

Patient Name: 환관주

Gender: M

Sample ID: N25-298

Primary Tumor Site: lung

Collection Date: 2025.10.28

Sample Cancer Type: Lung Cancer

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Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	11.37 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	BRCA1 deletion BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	2
IIC	ATRX deletion ATRX, chromatin remodeler Locus: chrX:76763769	None*	None*	1
IIC	BRIP1 deletion BRCA1 interacting protein C-terminal helicase 1 Locus: chr17:59760627	None*	None*	1
IIC	CDK12 deletion cyclin dependent kinase 12 Locus: chr17:37618286	None*	None*	1

* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	<i>CHEK1</i> deletion checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	<i>RAD51C</i> deletion RAD51 paralog C Locus: chr17:56769933	None*	None*	1
IIC	<i>RAD51D</i> deletion RAD51 paralog D Locus: chr17:33427950	None*	None*	1

* Public data sources included in relevant therapies: FDA¹, NCCN, EMA², ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

APC p.(Q1444*) c.4330C>T, *CUL4B* deletion, *MAP2K7* deletion, *Microsatellite stable*, *NF1* p.(Q1235*) c.3703C>T, *TP53* p.(P71Lfs*52) c.212_215delCCCCinsTCG, *ERAP2* deletion, *HLA-A* deletion, *NOTCH1* deletion, *NQO1* p.(P187S) c.559C>T, *CIC* deletion, *ZRSR2* deletion, *DDX3X* deletion, *KDM6A* deletion, *RBM10* deletion, *KDM5C* deletion, *SMC1A* deletion, *AMER1* deletion, *ZMYM3* deletion, *STAG2* deletion, *PHF6* deletion, *Tumor Mutational Burden*

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
APC	p.(Q1444*)	c.4330C>T	.	chr5:112175621	20.42%	NM_000038.6	nonsense
NF1	p.(Q1235*)	c.3703C>T	.	chr17:29560226	24.84%	NM_001042492.3	nonsense
TP53	p.(P71Lfs*52)	c.212_215delCCCCinsTCG	.	chr17:7579472	23.52%	NM_000546.6	frameshift Block Substitution
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	60.09%	NM_000903.3	missense
GKN2	p.(I127M)	c.381C>G	.	chr2:69173527	18.27%	NM_182536.3	missense
MAML3	p.(Q489Tfs*29)	c.1455_1506delACAGC AACAGCAACAGCAGC AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGinsGCAGCAACAGA CAGCCAGCAGCAGCA GCAGCAGCAGCAA	.	chr4:140811084	25.15%	NM_018717.5	frameshift Block Substitution
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGC AACAGCAACAGCAGC AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGinsGCAGCAACAGC AACAGCCAGCAGCAG CAGCAGCAGCAGCAA	.	chr4:140811084	71.17%	NM_018717.5	frameshift Block Substitution
HLA-A	p.(I121R)	c.362_363delTAinsGG	.	chr6:29911063	34.17%	NM_001242758.1	missense
BMP5	p.(R313Q)	c.938G>A	.	chr6:55638936	12.52%	NM_021073.4	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
RB1CC1	p.(V241A)	c.722T>C	.	chr8:53586685	33.19%	NM_014781.5	missense
ABL1	p.(E352*)	c.1054G>T	.	chr9:133748393	16.01%	NM_005157.6	nonsense
PARP4	p.(?)	c.3285_3285+5delinsA . GT	.	chr13:25021149	100.00%	NM_006437.4	unknown
PARP4	p.(Y214F)	c.641A>T	.	chr13:25068811	17.55%	NM_006437.4	missense
MLH3	p.(E799Q)	c.2395G>C	.	chr14:75513964	50.03%	NM_001040108.2	missense
DICER1	p.(P1724A)	c.5170C>G	.	chr14:95560419	17.46%	NM_030621.4	missense
STK11	p.(*434=)	c.1301G>A	.	chr19:1226645	19.27%	NM_000455.5	stoploss
DNMT1	p.(S328C)	c.983C>G	.	chr19:10273368	18.50%	NM_001130823.3	missense
KMT2B	p.(V2324L)	c.6970G>C	.	chr19:36224508	59.98%	NM_014727.3	missense
CHEK2	p.(Q10E)	c.28C>G	.	chr22:29130682	21.86%	NM_007194.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA1	chr17:41197602	1	0.83
ATRX	chrX:76763769	0	0.52
BRIP1	chr17:59760627	1	0.98
CDK12	chr17:37618286	1	0.81
CHEK1	chr11:125496639	1	0.77
RAD51C	chr17:56769933	1	0.96
RAD51D	chr17:33427950	1	0.89
CUL4B	chrX:119660593	0.02	0.57
MAP2K7	chr19:7968792	0.35	0.65
ERAP2	chr5:96219500	0	0.43
HLA-A	chr6:29910229	0.49	0.67
NOTCH1	chr9:139390441	0.53	0.68
CIC	chr19:42775916	0.42	0.66
ZRSR2	chrX:15808582	0	0.51
DDX3X	chrX:41193501	0.56	0.69
KDM6A	chrX:44732715	0	0.53
RBM10	chrX:47006798	0	0.54
KDM5C	chrX:53221892	0	0.54
SMC1A	chrX:53406966	0	0.53
AMER1	chrX:63409727	0	0.54

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
ZMYM3	chrX:70460753	0	0.52
STAG2	chrX:123156472	0	0.57
PHF6	chrX:133511628	0	0.51
FGFR3	chr4:1801456	0	0.56
FLT4	chr5:180030092	0.37	0.65
RUNX1T1	chr8:92982878	0.21	0.62
CD276	chr15:73991923	0.4	0.66
EIF1AX	chrX:20148599	0	0.55
ARAF	chrX:47422311	0	0.54
AR	chrX:66766015	0	0.48

Biomarker Descriptions

BRCA1 deletion

BRCA1, DNA repair associated

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{13,14}. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{13,14}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer^{15,16,17}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{15,18}.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{19,20,21,22,23,24,25,26}. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme^{5,6}.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)²⁷. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{28,29}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib³⁰ (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib³⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib³¹ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib³² (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib³² in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib³³ (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate³⁴ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported³⁵. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality³⁶.

Biomarker Descriptions (continued)

In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

ATR^X deletion

ATR^X, chromatin remodeler

Background: The ATR^X gene encodes the ATR^X chromatin remodeler and ATPase/helicase domain protein, which belongs to SWI/SNF family of chromatin remodeling proteins¹. The SWI/SNF proteins are a group of DNA translocases that use ATP hydrolysis to remodel chromatin structure and maintain genomic integrity by controlling transcriptional regulation, DNA repair, and chromosome stability through the regulation of telomere length^{138,139,140,141}. ATR^X is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair^{142,143,144}.

Alterations and prevalence: Somatic mutations of ATR^X are observed in 38% of brain lower grade glioma, 15% of uterine corpus endometrial carcinoma, 14% of sarcoma, 9% of glioblastoma multiforme and skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of lung adenocarcinoma, stomach adenocarcinoma, and cervical squamous cell carcinoma, 5% of bladder urothelial carcinoma and lung squamous cell carcinoma, 4% of adrenocortical carcinoma, head and neck squamous cell carcinoma and uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma, ovarian serous cystadenocarcinoma, breast invasive carcinoma, pheochromocytoma and paraganglioma, kidney renal clear cell carcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma and kidney chromophobe^{5,6}. Biallelic deletion of ATR^X is observed in 7% of sarcoma, 3% of kidney chromophobe, and 2% of brain lower grade glioma^{5,6}. Although alterations of ATR^X in pediatric populations are rare, somatic mutations are observed in 6% of gliomas, 4% of bone cancer, 3% of soft tissue sarcoma, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (3 in 332 cases), and leukemia (2 in 354 cases)⁶. Biallelic deletion of ATR^X is observed in 1% of peripheral nervous system tumors (1 in 91 cases) in and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)⁶.

Potential relevance: Currently, no therapies are approved for ATR^X aberrations. Loss of ATR^X protein expression correlates with the presence of ATR^X mutations^{145,146}. ATR^X deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)^{147,148}.

BRIP1 deletion

BRCA1 interacting protein C-terminal helicase 1

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA⁷⁰. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control⁷¹. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss^{66,67}. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)⁷². Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer^{72,73}. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer^{70,74}.

Alterations and prevalence: Somatic mutations in BRIP1 are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 4% of bladder urothelial carcinoma^{5,6}.

Potential relevance: The PARP inhibitor, olaparib³⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy^{66,75}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability^{174,175,176}. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes^{67,174,175,176,177}. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype^{67,176}. CDK12 is a tumor suppressor gene and loss of function

Biomarker Descriptions (continued)

mutations are observed in various solid tumors¹⁷⁷. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene¹⁷⁷.

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma^{1,5}. CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma^{1,5}.

Potential relevance: The PARP inhibitor, olaparib³⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib³² in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP inhibitors^{67,177}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CHEK1 deletion

checkpoint kinase 1

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2¹. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest¹⁶⁹. CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)^{170,171}. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR¹⁷⁰. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication^{170,172}.

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma cases^{5,173}. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases^{5,173}.

Potential relevance: The PARP inhibitor, olaparib³⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD51C deletion

RAD51 paralog C

Background: The RAD51C gene encodes the RAD51 paralog C protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs⁶⁰. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)⁶¹. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)⁶². The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing⁶³. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity^{64,65}. RAD51C is a tumor suppressor gene and loss of function mutations in RAD51C are implicated in the BRCAness phenotype, characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{66,67}.

Alterations and prevalence: Somatic mutations in RAD51C are observed in 1-3% of adrenocortical carcinoma, melanoma, squamous lung, bladder, and uterine cancers⁵.

Potential relevance: The PARP inhibitor, olaparib³⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51C. Additionally, talazoparib³² in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes RAD51C. In one study, RAD51C underexpression was observed in olaparib-sensitive gastric cancer cell lines, and olaparib treatment sensitized cells to irradiation⁶⁸. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

RAD51D deletion

RAD51 paralog D

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)⁶¹. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex⁶². The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP⁶³. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss^{66,67}. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer⁶⁹.

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer⁵.

Potential relevance: The PARP inhibitor, olaparib³⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors⁶⁶. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

APC p.(Q1444*) c.4330C>T

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β -catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation¹¹⁰. APC is an antagonist of WNT signaling as it targets β -catenin for proteasomal degradation^{111,112}. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine^{110,113}. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer¹¹⁴.

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma^{5,6,115}. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation^{116,117}.

Potential relevance: Currently, no therapies are approved for APC aberrations.

CUL4B deletion

cullin 4B

Background: The CUL4B gene encodes cullin 4B, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4a, CUL5, CUL7, and Parc^{1,2}. CUL4B belongs to the CUL4 subfamily which also includes CUL4A³. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy^{3,4}. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)². CUL4B is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the substrate recognition component of the CRL4 complex⁴. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4B in oncogenesis^{3,4}.

Alterations and prevalence: Somatic mutations in CUL4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 2% of bladder urothelial carcinoma, cervical squamous cell carcinoma, colorectal adenocarcinoma, uterine carcinosarcoma, brain lower grade glioma, and lung squamous cell carcinoma^{5,6}. Amplification of CUL4B is observed in 2% of diffuse large B-cell lymphoma^{5,6}. Biallelic loss of CUL4B is observed in 1% sarcoma and testicular germ cell tumors^{5,6}.

Potential relevance: Currently, no therapies are approved for CUL4B aberrations.

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7¹. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10^{160,161,162}. Activation of MAPK

Biomarker Descriptions (continued)

proteins occurs through a kinase signaling cascade^{160,161,163}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{160,161,163}. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation^{160,161,163}.

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma^{5,6}. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma^{5,6}.

Potential relevance: Currently, no therapies are approved for MAP2K7 aberrations.

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome⁸⁸. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{89,90}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁹¹. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250⁹². Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)⁹². Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{93,94,95,96,97}. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes⁹⁰. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{89,90,94,98}.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma^{89,90,99,100}. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers^{99,100}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab¹⁰¹ (2014) and nivolumab¹⁰² (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab¹⁰¹ is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication¹⁰¹. Dostarlimab¹⁰³ (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer^{95,104}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab¹⁰⁵ (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location^{95,106,107}. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients¹⁰⁷. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors^{108,109}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{108,109}.

NF1 p.(Q1235*) c.3703C>T

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family⁷. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state^{7,8}. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival⁷. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)^{7,9,10}.

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements⁷. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis^{7,11}. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)^{7,10}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)¹².

TP53 p.(P71Lfs*52) c.212_215delCCCCinsTCG

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair¹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis¹⁷⁸. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential¹⁷⁹. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{180,181}.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)^{5,6,125,182,183,184}. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282^{5,6}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{185,186,187,188}. Alterations in TP53 are also observed in pediatric cancers^{5,6}. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)^{5,6}. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)^{5,6}.

Potential relevance: The small molecule p53 reactivator, PC14586¹⁸⁹ (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{190,191}. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma¹⁴⁷. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)^{10,154,192,193,194}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant¹⁹⁵. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system¹⁹⁶.

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway^{166,167}. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules^{166,168}. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic¹⁶⁶.

Alterations and prevalence: Somatic mutations in ERAP2 are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma^{5,6}. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for ERAP2 aberrations.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A¹. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells⁵⁴. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁵⁵. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids,

Biomarker Descriptions (continued)

to the immune system to distinguish self from non-self^{56,57,58}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A⁵⁹.

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma^{5,6}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{5,6}.

Potential relevance: Currently, no therapies are approved for HLA-A aberrations.

NOTCH1 deletion

notch 1

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling¹¹⁸. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism^{119,120}. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members^{121,122,123,124}.

Alterations and prevalence: Somatic mutations in NOTCH1 are observed in 15-20% of head and neck cancer, 5-10% of glioma, melanoma, gastric, esophageal, lung, and uterine cancers^{5,6,125}. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia^{126,127}.

Potential relevance: Currently, no therapies are approved for NOTCH1 aberrations.

CIC deletion

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily^{1,128}. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes^{1,128}. CIC interacts with the HDAC complex and SWI/SNF to transcriptionally repress target genes, which include members of the E-Twenty Six (ETS) oncogene family ETV1, ETV4 and ETV5¹²⁸. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC¹²⁸.

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma^{5,6}. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)^{5,6}. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma^{128,129}.

Potential relevance: Currently, no therapies are approved for CIC aberrations. CIC fusions, including CIC::DUX4 fusion, t(10;19)(q26;q13) and t(4;19)(q35;q13), are ancillary diagnostic markers for CIC-Rearranged Sarcoma^{12,130}.

ZRSR2 deletion

zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2

Background: The ZRSR2 gene encodes the zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2 protein, a component of the spliceosome. Specifically, ZRSR2 encodes a splicing factor that is involved in the recognition of the 3' intron splice site¹⁵⁶. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer^{156,157}. Mutations in ZRSR2 can lead to deregulated global and alternative mRNA splicing, nuclear-cytoplasm export, and unspliced mRNA degradation while concurrently altering the expression of multiple genes^{156,158}.

Alterations and prevalence: ZRSR2 alterations including nonsense and frameshift mutations are observed in 5-10% of myelodysplastic syndromes (MDS) and 4% of uterine cancer. ZRSR2 deletions are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of head and neck and esophageal cancers^{6,10}.

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)^{10,154,159}.

Biomarker Descriptions (continued)

DDX3X deletion

DEAD-box helicase 3, X-linked

Background: The DDX3X gene encodes DEAD-box helicase 3 X-linked, a member of the DEAD-box protein family, which is part of the RNA helicase superfamily II^{1,76}. DEAD-box helicases contain twelve conserved motifs including a "DEAD" domain which is characterized by a conserved amino acid sequence of Asp-Glu-Ala-Asp (DEAD)^{76,77,78,79}. In DEAD-box proteins, the DEAD domain interacts with β - and γ -phosphates of ATP through Mg²⁺ and is required for ATP hydrolysis⁷⁶. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation^{80,81,82,83,84,85,86,87}. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance⁸⁰.

Alterations and prevalence: Somatic mutations in DDX3X are observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of diffuse large B-cell lymphoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and head and neck squamous cell carcinoma^{5,6}. Biallelic loss of DDX3X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma and lung squamous cell carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for DDX3X aberrations.

KDM6A deletion

lysine demethylase 6A

Background: The KDM6A gene encodes the lysine demethylase 6A protein¹. KDM6A is a histone demethylase that belongs to the KDM6 family of histone H3 lysine demethylases that also includes KDM6B and KDM6C¹⁶⁴. Methylation of histone lysine and arginine residues functions to regulate transcription and the DNA damage response, specifically in the recruitment of DNA repair proteins and transcriptional repression¹³⁶. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)^{135,164}. KDM6A also interacts with various transcription factors as well as KMT2C, KMT2D, and CBP/p300 chromatin-modifying enzymes, and the SWI/SNF chromatin-remodeling complex to facilitate transcriptional regulation¹⁶⁴. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression¹⁶⁴. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation^{164,165}.

Alterations and prevalence: Somatic mutations in KDM6A are observed in 26% of bladder urothelial carcinoma, 7% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, lung squamous cell carcinoma, and 4% of esophageal adenocarcinoma, kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, cervical squamous cell carcinoma, and head and neck squamous cell carcinoma^{5,6}. Biallelic loss of KDM6A is observed in 8% of esophageal adenocarcinoma, 4% of lung squamous cell carcinoma, 3% of head and neck squamous cell carcinoma, bladder urothelial carcinoma, and pancreatic adenocarcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for KDM6A aberrations. Pre-clinical data suggest that KDM6A loss of function or inactivating mutations may respond to EZH2 inhibitors¹⁶⁵.

RBM10 deletion

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family^{1,131}. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA^{131,132}. RBM10 is suggested to function as a tumor suppressor by promoting apoptosis and inhibiting cellular proliferation through regulation of the MDM2 and p53 feedback loops, as well as influencing BAX expression¹³¹. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10^{133,134}.

Alterations and prevalence: Somatic mutations in RBM10 are observed in 7% of lung adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 4% of bladder urothelial carcinoma, 3% of colorectal adenocarcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, and kidney chromophobe^{5,6}. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma^{5,6}. Amplification of RBM10 is observed in 5% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, and 2% of sarcoma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, and diffuse large B-cell lymphoma^{5,6}.

Potential relevance: Currently, no therapies are approved for RBM10 aberrations.

Biomarker Descriptions (continued)

KDM5C deletion

lysine demethylase 5C

Background: The KDM5C gene encodes the lysine demethylase 5C protein, a histone demethylase, also known as JARID1C^{1,135}. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response¹³⁶. KDM5C removes methylation of di- and trimethylated histone H3 lysine 4 (H3K4) and is involved in the repression of transcription in response to DNA damage^{135,136}. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication¹³⁷.

Alterations and prevalence: Somatic mutations in KDM5C are observed in 9% of uterine corpus endometrial carcinoma, 5% of kidney renal clear cell carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, 4% of lung adenocarcinoma and uterine carcinosarcoma^{5,6}. Biallelic loss of KDM5C is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for KDM5C aberrations.

SMC1A deletion

structural maintenance of chromosomes 1A

Background: SMC1A encodes the structural maintenance of chromosomes 1A and belongs to structural maintenance of chromosomes (SMCs) family, which consists of SMC1A, SMC1B, SMC2, SMC3, SMC4, SMC5, and SMC6^{1,44,45}. As a part of the cohesion-core complex, SMC1A plays a crucial role in chromosome segregation during mitosis and meiosis^{44,46}. SMC1A also plays a role in cell cycle regulation, DNA damage repair, gene transcription regulation, and genomic organization⁴⁴. SMC1A aberrations, including overexpression, have been observed in several cancer types and have been proposed to promote tumor formation and epithelial to mesenchymal transition^{45,47}.

Alterations and prevalence: Somatic mutations in SMC1A are observed in 11% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma and acute myeloid leukemia, 4% of colorectal adenocarcinoma and bladder urothelial carcinoma, 3% cervical squamous cell carcinoma and glioblastoma multiforme, 2% diffuse large B-Cell lymphoma, adrenocortical carcinoma, stomach adenocarcinoma, uterine carcinosarcoma, ovarian serous cystadenocarcinoma and lung adenocarcinoma^{5,6}. Amplification of SMC1A is found in 4% of diffuse large B-Cell lymphoma, 3% of sarcoma, and 2% of ovarian serous cystadenocarcinoma, adrenocortical carcinoma, and uterine carcinosarcoma^{5,6}. Biallelic loss of SMC1A is found in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for SMC1A aberrations.

AMER1 deletion

APC membrane recruitment protein 1

Background: The AMER1 gene encodes APC membrane recruitment protein 1¹. AMER1 works in complex with CTNNB1, APC, AXIN1, and AXIN2 to regulate the WNT pathway^{1,48}. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis^{49,50}. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types⁵⁰. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer⁵¹. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest⁴⁸.

Alterations and prevalence: Somatic mutations of AMER1 are observed in 13% of colorectal adenocarcinoma, 10% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 4% of stomach adenocarcinoma, and uterine carcinosarcoma, 3% of lung squamous cell carcinoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, and 2% of diffuse large B-cell lymphoma, liver hepatocellular carcinoma, head and neck squamous cell carcinoma, and breast invasive carcinoma^{5,6}. Biallelic deletion of AMER1 is observed in 2% of esophageal adenocarcinoma, diffuse large b-cell lymphoma, uterine carcinosarcoma, lung squamous cell carcinoma, and pancreatic adenocarcinoma, and 1% of stomach adenocarcinoma, sarcoma, liver hepatocellular carcinoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, uterine corpus endometrial carcinoma, and ovarian serous cystadenocarcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for AMER1 aberrations.

Biomarker Descriptions (continued)

ZMYM3 deletion

zinc finger MYM-type containing 3

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein¹. While the function is not fully understood, ZMYM3 is capable of binding histones and DNA, and may facilitate the repair of double-strand breaks (DSBs)⁵².

Alterations and prevalence: Somatic mutations in ZMYM3 are observed in 12% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, 3% of lung adenocarcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma^{5,6}. In prostate cancer, ZMYM3 mutations have been observed to be enriched in African American men compared to white men with one study demonstrating occurrence in 11.7% vs. 2.7% of patients, respectively⁵³. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe^{5,6}.

Potential relevance: Currently, no therapies are approved for ZMYM3 aberrations.

STAG2 deletion

stromal antigen 2

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division^{149,150}. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs^{151,152}. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer^{151,153}.

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, and splice site variants¹⁰. Somatic mutations in STAG2 are observed in 14% of bladder cancer, 10% of uterine cancer, 5% of glioblastoma multiforme, 4% of lung adenocarcinoma and skin cutaneous melanoma, 3% of acute myeloid leukemia, stomach adenocarcinoma, kidney renal papillary cell carcinoma, and lung squamous cell carcinoma, and 2% of cholangiocarcinoma, diffuse large B-cell lymphoma, colorectal adenocarcinoma, cervical squamous cell carcinoma, kidney renal clear cell carcinoma, uterine carcinosarcoma, breast invasive carcinoma, and esophageal adenocarcinoma⁶. Biallelic deletion of STAG2 is observed in 2% of uterine carcinosarcoma and 1% of sarcoma and acute myeloid leukemia⁶. Alterations in STAG2 are also observed in pediatric cancers⁶. Somatic mutations in STAG2 are observed in 10% of bone cancer (34 in 327 cases), 5% of soft tissue sarcoma (2 in 38 cases), 2% of embryonal tumors (5 in 332 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 252 cases) and peripheral nervous system cancers (1 in 1158 cases)⁶. Structural variants in STAG2 are observed in 2% of leukemia (1 in 64 cases) and less than 1% of bone cancer (1 in 150 cases)⁶. Biallelic deletion of STAG2 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of leukemia (1 in 250 cases)⁶.

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and acute myeloid leukemia^{10,154}. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors¹⁵⁵.

PHF6 deletion

PHD finger protein 6

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression^{38,39}.

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression^{38,40,41,42}. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)^{40,42}. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6⁴⁰. PHF6 mutations are frequently observed in hematologic malignancies from male patients^{38,40}.

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy⁴³.

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO10, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERFF1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFXH3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSP02, RSP03, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERFF1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFXH3, ZMYM3, ZRSR2

Relevant Therapy Summary

In this cancer type

In other cancer type

In this cancer type and other cancer types

No evidence

BRCA1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	×	×	×	×	● (II)
pamiparib, tislelizumab	×	×	×	×	● (II)

ATRX deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (II)

BRIP1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (II)

CDK12 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (II)

CHEK1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (II)

RAD51C deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (II)

RAD51D deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	44.42%
BRCA1	CNV, CN:1.0
BRCA1	LOH, 17q21.31(41197602-41276231)x1
BRIP1	CNV, CN:1.0
BRIP1	LOH, 17q23.2(59760627-59938976)x1
CDK12	CNV, CN:1.0
CDK12	LOH, 17q12(37618286-37687611)x1
CHEK1	CNV, CN:1.0
CHEK1	LOH, 11q24.2(125496639-125525271)x1
CHEK2	SNV, Q10E, AF:0.22
RAD51C	CNV, CN:1.0
RAD51C	LOH, 17q22(56769933-56811619)x1
RAD51D	CNV, CN:1.0
RAD51D	LOH, 17q12(33427950-33446720)x1

Homologous recombination repair (HRR) genes were defined from published evidence in relevant therapies, clinical guidelines, as well as clinical trials, and include - BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L.

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.1.1 data version 2025.10(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Res.* 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Sarikas et al. The cullin protein family. *Genome Biol.* 2011;12(4):220. PMID: 21554755
3. Sang et al. The role and mechanism of CRL4 E3 ubiquitin ligase in cancer and its potential therapy implications. *Oncotarget.* 2015 Dec 15;6(40):42590-602. PMID: 26460955
4. Cheng et al. The emerging role for Cullin 4 family of E3 ligases in tumorigenesis. *Biochim Biophys Acta Rev Cancer.* 2019 Jan;1871(1):138-159. PMID: 30602127
5. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
6. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
7. Philpott et al. The NF1 somatic mutational landscape in sporadic human cancers. 2017 Jun 21;11(1):13. doi: 10.1186/s40246-017-0109-3. PMID: 28637487
8. Scheffzek et al. The Ras-RasGAP complex: structural basis for GTPase activation and its loss in oncogenic Ras mutants. *Science.* 1997 Jul 18;277(5324):333-8. PMID: 9219684
9. Fioretos et al. Isochromosome 17q in blast crisis of chronic myeloid leukemia and in other hematologic malignancies is the result of clustered breakpoints in 17p11 and is not associated with coding TP53 mutations. *Blood.* 1999 Jul 1;94(1):225-32. PMID: 10381517
10. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
11. Brems et al. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. *Lancet Oncol.* 2009 May;10(5):508-15. PMID: 19410195
12. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
13. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. *Breast Cancer Res.* 2002;4(1):9-13. PMID: 11879553
14. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. *Oncogene.* 2002 Dec 16;21(58):8981-93. PMID: 12483514
15. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA.* 2017 Jun 20;317(23):2402-2416. PMID: 28632866
16. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J. Natl. Cancer Inst.* 2007 Dec 5;99(23):1811-4. PMID: 18042939
17. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. *Br. J. Cancer.* 2007 Jan 15;96(1):11-5. PMID: 17213823
18. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis . *JNCI Cancer Spectr.* 2020 Aug;4(4):pkaa029. PMID: 32676552
19. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. *GeneReviews®* [Internet]. PMID: 20301425
20. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. *Mayo Clin. Proc.* 2010 Dec;85(12):1111-20. PMID: 21123638
21. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc. Natl. Acad. Sci. U.S.A.* 2011 Nov 1;108(44):18032-7. PMID: 22006311
22. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J. Clin. Oncol.* 2012 Jul 20;30(21):2654-63. PMID: 22711857
23. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. *Cancer Epidemiol. Biomarkers Prev.* 2004 Dec;13(12):2078-83. PMID: 15598764
24. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science.* 2003 Oct 24;302(5645):643-6. PMID: 14576434
25. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br. J. Cancer.* 2000 Nov;83(10):1301-8. PMID: 11044354
26. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. *Environ Mol Mutagen.* 2022 Jul;63(6):308-316. PMID: 36054589
27. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. *Br. J. Cancer.* 2018 Nov;119(11):1401-1409. PMID: 30353044

References (continued)

28. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005 Apr 14;434(7035):913-7. PMID: 15829966
29. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005 Apr 14;434(7035):917-21. PMID: 15829967
30. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
31. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
32. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf
33. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214876s003s004lbl.pdf
34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
35. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. *J. Pathol.* 2013 Feb;229(3):422-9. PMID: 23165508
36. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. *DNA Repair (Amst.)*. 2018 Nov;71:172-176. PMID: 30177437
37. <https://www.senhwabio.com/en/news/20220125>
38. Wendorff et al. Phf6 Loss Enhances HSC Self-Renewal Driving Tumor Initiation and Leukemia Stem Cell Activity in T-ALL. *Cancer Discov.* 2019 Mar;9(3):436-451. PMID: 30567843
39. Lower et al. Mutations in PHF6 are associated with Börjeson-Forssman-Lehmann syndrome. *Nat. Genet.* 2002 Dec;32(4):661-5. PMID: 12415272
40. Van et al. PHF6 mutations in T-cell acute lymphoblastic leukemia. *Nat. Genet.* 2010 Apr;42(4):338-42. PMID: 20228800
41. Van et al. PHF6 mutations in adult acute myeloid leukemia. *Leukemia*. 2011 Jan;25(1):130-4. PMID: 21030981
42. Yoo et al. Somatic mutation of PHF6 gene in T-cell acute lymphoblastic leukemia, acute myelogenous leukemia and hepatocellular carcinoma. *Acta Oncol.* 2012 Jan;51(1):107-11. PMID: 21736506
43. Patel et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N. Engl. J. Med.* 2012 Mar 22;366(12):1079-89. PMID: 22417203
44. Musio. The multiple facets of the SMC1A gene. *Gene*. 2020 Jun 15;743:144612. PMID: 32222533
45. Nie et al. Clinical Significance and Integrative Analysis of the SMC Family in Hepatocellular Carcinoma. *Front Med (Lausanne)*. 2021;8:727965. PMID: 34527684
46. Yatskevich et al. Organization of Chromosomal DNA by SMC Complexes. *Annu Rev Genet.* 2019 Dec 3;53:445-482. PMID: 31577909
47. Yadav et al. SMC1A is associated with radioresistance in prostate cancer and acts by regulating epithelial-mesenchymal transition and cancer stem-like properties. *Mol Carcinog.* 2019 Jan;58(1):113-125. PMID: 30242889
48. Liu et al. Aging (Albany NY). 2020 May 4;12(9):8372-8396. PMID: 32365332
49. Komiya et al. Wnt signal transduction pathways. *Organogenesis*. 2008 Apr;4(2):68-75. PMID: 19279717
50. Zhang et al. *J Hematol Oncol.* 2020 Dec 4;13(1):165. PMID: 33276800
51. Rivera et al. An X chromosome gene, WTX, is commonly inactivated in Wilms tumor. *Science*. 2007 Feb 2;315(5812):642-5. PMID: 17204608
52. Leung et al. ZMYM3 regulates BRCA1 localization at damaged chromatin to promote DNA repair. *Genes Dev.* 2017 Feb 1;31(3):260-274. PMID: 28242625
53. Liu et al. Distinct Genomic Alterations in Prostate Tumors Derived from African American Men. *Mol Cancer Res.* 2020 Dec;18(12):1815-1824. PMID: 33115829
54. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
55. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. *Annu Rev Immunol.* 2013;31:529-61. PMID: 23298204
56. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
57. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
58. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
59. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. *Cancers (Basel)*. 2020 Jul 2;12(7). PMID: 32630675

References (continued)

60. Somyajit et al. RAD51C: a novel cancer susceptibility gene is linked to Fanconi anemia and breast cancer. *Carcinogenesis*. 2010 Dec;31(12):2031-8. PMID: 20952512
61. Sullivan et al. RAD-ical New Insights into RAD51 Regulation. *Genes (Basel)*. 2018 Dec 13;9(12). PMID: 30551670
62. Suwaki et al. RAD51 paralogs: roles in DNA damage signalling, recombinational repair and tumorigenesis. *Semin. Cell Dev. Biol.* 2011 Oct;22(8):898-905. PMID: 21821141
63. Chun et al. Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. *Mol. Cell. Biol.* 2013 Jan;33(2):387-95. PMID: 23149936
64. Badie et al. RAD51C facilitates checkpoint signaling by promoting CHK2 phosphorylation. *J. Cell Biol.* 2009 May 18;185(4):587-600. PMID: 19451272
65. Renglin et al. RAD51C (RAD51L2) is involved in maintaining centrosome number in mitosis. *Cytogenet. Genome Res.* 2007;116(1-2):38-45. PMID: 17268176
66. Lim et al. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. *Endocr. Relat. Cancer*. 2016 Jun;23(6):R267-85. PMID: 27226207
67. Lord et al. BRCAness revisited. *Nat. Rev. Cancer*. 2016 Feb;16(2):110-20. PMID: 26775620
68. Min et al. RAD51C-deficient cancer cells are highly sensitive to the PARP inhibitor olaparib. *Mol. Cancer Ther.* 2013 Jun;12(6):865-77. PMID: 23512992
69. Godin et al. Novel insights into RAD51 activity and regulation during homologous recombination and DNA replication. *Biochem. Cell Biol.* 2016 Oct;94(5):407-418. PMID: 27224545
70. Ali et al. BRIP-1 germline mutation and its role in colon cancer: presentation of two case reports and review of literature. *BMC Med Genet.* 2019 May 7;20(1):75. PMID: 31064327
71. Daino et al. Loss of the BRCA1-interacting helicase BRIP1 results in abnormal mammary acinar morphogenesis. *PLoS ONE*. 2013;8(9):e74013. PMID: 24040146
72. Taniguchi et al. Molecular pathogenesis of Fanconi anemia: recent progress. *Blood*. 2006 Jun 1;107(11):4223-33. PMID: 16493006
73. Weber-Lassalle et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. *Breast Cancer Res.* 2018 Jan 24;20(1):7. PMID: 29368626
74. Ramus et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. *J. Natl. Cancer Inst.* 2015 Nov;107(11). PMID: 26315354
75. Pennington et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin. Cancer Res.* 2014 Feb 1;20(3):764-75. PMID: 24240112
76. Rocak et al. DEAD-box proteins: the driving forces behind RNA metabolism. *Nat Rev Mol Cell Biol.* 2004 Mar;5(3):232-41. PMID: 14991003
77. Fuller-Pace. The DEAD box proteins DDX5 (p68) and DDX17 (p72): multi-tasking transcriptional regulators. *Biochim Biophys Acta*. 2013 Aug;1829(8):756-63. PMID: 23523990
78. Ali. DEAD-box RNA helicases: The driving forces behind RNA metabolism at the crossroad of viral replication and antiviral innate immunity. *Virus Res.* 2021 Apr 15;296:198352. PMID: 33640359
79. Linder et al. Looking back on the birth of DEAD-box RNA helicases. *Biochim Biophys Acta*. 2013 Aug;1829(8):750-5. PMID: 23542735
80. Lin. DDX3X Multifunctionally Modulates Tumor Progression and Serves as a Prognostic Indicator to Predict Cancer Outcomes. *Int J Mol Sci.* 2019 Dec 31;21(1). PMID: 31906196
81. Song et al. The mechanism of RNA duplex recognition and unwinding by DEAD-box helicase DDX3X. *Nat Commun.* 2019 Jul 12;10(1):3085. PMID: 31300642
82. Zhou et al. Comprehensive proteomic analysis of the human spliceosome. *Nature*. 2002 Sep 12;419(6903):182-5. PMID: 12226669
83. Yedavalli et al. Requirement of DDX3 DEAD box RNA helicase for HIV-1 Rev-RRE export function. *Cell*. 2004 Oct 29;119(3):381-92. PMID: 15507209
84. Chao et al. DDX3, a DEAD box RNA helicase with tumor growth-suppressive property and transcriptional regulation activity of the p21waf1/cip1 promoter, is a candidate tumor suppressor. *Cancer Res.* 2006 Jul 1;66(13):6579-88. PMID: 16818630
85. Chuang et al. Requirement of the DEAD-Box protein ded1p for messenger RNA translation. *Science*. 1997 Mar 7;275(5305):1468-71. PMID: 9045610
86. Shih et al. Candidate tumor suppressor DDX3 RNA helicase specifically represses cap-dependent translation by acting as an eIF4E inhibitory protein. *Oncogene*. 2008 Jan 24;27(5):700-14. PMID: 17667941

References (continued)

87. Lee et al. Human DDX3 functions in translation and interacts with the translation initiation factor eIF3. *Nucleic Acids Res.* 2008 Aug;36(14):4708-18. PMID: 18628297
88. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
89. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. *Front Oncol.* 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
90. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
91. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. *Front Microbiol.* 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133
92. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res.* 1998 Nov 15;58(22):5248-57. PMID: 9823339
93. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. *Cancer Res.* 2002 Jan 1;62(1):53-7. PMID: 11782358
94. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
95. NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2025]
96. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
97. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. *Medicine (Baltimore).* 2015 Dec;94(50):e2260. PMID: 26683947
98. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. *J. Clin. Oncol.* 2019 Feb 1;37(4):286-295. PMID: 30376427
99. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun.* 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
100. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
101. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
102. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
103. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
104. NCCN Guidelines® - NCCN-Rectal Cancer [Version 3.2025]
105. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
106. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N. Engl. J. Med.* 2003 Jul 17;349(3):247-57. PMID: 12867608
107. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. *Ann. Oncol.* 2015 Jan;26(1):126-32. PMID: 25361982
108. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
109. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
110. Wang et al. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. *Cell. Physiol. Biochem.* 2018;51(6):2647-2693. PMID: 30562755
111. Stamos et al. The β -catenin destruction complex. *Cold Spring Harb Perspect Biol.* 2013 Jan 1;5(1):a007898. PMID: 23169527
112. Minde et al. Messing up disorder: how do missense mutations in the tumor suppressor protein APC lead to cancer?. *Mol Cancer.* 2011 Aug 22;10:101. doi: 10.1186/1476-4598-10-101. PMID: 21859464
113. Aoki et al. Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. *J. Cell. Sci.* 2007 Oct 1;120(Pt 19):3327-35. PMID: 17881494
114. Miyoshi et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. *Hum. Mol. Genet.* 1992 Jul;1(4):229-33. PMID: 1338904
115. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
116. Rowan et al. APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". *Proc. Natl. Acad. Sci. U.S.A.* 2000 Mar 28;97(7):3352-7. PMID: 10737795

References (continued)

117. Laurent-Puig et al. APC gene: database of germline and somatic mutations in human tumors and cell lines. *Nucleic Acids Res.* 1998 Jan 1;26(1):269-70. PMID: 9399850
118. Sakamoto et al. Distinct roles of EGF repeats for the Notch signaling system. *Exp. Cell Res.* 2005 Jan 15;302(2):281-91. PMID: 15561108
119. Bray. Notch signalling in context. *Nat. Rev. Mol. Cell Biol.* 2016 Nov;17(11):722-735. PMID: 27507209
120. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. *Cell.* 2009 Apr 17;137(2):216-33. PMID: 19379690
121. Lobry et al. Oncogenic and tumor suppressor functions of Notch in cancer: it's NOTCH what you think. *J. Exp. Med.* 2011 Sep 26;208(10):1931-5. PMID: 21948802
122. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. *Nat Rev Urol.* 2018 Jun;15(6):345-357. PMID: 29643502
123. Wang et al. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. *Proc. Natl. Acad. Sci. U.S.A.* 2011 Oct 25;108(43):17761-6. PMID: 22006338
124. Xiu et al. The role of oncogenic Notch2 signaling in cancer: a novel therapeutic target. *Am J Cancer Res.* 2019;9(5):837-854. PMID: 31218097
125. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015 Jan 29;517(7536):576-82. PMID: 25631445
126. Weng et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science.* 2004 Oct 8;306(5694):269-71. PMID: 15472075
127. Breit et al. Activating NOTCH1 mutations predict favorable early treatment response and long-term outcome in childhood precursor T-cell lymphoblastic leukemia. *Blood.* 2006 Aug 15;108(4):1151-7. PMID: 16614245
128. Wong et al. Making heads or tails - the emergence of capicua (CIC) as an important multifunctional tumour suppressor. *J Pathol.* 2020 Apr;250(5):532-540. PMID: 32073140
129. Huang et al. Recurrent CIC Gene Abnormalities in Angiosarcomas: A Molecular Study of 120 Cases With Concurrent Investigation of PLCG1, KDR, MYC, and FLT4 Gene Alterations. *Am J Surg Pathol.* 2016 May;40(5):645-55. PMID: 26735859
130. NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2025]
131. Cao et al. RBM10 Regulates Tumor Apoptosis, Proliferation, and Metastasis. *Front Oncol.* 2021;11:603932. PMID: 33718153
132. Zhang et al. RNA binding motif protein 10 suppresses lung cancer progression by controlling alternative splicing of eukaryotic translation initiation factor 4H. *EBioMedicine.* 2020 Nov;61:103067. PMID: 33130397
133. Sun et al. Functional role of RBM10 in lung adenocarcinoma proliferation. *Int J Oncol.* 2019 Feb;54(2):467-478. PMID: 30483773
134. Loisel et al. RBM10 promotes transformation-associated processes in small cell lung cancer and is directly regulated by RBM5. *PLoS One.* 2017;12(6):e0180258. PMID: 28662214
135. Iwase et al. The X-linked mental retardation gene SMCX/JARID1C defines a family of histone H3 lysine 4 demethylases. *Cell.* 2007 Mar 23;128(6):1077-88. PMID: 17320160
136. Gong et al. Histone methylation and the DNA damage response. *Mutat Res.* 2017 Sep 23;780:37-47. PMID: 31395347
137. Rondinelli et al. H3K4me3 demethylation by the histone demethylase KDM5C/JARID1C promotes DNA replication origin firing. *Nucleic Acids Res.* 2015 Mar 11;43(5):2560-74. PMID: 25712104
138. Ryan et al. Snf2-family proteins: chromatin remodellers for any occasion. *Curr Opin Chem Biol.* 2011 Oct;15(5):649-56. PMID: 21862382
139. Heyer et al. Rad54: the Swiss Army knife of homologous recombination?. *Nucleic Acids Res.* 2006;34(15):4115-25. PMID: 16935872
140. Matsuda et al. Mutations in the RAD54 recombination gene in primary cancers. *Oncogene.* 1999 Jun 3;18(22):3427-30. PMID: 10362365
141. Abedalthagafi et al. The alternative lengthening of telomere phenotype is significantly associated with loss of ATRX expression in high-grade pediatric and adult astrocytomas: a multi-institutional study of 214 astrocytomas. *Mod. Pathol.* 2013 Nov;26(11):1425-32. PMID: 23765250
142. Clynes et al. ATRX dysfunction induces replication defects in primary mouse cells. *PLoS ONE.* 2014;9(3):e92915. PMID: 24651726
143. Tang et al. A novel transcription regulatory complex containing death domain-associated protein and the ATR-X syndrome protein. *J. Biol. Chem.* 2004 May 7;279(19):20369-77. PMID: 14990586
144. Xue et al. The ATRX syndrome protein forms a chromatin-remodeling complex with Daxx and localizes in promyelocytic leukemia nuclear bodies. *Proc. Natl. Acad. Sci. U.S.A.* 2003 Sep 16;100(19):10635-40. PMID: 12953102

References (continued)

145. Pisapia. The Updated World Health Organization Glioma Classification: Cellular and Molecular Origins of Adult Infiltrating Gliomas. *Arch. Pathol. Lab. Med.* 2017 Dec;141(12):1633-1645. PMID: 29189064
146. Jiao et al. Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. *Oncotarget.* 2012 Jul;3(7):709-22. PMID: 22869205
147. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021 Aug 2;23(8):1231-1251. PMID: 34185076
148. NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2025]
149. Mehta et al. Cohesin: functions beyond sister chromatid cohesion. *FEBS Lett.* 2013 Aug 2;587(15):2299-312. PMID: 23831059
150. Aquila et al. The role of STAG2 in bladder cancer. *Pharmacol. Res.* 2018 May;131:143-149. PMID: 29501732
151. Mullegama et al. De novo loss-of-function variants in STAG2 are associated with developmental delay, microcephaly, and congenital anomalies. *Am. J. Med. Genet. A.* 2017 May;173(5):1319-1327. PMID: 28296084
152. van et al. Synthetic lethality between the cohesin subunits STAG1 and STAG2 in diverse cancer contexts. *Elife.* 2017 Jul 10;6. PMID: 28691904
153. Solomon et al. Mutational inactivation of STAG2 causes aneuploidy in human cancer. *Science.* 2011 Aug 19;333(6045):1039-43. PMID: 21852505
154. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood.* 2022 Sep 22;140(12):1345-1377. PMID: 35797463
155. Solomon et al. Frequent truncating mutations of STAG2 in bladder cancer. *Nat. Genet.* 2013 Dec;45(12):1428-30. PMID: 24121789
156. Madan et al. Aberrant splicing of U12-type introns is the hallmark of ZRSR2 mutant myelodysplastic syndrome. *Nat Commun.* 2015 Jan 14;6:6042. doi: 10.1038/ncomms7042. PMID: 25586593
157. Tronchère et al. A protein related to splicing factor U2AF35 that interacts with U2AF65 and SR proteins in splicing of pre-mRNA. *Nature.* 1997 Jul 24;388(6640):397-400. PMID: 9237760
158. Chesnais et al. Spliceosome mutations in myelodysplastic syndromes and chronic myelomonocytic leukemia. *Oncotarget.* 2012 Nov;3(11):1284-93. PMID: 23327988
159. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2025]
160. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. *Clin. Cancer Res.* 2013 May 1;19(9):2301-9. PMID: 23406774
161. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. *Br J Pharmacol.* 2014 Jan;171(1):24-37. PMID: 24117156
162. Cargnello et al. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev.* 2011 Mar;75(1):50-83. PMID: 21372320
163. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. *Int J Mol Sci.* 2020 Feb 7;21(3). PMID: 32046099
164. Tran et al. Lysine Demethylase KDM6A in Differentiation, Development, and Cancer. *Mol Cell Biol.* 2020 Sep 28;40(20). PMID: 32817139
165. Ler et al. Loss of tumor suppressor KDM6A amplifies PRC2-regulated transcriptional repression in bladder cancer and can be targeted through inhibition of EZH2. *Sci Transl Med.* 2017 Feb 22;9(378). PMID: 28228601
166. Stratikos et al. A role for naturally occurring alleles of endoplasmic reticulum aminopeptidases in tumor immunity and cancer pre-disposition. *Front Oncol.* 2014;4:363. PMID: 25566501
167. López. How ERAP1 and ERAP2 Shape the Peptidomes of Disease-Associated MHC-I Proteins. *Front Immunol.* 2018;9:2463. PMID: 30425713
168. Serwold et al. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. *Nature.* 2002 Oct 3;419(6906):480-3. PMID: 12368856
169. Patil et al. Checkpoint kinase 1 in DNA damage response and cell cycle regulation. *Cell. Mol. Life Sci.* 2013 Nov;70(21):4009-21. PMID: 23508805
170. Bartek et al. Chk1 and Chk2 kinases in checkpoint control and cancer. *Cancer Cell.* 2003 May;3(5):421-9. PMID: 12781359
171. Huang et al. Chk1 and Chk2 are differentially involved in homologous recombination repair and cell cycle arrest in response to DNA double-strand breaks induced by camptothecins. *Mol. Cancer Ther.* 2008 Jun;7(6):1440-9. PMID: 18566216
172. Zhang et al. Roles of Chk1 in cell biology and cancer therapy. *Int. J. Cancer.* 2014 Mar 1;134(5):1013-23. PMID: 23613359
173. Sen et al. CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib. *Cancer Res.* 2017 Jul 15;77(14):3870-3884. PMID: 28490518

References (continued)

174. Malgorzata et al. CDK12 loss in cancer cells affects DNA damage response genes through premature cleavage and polyadenylation. *Nat Commun* . 2019 Apr 15;10(1):1757. PMID: 30988284
175. Joshi et al. Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. *J. Biol. Chem.* 2014 Mar 28;289(13):9247-53. PMID: 24554720
176. Blazek et al. The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. *Genes Dev.* 2011 Oct 15;25(20):2158-72. PMID: 22012619
177. Paculová et al. The emerging roles of CDK12 in tumorigenesis. . doi: 10.1186/s13008-017-0033-x. eCollection 2017. PMID: 29090014
178. Nag et al. The MDM2-p53 pathway revisited. *J Biomed Res.* 2013 Jul;27(4):254-71. PMID: 23885265
179. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell.* 2014 Mar 17;25(3):304-17. PMID: 24651012
180. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol.* 2010 Jan;2(1):a001008. PMID: 20182602
181. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. *Cold Spring Harb Perspect Med.* 2017 Apr 3;7(4). PMID: 28270529
182. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature.* 2012 Sep 27;489(7417):519-25. PMID: 22960745
183. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nat. Genet.* 2016 Jun;48(6):607-16. PMID: 27158780
184. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. *Nature.* 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
185. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. *Hum. Mutat.* 2002 Jun;19(6):607-14. PMID: 12007217
186. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. *Genes Cancer.* 2011 Apr;2(4):466-74. PMID: 21779514
187. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene.* 2007 Apr 2;26(15):2157-65. PMID: 17401424
188. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. *Hum. Mutat.* 2014 Jun;35(6):766-78. PMID: 24729566
189. <https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html>
190. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. *Front Oncol.* 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
191. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. *Cell. Mol. Life Sci.* 2017 Nov;74(22):4171-4187. PMID: 28643165
192. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
193. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 3.2025]
194. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
195. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]
196. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat. Med.* 2020 Aug 3. PMID: 32747829