

Demo User  
geneXplain GmbH  
info@genexplain.com

Data received on 10/04/2022 ; Run on 26/11/2024 ; Report generated on 26/11/2024

Genome Enhancer release 3.5 (GKDB version 20.0, CIViC version 01 October 2022)



## 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:

NCI-H1975
<a href="#">NCI-H1975</a>



Annotation diagram of experimental data used in the study.

The studied pathologies, which were selected during the Genome Enhancer analysis launch, were *Carcinoma, Non-Small-Cell Lung and Lung Neoplasms*. These diseases match the following pathologies, which were used as the input parameters for the [Molecular Tumor Board \(MTB\)](#) method to produce this report: *Lung cancer*.

The [Variant Effect Predictor](#) analysis was applied to the input vcf track, which was submitted for the analysis in the *NCI-H1975* 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.

Table 1. Report for Lung cancer

Gene	Variant	Disease	Known Variant	Association	Drugs	Evidence	PMID	Level
EGFR	L858R	Lung Acinar Adenocarcinoma	L858R (GoF)	response	erlotinib	FDA-approved	FDA	A1
EGFR	L858R	Lung Acinar Adenocarcinoma	L858R (GoF)	response	afatinib	FDA-approved	FDA	A1
EGFR	L858R	Lung Acinar Adenocarcinoma	L858R (GoF)	response	gefitinib	FDA-approved	FDA	A1
EGFR	T790M	Lung Acinar Adenocarcinoma	T790M (GoF)	response	osimertinib	FDapproved	FDA	A1
EGFR	T790M	Lung Acinar Adenocarcinoma	T790M (GoF)	resistance	erlotinib	NCCN guidelines	NCCN	A1
EGFR	T790M	Lung Acinar Adenocarcinoma	T790M (GoF)	resistance	afatinib	NCCN guidelines	NCCN	A1
BRCA2	R2034C R1911C V2466A V2343A	Epithelial Ovarian Cancer	any variant (LoF)	response	olaparib	FDA-approved	FDA	B1
BRCA2	R2034C R1911C V2466A V2343A	Epithelial Ovarian Cancer	any variant (LoF)	response	rucaparib	FDA-approved	FDA	B1
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G S1317G S104G S1572G S1635G ...	Epithelial Ovarian Cancer	any variant (LoF)	response	olaparib	FDA-approved	FDA	B1
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G S1317G S104G S1572G S1635G ...	Epithelial Ovarian Cancer	any variant (LoF)	response	rucaparib	FDA-approved	FDA	B1
EGFR	L858R	Lung Adenocarcinoma	L858R	sensitivity/response	Gefitinib	case report	15329413	A2
EGFR	T790M	Lung Adenocarcinoma	T790M	sensitivity/response	Osimertinib	case report	26181354, 26269204	A2
EGFR	L858R	Lung Adenocarcinoma	L858R	sensitivity/response	Afatinib	clin. trials	23816960, 22452895,	A2

							24439929	
EGFR	L858R	Lung Adenocarcinoma	Ex19 del L858R, L858R	sensitivity/response	Erlotinib	clin. trials	22285168, 27032107	A2
EGFR	L858R	Lung Adenocarcinoma	L858R	sensitivity/response	Gefitinib	clin. trials	22370314, 27022112	A2
EGFR	T790M	Lung Adenocarcinoma	T790M	resistance	Gefitinib	clin. trials	23470965	A2
EGFR	T790M	Lung Adenocarcinoma	T790M	resistance	Erlotinib	clin. trials	23470965	A2
EGFR	L858R	Lung Acinar Adenocarcinoma	L858R (GoF)	response	afatinib + cetuximab	early trials	ESMO 2012 (abstr 1289)	A2
EGFR	T790M	Lung Acinar Adenocarcinoma	T790M (GoF)	response	afatinib + cetuximab	early trials	25074459	A2
EGFR	T790M	Lung Acinar Adenocarcinoma	T790M (GoF)	response	afatinib + nimotuzumab	early trials	26667485	A2
EGFR	L858R	Lung Acinar Adenocarcinoma	L858R (GoF)	response	HSP90 inhibitors	early trials	ESMO 2012 (abstr 4380)	A2
EGFR	T790M	Lung Acinar Adenocarcinoma	T790M (GoF)	response	HSP90 inhibitors	early trials	ESMO 2012 (abstr 4380)	A2
EGFR	T790M	Lung Acinar Adenocarcinoma	T790M (GoF)	response	irreversible EGFR T790M inhibitors	early trials	ASCO 2014 (abstr 8009), ENA 2014 (abstr 10LBA), ENA 2014 (abstr 9LBA), ASCO 2015 (abstr 8001)	A2
PIK3CA	G118D I391M	Lung Acinar Adenocarcinoma	any variant (GoF)	no response	PI3K pathway inhibitors	early trials	ASCO 2017 (abstr 9054)	A2
EGFR	L858R	Lung Acinar Adenocarcinoma	L858R (GoF)	response	irreversible EGFR TKIs	late trials	22753918	A2
ATM	L1420F L1365F	Colon Cancer	any variant (LoF)	response	ATR inhibitors	case report	ENA 2015 (abstract A48)	B2
TSC2	H798Y H749Y H761Y H809Y H813Y H796Y	Gastric Adenocarcinoma	any variant (LoF)	response	everolimus	case report	26859683	B2
TSC2	H798Y H749Y H761Y H809Y H813Y H796Y	Thyroid Gland Papillary Carcinoma	any variant (LoF)	response	everolimus	case report	25295501	B2
NF1	D196Y	Hepatocellular Carcinoma	any mut. (LoF)	response	everolimus + pazopanib	case report	24931142	B2
SMARCA4	P228A	ovarian rhabdoid Cancer	any variant (LoF)	response	EZH2 inhibitor	case report	ESMO 2015 (abstract 302)	B2

PTPRD	R995C	angiosarcoma	any mut. (GoF)	response	IGF-1R antibodies	case report	23800680	B2
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G S1317G S104G S1572G S1635G ...	Pancreas Adenocarcinoma	any variant (LoF)	response	PARP inhibitors	case report	25366685, 25719666	B2
BRCA2	R2034C R1911C V2466A V2343A	Melanoma	any variant (LoF)	response	PD1 blockade	case report	26997480	B2
PIK3CA	G118D I391M	Gastric Adenocarcinoma	any variant (GoF)	response	PI3K alpha inhibitors	case report	ASCO 2015 (abstr 2501)	B2
PIK3CA	G118D I391M	Head And Neck Carcinoma	any variant (GoF)	response	PI3K pathway inhibitors	case report	26787751, 26763254	B2
PIK3CA	G118D I391M	Urothelial Carcinoma	any variant (GoF)	response	PI3K pathway inhibitors	case report	ASCO 2015 (abstr 2516)	B2
PIK3R1	M26I M56I M326I M301I M151I M5I M295I	Endometrial Cancer	any variant (LoF)	response	PI3K pathway inhibitors	case report	ASCO 2015 (abstr 11075)	B2
BRCA2	R2034C R1911C V2466A V2343A	Pancreas Adenocarcinoma	any variant (LoF)	response	platinum	case report	25719666	B2
NF1	D196Y	Melanoma	any variant (LoF)	resistance	selumetinib in BRAF mutant tumors	case report	23444215, 23288408	B2
TSC2	H798Y H749Y H761Y H809Y H813Y H796Y	Endometrial Cancer	any variant (GoF)	response	tensirolimus	case report	27016228	B2
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G	Cancer	any variant (LoF)	response	WEE1 inhibitors	case report	25964244	B2

	S1317G S104G S1572G S1635G ...							
ERCC2	K751Q		K751Q	resistance	Cisplatin	clin. trials	19434073	B2
FLT3	T227M	Renal Cell Carcinoma	T227M	adverse response	Sunitinib	clin. trials	19667267	B2
PIK3CA	G118D I391M	Inflammatory Breast Carcinoma	any variant (GoF)	response	AKT inhibitors	early trials	ASCO 2015 (abstr 2500)	B2
TP53	R273H R141H R180H R266H R234H R114H	Inflammatory Breast Carcinoma	any mut. (LoF)	resistance	CDK4/CDK6 inhibitor abemaciclib	early trials	27217383	B2
ERCC2	K751Q K710Q	Urothelial Carcinoma	any variant (LoF)	response	cisplatin	early trials	25096233	B2
ATM	L1420F L1365F	Urothelial Carcinoma	any variant (LoF)	response	cisplatin	early trials	26238431	B2
TP53	R273H R141H R180H R266H R234H R114H	Acute Promyelocytic Leukemia	any mut. (LoF)	response	decitabine	early trials	27959731	B2
TP53	R273H R141H R180H R266H R234H R114H	myelodysplastic syndrome	any mut. (LoF)	response	decitabine	early trials	27959731	B2
FANCA	G501S	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	26510020	B2
ATM	L1420F L1365F	Gastric Adenocarcinoma	any variant (LoF)	response	PARP inhibitors	early trials	ENA 2014 (abstr 8LBA)	B2
ATM	L1420F L1365F	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	26510020	B2
BRCA2	R2034C R1911C V2466A V2343A	Inflammatory Breast Carcinoma	any variant (LoF)	response	PARP inhibitors	early trials	20609467	B2
BRCA2	R2034C R1911C V2466A V2343A	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	26510020	B2
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G	Inflammatory Breast Carcinoma	any variant (LoF)	response	PARP inhibitors	early trials	20609467, 25366685	B2

	S463G S1317G S104G S1572G S1635G ...							
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G S1317G S104G S1572G S1635G ...	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	19553641, 25366685, 26510020	B2
BRCA2	R2034C R1911C V2466A V2343A	Epithelial Ovarian Cancer	any variant (LoF)	response	PARP inhibitors + chemotherapy	early trials	22307137, ASCO 2012 (abstr 1009)	B2
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G S1317G S104G S1572G S1635G ...	Epithelial Ovarian Cancer	any variant (LoF)	response	PARP inhibitors + chemotherapy	early trials	22307137, ASCO 2012 (abstr 1009)	B2
NF1	D196Y	Melanoma	any variant (LoF)	response	PD1 blockade	early trials	ASCO 2016 (abstr 105)	B2
PIK3CA	G118D I391M	Inflammatory Breast Carcinoma	any variant (GoF)	response	PI3K alpha inhibitors	early trials	28331003	B2
PIK3CA	G118D I391M	Cervix Carcinoma	any variant (GoF)	response	PI3K pathway inhibitors	early trials	22271473, ASCO 2013 (abstr 2531)	B2
PIK3CA	G118D I391M	Endometrial Cancer	any variant (GoF)	response	PI3K pathway inhibitors	early trials	22271473, 27672108	B2
PIK3CA	G118D I391M	Epithelial Ovarian Cancer	any variant (GoF)	response	PI3K pathway inhibitors	early trials	22271473, AACR 2013 (abstr LB-66), 25231405	B2
PIK3CA	G118D I391M	Inflammatory Breast	any variant	response	PI3K pathway	early trials	22271473	B2

		Carcinoma	(GoF)		inhibitors			
BRCA2	R2034C R1911C V2466A V2343A	Inflammatory Breast Carcinoma	any variant (LoF)	response	platinum agents	early trials	25847936	B2
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G S1317G S104G S1572G S1635G ...	Inflammatory Breast Carcinoma	any variant (LoF)	response	platinum agents	early trials	25847936	B2
BRCA2	R2034C R1911C V2466A V2343A	Inflammatory Breast Carcinoma	any variant (LoF)	response	veliparib + cisplatin	early trials	26801247	B2
BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G S1317G S104G S1572G S1635G ...	Inflammatory Breast Carcinoma	any variant (LoF)	response	veliparib + cisplatin	early trials	26801247	B2
TP53	R273H R141H R180H R266H R234H R114H	Epithelial Ovarian Cancer	any variant (GoF)	response	WEE1 inhibitors + carboplatin	early trials	ASCO2015 (abstr 2507)	B2
PIK3CA	G118D I391M	Colon Cancer	any variant (GoF)	response	aspirin in adjuvant setting	late trials	23094721	B2
PIK3CA	G118D I391M	Colon Cancer	any variant (GoF)	resistance	cetuximab	late trials	19223544, 20619739	B2
PIK3CA	G118D I391M	Inflammatory Breast Carcinoma	any variant (GoF)	response	everolimus + trastuzumab + chemotherapy (HER2 ampl)	late trials	27091708	B2
BRCA2	R2034C R1911C V2466A V2343A	Epithelial Ovarian Cancer	any variant (LoF)	response	platinum agents	late trials	22406760, 22711857	B2



BRCA1	S471G S1613G S1612G S509G S1634G S1571G S1611G S1587G S467G S1566G S463G S1317G S104G S1572G S1635G ...	Epithelial Ovarian Cancer	any variant (LoF)	response	platinum agents	late trials	22406760, 22711857	B2
EGFR	L858R	Lung Adenocarcinoma	L858R	sensitivity/response	Erlotinib	preclinical	27102076	A3
EGFR	L858R	Lung Small Cell Carcinoma	L858R	sensitivity/response	Erlotinib	preclinical	24893891	A3
EGFR	T790M	Lung Cancer	T790M	resistance	Gefitinib	preclinical	18227510	A3
EGFR	T790M	Lung Cancer	T790M	resistance	Multikinase Inhibitor AEE788	preclinical	18227510	A3
EGFR	L858R	Lung Acinar Adenocarcinoma	L858R (GoF)	sensitivity	MEK inhibitors (alone or in combination)	preclinical	23102728	A3
EGFR	T790M	Lung Acinar Adenocarcinoma	T790M (GoF)	sensitivity	MEK inhibitors (alone or in combination)	preclinical	23102728	A3
PIK3R1	M26I M56I M326I M301I M151I M5I M295I	Glioma	any variant (LoF)	sensitivity	AKT inhibitors	preclinical	23166678	B3
NF1	D196Y	Melanoma	any variant (LoF)	resistance	BRAF inhibitors in BRAF mutant tumor	preclinical	23288408, 24576830	B3
ERCC6	S43C	Epithelial Ovarian Cancer	any variant (LoF)	sensitivity	cisplatin	preclinical	25634215	B3
ATM	L1420F L1365F	Mantle Cell Lymphoma	any variant (LoF)	sensitivity	DNA-PKc inhibitors	preclinical	23761041	B3
MSH3	Q949R Q893R Q884R	Cancer	any variant (LoF)	sensitivity	DNA-PKcs inhibitors	preclinical	24556366	B3
EGFR	L858R	Cancer	L858R	sensitivity/response	Erlotinib	preclinical	17877814, 21132006	B3
EGFR	T790M	Cancer	T790M	resistance	Gefitinib	preclinical	19147750	B3
EGFR	T790M	Cancer	T790M	resistance	Erlotinib	preclinical	19147750	B3
EGFR	T790M	Cancer	T790M	resistance	Multikinase Inhibitor AEE788	preclinical	19147750	B3
EGFR	L858R	Cancer	L858R	sensitivity/response	Gefitinib	preclinical	19147750	B3

EGFR	L858R	Cancer	L858R	sensitivity/response	Multikinase Inhibitor AEE788	preclinical	19147750	B3
EGFR	L858R	Cancer	L858R	sensitivity/response	Erlotinib	preclinical	19147750	B3
TP53	R273H	Cancer	R273H	resistance	MDM2 Inhibitor AMGMS3	preclinical	25730903	B3
TP53	R273H		R273H	resistance	Methotrexate	preclinical	17363498	B3
TP53	R273H		R273H	resistance	Doxorubicin	preclinical	17363498	B3
TP53	R273H R141H R180H R266H R234H R114H	Urothelial Carcinoma	any mut. (LoF)	sensitivity	mitomycin C	preclinical	27397505	B3
TP53	R273H R141H R180H R266H R234H R114H	Urothelial Carcinoma	any mut. (LoF)	sensitivity	gemcitabine	preclinical	27397505	B3
TP53	R273H R141H R180H R266H R234H R114H	Urothelial Carcinoma	any mut. (LoF)	sensitivity	doxorubicin	preclinical	27397505	B3
NF1	D196Y	Glioma	any variant (LoF)	sensitivity	mTOR inhibitors	preclinical	19573811	B3
ATR	K297N M211T	Cancer	any variant (LoF)	sensitivity	PARP inhibitors	preclinical	23548269	B3
PIK3CA	G118D I391M	Glioma	any variant (GoF)	sensitivity	PI3K pathway inhibitors	preclinical	19671762	B3
PIK3CA	G118D I391M	Thyroid Gland Papillary Carcinoma	any variant (GoF)	sensitivity	PI3K pathway inhibitors	preclinical	21289267	B3
PIK3CA	G118D I391M	Colon Cancer	any variant (GoF)	sensitivity	PI3K pathway inhibitors (alone or in combination)	preclinical	23475782, 22392911	B3
APC	V1822D V1840D V1804D V1716D S2134C S2152C S2116C S2028C	Colon Cancer	any variant (LoF)	sensitivity	tankyrase inhibitors	preclinical	22440753, 23539443	B3
ATR	K297N M211T	Glioma	any variant (LoF)	sensitivity	temozolomide	preclinical	23960094	B3
ATM	L1420F L1365F	Glioma	any variant (LoF)	sensitivity	temozolomide	preclinical	23960094	B3
NF1	D196Y	Melanoma	any variant (LoF)	sensitivity	trametinib	preclinical	24576830	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).

**Disclaimer:** This report is intended for research use only and should not be used for medical or professional advice. GeneXplain GmbH makes no guarantee of the comprehensiveness, reliability or accuracy of the information contained in this report. You accept full responsibility for all risks associated with using of information, contained in this report.