삼광의료재단
서울특별시 서초구 바우뫼로41길 58 (양재동, 선화빌딩)
검사기관 11365200
Tel. 1661-5117
www.smlab.co.kr

Patient Name: 권순자
Gender: F
Sample ID: N26-60

Primary Tumor Site: peritoneum
Collection Date: 2025.10.30

Sample Cancer Type: Ovarian Cancer

Table of Contents	Page
Variant Details	3
Biomarker Descriptions	5
Alert Details	26
Relevant Therapy Summary	27

Report Highlights

9 Relevant Biomarkers
8 Therapies Available
29 Clinical Trials

Relevant Ovarian Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
BRCA1	None detected	NTRK2	None detected
BRCA2	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	***3.8 Mut/Mb measured***
Genomic Instability	***GIM 21 (High)***

HRD Status: ***HR Deficient (HRD+)***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Genomic Instability* GIM 21 (High)	**bevacizumab + olaparib** [1, 2 / II+] **niraparib** [1 / II+] bevacizumab [II+] bevacizumab + niraparib [II+] olaparib [II+]	None*	16
IIC	*SMARCB1 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 Locus: chr22:24129273	None*	cabozantinib pazopanib sunitinib	2

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	5
IIC	*FGFR1 amplification* fibroblast growth factor receptor 1 Locus: chr8:38271452	None*	None*	4
IIC	*CCND2 amplification* cyclin D2 Locus: chr12:4383227	None*	None*	2
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	2
IIC	*BRIP1 p.(A1081Cfs*5) c.3240_3241insT* BRCA1 interacting protein C-terminal helicase 1 Allele Frequency: 96.81% Locus: chr17:59761166 Transcript: NM_032043.3	None*	None*	1
IIC	*FBXW7 deletion* F-box and WD repeat domain containing 7 Locus: chr4:153243999	None*	None*	1
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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.

Alerts informed by public data sources: ⊘ Contraindicated, Resistance, Breakthrough, Fast Track

Genomic Instability	**pidnarulex** [1]

Public data sources included in alerts: FDA[1], NCCN, **EMA**[2], ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

ABRAXAS1 deletion, ATRX deletion, CUL4A deletion, CUL4B deletion, FANCG deletion, FANCM deletion, GNAS amplification, KMT2C deletion, LATS2 deletion, MLH3 deletion, Microsatellite stable, PMS2 deletion, RNASEH2B deletion, TP53 c.920-1G>T, TSC1 deletion, XRCC3 deletion, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, XPO1 amplification, TET2 deletion, INPP4B deletion, FAT1 deletion, HDAC9 deletion, POT1 deletion, NOTCH1 deletion, TPP2 deletion, DICER1 deletion, NQO1 p.(P187S) c.559C>T, SRC amplification, PLCG1 amplification, ZNF217 amplification, EP300 deletion, ZRSR2 deletion, BCOR deletion, USP9X 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
BRIP1	p.(A1081Cfs*5)	c.3240_3241insT	.	chr17:59761166	96.81%	NM_032043.3	frameshift Insertion
TP53	p.(?)	c.920-1G>T	.	chr17:7576927	93.46%	NM_000546.6	unknown
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	49.72%	NM_000903.3	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCGCCC	.	chr5:79950735	42.66%	NM_002439.5	nonframeshift Insertion
HLA-A	p.([H175R;E176V])	c.524_527delATGAinsGTGT	.	chr6:29911225	70.86%	NM_001242758.1	missense, missense
ARID1B	p.(G1563S)	c.4687G>A	.	chr6:157522166	19.85%	NM_001371656.1	missense
KNSTRN	p.(A6S)	c.16G>T	.	chr15:40675052	5.31%	NM_033286.3	missense
NCOR1	p.(V1541A)	c.4622T>C	.	chr17:15971327	95.71%	NM_006311.4	missense
NOTCH3	p.(G1347R)	c.4039G>C	.	chr19:15288700	54.55%	NM_000435.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
SMARCB1	chr22:24129273	1.21	0.69
CDKN2A	chr9:21968178	1.14	0.65
FGFR1	chr8:38271452	6.5	2.8
CCND2	chr12:4383227	4.79	2.11
RB1	chr13:48877953	1.05	0.62
FBXW7	chr4:153243999	1.01	0.6
NF2	chr22:29999923	1.18	0.67
ABRAXAS1	chr4:84383635	0.95	0.58
ATRX	chrX:76763769	0.68	0.47
CUL4A	chr13:113863977	1.21	0.69
CUL4B	chrX:119660593	0.74	0.5
FANCG	chr9:35074046	1.25	0.7
FANCM	chr14:45605157	1.15	0.66
GNAS	chr20:57415551	5.66	2.47
KMT2C	chr7:151833866	1.06	0.63
LATS2	chr13:21548922	1.08	0.63
MLH3	chr14:75483761	1.24	0.69
PMS2	chr7:6012922	1.1	0.64
RNASEH2B	chr13:51484145	1.14	0.65
TSC1	chr9:135771600	0.64	0.46

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
XRCC3	chr14:104165043	1.2	0.68
TNFRSF14	chr1:2488070	0.88	0.55
ERRFI1	chr1:8073246	0.84	0.54
ENO1	chr1:8921399	0.8	0.52
XPO1	chr2:61705889	5.05	2.22
TET2	chr4:106155068	0.96	0.59
INPP4B	chr4:142949914	1.01	0.6
FAT1	chr4:187509708	0.91	0.57
HDAC9	chr7:18201905	1.04	0.61
POT1	chr7:124464001	1.1	0.64
NOTCH1	chr9:139390441	1.09	0.63
TPP2	chr13:103249399	0.96	0.58
DICER1	chr14:95556791	1.15	0.66
SRC	chr20:36012492	5.2	2.28
PLCG1	chr20:39766236	4.95	2.18
ZNF217	chr20:52188253	5.1	2.24
EP300	chr22:41489001	1.25	0.7
ZRSR2	chrX:15808582	0.18	0.27
BCOR	chrX:39911340	0.15	0.26
USP9X	chrX:40982869	0.18	0.27
DDX3X	chrX:41193501	0.15	0.26
KDM6A	chrX:44732715	0.21	0.29
RBM10	chrX:47006798	0.18	0.27
KDM5C	chrX:53221892	0.18	0.27
SMC1A	chrX:53406966	0.14	0.26
AMER1	chrX:63409727	0.48	0.39
ZMYM3	chrX:70460753	0.64	0.46
STAG2	chrX:123156472	0.75	0.5
PHF6	chrX:133511628	0.65	0.46
PDGFRA	chr4:55131078	1.09	0.63
KIT	chr4:55589693	1.14	0.65
KDR	chr4:55955541	1.06	0.63
GLI3	chr7:42003880	1.1	0.64
EGFR	chr7:55211010	1.09	0.64

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
ABCB1	chr7:87145849	1.06	0.62
CDK6	chr7:92244380	1.13	0.65
RAD52	chr12:1022494	4.55	2.02
MAX	chr14:65472833	1.15	0.66
AKT1	chr14:105236628	1.11	0.65
SETBP1	chr18:42281265	1.16	0.66
BCL2	chr18:60795830	1.05	0.62
ASXL1	chr20:30954155	5.23	2.29
TOP1	chr20:39690023	5.05	2.22
PTPRT	chr20:40710527	4.63	2.05
EIF1AX	chrX:20148599	0.25	0.3
ARAF	chrX:47422311	0.16	0.27
AR	chrX:66766015	0.66	0.47

Biomarker Descriptions

Genomic Instability

Background: Homologous recombination repair (HRR) is a DNA repair mechanism that targets double stranded breaks (DSBs) and interstrand cross-links (ICL) in DNA[334]. Homologous recombination deficiency (HRD) is characterized by the cell's inability to repair these DSBs[334,335]. HRD is caused by genetic or epigenetic alterations in the HRR pathway genes, most notably BRCA1 and BRCA2 along with other genes such as ATM and PALB2[64,336,337,338]. A consequence of HRD due to the failure to repair DSBs is genomic instability[339,340]. Genomic instability is an increased tendency towards acquiring genomic alterations during cell division[341,342,343,344,345,346]. These alterations include small structural variations (i.e., single nucleotide variants (SNVs), insertions, and deletions) as well as significant structural variations (i.e., loss or gain of large chromosome fragments)[342,347,348]. Variations of genomic instability include chromosomal instability, intrachromosomal instability, microsatellite instability, and epigenetic instability[341]. Importantly, while the impact of frame-shift mutations in specific HRR genes can be mitigated by secondary mutations that restore the correct reading frame and thereby alleviate HRD, the effects of genomic instability are permanent and not reversible[349,350,351]. For this reason, the alterations characteristic of genomic instability are referred to as genomic scars[352,353]. Some of the genomic scar signatures that are characteristic of the HRD phenotype include loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transition (LST)[334,354]. Current methods for HRD detection are heterogeneous and the definition for HRD positive tumors varies depending on the cancer type[334]. Generally, these methods detect the causes of HRD (i.e., alterations in HRR genes) and/or the consequences (i.e., signatures of genomic instability/genomic scarring)[334,339,355,356].

Alterations and prevalence: In a pan-cancer analysis of HRR gene mutations and genomic scar signatures in 8847 tumors across 33 cancer types, 17.5% of tumors were HRD-positive and 4% of tumors were positive for the BRCA1/2 mutation[357]. Specifically, HRD-positive status was observed in over 50% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 35-45% of esophageal carcinoma, uterine carcinosarcoma, sarcoma, and lung adenocarcinoma, 20-30% of stomach adenocarcinoma, bladder urothelial carcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma, 5-15% of endometrial cancer, mesothelioma, cervical cancer, pancreatic adenocarcinoma, cutaneous melanoma, hepatocellular carcinoma, diffuse large B-cell lymphoma, and adrenocortical carcinoma, and 1-4% of rectum adenocarcinoma, prostate adenocarcinoma, colon adenocarcinoma, testicular germ cell tumors, kidney chromophobe, glioblastoma multiforme, low grade glioma, and renal clear cell carcinoma[357]. 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[358,359,360,361,362,363,364,365]. 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]. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma,

Biomarker Descriptions (continued)

cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme[5,6].

Potential relevance: HRD status is an important biomarker in advanced ovarian and prostate cancer because it predicts response to certain treatments including poly-ADP ribose polymerase (PARP) inhibitors and platinum chemotherapies[366,367,368]. Disruption of HRR or inhibition of PARP, are tolerated by cells through the utilization of complementary DNA repair pathways. However, presence of HRD and subsequent treatment with PARP inhibitors block DNA repair, causing accumulation of DNA damage and cell death through synthetic lethality[334,369,370,371]. Several PARP inhibitors are approved by the FDA for various cancers associated with markers of HRD. Olaparib[73] was the first PARP inhibitor originally approved in 2014 for ovarian cancer with germline mutations in BRCA1/2 (gBRCAm). The utility of olaparib has since expanded to include genomic instability markers and mutations in other HRR genes. Specifically, olaparib as monotherapy is now indicated for gBRCAm and somatic BRCA1/2 mutated (sBRCAm) ovarian cancer and in combination with bevacizumab for BRCA1/2 mutated or genomic instability positive ovarian cancer[73]. In addition, olaparib is approved in prostate cancer with germline or somatic mutations in HRR genes including ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L[73,337,372]. Olaparib is also approved for gBRCAm HER2 negative breast cancer and as maintenance therapies for gBRCAm pancreatic cancers[73]. Other PARP inhibitors that are FDA approved for BRCA mutated cancers include rucaparib[373] (2016) that is indicated for gBRCAm or sBRCAm ovarian and prostate cancers, niraparib[374] (2017) that is indicated for gBRCAm ovarian cancer, and talazoparib[375] (2018) that is indicated for gBRCAm HER2-negative metastatic breast cancer. Niraparib is also recommended for the treatment of HRD-positive ovarian cancer, defined by BRCA1/2 mutations and/or genomic instability[376]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA1/2 mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[75], for BRCA1/2, PALB2, or other HRR gene mutations in breast and ovarian cancers. Like PARP inhibitors, pidnarulex[75] causes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. Despite tolerability and efficacy, acquired resistance to PARP inhibitors such as olaparib has been clinically reported[377]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[378]. Other potential mechanisms of resistance to PARP inhibitors include restoration of HRR activity, stabilization of the replication forks, inhibition of PARP trapping, increased drug efflux mediated by P-glycoprotein, and cell cycle control alterations[378,379,380,381].

SMARCB1 deletion

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1

Background: The SMARCB1 gene encodes SWI/SNF related BAF chromatin remodeling complex subunit B1[1]. SMARCB1, also known as SNF5 or INI1, is a core member of the ATP-dependent, multi-subunit SWI/SNF chromatin-remodeling complex, along with SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1, and SMARCA2/BRM[44]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[44,45]. Independent of its functions in chromatin remodeling, SMARCB1 acts as a tumor suppressor and inhibits MYC activation, so loss of function in SMARCB1 enhances MYC activity[46]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[47,48].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[45]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[46]. Somatic mutations in SMARCB1 are observed in 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and kidney chromophobe[5,6]. Alterations in SMARCB1 are also observed in pediatric cancers[5,6]. Somatic mutations in SMARCB1 are observed in 10% of pediatric rhabdoid tumors, 6% of non-Hodgkin lymphoma, 4% of embryonal tumors, and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and Ewing sarcoma (1 in 354 cases)[5,6]. Biallelic deletion of SMARCB1 is observed in 22% of embryonal tumors and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5,6].

Potential relevance: Currently, no therapies are approved for SMARCB1 aberrations. Mutations and deletions of SMARCB1 are considered diagnostic markers of epithelioid sarcoma and SMARCB1-deficient renal medullary carcinoma[49,50].

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[144]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[145,146,147]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[148]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent

Biomarker Descriptions (continued)

its degradation[1,148,149]. CDKN2A aberrations commonly co-occur with CDKN2B[144]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[150]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[151,152].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[153]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[5,6]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[5,6]. Alterations in CDKN2A are also observed in pediatric cancers[6]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[6]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[6].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[50,154,155]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[156]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[157,158,159]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[160]. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[161,162,163,164].

FGFR1 amplification

fibroblast growth factor receptor 1

Background: The FGFR1 gene encodes fibroblast growth receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 3, and 4[1]. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain[1]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLCγ/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[292,293,294].

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions[295]. Amplification of FGFR1 is observed in 17% of lung squamous cell carcinoma, 11% of breast invasive carcinoma, 8% of bladder urothelial carcinoma, 7% of uterine carcinosarcoma and head and neck squamous cell carcinoma, 6% of esophageal adenocarcinoma, 5% of sarcoma, 4% of colorectal adenocarcinoma and pancreatic adenocarcinoma, 3% of prostate adenocarcinoma, ovarian serous cystadenocarcinoma, and lung adenocarcinoma, and 2% of uterine corpus endometrial carcinoma[5,6,296,297,298]. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types[299]. Somatic mutations in FGFR1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma[5,6]. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but are less common in solid tumors[300,301,302]. Alterations in FGFR1 are rare in pediatric cancers[6]. Amplification of FGFR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6]. Somatic mutations in FGFR1 are observed in 6% of non-Hodgkin Lymphoma, 3% of soft tissue sarcoma, 2% of glioma, and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), Wilms tumor (2 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[6].

Potential relevance: The FGFR kinase inhibitor, pemigatinib[303] (2022) is approved for the treatment of adults with relapsed/refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members[304]. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations[305,306,307,308,309,310,311]. Rearrangements in FGFR1 are associated with poor risk pediatric and adult acute lymphoblastic leukemia[312,313,314].

Biomarker Descriptions (continued)

CCND2 amplification

cyclin D2

Background: The CCND2 gene encodes the cyclin D2 protein, a member of the highly conserved D-cyclin family that also includes CCND1 and CCND3[278,279,280]. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein[278,279]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis[278,279,281]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND2[280,282].

Alterations and prevalence: Somatic mutations in CCND2 are observed in 2-3% of melanoma, diffuse large B-cell lymphoma (DLBCL), and uterine cancer[5]. Additionally, amplification of CCND2 is observed in 6-7% of ovarian and uterine carcinosarcoma, 4-5% of low grade gliomas and testicular cancer, and 2-3% of sarcomas, glioblastoma, squamous lung, colorectal, pancreatic, and head and neck cancers[5].

Potential relevance: Currently, no therapies are approved for CCND2 aberrations.

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer[36]. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[36,37]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[38]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[36,37,39]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[40].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in 20% of bladder urothelial carcinoma, 13% of uterine corpus endometrial carcinoma, and 10% of sarcoma and glioblastoma multiforme[5,6]. Biallelic loss of RB1 is also observed in several cancers including 15% of sarcoma, 10% of prostate adenocarciona, 9% of uterine carcinosarcoma, ovarian serous cystadenocarcinoma, and bladder urothelial carcinoma, 5% of liver hepatocellular carcinoma and adrenocortical carcinoma, and 4% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[5,6]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[41,42,43]. Alterations in RB1 are also observed in pediatric cancers[6]. Somatic mutations in RB1 are observed in 52% of retinoblastoma (16 in 31 cases), 3% of bone cancer (10 in 327 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (2 in 311 cases)[6]. Biallelic deletion of RB1 is observed in 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (28 in 731 cases), 3% of leukemia (7 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)[6]. Structural variants in RB1 are observed in 3% of bone cancer (5 in 150 cases)[6].

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

BRIP1 p.(A1081Cfs*5) c.3240_3241insT

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 DNA[67]. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control[68]. 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[11,69]. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)[70]. 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[70,71]. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer[67,72].

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, olaparib[73] 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

Biomarker Descriptions (continued)

platinum therapy[69,74]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[75], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FBXW7 deletion

F-box and WD repeat domain containing 7

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[1,81]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes[82]. Aberrations such as mutations or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[81,82,83,84,85,86,87].

Alterations and prevalence: Somatic mutations in FBXW7 occur at high frequencies in various malignancies, including 39% of uterine carcinosarcoma, 19% of uterine corpus endometrial carcinoma, 17% of colorectal adenocarcinoma, 12% of cervical squamous cell carcinoma, 8% of stomach adenocarcinoma and bladder urothelial carcinoma, 6% of head and neck squamous cell carcinoma and esophageal adenocarcinoma, 4% of lung squamous cell carcinoma and skin cutaneous melanoma, 3% of pancreatic adenocarcinoma, and 2% of lung adenocarcinoma and breast invasive carcinoma[5,6,88,89,90]. Biallelic deletion is observed in 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and brain lower grade glioma[5,6]. Alterations in FBXW7 are also observed in pediatric cancers[6]. Somatic mutations in FBXW7 are observed in 15% of T-lymphoblastic leukemia/lymphoma (6 in 41 cases), 2% of embryonal tumor (5 in 332 cases), and less than 1% of glioma (2 in 297 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and bone cancer (1 in 327 cases)[6]. Biallelic deletion of FBXW7 is observed in 2% of B-lymphoblastic leukemia/lymphoma (12 in 731 cases) and less than 1% of leukemia (2 in 250 cases)[6].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[91], in combination with camonsertib for the treatment of adult patients with FBXW7 mutated endometrial cancer and platinum resistant ovarian cancer. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[88]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment with the mTOR inhibitor temsirolimus[92].

NF2 deletion

neurofibromin 2

Background: The NF2 gene encodes the cytoskeletal Merlin (Moesin-ezrin-radixin-like) protein[1]. NF2 is also known as Schwannomin due to its prevalence in neuronal Schwann cells[76]. NF2 is structurally and functionally related to the Ezrin, Radixin, Moesin (ERM) family which is known to control plasma membrane function, thereby influencing cell shape, adhesion, and growth[77,78,79]. NF2 regulates several cellular pathways including the RAS/RAF/MEK/ERK, PI3K/AKT, and Hippo-YAP pathways, thus impacting cell motility, adhesion, invasion, proliferation, and apoptosis[77,78,79,80]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[76,78,79]. Specifically, deleterious germline mutations or deletion of NF2 leading to loss of heterozygosity (LOH) is causal of neurofibromatosis type 2, a tumor prone disorder characterized by early age onset of multiple Schwannomas and meningiomas[76,78,79].

Alterations and prevalence: Somatic mutations in NF2 are predominantly misssense or truncating and are observed in about 23% of mesothelioma, 6% of cholangiocarcinoma, 4% of uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma (pRCC), bladder urothelial carcinoma, and cervical squamous cell carcinoma, and 2% of colorectal adenocarcinoma, skin cutaneous melanoma, lung squamous cell carcinoma, and liver hepatocellular carcinoma[5,6]. Biallelic loss of NF2 is observed in 8% of mesothelioma and 2% of thymoma[5,6]. Structural variants in NF2 are observed in 3% of cholangiocarcinoma and 2% of mesothelioma[5,6]. Alterations in NF2 are also observed in pediatric cancers[6]. Somatic mutations in NF2 are observed in less than 1% of bone cancer (2 in 327 cases) and glioma (1 in 297 cases)[6]. Biallelic deletion of NF2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for NF2 aberrations.

ABRAXAS1 deletion

family with sequence similarity 175 member A

Background: The ABRAXAS1 gene encodes the abraxas 1, BRCA1-A complex subunit[1]. ABRAXAS1, also known as FAM175A, is capable of binding both BRCA1 and RAP80 which promotes the BRCA1-A complex formation along with BABAM2 and BRCC36[64,65]. Following formation, the BRCA1-A complex is capable of recognizing polyubiquitylated histones, including H2AX, through recognition by RAP80, resulting in complex localization to sites of DNA damage such as double-strand breaks[64]. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair[64]. Together with the rest of the BRCA1-A

Biomarker Descriptions (continued)

complex, ABRAXAS1 is suggested to function as a tumor suppressor where germline mutations in such genes have been associated with an increased risk of breast cancer[64,66].

Alterations and prevalence: Somatic mutations in ABRAXAS1 are observed in 3% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, and 1% of stomach adenocarcinoma and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ABRAXAS1 aberrations.

ATRX deletion

ATRX, chromatin remodeler

Background: The ATRX gene encodes the ATRX chromatin remodeler and ATPase/helicase domain protein, which belongs to SWI/SNF family of chromatin remodeling proteins[1]. 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[111,112,113,114]. ATRX is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair[115,116,117].

Alterations and prevalence: Somatic mutations of ATRX 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 ATRX is observed in 7% of sarcoma, 3% of kidney chromophobe, and 2% of brain lower grade glioma[5,6]. Although alterations of ATRX 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 ATRX 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 ATRX aberrations. Loss of ATRX protein expression correlates with the presence of ATRX mutations[118,119]. ATRX deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)[120,121].

CUL4A deletion

cullin 4A

Background: The CUL4A gene encodes cullin 4A, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4b, CUL5, CUL7, and Parc[1,2]. CUL4A belongs to the CUL4 subfamily which also includes CUL4B[3]. 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]. CUL4A 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 complex[4]. 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 CUL4A in oncogenesis[3,4].

Alterations and prevalence: Somatic mutations in CUL4A are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma[5,6]. Structural variants of CUL4A are observed in 3% of cholangiocarcinoma[5,6]. Amplification of CUL4A is observed in 4% of sarcoma and uterine carcinosarcoma, 3% of colorectal adenocarcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma[5,6]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[5,6].

Potential relevance: Currently, no therapies are approved for CUL4A 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 CUL4A[3]. 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

Biomarker Descriptions (continued)

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 complex[4]. 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.

FANCG deletion

Fanconi anemia complementation group G

Background: The FANCG gene encodes the FA complementation group G protein, a member of Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[7,8]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[7]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[9,10]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[11,12]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[13,14].

Alterations and prevalence: Somatic mutations in FANCG are observed in 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma[5,6].

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

FANCM deletion

FA complementation group M

Background: The FANCM gene encodes the FA complementation group M protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[7,8]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[7]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[9,10]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[11,12]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[13,14].

Alterations and prevalence: Somatic mutations in FANCM are observed in 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 6% of stomach adenocarcinoma, 5% colorectal adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for FANCM aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCM are shown to confer enhanced sensitivity in vitro to PARP inhibitors such as olaparib[15].

GNAS amplification

GNAS complex locus

Background: GNAS encodes the stimulatory alpha subunit of the guanine nucleotide-binding protein (G-protein)[1]. G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules[226]. GNAS links receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular responses[226].

Biomarker Descriptions (continued)

Alterations and prevalence: Recurrent somatic mutations at amino acid positions R201 and Q227 lead to constitutive activation of GNAS and are observed in pancreatic cancer as well as lung adenocarcinoma, colorectal, and gastric cancers.[5,6,227,228]. In colorectal cancer, GNAS mutations were enriched in right-sided tumors[229]. In lung adenocarcinoma, GNAS mutations were enriched in female patients with invasive mucinous adenocarcinoma[228]. Specifically, GNAS mutations in these patients were exclusively observed at R201C/H, along with concurrent mutations in KRAS or BRAF[228]. Recurrent somatic mutations in GNAS is observed in 5% of uterine corpus endometrial carcinoma, 4% of pancreatic adenocarcinoma, 3% of stomach adenocarcinoma and esophageal adenocarcinoma, and 2% of skin cutaneous melanoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, lung adenocarcinoma, and colorectal adenocarcinoma[5,6]. GNAS amplification is observed in 7% of colorectal adenocarcinoma, 6% of sarcoma, 5% of breast invasive carcinoma and lung adenocarcinoma, 4% of ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and uterine adenocarcinoma, 3% of esophageal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and pancreatic adenocarcinoma[5,6]. Alterations in GNAS are also observed in the pediatric population[6]. Somatic mutations in GNAS are observed in 1% of glioma (4 in 297 cases) and less than 1% of bone cancer (2 in 327 cases), embryonal tumor (2 in 332 cases), and Wilms tumor (2 in 332 cases)[6]. GNAS amplification is observed in less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia and lymphoma (1 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for GNAS aberrations. A case study of a patient with appendiceal adenocarcinoma harboring a GNAS R201H mutation reported a progression-free survival (PFS) of 4 months when treated with the MEK inhibitor trametinib[230].

KMT2C deletion

lysine methyltransferase 2C

Background: The KMT2C gene encodes the lysine methyltransferase 2C protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2C belongs to the SET domain protein methyltransferase superfamily[165]. KMT2C is capable of di- and tri-methylation of histone 3 lysine 4 (H3K4) at select transcriptional enhancers depending on the cell type[166]. KMT2C is also found to interact with BAP1 to control ubiquitin-mediated gene silencing of H2A by Polycomb group (PcG) complexes[167,168]. Specifically, KMT2C interaction with BAP1 promotes KMT2C histone recruitment/methyltransferase activity and, along with BAP1 deubiquitination of H2A, facilitates transcription of target genes[167,168]. Mutations that occur within the SET domain of KMT2C are frequently observed in cancer and alter the methylation activity and target methylation states, thereby impacting gene regulation[166].

Alterations and prevalence: Somatic mutations in KMT2C are observed in 20% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, 19% of skin cutaneous melanoma and cervical squamous cell carcinoma, 15% of lung squamous cell carcinoma, 14% of stomach adenocarcinoma and lung adenocarcinoma, and 11% of cholangiocarcinoma[5,6]. Biallelic deletion of KMT2C is observed in 3% of sarcoma, stomach adenocarcinoma, 2% of esophageal adenocarcinoma, acute myeloid leukemia, uterine carcinosarcoma, and head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KMT2C aberrations.

LATS2 deletion

large tumor suppressor kinase 2

Background: The LATS2 gene encodes the large tumor suppressor kinase 2[1]. LATS2 is a serine/threonine protein kinase and, along with LATS1, is a member of the AGC kinase family comprised of more than 60 members[222,223]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[224]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[224]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[225].

Alterations and prevalence: Somatic mutations in LATS2 are observed in 9% of mesothelioma, 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% stomach adenocarcinoma, and 3% of colorectal adenocarcinoma[5,6]. Biallelic deletion of LATS2 is observed in 2% of lung adenocarcinoma and uterine carcinosarcoma[5,6].

Potential relevance: Currently, no therapies are approved for LATS2 aberrations.

MLH3 deletion

mutL homolog 3

Background: The MLH3 gene encodes the mutL homolog 3 protein[1]. MLH3 heterodimerizes with MLH1 to form the MutLγ complex which functions as an endonuclease during meiosis, specifically in meiotic recombination[18]. MLH3 is considered a mismatch repair

Biomarker Descriptions (continued)

(MMR) gene due to its functional role in yeast, however, its exact MMR role in humans is less clear[18,19,20]. Low expression of MMR genes, including MLH3, have been associated with high levels of microsatellite instability (MSI-H) in colorectal cancer[21].

Alterations and prevalence: Somatic mutations in MLH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, skin cutaneous melanoma, and stomach adenocarcinoma[5,6]. Biallelic deletions are observed in 2% of kidney chromophobe[5,6].

Potential relevance: Currently, no therapies are approved for MLH3 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 genome[93]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[54,56]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[55]. 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 D17S250[94]. 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)[94]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[57,95,96,97,98]. 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 genes[56]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[54,56,57,58].

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[54,56,99,100]. 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 pembrolizumab[59] (2014) and nivolumab[60] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[59] 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 indication[59]. Dostarlimab[101] (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[96,102]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[61] (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[96,103,104]. 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 patients[104]. 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[105,106]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[105,106].

PMS2 deletion

PMS1 homolog 2, mismatch repair system component

Background: The PMS2 gene encodes the PMS1 homolog 2 protein[1]. PMS2 is a tumor suppressor gene that heterodimerizes with MLH1 to form the MutLα complex[18]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process[1]. Mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[51]. PMS2, along with MLH1, MSH6, and MSH2, form the core components of the MMR pathway[18,51]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[18]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[52]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[53,54,55]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[53,56]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[54,56,57,58].

Alterations and prevalence: Somatic mutations in PMS2 are observed in 7% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, and 4% of adrenocortical carcinoma[5,6]. Iterations in PMS2 are observed in pediatric cancers[5,6]. Somatic mutations are observed in 3% of soft tissue sarcoma, 2% of B-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), leukemia (1 in 311 cases), and peripheral nervous system tumors (1 in 1158 cases)[5,6].

Biomarker Descriptions (continued)

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[59]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[60,61]. PMS2 mutations are consistent with high grade in pediatric diffuse gliomas[62,63].

RNASEH2B deletion

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[1]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[262,263]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[262]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[262].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[5,6]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for RNASEH2B aberrations.

TP53 c.920-1G>T

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 repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[315]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[316]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[317,318].

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%)[5,6,238,296,319,320]. 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[321,322,323,324]. 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, PC14586[325] (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[326,327]. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[120]. 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)[129,130,187,312,328]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[171]. 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 system[329].

TSC1 deletion

tuberous sclerosis 1

Background: The TSC1 gene encodes the hamartin protein. TSC1 and TSC2 (also known as tuberin) form a complex through their respective coiled-coil domains[23]. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis[24]. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1)[24]. TSC1 and TSC2 are tumor suppressor genes and loss of function mutations in TSC1 and

Biomarker Descriptions (continued)

TSC2 lead to dysregulation of the mTOR pathway[23,25]. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs[23].

Alterations and prevalence: Somatic mutations are observed in 9% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 3% of colorectal adenocarcinoma, esophageal adenocarcinoma, kidney chromophobe, cholangiocarcinoma, and 2% of lung squamous cell carcinoma, cervical squamous cell carcinoma, liver hepatocellular carcinoma, and uterine carcinosarcoma[5,6]. Alterations in TSC1 are also observed in pediatric cancers[6]. Somatic mutations in TSC1 are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of Hodgkin lymphoma (1 in 61 cases), 1% of B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and less than 1% of bone cancer (3 in 327 cases), glioma (2 in 297 cases), and leukemia (1 in 311 cases)[6]. Biallelic deletion of TSC1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (7 in 731 cases) and Wilms tumor (1 in 136 cases)[6].

Potential relevance: Currently, no therapies are approved for TSC1 aberrations.

XRCC3 deletion

X-ray repair cross complementing 3

Background: The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs[1,64]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[64,122]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[123].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[5,6]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[123].

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14[1]. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines[169]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[169]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[169,170]. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival[169]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[170].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[5,6]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[171]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[172,173].

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,283]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[283,284]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[283,285]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[283,286,287,288,289]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[283,286,287,290,291].

Alterations and prevalence: Somatic mutations in ERRFI1 are observed in 4% of uterine corpus endometrial carcinoma and 2% of skin cutaneous melanoma, uterine carcinosarcoma, and colorectal adenocarcinoma[5,6]. Biallelic loss of ERRFI1 is observed in 6% of

Biomarker Descriptions (continued)

cholangiocarcinoma, 4% of adrenocortical carcinoma and diffuse large B-cell lymphoma, and 2% of liver hepatocellular carcinoma, pheochromocytoma and paraganglioma, and glioblastoma multiforme[5,6].

Potential relevance: Currently, no therapies are approved for ERRFI1 aberrations.

ENO1 deletion

enolase 1

Background: The ENO1 gene encodes enolase 1 and its alternatively spliced protein isoform, c-MYC promoter binding protein 1 (MBP1)[1,241]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[241]. In addition to its role in glycolysis, ENO1 acts as a cell surface plasminogen receptor and is involved in cytoskeleton reorganization, stabilization of the mitochondrial membrane, and modulation of several oncogenic pathways, including PI3K/AKT, AMPK/mTOR and Wnt/β-catenin[241,242,243]. ENO1 has been found to be overexpressed in various cancers contributing to upregulation of glycolysis, cancer cell survival and proliferation, chemoresistance, extracellular matrix degradation, migration, invasion, and metastases[241,242,244]. In contrast, MBP1 is known to repress c-MYC transcription under cellular stress and low glucose conditions, leading to suppression of cellular proliferation, migration, and invasion[241,242].

Alterations and prevalence: Somatic mutations in ENO1 are observed in 3% uterine corpus endometrial carcinoma and kidney chromophobe, and 2% of diffuse large B-cell lymphoma, skin cutaneous melanoma, and cervical squamous cell carcinoma[5,6]. Amplification of ENO1 is observed in 2% of adrenocortical carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and sarcoma[5,6]. Biallelic loss of ENO1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma, and 2% of pheochromocytoma and paraganglioma, liver hepatocellular carcinoma, and diffuse large B-cell lymphoma[5,6].

Potential relevance: Currently, no therapies are approved for ENO1 aberrations.

XPO1 amplification

exportin 1

Background: The XPO1 gene encodes exportin 1, a nuclear export protein[1,202]. XPO1, also known as CRM1, functions by binding nuclear localized signal-carrying proteins containing a leucine-rich nuclear export signal (NES) and facilitates their transport out of the nucleus[202]. Normally, nuclear protein export is tightly regulated and dysregulation is known to contribute to certain pathological conditions including cancer[202]. Specifically, XPO1 has been shown to contribute to the nuclear export of several proteins critical in oncogenesis, including RB1, TP53, and BRCA1 as well as the BCR::ABL1 fusion protein[202]. Aberrations in XPO1, including overexpression, have been shown to correlate with increased tumor size, tumor grade, and metastasis, supporting an oncogenic role for XPO1[202].

Alterations and prevalence: Somatic mutations in XPO1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of DLBC, and 2% of skin cutaneous melanoma and stomach adenocarcinoma[5,6]. Specifically, the E571K mutation has been observed to be recurrent and results in an increased affinity for NES and changes to nuclear transport[203]. Amplification of XPO1 is observed in 19% of diffuse large B-cell lymphoma (DLBCL), 5% of lung squamous cell carcinoma, and 2% of bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for XPO1 aberrations. The nuclear export inhibitor, selinexor (2019), inhibits XPO1 and is indicated for the treatment of relapsed or refractory multiple myeloma and DLBCL, although it is not indicated for specific alterations[204]. Overexpression of XPO1 is correlated with poor prognosis in ovarian cancer and decreased overall and progression-free survival in pancreatic cancer, osteosarcoma, and glioma[202]. A mutation in XPO1 is a diagnostic marker of primary mediastinal large B-cell lymphoma[171].

TET2 deletion

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to the ten-eleven translocation (TET) family, which also includes TET1 and TET3[1,181]. The TET enzymes are involved in DNA demethylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[182,183]. The TET proteins contain a C-terminal core catalytic domain that consists of a cysteine-rich domain and a double-stranded ß-helix domain (DSBH)[182,183]. TET1 and TET3 possess a DNA-binding N-terminal CXXC zinc finger domain, whereas TET2, lacking this domain, is regulated by the neighboring CXXC4 protein, which harbors a CXXC domain and recruits TET2 to unmethylated CpG sites[182,183]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[181,184,185].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense mutations, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40-60% chronic myelomonocytic leukemia (CMML)[129]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[184,186]. TET2 mutations are also observed in 9% of uterine corpus endometrial carcinoma and acute myeloid leukemia (AML), 8% of skin cutaneous melanoma, 7% of diffuse large B-cell lymphoma (DLBCL), 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and stomach adenocarcinoma, and 2% of sarcoma, esophageal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, uterine carcinosarcoma, and kidney chromophobe[5,6]. Alterations in TET2 are also observed in the pediatric population[6]. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than 1 % of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (5 in 1158 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[6]. Biallelic deletion of TET2 is observed in 2% of leukemia (6 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[6].

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[187]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[188]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[189].

INPP4B deletion

inositol polyphosphate-4-phosphatase type II B

Background: INPP4B encodes inositol polyphosphate 4-phosphatase type II, a member of the inositol polyphosphate 4-phosphatase family which also includes INPP4A[1,330]. INPP4B, along with PTEN and PIPP, is a phosphoinositide phosphatase that modulates the PI3K/AKT signaling pathway by hydrolyzing phosphatidylinositol 3,4-bisphosphate to generate phosphatidylinositol 3-phosphate, thereby suppressing the PI3K/AKT signaling cascade[331]. Although overexpression of INPP4B has been observed in several tumor types and is suggested to be associated with poor outcomes and response to therapy, alterations including mutations leading to loss of INPP4B function have been observed to result in enhanced AKT signaling, cell proliferation, and decreased survival in other tumor types, supporting a tumor suppressor role for INPP4B[332,333].

Alterations and prevalence: Somatic mutations in INPP4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, 3% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma, and 2% of cervical squamous cell carcinoma, lung squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, and uterine carcinosarcoma[5,6]. Biallelic loss of INPP4B is observed in 2% of bladder urothelial carcinoma, uterine carcinosarcoma, and brain lower grade glioma[5,6]. Amplification of INPP4B is observed in 3% of cholangiocarcinoma and esophageal adenocarcinoma, and 2% of sarcoma, stomach adenocarcinoma, and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for INPP4B aberrations.

FAT1 deletion

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[1,180]. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions[180]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[180]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[180]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[180].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[5,6]. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma[5,6]. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma[5,6].

Potential relevance: Currently, no therapies are approved for FAT1 aberrations.

Biomarker Descriptions (continued)

HDAC9 deletion

histone deacetylase 9

Background: The HDAC9 gene encodes the histone deacetylase 9 protein[1]. HDAC9 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[264]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[264,265]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[264]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[264,266].

Alterations and prevalence: Somatic mutations in HDAC9 are observed in 16% of skin cutaneous melanoma, 8% of lung adenocarcinoma, 7% of colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma and lung squamous cell carcinoma, 4% of esophageal adenocarcinoma, 3% of esophageal adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, diffuse large B-cell lymphoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, and kidney chromophobe[5,6]. Biallelic deletion of HDAC9 is observed in 2% of diffuse large B-cell lymphoma[6]. Alterations in HDAC9 are also observed in pediatric cancers[6]. Somatic mutations in HDAC9 are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), bone cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[6]. Biallelic deletion of HDAC9 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for HDAC9 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat[267] (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies. The pan-HDAC inhibitor, romidepsin[268] (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy. The pan-HDAC inhibitor, belinostat[269] (2014), is approved for the treatment of relapsed or refractory PTCL. The FDA granted fast track designation to the pan-HDAC inhibitor, panobinostat[270] (2024), for the treatment of recurrent glioblastoma.

POT1 deletion

protection of telomeres 1

Background: The POT1 gene encodes the protection of telomeres 1 protein, a nuclear protein and member of the Shelterin complex along with TERF1, TERF2, TPP1, TINF2, and TERF2IP[275]. The Shelterin complex is responsible for the protection and maintenance telomeres[1,275,276]. POT1 mediates the association of the Shelterin complex with single-stranded telomeric DNA, resulting in the prevention of telomerase binding and subsequent telomere elongation[275,277]. POT1 also inhibits inappropriate DNA damage response at telomeres by preventing the binding of RPA and inhibiting recruitment of ATR, thereby protecting telomeres from erroneous repair[276]. Loss of function POT1 germline mutations have been observed in melanoma, chronic lymphocytic leukemia (CLL), angiosarcoma, and glioma[276].

Alterations and prevalence: Somatic mutations in POT1 are observed in 5% of uterine corpus endometrial carcinoma, 3% of bladder urothelial carcinoma, 2% of lung adenocarcinoma, skin cutaneous melanoma, stomach adenocarcinoma, and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for POT1 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 signaling[231]. 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[232,233]. 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[234,235,236,237].

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[5,6,238]. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia[239,240].

Biomarker Descriptions (continued)

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

TPP2 deletion

tripeptidyl peptidase 2

Background: The TPP2 gene encodes the tripeptidyl peptidase 2[1]. TPP2 is a serine peptidase that becomes activated upon homopolymer complex formation[22]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[22]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[22].

Alterations and prevalence: Somatic mutations in TPP2 are observed in 8% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 4% of bladder urothelial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL), kidney renal papillary cell carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma[5,6]. Biallelic deletions in TPP2 are observed in 2% of DLBCL[5,6].

Potential relevance: Currently, no therapies are approved for TPP2 aberrations.

DICER1 deletion

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[1]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[196]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[196,197]. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is then cleaved by DICER1 resulting in the production of mature miRNA[196]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[196,197]. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[197,198,199,200]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[201].

Alterations and prevalence: Somatic mutations in DICER1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[5,6], 3% of lung squamous cell carcinoma, cholangiocarcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, and stomach adenocarcinoma, and 2% of head and neck squamous cell carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, kidney chromophobe, and glioblastoma multiforme[6]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% of kidney chromophobe[5,6]. Alterations in DICER1 are also observed in pediatric cancers[6]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 2% of Hodgkin lymphoma (1 in 61 cases) and bone cancer (5 in 327 cases), 1% of glioma (4 in 297 cases), and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), peripheral nervous system cancers (2 in 1158 cases), and Wilms tumor (1 in 710 cases)[6]. Biallelic deletion of DICER1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for DICER1 aberrations.

SRC amplification

SRC proto-oncogene, non-receptor tyrosine kinase

Background: The SRC gene encodes the SRC proto-oncogene, non-receptor tyrosine kinase[1]. SRC belongs to the Src family that also includes proteins Fgr, Yes, Fyd, Lck, Hck, Lyn, and Blk[1,205]. SRC interacts with transmembrane receptor tyrosine kinases (RTKs), including EGFR, HER2, PDGFR, IGF-1R, and HGFR, to directly transduce extracellular signals from these receptors to downstream effector molecules such as PI3Ks, AKT, and STAT3[206]. SRC is known be critical in tumor progression and metastasis due to its impact in the regulation of cell migration, adhesion, invasion, and stabilization of focal adhesion complexes[206]. Specifically, interaction of SRC with the EGF receptor family members, including EGFR and HER2, has been shown to promote cell survival and tumorigenesis, supporting an oncogenic role for SRC[207].

Alterations and prevalence: Somatic mutations in SRC are observed in 2% of melanoma, and 1% of uterine and bladder cancer[5,6]. Amplifications are observed in 7% of colorectal cancer, and 2-3% of uterine, stomach, and esophageal cancer[5,6]. Overexpression of SRC and its kinase activity has been reported in lung, neural, ovarian, esophageal, and gastric cancer[208].

Potential relevance: Currently, no therapies are approved for SRC aberrations. Dasatinib is a tyrosine kinase inhibitor targeting SRC that is FDA approved for use in chronic myeloid leukemia or Philadelphia-chromosome positive acute lymphocytic leukemia[209].

Biomarker Descriptions (continued)

PLCG1 amplification

phospholipase C gamma 1

Background: The PLCG1 gene encodes phospholipase C gamma 1, one of 13 phospholipase C (PLC) isozymes, that catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate to generate the second messenger molecules, inositol 1,4,5-trisphosphate and diacylglycerol[1,271]. PLCG1 interacts with several signaling molecules, including phosphoinositide-dependent kinase 1 (PDK1) and AKT[272,273]. PLCG1 has also been implicated in the regulation of mitogen-mediated signaling cascades, including the RAS/RAF/MEK/ERK pathway, and positively regulates several cellular and physiological functions including cell proliferation, migration/invasion and angiogenesis[272,273,274]. Overexpression of PLCG1 has been found in many cancers, including head and neck cancer, breast cancer, pancreatic cancer, and colon cancer, and is associated with tumor growth and progression[272].

Alterations and prevalence: Somatic mutations in PLCG1 are predominantly missense and observed in 5% of uterine corpus endometrial carcinoma, skin cutaneous melanoma, and stomach adenocarcinoma, 3% of adrenocortical carcinoma, esophageal adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, and cholangiocarcinoma, and 2% of sarcoma, head and neck squamous cell carcinoma, lung adenocarcinoma, cervical squamous cell carcinoma, diffuse large B-cell lymphoma, liver hepatocellular carcinoma, kidney chromophobe, and glioblastoma multiforme[5,6]. Amplification of PLCG1 is observed in about 7% of colorectal adenocarcinoma, 5% of uterine carcinosarcoma, 4% of stomach adenocarcinoma, 3% of adrenocortical carcinoma, and 2% of esophageal adenocarcinoma and sarcoma[5,6]

Potential relevance: Currently, no therapies are approved for PLCG1 aberrations.

ZNF217 amplification

zinc finger protein 217

Background: ZNF217 encodes zinc finger protein 217, a member of the Krüppel-like family of transcription factors[1,132]. While ZNF217 positively regulates gene expression, it also interacts with corepressors and histone-modifying proteins demonstrating its complexity as a transcriptional regulator[132,133,134]. ZNF217 coordinates several cellular processes involved in tumorigenesis, such as proliferation, survival, invasion, and metastasis[134]. In breast cancer, functional crosstalk between the estrogen receptor and ZNF217 has been a suggested mechanism for endocrine therapy resistance and high expression of ZNF217 may confer poor prognosis[135].

Alterations and prevalence: Somatic mutations in ZNF217 are observed in 7% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma, colorectal adenocarcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, lung adenocarcinoma, and head and neck squamous cell carcinoma[5,6]. Amplification of ZNF217 is found in 9% of uterine carcinosarcoma, 8% of stomach adenocarcinoma, 7% of colorectal adenocarcinoma and breast invasive carcinoma, 5% of esophageal adenocarcinoma and lung adenocarcinoma, 4% of ovarian serous cystadenocarcinoma, 3% of uterine corpus endometrial carcinoma, and 2% of sarcoma, pancreatic adenocarcinoma, and liver hepatocellular carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ZNF217 aberrations.

EP300 deletion

E1A binding protein p300

Background: The EP300 gene encodes the E1A binding protein p300[1]. EP300 is a member of the KAT3 family of lysine acetyl transferases, which, along with CREBBP (also known as CBP), interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[174,175]. EP300 functions as a transcriptional coactivator and has been observed to activate members of the E2F transcription factor family, thereby regulating expression of genes required for cell cycle G1/S phase transition[176,177]. Along with transcriptional coactivation, EP300 also functions in the formation of the transcription pre-initiation complex[176]. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[178].

Alterations and prevalence: Somatic mutations in EP300 are observed in 15% of bladder urothelial carcinoma, 14% of uterine corpus endometrial carcinoma, 12% of cervical squamous cell carcinoma, 8% of skin cutaneous melanoma, 7% of head and neck squamous cell carcinoma, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and colorectal adenocarcinoma[5,6]. Inactivating EP300 mutations are associated with lack of acetylation activity of EP300, resulting in altered expression of protein targets[179].

Potential relevance: Currently, no therapies are approved for EP300 aberrations.

Biomarker Descriptions (continued)

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 site[136]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[136,137]. 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[136,138].

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[6,129].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[129,130,139].

BCOR deletion

BCL6 corepressor

Background: The BCOR gene encodes the B-cell CLL/lymphoma 6 (BCL6) co-repressor protein, which potentiates transcriptional repression by BCL6[245,246]. BCOR also associates with class I and II histone deacetylases (HDACs), suggesting an alternate mechanism for BCOR-mediated transcriptional repression independent of BCL6[246]. Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene[247,248,249].

Alterations and prevalence: Genetic alterations in BCOR include missense, nonsense, and frameshift mutations that result in loss of function and have been observed in up to 5% of myelodysplastic syndromes (MDS), 5-10% of chronic myelomonocytic leukemia (CMML), and 1-5% of acute myeloid leukemia (AML)[5,129,250,251]. Higher mutational frequencies are reported in some solid tumors, including up to 15% of uterine cancer and 5-10% of colorectal cancer, stomach cancer, cholangiocarcinoma, and melanoma[5,6]. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[252,253,254]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[255,256]. Alterations in BCOR are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 13% of soft tissue sarcoma, 4% of glioma, 3% of retinoblastoma, 2% of bone cancer, 1% of B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and less than 1% of embryonal tumors (3 in 332 cases), leukemia (2 in 311 cases), and Wilms tumor (2 in 710 cases)[5,6]. Other alterations have been reported in clear cell carcinoma of the kidney, a rare pediatric renal malignant tumor, with one study reporting the presence of BCOR ITDs in more than 90% of cases[252].

Potential relevance: BCOR rearrangement, including inv(X)(p11.4p11.22) resulting in BCOR::CCNB3 fusion, is diagnostic of sarcoma with BCOR genetic alterations, a subset of undifferentiated round cell sarcomas[50,257]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[50]. Somatic mutation in BCOR is one of the possible molecular abnormality requirements for the diagnosis of myelodysplasia-related AML (AML-MR) and is associated with poor prognosis in AML and MDS[129,130,139,250,258]. In FLT3-ITD negative AML patients under 65 with intermediate cytogenetic prognosis, mutations in BCOR confer inferior overall survival (OS) as well as relapse-free survival (RFS) compared to those without BCOR abnormalities (OS = 13.6% vs. 55%; RFS = 14.3% vs. 44.5%)[251]. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas[259,260].

USP9X deletion

ubiquitin specific peptidase 9 X-linked

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-linked protein[1]. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases[16]. DUBs catalyze the removal of ubiquitin from target proteins, thereby counter-regulating post-translational ubiquitin modifications within the cell[16,17]. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X[17]. Conversely, in some cancer types, USP9X has been observed to function as a tumor suppressor, suggesting its exact role in cancer may be dependent on its substrates[17]. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair[17].

Alterations and prevalence: Somatic mutations are observed in 16% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of cholangiocarcinoma, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, diffuse large B-cell lymphoma (DLBCL), and head and neck squamous cell carcinoma[5,6]. Biallelic deletion in USP9X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma, uterine

Biomarker Descriptions (continued)

carcinosarcoma, and lung squamous cell carcinoma[5,6]. Alterations in USP9X are also observed in the pediatric population[6]. Somatic mutations are observed in 2% of Hodgkin lymphoma (1 in 61 cases) and bone cancer (5 in 327 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (1 in 311 cases)[6]. Biallelic deletion in USP9X is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for USP9X aberrations.

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[1,210]. 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)[210,211,212,213]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[210]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[214,215,216,217,218,219,220,221]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[214].

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 protein[1]. KDM6A is a histone demethylase that belongs to the KDM6 family of histone H3 lysine demethylases that also includes KDM6B and KDM6C[140]. 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 repression[141]. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)[140,142]. 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 regulation[140]. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression[140]. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation[140,143].

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 inhibitors[143].

RBM10 deletion

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family[1,107]. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA[107,108]. 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 expression[107]. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10[109,110].

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

Biomarker Descriptions (continued)

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.

KDM5C deletion

lysine demethylase 5C

Background: The KDM5C gene encodes the lysine demethylase 5C protein, a histone demethylase, also known as JARID1C[1,142]. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response[141]. 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[141,142]. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication[261].

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[1,26,27]. As a part of the cohesion-core complex, SMC1A plays a crucial role in chromosome segregation during mitosis and meiosis[26,28]. SMC1A also plays a role in cell cycle regulation, DNA damage repair, gene transcription regulation, and genomic organization[26]. SMC1A aberrations, including overexpression, have been observed in several cancer types and have been proposed to promote tumor formation and epithelial to mesenchymal transition[27,29].

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 1[1]. AMER1 works in complex with CTNNB1, APC, AXIN1, and AXIN2 to regulate the WNT pathway[1,30]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[31,32]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[32]. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer[33]. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest[30].

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,

Biomarker Descriptions (continued)

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.

ZMYM3 deletion

zinc finger MYM-type containing 3

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein[1]. 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)[34].

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, and 2% of thymoma, diffuse large B-cell lymphoma, head and neck squamous cell carcinoma, stomach adenocarcinoma, prostate adenocarcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, and breast invasive 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, respectively[35]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[5,6]. Alterations in ZMYM3 are also observed in pediatric cancers[6]. Somatic mutations in ZMYM3 are observed in 2% of embryonal tumors (8 in 332 cases), 1% of bone cancer (4 in 327 cases), and less than 1% of glioma (1 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)[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[124,125]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[126,127]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[126,128].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, and splice site variants[129]. 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 adenocarcinoma[6]. Biallelic deletion of STAG2 is observed in 2% of uterine carcinosarcoma and 1% of sarcoma and acute myeloid leukemia[6]. Alterations in STAG2 are also observed in pediatric cancers[6]. 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[129,130]. 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 tumors[131].

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[190,191].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[190,192,193,194]. 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,

Biomarker Descriptions (continued)

and 2.6% of hepatocellular carcinoma (HCC)[192,194]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[192]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[190,192].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[195].

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search www.fda.gov.

Genomic Instability

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer **Variant class:** HR Deficient

Supporting Statement:
The FDA has granted Fast Track designation to the small molecule inhibitor, pidnarulex, for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

Reference:

https://www.senhwabio.com//en/news/20220125

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, MYOD1, 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, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, 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, ERRFI1, 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, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed (continued)

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, RSPO2, RSPO3, 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, ERRFI1, 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, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

Genomic Instability

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + olaparib	●	●	●	●	✖
niraparib	●	●	✖	●	● (II)
olaparib	✖	●	✖	✖	● (IV)
bevacizumab	✖	●	✖	✖	✖
bevacizumab + niraparib	✖	●	✖	✖	✖
fluzoparib, bevacizumab	✖	✖	✖	✖	● (III)
IMNN-001, chemotherapy, olaparib, niraparib	✖	✖	✖	✖	● (III)
olaparib, bevacizumab	✖	✖	✖	✖	● (III)
atezolizumab + talazoparib	✖	✖	✖	✖	● (II)
fluzoparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/II)
cirtuvivint, olaparib	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

Genomic Instability (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
HS-10502	✖	✖	✖	✖	● (I)
MOMA-313, olaparib	✖	✖	✖	✖	● (I)
pidnarulex	✖	✖	✖	✖	● (I)
SIM-0501	✖	✖	✖	✖	● (I)
XL-309, olaparib	✖	✖	✖	✖	● (I)

SMARCB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	✖	✖	○	✖
pazopanib	✖	✖	✖	○	✖
sunitinib	✖	✖	✖	○	✖
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✖	✖	✖	✖	● (II)
tazemetostat, nivolumab, ipilimumab	✖	✖	✖	✖	● (I/II)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)
ABSK-131	✖	✖	✖	✖	● (I)
CID-078	✖	✖	✖	✖	● (I)

FGFR1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pemigatinib	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
BBI-355, futibatinib	✖	✖	✖	✖	● (I/II)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

CCND2 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)

RB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/II)
CID-078	✖	✖	✖	✖	● (I)

BRIP1 p.(A1081Cfs*5) c.3240_3241insT

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✖	✖	✖	✖	● (II)

FBXW7 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/II)

NF2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BPI-460372	✖	✖	✖	✖	● (I)

* 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
Not Detected	***Not Applicable***

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 Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.2.4 data version 2025.12(007)). 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 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. 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. Niraj et al. The Fanconi Anemia Pathway in Cancer. Annu Rev Cancer Biol. 2019 Mar;3:457-478. PMID: 30882047
8. Rodríguez et al. Fanconi anemia pathway. Curr Biol. 2017 Sep 25;27(18):R986-R988. PMID: 28950089
9. Garcia-Higuera et al. Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. Mol. Cell. 2001 Feb;7(2):249-62. PMID: 11239454
10. Hussain et al. Direct interaction of FANCD2 with BRCA2 in DNA damage response pathways. Hum. Mol. Genet. 2004 Jun 15;13(12):1241-8. PMID: 15115758
11. Lord et al. BRCAness revisited. Nat. Rev. Cancer. 2016 Feb;16(2):110-20. PMID: 26775620
12. Byrum et al. Defining and Modulating 'BRCAness'. Trends Cell Biol. 2019 Sep;29(9):740-751. PMID: 31362850
13. Michl et al. Interplay between Fanconi anemia and homologous recombination pathways in genome integrity. EMBO J. 2016 May 2;35(9):909-23. PMID: 27037238
14. Abbasi et al. A rare FANCA gene variation as a breast cancer susceptibility allele in an Iranian population. Mol Med Rep. 2017 Jun;15(6):3983-3988. PMID: 28440412
15. Stoepker et al. DNA helicases FANCM and DDX11 are determinants of PARP inhibitor sensitivity. DNA Repair (Amst). 2015 Feb;26:54-64. PMID: 25583207
16. Dufner et al. Ubiquitin-specific protease 8 (USP8/UBPy): a prototypic multidomain deubiquitinating enzyme with pleiotropic functions. Biochem Soc Trans. 2019 Dec 20;47(6):1867-1879. PMID: 31845722
17. Lu et al. USP9X stabilizes BRCA1 and confers resistance to DNA-damaging agents in human cancer cells. Cancer Med. 2019 Nov;8(15):6730-6740. PMID: 31512408
18. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
19. Kadyrova et al. Human MutLγ, the MLH1-MLH3 heterodimer, is an endonuclease that promotes DNA expansion. Proc Natl Acad Sci U S A. 2020 Feb 18;117(7):3535-3542. PMID: 32015124
20. Al-Sweel et al. mlh3 mutations in baker's yeast alter meiotic recombination outcomes by increasing noncrossover events genome-wide. PLoS Genet. 2017 Aug;13(8):e1006974. PMID: 28827832
21. Narayanan et al. Tumor Infiltrating Lymphocytes and Macrophages Improve Survival in Microsatellite Unstable Colorectal Cancer. Sci Rep. 2019 Sep 17;9(1):13455. PMID: 31530839
22. Wiemhoefer et al. Tripeptidyl Peptidase II Mediates Levels of Nuclear Phosphorylated ERK1 and ERK2. Mol Cell Proteomics. 2015 Aug;14(8):2177-93. PMID: 26041847
23. Rosset et al. TSC1 and TSC2 gene mutations and their implications for treatment in Tuberous Sclerosis Complex: a review. Genet Mol Biol. 2017 Jan-Mar;40(1):69-79. PMID: 28222202
24. Henske et al. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016 May 26;2:16035. PMID: 27226234
25. Santiago Lima et al. Identification of regions critical for the integrity of the TSC1-TSC2-TBC1D7 complex. PLoS ONE. 2014;9(4):e93940. PMID: 24714658
26. Musio. The multiple facets of the SMC1A gene. Gene. 2020 Jun 15;743:144612. PMID: 32222533
27. Nie et al. Clinical Significance and Integrative Analysis of the SMC Family in Hepatocellular Carcinoma. Front Med (Lausanne). 2021;8:727965. PMID: 34527684
28. Yatskevich et al. Organization of Chromosomal DNA by SMC Complexes. Annu Rev Genet. 2019 Dec 3;53:445-482. PMID: 31577909
29. 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
30. Liu et al. Aging (Albany NY). 2020 May 4;12(9):8372-8396. PMID: 32365332

References (continued)

31. Komiya et al. Wnt signal transduction pathways. Organogenesis. 2008 Apr;4(2):68-75. PMID: 19279717
32. Zhang et al. J Hematol Oncol. 2020 Dec 4;13(1):165. PMID: 33276800
33. Rivera et al. An X chromosome gene, WTX, is commonly inactivated in Wilms tumor. Science. 2007 Feb 2;315(5812):642-5. PMID: 17204608
34. 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
35. 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
36. Korenjak et al. E2F-Rb complexes regulating transcription of genes important for differentiation and development. Curr Opin Genet Dev . 2005 Oct;15(5):520-7. doi: 10.1016/j.gde.2005.07.001. PMID: 16081278
37. Sachdeva et al. Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma. J. Clin. Invest. 2012 Feb;122(2):425-34. PMID: 22293180
38. Dyson. RB1: a prototype tumor suppressor and an enigma. Genes Dev. 2016 Jul 1;30(13):1492-502. PMID: 27401552
39. Cobrinik. Pocket proteins and cell cycle control. Oncogene. 2005 Apr 18;24(17):2796-809. PMID: 15838516
40. Dommering et al. RB1 mutations and second primary malignancies after hereditary retinoblastoma. Fam. Cancer. 2012 Jun;11(2):225-33. PMID: 22205104
41. Anasua et al. Acute lymphoblastic leukemia as second primary tumor in a patient with retinoblastoma. Oman J Ophthalmol . May-Aug 2016;9(2):116-8. PMID: 27433042
42. Tanaka et al. Frequent allelic loss of the RB, D13S319 and D13S25 locus in myeloid malignancies with deletion/translocation at 13q14 of chromosome 13, but not in lymphoid malignancies. Leukemia. 1999 Sep;13(9):1367-73. PMID: 10482987
43. Gombos et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: is chemotherapy a factor?. Ophthalmology. 2007 Jul;114(7):1378-83. PMID: 17613328
44. Wilson et al. SWI/SNF nucleosome remodellers and cancer. Nat. Rev. Cancer. 2011 Jun 9;11(7):481-92. PMID: 21654818
45. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. Nat Commun. 8;14648. PMID: 28262751
46. Weissmiller et al. Inhibition of MYC by the SMARCB1 Tumor Suppressor. Nat Commun. 10 (1). PMID: 31043611
47. Vitte et al. Timing of Smarcb1 and Nf2 Inactivation Determines Schwannoma Versus Rhabdoid Tumor Development. Nat. Commun. 2017 Aug 21;8(1):300. PMID: 28824165
48. Fitzhugh. Rhabdoid Tumor Predisposition Syndrome and Pleuropulmonary Blastoma Syndrome. J Pediatr Genet. 2016 Jun;5(2):124-8. PMID: 27617153
49. Moch et al. The 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2022 Nov;82(5):458-468. PMID: 35853783
50. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
51. Zhao et al. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for anti-PD-1/PD-L1 Immunotherapy Efficacy. J Hematol Oncol. 12(1),54. PMID: 31151482
52. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. Clin Cancer Res. 2010 Nov 1;16(21):5107-13. PMID: 20823149
53. Lynch et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. 2009 Jul;76(1):1-18. PMID: 19659756
54. 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
55. 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
56. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
57. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
58. 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
59. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
60. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf

References (continued)

61. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
62. Buccoliero et al. Pediatric High Grade Glioma Classification Criteria and Molecular Features of a Case Series. Genes (Basel). 2022 Mar 31;13(4). PMID: 35456430
63. Friker et al. MSH2, MSH6, MLH1, and PMS2 immunohistochemistry as highly sensitive screening method for DNA mismatch repair deficiency syndromes in pediatric high-grade glioma. Acta Neuropathol. 2025 Feb 2;149(1):11. PMID: 39894875
64. Prakash et al. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harb Perspect Biol. 2015 Apr 1;7(4):a016600. PMID: 25833843
65. Wang et al. Ubc13/Rnf8 ubiquitin ligases control foci formation of the Rap80/Abraxas/Brca1/Brcc36 complex in response to DNA damage. Proc Natl Acad Sci U S A. 2007 Dec 26;104(52):20759-63. PMID: 18077395
66. Solyom et al. Breast cancer-associated Abraxas mutation disrupts nuclear localization and DNA damage response functions. Sci Transl Med. 2012 Feb 22;4(122):122ra23. PMID: 22357538
67. 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
68. Daino et al. Loss of the BRCA1-interacting helicase BRIP1 results in abnormal mammary acinar morphogenesis. PLoS ONE. 2013;8(9):e74013. PMID: 24040146
69. 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
70. Taniguchi et al. Molecular pathogenesis of Fanconi anemia: recent progress. Blood. 2006 Jun 1;107(11):4223-33. PMID: 16493006
71. 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
72. 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
73. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
74. 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
75. https://www.senhwabio.com//en/news/20220125
76. Evans. Neurofibromatosis Type 2 (NF2): A Clinical and Molecular Review. Orphanet J Rare Dis. 2009 Jun 19;4:16. doi: 10.1186/1750-1172-4-16. PMID: 19545378
77. Bretscher et al. ERM-Merlin and EBP50 protein families in plasma membrane organization and function. Annu. Rev. Cell Dev. Biol. 2000;16:113-43. PMID: 11031232
78. Petrilli et al. Role of Merlin/NF2 inactivation in tumor biology. Oncogene. 2016 Feb 4;35(5):537-48. PMID: 25893302
79. Morrow et al. Merlin: the wizard requires protein stability to function as a tumor suppressor. Biochim. Biophys. Acta. 2012 Dec;1826(2):400-6. PMID: 22750751
80. Mia et al. Targeting NF2-Hippo/Yap signaling pathway for cardioprotection after ischemia/reperfusion injury. Ann Transl Med. 2016 Dec; 4(24): 545. PMID: 28149906
81. Yeh et al. FBXW7: a critical tumor suppressor of human cancers. Mol Cancer. 2018 Aug 7;17(1):115. doi: 10.1186/s12943-018-0857-2. PMID: 30086763
82. Wang et al. Tumor suppressor functions of FBW7 in cancer development and progression. FEBS Lett. 2012 May 21;586(10):1409-18. PMID: 22673505
83. Uhlén et al. Proteomics. Tissue-based map of the human proteome. Science. 2015 Jan 23;347(6220):1260419. doi: 10.1126/science.1260419. PMID: 25613900
84. Yada et al. Phosphorylation-dependent degradation of c-Myc is mediated by the F-box protein Fbw7. EMBO J. 2004 May 19;23(10):2116-25. PMID: 15103331
85. Hori et al. Notch signaling at a glance. J. Cell. Sci. 2013 May 15;126(Pt 10):2135-40. PMID: 23729744
86. Aydin et al. FBXW7 mutations in melanoma and a new therapeutic paradigm. J. Natl. Cancer Inst. 2014 Jun;106(6):dju107. PMID: 24838835
87. Jardim et al. FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors. PLoS ONE. 2014;9(2):e89388. PMID: 24586741
88. Korphaisarn et al. FBXW7 missense mutation: a novel negative prognostic factor in metastatic colorectal adenocarcinoma. Oncotarget. 2017 Jun 13;8(24):39268-39279. PMID: 28424412

References (continued)

89. Donna M et al. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7. PMID: 22810696
90. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
91. https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda
92. Villaruz et al. Temsirolimus therapy in a patient with lung adenocarcinoma harboring an FBXW7 mutation. Lung Cancer. 2014 Feb;83(2):300-1. PMID: 24360397
93. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
94. 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
95. 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
96. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
97. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
98. 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
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/2024/761174s009lbl.pdf
102. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
103. 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
104. 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
105. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
106. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
107. Cao et al. RBM10 Regulates Tumor Apoptosis, Proliferation, and Metastasis. Front Oncol. 2021;11:603932. PMID: 33718153
108. 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
109. Sun et al. Functional role of RBM10 in lung adenocarcinoma proliferation. Int J Oncol. 2019 Feb;54(2):467-478. PMID: 30483773
110. Loiselle 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
111. Ryan et al. Snf2-family proteins: chromatin remodellers for any occasion. Curr Opin Chem Biol. 2011 Oct;15(5):649-56. PMID: 21862382
112. Heyer et al. Rad54: the Swiss Army knife of homologous recombination?. Nucleic Acids Res. 2006;34(15):4115-25. PMID: 16935872
113. Matsuda et al. Mutations in the RAD54 recombination gene in primary cancers. Oncogene. 1999 Jun 3;18(22):3427-30. PMID: 10362365
114. 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
115. Clynes et al. ATRX dysfunction induces replication defects in primary mouse cells. PLoS ONE. 2014;9(3):e92915. PMID: 24651726
116. 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
117. 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)

118. 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
119. 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
120. 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
121. NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2025]
122. Liu et al. Role of RAD51C and XRCC3 in genetic recombination and DNA repair. J Biol Chem. 2007 Jan 19;282(3):1973-9. PMID: 17114795
123. Wilson et al. FANCG promotes formation of a newly identified protein complex containing BRCA2, FANCD2 and XRCC3. Oncogene. 2008 Jun 12;27(26):3641-52. PMID: 18212739
124. Mehta et al. Cohesin: functions beyond sister chromatid cohesion. FEBS Lett. 2013 Aug 2;587(15):2299-312. PMID: 23831059
125. Aquila et al. The role of STAG2 in bladder cancer. Pharmacol. Res. 2018 May;131:143-149. PMID: 29501732
126. 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
127. van der Lelij et al. Synthetic lethality between the cohesin subunits STAG1 and STAG2 in diverse cancer contexts. Elife. 2017 Jul 10;6. PMID: 28691904
128. Solomon et al. Mutational inactivation of STAG2 causes aneuploidy in human cancer. Science. 2011 Aug 19;333(6045):1039-43. PMID: 21852505
129. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
130. 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
131. Solomon et al. Frequent truncating mutations of STAG2 in bladder cancer. Nat. Genet. 2013 Dec;45(12):1428-30. PMID: 24121789
132. Vendrell et al. ZNF217 is a marker of poor prognosis in breast cancer that drives epithelial-mesenchymal transition and invasion. Cancer Res. 2012 Jul 15;72(14):3593-606. PMID: 22593193
133. Quinlan et al. Amplification of zinc finger gene 217 (ZNF217) and cancer: when good fingers go bad. Biochim Biophys Acta. 2007 Jun;1775(2):333-40. PMID: 17572303
134. Cohen et al. The dark side of ZNF217, a key regulator of tumorigenesis with powerful biomarker value. Oncotarget. 2015 Dec 8;6(39):41566-81. PMID: 26431164
135. Vendrell et al. Evaluating ZNF217 mRNA Expression Levels as a Predictor of Response to Endocrine Therapy in ER+ Breast Cancer. Front Pharmacol. 2018;9:1581. PMID: 30740056
136. 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
137. 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
138. Chesnais et al. Spliceosome mutations in myelodysplastic syndromes and chronic myelomonocytic leukemia. Oncotarget. 2012 Nov;3(11):1284-93. PMID: 23327988
139. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2026]
140. Tran et al. Lysine Demethylase KDM6A in Differentiation, Development, and Cancer. Mol Cell Biol. 2020 Sep 28;40(20). PMID: 32817139
141. Gong et al. Histone methylation and the DNA damage response. Mutat Res. 2017 Sep 23;780:37-47. PMID: 31395347
142. 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
143. 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
144. Xia et al. Dominant role of CDKN2B/p15INK4B of 9p21.3 tumor suppressor hub in inhibition of cell-cycle and glycolysis. Nat Commun. 2021 Apr 6;12(1):2047. PMID: 33824349
145. Scruggs et al. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. Am. J. Respir. Cell Mol. Biol. 2018 Aug;59(2):200-214. PMID: 29420051
146. Roussel. The INK4 family of cell cycle inhibitors in cancer. Oncogene. 1999 Sep 20;18(38):5311-7. PMID: 10498883

References (continued)

147. Aytac et al. Rb independent inhibition of cell growth by p15(INK4B). Biochem. Biophys. Res. Commun. 1999 Aug 27;262(2):534-8. PMID: 10462509
148. Hill et al. The genetics of melanoma: recent advances. Annu Rev Genomics Hum Genet. 2013;14:257-79. PMID: 23875803
149. Kim et al. The regulation of INK4/ARF in cancer and aging. Cell. 2006 Oct 20;127(2):265-75. PMID: 17055429
150. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. Mayo Clin. Proc. 2008 Jul;83(7):825-46. PMID: 18613999
151. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. J. Invest. Dermatol. 2007 May;127(5):1234-43. PMID: 17218939
152. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. Ann. Surg. 2002 Dec;236(6):730-7. PMID: 12454511
153. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. Clin Cancer Res. 2021 Jul 15;27(14):4025-4035. PMID: 34074656
154. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2026]
155. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2026]
156. Louis et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol. 2020 Jul;30(4):844-856. PMID: 32307792
157. Longwen et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. J Transl Med. 2019 Jul 29;17(1):245. PMID: 31358010
158. Logan et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. Anticancer Res. 2013 Aug;33(8):2997-3004. PMID: 23898052
159. von Witzleben et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmocological Inhibitors of the CDK4/6 Cell-Cycle Pathway. Cancer Res. 2015 Sep 15;75(18):3823-31. PMID: 26183925
160. Cen et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. Neuro-oncology. 2012 Jul;14(7):870-81. PMID: 22711607
161. Vitzthum et al. The role of p16 as a biomarker in nonoropharyngeal head and neck cancer. Oncotarget. 2018 Sep 7;9(70):33247-33248. PMID: 30279955
162. Chung et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J. Clin. Oncol. 2014 Dec 10;32(35):3930-8. PMID: 25267748
163. Bryant et al. Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer. J. Natl. Cancer Inst. 2018 Dec 1;110(12):1393-1399. PMID: 29878161
164. Stephen et al. Significance of p16 in Site-specific HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma. Cancer Clin Oncol. 2013;2(1):51-61. PMID: 23935769
165. Froimchuk et al. Histone H3 lysine 4 methyltransferase KMT2D. Gene. 2017 Sep 5;627:337-342. PMID: 28669924
166. Fagan et al. COMPASS Ascending: Emerging clues regarding the roles of MLL3/KMT2C and MLL2/KMT2D proteins in cancer. Cancer Lett. 2019 Aug 28;458:56-65. PMID: 31128216
167. Wang et al. Resetting the epigenetic balance of Polycomb and COMPASS function at enhancers for cancer therapy. Nat Med. 2018 Jun;24(6):758-769. PMID: 29785026
168. Masclef et al. Roles and mechanisms of BAP1 deubiquitinase in tumor suppression. Cell Death Differ. 2021 Feb;28(2):606-625. PMID: 33462414
169. So et al. The TNF-TNFR Family of Co-signal Molecules. Adv Exp Med Biol. 2019;1189:53-84. PMID: 31758531
170. Costello et al. Stimulation of non-Hodgkin's lymphoma via HVEM: an alternate and safe way to increase Fas-induced apoptosis and improve tumor immunogenicity. Leukemia. 2003 Dec;17(12):2500-7. PMID: 14562115
171. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]
172. Launay et al. High rate of TNFRSF14 gene alterations related to 1p36 region in de novo follicular lymphoma and impact on prognosis. Leukemia. 2012 Mar;26(3):559-62. PMID: 21941365
173. Cheung et al. Acquired TNFRSF14 mutations in follicular lymphoma are associated with worse prognosis. Cancer Res. 2010 Nov 15;70(22):9166-74. PMID: 20884631
174. Zhang et al. The CREBBP Acetyltransferase Is a Haploinsufficient Tumor Suppressor in B-cell Lymphoma. Cancer Discov. 2017 Mar;7(3):322-337. PMID: 28069569
175. Bedford et al. Target gene context influences the transcriptional requirement for the KAT3 family of CBP and p300 histone acetyltransferases. Epigenetics. 2010 Jan 1;5(1):9-15. PMID: 20110770

References (continued)

176. Attar et al. Exploitation of EP300 and CREBBP Lysine Acetyltransferases by Cancer. Cold Spring Harb Perspect Med. 2017 Mar 1;7(3). PMID: 27881443
177. Gocho et al. A novel recurrent EP300-ZNF384 gene fusion in B-cell precursor acute lymphoblastic leukemia. Leukemia. 2015 Dec;29(12):2445-8. PMID: 25943178
178. Schorry et al. Genotype-phenotype correlations in Rubinstein-Taybi syndrome. Am. J. Med. Genet. A. 2008 Oct 1;146A(19):2512-9. PMID: 18792986
179. Pasqualucci et al. Inactivating mutations of acetyltransferase genes in B-cell lymphoma. Nature. 2011 Mar 10;471(7337):189-95. PMID: 21390126
180. Peng et al. Role of FAT1 in health and disease. Oncol Lett. 2021 May;21(5):398. PMID: 33777221
181. Pan et al. The TET2 interactors and their links to hematological malignancies. IUBMB Life. 2015 Jun;67(6):438-45. PMID: 26099018
182. An et al. TET family dioxygenases and DNA demethylation in stem cells and cancers. Exp. Mol. Med. 2017 Apr 28;49(4):e323. PMID: 28450733
183. Rasmussen et al. Role of TET enzymes in DNA methylation, development, and cancer. Genes Dev. 2016 Apr 1;30(7):733-50. PMID: 27036965
184. Ko et al. Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature. 2010 Dec 9;468(7325):839-43. PMID: 21057493
185. Solary et al. The Ten-Eleven Translocation-2 (TET2) gene in hematopoiesis and hematopoietic diseases. Leukemia. 2014 Mar;28(3):485-96. PMID: 24220273
186. Kosmider et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). Blood. 2009 Oct 8;114(15):3285-91. PMID: 19666869
187. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
188. Lundberg et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood. 2014 Apr 3;123(14):2220-8. PMID: 24478400
189. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2025]
190. 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
191. Lower et al. Mutations in PHF6 are associated with Börjeson-Forssman-Lehmann syndrome. Nat. Genet. 2002 Dec;32(4):661-5. PMID: 12415272
192. Van Vlierberghe et al. PHF6 mutations in T-cell acute lymphoblastic leukemia. Nat. Genet. 2010 Apr;42(4):338-42. PMID: 20228800
193. Van Vlierberghe et al. PHF6 mutations in adult acute myeloid leukemia. Leukemia. 2011 Jan;25(1):130-4. PMID: 21030981
194. Yoo et al. Somatic mutation of PHF6 gene in T-cell acute lymphoblatic leukemia, acute myelogenous leukemia and hepatocellular carcinoma. Acta Oncol. 2012 Jan;51(1):107-11. PMID: 21736506
195. 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
196. Aharoni et al. Dynamical comparison between Drosha and Dicer reveals functional motion similarities and dissimilarities. PLoS One. 2019;14(12):e0226147. PMID: 31821368
197. Lee et al. MicroRNAs in cancer. Annu Rev Pathol. 2009;4:199-227. PMID: 18817506
198. Hammond. An overview of microRNAs. Adv Drug Deliv Rev. 2015 Jun 29;87:3-14. PMID: 25979468
199. Wen et al. Biosci Rep. 2018 Jun 29;38(3). PMID: 29654164
200. Kumar et al. Impaired microRNA processing enhances cellular transformation and tumorigenesis. Nat Genet. 2007 May;39(5):673-7. PMID: 17401365
201. Robertson et al. DICER1 Syndrome: DICER1 Mutations in Rare Cancers. Cancers (Basel). 2018 May 15;10(5). PMID: 29762508
202. Turner et al. Nuclear export of proteins and drug resistance in cancer. Biochem Pharmacol. 2012 Apr 15;83(8):1021-32. PMID: 22209898
203. Camus et al. XPO1 in B cell hematological malignancies: from recurrent somatic mutations to targeted therapy. J Hematol Oncol. 2017 Feb 14;10(1):47. PMID: 28196522
204. Kasamon et al. FDA Approval Summary: Selinexor for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Oncologist. 2021 Oct;26(10):879-886. PMID: 34132444

References (continued)

205. Shen et al. The Src family kinase Fgr is a transforming oncoprotein that functions independently of SH3-SH2 domain regulation. Sci Signal. 2018 Oct 23;11(553). PMID: 30352950
206. Zhang et al. Targeting Src family kinases in anti-cancer therapies: turning promise into triumph. Trends Pharmacol Sci. 2012 Mar;33(3):122-8. PMID: 22153719
207. Biscardi et al. Tyrosine kinase signalling in breast cancer: epidermal growth factor receptor and c-Src interactions in breast cancer. Breast Cancer Res. 2000;2(3):203-10. PMID: 11250711
208. Irby et al. Role of Src expression and activation in human cancer. Oncogene. 2000 Nov 20;19(49):5636-42. PMID: 11114744
209. Wheeler et al. The role of Src in solid tumors. Oncologist. 2009 Jul;14(7):667-78. PMID: 19581523
210. 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
211. 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
212. 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
213. Linder et al. Looking back on the birth of DEAD-box RNA helicases. Biochim Biophys Acta. 2013 Aug;1829(8):750-5. PMID: 23542735
214. 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
215. 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
216. Zhou et al. Comprehensive proteomic analysis of the human spliceosome. Nature. 2002 Sep 12;419(6903):182-5. PMID: 12226669
217. 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
218. 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
219. Chuang et al. Requirement of the DEAD-Box protein ded1p for messenger RNA translation. Science. 1997 Mar 7;275(5305):1468-71. PMID: 9045610
220. 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
221. 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
222. Furth et al. The LATS1 and LATS2 tumor suppressors: beyond the Hippo pathway. Cell Death Differ. 2017 Sep;24(9):1488-1501. PMID: 28644436
223. Leroux et al. AGC kinases, mechanisms of regulation #and innovative drug development. Semin Cancer Biol. 2018 Feb;48:1-17. PMID: 28591657
224. Meng et al. Mechanisms of Hippo pathway regulation. Genes Dev. 2016 Jan 1;30(1):1-17. PMID: 26728553
225. Yu et al. Mutation analysis of large tumor suppressor genes LATS1 and LATS2 supports a tumor suppressor role in human cancer. Protein Cell. 2015 Jan;6(1):6-11. PMID: 25482410
226. Neves et al. G protein pathways. Science. 2002 May 31;296(5573):1636-9. PMID: 12040175
227. Landis et al. GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. Nature. 1989 Aug 31;340(6236):692-6. PMID: 2549426
228. Ritterhouse et al. GNAS mutations in primary mucinous and non-mucinous lung adenocarcinomas. Mod. Pathol. 2017 Dec;30(12):1720-1727. PMID: 28776576
229. Loree et al. Classifying Colorectal Cancer by Tumor Location Rather than Sidedness Highlights a Continuum in Mutation Profiles and Consensus Molecular Subtypes. Clin. Cancer Res. 2018 Mar 1;24(5):1062-1072. PMID: 29180604
230. Ang et al. Clinical Benefit from Trametinib in a Patient with Appendiceal Adenocarcinoma with a GNAS R201H Mutation. Case Rep Oncol. 2017 Jun 22;10(2):548-552. doi: 10.1159/000477562. eCollection 2017 May-Aug. PMID: 28868010
231. 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
232. Bray. Notch signalling in context. Nat. Rev. Mol. Cell Biol. 2016 Nov;17(11):722-735. PMID: 27507209

References (continued)

233. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. Cell. 2009 Apr 17;137(2):216-33. PMID: 19379690
234. 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
235. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. Nat Rev Urol. 2018 Jun;15(6):345-357. PMID: 29643502
236. 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
237. 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
238. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
239. Weng et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science. 2004 Oct 8;306(5694):269-71. PMID: 15472075
240. 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
241. Huang et al. ENO1 and Cancer. Mol Ther Oncolytics. 2022 Mar 17;24:288-298. PMID: 35434271
242. Almaguel et al. Alpha-Enolase: Emerging Tumor-Associated Antigen, Cancer Biomarker, and Oncotherapeutic Target. Front Genet. 2020;11:614726. PMID: 33584813
243. Qiao et al. Enolase 1, a Moonlighting Protein, as a Potential Target for Cancer Treatment. Int J Biol Sci. 2021;17(14):3981-3992. PMID: 34671213
244. Xu et al. Enolase 1 Correlated With Cancer Progression and Immune-Infiltrating in Multiple Cancer Types: A Pan-Cancer Analysis. Front Oncol. 2020;10:593706. PMID: 33643901
245. Gearhart et al. Polycomb group and SCF ubiquitin ligases are found in a novel BCOR complex that is recruited to BCL6 targets. Mol. Cell. Biol. 2006 Sep;26(18):6880-9. PMID: 16943429
246. Huynh et al. BCoR, a novel corepressor involved in BCL-6 repression. Genes Dev. 2000 Jul 15;14(14):1810-23. PMID: 10898795
247. Kelly et al. Bcor loss perturbs myeloid differentiation and promotes leukaemogenesis. Nat Commun. 2019 Mar 22;10(1):1347. PMID: 30902969
248. Cao et al. BCOR regulates myeloid cell proliferation and differentiation. Leukemia. 2016 May;30(5):1155-65. PMID: 26847029
249. Yamamoto et al. Clarifying the impact of polycomb complex component disruption in human cancers. Mol. Cancer Res. 2014 Apr;12(4):479-84. PMID: 24515802
250. Damm et al. BCOR and BCORL1 mutations in myelodysplastic syndromes and related disorders. Blood. 2013 Oct 31;122(18):3169-77. PMID: 24047651
251. Terada et al. Usefulness of BCOR gene mutation as a prognostic factor in acute myeloid leukemia with intermediate cytogenetic prognosis. Genes Chromosomes Cancer. 2018 Aug;57(8):401-408. PMID: 29663558
252. Wong et al. Clear cell sarcomas of the kidney are characterised by BCOR gene abnormalities, including exon 15 internal tandem duplications and BCOR-CCNB3 gene fusion. Histopathology. 2018 Jan;72(2):320-329. PMID: 28833375
253. Cramer et al. Successful Treatment of Recurrent Primitive Myxoid Mesenchymal Tumor of Infancy With BCOR Internal Tandem Duplication. J Natl Compr Canc Netw. 2017 Jul;15(7):868-871. PMID: 28687574
254. Peters et al. BCOR-CCNB3 fusions are frequent in undifferentiated sarcomas of male children. Mod. Pathol. 2015 Apr;28(4):575-86. PMID: 25360585
255. Puls et al. BCOR-CCNB3 (Ewing-like) sarcoma: a clinicopathologic analysis of 10 cases, in comparison with conventional Ewing sarcoma. Am. J. Surg. Pathol. 2014 Oct;38(10):1307-18. PMID: 24805859
256. Kao et al. BCOR-CCNB3 Fusion Positive Sarcomas: A Clinicopathologic and Molecular Analysis of 36 Cases With Comparison to Morphologic Spectrum and Clinical Behavior of Other Round Cell Sarcomas. Am. J. Surg. Pathol. 2018 May;42(5):604-615. PMID: 29300189
257. NCCN Guidelines® - NCCN-Bone Cancer [Version 1.2026]
258. Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719. PMID: 35732831
259. Torre et al. Recurrent EP300-BCOR Fusions in Pediatric Gliomas With Distinct Clinicopathologic Features. J Neuropathol Exp Neurol. 2019 Apr 1;78(4):305-314. PMID: 30816933

References (continued)

260. Wang et al. Clinical, pathological, and molecular features of central nervous system tumors with BCOR internal tandem duplication. Pathol Res Pract. 2024 Jul;259:155367. PMID: 38797130
261. 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
262. D'Alessandro et al. BRCA2 controls DNA:RNA hybrid level at DSBs by mediating RNase H2 recruitment. Nat Commun. 2018 Dec 18;9(1):5376. PMID: 30560944
263. Aden et al. Epithelial RNase H2 Maintains Genome Integrity and Prevents Intestinal Tumorigenesis in Mice. Gastroenterology. 2019 Jan;156(1):145-159.e19. PMID: 30273559
264. Falkenberg et al. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014 Sep;13(9):673-91. PMID: 25131830
265. Li et al. HDAC2 promotes the migration and invasion of non-small cell lung cancer cells via upregulation of fibronectin. Biomed Pharmacother. 2016 Dec;84:284-290. PMID: 27665474
266. Li et al. HDACs and HDAC Inhibitors in Cancer Development and Therapy. Cold Spring Harb Perspect Med. 2016 Oct 3;6(10). PMID: 27599530
267. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021991s009lbl.pdf
268. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022393s017lbl.pdf
269. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206256Orig1s006lbl.pdf
270. https://biodexapharma.com/fast-track-designation-granted-to-mtx110-development-for-the-treatment-of-recurrent-glioblastoma/
271. Hajicek et al. Structural basis for the activation of PLC-γ isozymes by phosphorylation and cancer-associated mutations. Elife. 2019 Dec 31;8. PMID: 31889510
272. Mandal et al. Recent advances in understanding the molecular role of phosphoinositide-specific phospholipase C gamma 1 as an emerging onco-driver and novel therapeutic target in human carcinogenesis. Biochim Biophys Acta Rev Cancer. 2021 Dec;1876(2):188619. PMID: 34454048
273. Jang et al. PLCγ1: Potential arbitrator of cancer progression. Adv Biol Regul. 2018 Jan;67:179-189. PMID: 29174396
274. Li et al. Phospholipase Cγ1 (PLCG1) overexpression is associated with tumor growth and poor survival in IDH wild-type lower-grade gliomas in adult patients. Lab Invest. 2022 Feb;102(2):143-153. PMID: 34697421
275. Schmutz et al. Shelterin. Curr Biol. 2016 May 23;26(10):R397-9. PMID: 27218840
276. Wu et al. Role of POT1 in Human Cancer. Cancers (Basel). 2020 Sep 24;12(10). PMID: 32987645
277. Liu et al. PTOP interacts with POT1 and regulates its localization to telomeres. Nat Cell Biol. 2004 Jul;6(7):673-80. PMID: 15181449
278. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
279. Koyama-Nasu et al. The critical role of cyclin D2 in cell cycle progression and tumorigenicity of glioblastoma stem cells. Oncogene. 2013 Aug 15;32(33):3840-5. PMID: 22964630
280. Ding et al. Prognostic role of cyclin D2/D3 in multiple human malignant neoplasms: A systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):2717-2729. PMID: 30950241
281. Bartek et al. Pathways governing G1/S transition and their response to DNA damage. FEBS Lett. 2001 Feb 16;490(3):117-22. PMID: 11223026
282. Shan et al. Cyclin D1 overexpression correlates with poor tumor differentiation and prognosis in gastric cancer. Oncol Lett. 2017 Oct;14(4):4517-4526. PMID: 28943959
283. Cui et al. ERRFI1 induces apoptosis of hepatocellular carcinoma cells in response to tryptophan deficiency. Cell Death Discov. 2021 Oct 4;7(1):274. PMID: 34608122
284. Hackel et al. Mig-6 is a negative regulator of the epidermal growth factor receptor signal. Biol Chem. 2001 Dec;382(12):1649-62. PMID: 11843178
285. Frosi et al. A two-tiered mechanism of EGFR inhibition by RALT/MIG6 via kinase suppression and receptor degradation. J Cell Biol. 2010 May 3;189(3):557-71. PMID: 20421427
286. Wendt et al. The antitumorigenic function of EGFR in metastatic breast cancer is regulated by expression of Mig6. Neoplasia. 2015 Jan;17(1):124-33. PMID: 25622905
287. Lin et al. Mitogen-inducible gene-6 is a multifunctional adaptor protein with tumor suppressor-like activity in papillary thyroid cancer. J Clin Endocrinol Metab. 2011 Mar;96(3):E554-65. PMID: 21190978
288. Xu et al. Upregulation of mitogen-inducible gene 6 triggers antitumor effect and attenuates progesterone resistance in endometrial carcinoma cells. Cancer Gene Ther. 2015 Nov;22(11):536-41. PMID: 26450625

References (continued)

289. Li et al. Low expression of Mig-6 is associated with poor survival outcome in NSCLC and inhibits cell apoptosis via ERK-mediated upregulation of Bcl-2. Oncol Rep. 2014 Apr;31(4):1707-14. PMID: 24573418
290. Li et al. Downregulation of Mig-6 in nonsmall-cell lung cancer is associated with EGFR signaling. Mol Carcinog. 2012 Jul;51(7):522-34. PMID: 21739478
291. Ferby et al. Mig6 is a negative regulator of EGF receptor-mediated skin morphogenesis and tumor formation. Nat Med. 2006 May;12(5):568-73. PMID: 16648858
292. Babina et al. Advances and challenges in targeting FGFR signalling in cancer. Nat. Rev. Cancer. 2017 May;17(5):318-332. PMID: 28303906
293. Ahmad et al. Mechanisms of FGFR-mediated carcinogenesis. Biochim. Biophys. Acta. 2012 Apr;1823(4):850-60. PMID: 22273505
294. Sarabipour et al. Mechanism of FGF receptor dimerization and activation. Nat Commun. 2016 Jan 4;7:10262. doi: 10.1038/ncomms10262. PMID: 26725515
295. Helsten et al. The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing. Clin. Cancer Res. 2016 Jan 1;22(1):259-67. PMID: 26373574
296. Peter S et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
297. Ciriello et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. Cell. 2015 Oct 8;163(2):506-19. PMID: 26451490
298. Cancer Genome Atlas Research et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73. PMID: 23636398
299. Lew et al. The precise sequence of FGF receptor autophosphorylation is kinetically driven and is disrupted by oncogenic mutations. Sci Signal. 2009 Feb 17;2(58):ra6. PMID: 19224897
300. Jackson et al. 8p11 myeloproliferative syndrome: a review. Hum. Pathol. 2010 Apr;41(4):461-76. PMID: 20226962
301. Li et al. Identification of a novel partner gene, TPR, fused to FGFR1 in 8p11 myeloproliferative syndrome. Genes Chromosomes Cancer. 2012 Sep;51(9):890-7. PMID: 22619110
302. Wasag et al. The kinase inhibitor TKI258 is active against the novel CUX1-FGFR1 fusion detected in a patient with T-lymphoblastic leukemia/lymphoma and t(7;8)(q22;p11). Haematologica. 2011 Jun;96(6):922-6. PMID: 21330321
303. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213736s002lbl.pdf
304. Helsten et al. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: biologic and clinical implications. Cancer Metastasis Rev. 2015 Sep;34(3):479-96. PMID: 26224133
305. Cha et al. FGFR2 amplification is predictive of sensitivity to regorafenib in gastric and colorectal cancers in vitro. Mol Oncol. 2018 Jun;12(7):993-1003. PMID: 29573334
306. Chae et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. Oncotarget. 2017 Feb 28;8(9):16052-16074. PMID: 28030802
307. Porta et al. FGFR a promising druggable target in cancer: Molecular biology and new drugs. Crit. Rev. Oncol. Hematol. 2017 May;113:256-267. PMID: 28427515
308. Gozgit et al. Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models. Mol. Cancer Ther. 2012 Mar;11(3):690-9. PMID: 22238366
309. Yamamoto et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014 Sep 6;6:18. doi: 10.1186/2045-824X-6-18. eCollection 2014. PMID: 25197551
310. Kim et al. Pazopanib, a novel multitargeted kinase inhibitor, shows potent in vitro antitumor activity in gastric cancer cell lines with FGFR2 amplification. Mol. Cancer Ther. 2014 Nov;13(11):2527-36. PMID: 25249557
311. Hibi et al. FGFR gene alterations in lung squamous cell carcinoma are potential targets for the multikinase inhibitor nintedanib. Cancer Sci. 2016 Nov;107(11):1667-1676. PMID: 27581340
312. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
313. NCCN Guidelines® - NCCN-Pediatric Acute Lymphoblastic Leukemia [Version 1.2026]
314. Brown et al. Biological and clinical implications of FGFR aberrations in paediatric and young adult cancers. Oncogene. 2023 Jun;42(23):1875-1888. PMID: 37130917
315. Nag et al. The MDM2-p53 pathway revisited. J Biomed Res. 2013 Jul;27(4):254-71. PMID: 23885265
316. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012

References (continued)

317. 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
318. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
319. 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
320. 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
321. 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
322. 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
323. 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
324. 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
325. 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
326. 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
327. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165
328. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2026]
329. 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
330. Rodgers et al. Regulation of PI3K effector signalling in cancer by the phosphoinositide phosphatases. Biosci Rep. 2017 Feb 28;37(1). PMID: 28082369
331. Wang et al. Inositol Polyphosphate 4-Phosphatase Type II Is a Tumor Suppressor in Multiple Myeloma. Front Oncol. 2021;11:785297. PMID: 35070988
332. Yang et al. INPP4B exerts a dual function in the stemness of colorectal cancer stem-like cells through regulating Sox2 and Nanog expression. Carcinogenesis. 2020 Mar 13;41(1):78-90. PMID: 31179504
333. Woolley et al. Phosphoinositide signaling in cancer: INPP4B Akt(s) out. Trends Mol Med. 2015 Sep;21(9):530-2. PMID: 26150301
334. Stewart et al. Homologous Recombination Deficiency: Concepts, Definitions, and Assays. Oncologist. 2022 Mar 11;27(3):167-174. PMID: 35274707
335. Creeden et al. Homologous recombination proficiency in ovarian and breast cancer patients. BMC Cancer. 2021 Oct 28;21(1):1154. PMID: 34711195
336. Sokol et al. Pan-Cancer Analysis of BRCA1 and BRCA2 Genomic Alterations and Their Association With Genomic Instability as Measured by Genome-Wide Loss of Heterozygosity. JCO Precis Oncol. 2020;4:442-465. PMID: 32903788
337. Heeke et al. Prevalence of Homologous Recombination-Related Gene Mutations Across Multiple Cancer Types. JCO Precis Oncol. 2018;2018. PMID: 30234181
338. Kondrashova et al. Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma. Nat Commun. 2018 Sep 28;9(1):3970. PMID: 30266954
339. Hoppe et al. Biomarkers for Homologous Recombination Deficiency in Cancer. J. Natl. Cancer Inst. 2018 Jul 1;110(7):704-713. PMID: 29788099
340. Wagener-Ryczek et al. Biomarkers for Homologous Recombination Deficiency in Cancer. J Pers Med. 2021 Jun 28;11(7). PMID: 34203281
341. Negrini et al. Genomic instability--an evolving hallmark of cancer. Nat Rev Mol Cell Biol. 2010 Mar;11(3):220-8. PMID: 20177397
342. Yao et al. Genomic Instability and Cancer. J Carcinog Mutagen. 2014;5. PMID: 25541596
343. Chen et al. GSA: an independent development algorithm for calling copy number and detecting homologous recombination deficiency (HRD) from target capture sequencing. BMC Bioinformatics. 2021 Nov 23;22(1):562. PMID: 34814825

References (continued)

344. Popova et al. Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation. Cancer Res. 2012 Nov 1;72(21):5454-62. PMID: 22933060
345. Timms et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. Breast Cancer Res. 2014 Dec 5;16(6):475. PMID: 25475740
346. Birkbak et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. Cancer Discov. 2012 Apr;2(4):366-375. PMID: 22576213
347. Duijf et al. Mechanisms of Genomic Instability in Breast Cancer. Trends Mol Med. 2019 Jul;25(7):595-611. PMID: 31078431
348. Stoler et al. The onset and extent of genomic instability in sporadic colorectal tumor progression. Proc Natl Acad Sci U S A. 1999 Dec 21;96(26):15121-6. PMID: 10611348
349. Sakai et al. Functional restoration of BRCA2 protein by secondary BRCA2 mutations in BRCA2-mutated ovarian carcinoma. Cancer Res. 2009 Aug 15;69(16):6381-6. PMID: 19654294
350. Sakai et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature. 2008 Feb 28;451(7182):1116-20. PMID: 18264087
351. Swisher et al. Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. Cancer Res. 2008 Apr 15;68(8):2581-6. PMID: 18413725
352. Watkins et al. Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers. Breast Cancer Res. 2014 Jun 3;16(3):211. PMID: 25093514
353. Marquard et al. Pan-cancer analysis of genomic scar signatures associated with homologous recombination deficiency suggests novel indications for existing cancer drugs. Biomark Res. 2015;3:9. PMID: 26015868
354. Chao et al. Genomic scar signatures associated with homologous recombination deficiency predict adverse clinical outcomes in patients with ovarian clear cell carcinoma. J Mol Med (Berl). 2018 Jun;96(6):527-536. PMID: 29725737
355. Doig et al. Homologous Recombination Repair Deficiency: An Overview for Pathologists. Mod Pathol. 2023 Mar;36(3):100049. PMID: 36788098
356. Nguyen et al. Pan-cancer landscape of homologous recombination deficiency. Nat Commun. 2020 Nov 4;11(1):5584. PMID: 33149131
357. Rempel et al. Pan-cancer analysis of genomic scar patterns caused by homologous repair deficiency (HRD). NPJ Precis Oncol. 2022 Jun 9;6(1):36. PMID: 35681079
358. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
359. 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
360. 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
361. 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
362. 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
363. 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
364. 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
365. 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
366. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823
367. Ferrone et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009 Jan 20;27(3):433-8. PMID: 19064968
368. Cavanagh et al. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hered Cancer Clin Pract. 2015;13(1):16. PMID: 26236408
369. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019 Jul 1;25(13):3759-3771. PMID: 30760478
370. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823

References (continued)

371. Iglehart et al. Synthetic lethality--a new direction in cancer-drug development. N Engl J Med. 2009 Jul 9;361(2):189-91. PMID: 19553640

372. de Bono et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020 May 28;382(22):2091-2102. PMID: 32343890

373. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf

374. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214876s003s004lbl.pdf

375. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf

376. NCCN Guidelines® - NCCN-Ovarian Cancer [Version 3.2025]

377. 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

378. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437

379. Dias et al. Understanding and overcoming resistance to PARP inhibitors in cancer therapy. Nat Rev Clin Oncol. 2021 Dec;18(12):773-791. PMID: 34285417

380. Giudice et al. PARP Inhibitors Resistance: Mechanisms and Perspectives. Cancers (Basel). 2022 Mar 10;14(6). PMID: 35326571

381. Kim et al. Alternate therapeutic pathways for PARP inhibitors and potential mechanisms of resistance. Exp Mol Med. 2021 Jan;53(1):42-51. PMID: 33487630