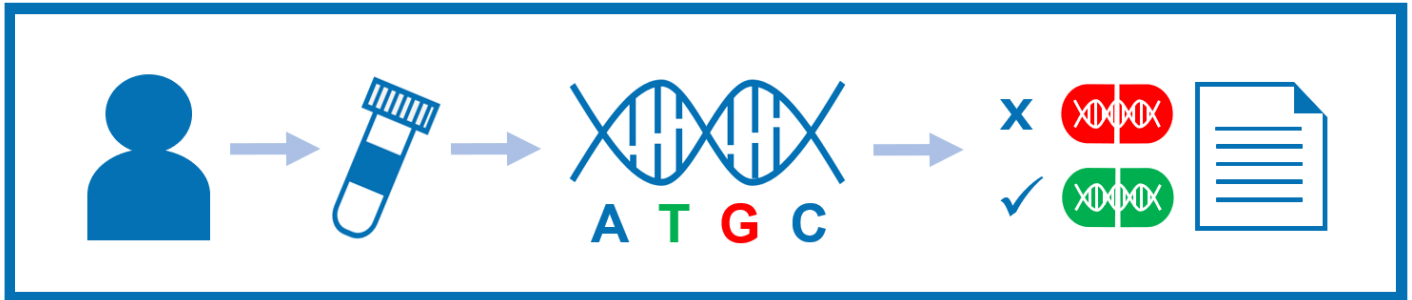


Demo User  
 geneXplain GmbH  
 info@genexplain.com

Data received on 28/10/2020 ; Run on 29/01/2021 ; Report generated on 29/01/2021

Genome Enhancer release 2.2 (GKDB version 20.0, CIViC version 01 MAY 2020)

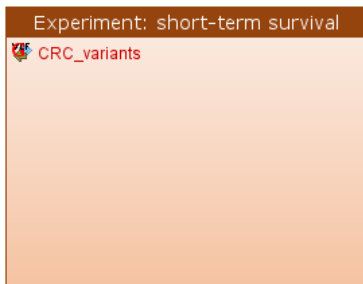


## MTB Report - From somatic variants to treatment options

### GENE-DRUG PREDICTIVE ASSOCIATIONS

This report is based on the following genomics data, which was submitted for the current study in the Genome Enhancer pipeline:

<b>Experiment: short-term survival</b>
<a href="#">CRC_variants</a>



Annotation diagram of experimental data used in the study.

The studied pathology, which was selected during the Genome Enhancer analysis launch, was *Colorectal Neoplasms*. This disease matches the following pathology, which was used as the input parameter for the [Molecular Tumor Board \(MTB\)](#) method to produce this report: *Colorectal Cancer*.

The [Variant Effect Predictor](#) analysis was applied to the input vcf track, which was submitted for the analysis in the *Experiment: short-term survival* condition. All mutations, which were found in the studied data in comparison to the reference genome, were annotated with the predicted effects. The gene-drug predictive associations were further retrieved with the use of the [MTB method](#).

**Gene-drug predictive associations method used in the MTB report:** somatic variants of the studied input data (mutations, amplifications, deletions, rearrangements) were searched in curated databases of predictive biomarkers ([GKDB](#), [CIViC](#)) and reported according to their clinical evidence (Levels of Evidence).

Levels of Evidence: Findings are classified into six levels of evidence combining the axis A-B and the axis 1-2-3. Level A means evidence was found in the same cancer type as the one being studied. Level B means evidence was found in any other cancer type. On the 1-2-3 axis, level 1 means the evidence is supported by drug approval organizations or clinical guidelines, level 2 contains a clinical evidence (clinical trials, case reports) and level 3 consists of a preclinical evidence.

The report summarizes all predictive associations in a detailed table. The results are sorted by the level of evidence (A1-B1-A2-B2-A3-B3). To allow a quick interpretation, the type of the association (response, resistance) is colored (green, red) and new variants are displayed in gray.

Gene	Variant	Disease	Known Variant	Association	Drugs	Evidence	PMID	Level
BRCA1	S408I S408I S370I S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...	Cancer	any mut.	sensitivity/response	Olaparib	approved	19553641	B1
BRCA2	V2466A V2466A	Cancer	any mut.	sensitivity/response	Olaparib	approved	19553641	B1
BRCA1	S408I S370I S1512I S1512I S1533I S3I F304L S1465I S362I F170L F278L F257L S283I F8L F263L F88L	Epithelial Ovarian Cancer	any variant (LoF)	response	olaparib, rucaparib	FDA-approved	FDA	B1
BRCA2	V2466A	Epithelial Ovarian Cancer	any variant (LoF)	response	olaparib, rucaparib	FDA-approved	FDA	B1
POLE	V384L V411L	Colon Cancer	any variant (LoF)	response	PD1 blockade	case report	28188185	A2
RNF43	L291M L418M R343H R216H L377M R302H P231L P104L P190L I47V	Colon Cancer	any variant (GoF)	response	porcupine inhibitors	case report	ENA 2015 (abstract C45)	A2
GSTP1	I105V	Colorectal Cancer	I105V	sensitivity/response	FolfoxProtocol	clin. trials	19922504	A2
FBXW7	D511Y D511Y D415Y D415Y D591Y D591Y D473Y D473Y	Colorectal Cancer	any mut.	resistance	Panitumumab,Cetuximab	clin. trials	26508446	A2
PTEN	R130Q	Colon Cancer	any variant (LoF)	resistance	anti-EGFR mAbs	late trials	21163703, 19398573	A2
PTEN	R130Q	Pancreas Adenocarcinoma	any variant (LoF)	response	AKT inhibitors	case report	22025163	B2
TSC1	M322T M271T	angiosarcoma	any variant (LoF)	response	everolimus	case report	26859683	B2
TSC1	M322T M271T	Renal Cell Carcinoma	any variant (LoF)	response	everolimus	case report	24622468, 26859683, ASCO 2015 (abstr 11010), ASCO 2015 (abstr 4519)	B2
PTPRD	R995C	angiosarcoma	any mut. (GoF)	response	IGF-1R antibodies	case report	23800680	B2
PTEN	R130Q	Endometrial Cancer	any variant (LoF)	response	PARP inhibitors	case report	21468130, 20944090	B2
BRCA1	S408I S370I S1512I S1512I S1533I S3I F304L S1465I S362I F170L F278L F257L S283I F8L	Pancreas Adenocarcinoma	any variant (LoF)	response	PARP inhibitors	case report	25366685, 25719666	B2

	F263L F88L								
B2M	C45G F64V F82V L41W F34V	Melanoma	any variant (LoF)	resistance	PD1 blockade	case report	27433843	B2	
BRCA2	V2466A	Melanoma	any variant (LoF)	response	PD1 blockade	case report	26997480	B2	
PTEN	R130Q	Prostate Cancer	any variant (LoF)	response	PI3K beta inhibitor	case report	ASCO 2014 (abstr 2514)	B2	
BRCA2	V2466A	Pancreas Adenocarcinoma	any variant (LoF)	response	platinum	case report	25719666	B2	
TP53	V157A V157A V25A V25A V118A V118A V146A V146A P72R P72R P33R P33R V64A V64A	Breast Cancer	any mut.	resistance	Tamoxifen	case report	10786679	B2	
TSC1	M322T M271T	Endometrial Cancer	any variant (GoF)	response	tensirolimus	case report	27016228	B2	
BRCA1	S408I S370I S1512I S1533I S3I F304L S1465I S362I F170L F278L F257L S283I F8L F263L F88L	Cancer	any variant (LoF)	response	WEE1 inhibitors	case report	25964244	B2	
TP53	V157A V157A V25A V25A V118A V118A V146A V146A P72R P72R P33R P33R V64A V64A	Chronic Lymphocytic Leukemia	any mut.	sensitivity/response	Alemtuzumab	clin. trials	14726385	B2	
GNA11	R63S R63S R214S R214S	Uveal Melanoma	any mut.	sensitivity/response	Cabozantinib	clin. trials	28103611	B2	
TP53	V157A V157A V25A V25A V118A V118A V146A V146A P72R P72R P33R P33R V64A V64A	Gastric Adenocarcinoma	any mut.	sensitivity/response	Chemotherapy	clin. trials	24740294	B2	
XRCC1	Q399R R157W Q368R R194W R170W R163W R123W R201W	Cervical Cancer	Q399R	sensitivity/response	Cisplatin, Carboplatin	clin. trials	16875718	B2	
BRCA1	S408I S408I S370I S370I S1512I S1512I	Triple receptor Negative Breast Cancer	any mut.	sensitivity/response	Cisplatin, Carboplatin	clin. trials	25847936	B2	

	S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...								
BRCA2	V2466A V2466A	Triple receptor Negative Breast Cancer	any mut.	sensitivity/response	Cisplatin,Carboplatin	clin. trials	25847936	B2	
BRCA2	V2466A V2466A	Pancreatic Cancer	any mut.	sensitivity/response	Cisplatin,Veliparib,Gemcitabine	clin. trials	29338080	B2	
PTEN	R130Q R130Q	Endometrial Carcinoma	any mut.	sensitivity/response	Everolimus	clin. trials	23238879	B2	
XRCC1	Q399R R157W Q368R R194W R170W R163W R123W R201W	Non-small Cell Lung Carcinoma	R194W	sensitivity/response	Gemcitabine,Vinorelbine,Docetaxel	clin. trials	19157633	B2	
FBXW7	D511Y D511Y D415Y D415Y D591Y D591Y D473Y D473Y	Cancer	any mut.	sensitivity/response	MTOR Inhibitors	clin. trials	24586741	B2	
BRCA1	S408I S408I S370I S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...	Triple receptor Negative Breast Cancer	any mut.	resistance	Olaparib	clin. trials	21862407	B2	
BRCA1	S408I S408I S370I S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...	Breast Cancer	any mut.	sensitivity/response	Olaparib	clin. trials	28792849	B2	
BRCA2	V2466A V2466A	Breast Cancer	any mut.	sensitivity/response	Olaparib	clin. trials	28792849	B2	
BRCA2	V2466A V2466A	Triple receptor Negative Breast Cancer	any mut.	sensitivity/response	Olaparib	clin. trials	21862407	B2	
BRCA1	S408I S408I S370I S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...	Ovarian Cancer	any mut.	sensitivity/response	Olaparib,Cediranib	clin. trials	25218906	B2	
BRCA2	V2466A V2466A	Ovarian Cancer	any mut.	sensitivity/response	Olaparib,Cediranib	clin. trials	25218906	B2	
BRCA1	S408I S408I S370I	Ovarian Carcinoma	any mut.	sensitivity/response	PLATINUM	clin. trials	24240112	B2	

	S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...							
BRCA1	S408I S408I S370I S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...	Pancreatic Cancer	any mut.	sensitivity/response	PLATINUM	clin. trials	25072261	B2
BRCA2	V2466A V2466A	Ovarian Carcinoma	any mut.	sensitivity/response	PLATINUM	clin. trials	24240112	B2
BRCA2	V2466A V2466A	Pancreatic Cancer	any mut.	sensitivity/response	PLATINUM	clin. trials	25072261	B2
BRCA1	S408I S408I S370I S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...	Ovarian Cancer	any mut.	sensitivity/response	Rucaparib	clin. trials	27908594	B2
ERBB2	I655V I655V I640V I640V I24V I24V I379V I379V I625V I625V I95V I95V	Non-small Cell Lung Carcinoma	any mut.	sensitivity/response	Trastuzumab,Pertuzumab	clin. trials	29320312	B2
BRCA1	S408I S408I S370I S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I S1465I S362I S362I F1...	Pancreatic Cancer	any mut.	sensitivity/response	Veliparib	clin. trials	29223478	B2
BRCA2	V2466A V2466A	Pancreatic Cancer	any mut.	sensitivity/response	Veliparib	clin. trials	29223478	B2
BRCA1	S408I S408I S370I S370I S1512I S1512I S1533I S1533I S3I S3I F304L F304L S1465I	Pancreatic Cancer	any mut.	sensitivity/response	Veliparib,Gemcitabine,Cisplatin	clin. trials	29338080	B2

	S1465I S362I S362I F1...								
PTEN	R130Q	Melanoma	any variant (LoF)	resistance	BRAF inhibitors in BRAF mutant tumor	early trials	10.1200/PO.16.00054	B2	
TP53	V157A V25A V118A V146A P72R P33R V64A	Inflammatory Breast Carcinoma	any mut. (LoF)	resistance	CDK4/CDK6 inhibitor abemaciclib	early trials	27217383	B2	
TP53	V157A V25A V118A V146A P72R P33R V64A	Acute Promyelocytic Leukemia	any mut. (LoF)	response	decitabine	early trials	27959731	B2	
TP53	V157A V25A V118A V146A P72R P33R V64A	myelodysplastic syndrome	any mut. (LoF)	response	decitabine	early trials	27959731	B2	
TSC1	M322T M271T	Urothelial Carcinoma	any variant (LoF)	response	everolimus	early trials	22923433	B2	
PTEN	R130Q	Prostate Cancer	any variant (LoF)	response	everolimus	early trials	23582881	B2	
FGFR2	D101N D84N	Bile Duct Adenocarcinoma	multiple, any mut. (GoF)	resistance	FGFR inhibitors	early trials	28034880, ASCO 2017 (abstr 2500)	B2	
PTEN	R130Q	Endometrial Cancer	any variant (LoF)	no response	mTOR inhibitors	early trials	21788564, 23238879	B2	
FANCA	G37D G809D G501S T266A H209R T92A L63V T234A	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	26510020	B2	
BRCA1	S408I S370I S1512I S1533I S3I F304L S1465I S362I F170L F278L F257L S283I F8L F263L F88L	Inflammatory Breast Carcinoma	any variant (LoF)	response	PARP inhibitors	early trials	20609467, 25366685	B2	
BRCA1	S408I S370I S1512I S1533I S3I F304L S1465I S362I F170L F278L F257L S283I F8L F263L F88L	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	19553641, 25366685, 26510020	B2	
BRCA2	V2466A	Inflammatory Breast Carcinoma	any variant (LoF)	response	PARP inhibitors	early trials	20609467	B2	
BRCA2	V2466A	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	26510020	B2	
BRCA1	S408I S370I S1512I S1533I S3I F304L S1465I S362I F170L F278L	Epithelial Ovarian Cancer	any variant (LoF)	response	PARP inhibitors + chemotherapy	early trials	22307137, ASCO 2012 (abstr 1009)	B2	

	F257L S283I F8L F263L F88L							
BRCA2	V2466A	Epithelial Ovarian Cancer	any variant (LoF)	response	PARP inhibitors + chemotherapy	early trials	22307137, ASCO 2012 (abstr 1009)	B2
PTEN	R130Q	Melanoma	any variant (LoF)	resistance	PD1 inhibitors	early trials	26645196	B2
BRCA1	S408I S370I S1512I S1533I S3I F304L S1465I S362I F170L F278L F257L S283I F8L F263L F88L	Inflammatory Breast Carcinoma	any variant (LoF)	response	platinum agents	early trials	25847936	B2
BRCA2	V2466A	Inflammatory Breast Carcinoma	any variant (LoF)	response	platinum agents	early trials	25847936	B2
PTEN	R130Q	Cancer	any variant (LoF)	response	sirolimus	early trials	ASCO 2013 (abstr 2532)	B2
BRCA1	S408I S370I S1512I S1533I S3I F304L S1465I S362I F170L F278L F257L S283I F8L F263L F88L	Inflammatory Breast Carcinoma	any variant (LoF)	response	veliparib + cisplatin	early trials	26801247	B2
BRCA2	V2466A	Inflammatory Breast Carcinoma	any variant (LoF)	response	veliparib + cisplatin	early trials	26801247	B2
TP53	V157A V25A V118A V146A P72R P33R V64A	Epithelial Ovarian Cancer	any variant (GoF)	response	WEE1 inhibitors + carboplatin	early trials	ASCO2015 (abstr 2507)	B2
PTEN	R130Q	Inflammatory Breast Carcinoma	any variant (LoF)	response	everolimus + trastuzumab + chemotherapy (HER2 ampl)	late trials	27091708	B2
BRCA1	S408I S370I S1512I S1533I S3I F304L S1465I S362I F170L F278L F257L S283I F8L F263L F88L	Epithelial Ovarian Cancer	any variant (LoF)	response	platinum agents	late trials	22406760, 22711857	B2
BRCA2	V2466A	Epithelial Ovarian Cancer	any variant (LoF)	response	platinum agents	late trials	22406760, 22711857	B2
FBXW7	D511Y D415Y D591Y D473Y	B-cell Adult Acute Lymphocytic Leukemia	any variant (LoF)	response	steroids in early setting	late trials	20861909	B2
APC	V1822D	Colon Cancer	any variant (LoF)	sensitivity	tankyrase inhibitors	preclinical	22440753, 23539443	A3
PIK3CB	R321Q	Head And Neck Carcinoma	any variant (GoF)	sensitivity	AKT inhibitor, mTORC1/2 inhibitors	preclinical	23619167	B3
FBXW7	D511Y D415Y D591Y D473Y	Cancer	any variant (LoF)	resistance	anti-tubulin agents	preclinical	21368834	B3
PTEN	R130Q	Inflammatory Breast	any variant	sensitivity	ATM inhibitor	preclinical	27397505	B3

		Carcinoma	(LoF)						
SUZ12	E324K E347K	Cancer	any variant (LoF)	sensitivity	BET inhibitors	preclinical	25119042	B3	
FAT1	V482I S89G E4158G D2309N D2311N E4156G S404R K4059N V862L K4061N	Head And Neck Carcinoma	any mut. (LoF)	sensitivity	BET inhibitors	preclinical	27397505	B3	
ERCC6	M1097V Q1413R	Epithelial Ovarian Cancer	any variant (LoF)	sensitivity	cisplatin	preclinical	25634215	B3	
MSH3	A1045T I79V	Cancer	any variant (LoF)	sensitivity	DNA-PKcs inhibitors	preclinical	24556366	B3	
TP53	V157A V157A V25A V25A V118A V118A V146A V146A P72R P72R P33R P33R V64A V64A	Non-small Cell Lung Carcinoma	any mut.	resistance	Docetaxel	preclinical	22425996	B3	
RNF43	L291M L418M R343H R216H L377M R302H P231L P104L P190L I47V	Pancreas Adenocarcinoma	any variant (GoF)	sensitivity	FZD5 antibodies	preclinical	27869803	B3	
PTEN	R130Q	Melanoma	any variant (LoF)	resistance	MEK inhibitors in BRAF mutant tumors	preclinical	23039341	B3	
TP53	V157A V25A V118A V146A P72R P33R V64A	Urothelial Carcinoma	any mut. (LoF)	sensitivity	mitomycin C, gemcitabine, doxorubicin	preclinical	27397505	B3	
STAG2	I1257L I1220L	Glioma	any variant (LoF)	sensitivity	PARP inhibitors	preclinical	24356817	B3	
ATR	M211T R2425Q R272Q	Cancer	any variant (LoF)	sensitivity	PARP inhibitors	preclinical	23548269	B3	
PTEN	R130Q	Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	21673091, 23287563, 21998291	B3	
PTEN	R130Q	Endometrial Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	22662154	B3	
PTEN	R130Q	Epithelial Ovarian Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	21632463	B3	
PTEN	R130Q	Inflammatory Breast Carcinoma	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	23085766, 22932669	B3	
PTEN	R130Q	Thyroid Gland Papillary Carcinoma	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	21289267	B3	
INPP4B	R653C R838C	Inflammatory Breast Carcinoma	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	23551093	B3	
PTEN	R130Q	Glioma	any variant (LoF)	sensitivity	PI3K pathway inhibitors (alone or in combination)	preclinical	21325073, 21191045, 17804702	B3	
PTEN	R130Q	Lung Acinar Adenocarcinoma	any variant (LoF)	sensitivity	PI3K pathway inhibitors (alone or in combination)	preclinical	23136191	B3	
PTEN	R130Q	Prostate Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors + AR antagonists	preclinical	21575859	B3	
PTEN	R130Q	Epithelial Ovarian Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors + MEK inhibitors	preclinical	21632463	B3	
PTEN	R130Q R130Q	Head And Neck Squamous Cell Carcinoma	any mut.	resistance	Taselisib (GDC-0032)	preclinical	26589432	B3	



ATR	M211T R2425Q R272Q	Glioma	any variant (LoF)	sensitivity	temozolomide	preclinical	23960094	B3
SETD2	R2077Q A1958T A1592T A508T	Cancer	any variant (LoF)	sensitivity	WEE1 inhibitors	preclinical	ENA 2014 (abstr 211)	B3
TP53	V157A V25A V118A V146A P72R P33R V64A	Head And Neck Carcinoma	any variant (LoF)	sensitivity	WEE1 inhibitors	preclinical	25125259	B3

The [MTB method](#) and the corresponding report structure were developed by Julia Perera-Bel in the research group of Prof. Dr. Tim Beißbarth at the University Medical Center Göttingen (UMG). Perera-Bel J, Hutter B, Heining C, et al. From somatic variants towards precision oncology: Evidence-driven reporting of treatment options in molecular tumor boards. *Genome Med.* 2018;10(1):18. Published 2018 Mar 15. doi:10.1186/s13073-018-0529-2).

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