MTB Report

Bioinformatics Center, University of Eastern Finland, May 15, 2023

PATIENT INFORMATION

Patient ID		**Tissue Type**	
Gender		**Tumor Content (%)**	
Disease	unspecified	**Number SNVs**	151
Stage			
Previous Therapies			

GENE-DRUG PREDICTIVE ASSOCIATIONS

Method: Somatic variants of the patient (mutations, amplifications, deletions, rearrangments) are searched in curated databases of predictive biomarkers (GKDB[1], CIViC[2]) and reported according to their clinical evidence (see Levels of Evidence). In the following two tables, basic information of the somatic variants with relevant clinical implications can be found:

Gene	Patient's Variant	Level of Evidence
ALK	D461E, D1529E, D1152E, K423R, K1491R, K1114R, I393V, I1461V, I1084V, F79L, W73*	**B1** ,**B2** ,**B3**
ARID1A	T292P, T294P, PQ942, 943P, PQ1326, 1327P, PQ943, 944P, PQ944, 945P, RS96, 97R, P1243A, P1627A, P1410A, P1244A, P1245A, H79Q	**B2** ,**B3**
BRCA1	S1613G, S471G, S1634G, S509G, S467G, S104G, S1566G, S463G, S482G, L210P, L201P, K1183R, K1136R, E1038G, E991G, P871L, P824L	**B1** ,**B2** ,**B3**
BRCA2	V2466A	**B1** ,**B2**
EGFR	R521K, R476K, R468K, L79Q, S237N	**B1** ,**B2** ,**B3**
ERBB2	P8T, P1140A, P1155A, P894A, P1170A	**B2** ,**B3**
NF1	A17V, D196Y, L640P	**B2** ,**B3**
PALB2	L337S, L42S	**B2** ,**B3**
POLE	I2255F, I2228F1446, 1447-1419, 1420-	**B2**
PTEN	C65S, D268E, D441E, D253E, T244K	**B2** ,**B3**
RET	S13G, I220V, I36V, G691S, G559S	**B2** ,**B3**
ROS1	S2223C, S2229C, K2222Q, K2228Q, D2207N, D2213N, R176Q, R167Q	**B2** ,**B3**
SMARCA4	1284, 1285-1089, 1090-832, 834-803, 804-779, 780-780, 781-736, 737-717, 719-712, 714-404, 406-134, 135-	**B2** ,**B3**
TP53	P72R, P33R	**B2** ,**B3**

Levels of Evidence: Findings are classified into 6 levels of evidence combining the **axis A-B** and the **axis 1-2-3**. Level A means evidence in the same cancer type. Level B means evidence in any other cancer type. On the 1-2-3 axis, level 1 means evidence supported by drug approval organizations or clinical guidelines, level 2 contains clinical evidence (clinical trials, case reports) and level 3 consists of preclinical evidence

Table of Results: All the predictive associations are detailed in this table. The results are sorted by 1) drug frequency, 2) levels of evidence (A1-B1-A2-B2-A3-B3). To allow a quick interpretation, the type of association (response, resistance) is colored (green, red) and new variants are gray.

Patient				Gene-Drug	Associations			
Gene	**Variant**	**Disease**	**Known Variant**	**Predicts**	**Drugs**	**Evidence**	**PMID**	**Level**
ERBB2	P8T, P1140A, P1155A, P894A, P1170A	lung	A775-G776insYVMA, G776delinsVC, V659E, S310F (GoF)	response	Ado-trastuzumab Emtansine	early trials	ASCO 2017 (abstr 8510)	**B2**

[1] Dienstmann et al., Cancer Discov (2015), gdkd
[2] Griffith et al., Nat Genet (2017), civic

Patient				Gene-Drug	Associations			
Gene	**Variant**	**Disease**	**Known Variant**	**Predicts**	**Drugs**	**Evidence**	**PMID**	**Level**
EGFR	R521K, R476K, R468K, L79Q, S237N	lung	T790M (GoF), exon 19 p.729-761 (GoF), L861Q, G719A, G719S, G719C, G719D, L747S, S768I, L861P, L861R (GoF), L858R (GoF)	sensitivity	MEK Inhibitors (alone Or In Combination)	preclinical	23102728	B3
PTEN	C65S, D268E, D441E, D253E, T244K	glioma	any variant (LoF)	sensitivity	PI3K Pathway Inhibitors (alone Or In Combination)	preclinical	21325073, 21191045, 17804702	B3
		lung	any variant (LoF)	sensitivity	PI3K Pathway Inhibitors (alone Or In Combination)	preclinical	23136191	B3
BRCA1	S1613G, S471G, S1634G, S509G, S467G, S104G, S1566G, S463G, S482G, L210P, L201P, K1183R, K1136R, E1038G, E991G, P871L, P824L	ovarian	any variant (LoF)	response	Olaparib, Rucaparib	FDA-approved	FDA	B1
		Cancer	any mut.	sensitivity/response	Olaparib	approved	19553641	B1
		Ovarian Cancer	any mut.	sensitivity/response	Olaparib	approved	30345884	B1
BRCA2	V2466A	ovarian	any variant (LoF)	response	Olaparib, Rucaparib	FDA-approved	FDA	B1
		Cancer	any mut.	sensitivity/response	Olaparib	approved	19553641	B1
		Ovarian Cancer	any mut.	sensitivity/response	Olaparib	approved	30345884	B1
BRCA1	S1613G, S471G, S1634G, S509G, S467G, S104G, S1566G, S463G, S482G, L210P, L201P, K1183R, K1136R, E1038G, E991G, P871L, P824L	Triple-receptor Negative Breast Cancer	any mut.	sensitivity/response	Carboplatin, Cisplatin	clin_trials	25847936	B2
		Pancreatic Cancer	any mut.	sensitivity/response	Cisplatin, Gemcitabine, Veliparib	clin_trials	29338080	B2
		Triple-receptor Negative Breast Cancer	any mut.	resistance	Olaparib	clin_trials	21862407	B2
		Her2-receptor Negative Breast Cancer	(LoF), any mut.	sensitivity/response	Olaparib	clin_trials	28578601, 28792849	B2
		Ovarian Cancer	(LoF), any mut.	sensitivity/response	Olaparib	clin_trials	23346317, 21862407	B2
		Pancreatic Cancer	any mut.	sensitivity/response	Olaparib	clin_trials	25366685	B2
		Ovarian Cancer	any mut.	sensitivity/response	Cediranib, Olaparib	clin_trials	25218906	B2
		Ovarian Cancer	any mut.	sensitivity/response	Rucaparib	clin_trials	27908594	B2
		Pancreatic Cancer	any mut.	sensitivity/response	Veliparib	clin_trials	29223478	B2
		breast	any variant (LoF)	response	Veliparib + Cisplatin	early trials	26801247	B2
BRCA2	V2466A	Pancreatic Cancer	any mut.	sensitivity/response	Iniparib	case_report	21508395	B2

Patient				Gene-Drug	Associations			
Gene	**Variant**	**Disease**	**Known Variant**	**Predicts**	**Drugs**	**Evidence**	**PMID**	**Level**
		Ovarian Cancer	M1R, M1I, V159M, V211L, V211I, R2336P	sensitivity/ response	Rucaparib	case_report	27908594	B2
		Triple-receptor Negative Breast Cancer	any mut.	sensitivity/ response	Carboplatin, Cisplatin	clin_trials	25847936	B2
		Breast Cancer	any mut.	sensitivity/ response	Olaparib	clin_trials	28792849	B2
		Ovarian Cancer	(LoF), any mut.	sensitivity/ response	Olaparib	clin_trials	23346317, 21862407	B2
		Pancreatic Cancer	any mut.	sensitivity/ response	Olaparib	clin_trials	25366685	B2
		Triple-receptor Negative Breast Cancer	any mut.	sensitivity/ response	Olaparib	clin_trials	21862407	B2
		Ovarian Cancer	any mut.	sensitivity/ response	Cediranib, Olaparib	clin_trials	25218906	B2
		Ovarian Cancer	any mut.	sensitivity/ response	Rucaparib	clin_trials	27908594	B2
		Pancreatic Cancer	any mut.	sensitivity/ response	Veliparib	clin_trials	29223478	B2
		Pancreatic Cancer	any mut.	sensitivity/ response	Cisplatin, Gemcitabine, Veliparib	clin_trials	29338080	B2
		breast	any variant (LoF)	response	Veliparib + Cisplatin	early trials	26801247	B2
TP53	P72R, P33R	Ovarian Cancer	R273L, Y234C	resistance	Carboplatin, Cisplatin	case_report	11595686	B2
		ovarian	any variant (GoF)	response	WEE1 Inhibitors + Carboplatin	early trials	ASCO2015 (abstr 2507)	B2
BRCA1	S1613G, S471G, S1634G, S509G, S467G, S104G, S1566G, S463G, S482G, L210P, L201P, K1183R, K1136R, E1038G, E991G, P871L, P824L	Endometrioid Ovary Carcinoma	W1815X	sensitivity/ response	Olaparib	preclinical	23415752	B3
PTEN	C65S, D268E, D441E, D253E, T244K	Prostate Cancer	any mut.	sensitivity/ response	Alpelisib, Enzalutamide, PI3Kbeta Inhibitor AZD8186	preclinical	25544636	B3
ARID1A	T292P, T294P, PQ942, 943P, PQ1326, 1327P, PQ943, 944P, PQ944, 945P, RS96, 97R, P1243A, P1627A, P1410A, P1244A, P1245A, H79Q	breast cancer	any mut. (LoF)	resistance	Trastuzumab (ANXA1 High)	early trials	27172896	B2
ERBB2	P8T, P1140A, P1155A, P894A, P1170A	lung_adeno	G776L (GoF)	response	Trastuzumab-based Therapy	case report	16775247	B2
		Colorectal Adenocarcinoma	L755S	sensitivity/ response	Fluorouracil, Leucovorin, Trastuzumab	case_report	27626067	B2
		Lung Adenocarcinoma	kinase domain any mut.	sensitivity/ response	Trastuzumab	case_report	26598547	B2
		Lung Non-small Cell Carcinoma	any mut.	sensitivity/ response	Pertuzumab, Trastuzumab	clin_trials	29320312	B2
		Lung Non-small Cell Carcinoma	exon 20 insertion	sensitivity/ response	Trastuzumab Deruxtecan	clin_trials	34534430	B2
		lung_adeno	proximal exon 20 p.775-881 (GoF)	response	Afatinib, Lapatinib, Neratinib, Trastuzumab	early trials	26598547, ASCO 2017 (abstr 9071)	B2

Patient				Gene-Drug	Associations			
Gene	**Variant**	**Disease**	**Known Variant**	**Predicts**	**Drugs**	**Evidence**	**PMID**	**Level**
PTEN	C65S, D268E, D441E, D253E, T244K	breast	any variant (LoF)	response	Everolimus + Trastuzumab + Chemotherapy (HER2 Ampl)	late trials	27091708	**B2**
ERBB2	P8T, P1140A, P1155A, P894A, P1170A	Colon Cancer	V777L	sensitivity/ response	Lapatinib, Neratinib, Trastuzumab	preclinical	26243863	**B3**
		Colon Cancer	V842I	sensitivity/ response	Lapatinib, Neratinib, Trastuzumab	preclinical	26243863	**B3**
		Colon Cancer	L866M	sensitivity/ response	Lapatinib, Neratinib, Trastuzumab	preclinical	26243863	**B3**
		breast	D769Y, D769H, R896C (GoF)	sensitivity	Lapatinib, Neratinib, Trastuzumab	preclinical	23220880	**B3**

SPECIFIC VARIANT-DISEASE CONNECTIONS

ClinVar variant information: This is a list of the patient's variants which could be found in the NCBI ClinVar database.[3] These include both germline and somatic variants as well as their related traits. Further information about these variants and related publications can be found at www.ncbi.nlm.nih.gov/clinvar/ by searching for the variant accession numbers.

Gene	Patient's Variant	Trait	Pathogenicity	Evidence	Accession
ALK	D461E, D1529E	Hereditary cancer-predisposing syndrome	Benign	multiple submitters	VCV000133476
	D461E, D1529E	Neuroblastoma, susceptibility to, 3	Benign	multiple submitters	VCV000133476
	K423R, K1491R	Neuroblastoma, susceptibility to, 3	Uncertain significance	single submitter	VCV000968430
	I393V, I1461V	Neuroblastoma, susceptibility to, 3	Uncertain significance	single submitter	VCV001047157
ARID1A	P1627A, P1410A	Intellectual disability, autosomal dominant 14	Benign/Likely benign	multiple submitters	VCV001257586
ARID5B	R335S, R92S	Inborn genetic diseases	Uncertain significance	single submitter	VCV002372142
BARD1	R378S, R359S	Familial cancer of breast	Benign	multiple submitters	VCV000142769
	R378S, R359S	Hereditary breast ovarian cancer syndrome	Benign	multiple submitters	VCV000142769
	R378S, R359S	Hereditary cancer-predisposing syndrome	Benign	multiple submitters	VCV000142769
BRCA1	P824L	Breast-ovarian cancer, familial, susceptibility to, 1	Benign	reviewed by expert panel	VCV000041812
	E1038G	Breast-ovarian cancer, familial, susceptibility to, 1	Benign	reviewed by expert panel	VCV000041815
	S471G, S1634G	Breast-ovarian cancer, familial, susceptibility to, 1	Benign	reviewed by expert panel	VCV000041827
	P871L	Hereditary breast ovarian cancer syndrome	Conflicting interpretations	conflicting interpretations	VCV000419626
	S467G	Hereditary breast ovarian cancer syndrome	Conflicting interpretations	conflicting interpretations	VCV000846197
	K1183R, K1136R	Hereditary breast ovarian cancer syndrome	Conflicting interpretations	conflicting interpretations	VCV000920987
	E991G	Hereditary breast ovarian cancer syndrome	Conflicting interpretations	conflicting interpretations	VCV001477696
	P871L	Hereditary cancer-predisposing syndrome	Conflicting interpretations	conflicting interpretations	VCV000419626
	S467G	Hereditary cancer-predisposing syndrome	Conflicting interpretations	conflicting interpretations	VCV000846197
	K1183R, K1136R	Hereditary cancer-predisposing syndrome	Conflicting interpretations	conflicting interpretations	VCV000920987
	E991G	Hereditary cancer-predisposing syndrome	Conflicting interpretations	conflicting interpretations	VCV001477696
	L201P	Breast-ovarian cancer, familial, susceptibility to, 1	Uncertain significance	multiple submitters	VCV000808279
	S509G	Hereditary breast ovarian cancer syndrome	Uncertain significance	multiple submitters	VCV000182159
	L201P	Hereditary breast ovarian cancer syndrome	Uncertain significance	multiple submitters	VCV000808279
	S509G	Hereditary cancer-predisposing syndrome	Uncertain significance	multiple submitters	VCV000182159
	L201P	Hereditary cancer-predisposing syndrome	Uncertain significance	multiple submitters	VCV000808279
BRCA2	V2466A	Hereditary breast ovarian cancer syndrome	Likely benign	single submitter	VCV001157128
BRIP1	S919P	Familial cancer of breast	Likely benign	single submitter	VCV002127109
	S919P	Fanconi anemia complementation group J	Likely benign	single submitter	VCV002127109
EGFR	R521K, R476K, R468K	EGFR-related lung cancer	Benign	multiple submitters	VCV000134021
	R521K, R476K, R468K	Inflammatory skin and bowel disease, neonatal, 2	Benign	multiple submitters	VCV000134021

[3]Landrum et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res . 2018 Jan 4.

EPCAM	M115T	Hereditary nonpolyposis colorectal neoplasms	Benign	multiple submitters	VCV000215500
MSH2	G256D, G322D	Lynch syndrome	Benign	reviewed by expert panel	VCV000001762
MSH6	G39E	Lynch syndrome	Benign	reviewed by expert panel	VCV000036581
PALB2	L337S	Breast and/or ovarian cancer	Conflicting interpretations	conflicting interpretations	VCV000126582
	L337S	Familial cancer of breast	Conflicting interpretations	conflicting interpretations	VCV000126582
	L337S	Fanconi anemia complementation group N	Conflicting interpretations	conflicting interpretations	VCV000126582
	L337S	Hereditary cancer-predisposing syndrome	Conflicting interpretations	conflicting interpretations	VCV000126582
PMS2	K541E, K406E, K489E, K435E, K350E, K354E	Hereditary nonpolyposis colorectal neoplasms	Benign	multiple submitters	VCV000135065
	K541E, K406E, K489E, K435E, K350E, K354E	Lynch syndrome 4	Benign	multiple submitters	VCV000135065
	K541E, K406E, K489E, K435E, K350E, K354E	Mismatch repair cancer syndrome 4	Benign	multiple submitters	VCV000135065
	G805A, G751A, G666A, G733A, G868A, G670A	Lynch syndrome	Benign	reviewed by expert panel	VCV000036691
	K603E	Hereditary cancer-predisposing syndrome	Uncertain significance	single submitter	VCV001789569
	K475E	Hereditary nonpolyposis colorectal neoplasms	Uncertain significance	single submitter	VCV001016843
POLE	I2255F, I2255F	Colorectal cancer, susceptibility to, 12	Conflicting interpretations	conflicting interpretations	VCV000221175
	I2255F	Facial dysmorphism-immunodeficiency-livedo-short stature syndrome	Conflicting interpretations	conflicting interpretations	VCV000221175
	I2255F	Hereditary cancer-predisposing syndrome	Conflicting interpretations	conflicting interpretations	VCV000221175
	I2255F	Intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies, and immunodeficiency	Conflicting interpretations	conflicting interpretations	VCV000221175
PTEN	D268E, D441E	Hereditary cancer-predisposing syndrome	Uncertain significance	single submitter	VCV001761790
RET	G559S	Hereditary cancer-predisposing syndrome	Conflicting interpretations	conflicting interpretations	VCV000024934
	G559S	Hirschsprung disease, susceptibility to, 1	Conflicting interpretations	conflicting interpretations	VCV000024934
	G559S	Multiple endocrine neoplasia	Conflicting interpretations	conflicting interpretations	VCV000024934
	G559S	Multiple endocrine neoplasia, type 2	Conflicting interpretations	conflicting interpretations	VCV000024934
	G559S	Multiple endocrine neoplasia, type 2a	Conflicting interpretations	conflicting interpretations	VCV000024934
	G559S	Pheochromocytoma	Conflicting interpretations	conflicting interpretations	VCV000024934
	G559S	Renal hypodysplasia/aplasia 1	Conflicting interpretations	conflicting interpretations	VCV000024934
TP53	P72R, P33R	Hereditary cancer-predisposing syndrome	Likely benign	multiple submitters	VCV000237944
	P72R, P33R	Li-Fraumeni syndrome	Likely benign	multiple submitters	VCV000237944
	P72R, P33R	Li-Fraumeni syndrome 1	Likely benign	multiple submitters	VCV000237944

Other genes: here you can find other genes that might be interesting to check (information from Target DB[4] and Meric-Bernstam list[5]). No level information is provided in this section.

[1] "No other genes found"

[4] Van Allen et al., Nature medicine 20.6 (2014): 682-688, v3

[5] Meric-Bernstam et al., J Natl Cancer Inst. 107(7) (2015)