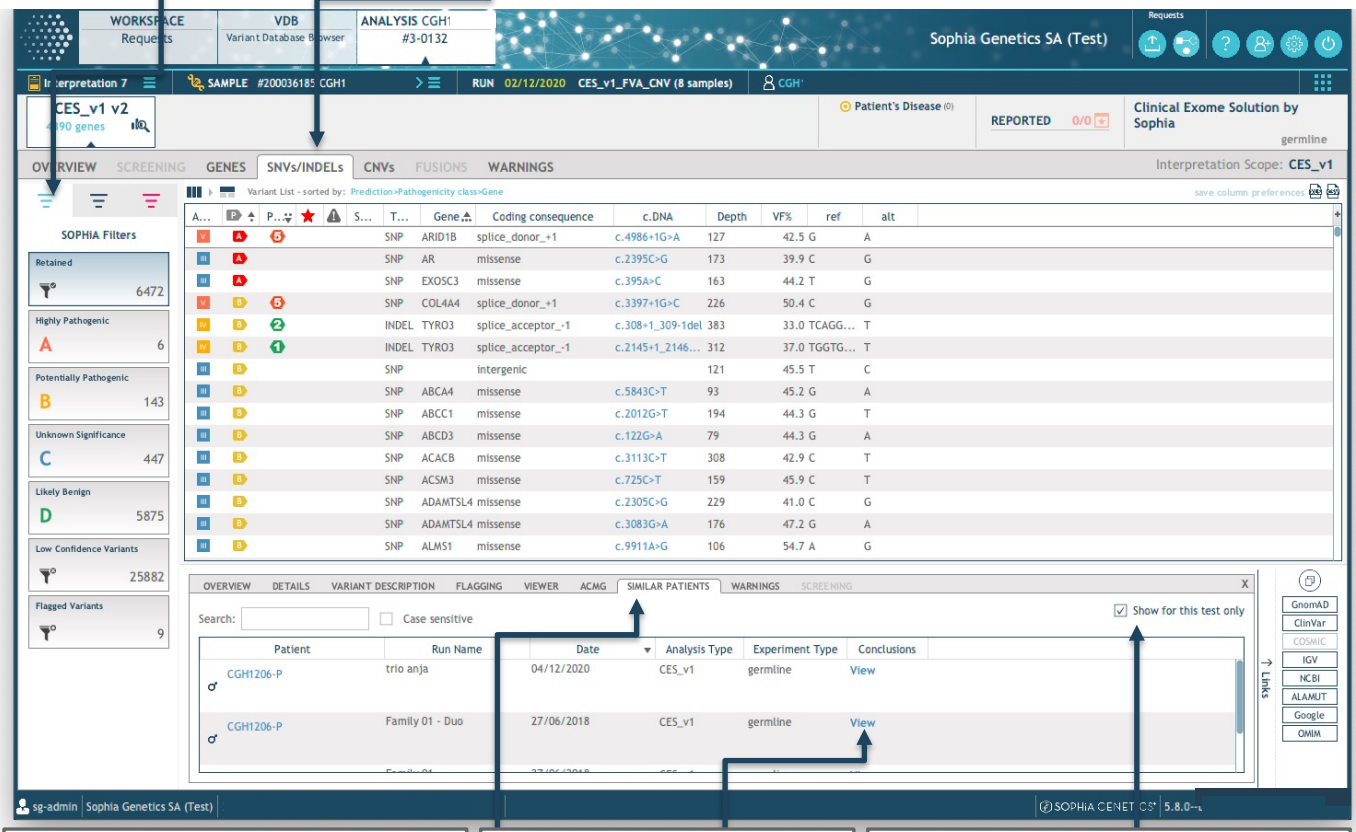
Rules to define ACMG score

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

4. Data Analysis
4.9 SNVs/Indels
4.9.12 Similar Patients* (1)

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)



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

View
Opens the corresponding analysis in a new window

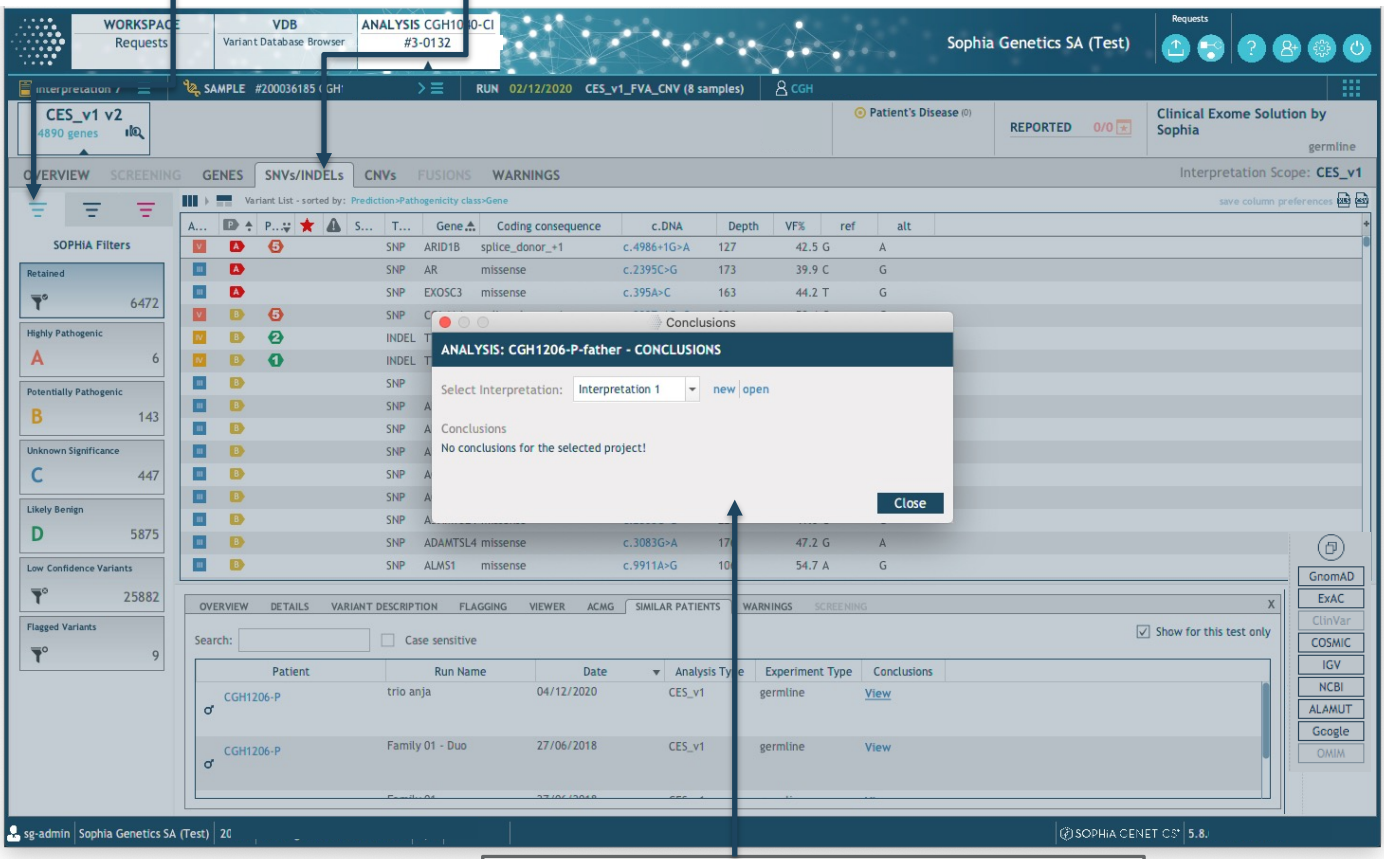
Checkbox
Checkbox to show similar patients* for same application or across application(s)

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 Vitual Panel).

4. Data Analysis
4.9 SNVs/Indels
4.9.12 Similar Patients* (2)

Retained variants
Active filter (blue)

SNVs/Indels
Active sub page (white)

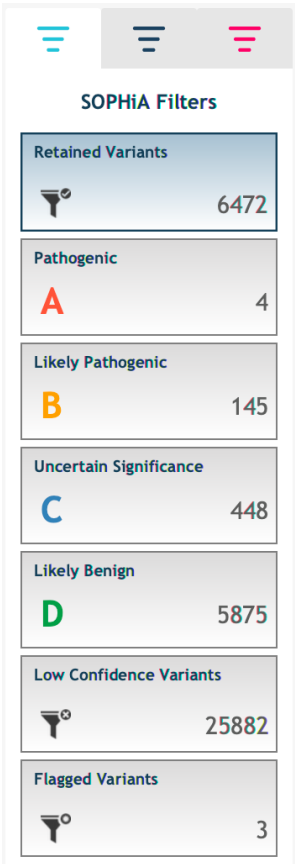


Project*
Select an Interpretation Project* from the dropdown menu to open similar patients* or create a new Project*

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



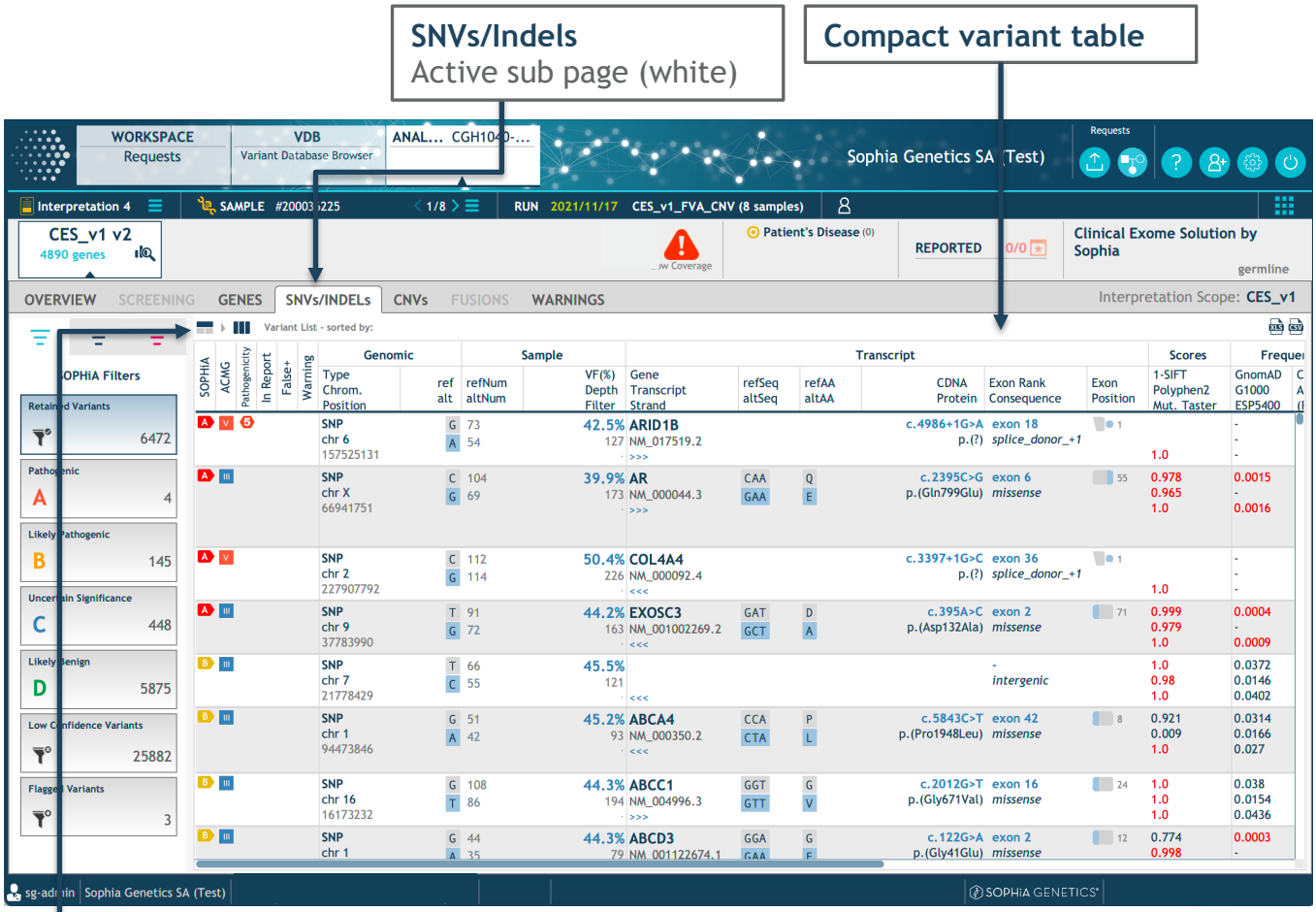
Light blue filter: predefined filters (SOPHiA DDM™ filters)
Dark blue filter: custom filters (Variant Filter Builder)
Pink filter: Cascading filters

Retained variants
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

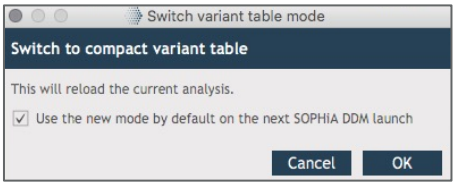
Flagged variants
Variants flagged by the user

4. Data Analysis
4.9 SNVs/Indels
4.9.14 Compact Variant Table

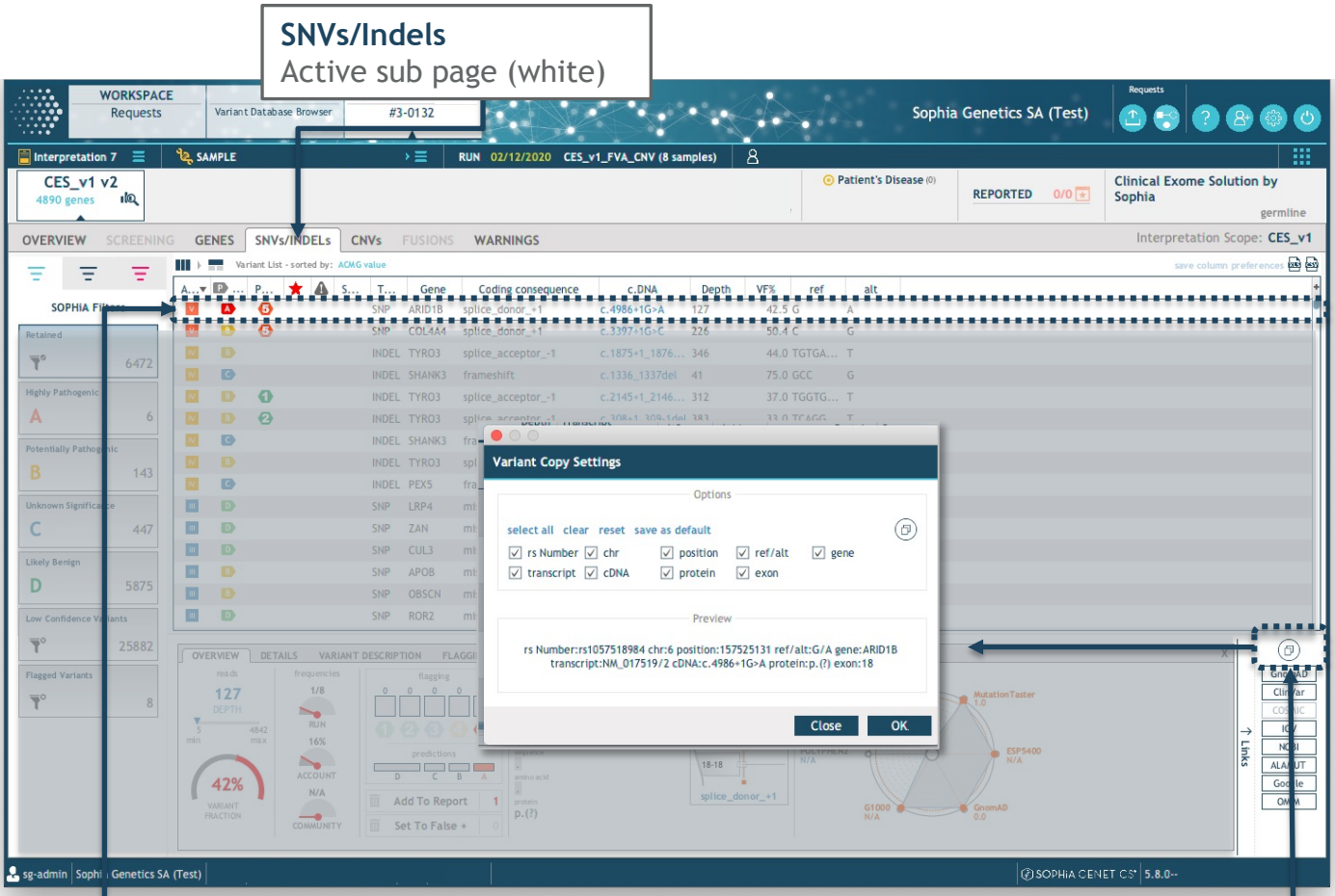


Variant table switch

- 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



4. Data Analysis
4.9 SNVs/Indels
4.9.15 Variant Copy Function



Copy variant information
- Select variant
- Press CTRL+C (Mac ⌘CMD+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.

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.

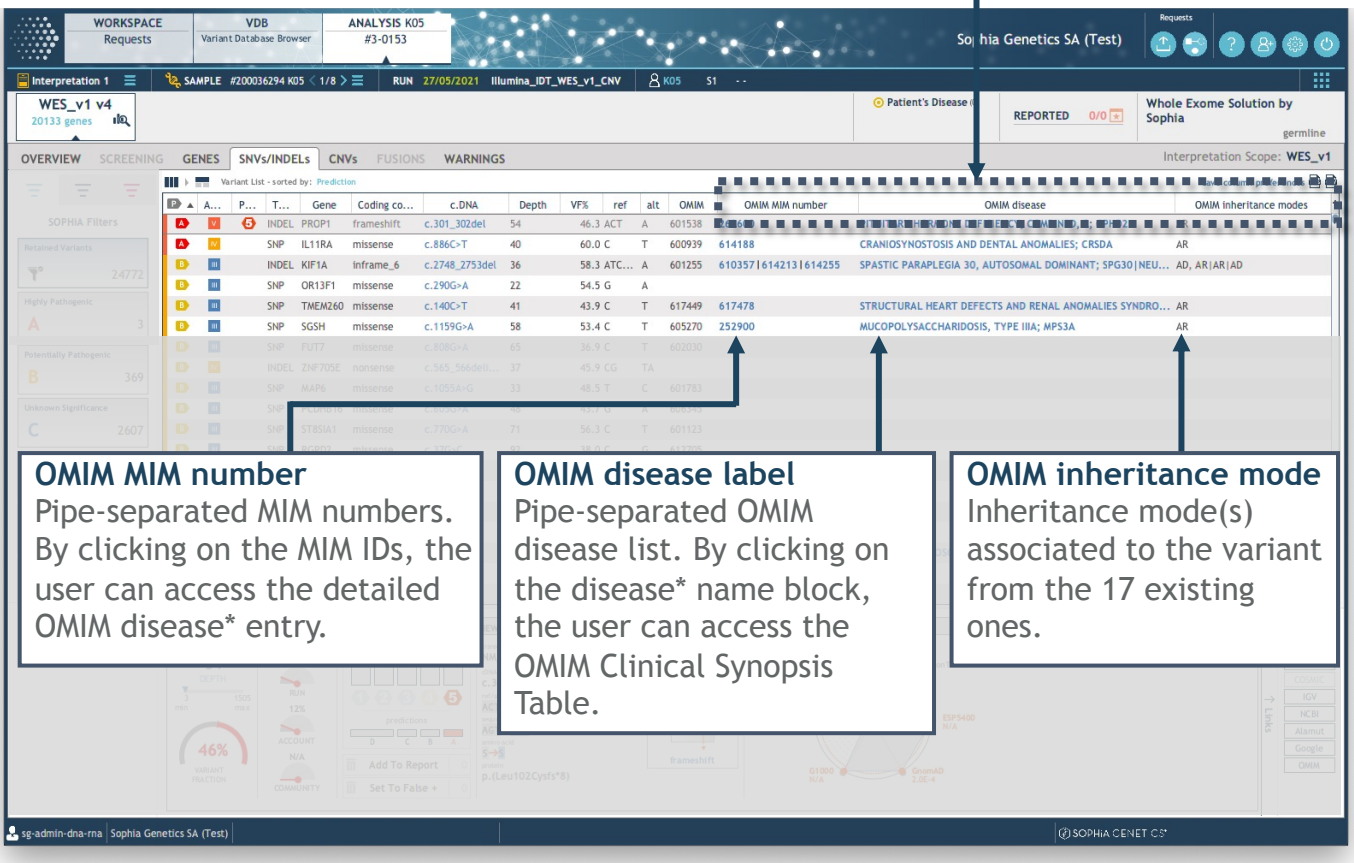
In addition, the user can select these variables to filter out the variant list through the Cascade Filters (see chapter 6. Cascading Filters) and the Variant Filter Builder (see chapter 5. Variant Filter Builder) for a faster and easier variant filtration and prioritization.

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.



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.

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.

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.

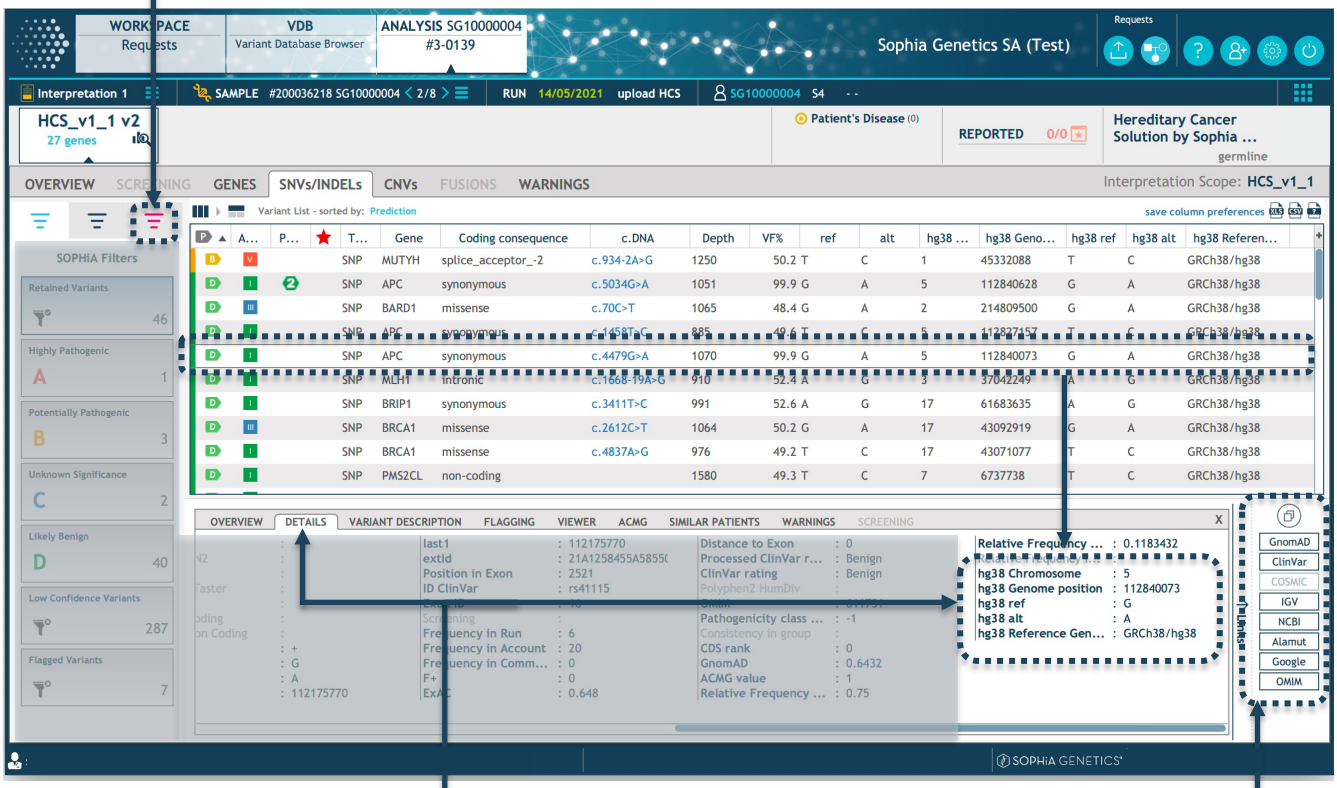
hg38 annotation information

- 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))



hg38 annotation information in Details sub-tab

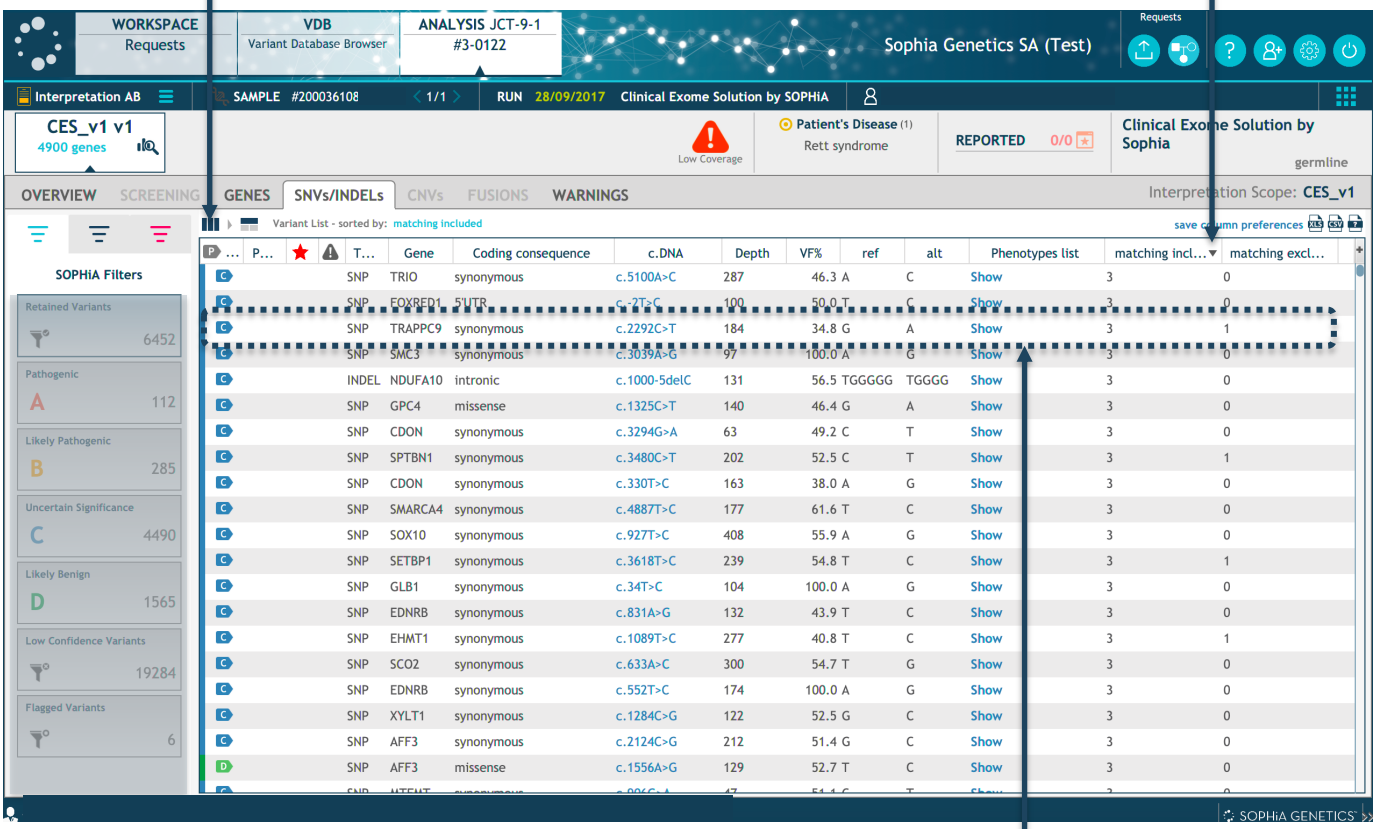
Variant copy details and link-out to GnomAD are based on the selected product (i.e., based on hg19 or hg38 reference genome).

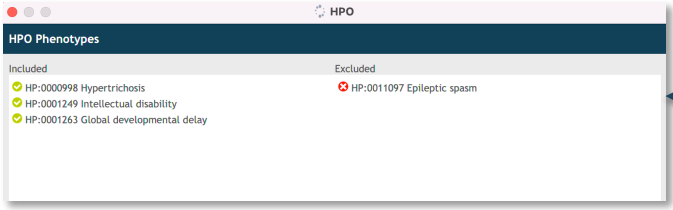
NOTE: The content of these columns is filled from different sources. Please refer to the previous pages for details.

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





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

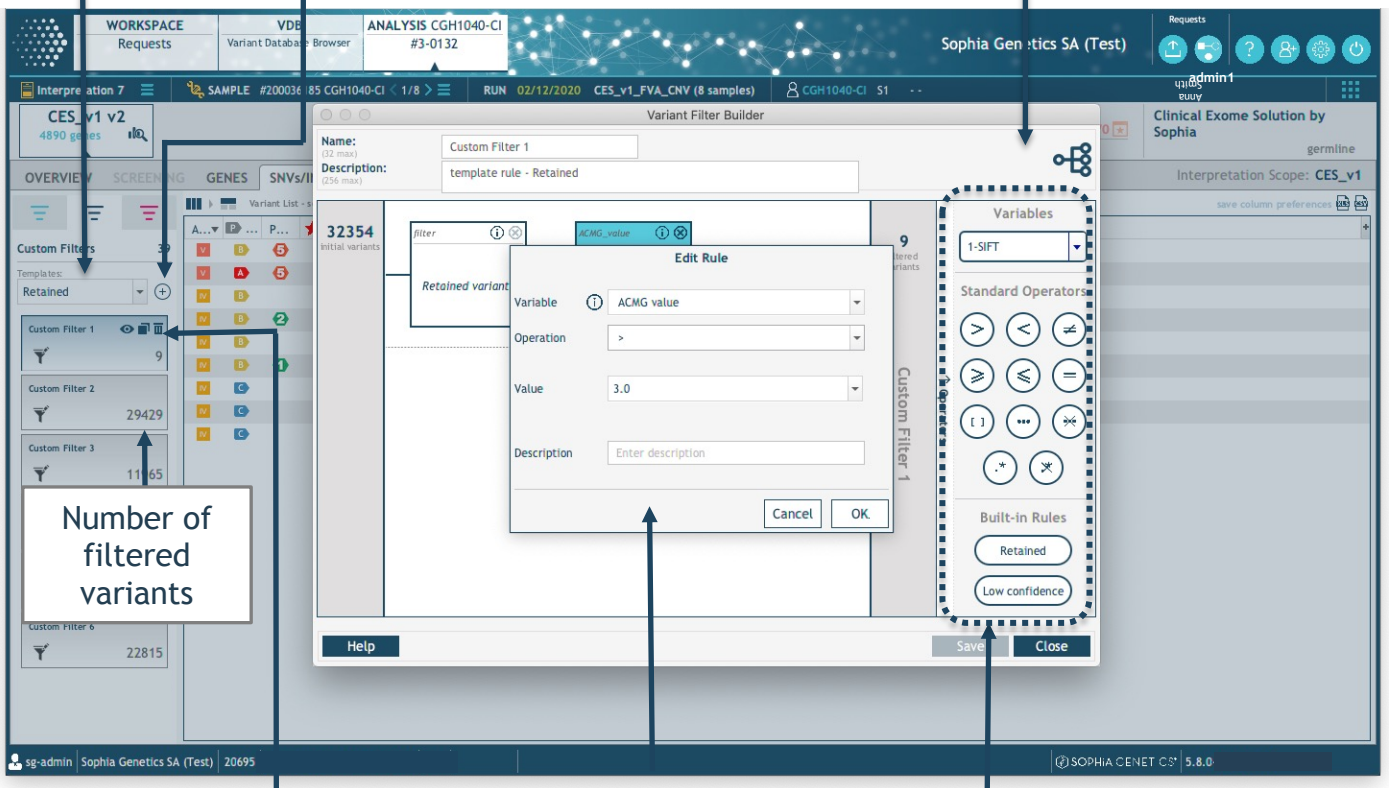
NOTE: These columns are also available in the compact view of the table.

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)

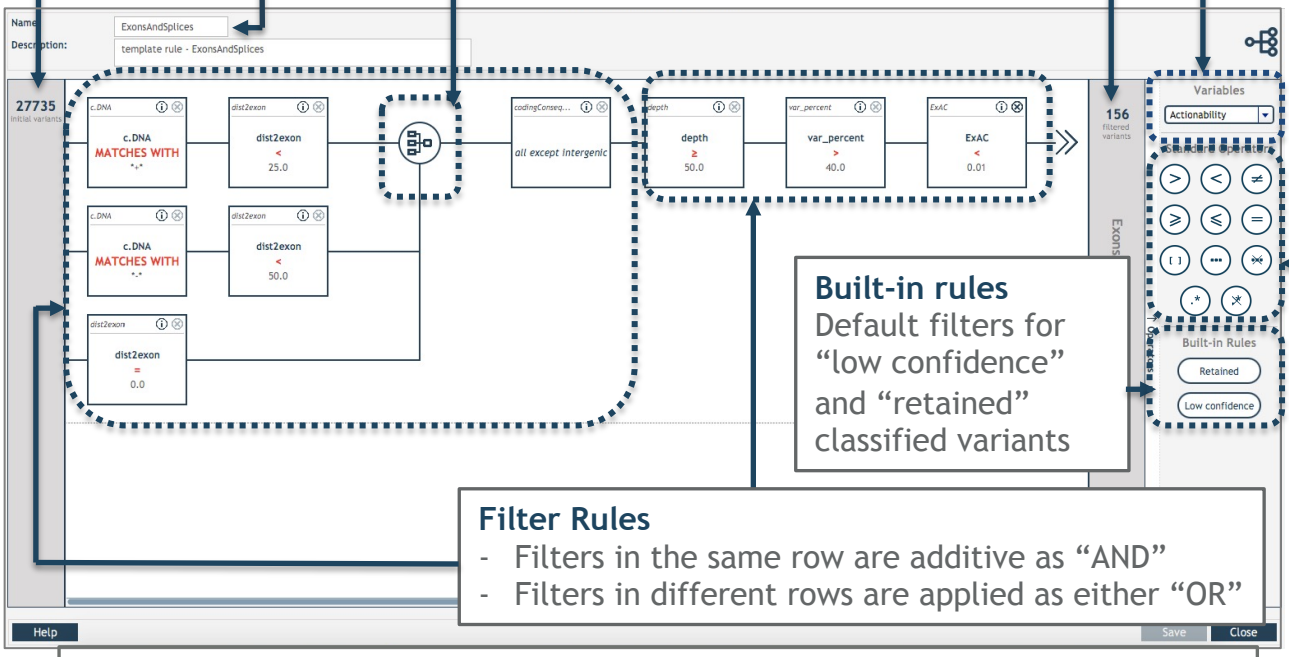
Branching
"Or" function can be used to combine filters (see chapter 5.3 – Branching)

"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

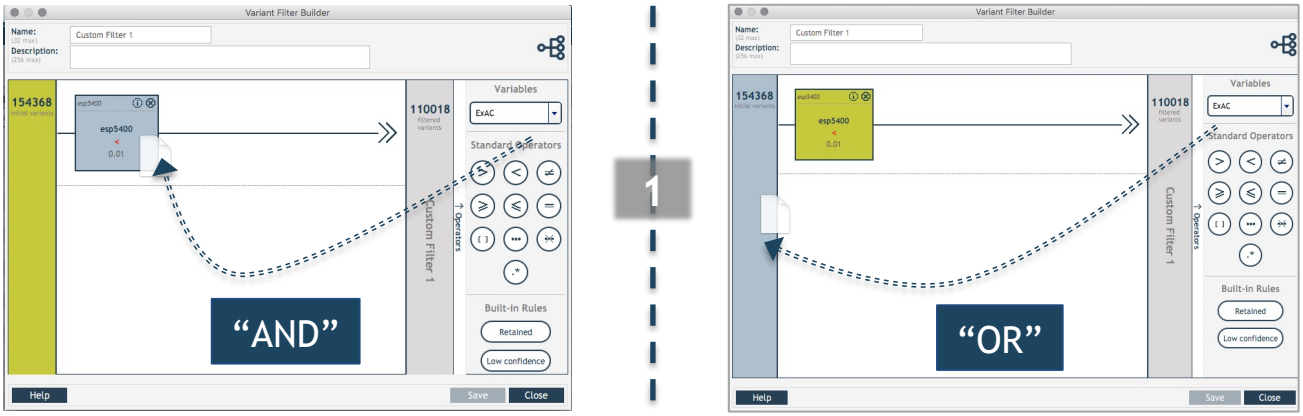
>	Greater than	≥	Greater than or equal to
<	Less than	≤	Less than or equal to
≠	Not equal	[ ]	Between (value 1 & 2)

●●●	In
●●●	Not in
.*	Matches with
.*	Does not match with

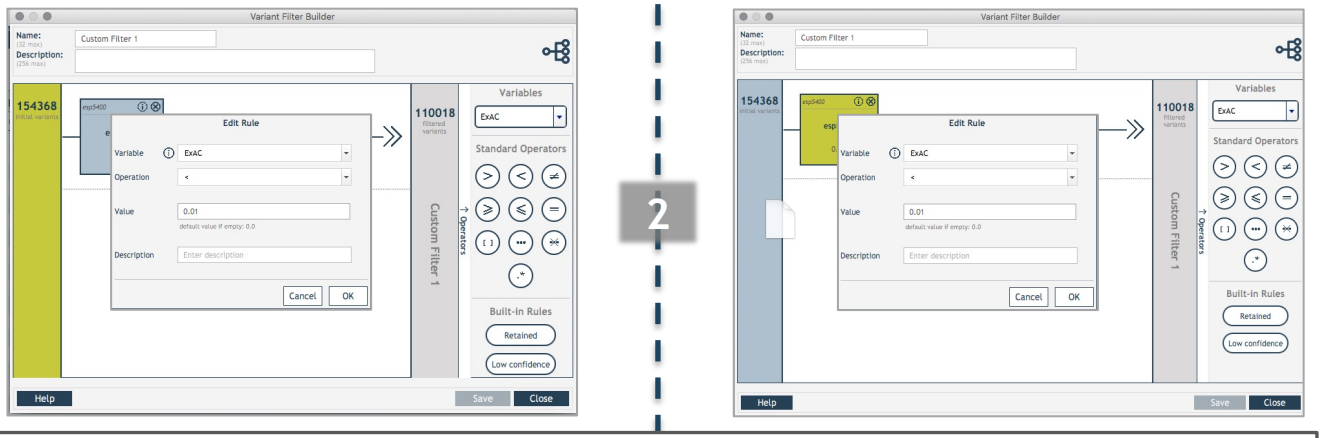
- If the IN operator is used, the exact naming of a variant attribute (e.g., gene name) needs to be specified e.g., *variable: gene + operator: IN + value: BRCA1.*
- If the MATCHES WITH or DOES NOT MATCH operators are used, an asterisk can be added to simulate "starts with", "ends with", "contains", "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

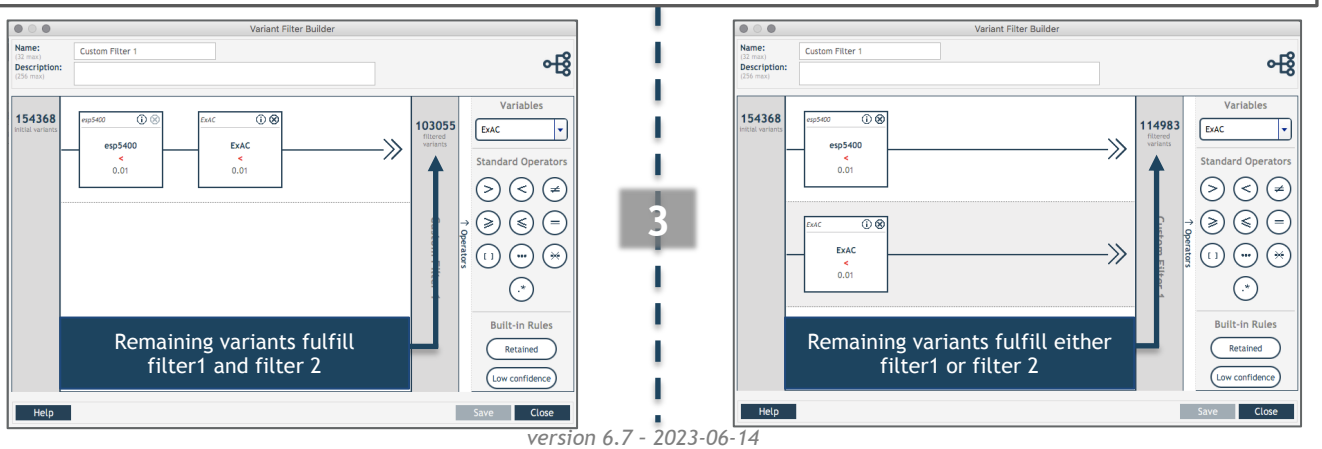
Drag and drop an operator or variable to the corresponding box (box will turn blue).



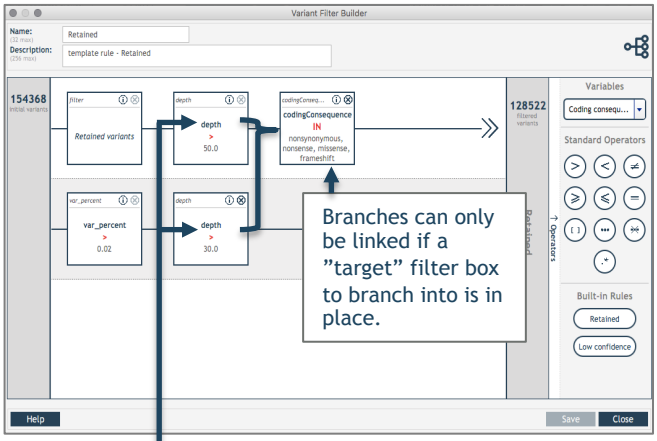
“Edit rule” window enables modification of variables, operators and values.



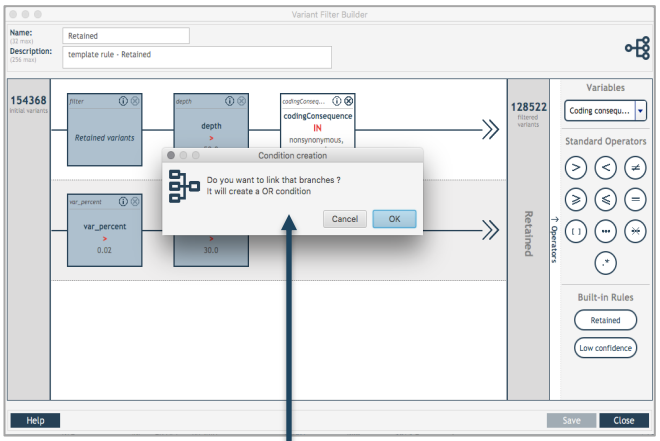
Filter boxes placed in same (AND) or separate row (OR). Click close to save custom filter.



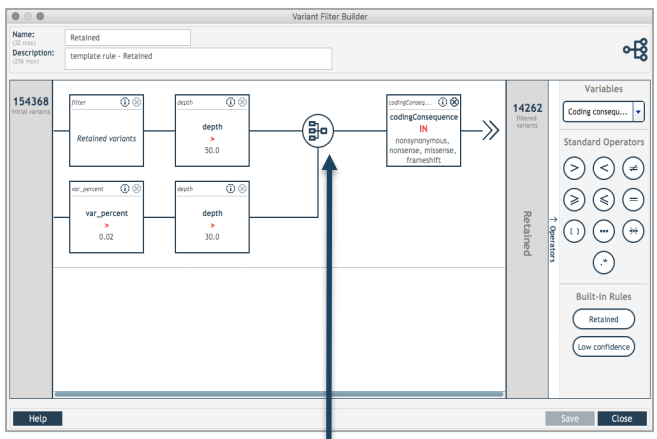
5. Variant Filter Builder
5.3 “Branching” of Filters



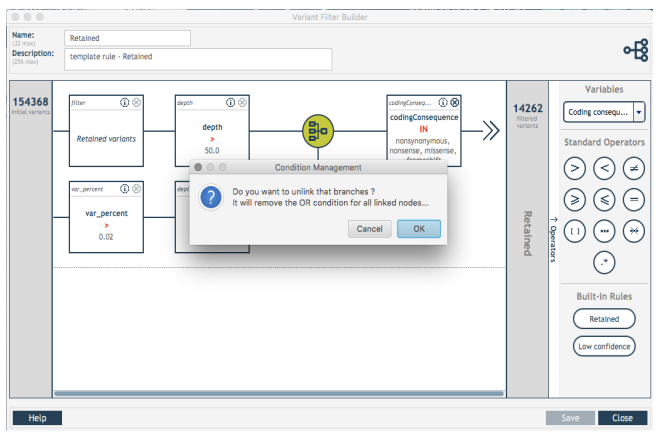
1 Connect the first branch with the second branch by selecting the boxes to connect and holding the “CTRL” key (boxes will turn blue).



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

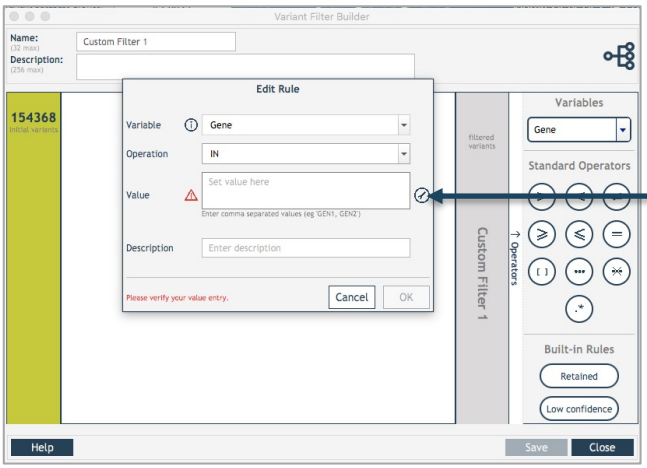


3 Both branches are now linked. Here the first two filters of row 1 and 2 are additive (“AND”). After linking the branches, the ”codingConsequences" filter will be applied to both rows.

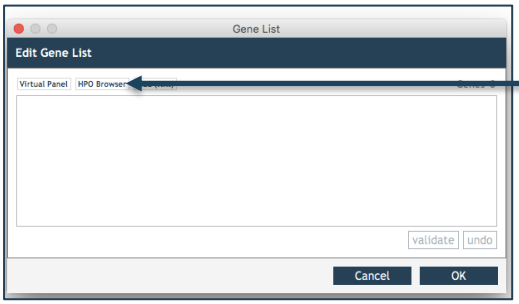


4 To unlink both branches again, click the branching tree button and click OK.

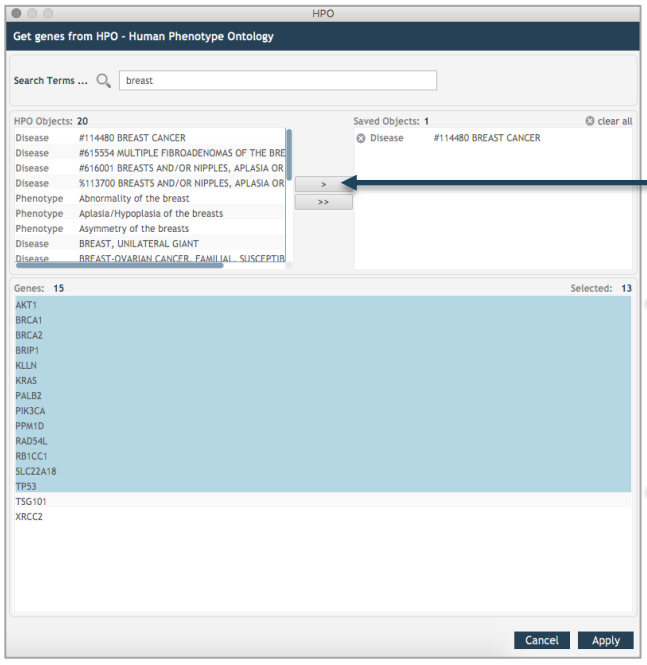
5. Variant Filter Builder
5.4 HPO Search



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.



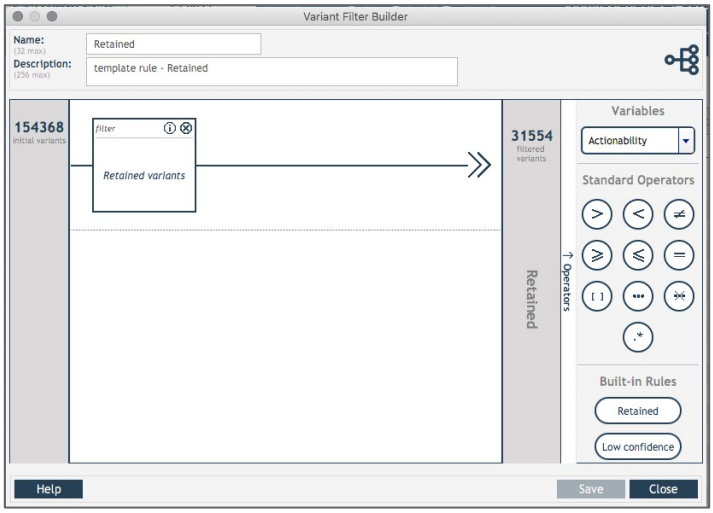
2 Select HPO browser in the pop-up window. Alternatively, genes can be imported from a txt-file or from selecting an existing Virtual Panel.



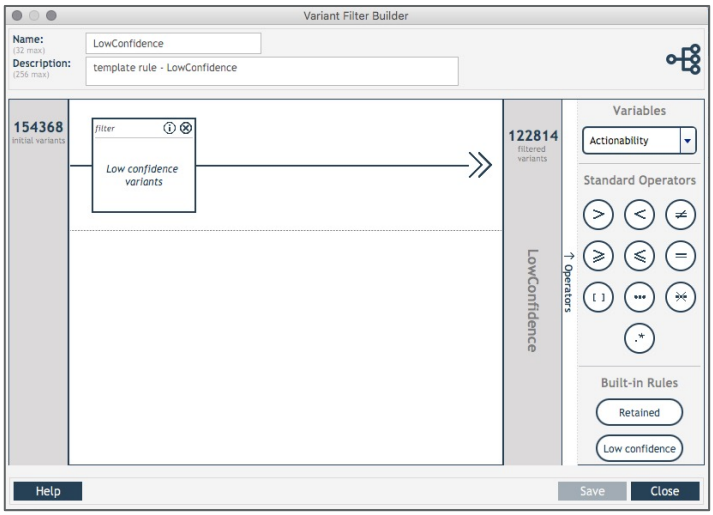
3 Type in the disease* name. Select the disease* from list and click. Several diseases* can be selected by holding shift.

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)



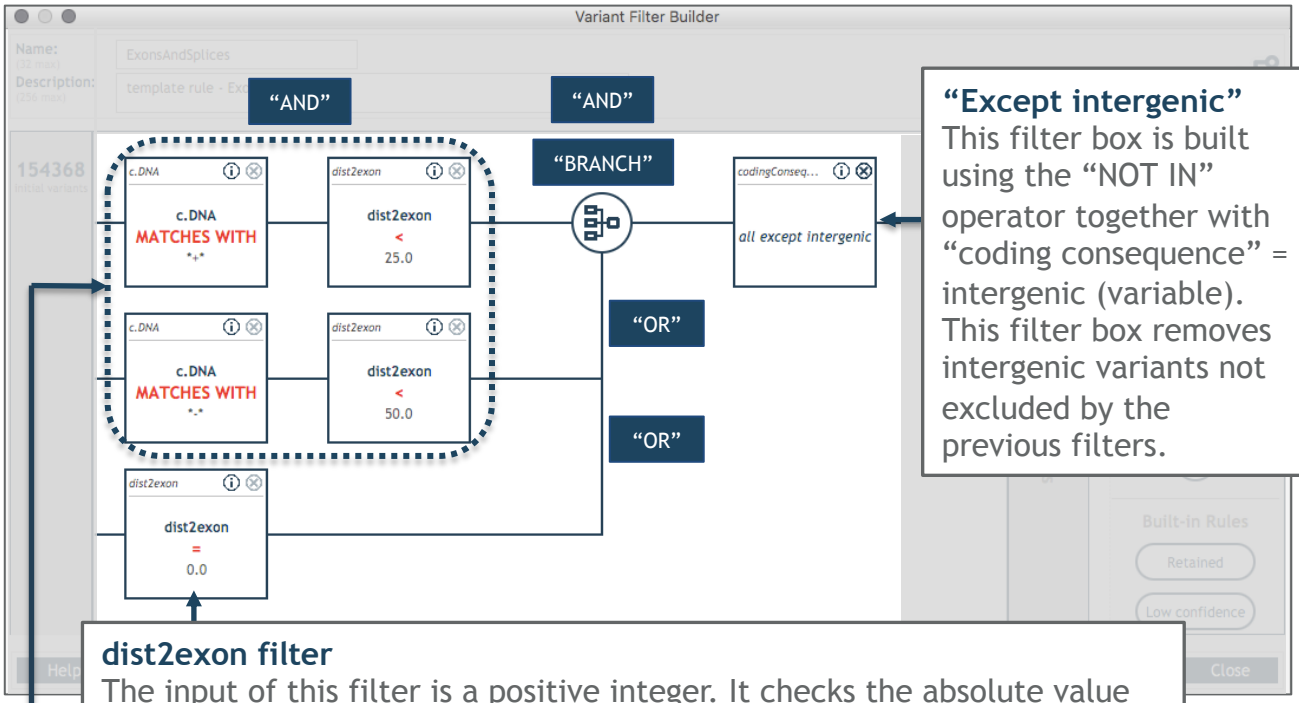
Template "Retained"
- Build your custom filter starting with the variants classified as "retained"
- To remove the "retained" filter box, click X



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

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.

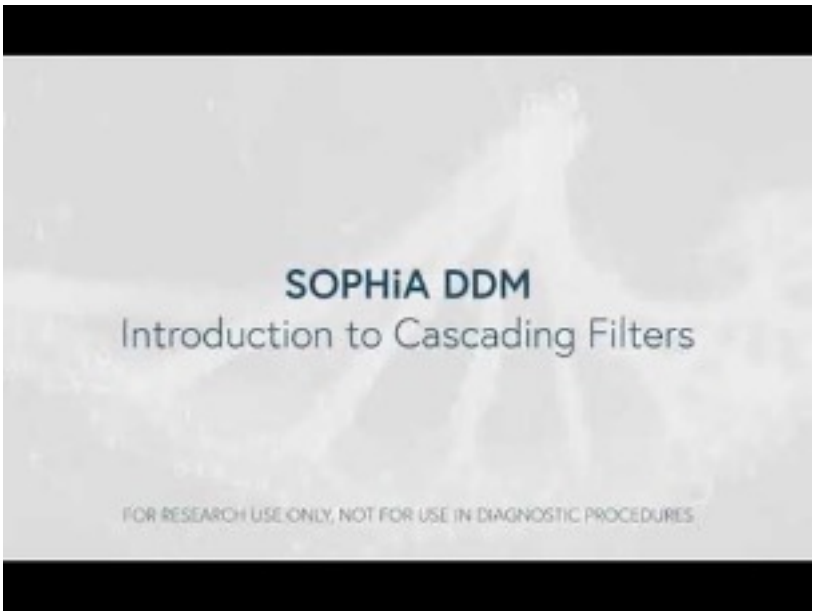
6. Cascading Filters

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:

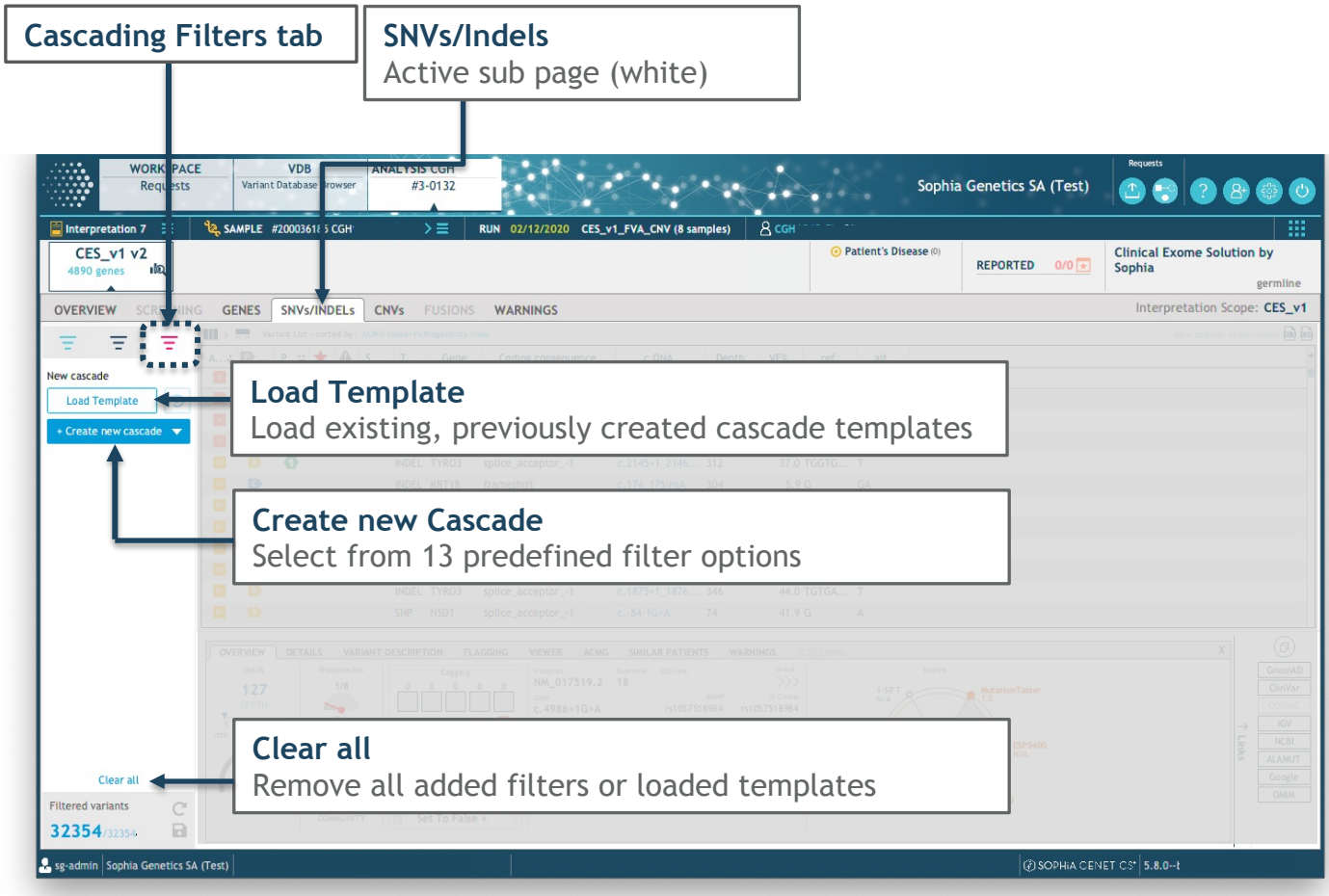
- Quickly create and edit combination of filters tailored to your needs
- Save and re-use cascades of filters throughout your account
- Track and report your filtering strategies

An explanation of this functionality can be found here:



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

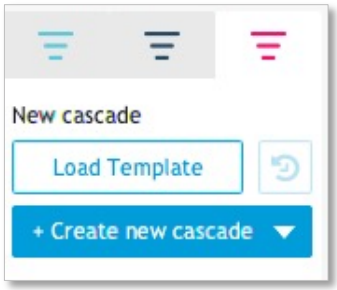
6. Cascading Filters
6.1 Overview

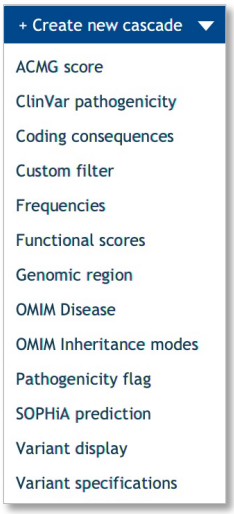


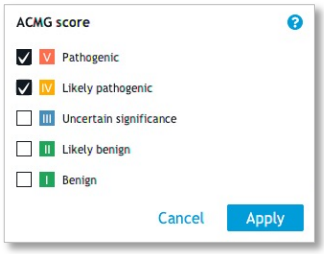
NOTE: Cascades are saved within the interpretation*. If you create a cascade and leave an interpretation project*, the cascade will be auto-saved and can be retrieved when you come back in the interpretation*.

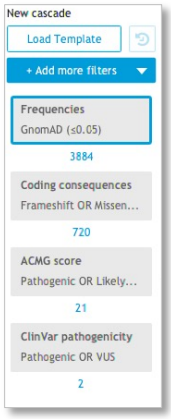
6. Cascading Filters
6.2 Create a new Cascade

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 ≤ or ≥ 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 ≤ or ≥ 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 ≤ or ≥ 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 ≤ or ≥ 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

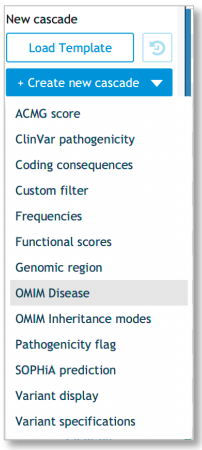
6. Cascading Filters
6.7 OMIM disease* browser

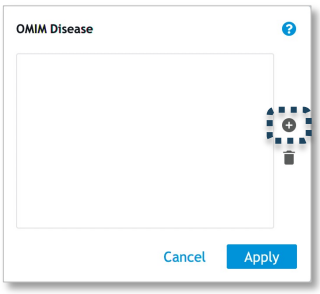
The user can use the OMIM disease* browser to select a disease* in order to filter variants by OMIM disease*.

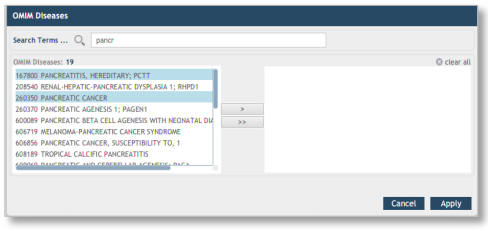
1 Click “Create new cascade” button and select “OMIM disease*” from the list.

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.



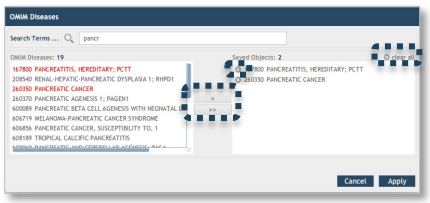


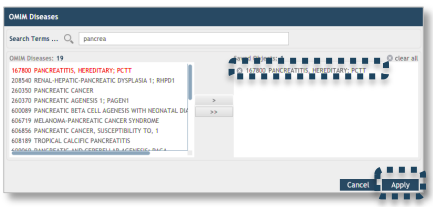


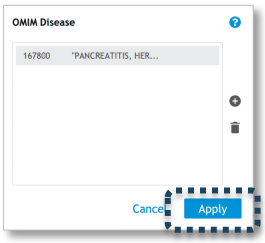
4 Click > to add disease(s)*, or >> to add all diseases to your selection. A maximum of 100 disease* entries can be manually added. Click x to remove individual disease(s)* or “clear all” to remove all items from the list.

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

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



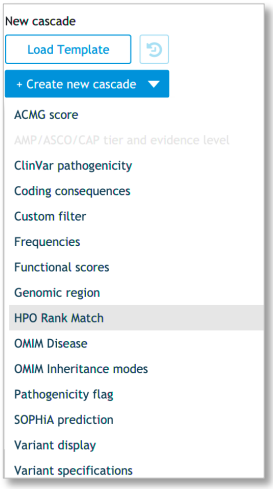




6. Cascading Filters
6.8 HPO Rank match filter

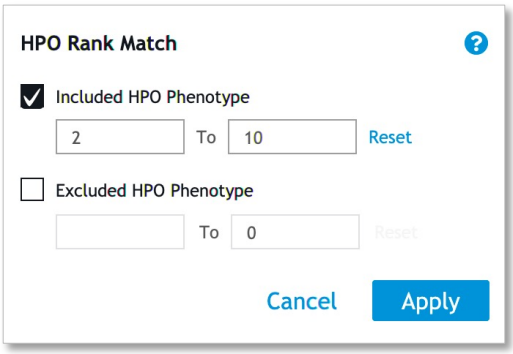
The user can use the HPO Rank match filter in order to select variants matching the user-entered HPO phenotypes.

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



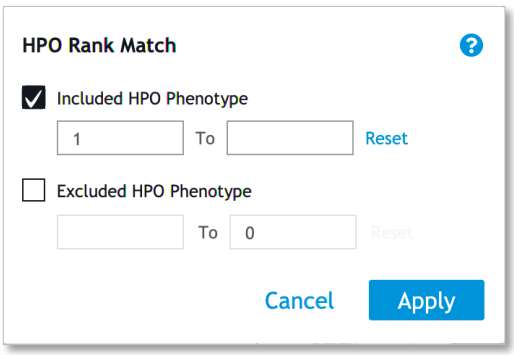
2 Enter the range [min, max] of included or excluded HPO terms for your filtering rule.

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.



3 To apply a ≤ or ≥ rule, leave the left or right text field empty.

By default the number of matching excluded phenotypes is zero.



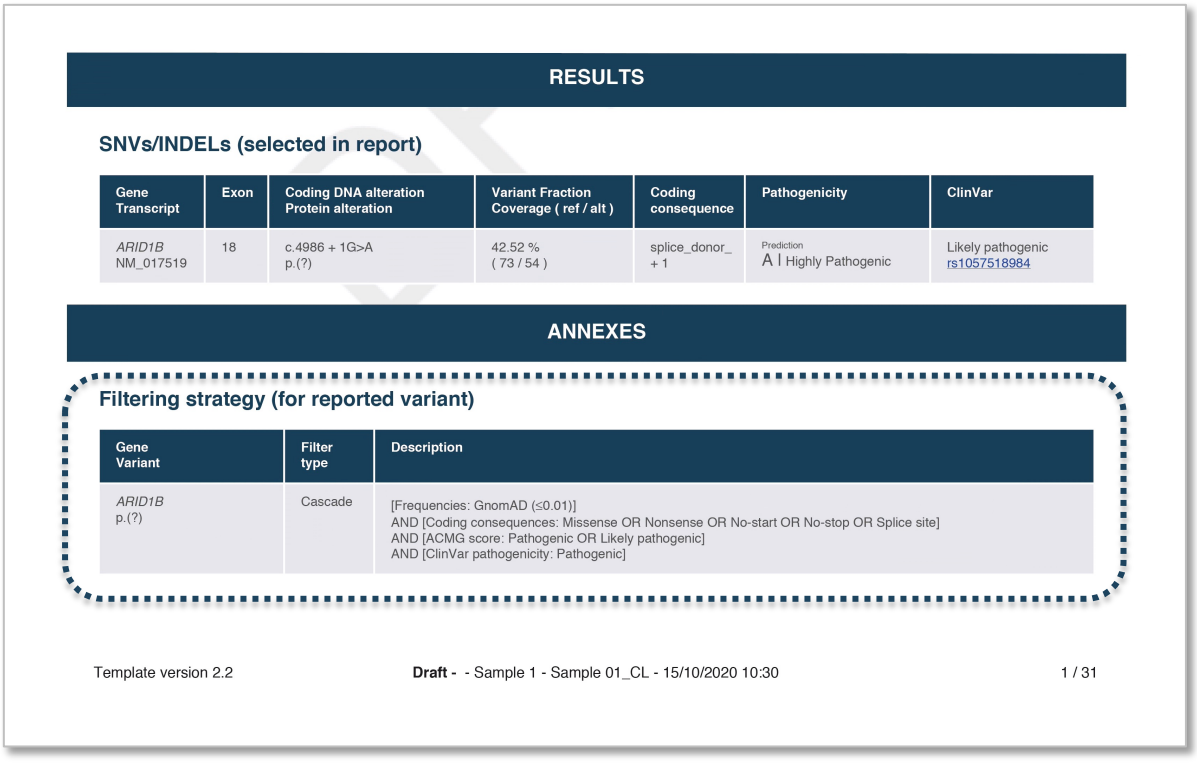
4 Click “Apply” to add the filter to cascade.

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 I 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]

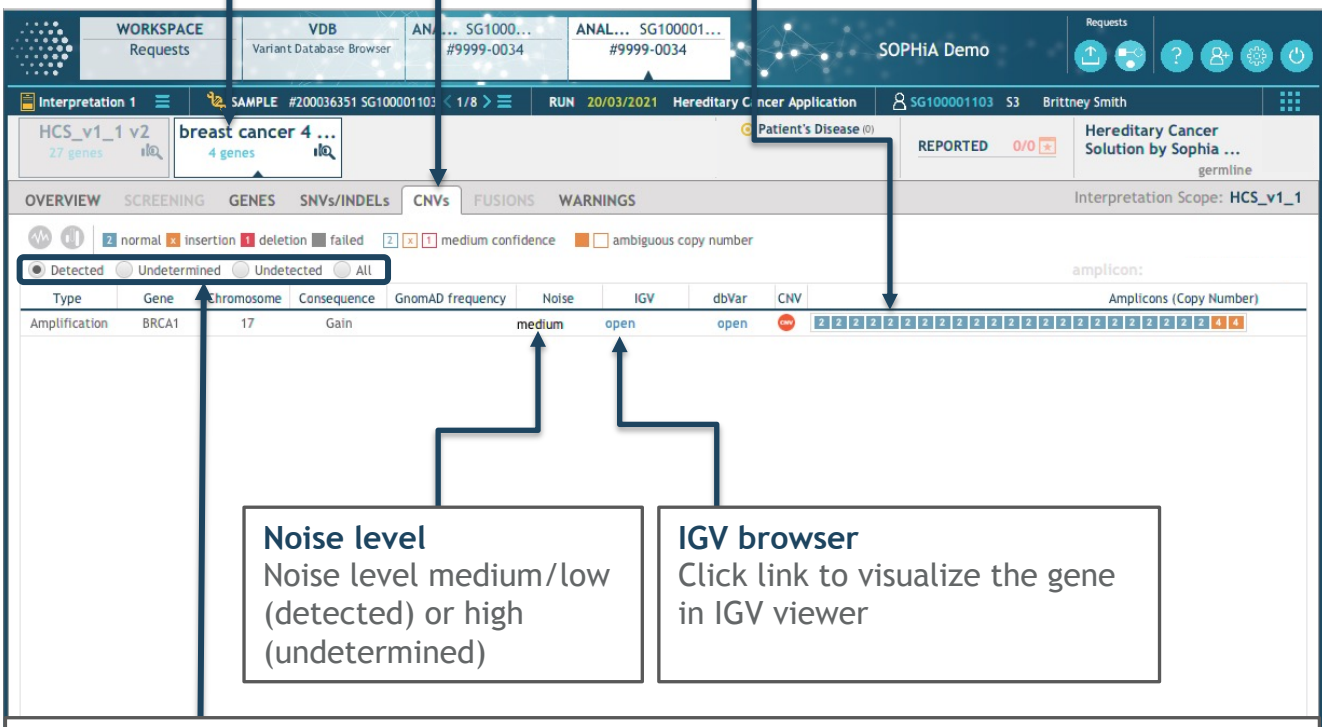
Template version 2.2 **Draft -** - Sample 1 - Sample 01_CL - 15/10/2020 10:30 1 / 31

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 (undetermined)

IGV browser
Click link to visualize the gene in IGV viewer

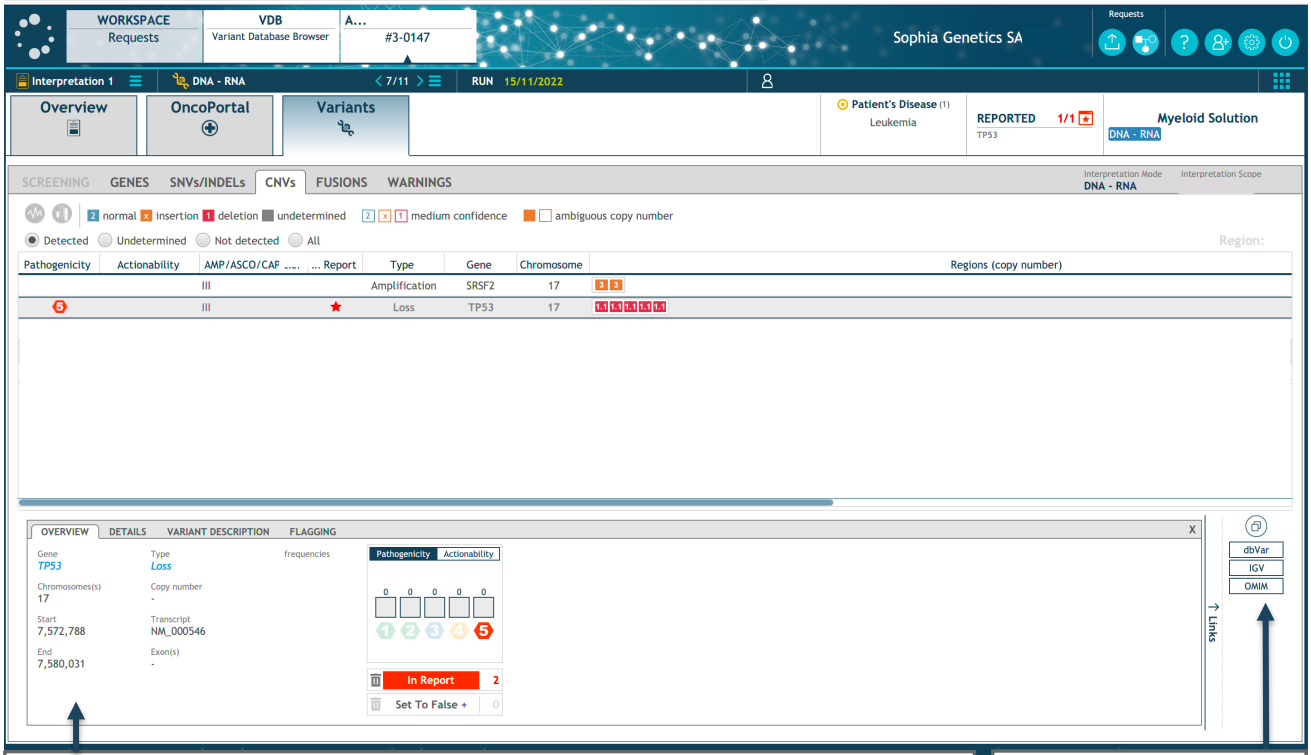
Filter view (according to scope of Project* or applied Virtual Panel)
Detected: genes with CNVs
Undetermined: genes with regions where CNV could not be determined (high noise level)
Undetected: genes with normal copy numbers
All: status of all genes of the panel where CNV detection is available

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.



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

NOTE:

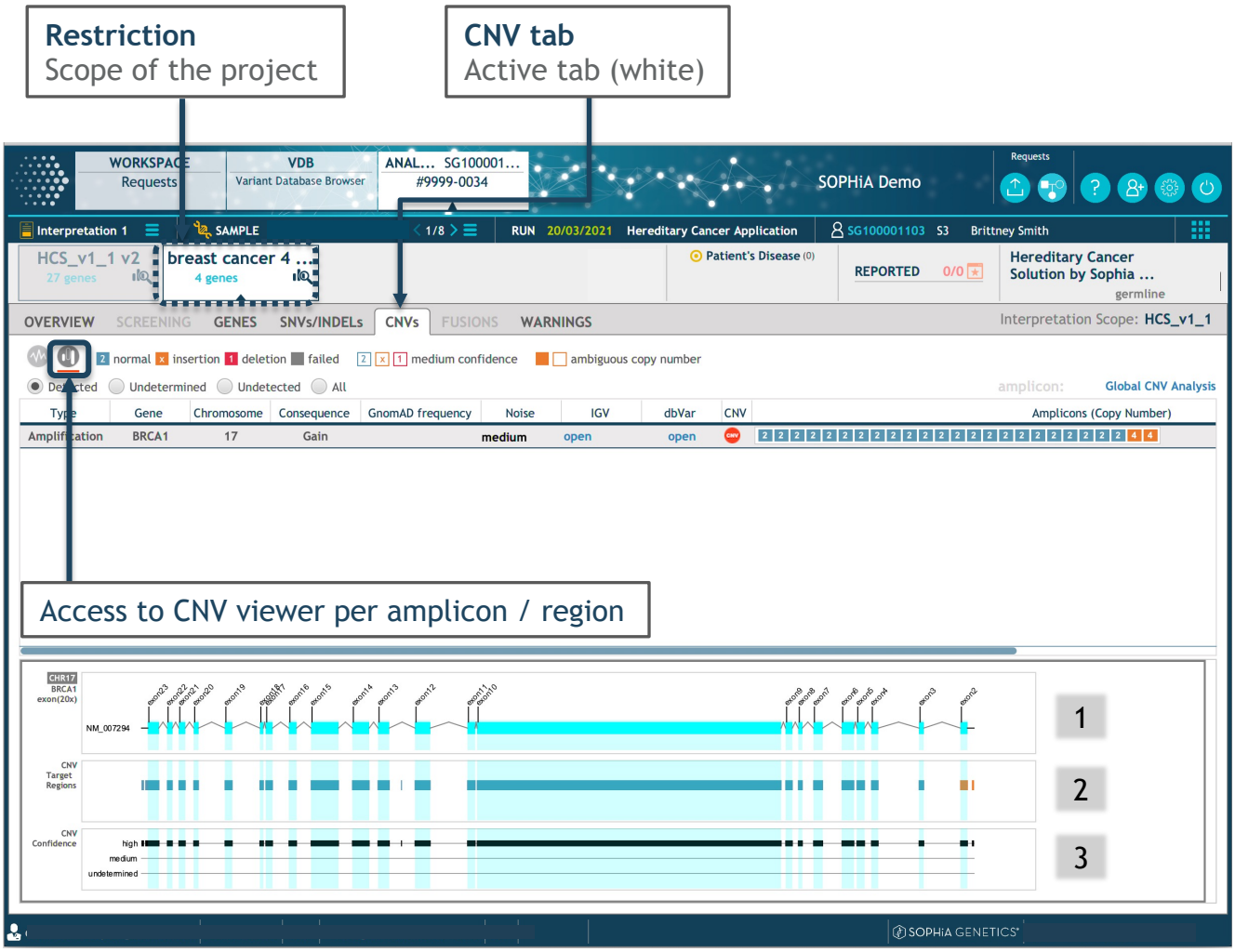
- **Analyses prior to pipeline version 5.5.68 or CE-IVD analyses:**

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.

7. CNV Analysis
7.1 Germline and liquid tumor applications
7.1.2 Gene viewer

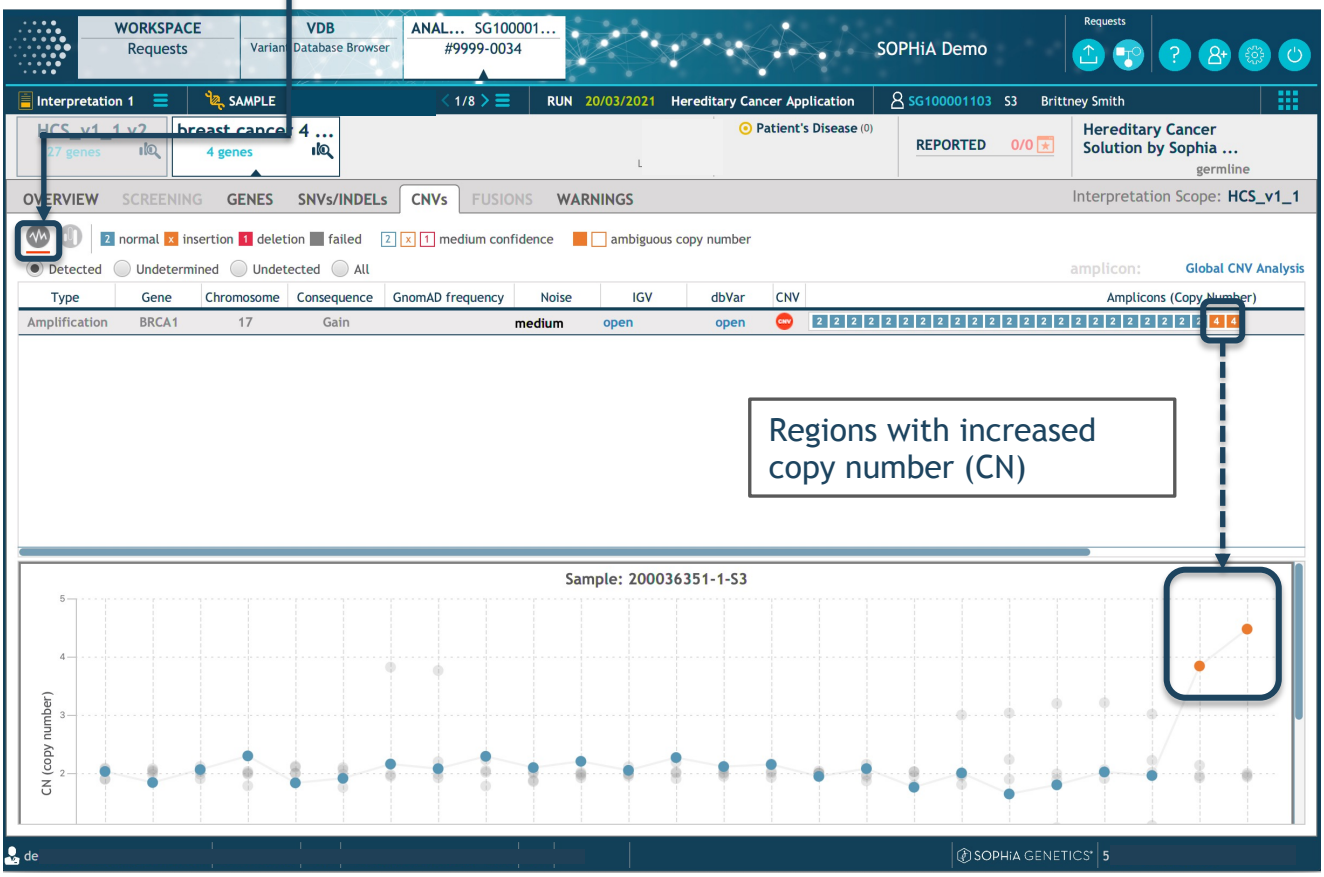


1	Exon view of the current gene (gene in bold)
2	Amplicons / regions of the application
3	Confidence level per region (high, medium or undetermined)

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)



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

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

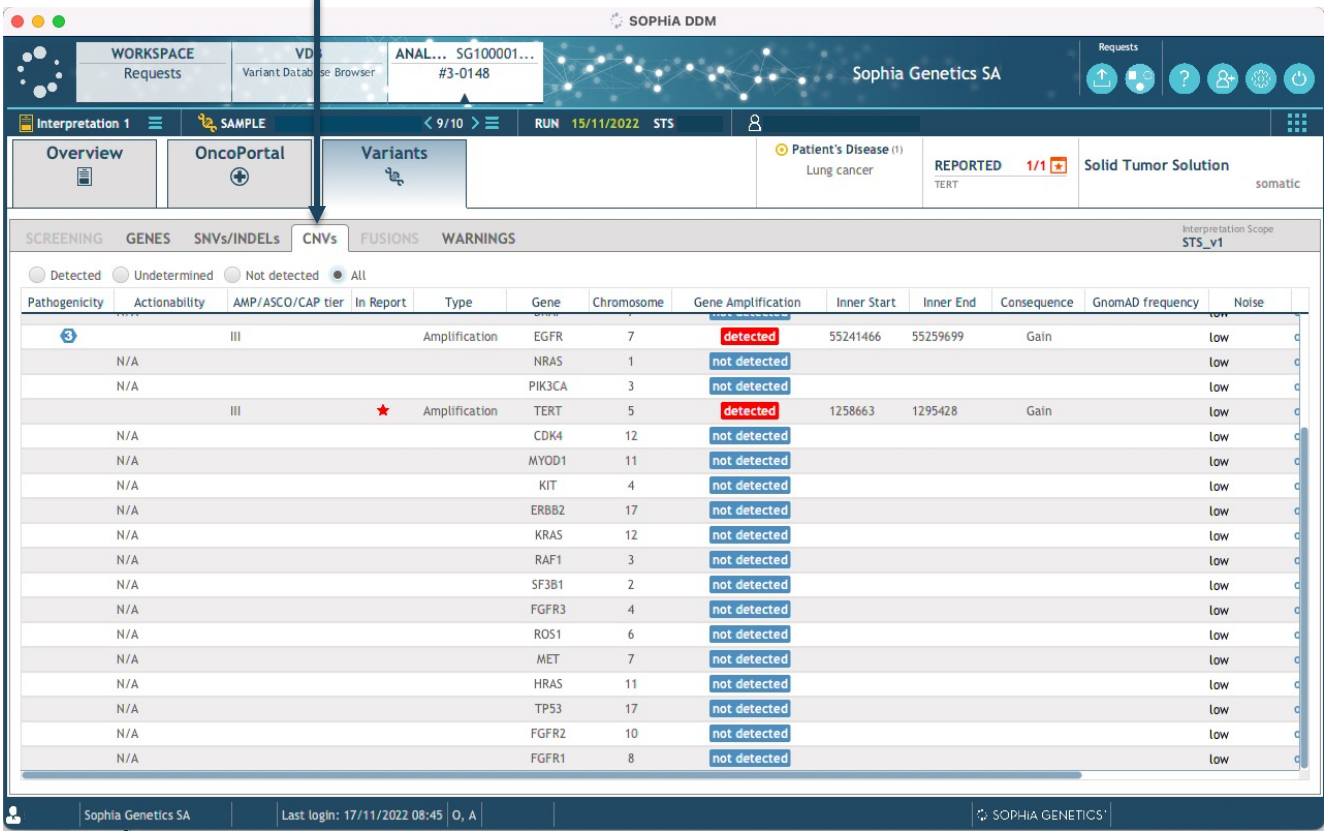
Deletion called with high confidence

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)

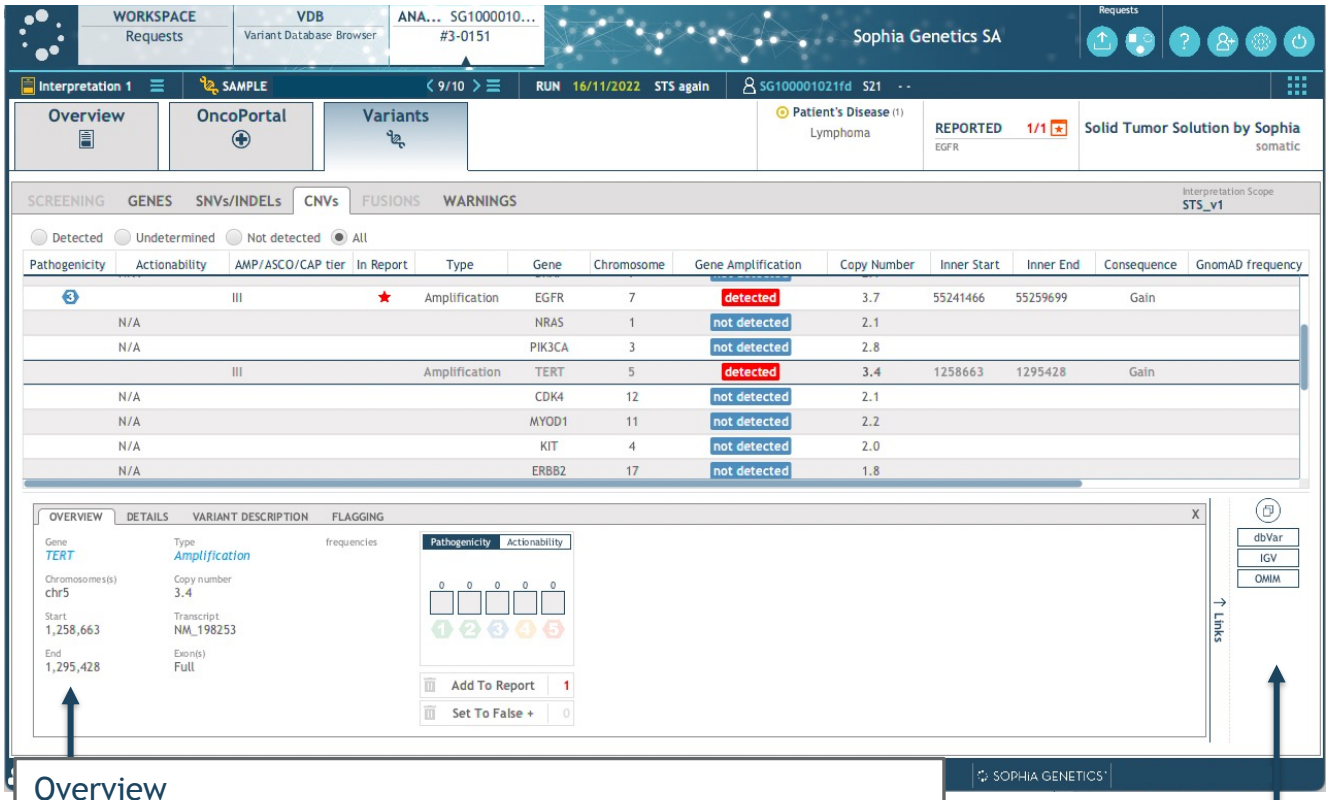


NOTE: The minimal resolution for gene amplification detection of the SOPHiA DDM™ solid tumor solutions is 3.25 copies (6 for high confidence level).

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.

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.

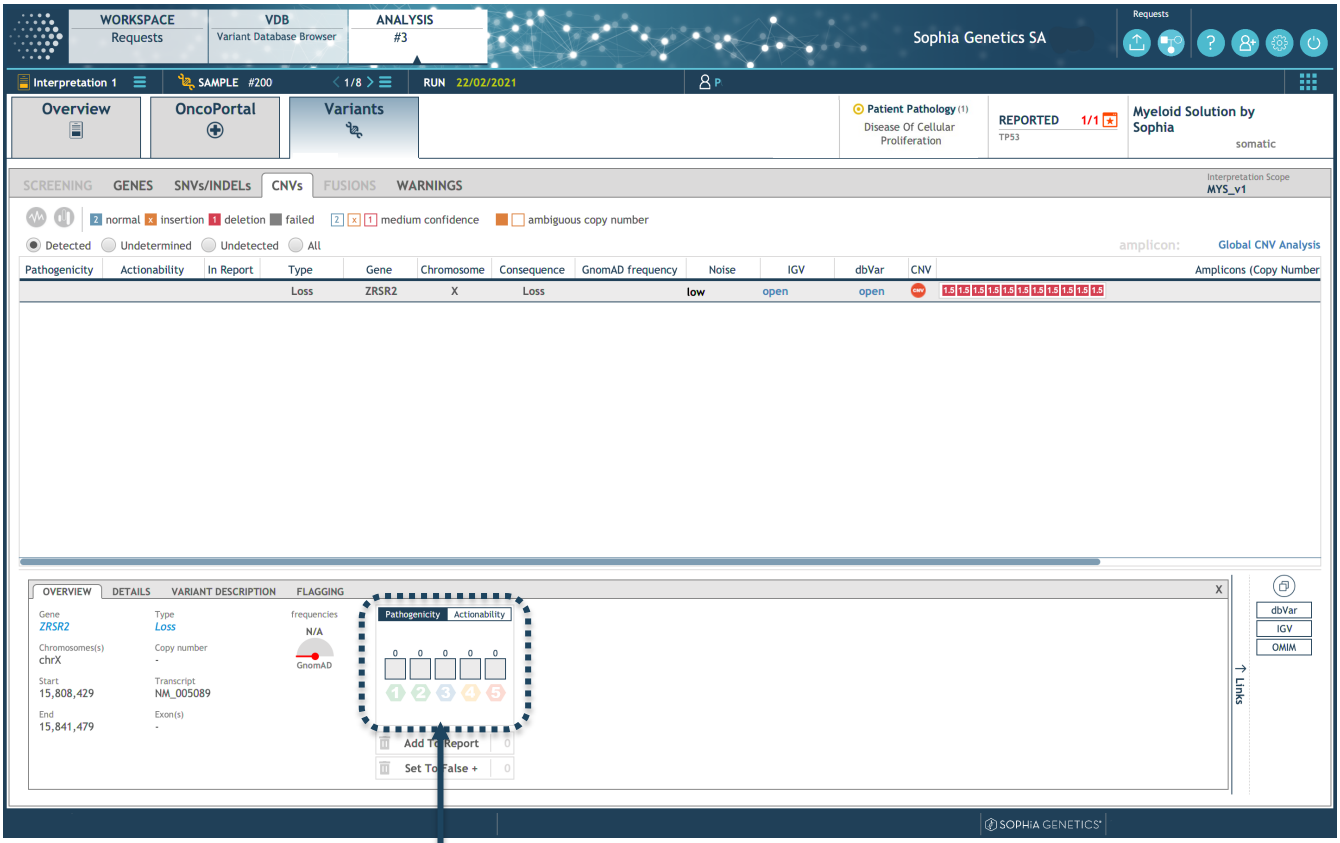


Overview
Information for the selected CNV:
- Gene, transcript, chromosome, positions
- Copy number
- Pathogenicity
- Actionability
- In Report Indicator
- False + indicator

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

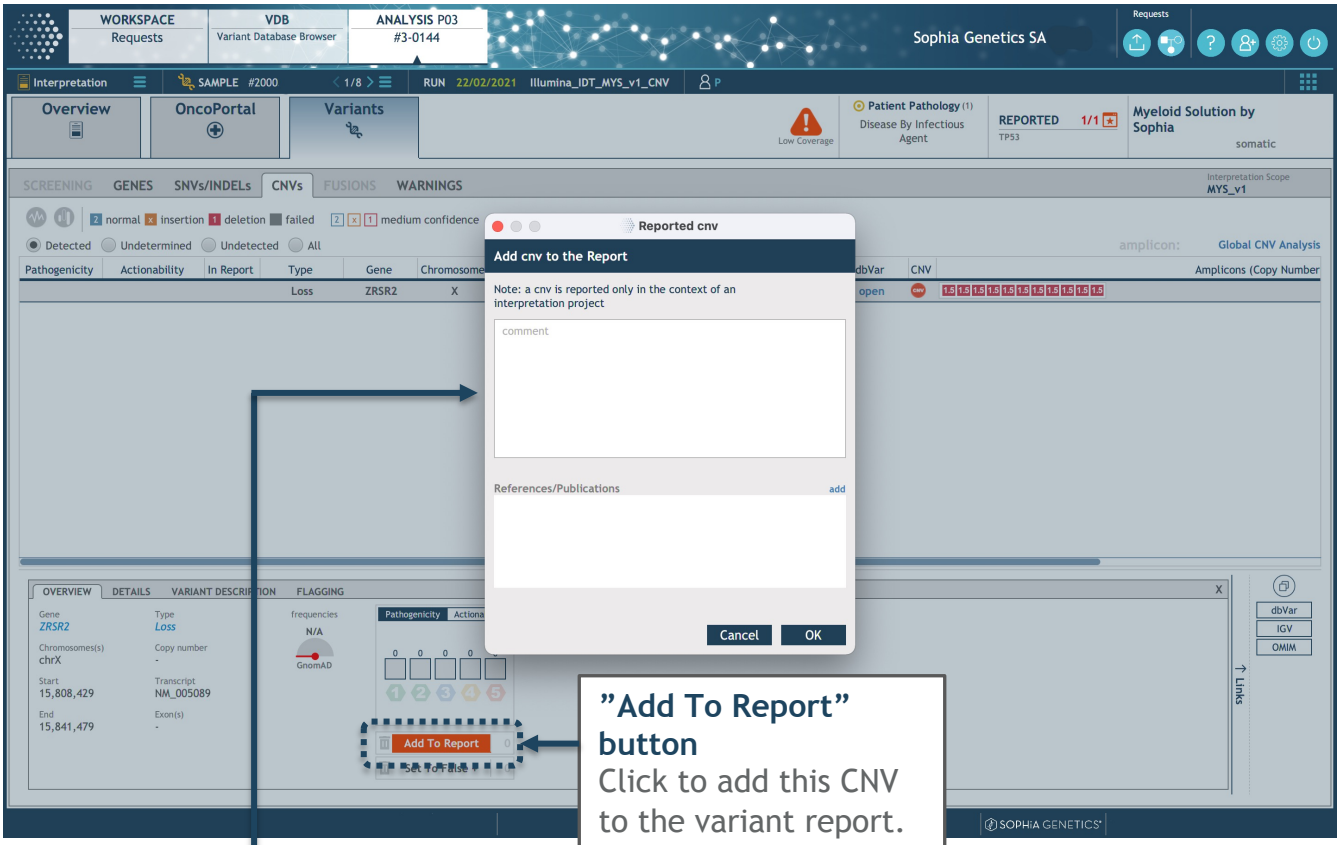
Links
Additional variant information in external sources

7. CNV Analysis
7.3 Somatic applications
7.3.1 Add pathogenicity flag



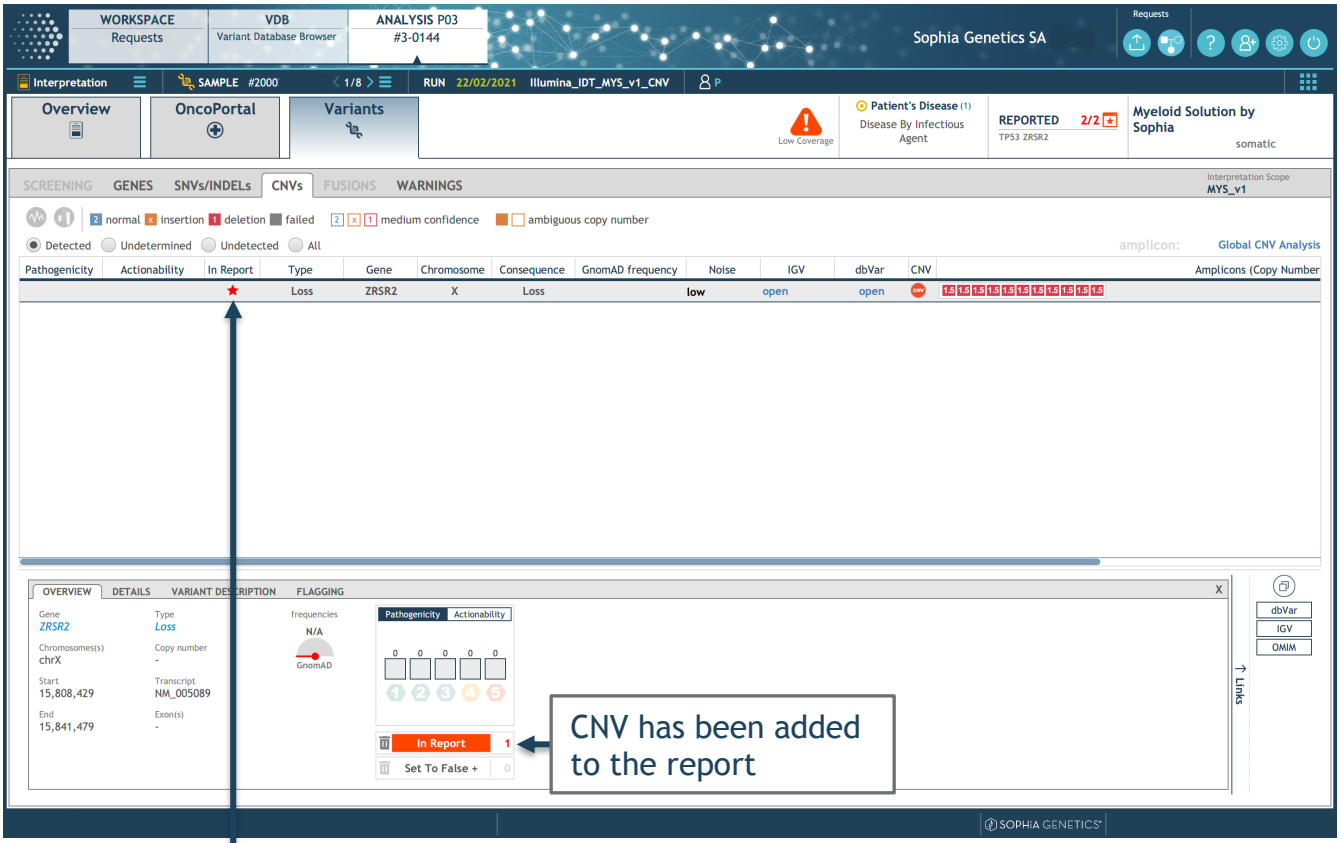
Pathogenicity flag distribution (community) and account pathogenicity flag
The numbers above the boxes indicate the number of community users having flagged the variant for each pathogenicity category. The colored numbers (1-5) indicate the pathogenicity level of the variant in your account.

7. CNV Analysis
7.3 Somatic applications
7.3.2 Add to report (1)



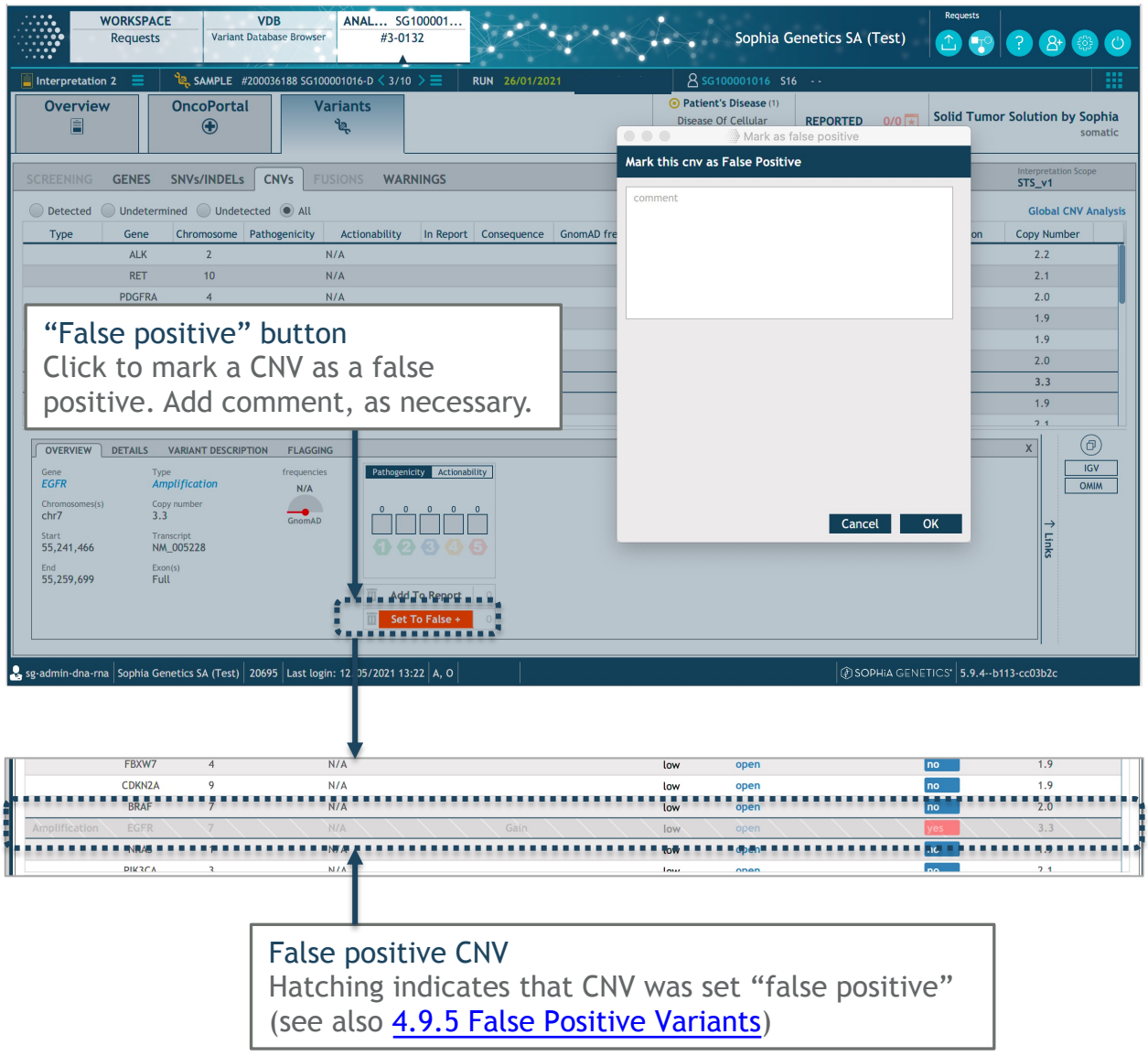
Reported CNV
Complete the sections with relevant information, such as:
- Comment that you would like to add to the report
- References/Publications

7. CNV Analysis
7.3 Somatic applications
7.3.2 Add to report (2)



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

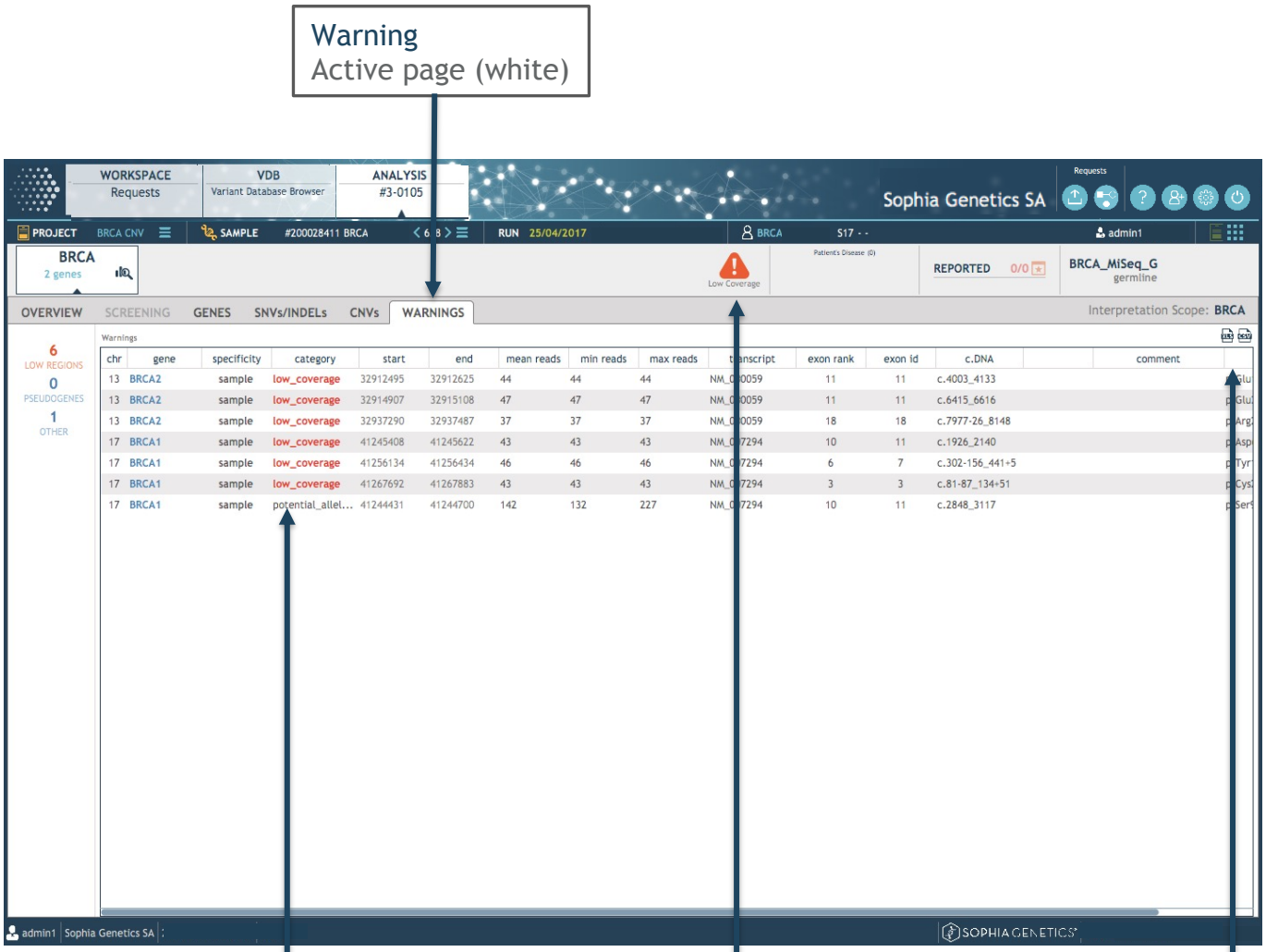
7. CNV Analysis
7.3 Somatic applications
7.3.3 Mark as false positive



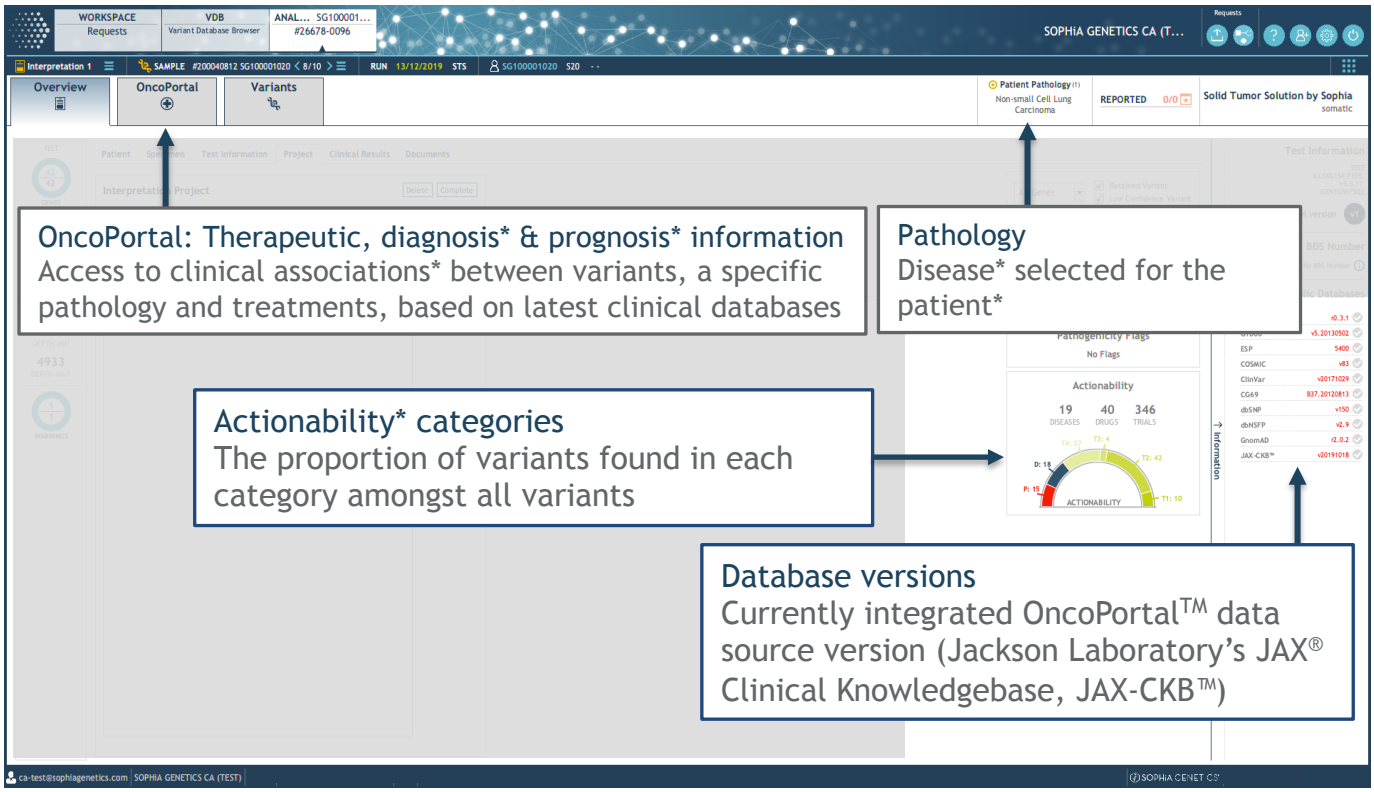
"False positive" button
Click to mark a CNV as a false positive. Add comment, as necessary.

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)
WORKSPACE
Requests
VDB
Variant Database Browser
ANALYSIS
#3-0105
Sophia Genetics SA
PROJECT BRCA CNV
SAMPLE #200028411 BRCA
RUN 25/04/2017
BRCA
admin1
BRCA
2 genes
Low Coverage
REPORTED 0/0
BRCA_MiSeq_G
germline
OVERVIEW
SCREENING
GENES
SNVs/INDELs
CNVs
WARNINGS
Interpretation Scope: BRCA
6
LOW REGIONS
0
PSEUDOGENES
1
OTHER
Warnings
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_000059 11 11 c.4003_4133
13 BRCA2 sample low_coverage 32914907 32915108 47 47 47 NM_000059 11 11 c.6415_6616
13 BRCA2 sample low_coverage 32937290 32937487 37 37 37 NM_000059 18 18 c.7977-26_8148
17 BRCA1 sample low_coverage 41245408 41245622 43 43 43 NM_007294 10 11 c.1926_2140
17 BRCA1 sample low_coverage 41256134 41256434 46 46 46 NM_007294 6 7 c.302-156_441+5
17 BRCA1 sample low_coverage 41267692 41267883 43 43 43 NM_007294 3 3 c.81-87_134+51
17 BRCA1 sample potential_allel... 41244431 41244700 142 132 227 NM_007294 10 11 c.2848_3117
admin1 Sophia Genetics SA
SOPHIA GENETICS
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

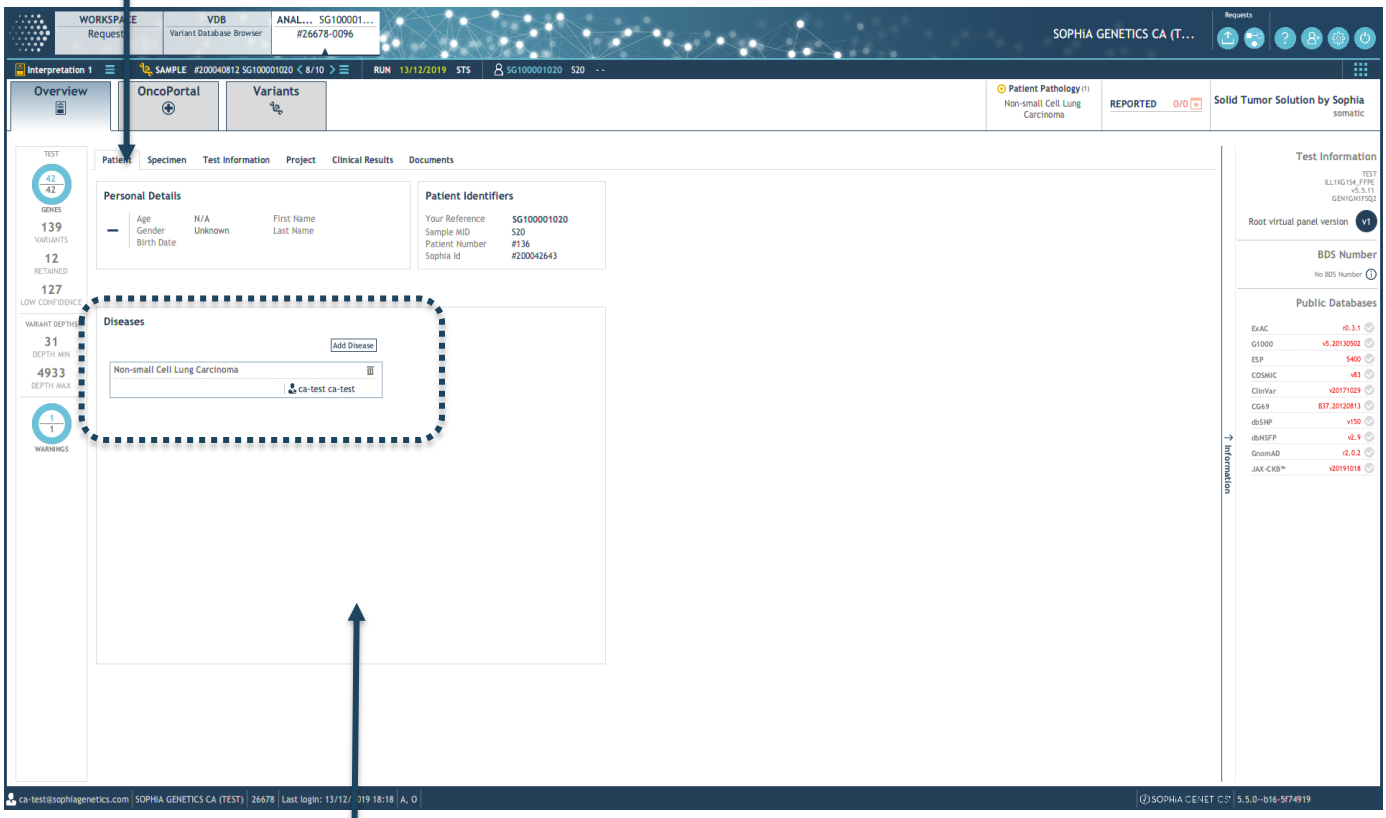


Actionability*
Quick overview on the actionable variants with related medical information

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



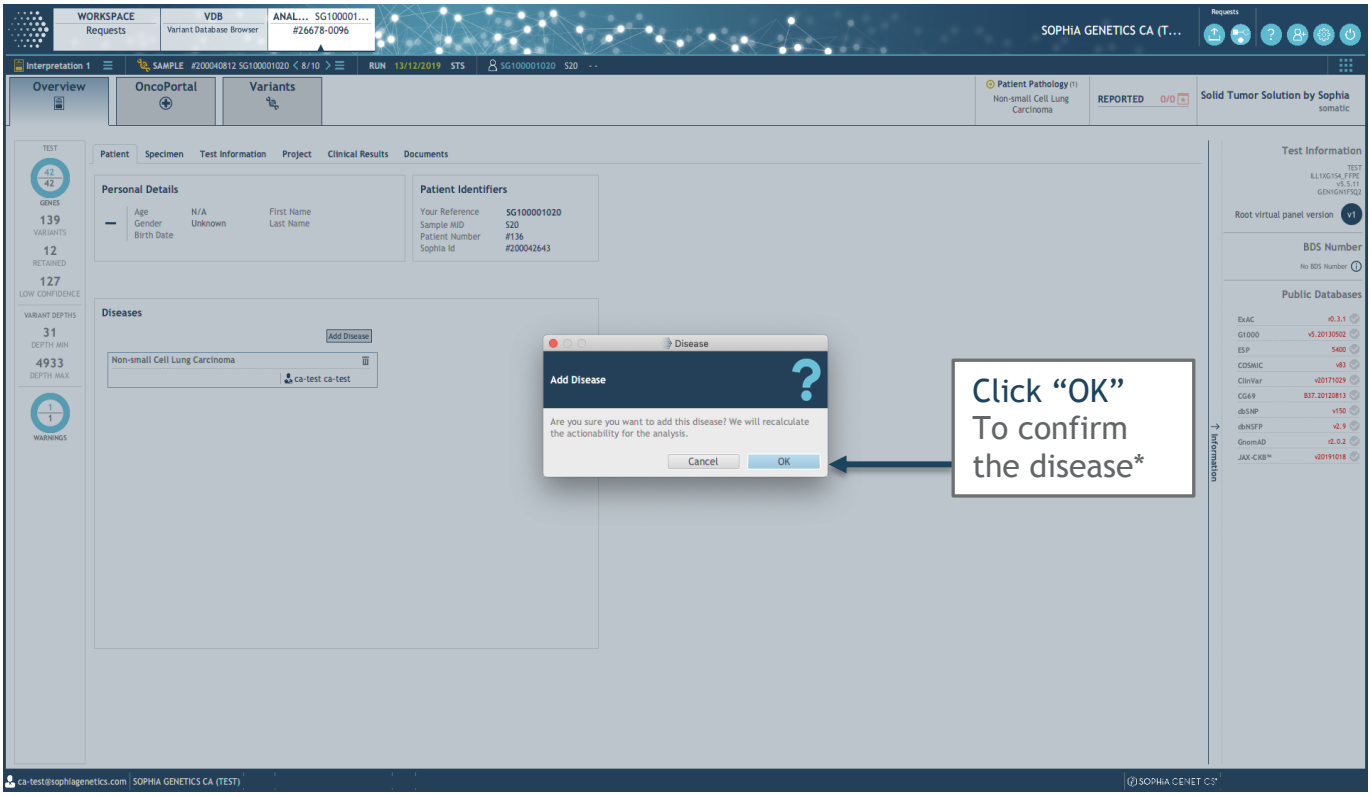
Disease*

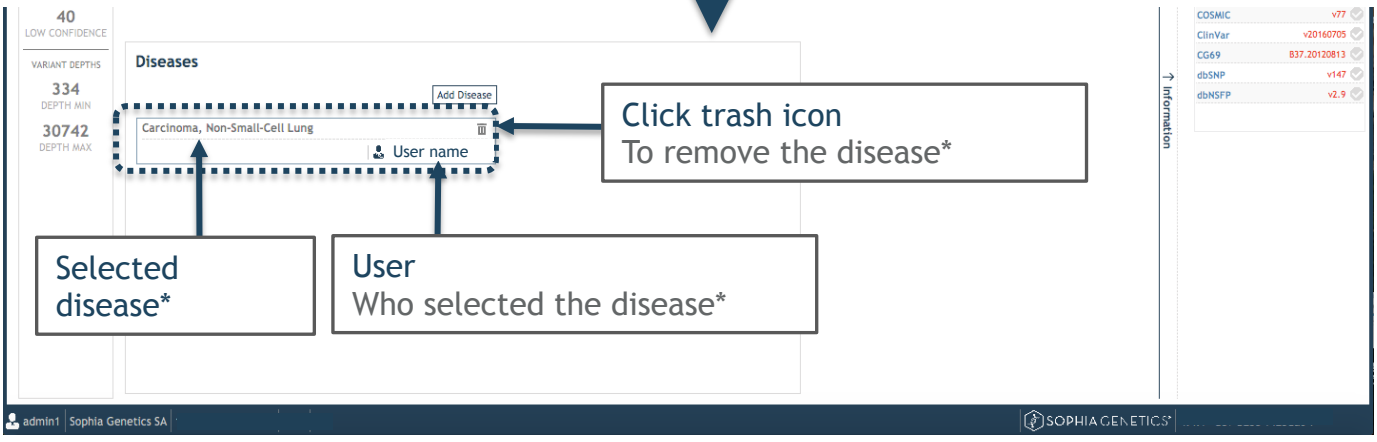
Users with access to the OncoPortal™:

- 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*.

9. OncoPortal™
9.2 Disease* Selection (2)

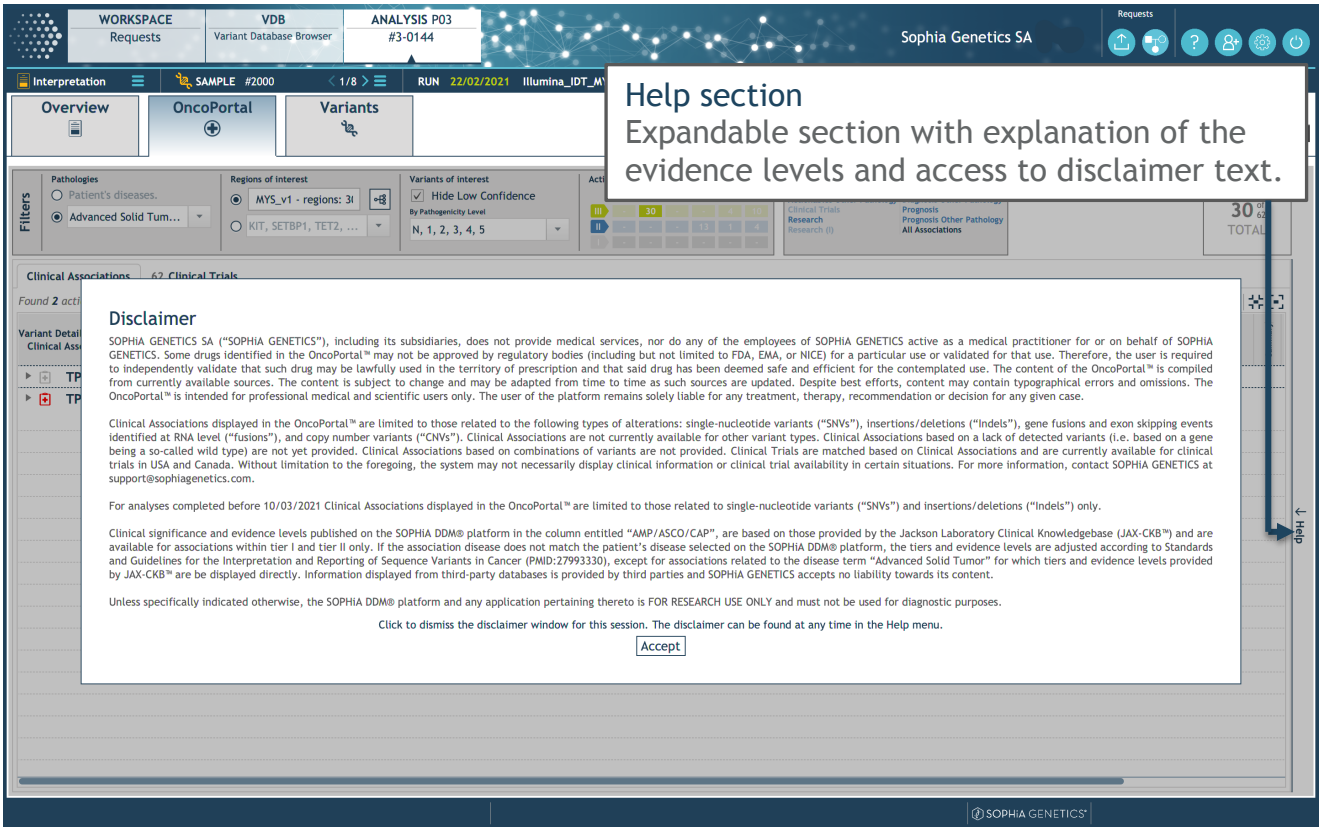




9. OncoPortal™

9.3 Actionability* – Diagnosis* – Prognosis*

9.3.1 Overview (1)



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

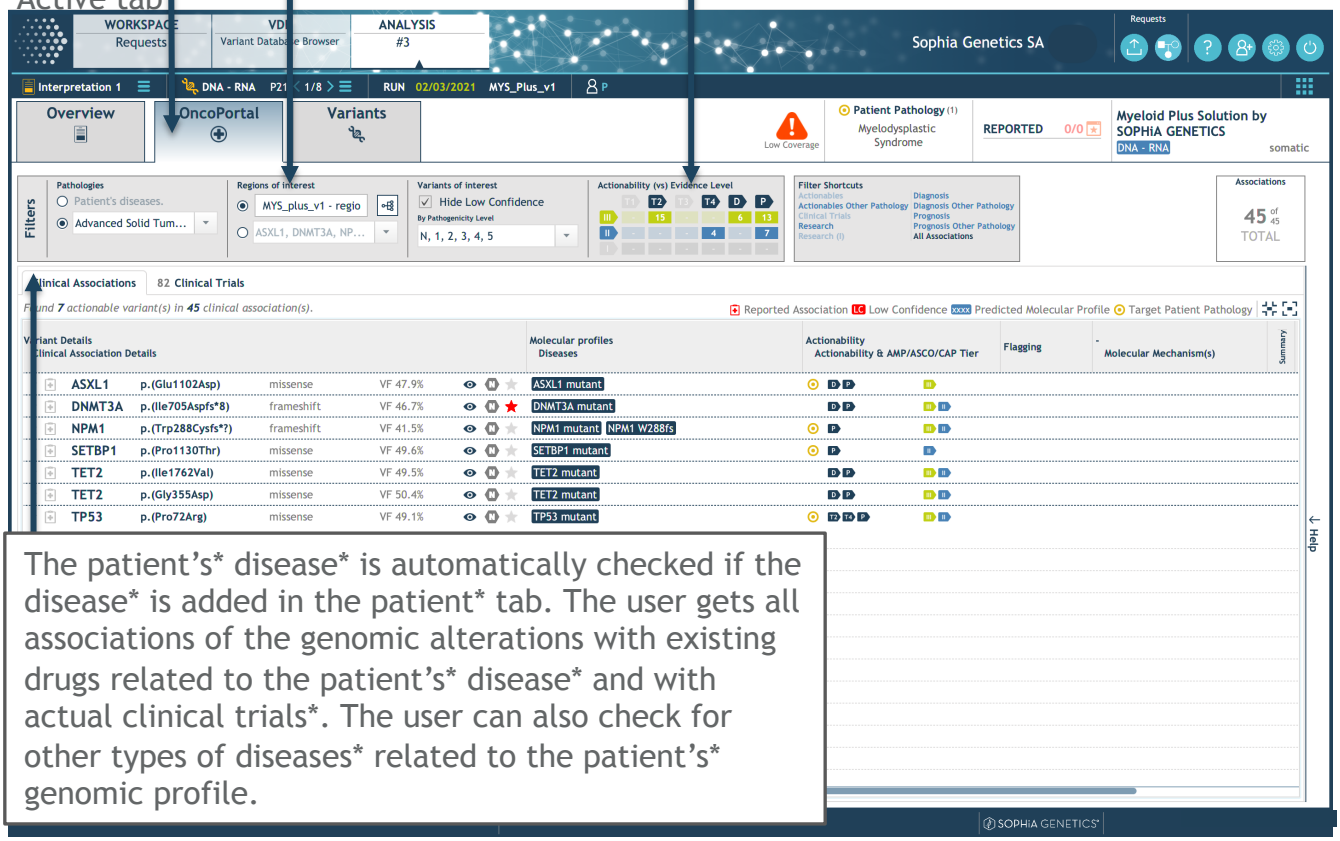
9. OncoPortal™
9.3 Actionability* – Diagnosis* – Prognosis*
9.3.1 Overview (2)

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)

Active tab



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™

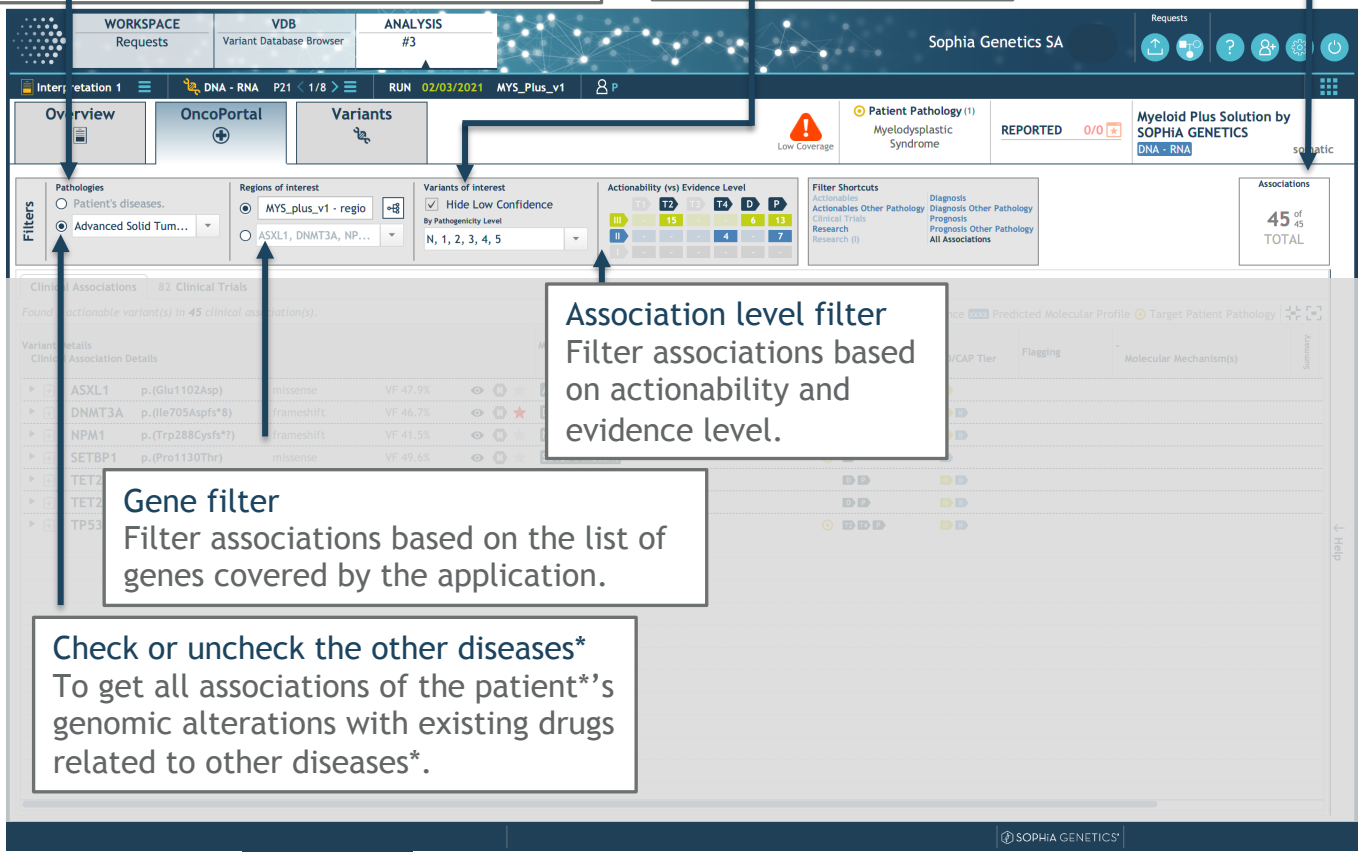
9.3 Actionability* – Diagnosis* – Prognosis*

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.*



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 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 II

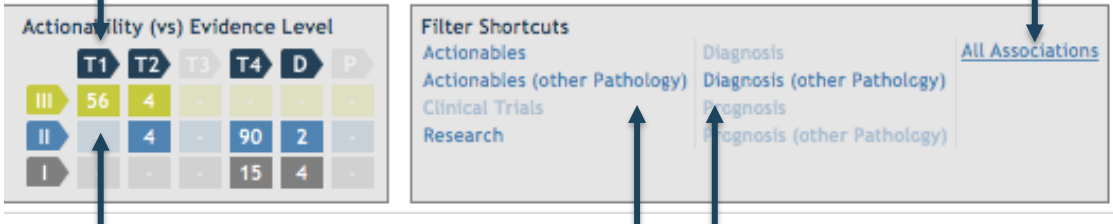
The clinical association* has agreements from different sources but is not approved by any regulatory agency or clinical society of international standing.
The confidence level is intermediate

Level I 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.



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

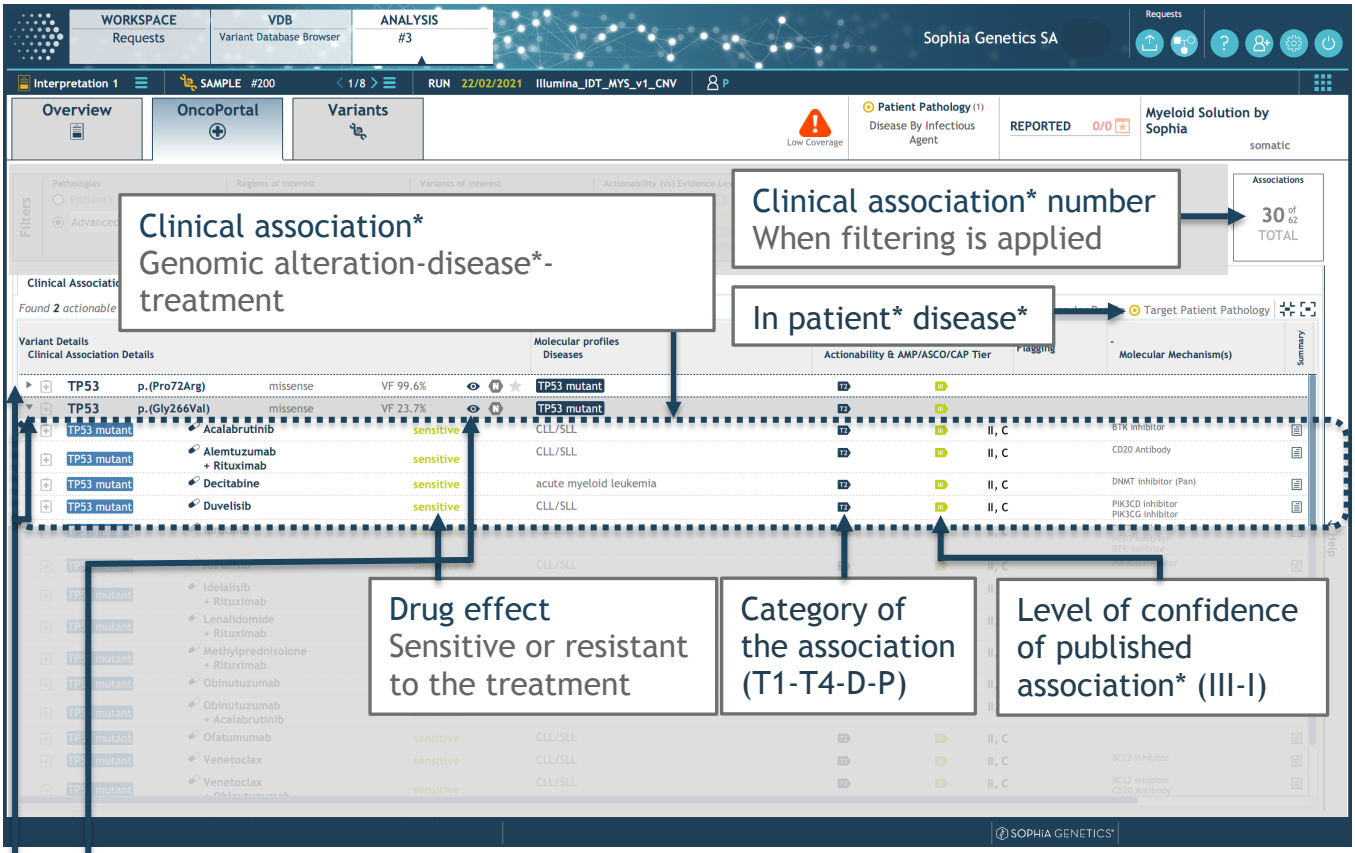
T3 - T3: Drugs in clinical trials* phase 1 to phase 4

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

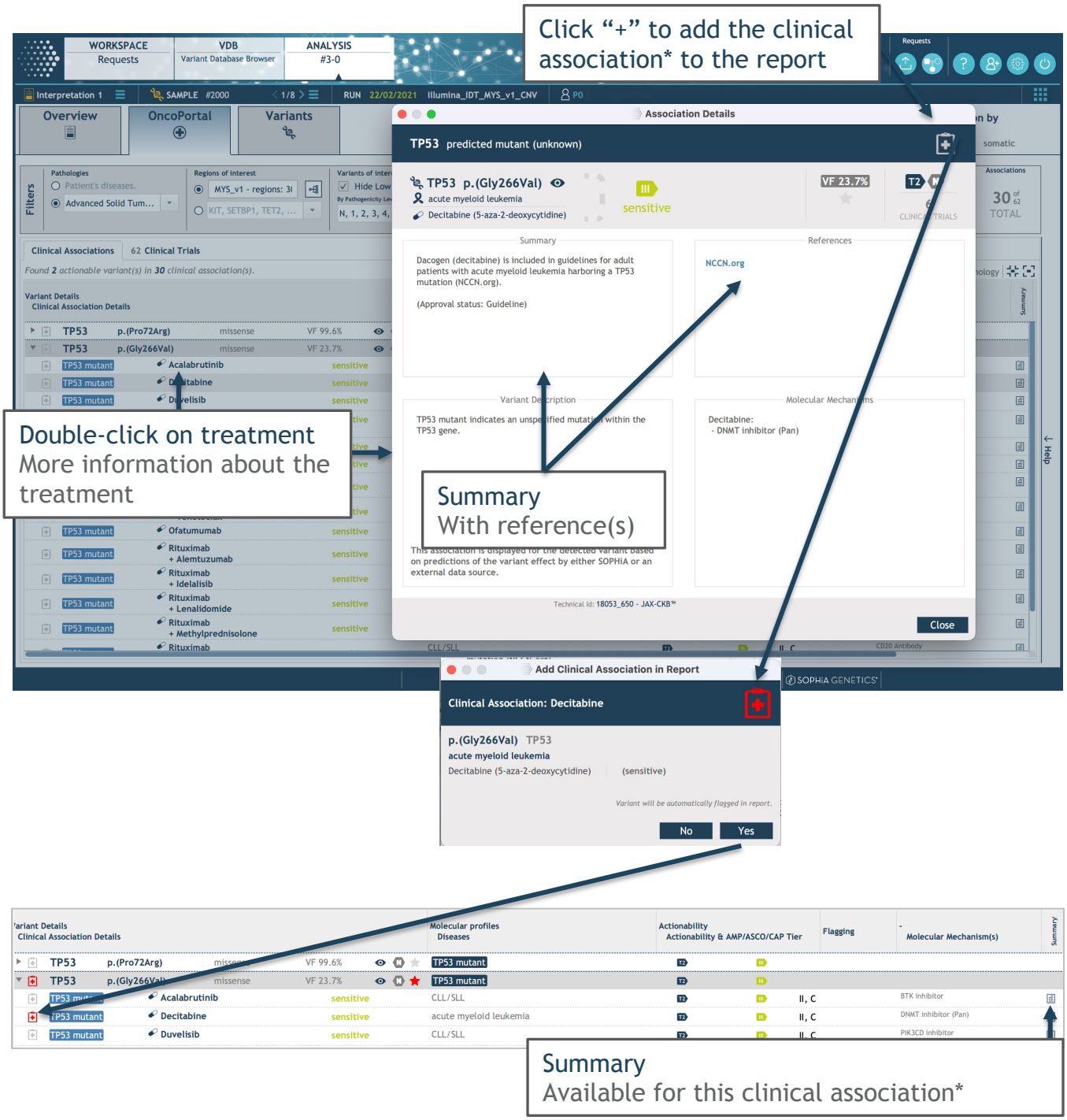
Click ▼ for variant of interest:
Information about the diseases* associated with the genomic profile of the patient*

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)



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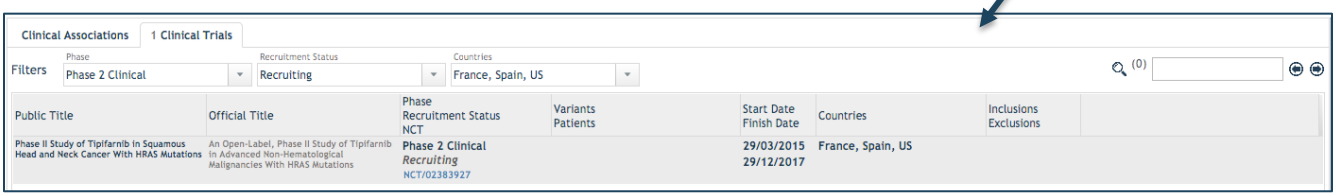
** Please refer to the Disclaimer (page 3).*
Research Use Only. Not for use in diagnostic procedures.

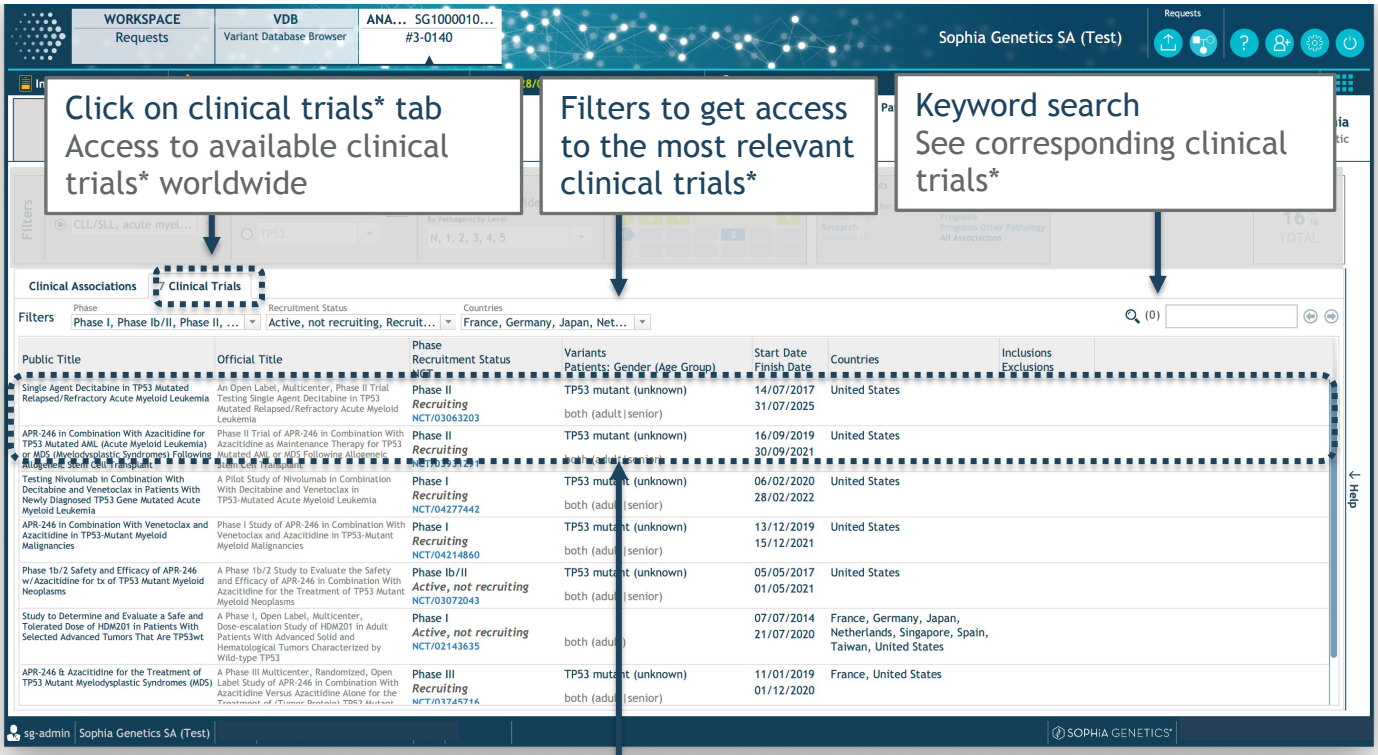
9. OncoPortal™
9.3 Actionability* – Diagnosis* – Prognosis*
9.3.5 Clinical Trials* (1)

Access to clinical trials*:
1) Through a chosen clinical association*
2) Through the clinical trials* tab



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

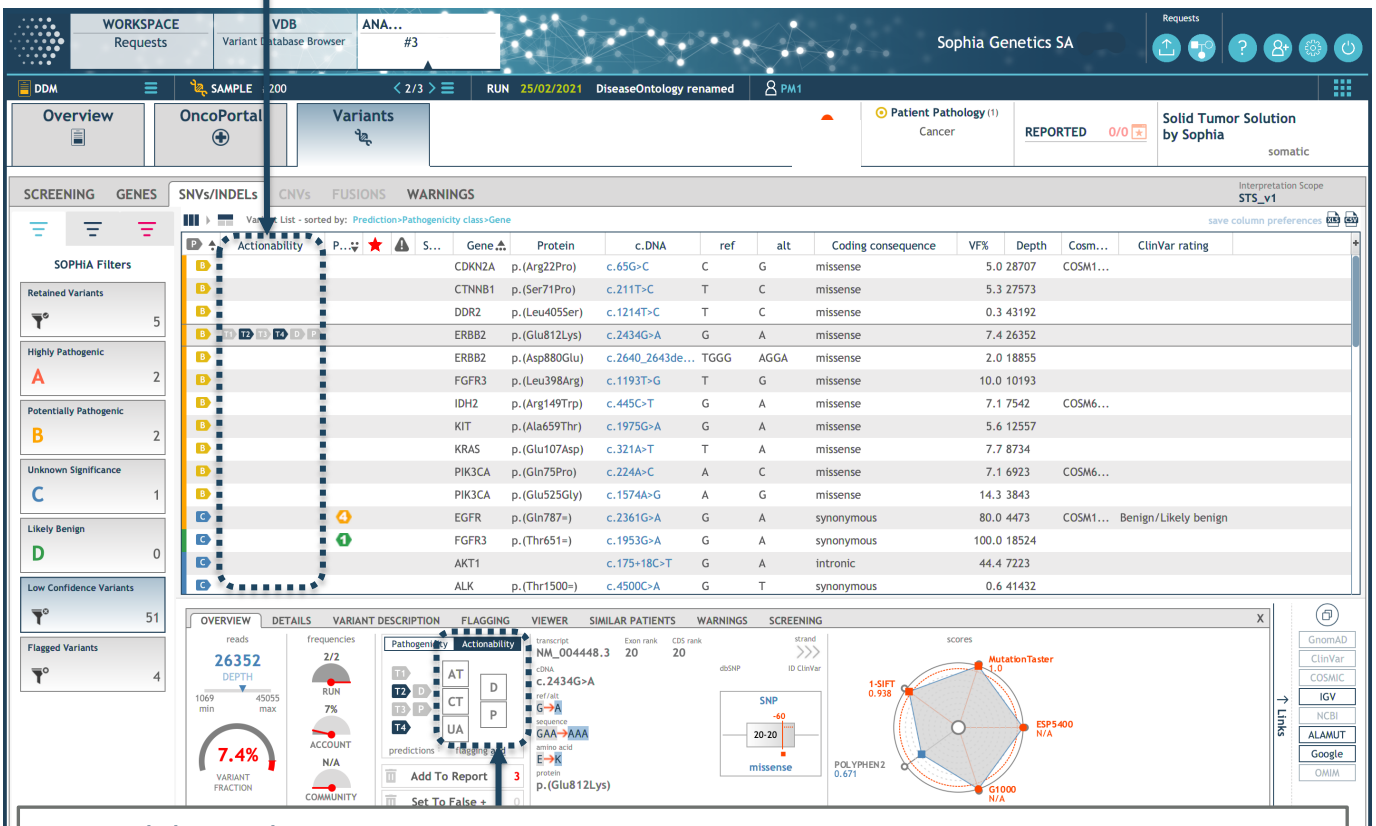


Details for each clinical trial*:
- Public and official titles of the clinical trial*
- Phase and recruitment status
- Genomic alteration status
- Available countries
- Inclusion/exclusion
- End dates
- NCT number if available

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



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

9. OncoPortal™

9.3 Actionability* – Diagnosis* – Prognosis*

9.3.6 User Clinical Associations*

9.3.6.1 Creation of a Clinical Association* (1)

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

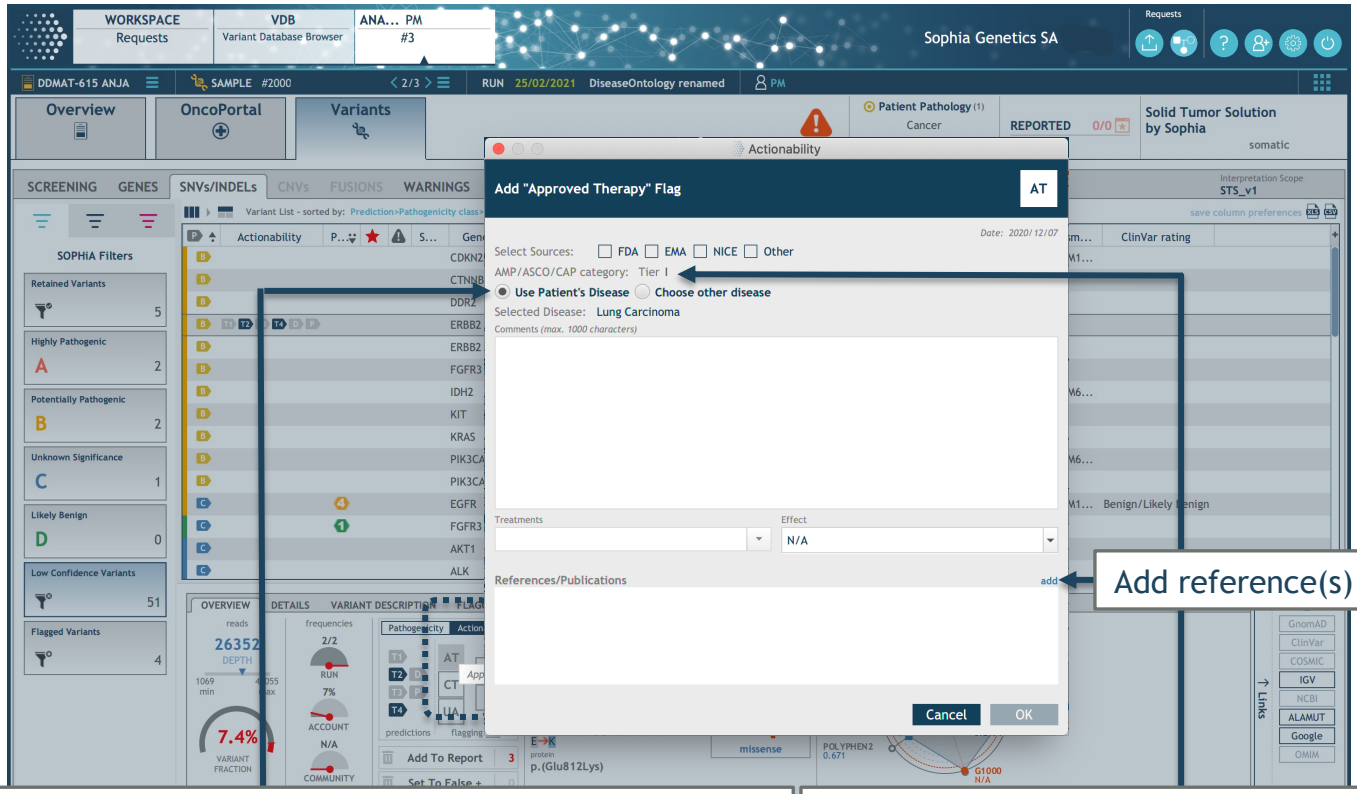
NOTE: Association flags are shared between Interpretation Projects* of the same sample.

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).

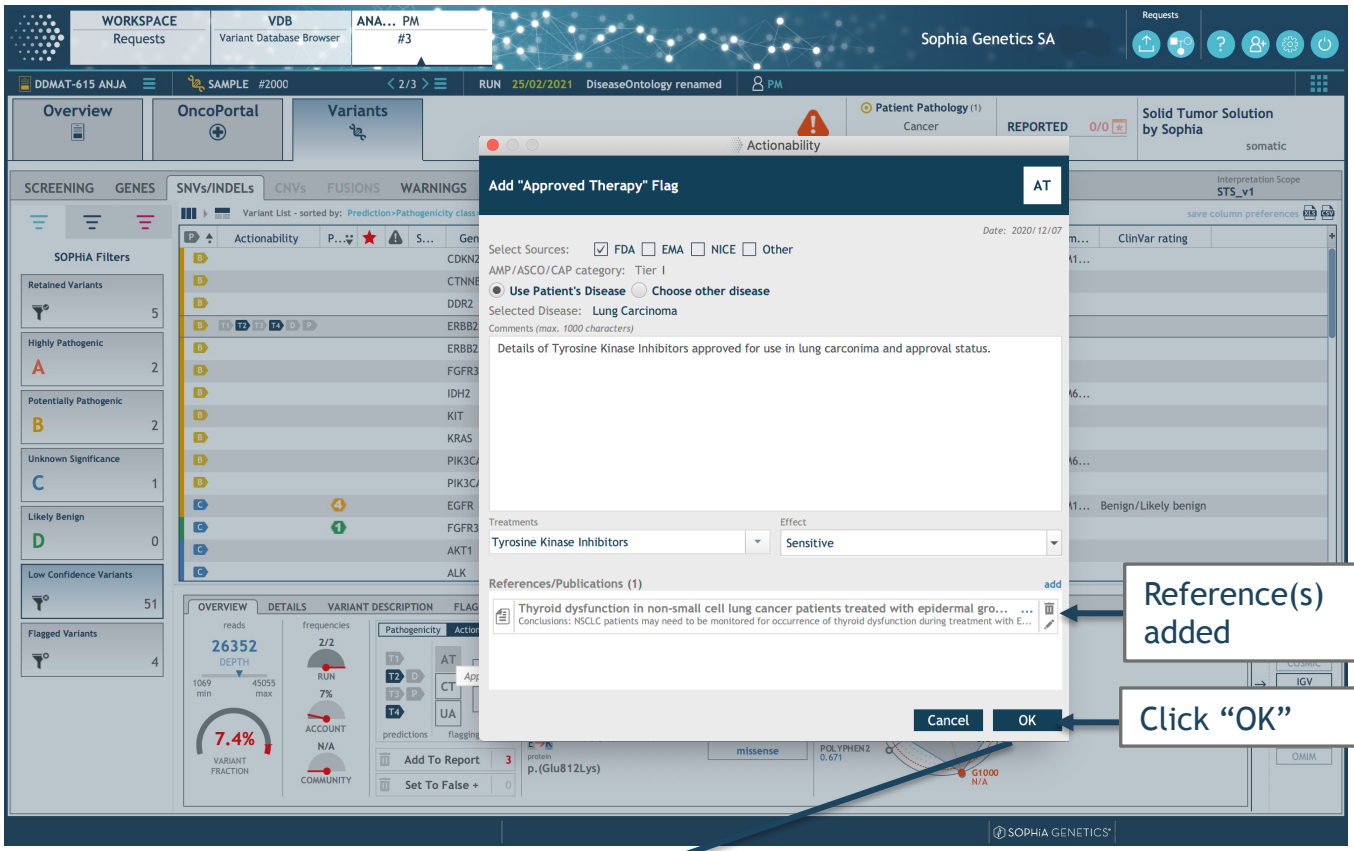
NOTE: Information provided will be displayed in the OncoPortal™ tab and will be available to add to the report. Providing accurate information is therefore important.

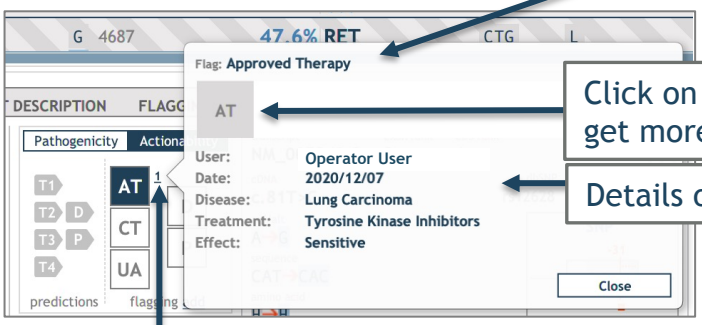
9. OncoPortal™

9.3 Actionability* – Diagnosis* – Prognosis*

9.3.6 User Clinical Associations*

9.3.6.1 Creation of a Clinical Association* (3)





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** Please refer to the Disclaimer (page 3).*
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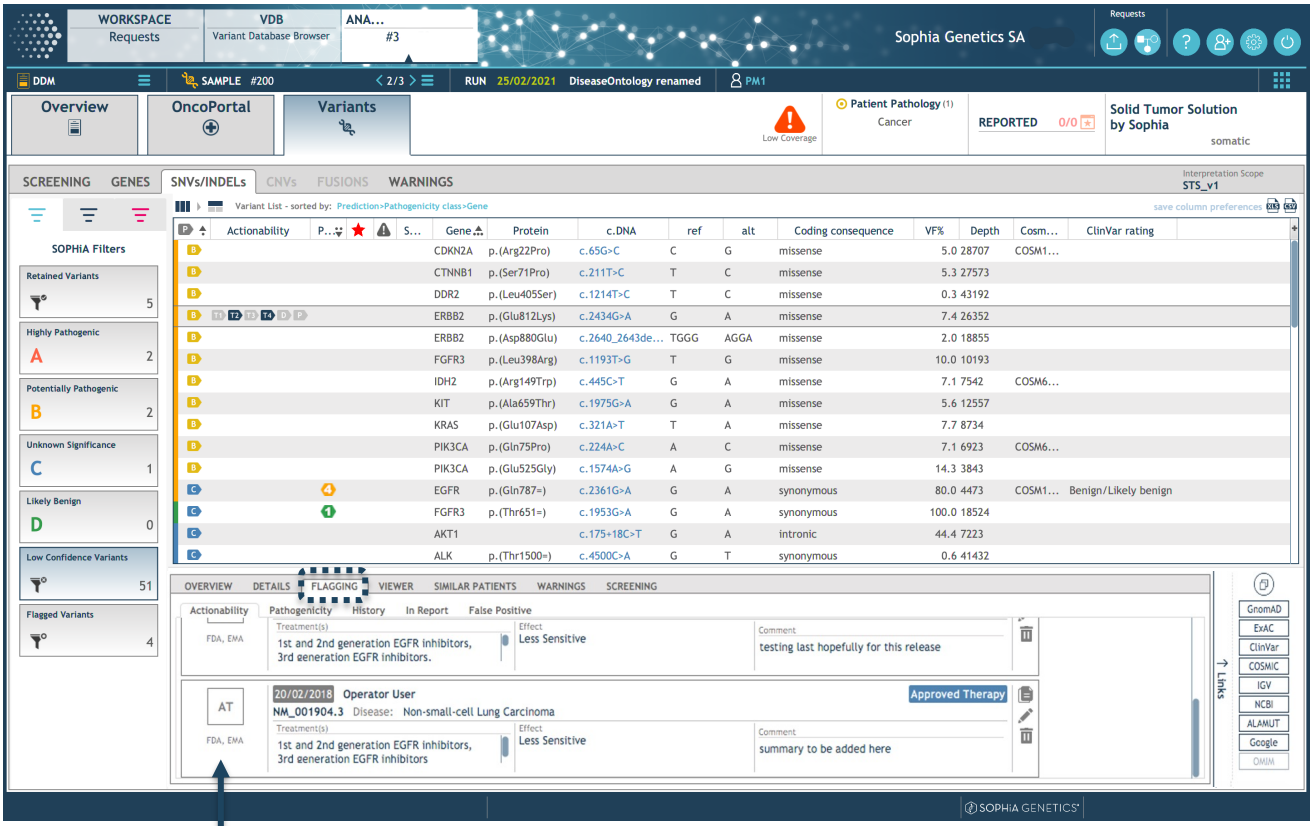
9. OncoPortal™

9.3 Actionability* – Diagnosis* – Prognosis*

9.3.6 User Clinical Associations*

9.3.6.2 Traceability of a Clinical Association* Created by a User



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.

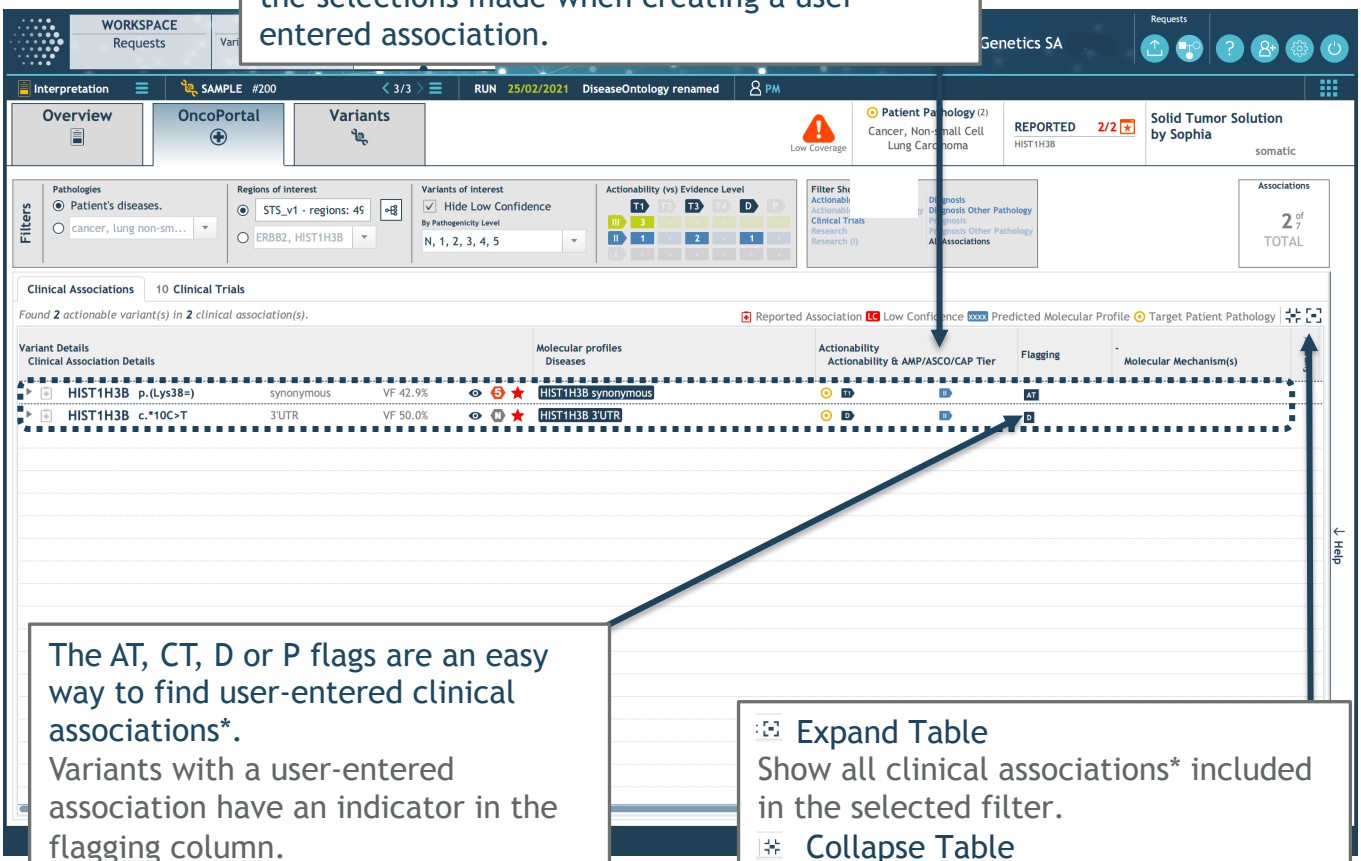
9. OncoPortal™

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 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.

Expand Table
Show all clinical associations* included in the selected filter.

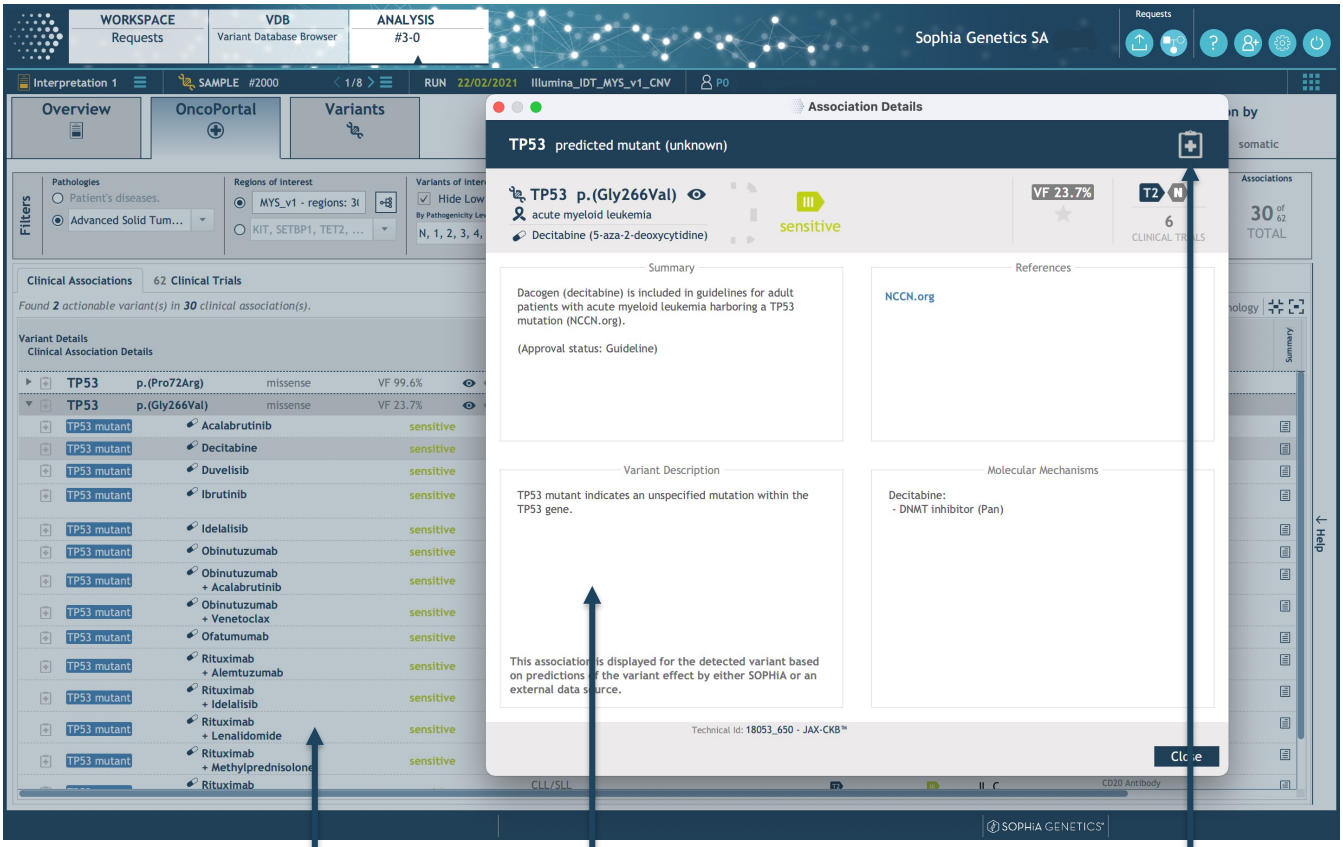
Collapse Table
Quick overview of the number and type of variants associated with clinical associations*.

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



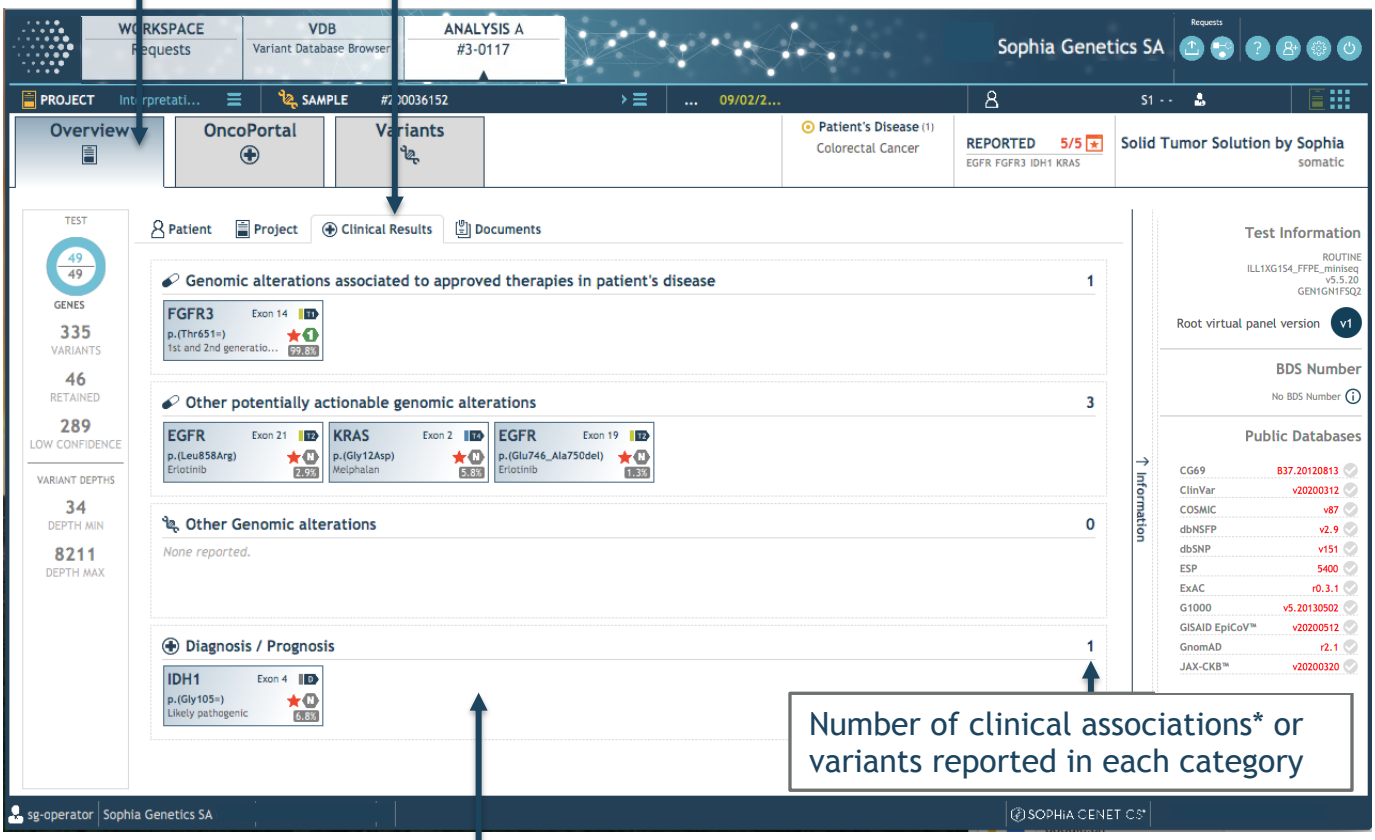
Double-click on the user clinical association* of interest:
All of the information previously provided is displayed. This information are also displayed in the report.

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

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)

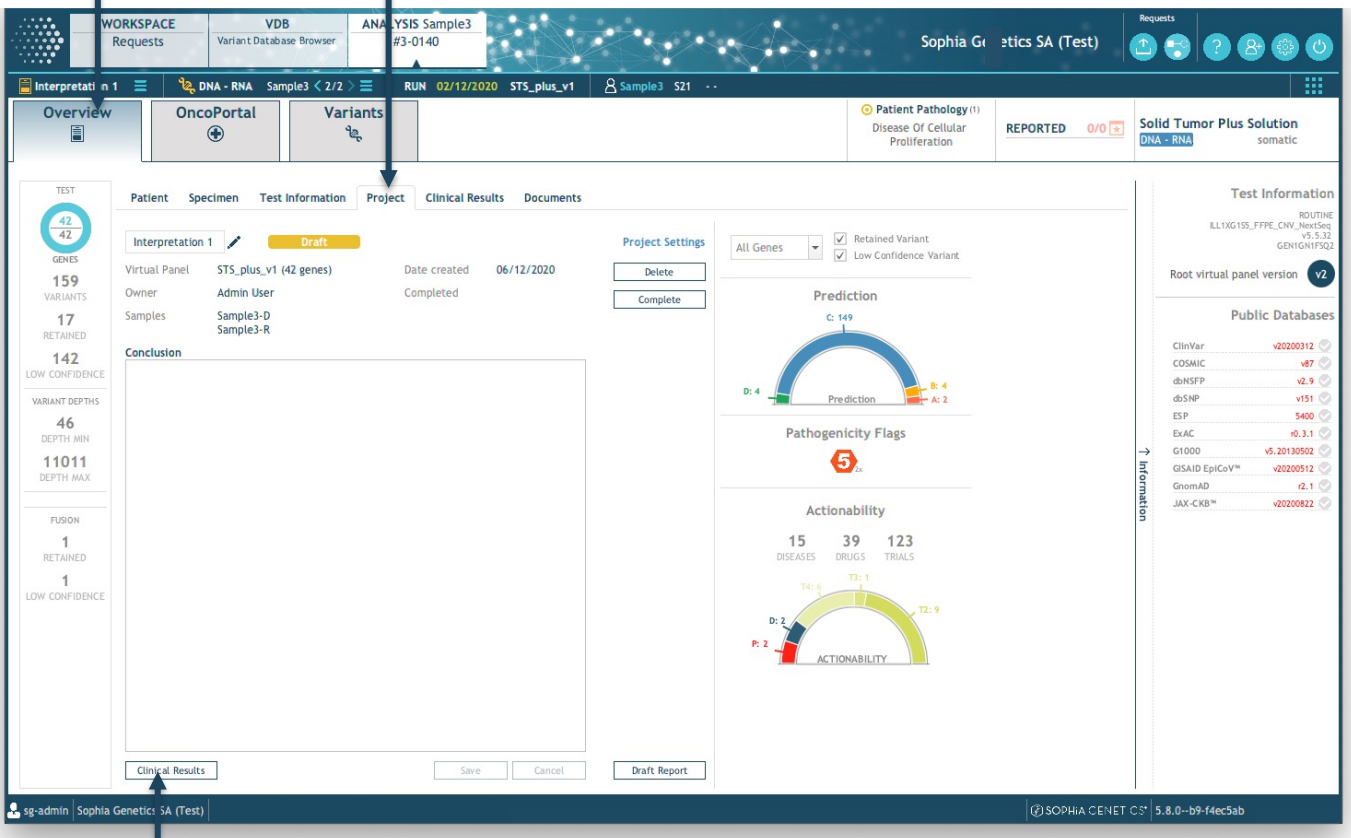
9. OncoPortal™

9.3 Actionability* – Diagnosis* – Prognosis*

9.3.8 Automatically Generated Conclusions (1)

Overview tab
Active

Project tab
Active



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

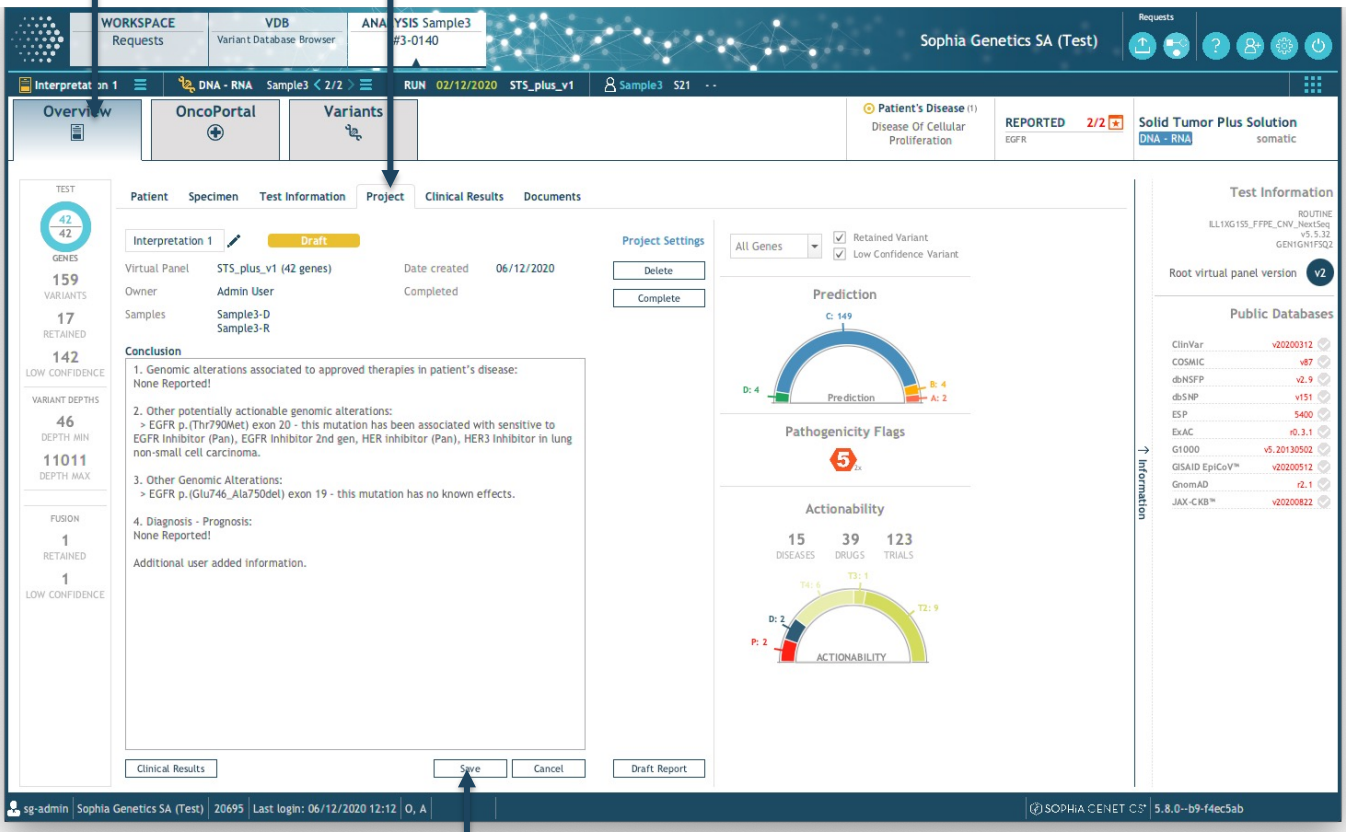
9. OncoPortal™

9.3 Actionability* – Diagnosis* – Prognosis*

9.3.8 Automatically Generated Conclusions (2)

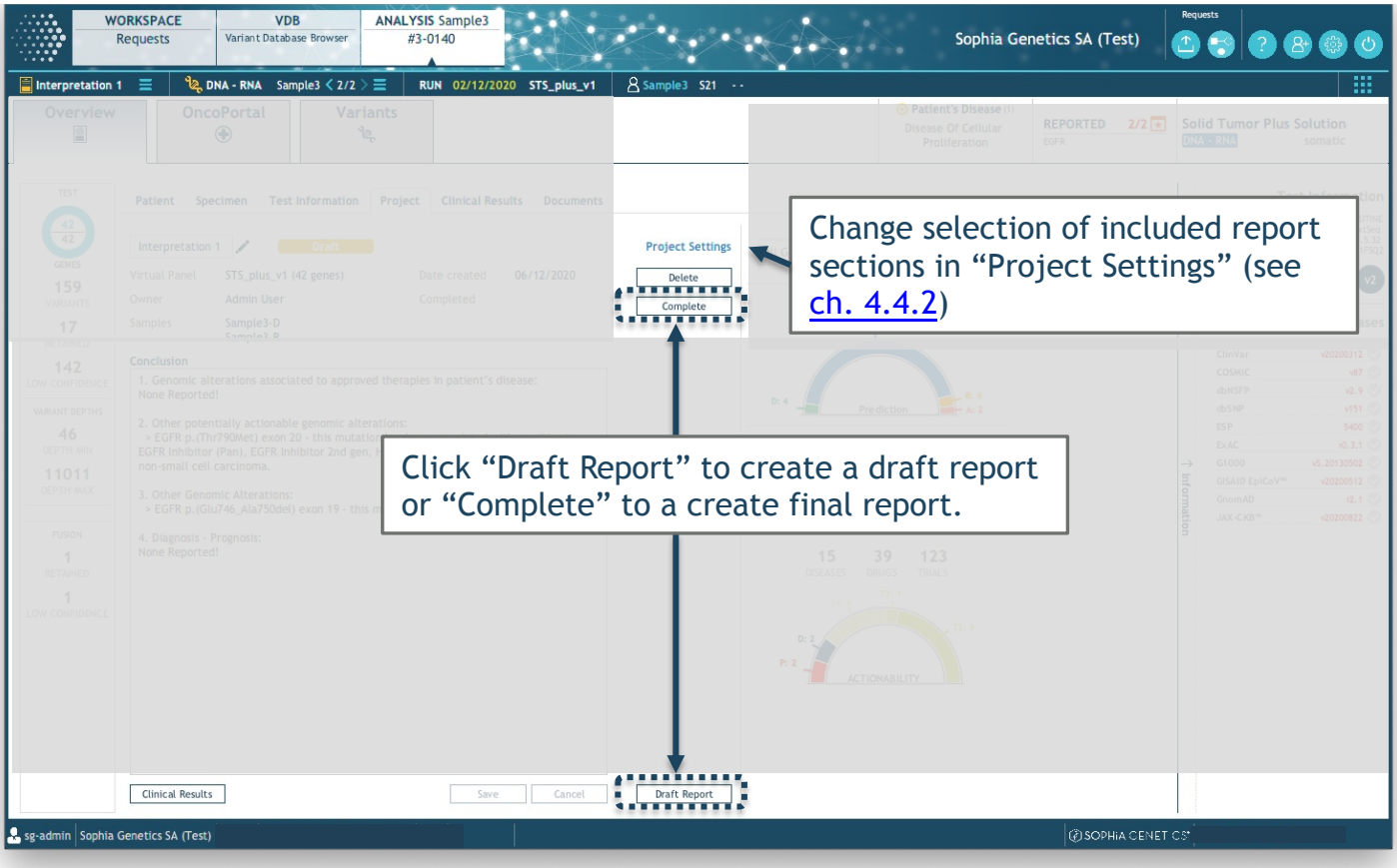
Overview tab
Active

Project tab
Active



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



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

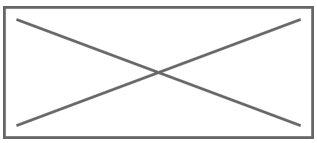
9. OncoPortal™
9.4 Somatic Report
9.4.2 Header

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

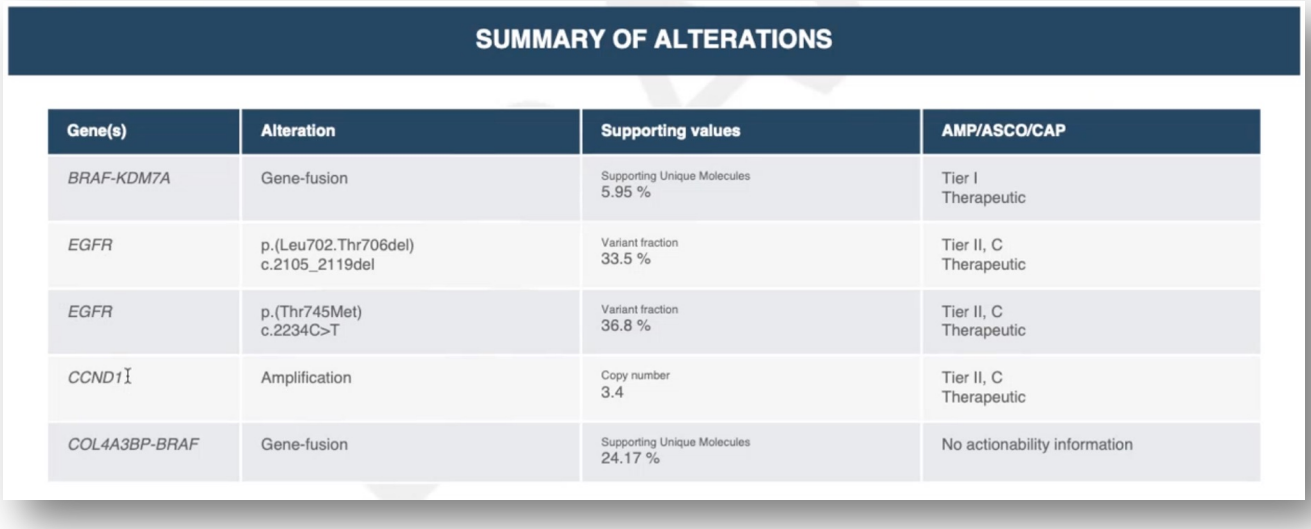
Analysis
Analysis ID: 388248
MID: S17
Run date: 2020/09/16
Run name: upload
Sequencer: Illumina MiniSeq

Medical history

49 year old female with new diagnosis of lung adenocarcinoma

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)

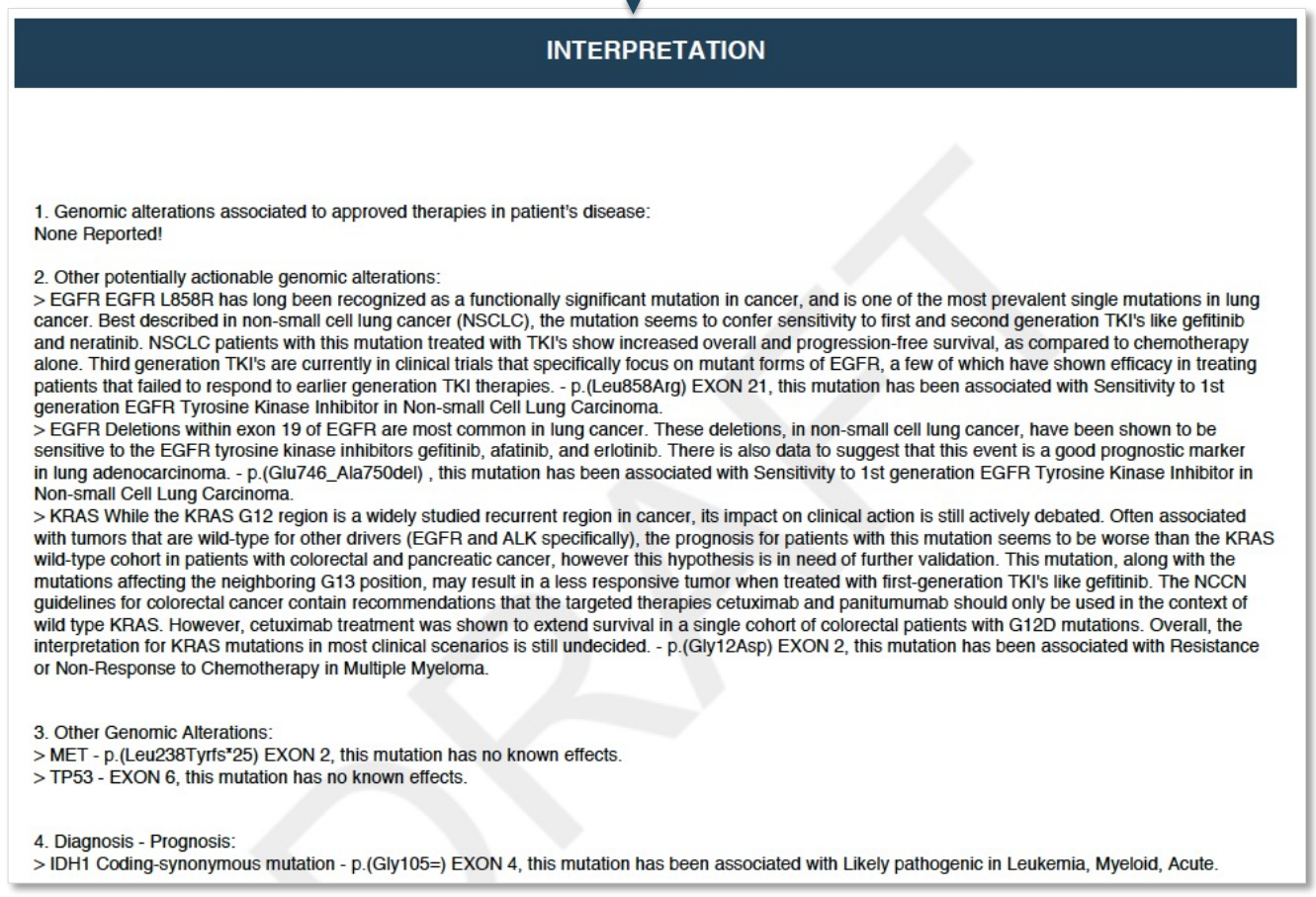


SUMMARY OF ALTERATIONS

Gene(s)	Alteration	Supporting values	AMP/ASCO/CAP
BRAF-KDM7A	Gene-fusion	Supporting Unique Molecules 5.95 %	Tier I Therapeutic
EGFR	p.(Leu702.Thr706del) c.2105_2119del	Variant fraction 33.5 %	Tier II, C Therapeutic
EGFR	p.(Thr745Met) c.2234C>T	Variant fraction 36.8 %	Tier II, C Therapeutic
CCND1	Amplification	Copy number 3.4	Tier II, C Therapeutic
COL4A3BP-BRAF	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.

DRAFT

Validated by:	Analysed by: Operator User
Date:	Date: 13-02-2018 I 16:17:13
Signature:	Signature:

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
MET 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
IDH1 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

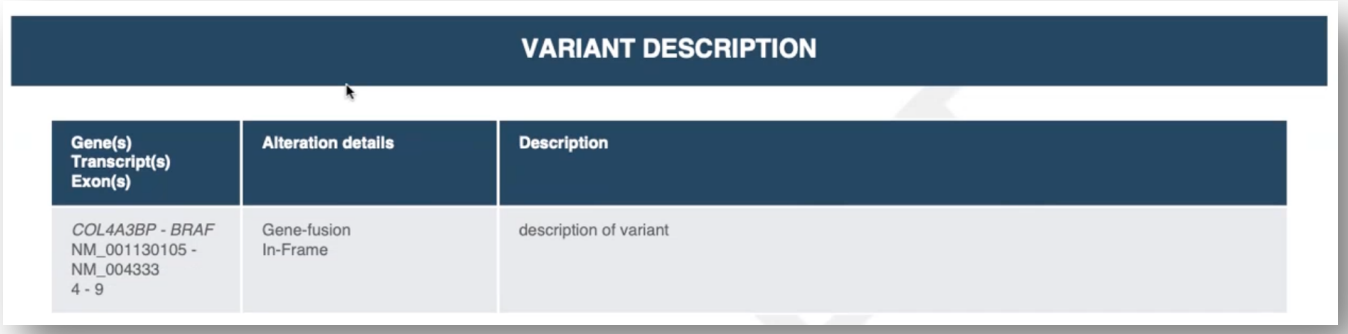
Gene(s) Transcript(s) Exon(s)	Chromosome Positions	Alteration details	Supporting Values	Clinvar	Pathogenicity
IDH2 NM_002168 4	15 90631837	c.516G>T p.(Arg172Ser)	Variant fraction 49.2 % Depth 11148		Flagged Pathogenicity 3: Uncertain

Diagnosis - Prognosis

Gene(s) Transcript(s) Exon(s)	Chromosome Positions	Alteration details	Supporting Values	Clinvar	Actionability
KRAS 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

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
MET 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)
EGFR 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)
KRAS 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)

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

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.

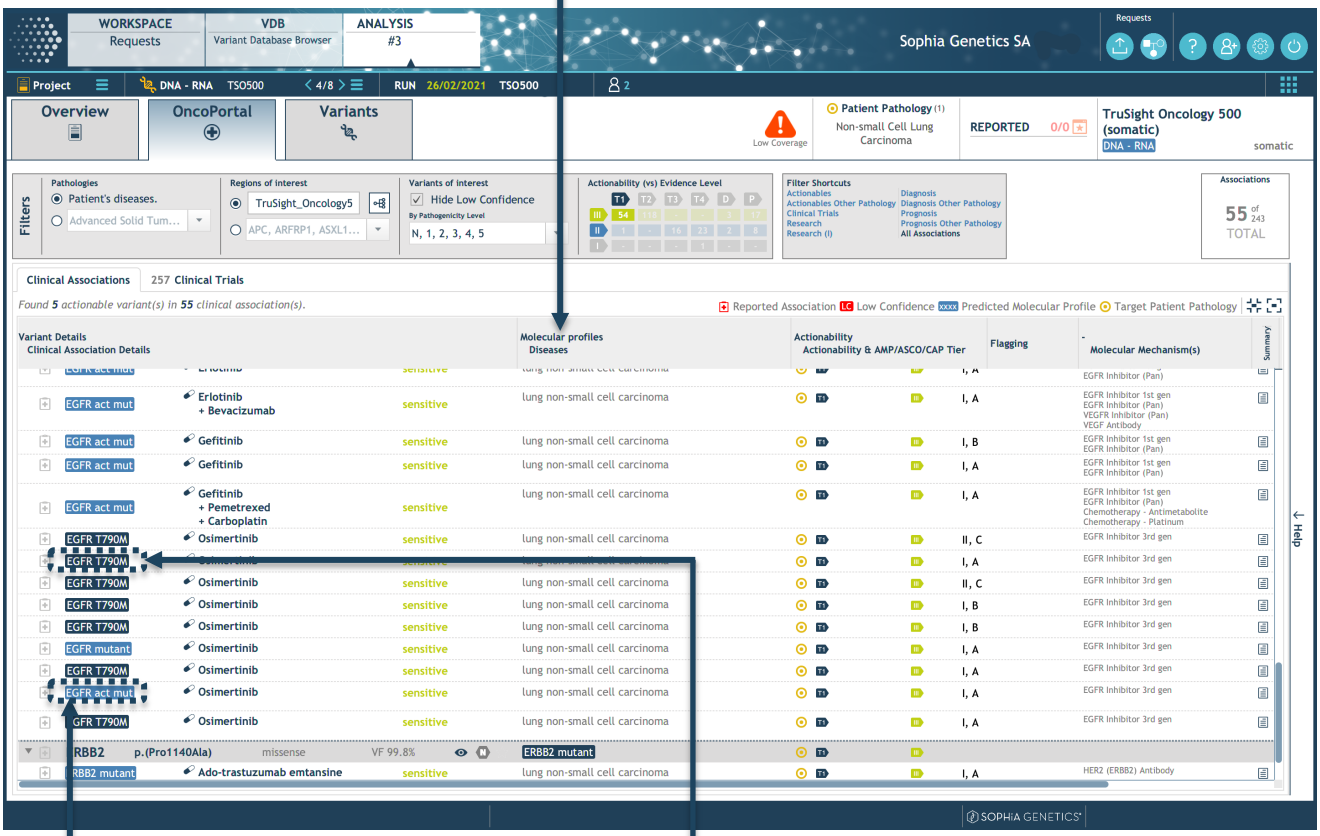
- **amp**: refers to increased number of copies of the gene and is used when a gene is located in a CNV with increased copy number
- **del**: refers to deletion of the gene and is used when a gene is located in a deleted region (CNV with copy number = 0)
- **loss**: refers to loss of the gene, mRNA, 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)

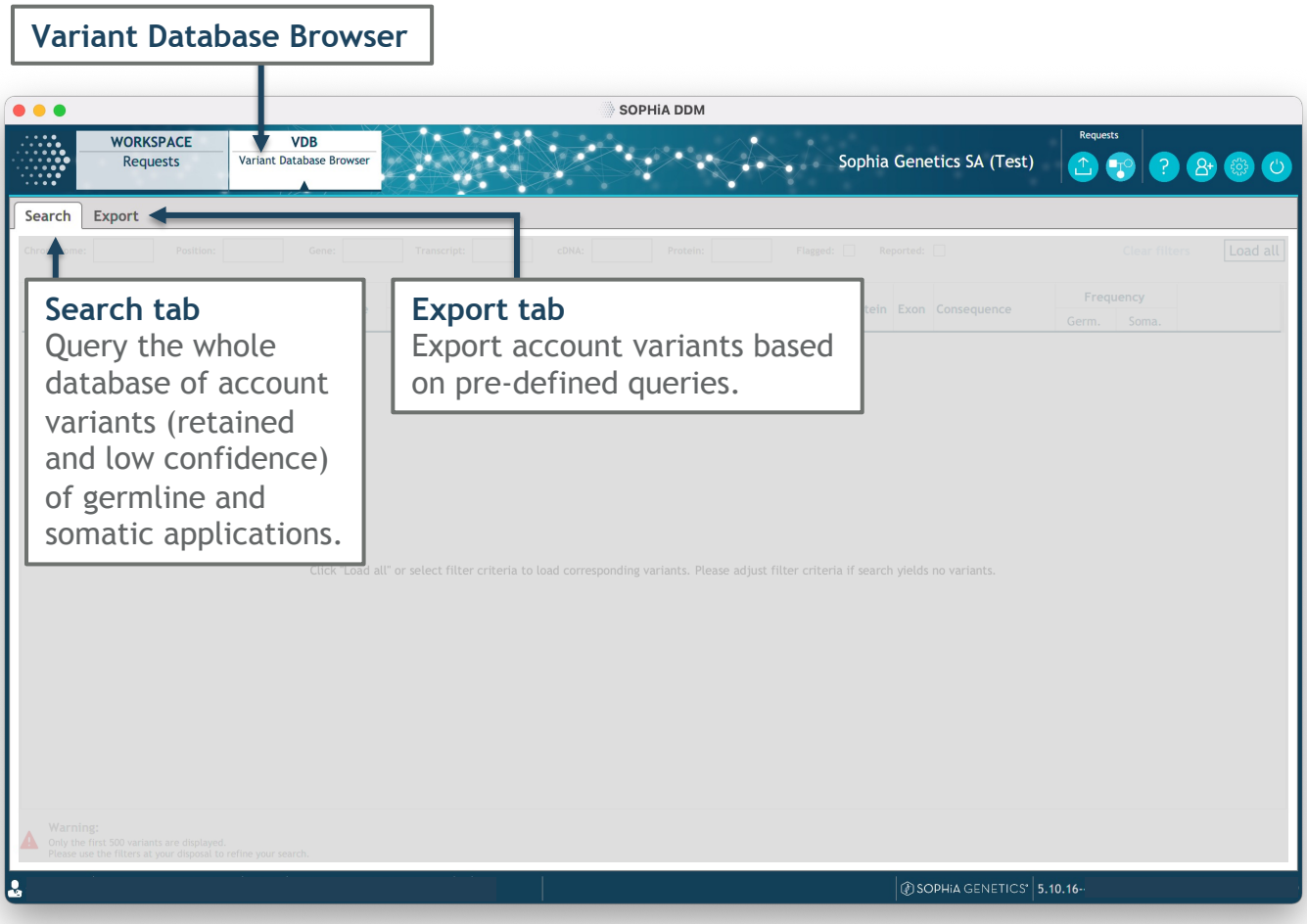
"Molecular profiles"
The column displaying the molecular profiles and linked diseases



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

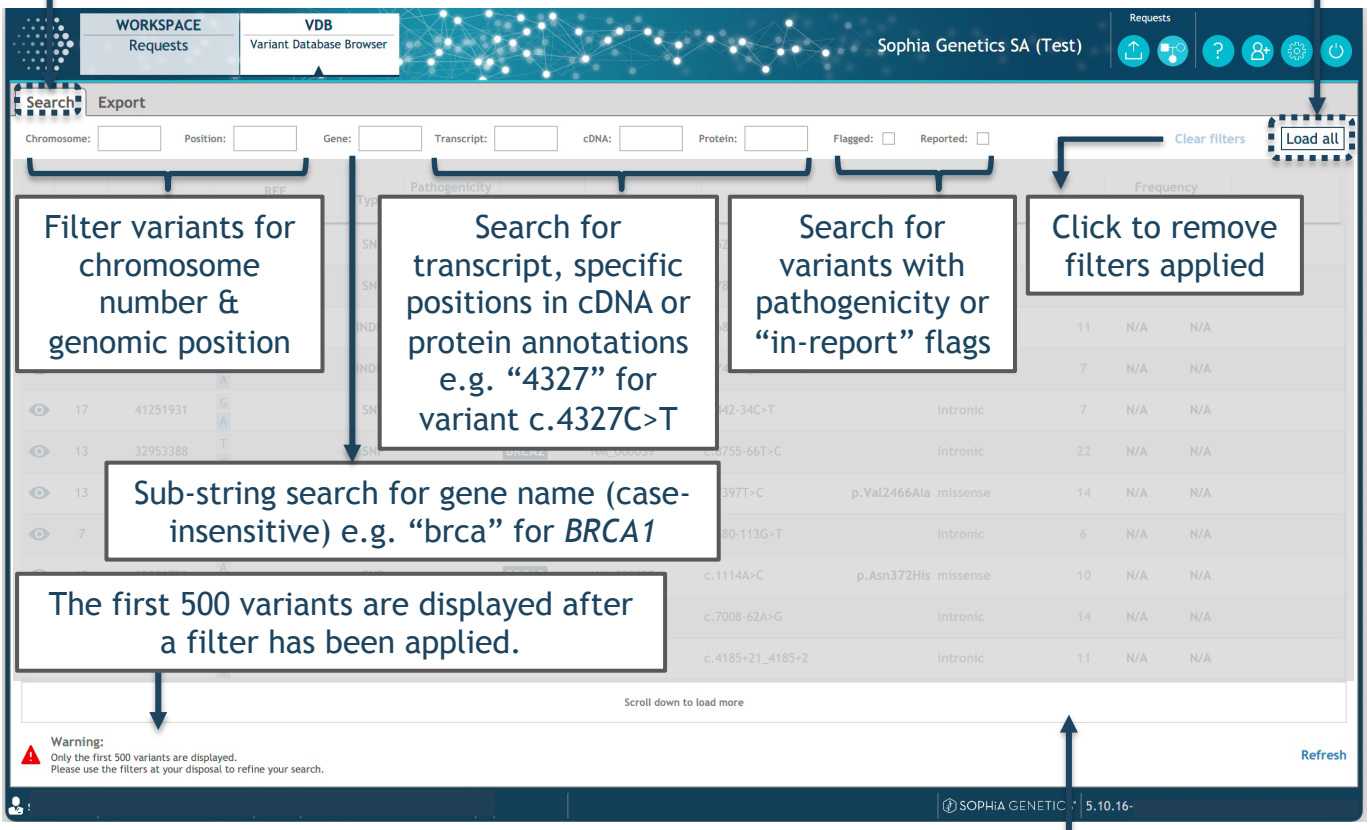
10. Variant Database Browser
10.1 Overview



10. Variant Database Browser
10.2 Variant Search (1)

Search tab

Click to “Load all” variants



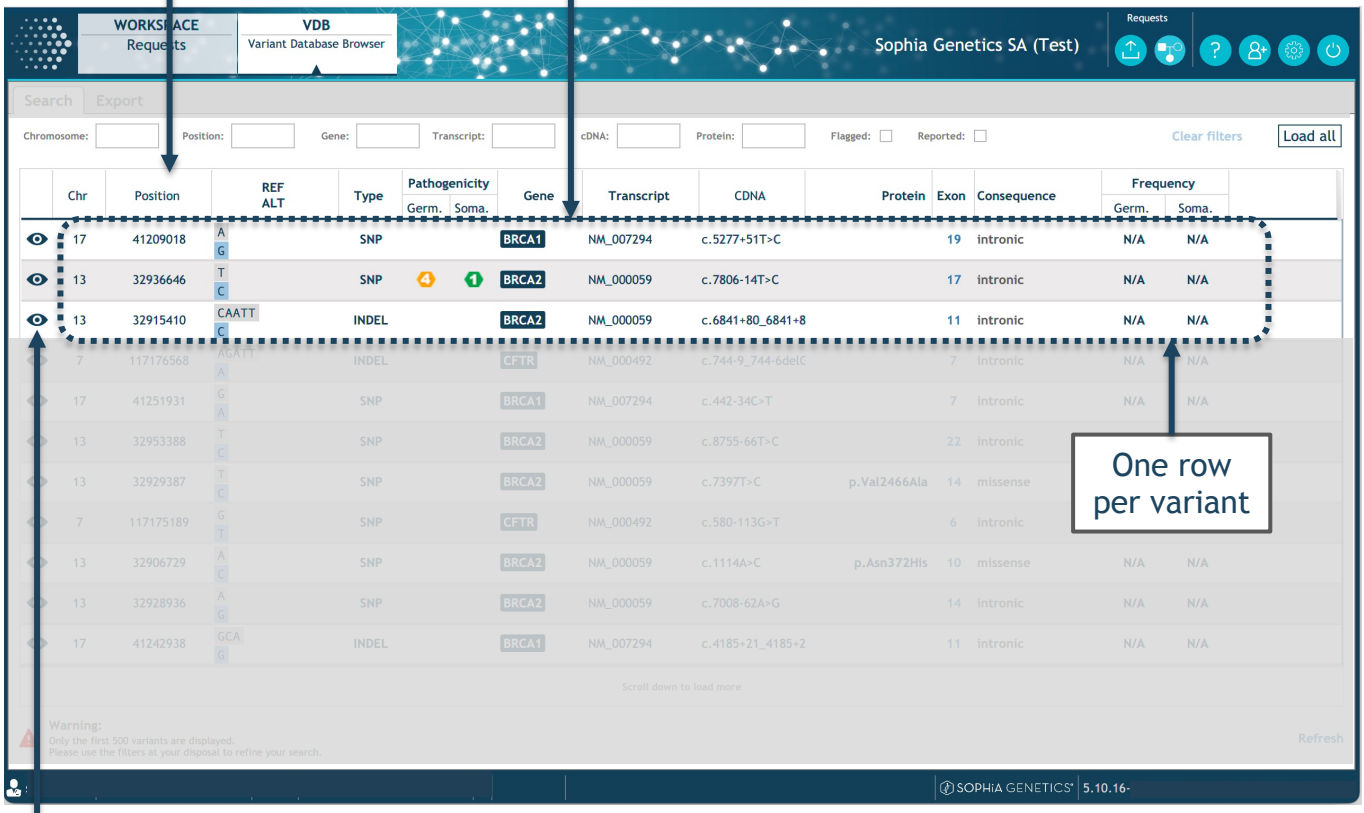
- Apply one or several filters to search your account’s variant database:
  - by chromosome number, genomic position, gene name, cDNA or protein annotation
  - Select checkbox to restrict to “reported” or “flagged” variants
- Press Enter or click “Search”
- A notification informs the user once variants 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



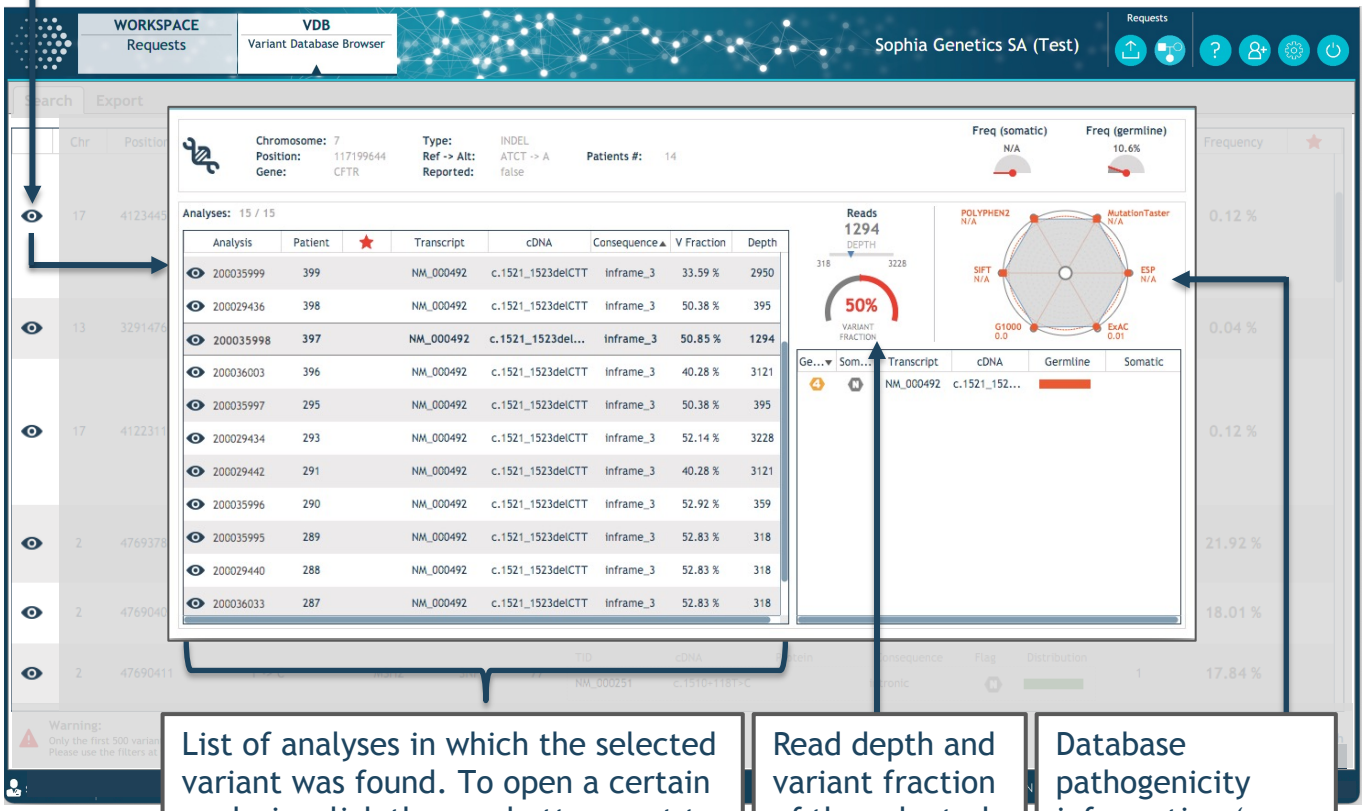
One row per variant

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.

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.



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

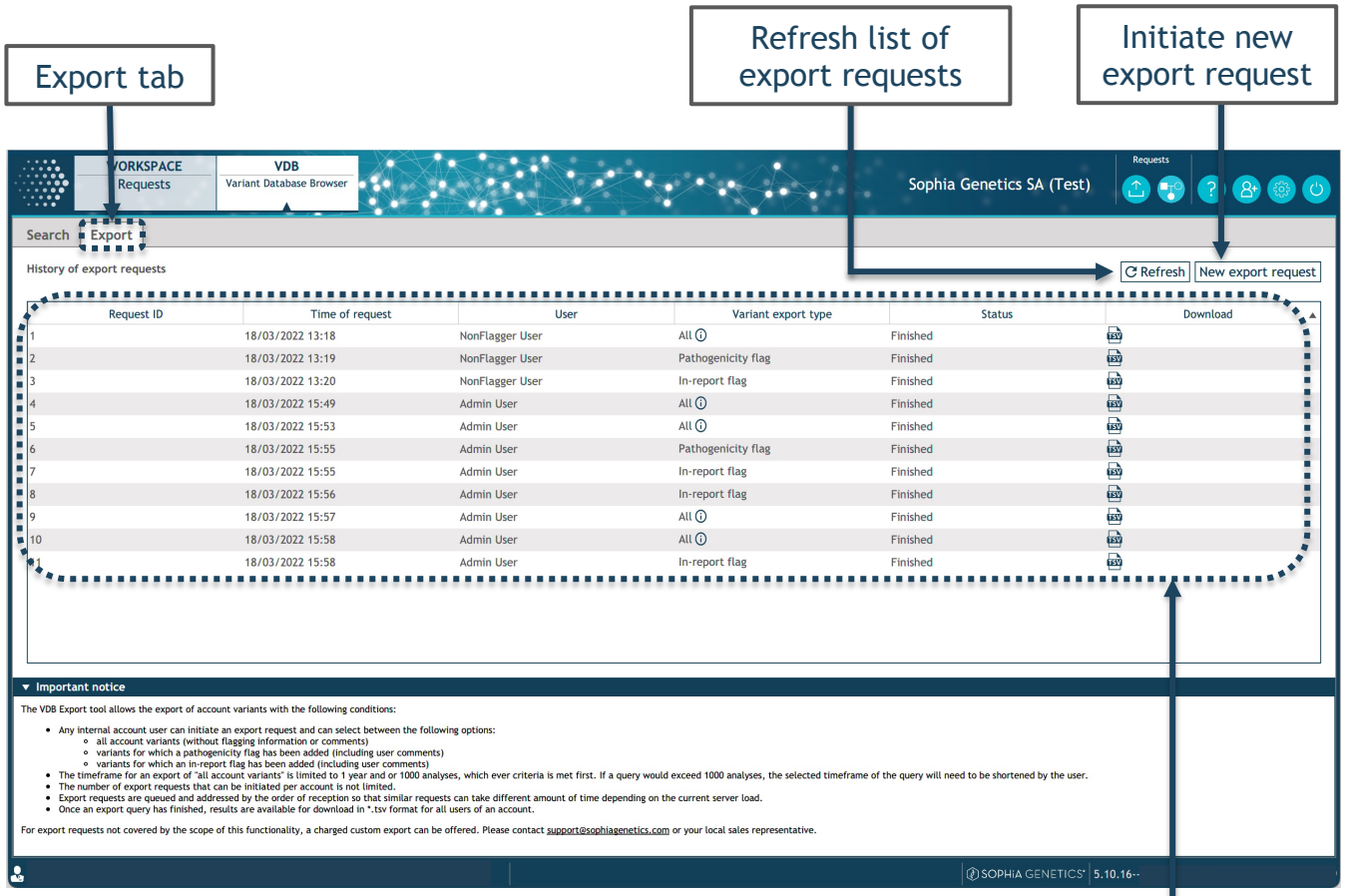
Once an export query has finished, results are available for download in compressed, tab-separated values format (*.tsv.gz) for all internal users of an account.

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.

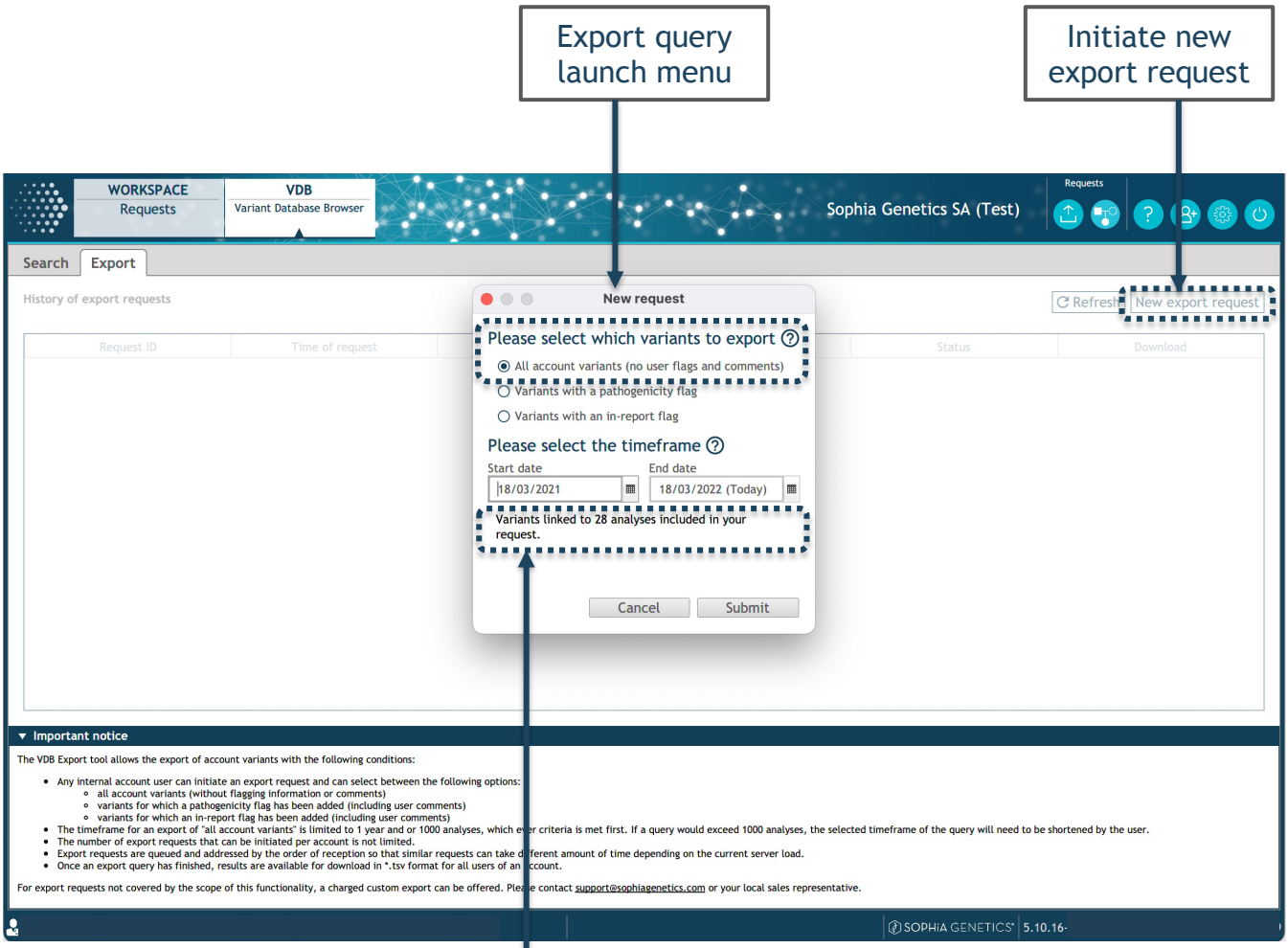
10. Variant Database Browser
10.4 Export variants
10.4.1 Overview (2)



- 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.

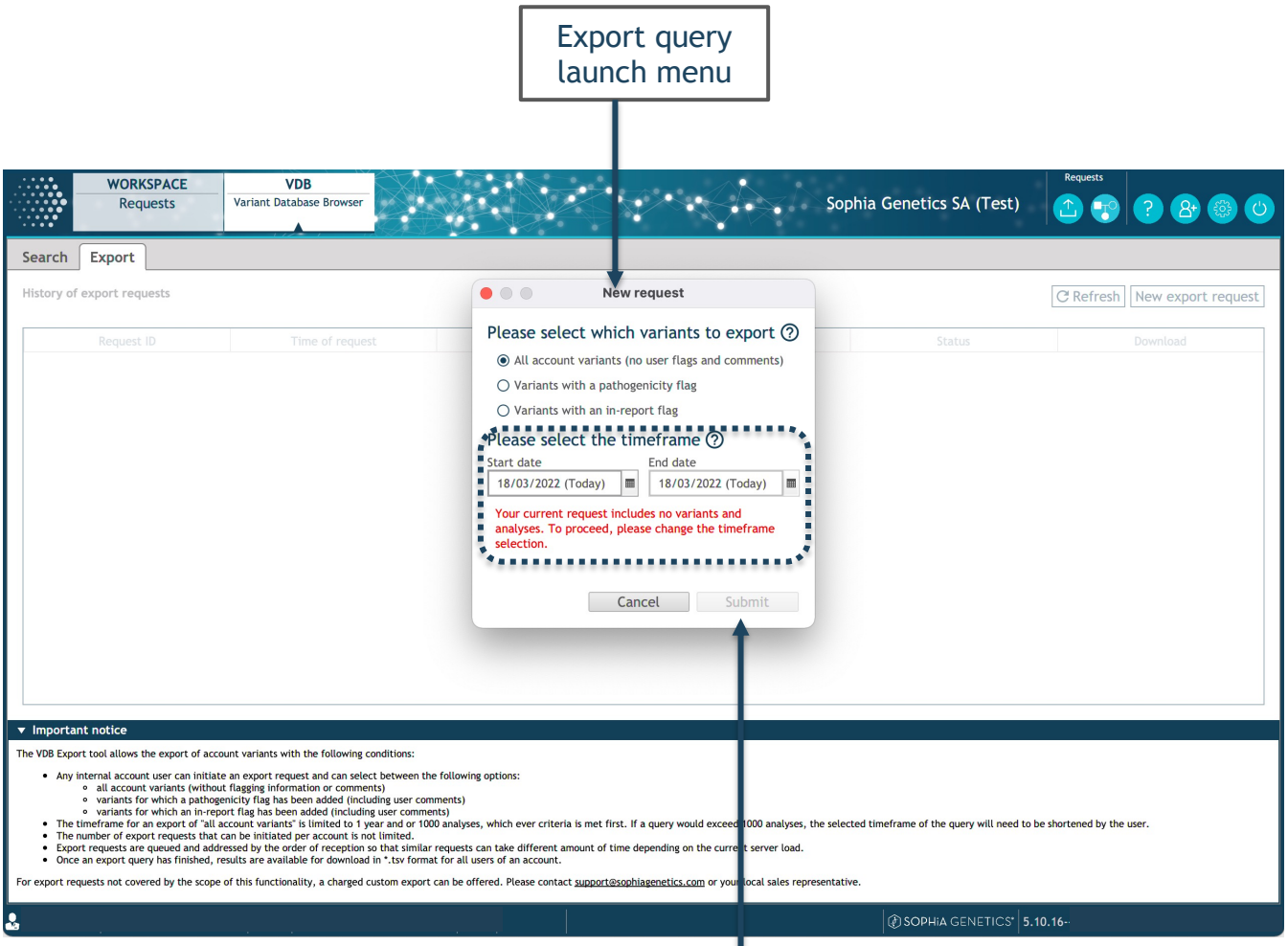
10. Variant Database Browser
10.4 Export variants
10.4.1 Create request – all variants (1)



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)



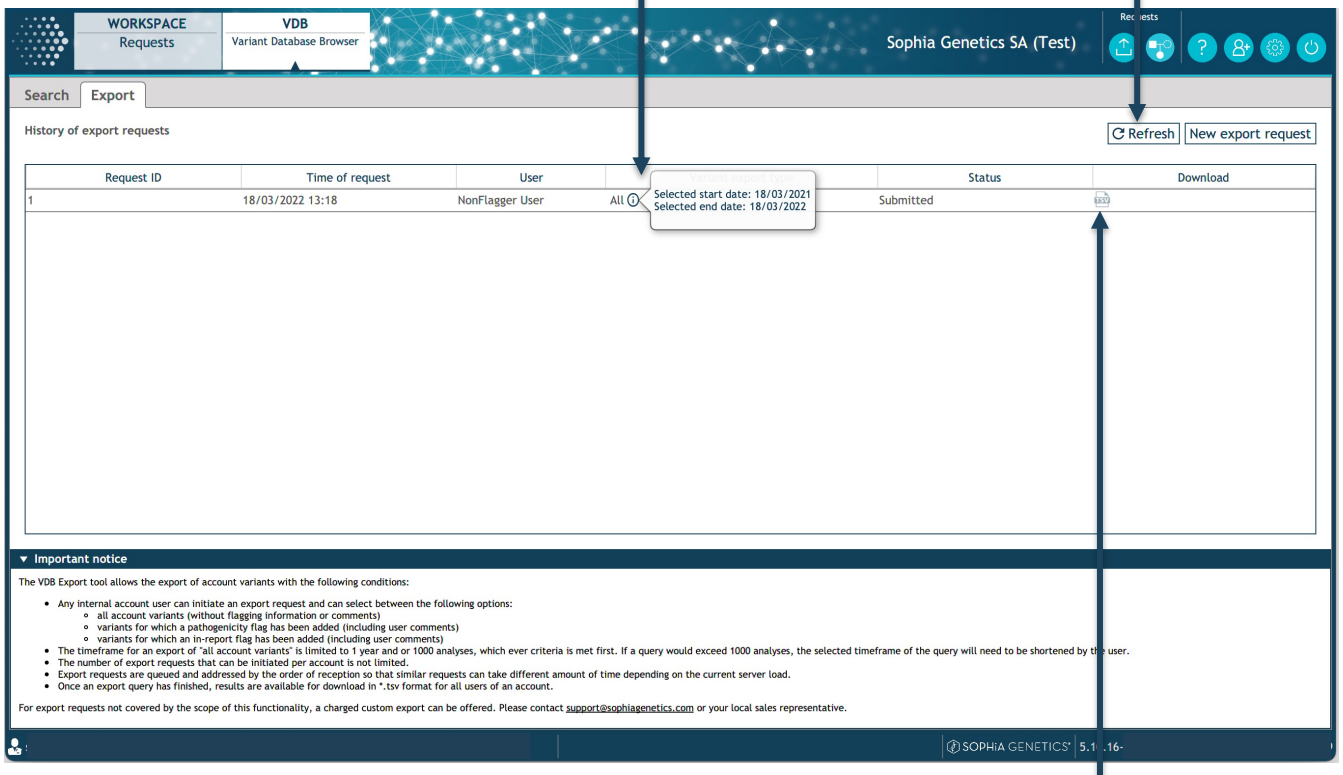
If 0 or >1000 analyses would be included in an export request, the timeframe selection needs to be adapted to proceed with the submission of the query.

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.

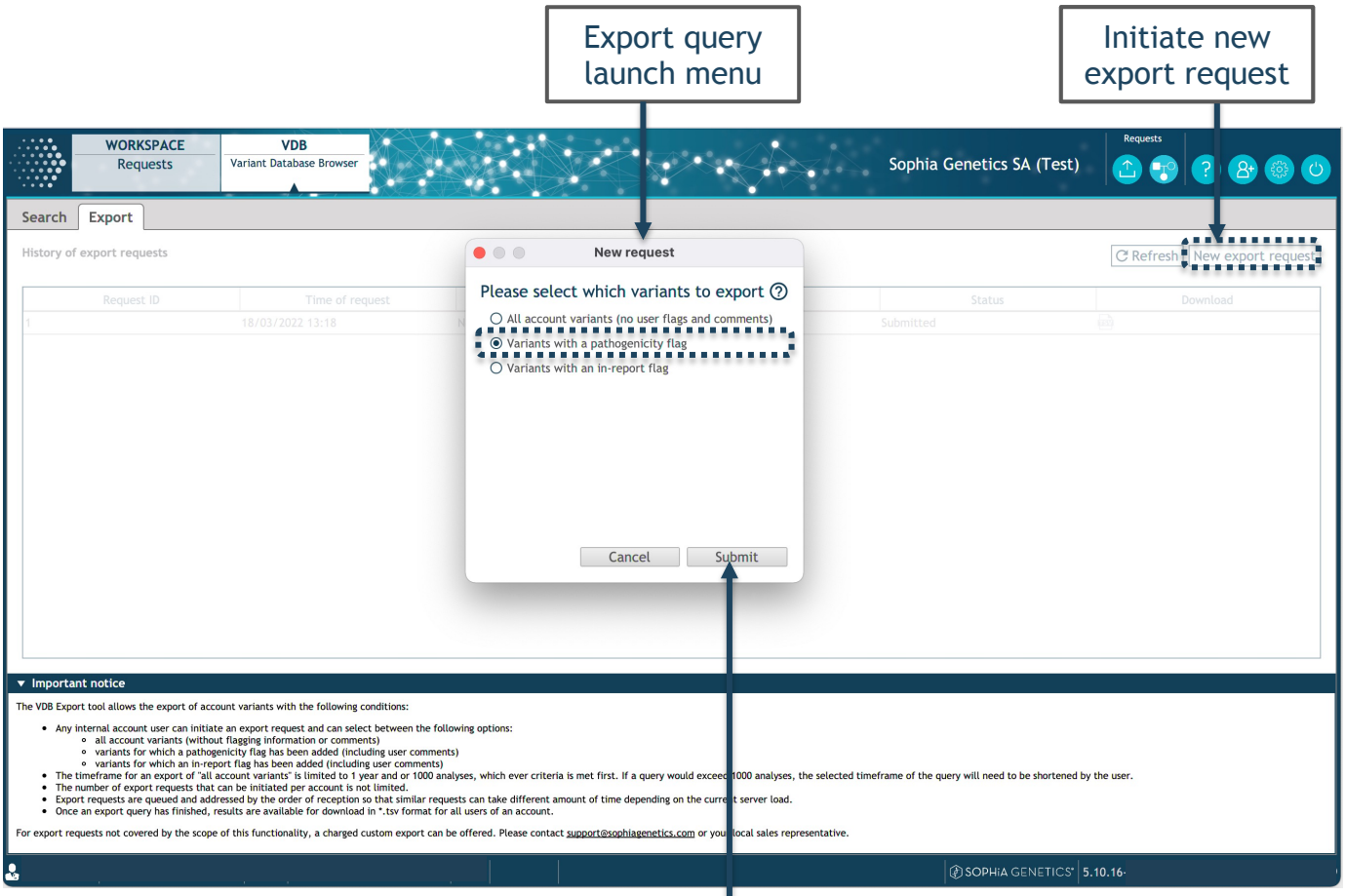
Click to see the updated status of a request.



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



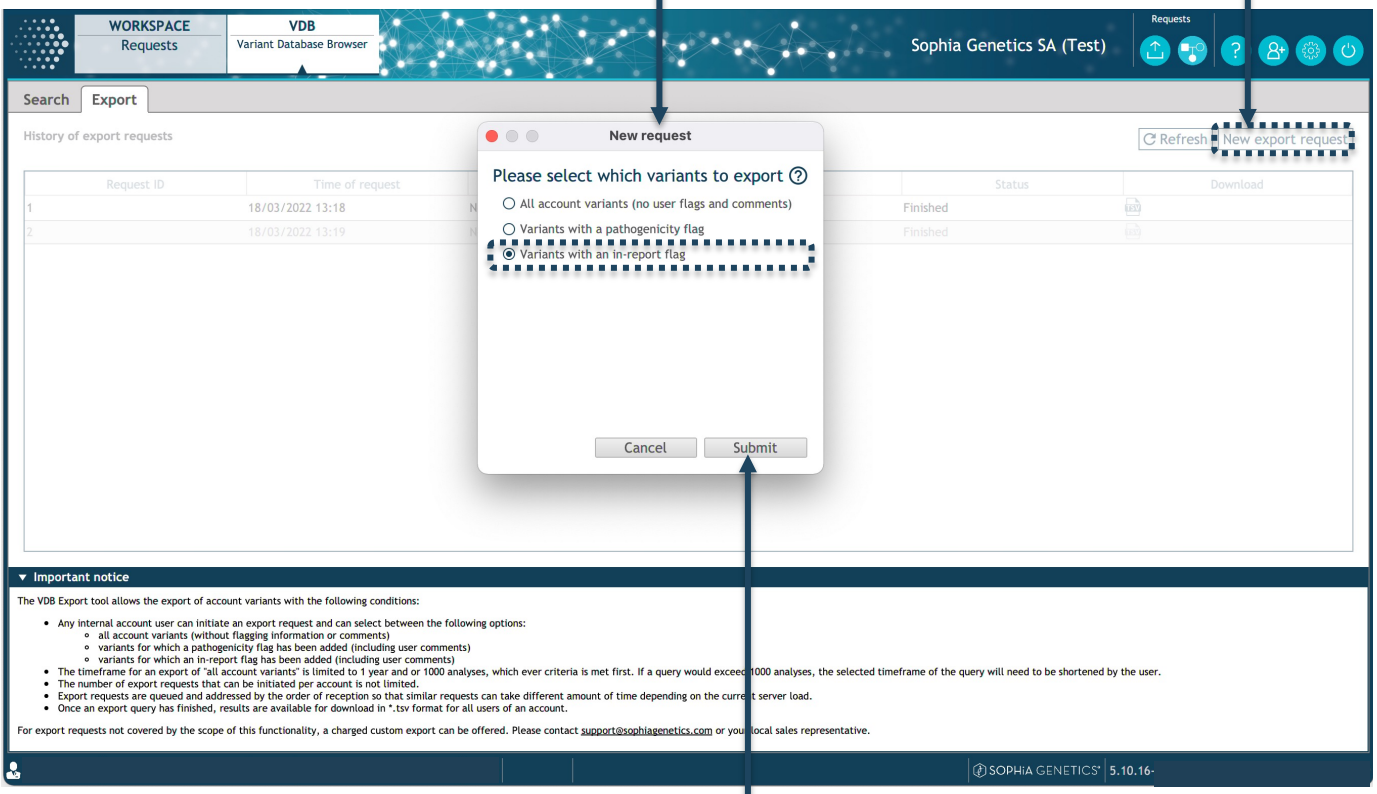
All variants with a pathogenicity annotation (flag and comment) are included in the export without any timeframe or analyses number restriction.

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

Export query launch menu

Initiate new export request



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.

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	*Tramscript 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)*	*.*
dbSnpID	*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

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	*Tramscript 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

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*

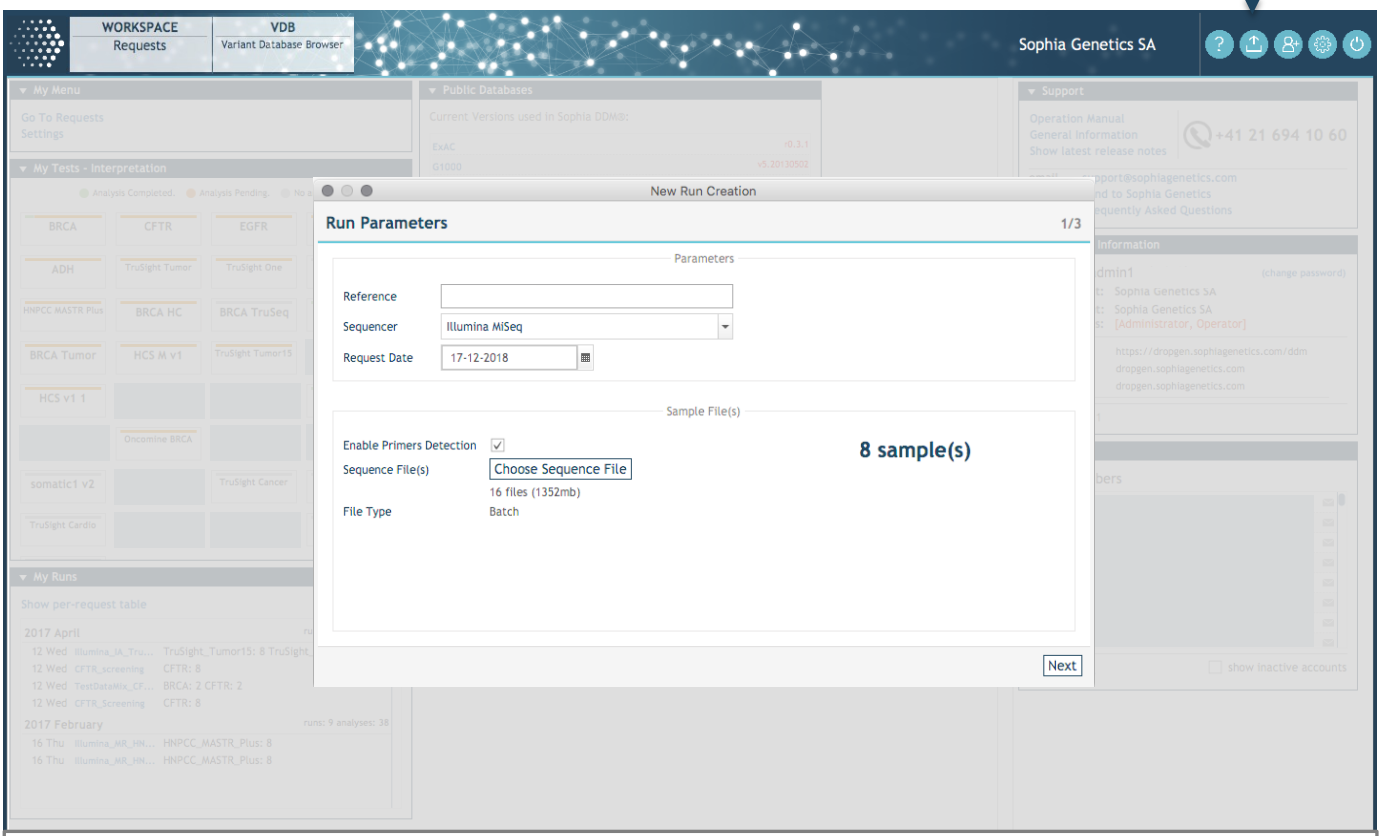
The export file
- includes low confidence and retained variants (SNVs / Indels) with an in-report flag
- displays one row per variant, sample and interpretation project
- is sorted by variant ID, then sample ID, then interpretation project name

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…).

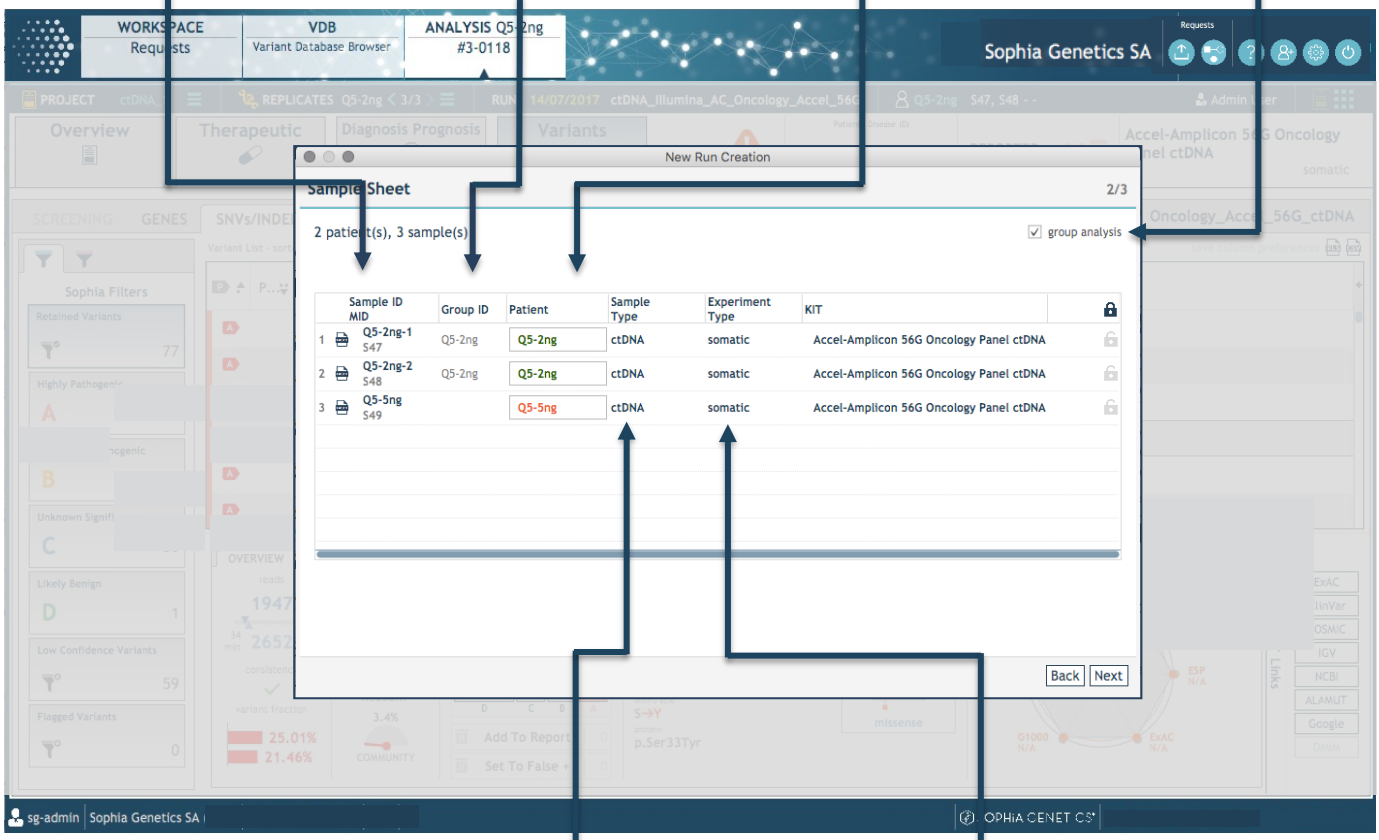
11. Replicate Analysis
11.1 Create a New Request (2)

"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



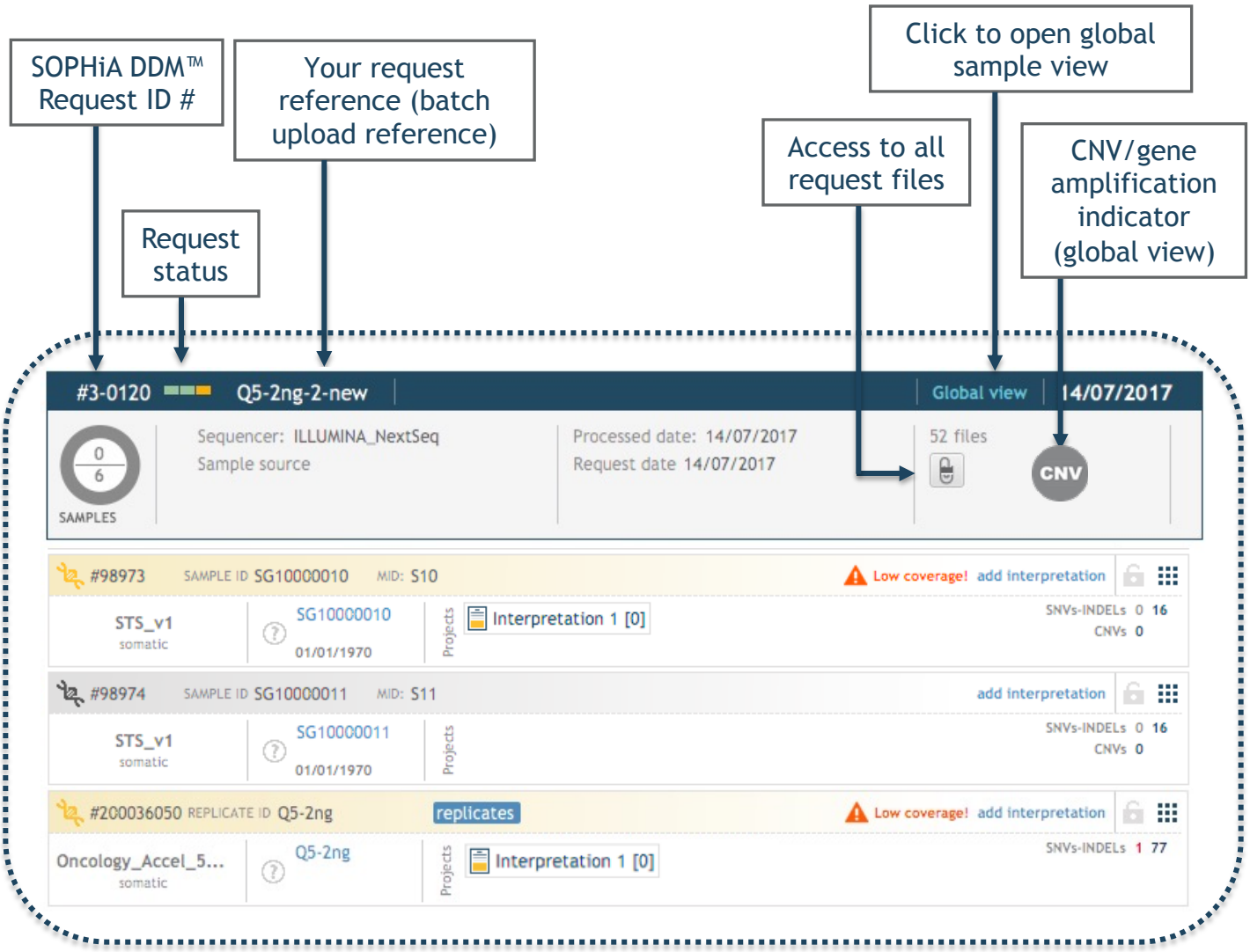
"Sample type"
Sample material used

"Experiment type"
Recognized automatically

Note: To proceed with a replicate analysis kit, experiment type and sample type need to by identical for replicate group.

11. Replicate Analysis
11.2 Analysis Card Overview

Request card summary



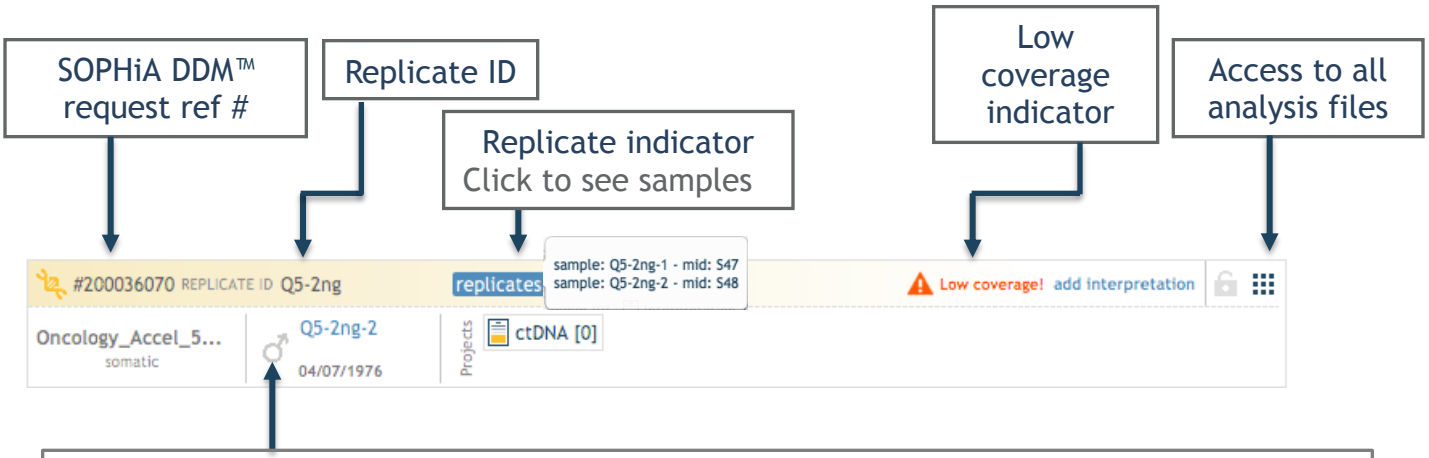
Indicators

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

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

replicates — 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

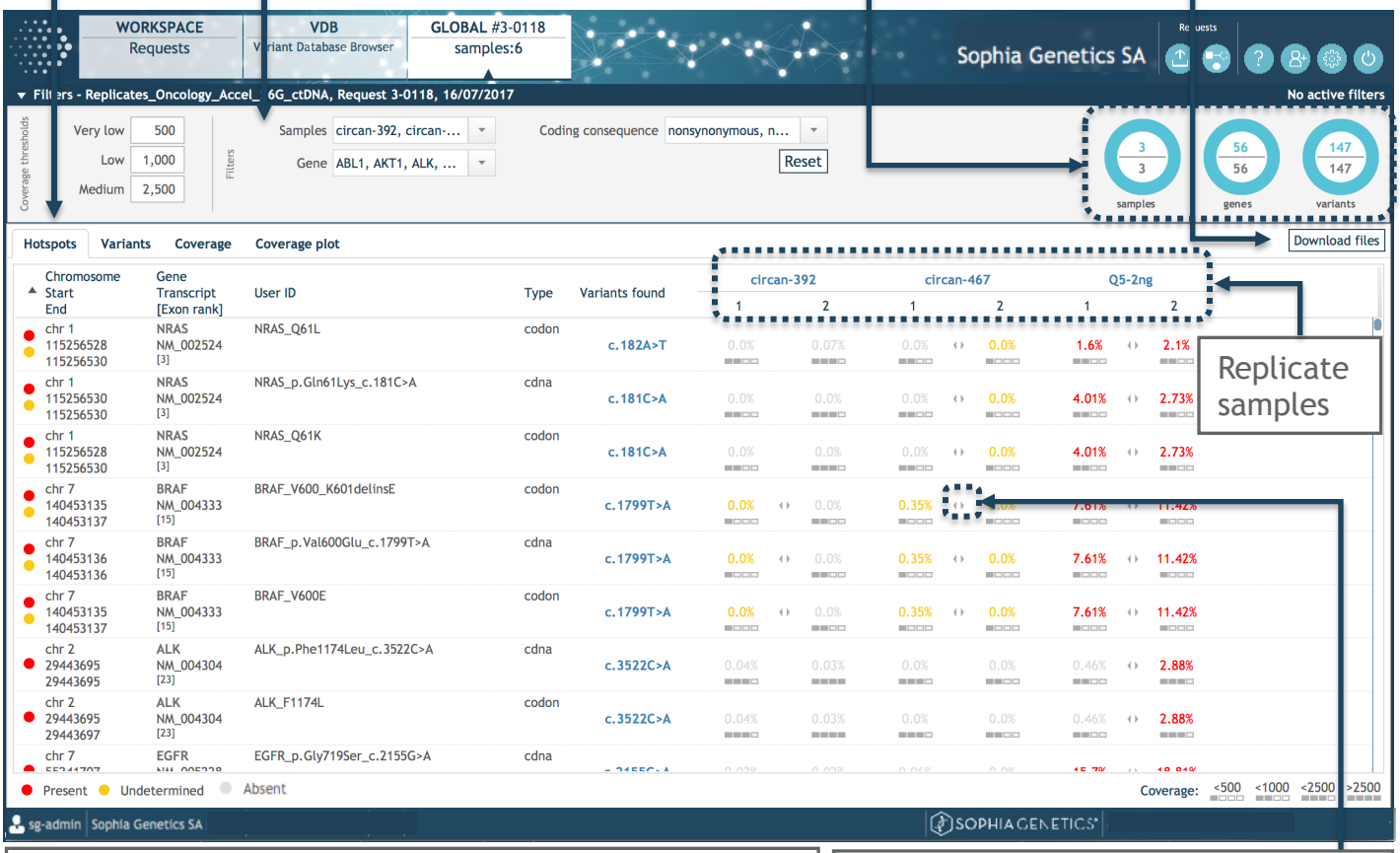
The global view lets the user quickly screen hotspots and variants for all samples in a run. Variants are represented in a "unified" view which also gives details on very low variant fractions. The global view can be accessed from the analysis card (see p. 214)

"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



Replicate samples

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*

- Variant is *present* in at least one of the samples
- Variant is *undetermined* in at least one of the samples
- Variant is *absent* (wild type) in at least one of the samples

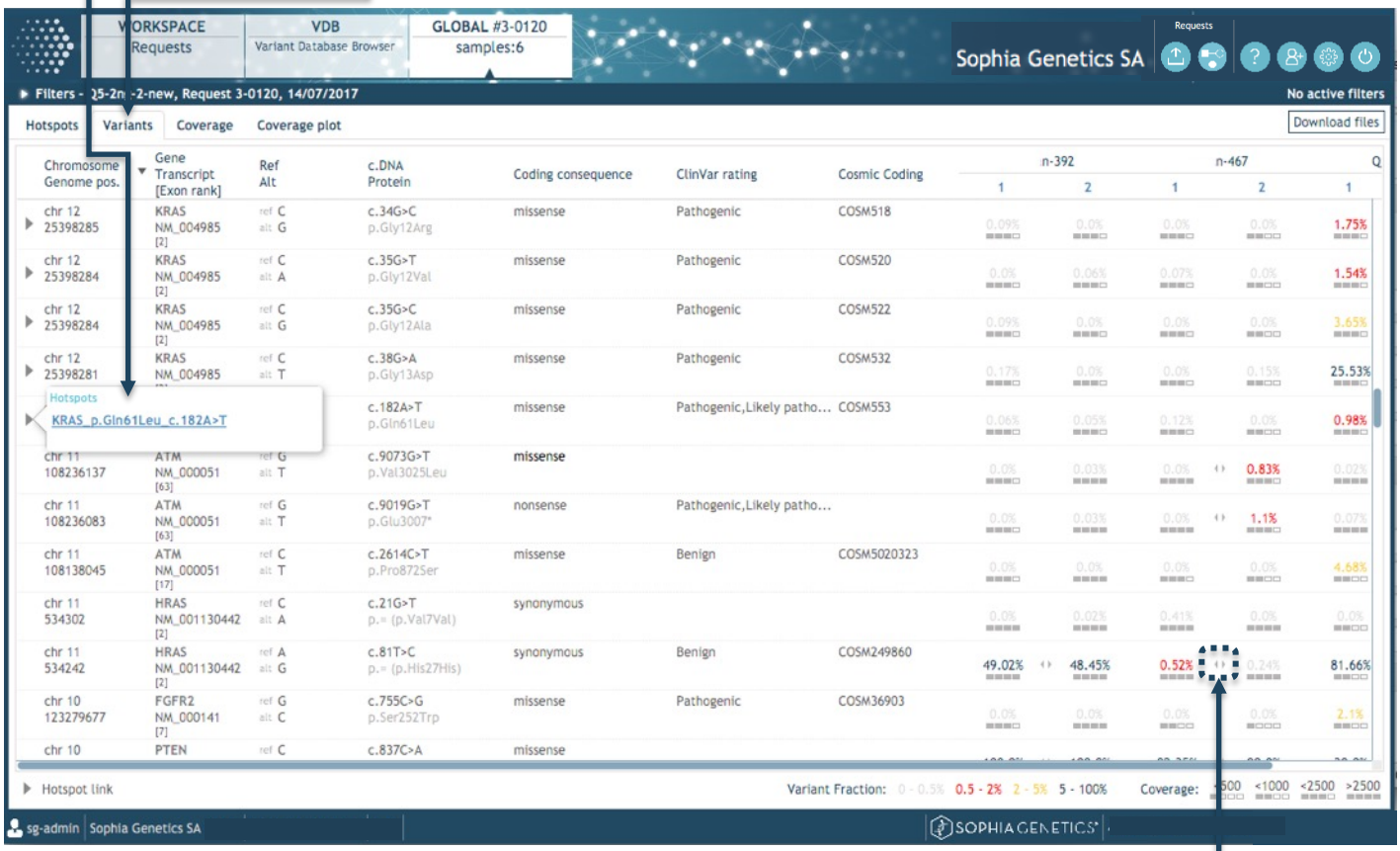
Coverage Indicators (variable)

<500 <1000 <2500 >2500

11. Replicate Analysis
11.5 Global Sample View Variants

"Hotspot link"
Variant present in hotspot screen

"Variants"
Active tab



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)

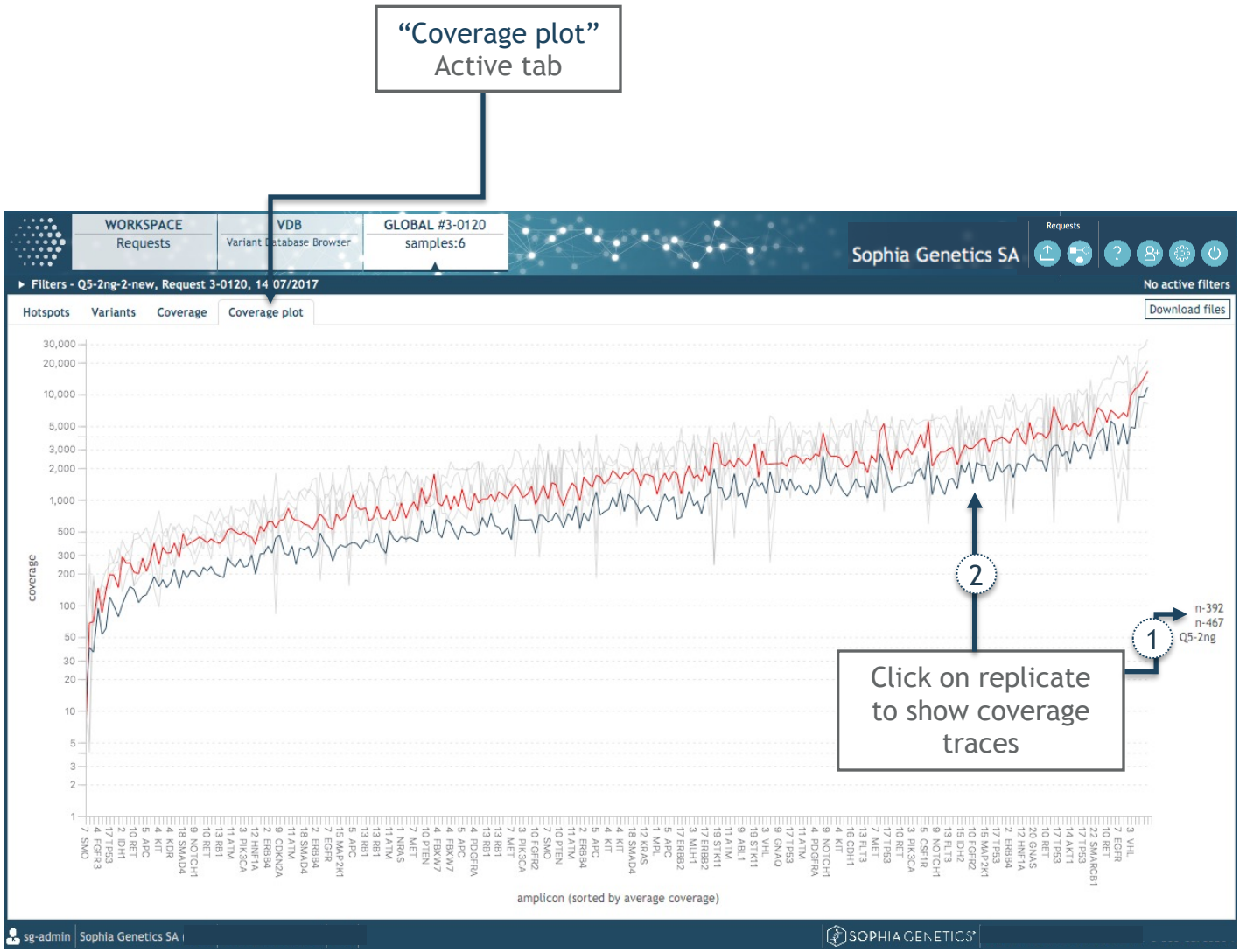
<500 <1000 <2500 >2500

11. Replicate Analysis
11.6 Global Sample View Coverage (1)

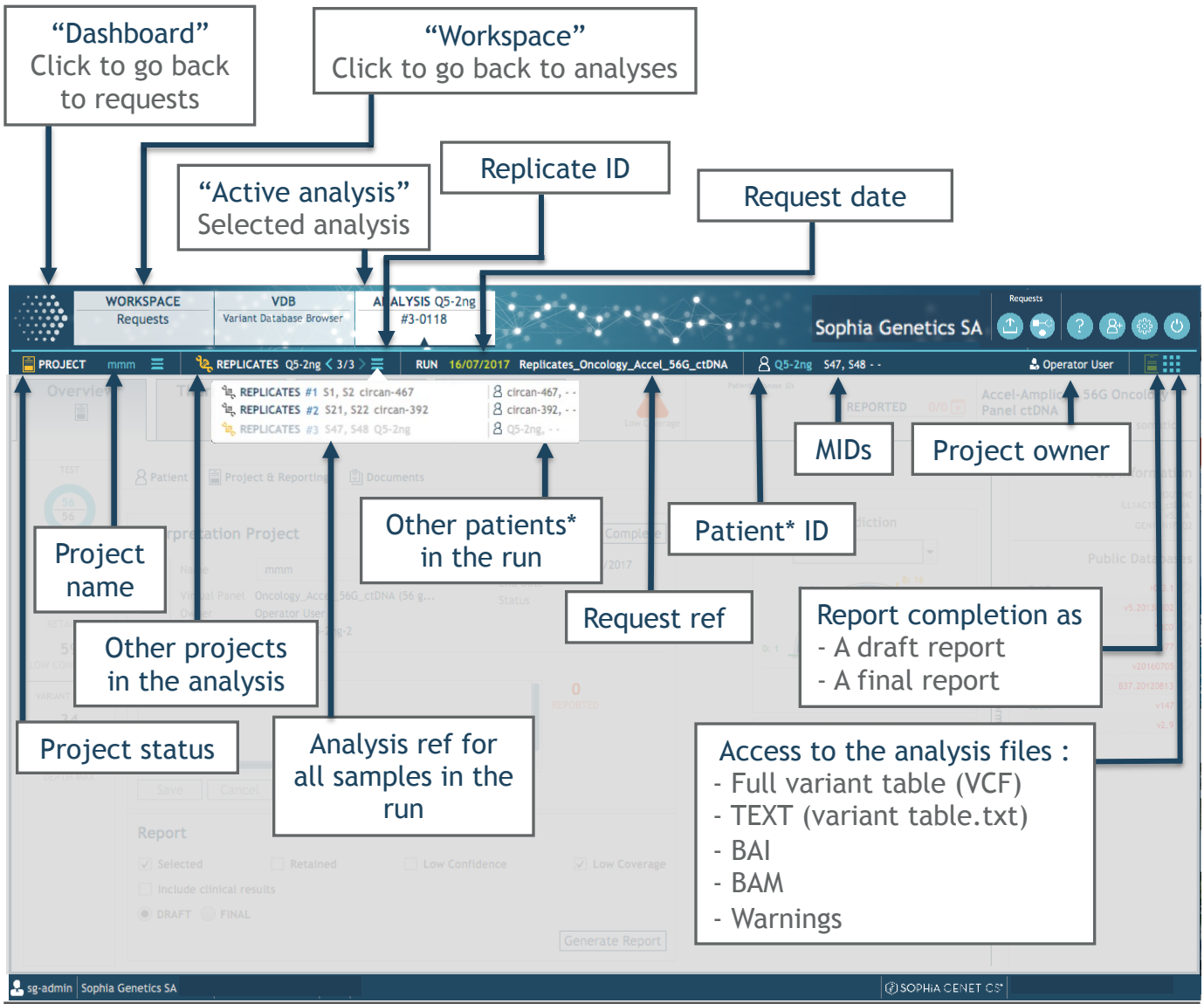
Coverage Indicators (variable)

- Coverage is < 500
- Coverage is < 1000
- Coverage is < 2500
- Coverage is > 2500

11. Replicate Analysis
11.6 Global Sample View Coverage (2)



11. Replicate Analysis
11.7 Analysis 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.

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™.

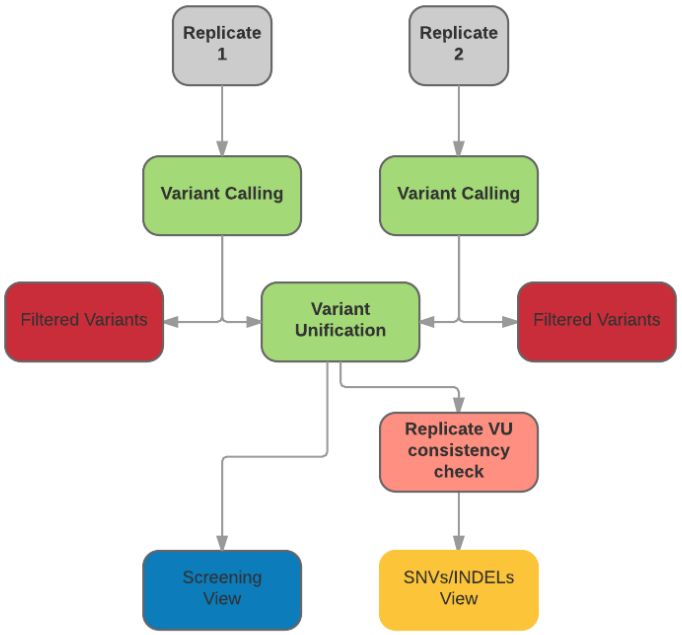
	Variant Fraction (%)				
Sample Name	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
VF % (Genomic Position A)	1%	Filter Flag: low VF	Filter Flag: low VF	2%	0.50%
VF% (Genomic Position B)	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF	Filter Flag: low VF

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.

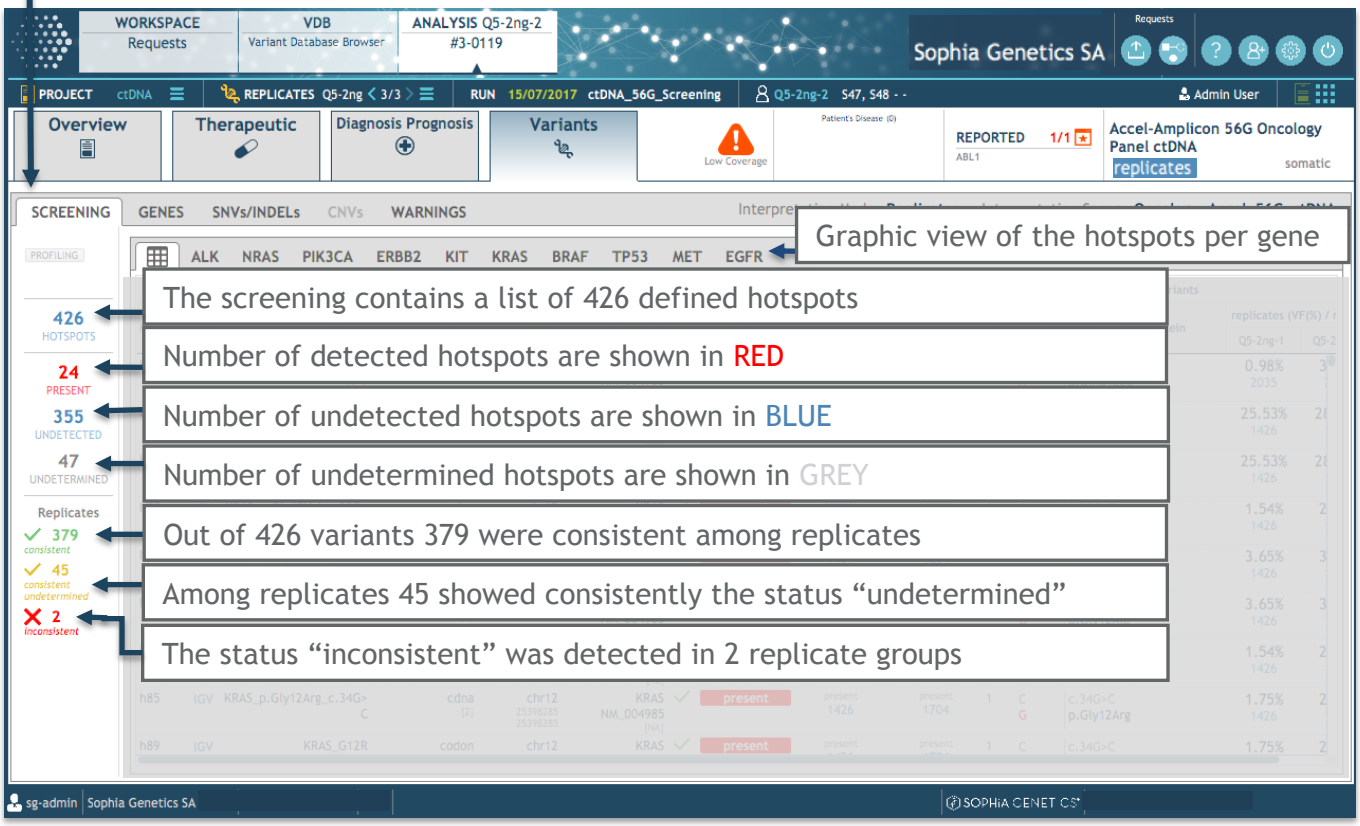
Variant unification:
During variant unification (VU), variants are unified and variants that have been below the variant fraction cut-off will be flagged “VU”. Variants are only flagged VU if the same variant has been called with high confidence in at least one other sample in the same run.

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

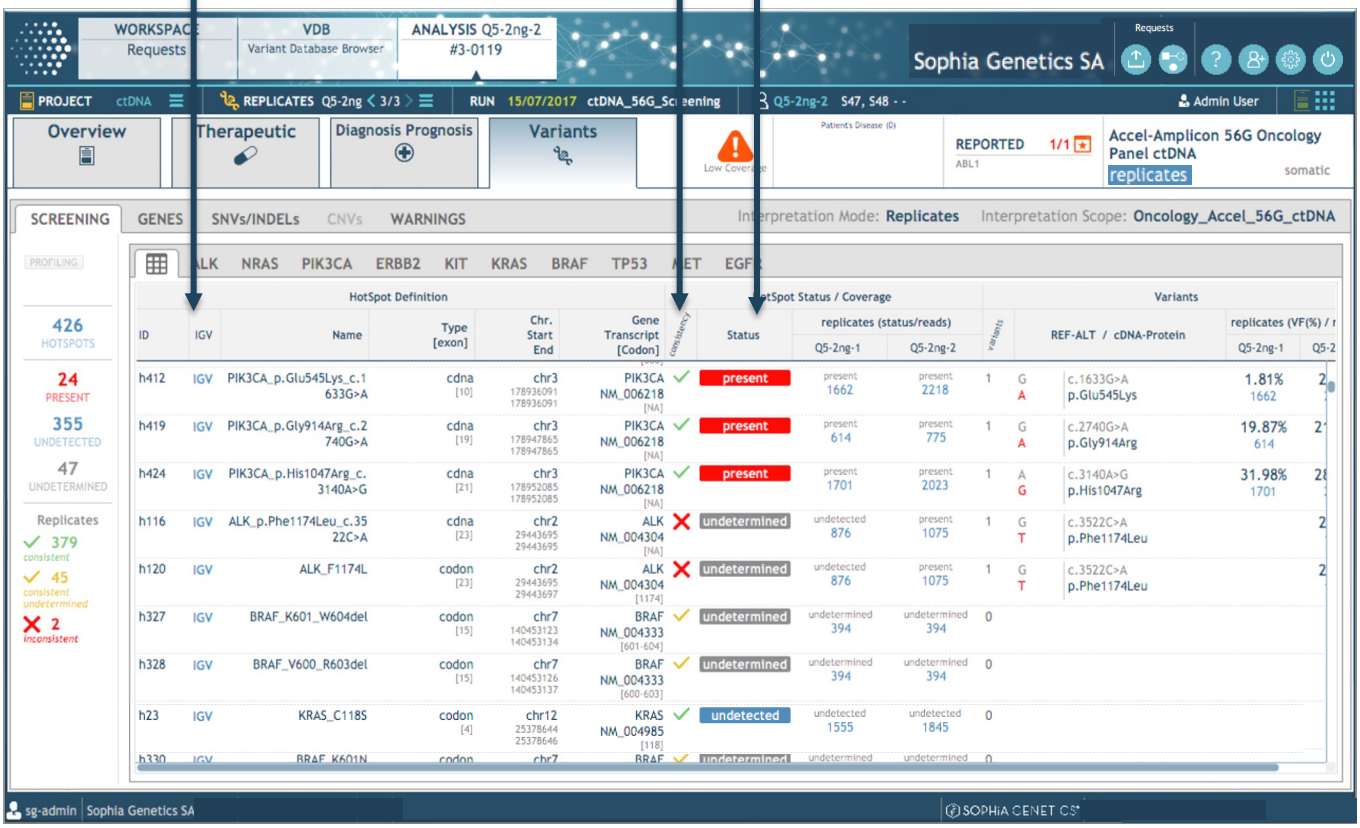
Using the screening view for replicates the user can not only quickly visualize pre-defined hotspots but also inspect if replicate samples are consistent.
Consistent: Replicate group shows the same status (present, undetected or undetermined)
Consistent undetermined: All replicates in a group are undetermined
Inconsistent: Replicates in a group show different statuses (e.g. present and undetected)

11. Replicate Analysis
11.10 Screening (2)

"IGV"
Opens replicates in IGV

"Consistency"
Indicates if replicates are consistent for this variant

"Status"
Combined replicate status



Status:

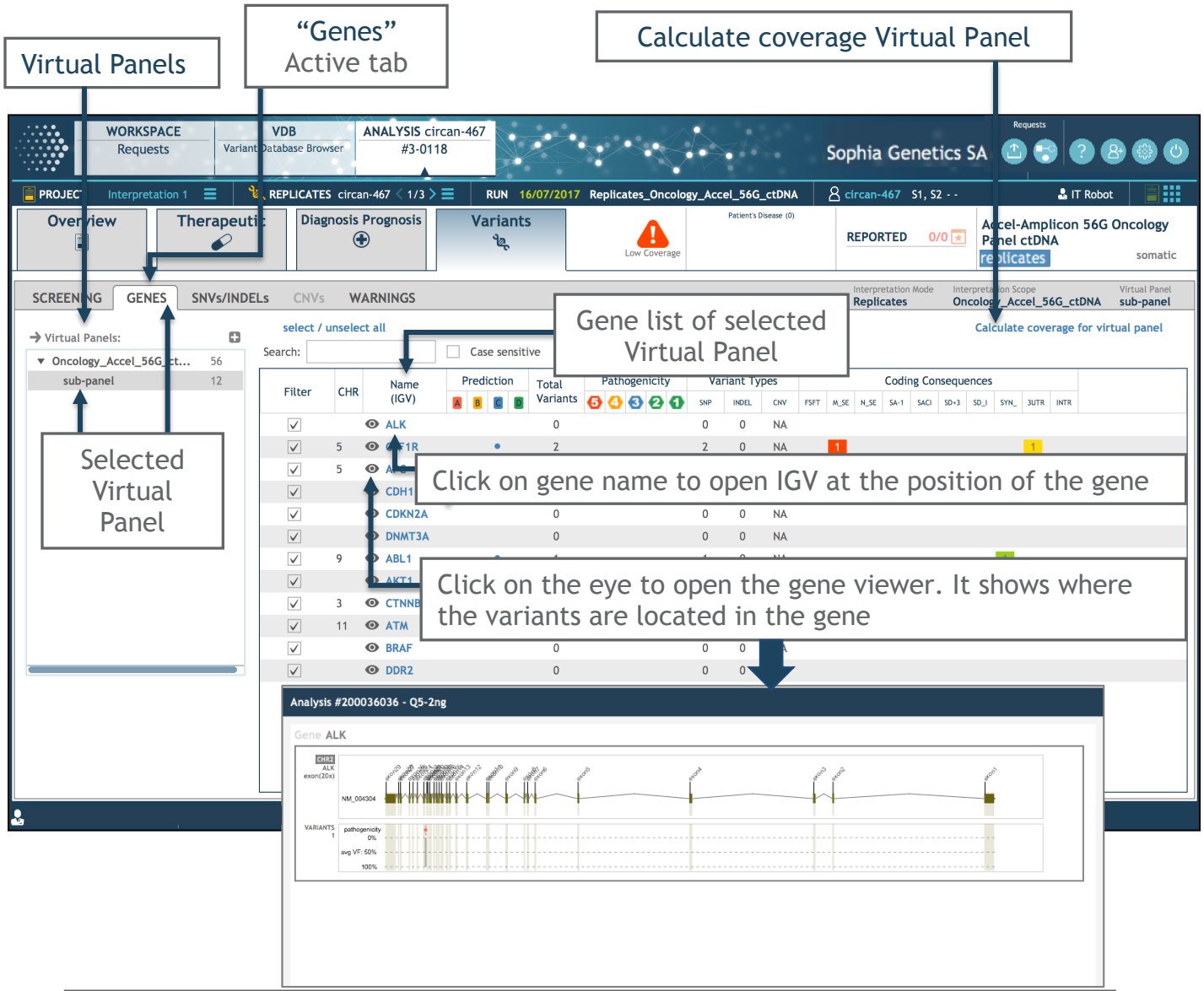
present — Variant is present with high confidence in all replicates

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

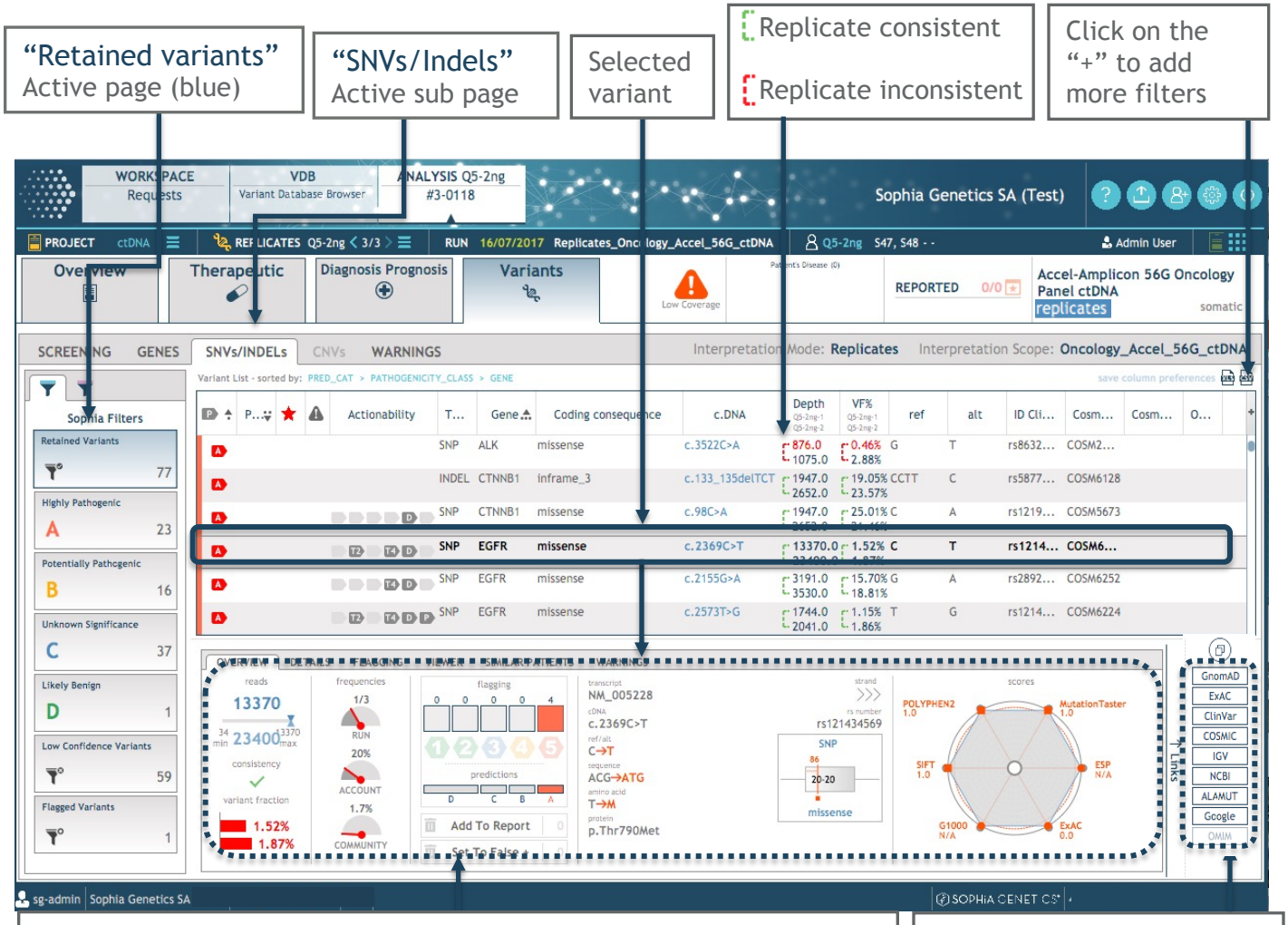
11. Replicate Analysis
11.11 Genes

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.



Note gene viewer: In the replicate interpretation mode, VF% is represented as an average of replicates.

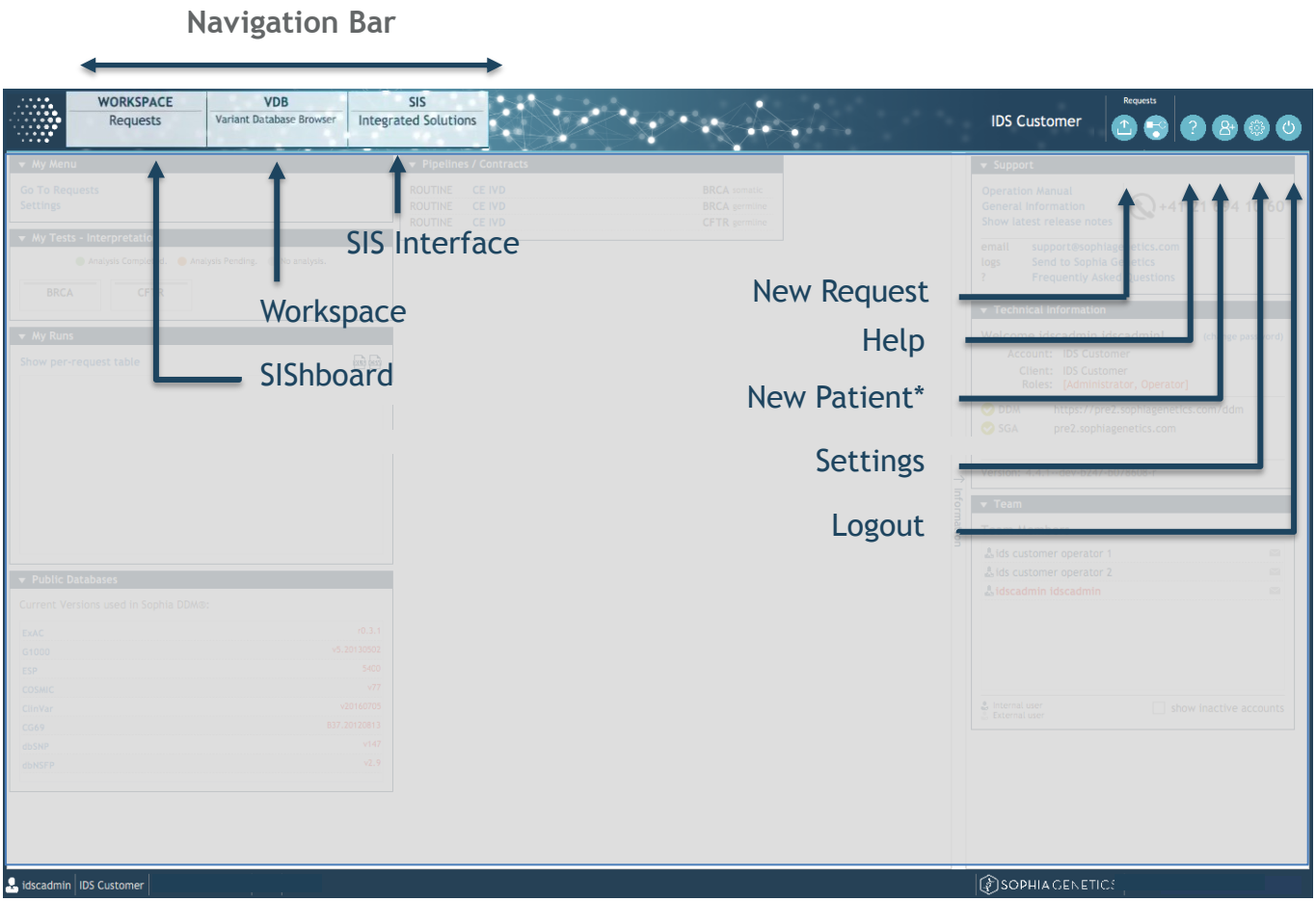
11. Replicate Analysis
11.12 SNVs/Indels



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

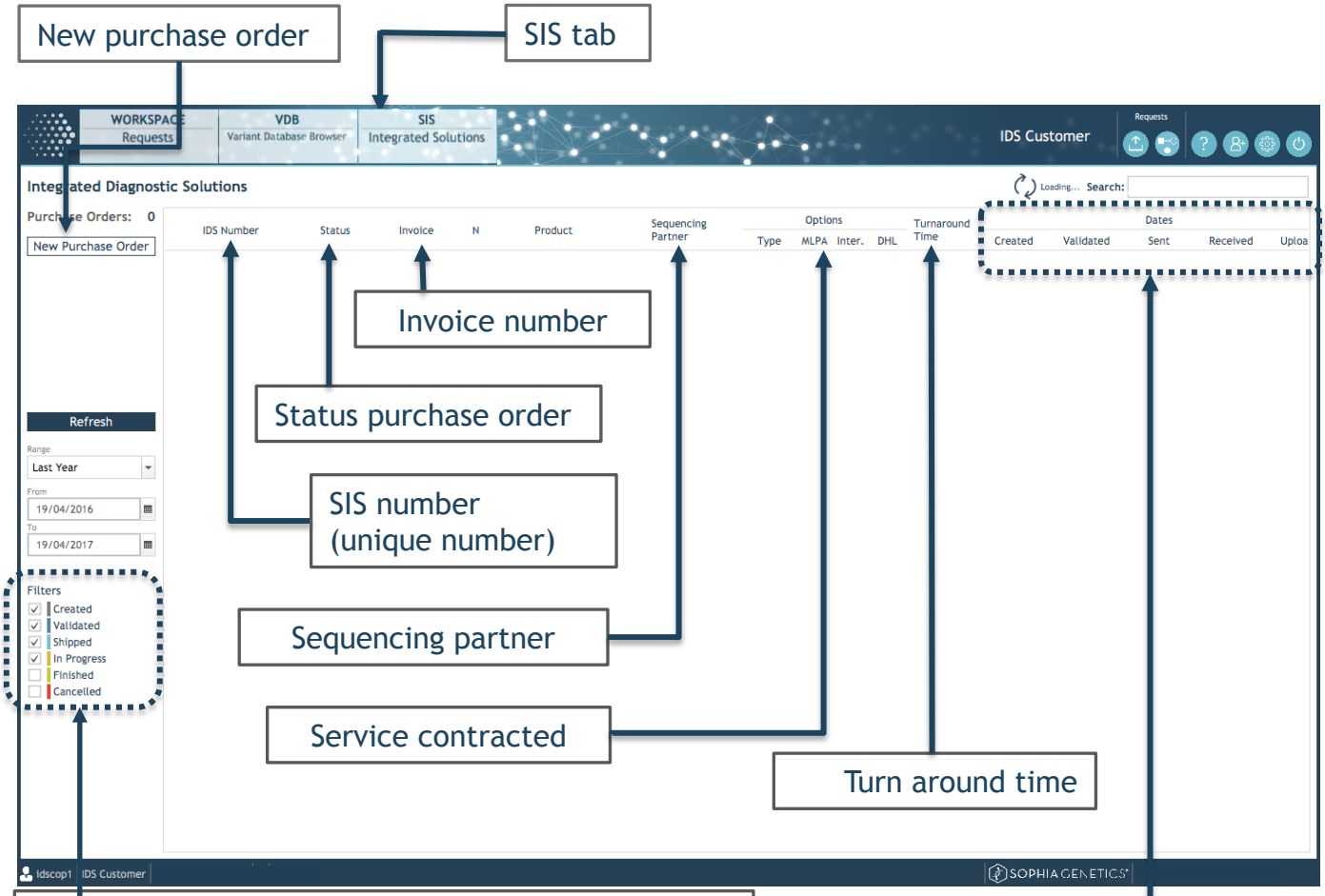
Links
Possibility to retrieve more external information about the variant by clicking on the corresponding database link.

12. SIS client
12.1 Dashboard



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™.

12. SIS Client
12.2 Purchase Orders
12.2.1 Purchase Orders – Overview



Purchase order statuses

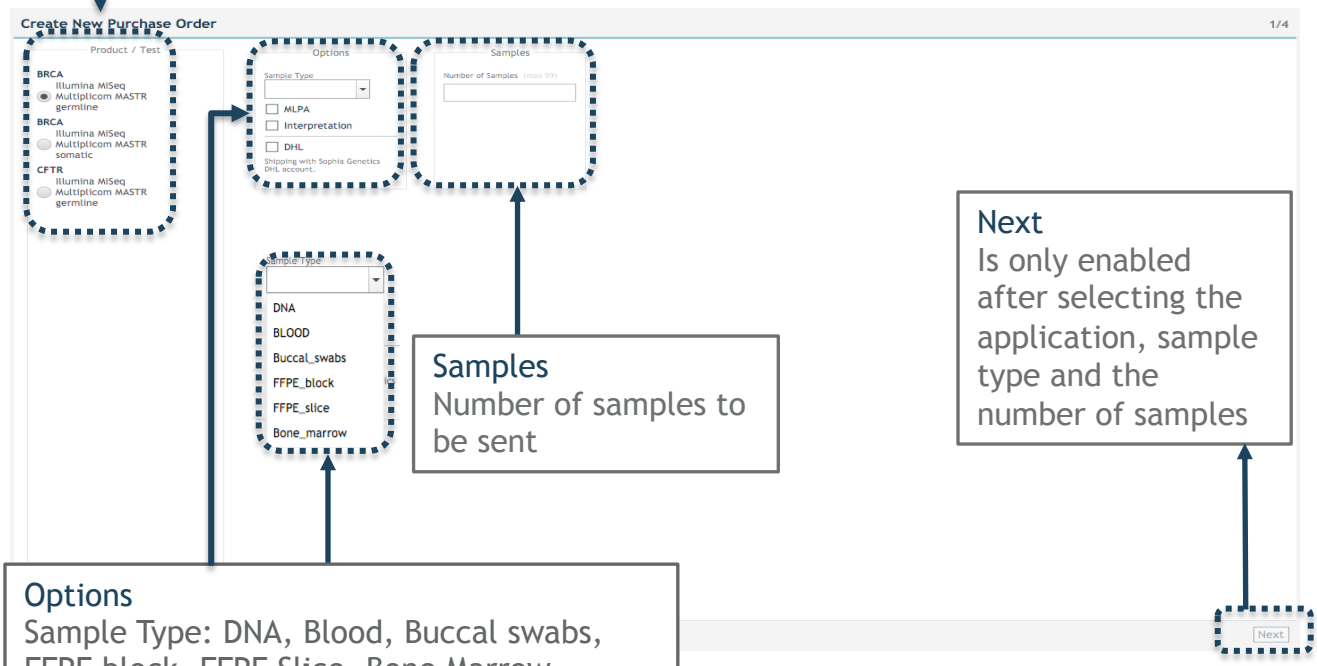
- Created: Awaiting validation
- Validated: Ready to ship samples
- Shipped: The client has shipped the samples
- In Progress: The sequencing partner has received the samples
- Finished: The run has been uploaded
- Canceled: The purchase order has been canceled by the client

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

12. SIS Client
12.2 Purchase Orders
12.2.2 Purchase Order Creation (1)

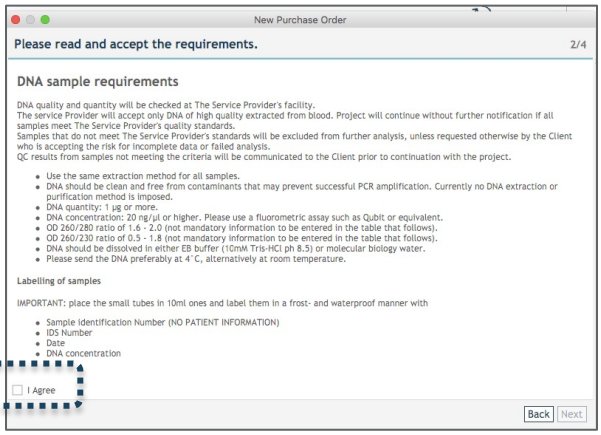
Product/Application
Applications available for the client



Samples
Number of samples to be sent

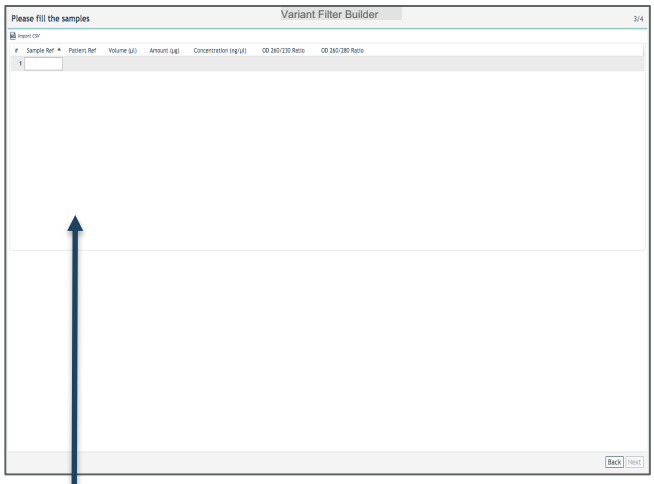
Next
Is only enabled after selecting the application, sample type and the number of samples

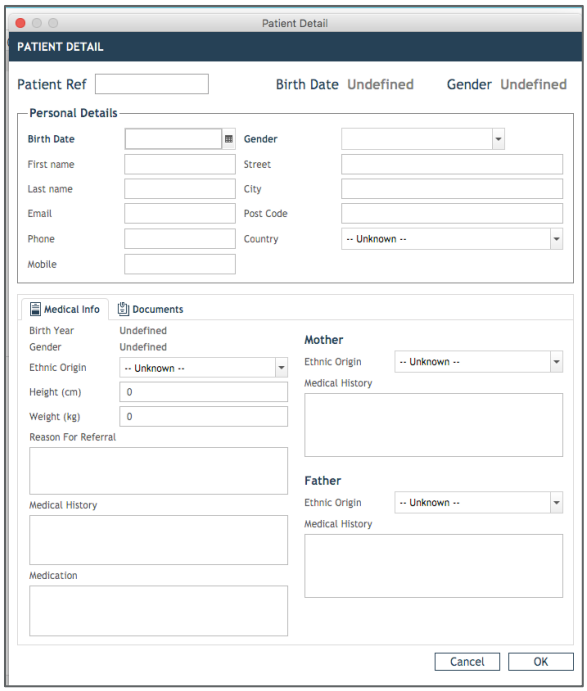
Options
Sample Type: DNA, Blood, Buccal swabs, FFPE block, FFPE Slice, Bone Marrow
MLPA: Request MLPA Analysis
Interpretation: Request interpretation*
DHL: Shipment with SOPHiA GENETICS DHL account



Validation check box

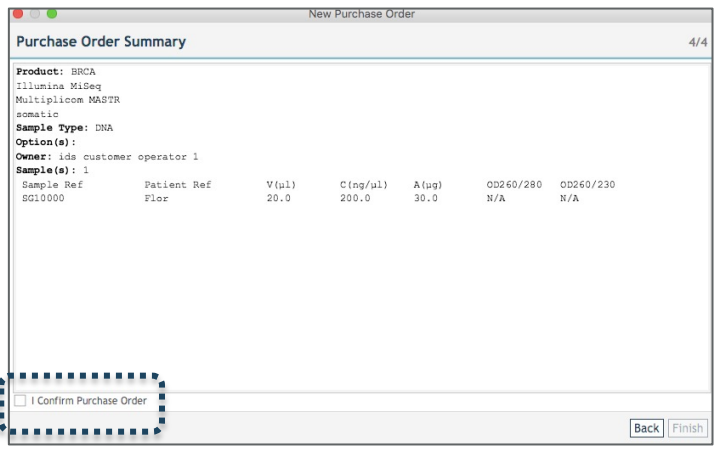
12. SIS Client
12.2 Purchase Orders
12.2.2 Purchase Order Creation (2)





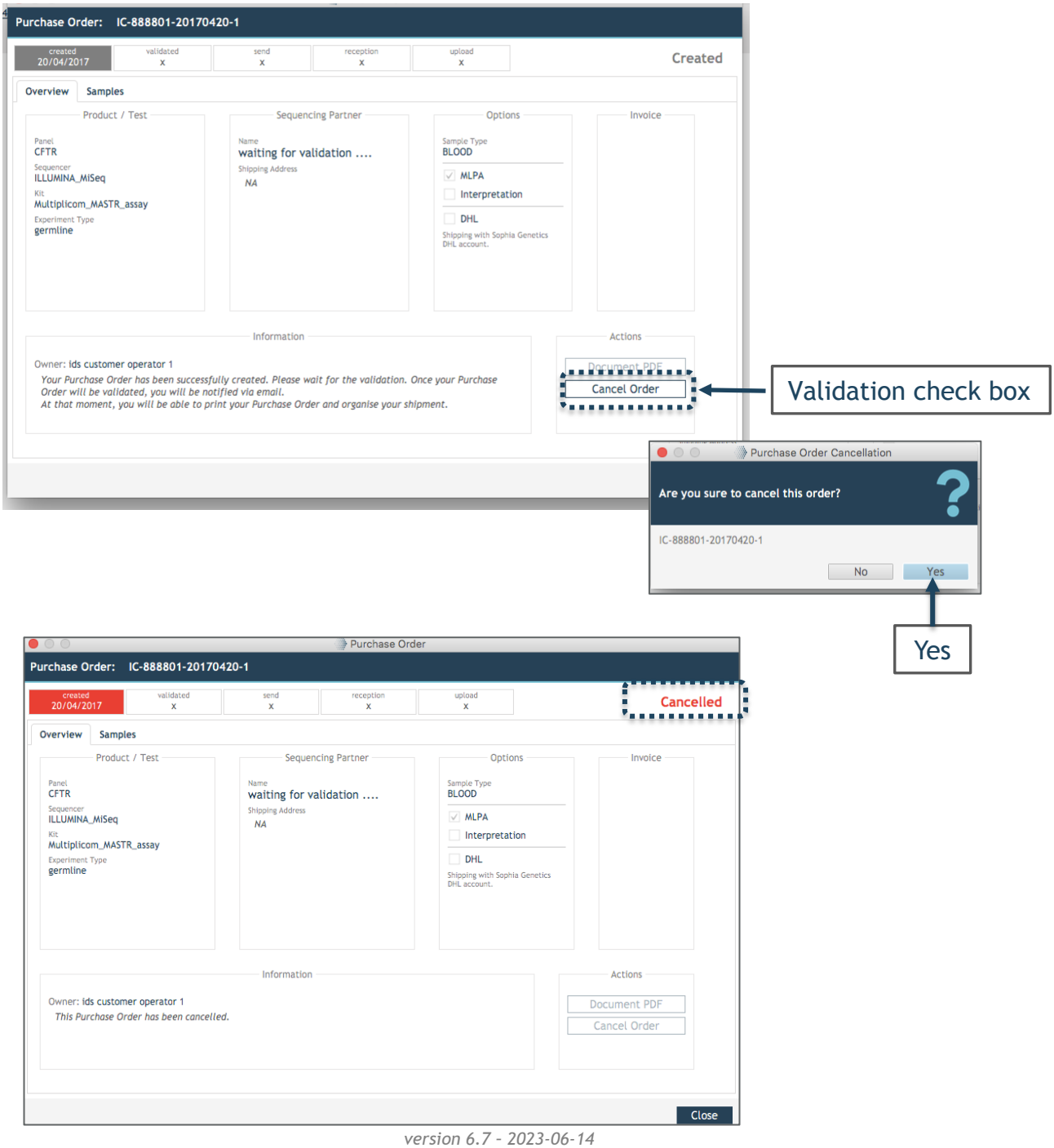
1 Depending on the sample type selected:
Sample ref: Give a ref alphanumeric code
Patient* ref: See box 2
Volume: Sample volume
Amount: Sample amount
Concentration: Sample concentration
OD 260/230 Ratio
OD 269/280 Ratio

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

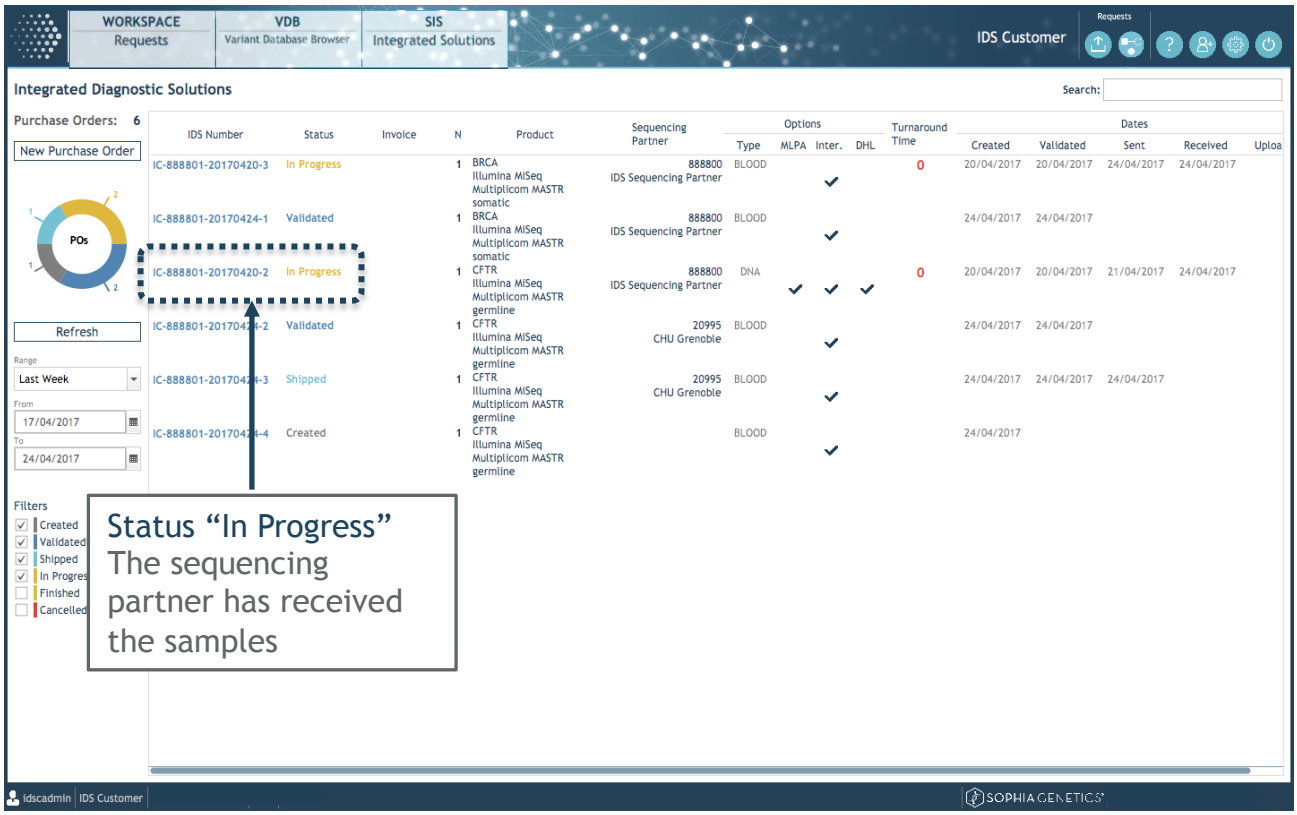


12. SIS Client

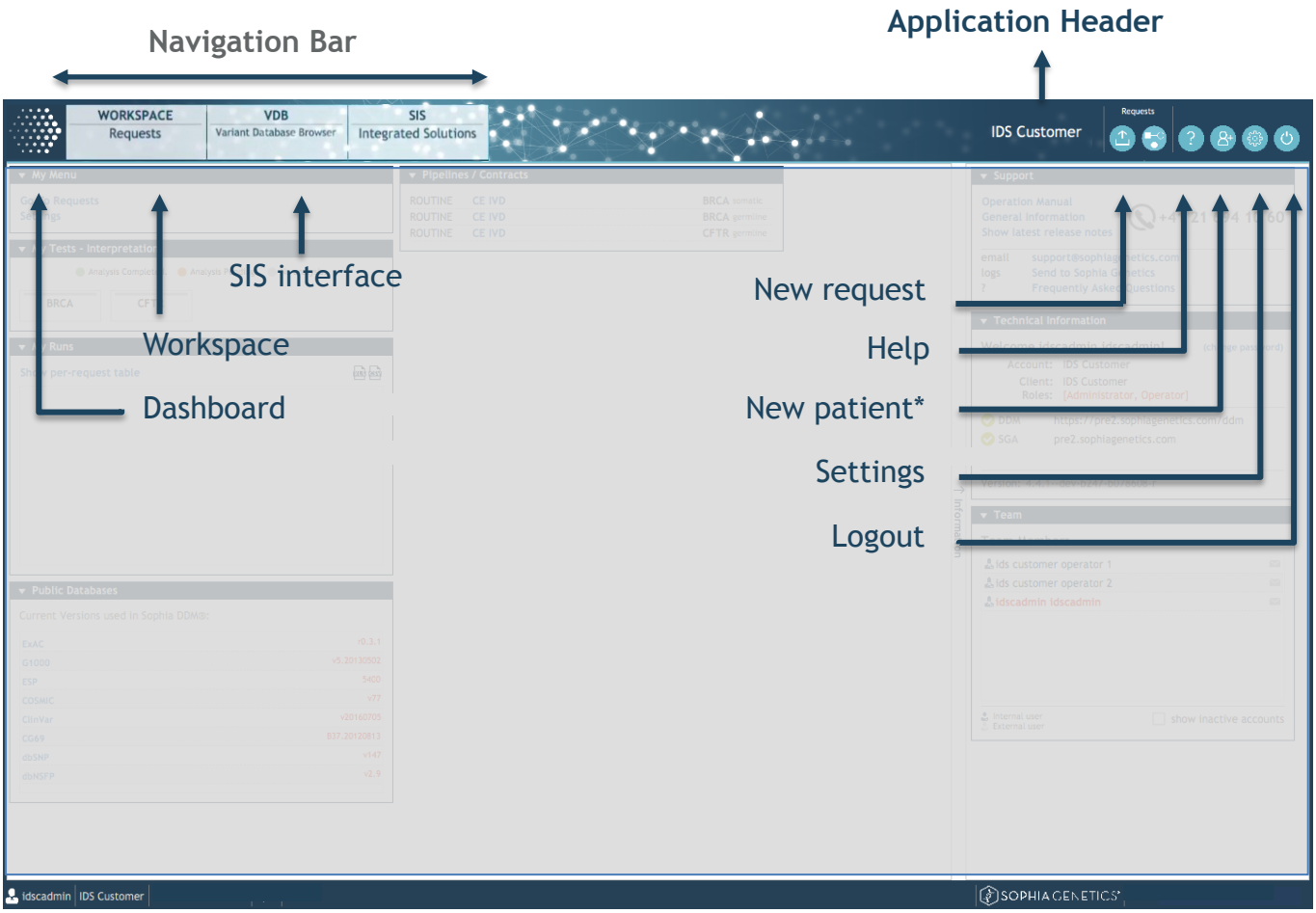
12.2 Purchase Orders

12.2.4 Validated PO Sample Shipment

12. SIS Client
12.2 Purchase Orders
12.2.5 Status Overview



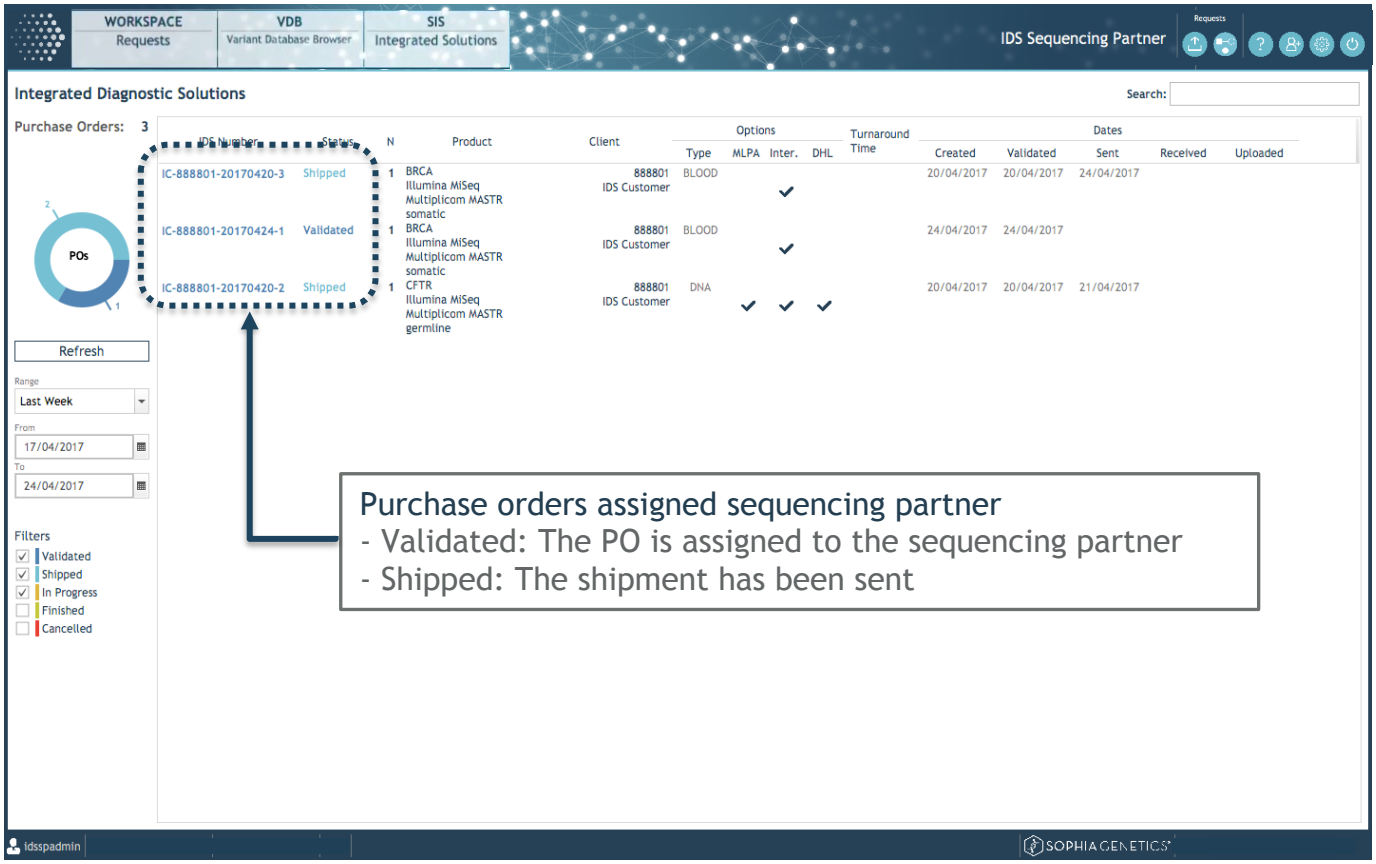
13. SIS - Sequencing Partner
13.1 Dashboard



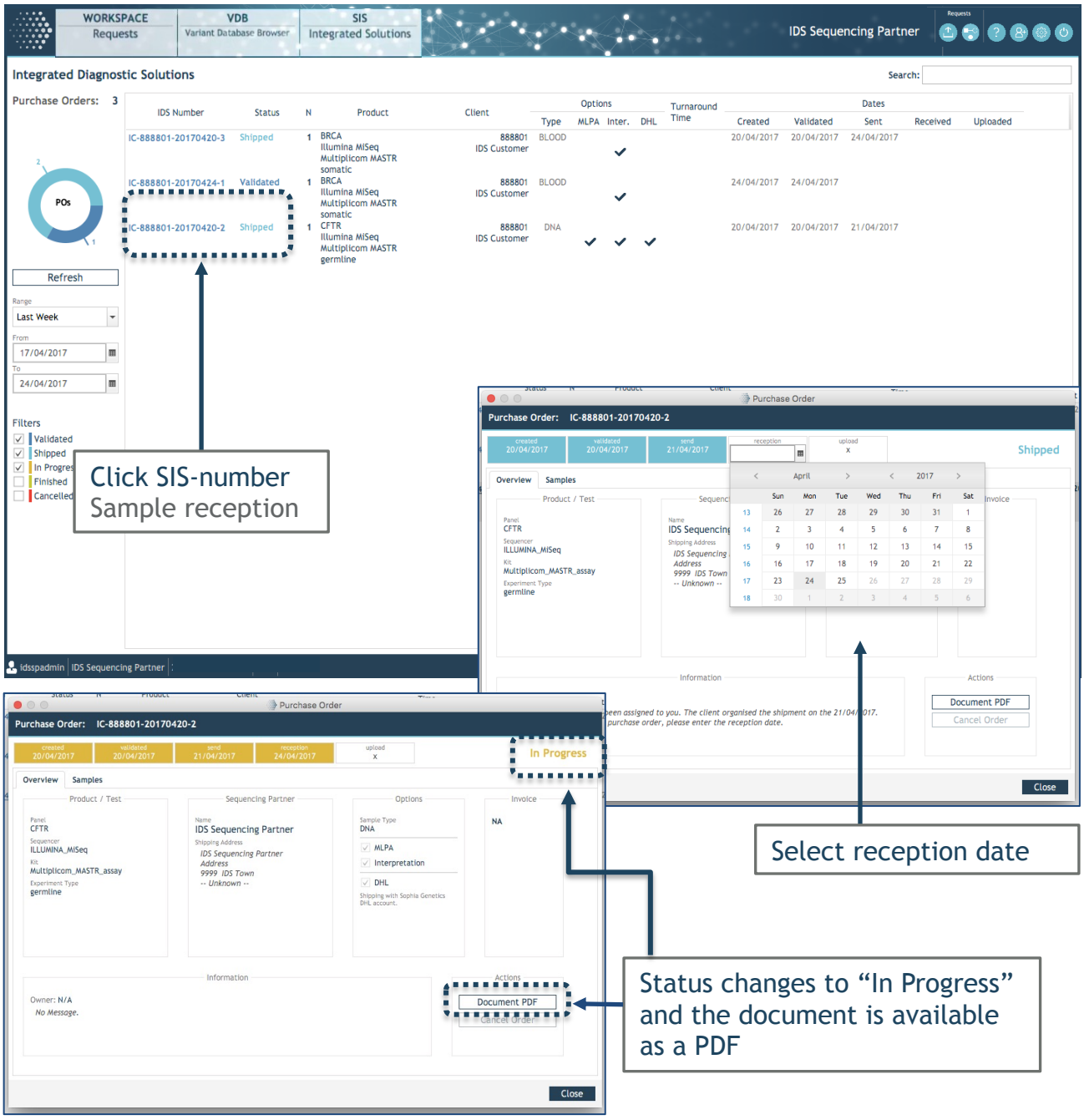
User Information:
- Username
- Client
- Starting date of the session

SOPHiA DDM™ release version

13. SIS - Sequencing Partner
13.2 Assigned Purchase Orders
13.2.1 Assigned POs – Overview

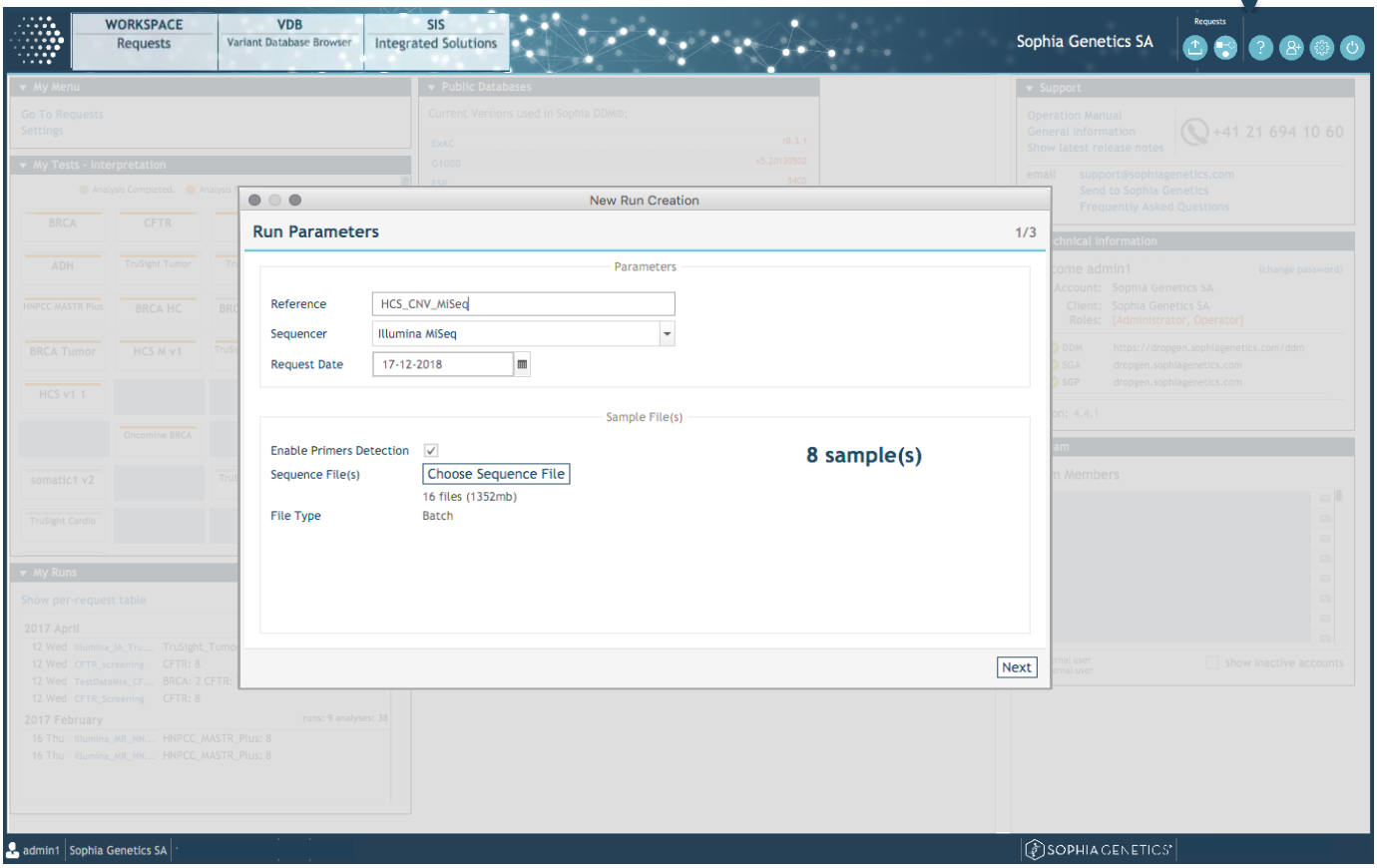


13. SIS - Sequencing Partner
13.2 Assigned Purchase Orders
13.2.2 Sample Reception



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.

13. SIS Sequencing Partner
13.2 Assigned Purchase Orders
13.2.3 Manual Sample Upload (2)

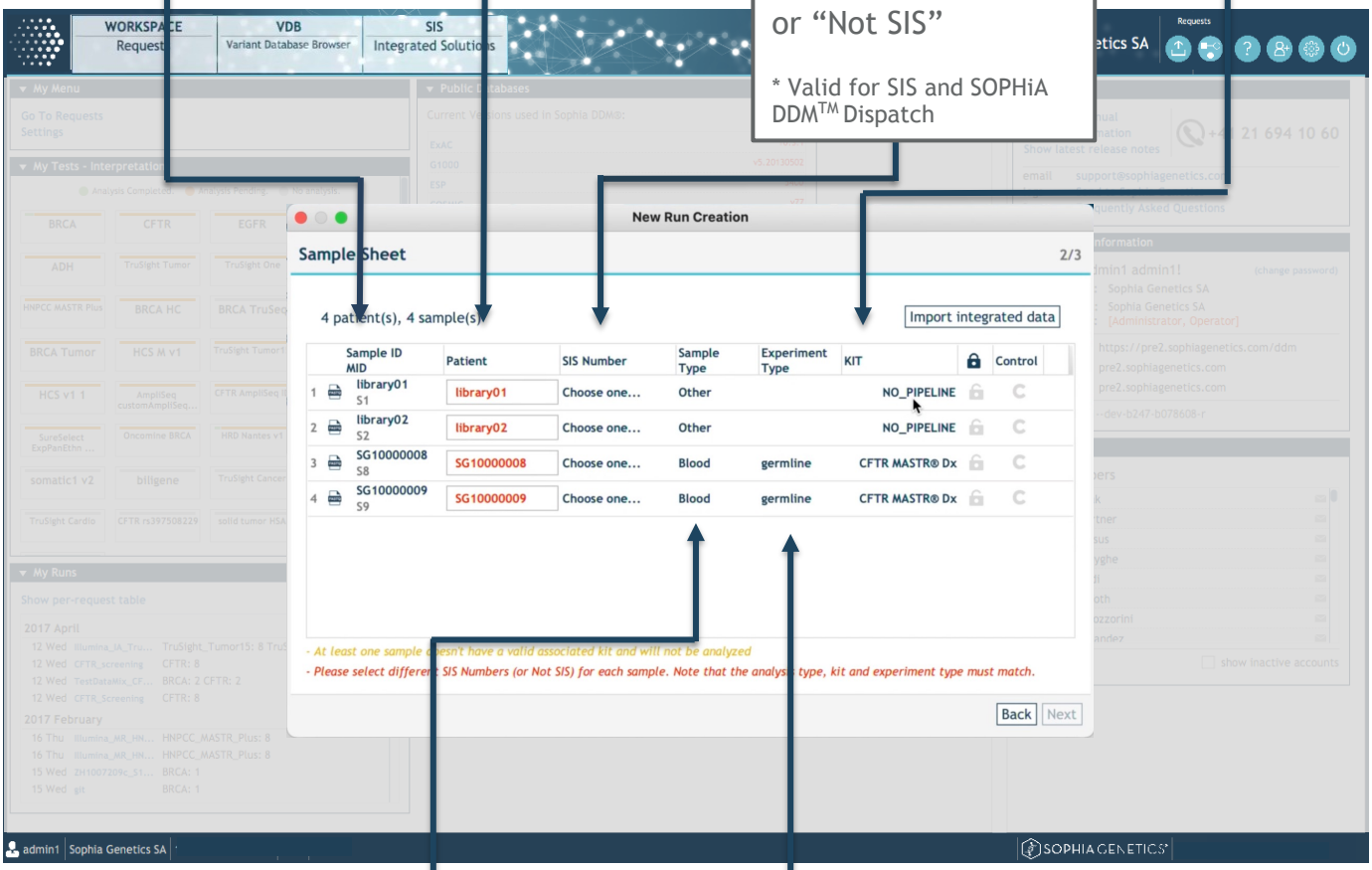
"MID"
Index used for sample identification

"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

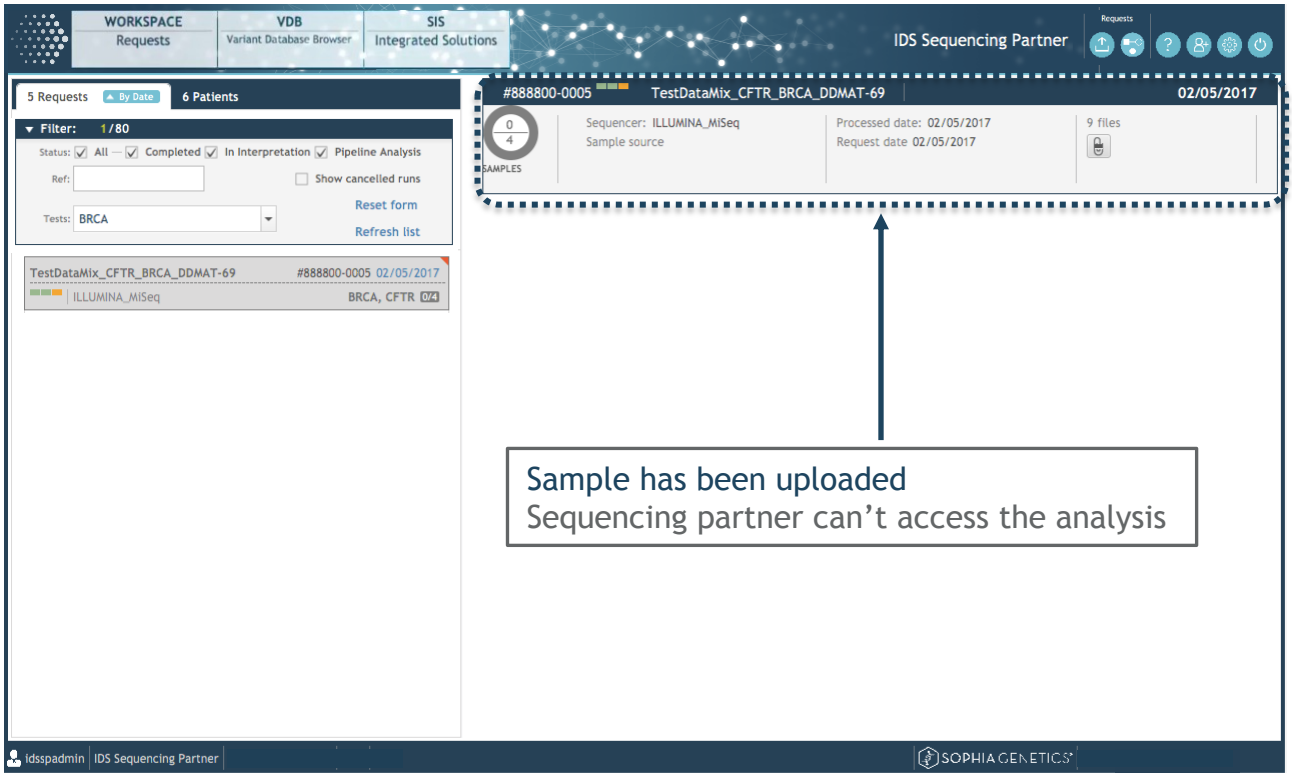
"Kit"
Library prep kit used (see p. 22)



"Sample 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)

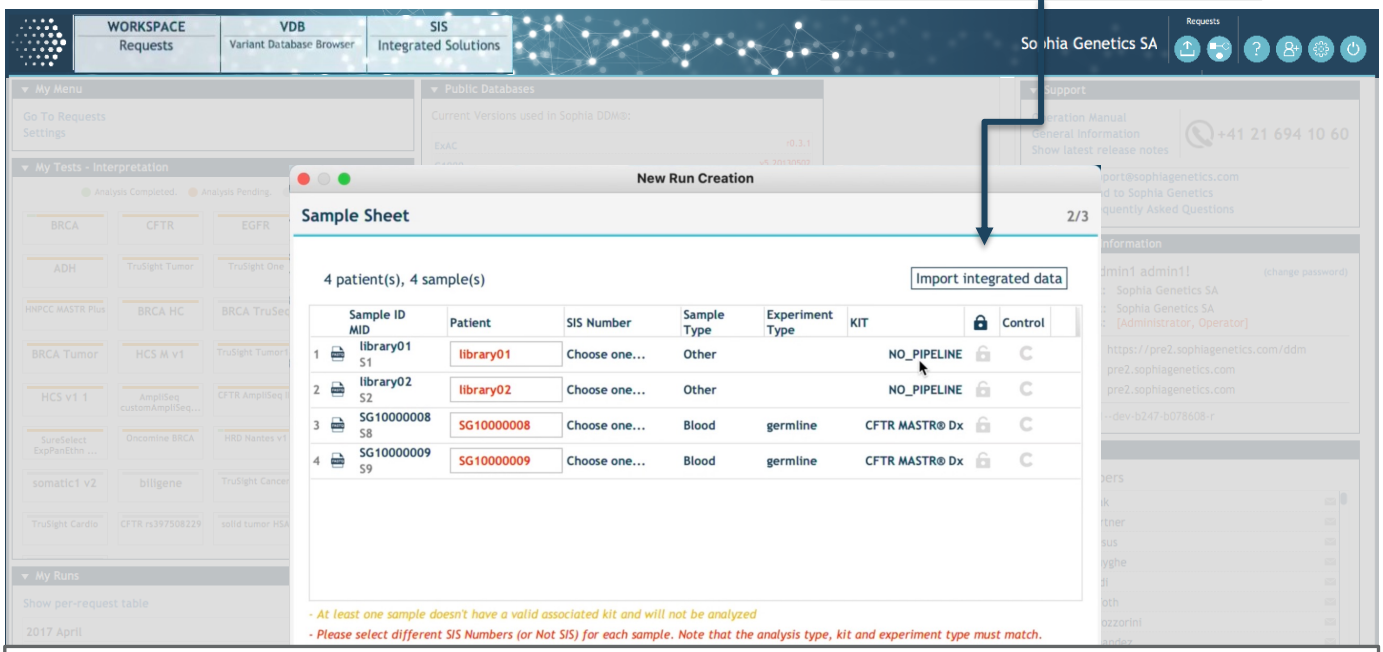


Note: Independently of the selected upload method (manual or semi-automatic), the Sequencing Partner can view the list of uploads without access to results in their account. The Sequencing Client can access the result of the analysis in their account and the FASTQ file(s) and QA report per patient* are accessible for download from the sample card of the respective sample.

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

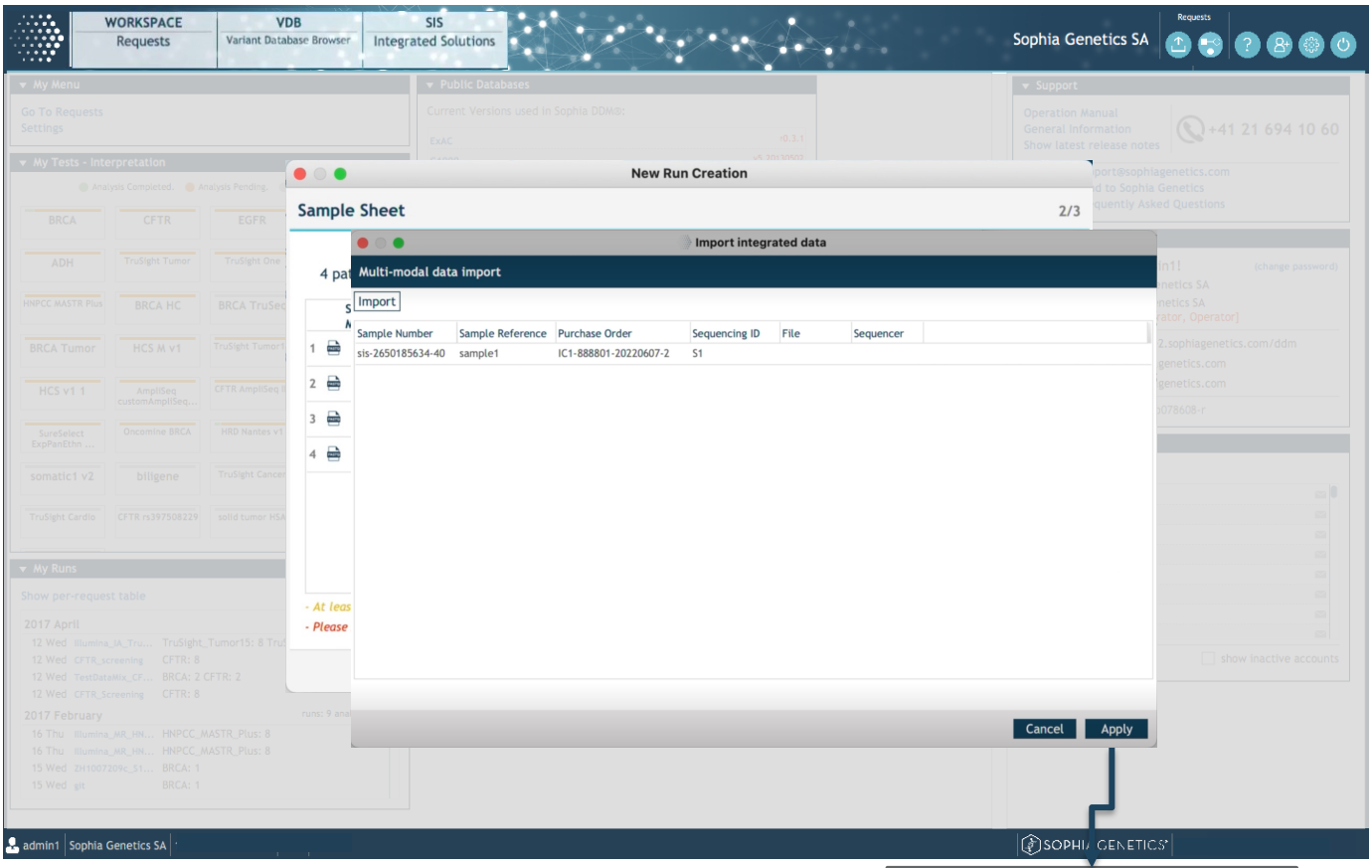
"Import Integrated Data"
Import a *.csv file with a link between your sample and the sequencing data



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)



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.**

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

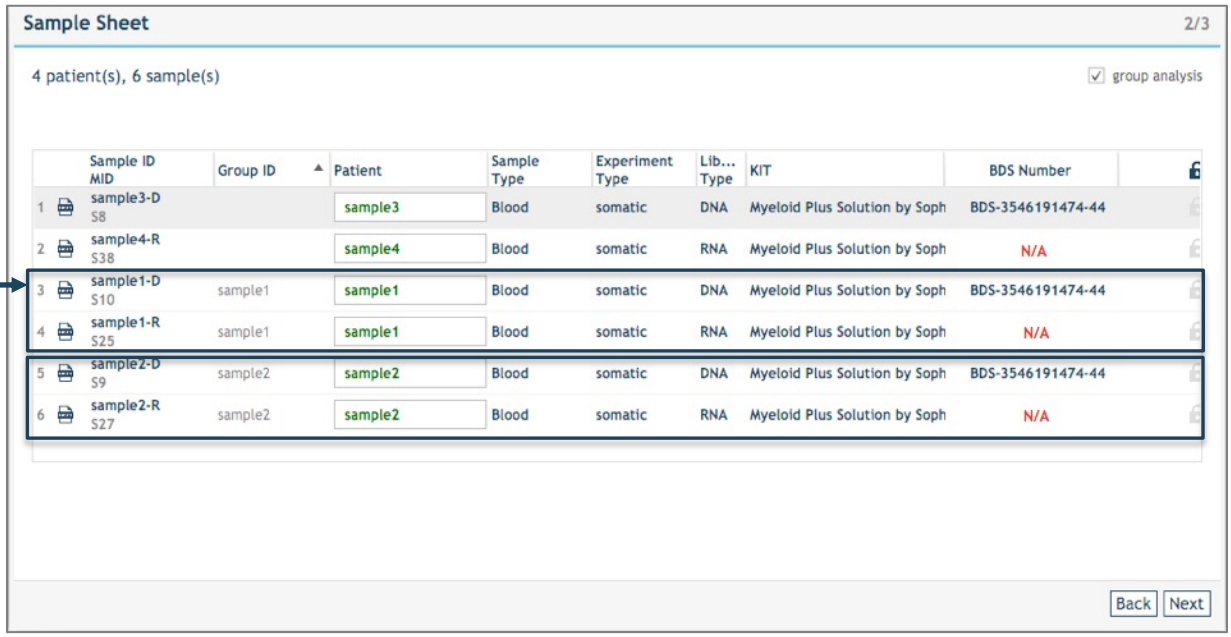
For MYS+ and STS+, SNV/Indel detection is performed on DNA samples and fusion gene detection on RNA samples. This requires a joint upload of DNA and RNA samples (see chapter 14.1.1 - Dual DNA RNA upload).
For the Archer FusionPlex® CTL application, SNV and fusion gene detection is performed on a single 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.



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+	• The RNA files need to have -R in the file name and the DNA files –D 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	*.fastq	• The number of DNA FASTQ files (-D) should be equal or greater than the number of RNA FASTQ files (-R).
Oncomine™ Focus	• 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 Example: IonXpress013-D_R_2018_12_12_08_05_16_user_GSS5-0087-12-181211_KFJ_Oncomine_RNA_DNA_1_Auto_user_GSS5-0087-12-181211_KFJ_Oncomine_RNA_DNA_1_154.bam	*.bam	• No restrictions
TruSight™ Tumor 170 (TST170) & TruSight™ Oncology 500 (TSO500)	• Naming convention (-D and –R) has to be applied to the DNA and RNA samples, respectively 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	*.fastq	• 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

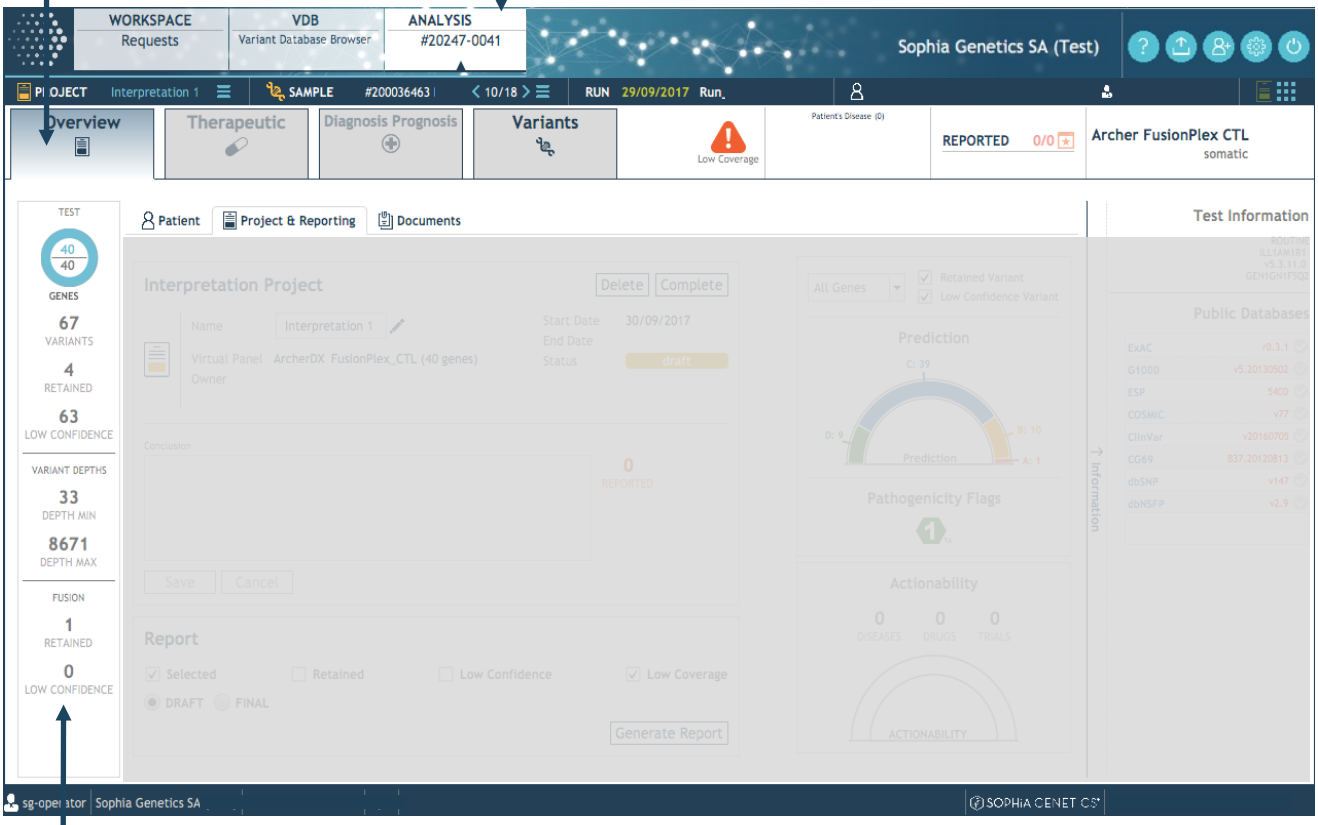
For the following applications fusion detection and SNV/Indel calling is available on the RNA sample.

Application	Naming convention / Example	Impacted Files	Upload restrictions
Archer Fusion Plex CTL	• No naming convention has to be applied, all samples are automatically considered RNA • SNVs/Indels and Fusions are detected from the RNA sample	*.fastq	• No restrictions

14. Gene Fusion Analysis
14.2 Analysis overview

Overview
Overview tab is highlighted

Analysis
Active analysis (highlighted in white)

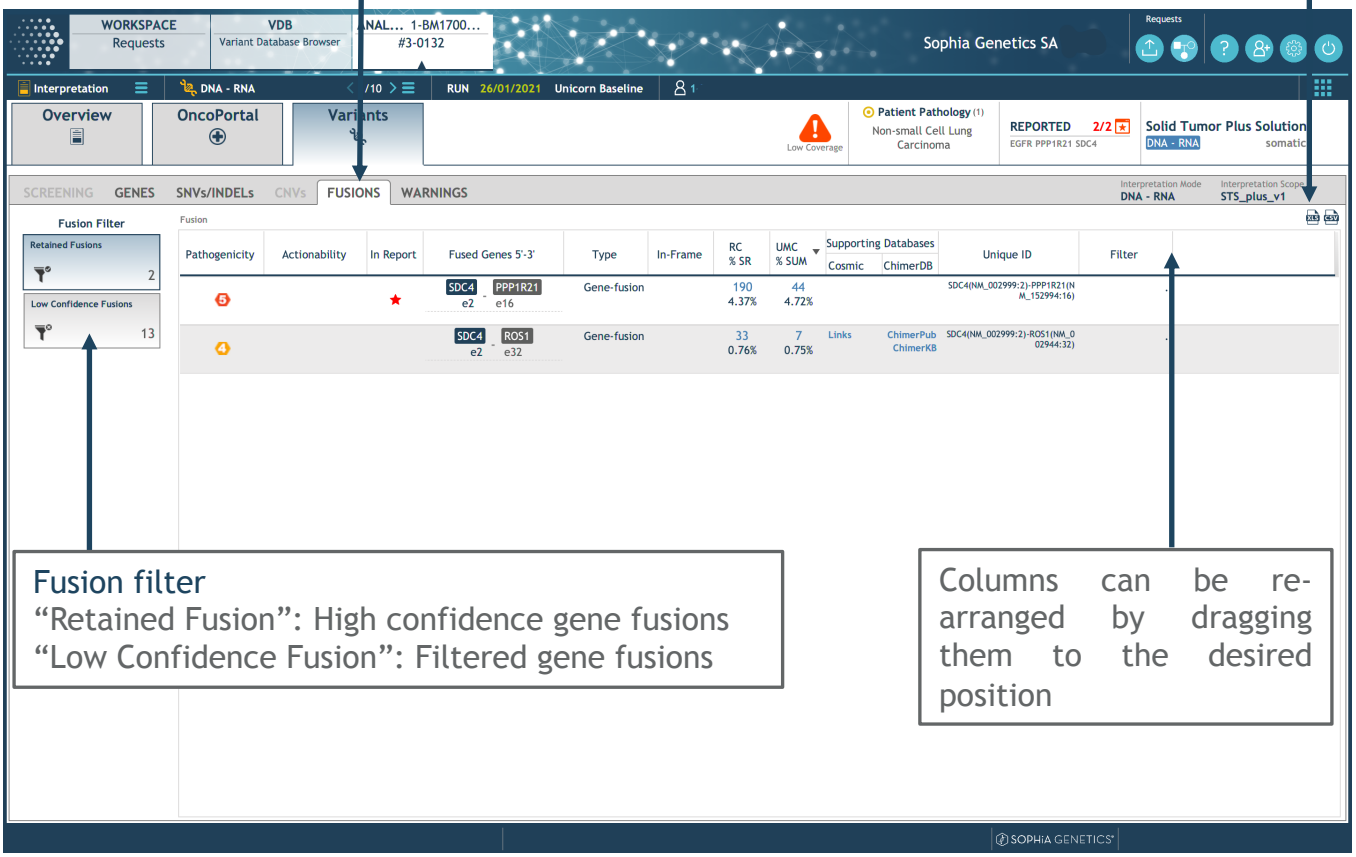


Application information column
In addition to the SNV/Indel information, the column also indicates how many fusion genes have been called with high confidence (retained) or low confidence

14. Gene Fusion Analysis
14.3 Fusion Tab

Fusion
Active tab

Download
Data can be downloaded as CSV or XLS files

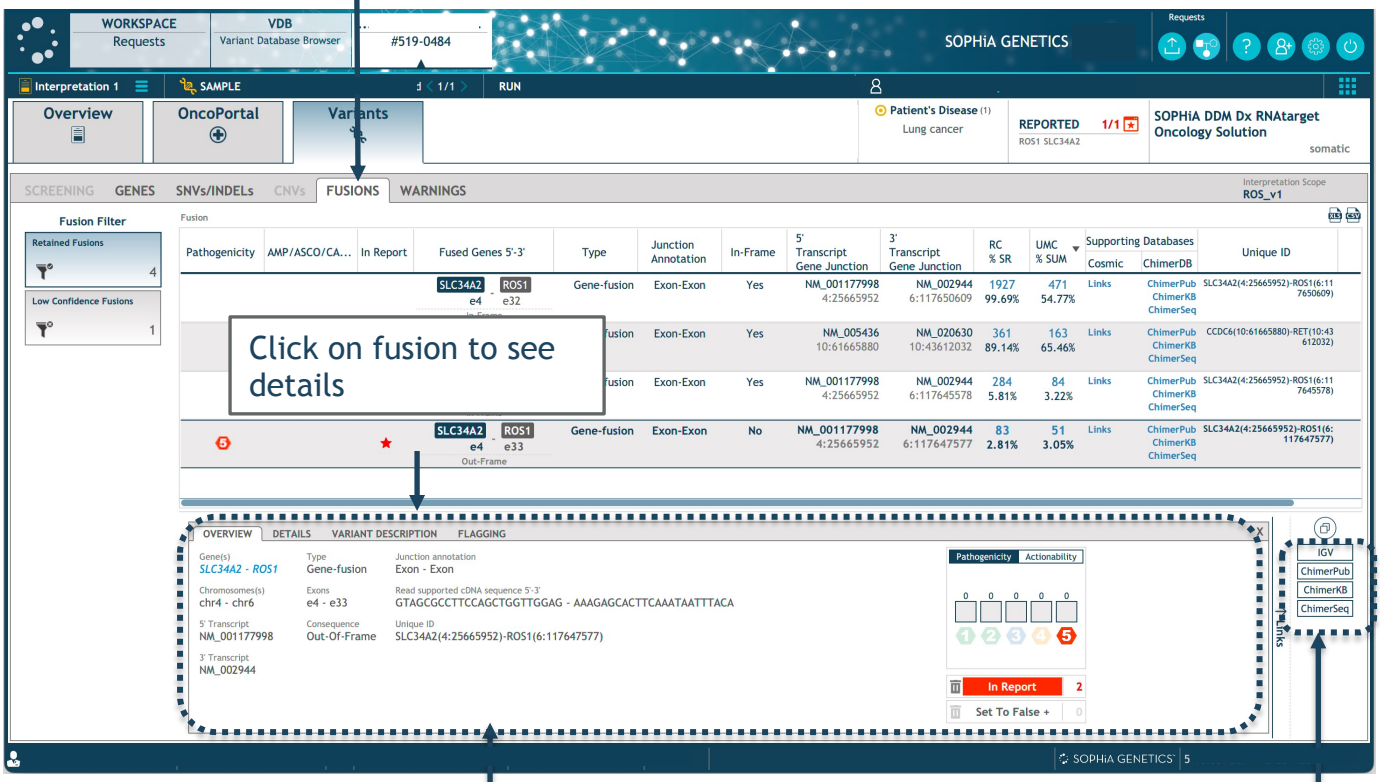


Fusion filter
"Retained Fusion": High confidence gene fusions
"Low Confidence Fusion": Filtered gene fusions

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



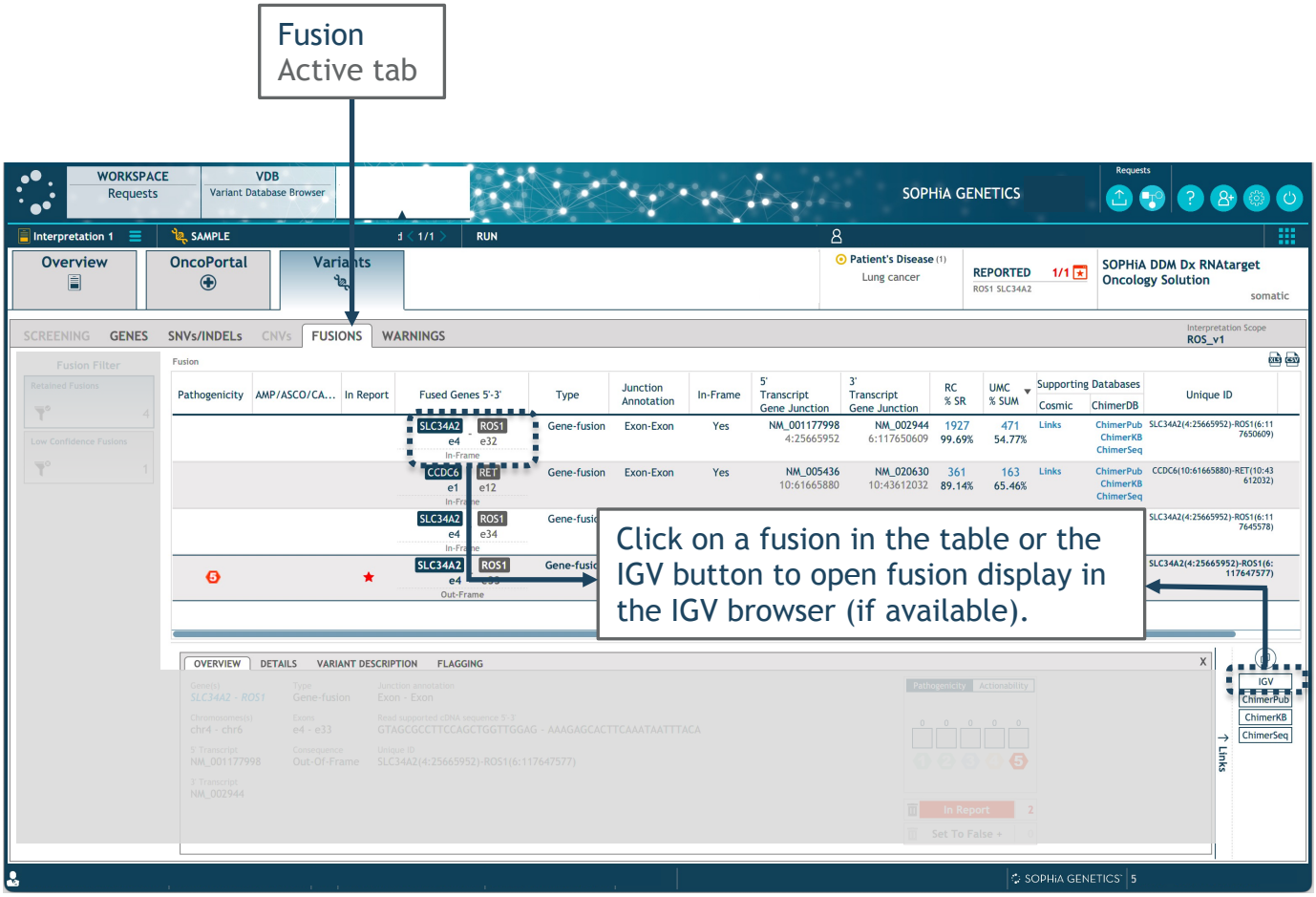
Overview
Information about the currently selected fusion:
Genes, chromosome, transcript, junction annotation

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



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 Oncomine™ 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.

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

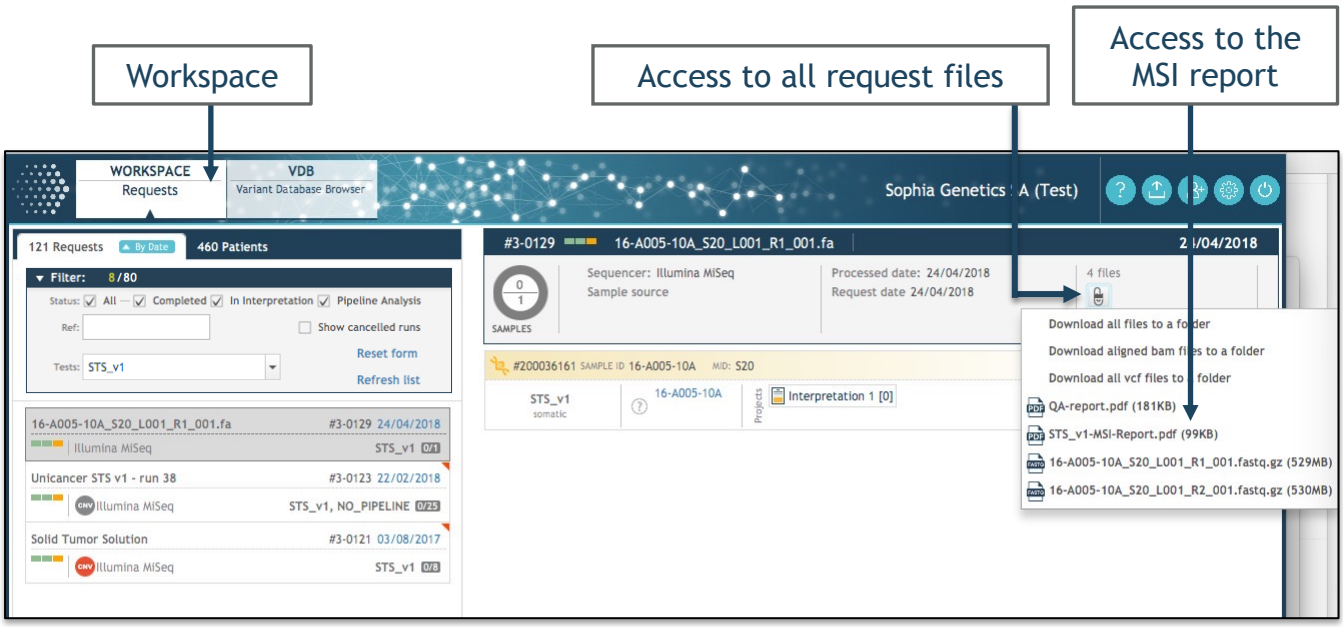
MSI-LC (MSI with low confidence) with a score between 6 and 14

The algorithm displays 2 MSI scores per analysis:

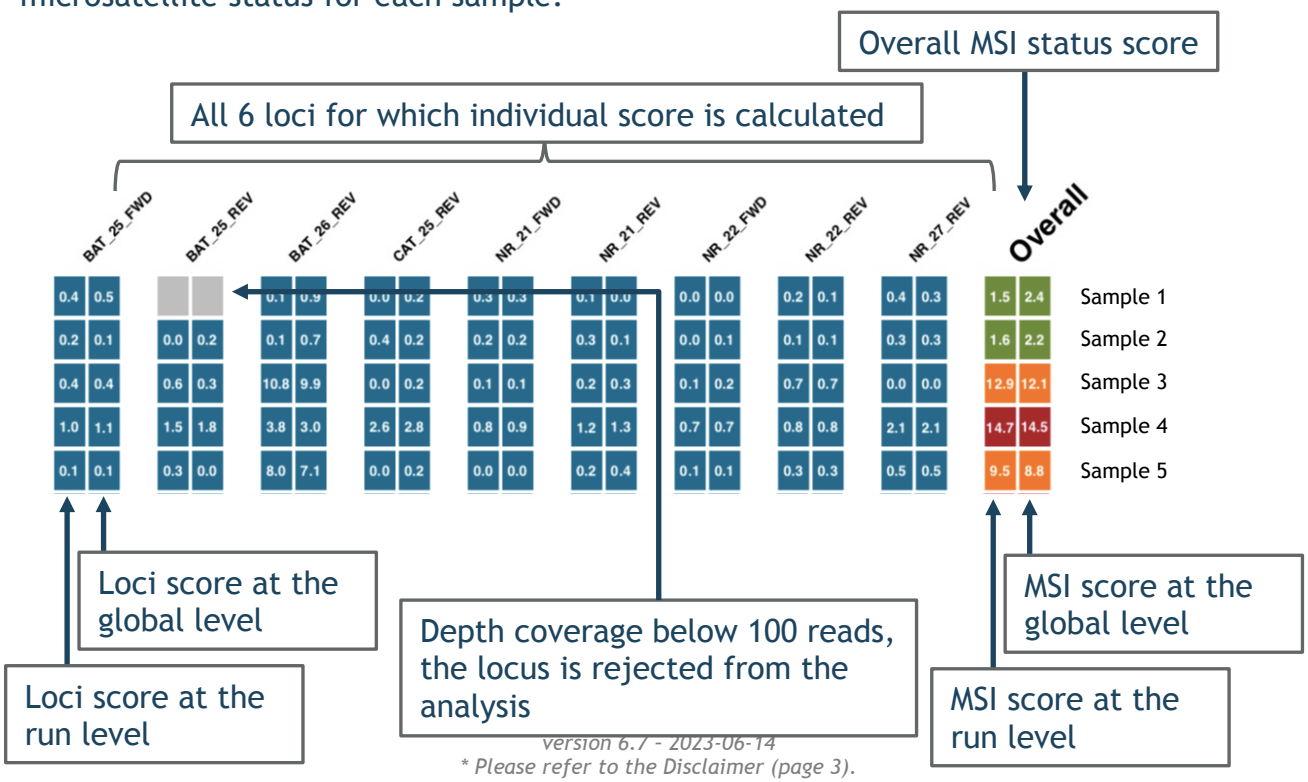
- At the run level
- At the global level, calculated on a dataset of over 400 clinical research FFPE samples (independent dataset)

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)

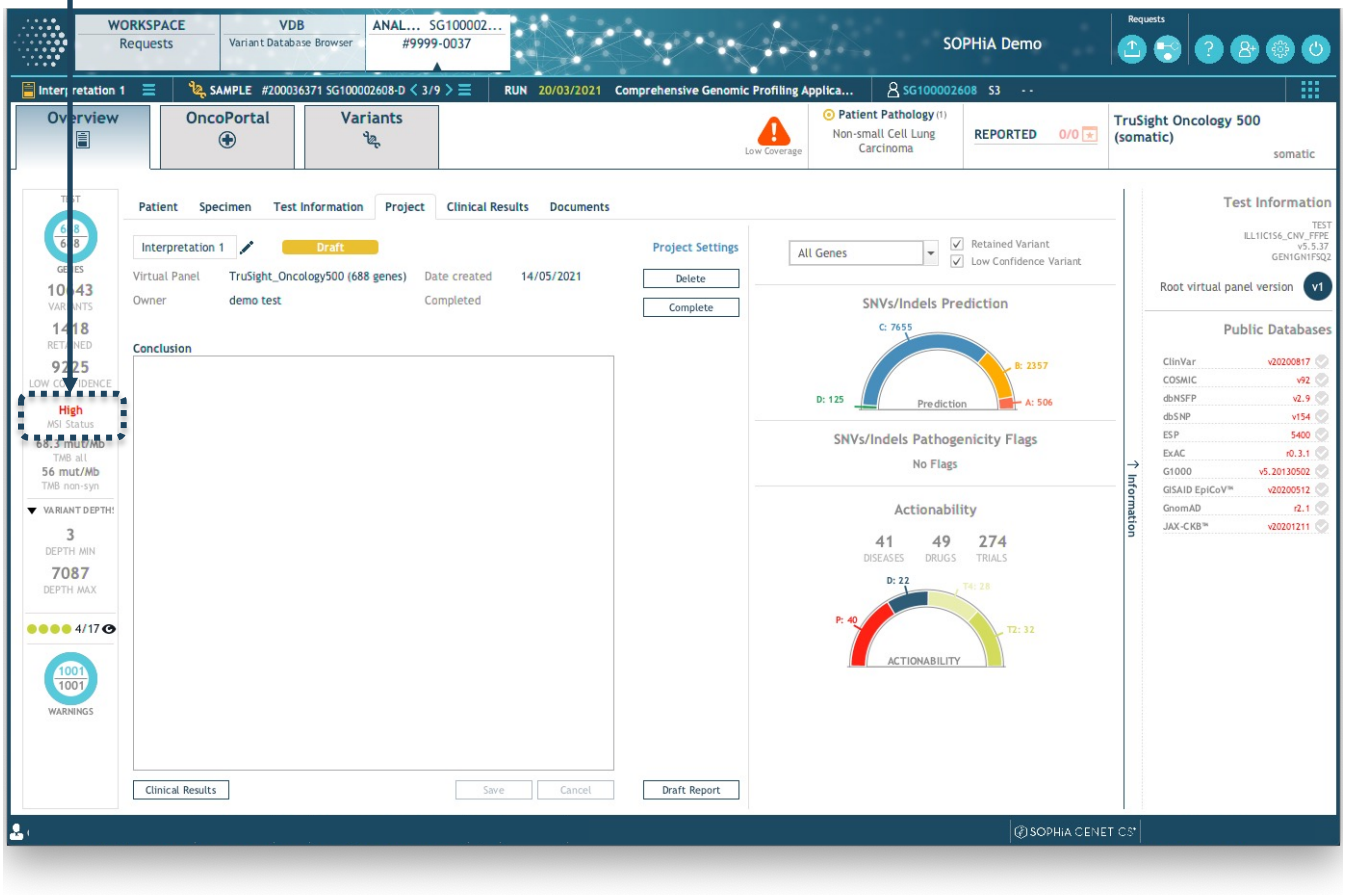


The MSI status report can be downloaded in pdf format from the run overview in the workspace of SOPHiA DDM™. This comprehensive report displays a summary table of the microsatellite status for each sample.



15. MSI Status Analysis
15.3 MSI status display (TSO500)

For the TSO500 application the MSI status is displayed in the Overview tab.



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.

16. Familial Variant Analysis

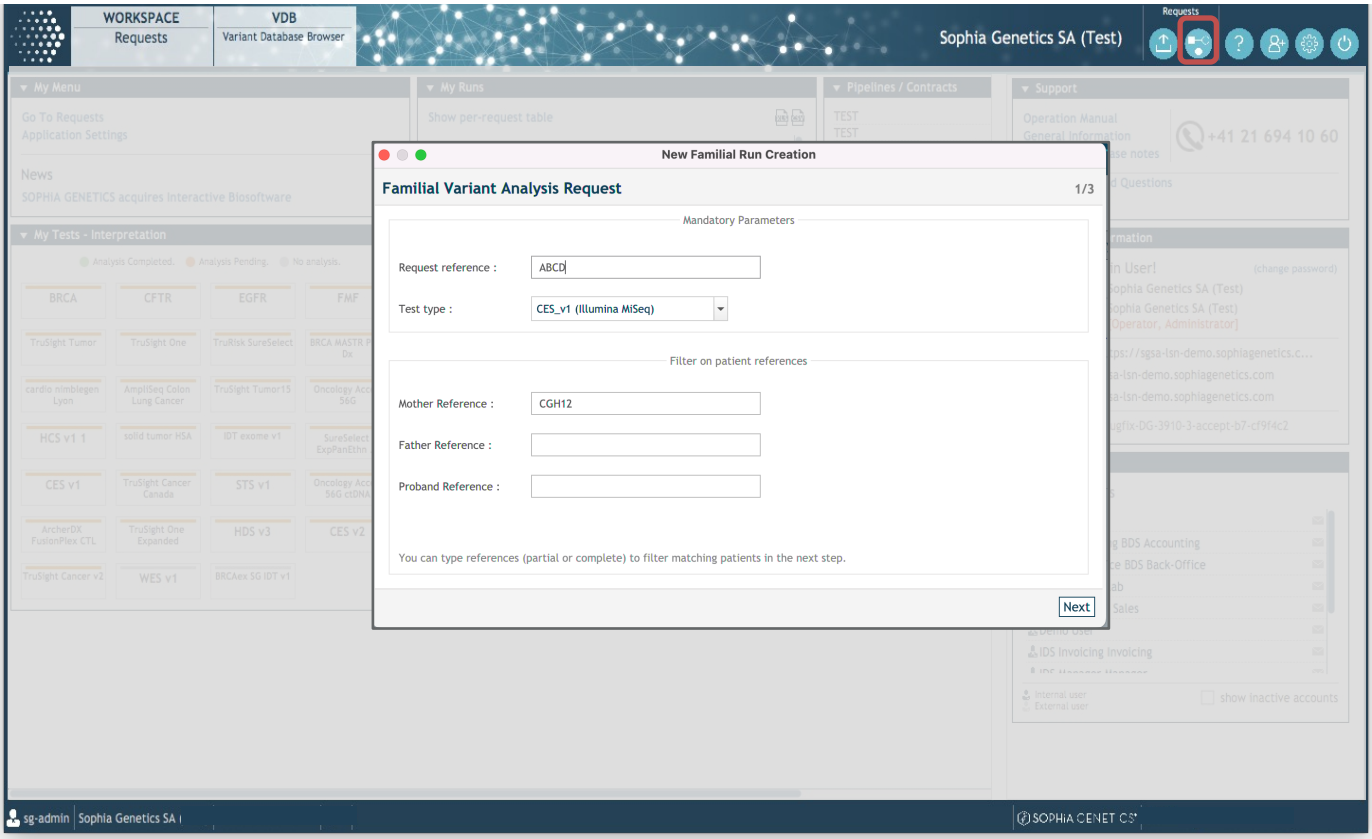
16.1 Overview

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.

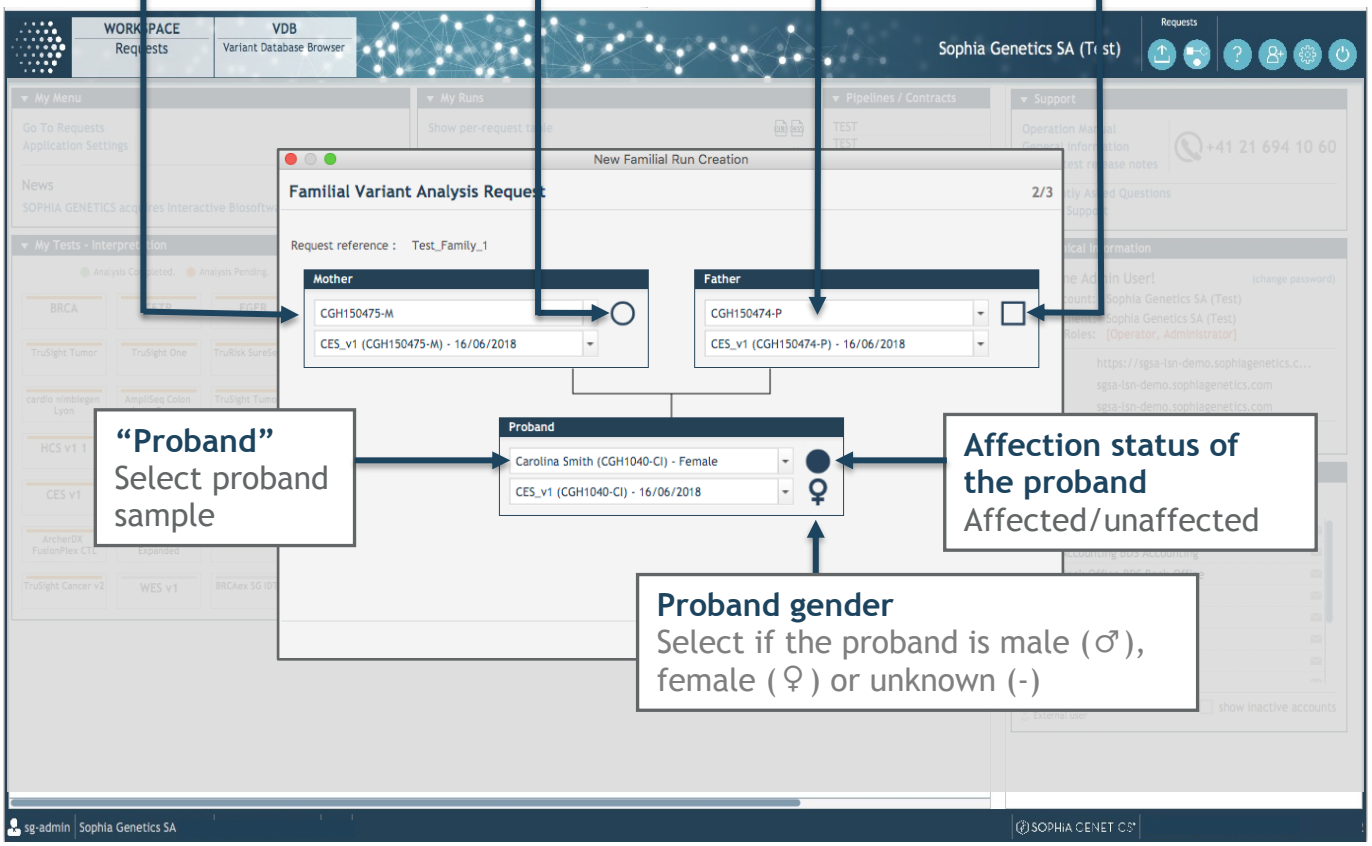
16. Familial Variant Analysis
16.2 Create a New FVA Request (2)

"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

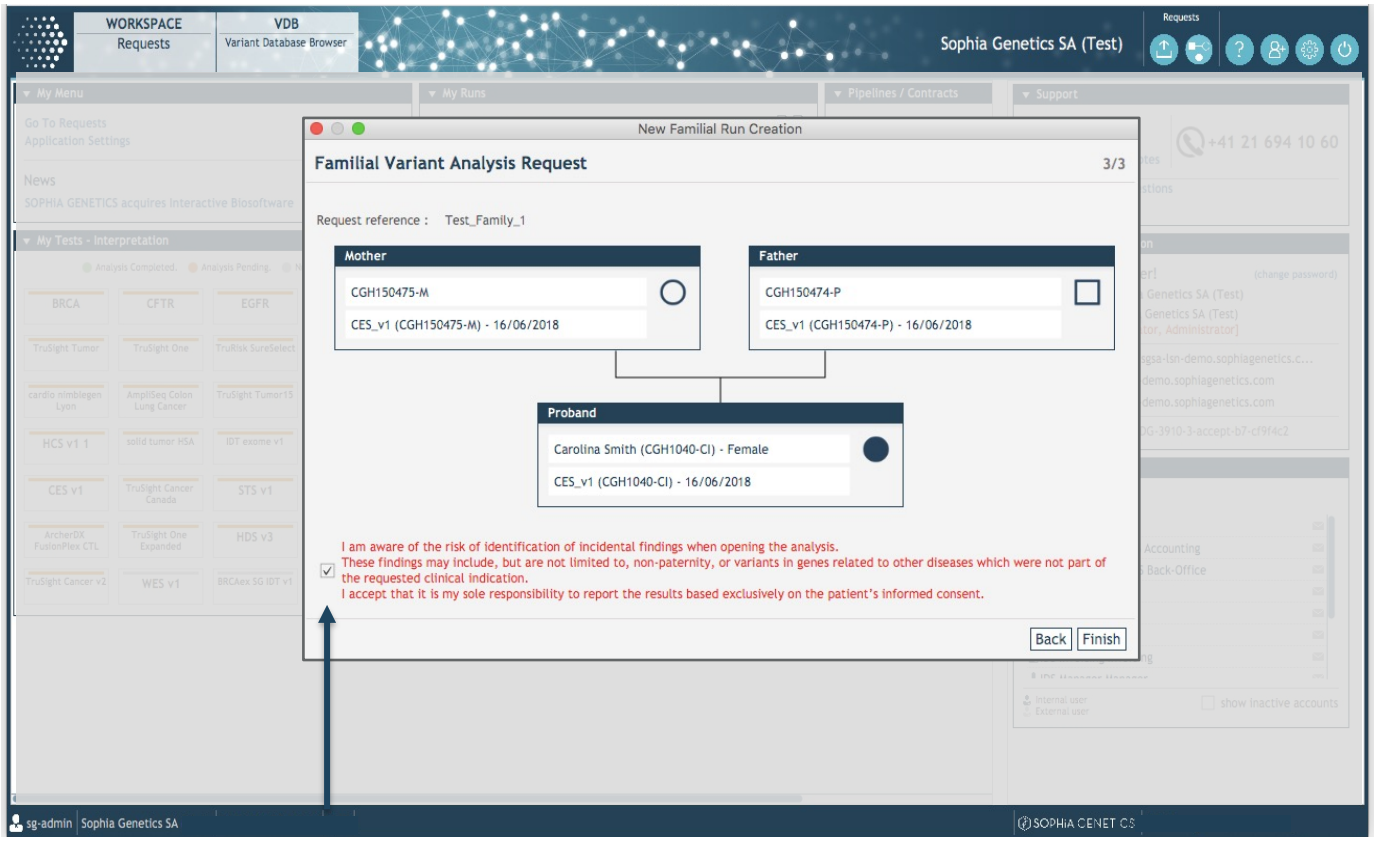
Affection status of the proband
Affected/unaffected

Proband gender
Select if the proband is male (♂), female (♀) or unknown (-)

- Chose 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).

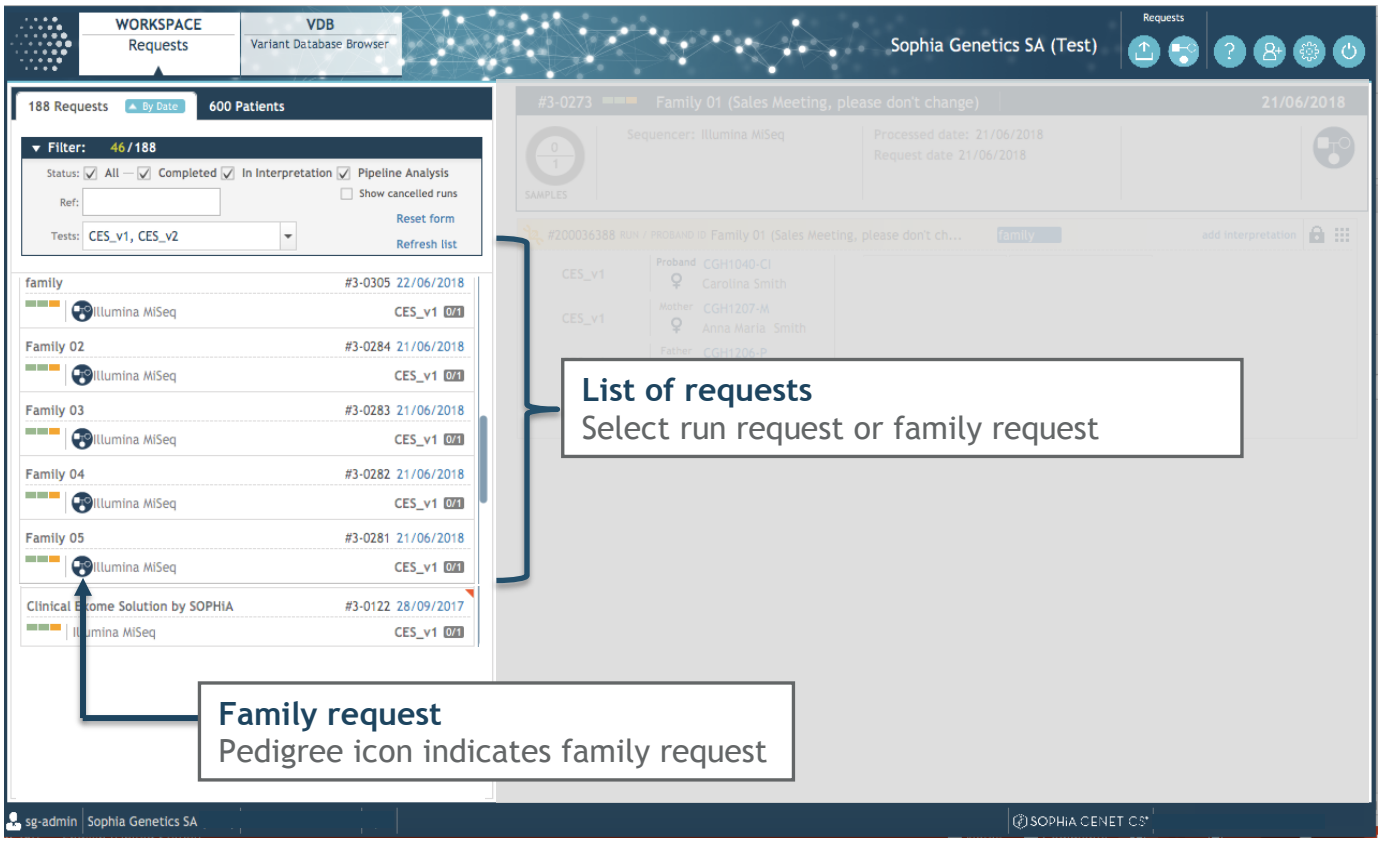
16. Familial Variant Analysis
16.2 Create a New FVA Request (3)



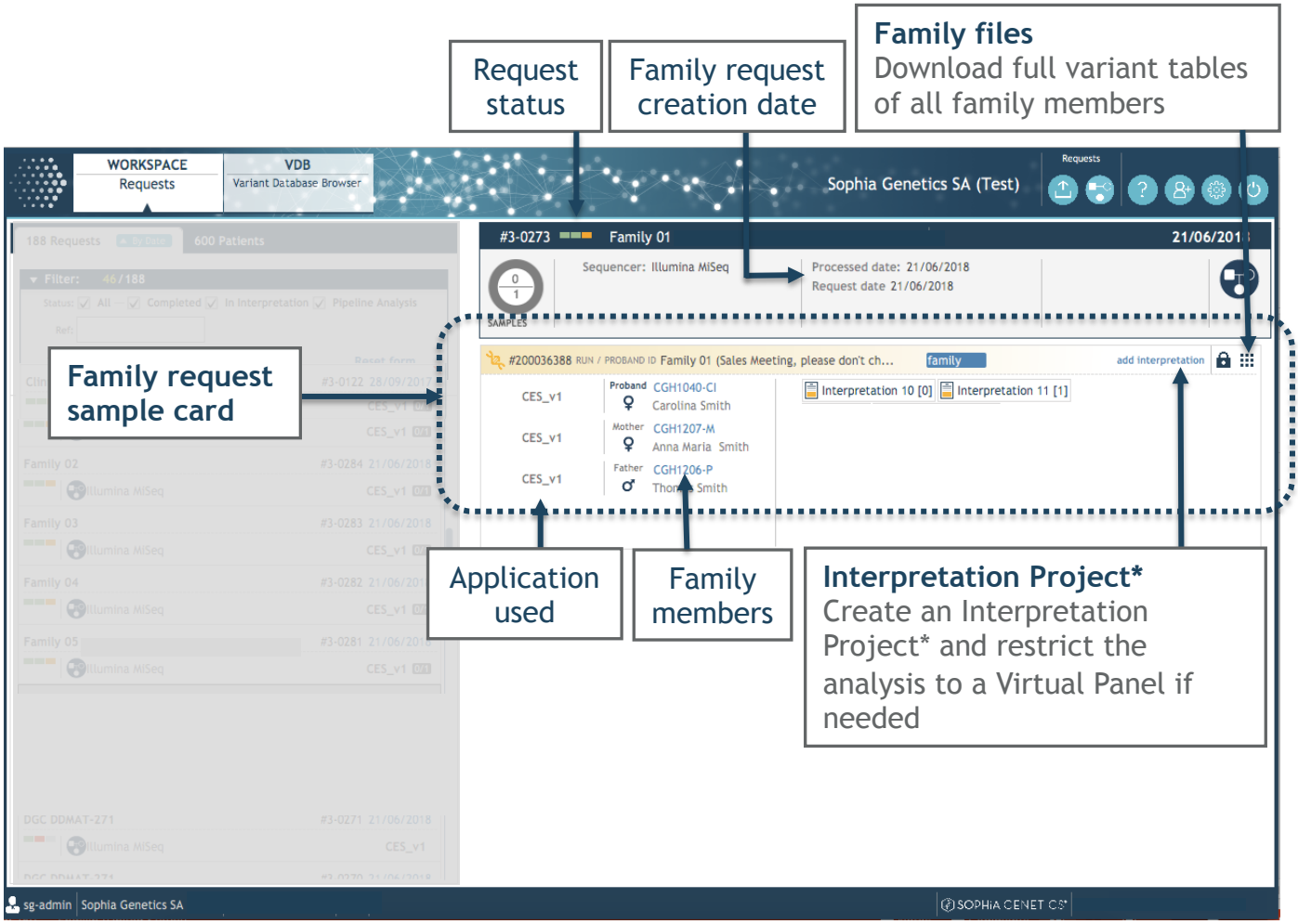
- Select checkbox to confirm that the risk of incidental findings is known
- Click "Finish" to create the new FVA request
- When completed, the user receives an email notification

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.

16. Familial Variant Analysis
16.3 Open a Family Request (1)



16. Familial Variant Analysis
16.3 Open a Family Request (2)



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.

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).

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

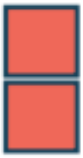
Variant is confidently absent (wildtype)

Variant is confidently heterozygous

Variant is confidently homozygous

Variant is confidently present but genotype (hetero- or homozygous) cannot be defined

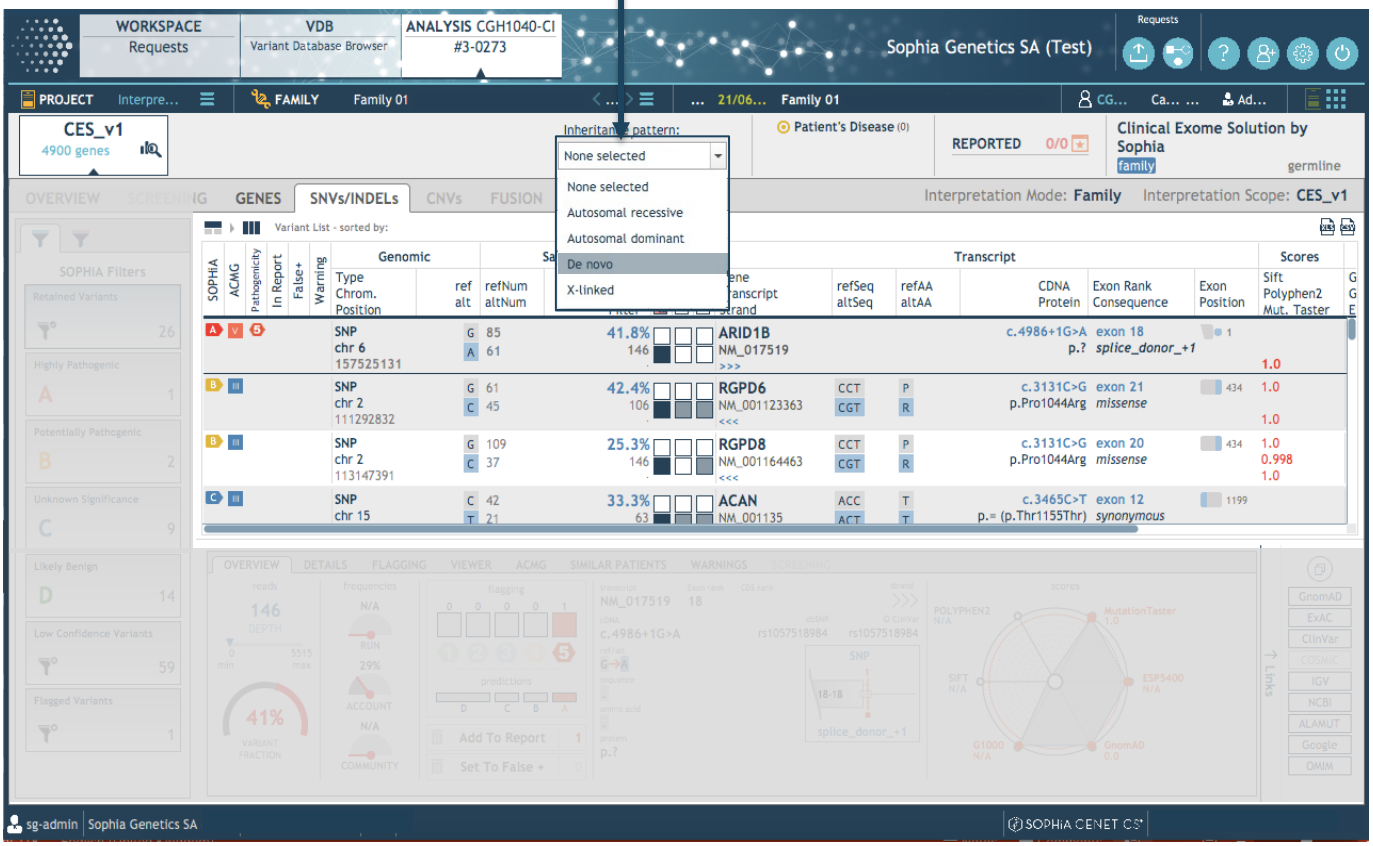
Homozygous state can be excluded but genotype (heterozygous or absent) cannot be defined



Noisy region (genotype cannot be determined)

16. Familial Variant Analysis
16.6 Inheritance Mode Filter

Inheritance mode
Select and test different modes of inheritance. Variants are filtered accordingly.



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.

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

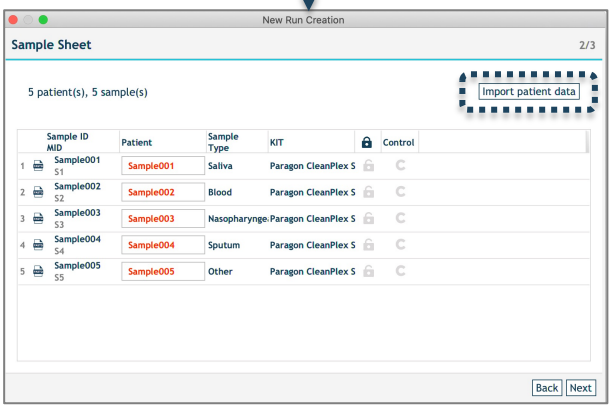
- **Global viral allele frequencies:** Allele-frequencies retrieved from the GISAID EpiCoV™ database are available in the full variant table

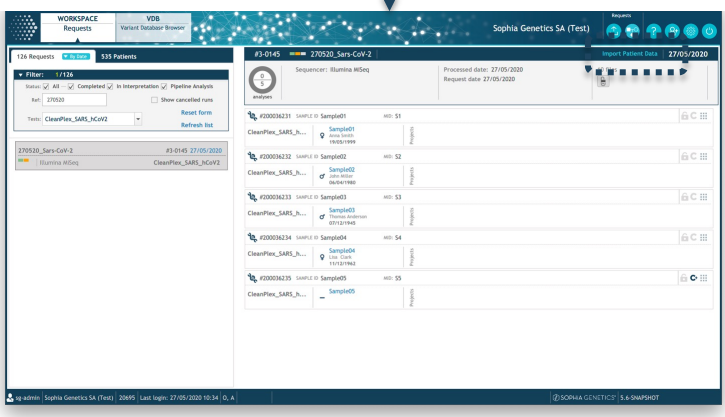
Note: With exception of the quality indicators, described functionalities are specific to this application and are not available for other panels. Viral allele frequencies are not updated dynamically.

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*

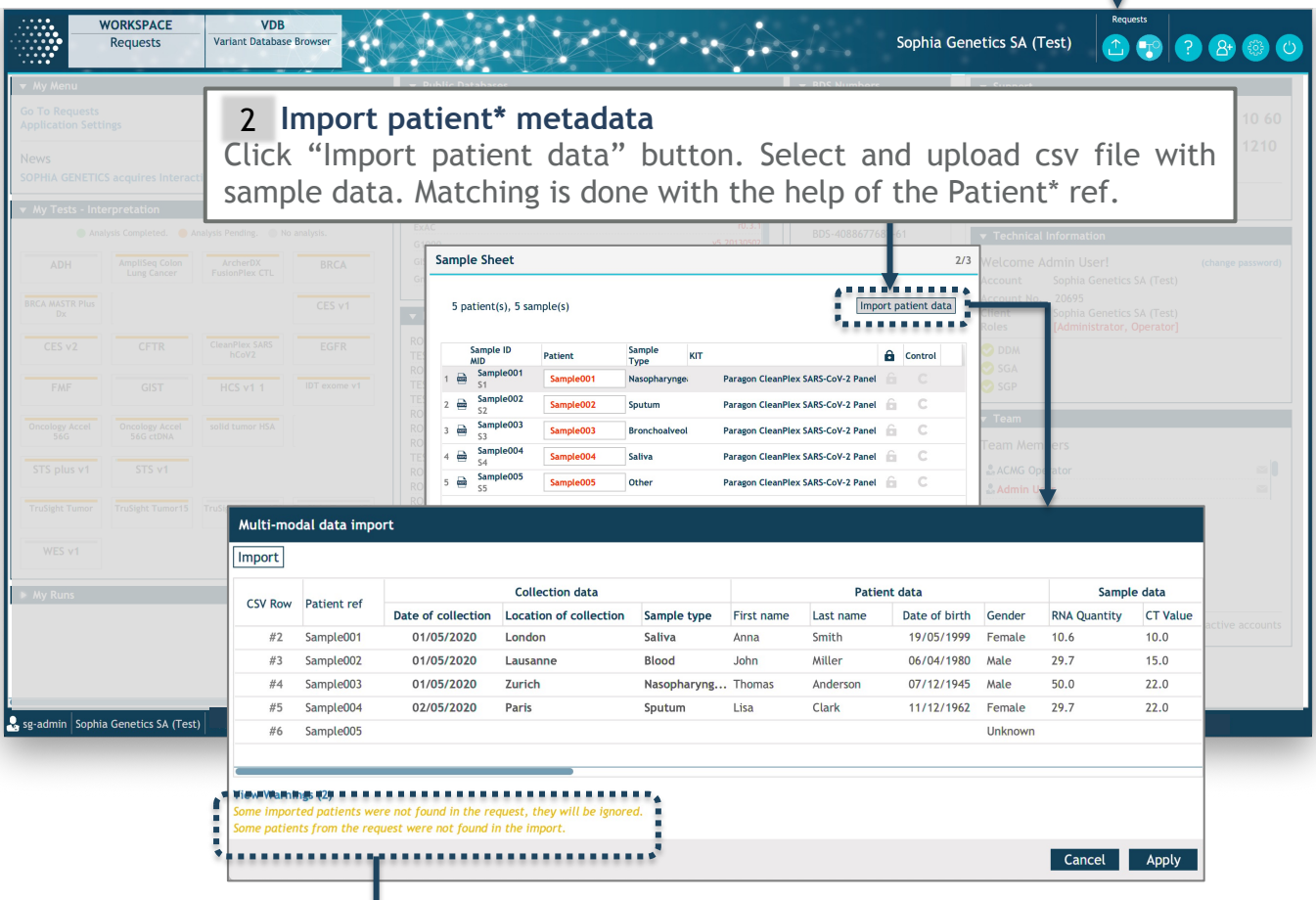
	*Medical history / Diseases**							
Column name	Hypertension	Cardiovascular disease	Diabetes	Chronic respiratory disease	COPD	Asthma	Renal disease	Obesity
Possible entries	yes no	yes no	yes no	yes no	yes no	yes no	yes no	yes no
Example	*yes*	*no*	*yes*	*no*	*no*	*yes*	*no*	*no*

	*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.

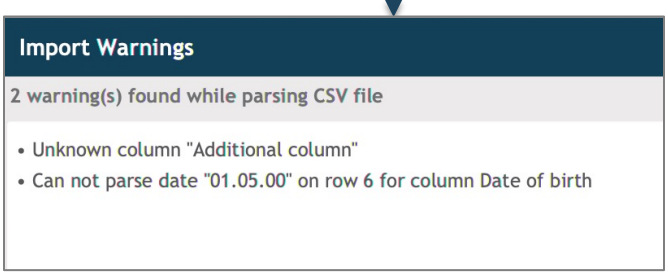
17. SARS-CoV-2 application
17.1 Metadata import (3)

1 Create New Batch Request



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.



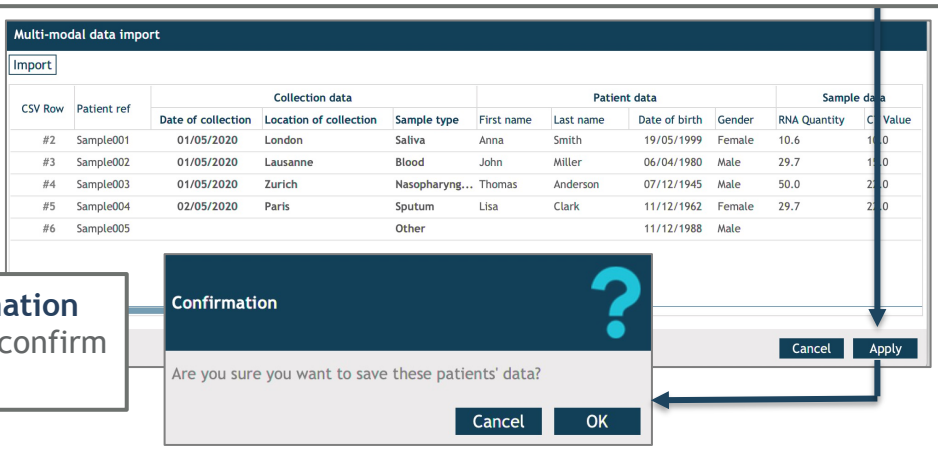
3 Check warnings (if any)

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.

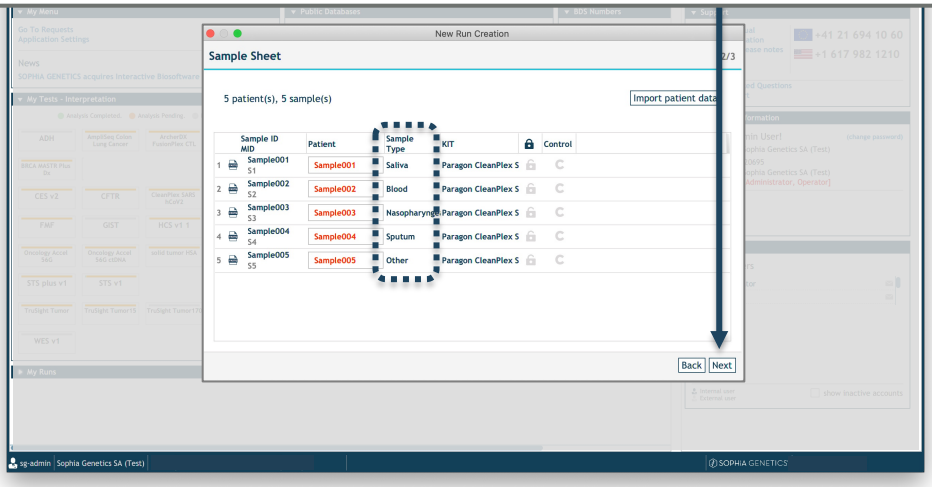


5 Confirmation

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.



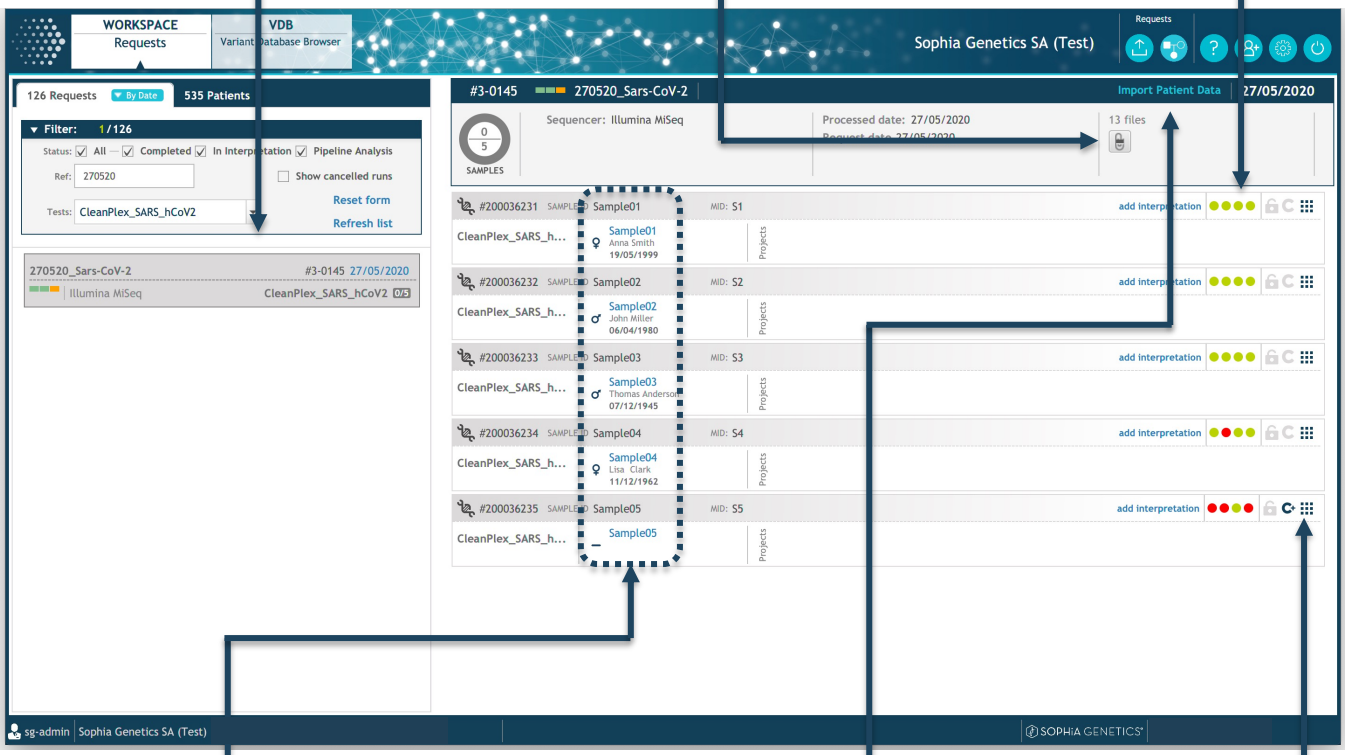
Note: If a “Patient* Ref» is already present in the database, existing values (e.g., Birth date or Gender) are not overwritten. Only new entries are added.

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)

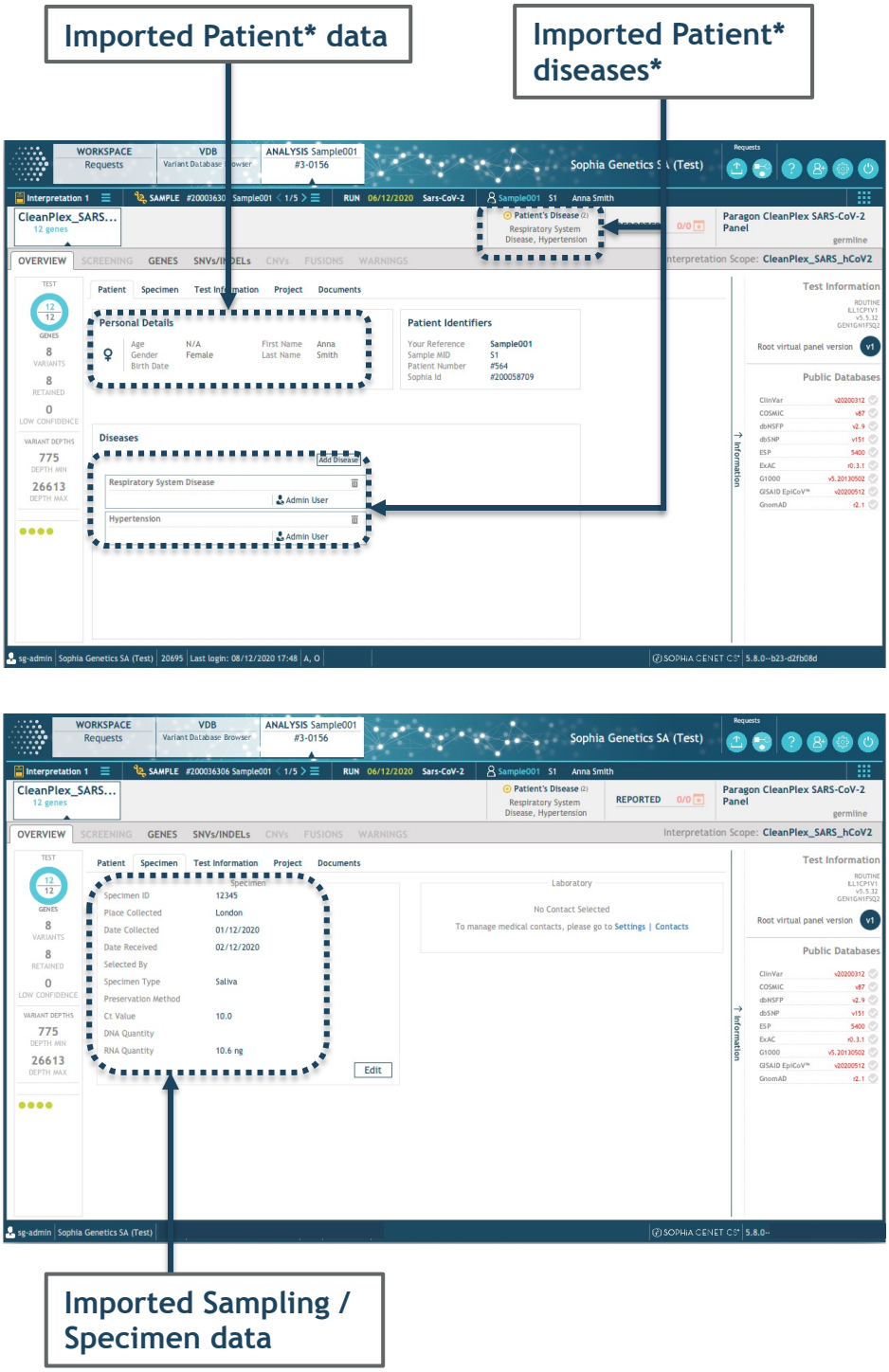
Virus presence report
A csv format report for all/individual samples of the batch request stating status of virus presence (positive, negative, unknown), clade naming based on Nextstrain and Pangolin lineage, number of amplicons covered, imported sampling info (collection date & place, sample type, patient*`s 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.

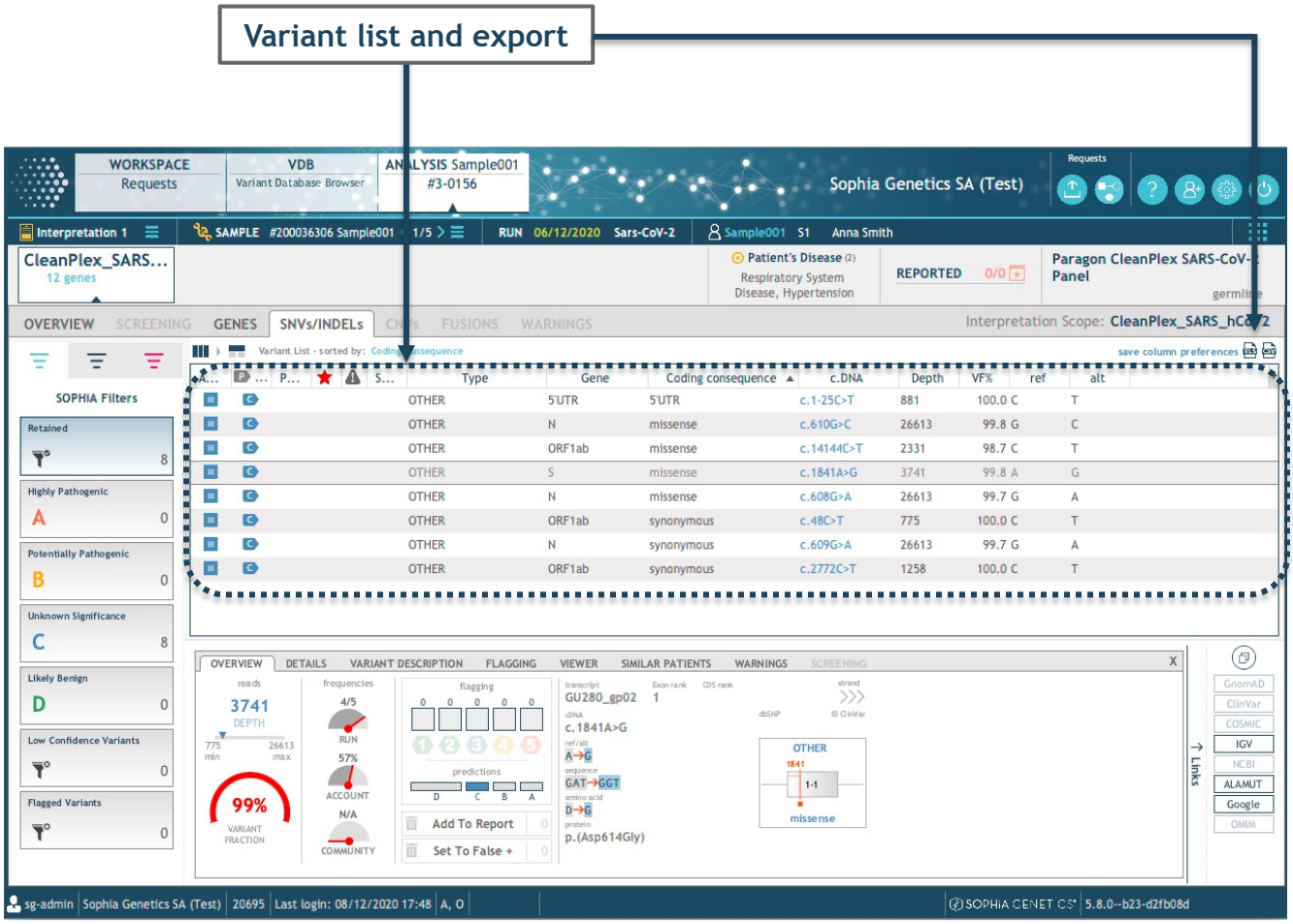
Full variant table
Available in txt and vcf format.

17. SARS-CoV-2 application
17.3 Analysis View (1)



version 6.7 - 2023-06-14
** Please refer to the Disclaimer (page 3).*
Research Use Only. Not for use in diagnostic procedures.

17. SARS-CoV-2 application
17.3 Analysis View (2)



Note: No particular experiment type is existent for viral samples, they are displayed as "germline". This has no impact on the displayed variant list.

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)

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
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:

SOPHiA GENETICS SA
Rue du Centre 172,
1025 Saint-Sulpice
www.sophiagenetics.com

Document Approvals

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Approval Verdict: Approve	Dawn Little, (DLittle@sophiagenetics.com) Regulatory Approval 13-Jun-2023 14:53:29 GMT+0000

Approval Verdict: Approve	Anja Seffner, (aseffner@sophiagenetics.com) Technical Approval 14-Jun-2023 07:52:48 GMT+0000

QA Approval Verdict: Approve	Brian Acon, (bacon@sophiagenetics.com) Quality Assurance Approval 14-Jun-2023 07:54:53 GMT+0000

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