OncoPortal[™] Plus

APP NOTE



Streamline clinical interpretation of comprehensive genomic profiling with OncoPortal[™] Plus

Comprehensive genomic profiling (CGP) of tumors using next-generation sequencing (NGS) is increasingly being used to aid decision making. These broad sequencing panels have the potential to identify more possible treatment targets than smaller panels, but generate hundreds of variants so that pinpointing actionable information is challenging. Complex molecular profiles of SNVs/Indels, copy number variations (CNVs), fusions, microsatellite instability (MSI) status and tumor mutational burden (TMB) need to be consistently, accurately, and efficiently interpreted without missing key actionable insights. The key findings then need to be summarized in a comprehensive genomic report that can be customized to individual preferences and standards. OncoPortal[™] Plus is an evidence-based decision support software fully integrated into the SOPHiA DDM[™] workflow to aid the interpretation of genomic variants identified through NGS assays (Figure 1). SOPHiA DDM[™] automatically detects, annotates, and pre-classifies genomic variants from raw sequencing data. Subsequently, the user-friendly OncoPortal[™] Plus web application, exclusively accessible through SOPHiA DDM[™], characterizes biomarkers associated with specific solid and hematological malignancies and their Clinical Associations (including available therapies, clinical trials, diagnosis, and prognosis) using published literature and guidelines. Finally, laboratories can customize state-of-the-art comprehensive genomic and genetic reports using an unlimited number of customizable templates to address their unique needs.



Here, we will demonstrate the power of OncoPortal[™] Plus for the interpretation of genomic data obtained with SOPHiA DDM[™] for TruSight[®] Oncology 500 (TSO500). TSO500 is a CGP assay that profiles >500 genes to detect multiple variant types and complex biomarkers such as MSI and TMB. OncoPortal[™] Plus is able to identify variants (biomarkers) and their Clinical Associations from SOPHiA DDM[™] for TSO500, facilitating the generation of detailed and intuitive reports to support decision making.



Starting variant interpretation in the SOPHiA DDM[™] Platform

When accessing SOPHiA DDM[™], all available applications (bioinformatic workflows) are displayed on the Dashboard (Figure 2). When SOPHiA DDM[™] has completed the TSO500 sequencing analysis, users receive an email notification to securely log in and begin the interpretation. Clicking on "TruSight Oncology500" provides access to the TSO500 workspace.

Go To Requests Application Settings Current Versions used in SOPHIA DDM: News Introducing the new Cascading Filters functionality ClinVar Maiyris Completed. Maiyris Pending. No analysis. Trusight Cncology500 ClinVar v My Runs Show per-request table The Readhow - ST3 + 31 Sun Readhow - ST3 + 31 Sun Readhow - ST3 + 31 Sun Readhow - ST5 Versight Concology500: 12 Statisphic Concology500: 12 Statisphic Contracts Trusight Concology500: 12 Statisphic Concology500: 12	lons used in SOPHIA DDM: v2020617 v22 v2. v2. v2. v2. v2. v3. v4. v4. v5. v5. v6. v6. v6. v6. v6. v6. v6. v6	cLinvar cClinvar cClinvar cOSMIC db/SFP db/SFP db/SFP (hg38) esp	Go To Requests Application Settings News introducing the new Cascading Filters fu			
Vews ClinVar Adaysis Coskil C My Tests - Interpretation MiSFP My Runs MiSFP Adaysis Readings - Sts - Sts_plus_v1: 8 TEST 18 Thu Readshow -STS + STS_plus_v1: 8 Sts In Readshow -STS + STS_plus_v1: 8 13 Sun Readshow v515 STS Sts_plus_v1: 8 31 Sun Readshow v515 STS_plus_v1: 8	۷۵۵۵۵۵۲۲ ۷۵۵۶ ۱) ۷۹۵۶ ۱) ۷۹۶۶ ۱۹۵۶ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶۲ ۱۹۵۶ ۱۹۵۶ ۱۹۵۶ ۱۹۵۶ ۱۹۵۶ ۱۹۵۶ ۱۹۵۶ ۱۹۵۶	ClinVar COSNIC dbNSFP dbNSFP dbNSFP dbSNP cosn	News News the new Cascading Filters fur			
News Accolor of the new Cascading Filters functionality Accolor of the new Cascading Filters functionality filters f	902 12.9 1 24.9 15 15 15 15 15 10 10 10 10 10 10 10 10 10 10 10 10 10	ccoskic dbNSFP dbNSFP (hg38) dbSNP	News ntroducing the new Cascading Filters fu			
Avg Tests - Interpretation dbNSFP My Tests - Interpretation dbNSFP (hg38) My Tests - Interpretation dbNSFP (hg38) Trustight Oncology500 manatysis STS plus v1 Trustight Oncology500 My Runs Pipelines / Contracts TEST NO 2021 November russ: 1 analyses: 8 18 Thu Roadshow -STS + STS.plus_v1: 8 31 Sun Readshow -STS STS.plus_v1: 8 31 Sun Readshow v515 STS.plus_v1: 8	0,0,0 () v4,1 v54 v54 v54 v54 v54 v54 v54 v54 v54 v54	nctionality dbNSFP dbNSFP (hg38) dbSNP dbSNP csp	ntroducing the new Cascading Filters fu			
My Tests - Interpretation dxiSFP (hg38) Wy Tests - Interpretation dxiSFP (hg38) My Tests - Interpretation dxiSFP Image: State of the state)	dbNSFP (hg38) dbSNP				
My Tests - Interpretation doSNP	v 154 5400 (0.3.1 v5.20130502 / Contracts	dbSNP ECD				
Avalysis Completed. Avalysis Pending. No analysis. STS plus v1 Trusight Concelegr500 My Runs Now per-request table 2021 November 18 Thu. Readshow - STS + 13 Sun. Readshow - STS + 31 Sun. Readshow - STS + 31 Sun. Readshow - STS - 31 Sun. Readshow -	5400 6500 63.1 43.1 45.20130502 7 Contracts	ESD	My Tests - Interpretation			
STS plus v1 Trustight Oncodegr500 ESP (hg.8) My Runs ExAC Grodo how per-request table Image: Standard	6500 10.3.1 V5.20130502 / Contracts	Pending. No analysis.	Analysis Completed. Analysis F			
STS plus v1 Truslight Oncodeg/500 EAC. My Runs Image: Contracts G1000 how per-request table Image: Contracts TEST NO, TEST NO, TOUTINE 2021 November Truslight_Oncolog/500:12 S15 S15 S15 S15 31 Sun Readshow - STS + S15 S15 S15 Truslight_Oncolog/500:12 S15	r0.3.1 v5.20130502 / Contracts	ESP (hg38)				
Viceopysio Groom My Runs • Pipelines / Contracts how per-request table • • Pipelines / Contracts 2021 November runs: 1 analyse: 8 18 Thu Readshow -STS + STS_plus_v1: 8 31 Sun Readshow -STS + STS_plus_v1: 8 31 Sun Readshow -STS + STS_plus_v1: 8	v5.20130502 / Contracts	ExAC	STS plus v1 TruSight			
Wy Runs Y Pipelines / Contracts how per-request table TEST NO 2021 November runs: 1 analyses 8 TEST NO 18 Thu Roadshow -STS + STS_plus_v1: 8 STS STS 31 Sun Readshow -STS + STS_plus_v1: 8 TruSight_Oncology500: 12 STS_plus_v1: 8	Contracts	G1000	Oncology500			
Z021 November runs: 1 analyses: 8 NO 18 Thu Roadshow -TS + STS_plus_v1: 8 ROUTINE STS 31 Sun Roadshow -TS > TruSight_Oncology500: 12 ROUTINE TruSight_Oncology500: 12 31 Sun Roadshow -TS > STS_plus_v1: 8 STS_plus_v1: 8 TruSight_Oncology500: 12	NO_PIPELINE germlir	📾 🔤 📔 TEST	how per-request table			
ZU21 November run: 1 anayex 8 ROUTINE STS 18 Thu Roadshow - STS + STS_plus_v1: 8 ROUTINE TruSight_Onc 31 Sun Roadshow - STS + STS_plus_v1: 8 STS_plus_v1: 8 STS	NO_PIPELINE germlir	TEST				
To Tru Readshow - 355 + S15_DUS_V1: 8 ROUTINE TruSlight_Onc 31 Sun Readshow - 575 + S15_DUS_V1: 8 S15_DUS_V1: 8 S15_DUS_V1: 8	STS_plus_v1 somation	ROUTINE	2021 November			
31 Sun Roadshow - 150 SUO Trusight_OffCology500: 12	TruSight_Oncology500 somation	SIS_PLUS_VI: 8 ROUTINE	18 Thu Roadshow - STS +			
515_p(d2_11) 0		STS plue v1: 8	31 Sun Roadshow - 150 500			
2021 Octobor runs: 2 analyses: 20		runs: 2 analyses: 20	2021 October			
			2021 October			

Figure 2. SOPHiA DDM™ home screen displaying all available applications.

2. Initiating a new interpretation project

The TSO500 workspace automatically displays all available runs and samples, ready for interpretation. To start the assessment of Sample 01-153-19, we create a "New Interpretation Project". First, click "add interpretation", select the disease from a drop-down menu (in this case "Colorectal cancer"), give the interpretation a name, and click "Finish" (Figure 3).

WORKSPACE VDB Requests Variant Database Brewser			•	Onci	oportal Roadshow D.	·· 🙆 😨 😨 🕲 🕲 🕲		
3 Requests V by Sere 13 Patients	#999666-0002 ==== 1	#599666-0002 ==== Roadshow - TSD 500 01/11/202						
	Sequencer:	Illumina NextSeq	Processed e Request da	date: 01/11/2021 tte 01/11/2021	37 files	CNV		
Traile TruSiete Oncology/200 * Reset form	12, #200240343 SAMPLE ID 01	-153-19 AID: S1	(New Interpretation Project		add interpretative 0000 4/50 🔒 C III		
Refresh list	TruSight_Oncology	01-153-19	Interpretation Pr	roject	2/2	OTS		
Roadshow - TSO 500 #999666-0002_01/11/2021	10, #200240344 SUMPLE ID 02	-154-19 MD: 52	Country Many Indonesia	union Benjam		add interpretation		
Uurnina NextSeq TruSight_Oncology300 22	TruSight_Oncology	02-154-19 stool og	Name In	nterpretation 1		om		
	12 #200240345 SAMPLE ID 03	-331-19 MD: 53	Virtual Panel Ti Scope	ru5ight_Oncology500		add interpretation 0000 4/50 🔒 C III		
	TruSight_Oncology	03-331-19	Start Date 16/ Owner Mar	/02/2022 rian Novak		om		
	10, 1200240346 SUMPLE 10 04	-332-19 MD: 54				add interpretation 🛛 😔 😁 4/5 👁 🔓 C 🔛		
	TruSight_Oncology =	04-332-19 to day				0m		
	12, #200240347 SAMPLE ID 15	1 MD: 56			Back Finish	▲ Low coveraget add interpretation 🔒 C III		
	TruSight_Oncology	151 II alog				000		
	10, #200240348 Group 12 152	DNA - 8N	A			🛦 Low coveraget add interpretation 🔓 C III		
	TruSight_Oncology	152 TD 152				005		
	12, #200240349 Group 10 155	DNA - RN	A.		Low coverage	add interpretation 👓 👓 4/5 👁 🔂 C 🖽		
	TruSight_Oncology	155 stoolog	hterpretation 2 [0]			om		
	12, #200240350 SAMPLE ID 15	6 MD: \$11			A Low coverage	add interpretation 0000 4/50 🛱 C III		
	TruSight_Oncology	156 19 direct				005		
	12, #200240351 Group 10 157	DNA - RN	A.		A Low coverage	add interpretation 🛛 🕶 🗢 4/5 👁 🔂 C 🖽		
	TruSight_Oncology =	157 spolar	interpretation 1 [0]			om		

Figure 3. SOPHiA DDM[™] TSO500 workspace, and initiation of a new interpretation project for the selected sample.

3. Viewing an overview of a sample's genomic variants

After creating a new interpretation project, the platform offers a glimpse of the detected variants in the "Overview" tab (Figure 4). This tab provides a high-level summary of the findings, including the number of variants, retained variants, MSI status, and TMB.



Figure 4. SOPHiA DDM[™] Overview tab for the selected sample.

4. Accessing OncoPortal™ Plus through SOPHiA DDM™

There are two ways to review SNVs/Indels, fusions, and CNVs. The variants can be reviewed individually in the "Variants" tab in SOPHiA DDM[™], or the results can be interpreted using OncoPortal[™] Plus by clicking on the "OncoPortal" tab. Clicking on "OncoPortal" will display a pop-up that gives the option to access the "NEW OncoPortal web app!" or "Legacy OncoPortal" (Figure 5). We will explore OncoPortal[™] Plus through the new OncoPortal web app.



Figure 5. Access to OncoPortal™ Plus via SOPHiA DDM™.

5. Viewing Molecular Profiles in the OncoPortal[™] Plus web application

OncoPortal[™] Plus opens as a new web browser window. Information flows securely between the SOPHiA DDM[™] Platform and the web application, so that the top panel of OncoPortal[™] Plus is automatically populated with the same case details as in SOPHiA DDM[™] (Figure 6). Viewing OncoPortal[™] Plus in a web browser allows multiple projects to be opened at the same time, in different tabs.

The web application has a range of intuitive features. On the left-hand side, it is possible to switch between "Molecular Profiles" and "Clinical Trials" views. The "Molecular Profiles" view is a key feature of OncoPortal[™] Plus. Molecular Profiles detail interactions between co-occurring biomarkers, which are listed in the main table. This display captures the potential biological interaction of different biomarkers present in the same sample. For example, one biomarker might indicate sensitivity to a targeted agent, whereas another co-occurring biomarker might indicate resistance to the same agent. Rather than considering each variant individually, this feature supports the assessment of the relationship between multiple tumor alterations and their compound impact on therapeutic efficacy, diagnosis, prognosis, or access to clinical trials.

• • • Incoportal x +								
C C C (a) pre-prod.sophiagenetics.com/app/onco/molecular-profiles								
OncoPortal	I Plus > Molecular Profiles				•	OncoPortal Plus		
ণ্ড ক	Molecular Profiles	01-153-19 Unknown, Unknown Colorectal cancer	Interpretation name Sample reference Interpretation 1 01-153-19 Gene Panel	e Analysis ID Date of analysis 200240343 01/11/2021 Analysis type MSI TMB (ali)	TMB (non-synomous)	MY REPORT 0 0 Profiles Clinical Associations		
	40/256 Rank V R Patient disease(6) MSI high + BRAF V600E 100% Colorectal cancer 4	8 IA © IB Ø IIC Ø IID Ø Ø ¹ 10 III III III III III III III III III	TruSight Oncology 500 (somatic)	CNV High (46.2 m	tl/Mb 36.2 mut/Mb	Preview Create		
	BRAF V600E + KRAS wild-type 100% Colorectal cancer (+ 2 diseases) 4	@3 10 111 112						
	KRAS wild-type + BCL2L1 wild-type	 €] 1 1 <l< th=""><th></th><th></th><th></th><th></th></l<>						
	BRAF mutant + TP53 wild-type 100% Colorectal cancer + 2 diseases 4	 						

Figure 6. OncoPortal™ Plus web application Molecular Profiles display for a selected sample.



6. Filtering Molecular Profiles

A useful feature in OncoPortal[™] Plus is the ability to filter the results and focus on the most actionable information first. Filters include cancer type (disease), AMP/ ASCO/CAP tier, association type, approval authority (FDA, EMA, TGA), and response type (therapy, diagnosis, prognosis) (Figure 7). After filtering, it is possible to rank the results in different orders, according to preference.

Disease	×	Tier	×	Association Type	×
Approval Authority	×	Response Type	×	TMB Status	~
Hide low confidence: False	~	Variant Annotations	~	In Report: False	~
E CONTRACTOR AND A CONT					
Colorectai cancer		1 3 11 0 11 0			
BRAF V600E (100%) Colorectal cancer	• + 55 di	[]3]0 ∭0 €]357 357 357 1]7 ∐]58 ∭58			

Figure 7. Filtering feature in OncoPortal™ Plus.

7. Exploring Molecular Profiles

After filtering and ranking, in this example, the number of Molecular Profiles was narrowed down from 256 to 5. *BRAF* V600E was identified as the most relevant variant (Figure 8). To explore this biomarker in more detail, click on the associated Molecular Profile and then click "①" next to the variant name. This displays rich interpretive information related to both normal gene function and biomarker function, supported by up-to-date scientific sources.

We also see a list of Clinical Associations related to the *BRAF* V600E Molecular Profile in the main table. The labels on the right enable a quick review of the key details, such as whether the biomarker is sensitive or resistant to the targeted agent, therapy approval status, clinical trial phase, and AMP/ASCO/CAP tier/evidence level.

O Coportal X +								
\leftrightarrow \rightarrow C \triangle (a) pre-prod.sophiagenetics.com/app/	onco/molecular-profiles	🗅 ☆ 🌟 🍔 i						
OncoPortal Plus > Molecular Profiles		OncoPortal Plus						
 Molecular Profiles 5/256 	01-153-19 Interpretation name Interpretation 1 Sample reference 01-153-19 Analysis ID 200240343 Date of analysis 01/11/2021 Colorectal cancer Gene Panel TruSight Oncology 500 (somatic) Analysis type CNV MSI TMB (all) TMB (non-synomous)	MY REPORT O O Profiles Clinical Associations (Create						
■ Sample overlap ∨ ■ 6 BRAF V600E 100% Colorectal cancer + 55 diseases Colorectal cancer + 55 diseases 1 NRAS wild-type 100% Colorectal cancer + 3 diseases KRAS wild-type 100% Colorectal cancer + 13 diseases	BRAF V600E Gene BRAF, seine/threonine-protein kinase B-raf, is a member of the Raf family of serine/threonine protein kinases, which signals through the MAP kinase pathway to regulate cell proliferation and cell growth (PMID: 24737949, PMID: 29540830). BRAF mutations and trusions have been identified in a variety of cancers, including, colorectal (PMID: 30122882), lung (PMID: 29729493), and a number of mutations have also been demonstrated to confer drug resistance (PMID: 27478040). Biomarker Colorectal	Clinical Trials Idd selection to report Icancer censitive						
MSI high (190%) Colorectal cancer (+ 27 diseases)	Colorectal cancer (sensitive) (Preclinica) Colorectal cancer (sensitive) (Preclinica) T 12 T 14 T 14	- Cell culture (ID) FDA						

Figure 8. Further exploration of the BRAF V600E Molecular Profile in OncoPortal™ Plus.

8. Gaining additional insights into Clinical Associations for a given biomarker

Clicking on a Clinical Association reveals additional details, such as the mechanism of action of a given drug (Figure 9). Molecular Profiles can be added to the report by selecting the Clinical Association of interest and checking the "Add selection to report" box, or by clicking the "Add to report" button when viewing the Clinical Association. The entry can be customized with a user-entered note, e.g., to explain why a specific Molecular Profile and Clinical Association have been selected.



Figure 9. Further details about Clinical Associations and adding items to the OncoPortal™ Plus report.

9. Customizing templates for comprehensive reports

$\leftarrow \ \ \rightarrow$	C 🛆 🗎 staging	.sophiage	netics.com/st-reporting-onco/app/reporting/editor/20695/785f01fa-2ce6-4be2-8fc7-c0e46f26d7c6	ô \$	20	: چ
Home	> Template Manager -> Er	ditor		Reporting Web Reparting		R
A	LAYOUT	^	Default Somatic Oncoportal Report T 🖍			
•	Tr Page break	vi	Scope	Default Somatic Oncoportal Rep	• •	1
au,	TT Header	v1 v2				-
B	Tr Footer	vt	E Header v2			~
	TABLE	~	BODY			_
	GENERIC	×	Patient Information VI		ΪΪ.	~
		- 1	H Admin information (S) VI		Î	~
		- 1	Conclusion V1		T	~
		- 1	Clinical Overview (S) VI		ii.	~
		- 1	Elinical Question VI		Î	~
			Clinical Actionable biomarkers table (S)		Î	<u> </u>
		L	Elinical Overview (S) VI		ĩ	~
			Reported Variants (S) VI		î.	~

In SOPHiA DDM[™], the Template Manager provides a user-friendly interface for the preparation of custom reporting templates (Figure 10). First, we select one of the provided templates. Then, the Editor can be used to activate/deactivate, rename, and configure individual report sections (stencils) with granular information fields. The final customized template can be previewed and saved, and then used for subsequent reports.

Figure 10. The SOPHiA DDM™ Template Manager Editor for configuring custom reporting templates.





10. Completing a comprehensive genomic report

During the clinical interpretation, information flows securely between OncoPortal[™] Plus and SOPHiA DDM[™], so that after selecting Molecular Profiles and Clinical Associations in OncoPortal[™] Plus, the report can be completed in the SOPHiA DDM[™] Overview tab (Figure 11), where the case information can be edited, and the Conclusion written. The 'Complete' button launches the web-based Reporting app (Figure 12), where a previously configured template can be selected. The reporting app populates the template with the case, biomarker, and interpretive information from OncoPortal[™] Plus and SOPHiA DDM[™]. Approval of the final report can then be initiated from the reporting app, so that the approver is notified that the report is ready for review and approval.

W	ORKSPACE Requests	VDB Variant Database Browser	SIS Integrated Solu	utions #3	IS 01-153-19 3-0456	
Interpretation	ı ≡ 🔌 s Onc	AMPLE #200240322 01-15 oPortal Va	3-19 < 1/9 > ☰ triants थेक्	RUN 27/10/202	Roadshow TSO5	00 8 01
TEST 655 665 000 000 000 000 000 000	Patient Spe Interpretation Virtual Panel Owner	1 Pratt TruSight_Oncology500 (6 Marian Novak	n Project Doc	uments eated 02/12/20 ted	Proj 21	ect Settings Delete
36.2 mut/Mb TMB non-syn VARIANT DEPTHS 4 DEPTH MIN						

Figure 11. The SOPHiA DDM[™] Overview tab for completion of the report.



Conclusion

OncoPortal[™] Plus is a user-friendly module of SOPHiA DDM[™], integrated into the platform's streamlined sample-to-report workflow. The OncoPortal[™] Plus web application intuitively displays and reviews co-occurring biomarkers as Molecular Profiles, to reduce the chance of missing interfering variants and speed up interpretation. Molecular Profiles can be filtered to display the most actionable biomarker first, further streamlining assessment. OncoPortal[™] Plus provides detailed descriptions of gene and biomarker functions, and rich information to support the Clinical Associations between Molecular Profiles and therapeutic options, clinical trials, diagnosis, and prognosis of specific cancer types, using up-todate published scientific sources. OncoPortal[™] Plus gives users the confidence to make fast decisions with consistent and accurate interpretation of clinically significant biomarkers. Users are able to save time and reduce errors from manual interpretation of comprehensive data sets like the TSO500 CGP, and can efficiently communicate results via customizable, comprehensive, state-of-theart reports generated in SOPHiA DDM[™].



About SOPHIA GENETICS

SOPHiA GENETICS (Nasdaq: SOPH) is a healthcare technology company dedicated to establishing the practice of data-driven medicine as the standard of care and for life sciences research. It is the creator of the SOPHiA DDM[™] platform, a cloud-based SaaS platform capable of analyzing data and generating insights from complex multimodal data sets and different diagnostic modalities. The SOPHiA DDM[™] platform and related solutions, products and services are currently used by more than 780 hospital, laboratory, and biopharma institutions globally.

Want to know more?

Contact us at: info@sophiagenetics.com

OncoPortal™ Plus is for Clinical Decision Support Use Only - Not intended as a primary diagnostic tool.

SOPHiA DDM[™] for TSO500 is for Research Use Only and is not intended for purposes other than research. SOPHiA DDM[™] for TSO500 is not for diagnostic, therapeutic, or treatment purposes.

© 2022 SOPHiA GENETICS. All rights reserved. All trademarks are the property of SOPHiA GENETICS and/or its affiliate(s) in the U.S. and/or other countries. All other names, logos, and other trademarks are the property of their respective owners.



