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Patient Name: 김동균
Gender: Male
Sample ID: N26-86

Primary Tumor Site: urinary bladder
Collection Date: 2025.04.07

Sample Cancer Type: Bladder Cancer

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Relevant Bladder Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR2	None detected	NTRK3	None detected
FGFR3	None detected	RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***1.9 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
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
IIC	*SMARCA4 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 Locus: chr19:11094814	None*	None*	2
IIC	*CHEK2 deletion* checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	*FANCA deletion* Fanconi anemia complementation group A Locus: chr16:89804984	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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	1
IIC	*SMAD4 deletion* SMAD family member 4 Locus: chr18:48573387	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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

*ERCC2 deletion, JAK3 deletion, KMT2B deletion, MAP2K4 deletion, MAP2K7 deletion, Microsatellite stable, PARP1 deletion, RAD54L deletion, RNASEH2A deletion, RPA1 deletion, SDHB deletion, STK11 deletion, TP53 deletion, XRCC3 deletion, SPEN deletion, EPHA2 deletion, ACVR2A deletion, FAT1 p.(T2369Rfs*2) c.7105delA, PRDM1 deletion, CSMD3 deletion, RECQL4 deletion, NQO1 p.(P187S) c.559C>T, ZFHX3 deletion, GPS2 deletion, NCOR1 deletion, DSC3 deletion, DSC1 deletion, SMAD2 deletion, KEAP1 deletion, NOTCH3 deletion, CIC deletion, ARHGAP35 deletion, ASXL1 deletion, TOP1 deletion, EP300 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
FAT1	p.(T2369Rfs*2)	c.7105delA	.	chr4:187540634	23.64%	NM_005245.4	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	48.55%	NM_000903.3	missense
ARID1A	p.(N1068D)	c.3202A>G	.	chr1:27097613	39.96%	NM_006015.6	missense
HLA-B	p.([R68=;E69M])	c.204_206delAGAinsGAT	.	chr6:31324602	52.38%	NM_005514.8	synonymous, missense
KMT2C	p.(F3947S)	c.11840T>C	.	chr7:151853115	46.87%	NM_170606.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
SMARCB1	chr22:24129273	1.11	0.61
SMARCA4	chr19:11094814	1.09	0.6
CHEK2	chr22:29083868	1	0.54
FANCA	chr16:89804984	1.03	0.58
NF2	chr22:29999923	1.02	0.57
SMAD4	chr18:48573387	0.97	0.55
ERCC2	chr19:45854865	1.08	0.6
JAK3	chr19:17937461	1.11	0.61

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
KMT2B	chr19:36209128	1.08	0.6
MAP2K4	chr17:11924164	1.1	0.61
MAP2K7	chr19:7968792	0.84	0.5
PARP1	chr1:226549124	1.05	0.59
RAD54L	chr1:46714017	1	0.61
RNASEH2A	chr19:12917452	1.1	0.61
RPA1	chr17:1733385	1.09	0.61
SDHB	chr1:17345303	1.11	0.61
STK11	chr19:1206847	1.23	0.66
TP53	chr17:7572848	1.15	0.63
XRCC3	chr14:104165043	1.02	0.58
SPEN	chr1:16174516	1.08	0.6
EPHA2	chr1:16451707	1.09	0.61
ACVR2A	chr2:148602708	1.06	0.59
PRDM1	chr6:106534408	1.02	0.58
CSMD3	chr8:113237020	0.69	0.43
RECQL4	chr8:145736758	0.97	0.55
ZFHX3	chr16:72820995	1.08	0.6
GPS2	chr17:7216071	1.22	0.66
NCOR1	chr17:15935586	1.05	0.58
DSC3	chr18:28574139	1.05	0.59
DSC1	chr18:28710424	0.99	0.56
SMAD2	chr18:45368152	1.05	0.59
KEAP1	chr19:10597314	1.09	0.61
NOTCH3	chr19:15271451	1.13	0.62
CIC	chr19:42775916	1	0.56
ARHGAP35	chr19:47421913	1.02	0.57
ASXL1	chr20:30954155	1.01	0.57
TOP1	chr20:39690023	0.87	0.51
EP300	chr22:41489001	1.08	0.6
AKT3	chr1:243663007	0.78	0.47
MYC	chr8:128748847	1.01	0.57
FAM135B	chr8:139144776	0.93	0.54
YES1	chr18:724481	0.95	0.54

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
SETBP1	chr18:42281265	1.09	0.6
BCL2	chr18:60795830	1.24	0.67
PIK3R2	chr19:18266737	1.25	0.68
MEF2B	chr19:19256562	1.11	0.61
ZNF429	chr19:21688488	0.8	0.48
CCNE1	chr19:30303647	1.09	0.6
AKT2	chr19:40739751	1.07	0.6
AXL	chr19:41725295	1.1	0.61
SRC	chr20:36012492	1.05	0.59
PLCG1	chr20:39766236	1.07	0.6
U2AF1L5	chr21:44513260	1.13	0.62
MAPK1	chr22:22123473	0.99	0.56

Biomarker Descriptions

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[74]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[74,75]. 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[76]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[77,78].

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[75]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[76]. 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[79,80].

SMARCA4 deletion

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4

Background: The SMARCA4 gene encodes the SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4 protein[1]. SMARCA4, also known as BRG1, is a core member of ATP-dependent, multisubunit SWI/SNF chromatin-remodeling complex, along with SMARCB1/SNF5, SMARCC1/BAF155, SMARCC2/BAF170, and SMARCA2/BRM[74]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[74,75]. SMARCA4 and SMARCA2 are highly homologous and are mutually exclusive ATPase catalytic subunits for SWI/SNF chromatin remodeling complexes[74,75]. Germline loss of function mutations in SMARCA4 are associated with atypical teratoid/rhabdoid tumors (AT/RT), and a rare form of

Biomarker Descriptions (continued)

ovarian cancer called small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), which highlights the tumor suppressor function of SMARCA4.[213,214].

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[75]. Recurrent somatic mutations in SMARCA4 are observed in 11% of skin cutaneous melanoma, 10% of uterine corpus endometrial carcinoma, 8% of lung adenocarcinoma, 7% of esophageal adenocarcinoma, 6% of bladder urothelial carcinoma and stomach adenocarcinoma, 5% of colorectal adenocarcinoma and brain lower grade glioma, 4% of head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, lung squamous cell carcinoma, and uterine carcinosarcoma, 3% of cervical squamous cell carcinoma, liver hepatocellular carcinoma, and kidney renal clear cell carcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, thymoma, and breast invasive carcinoma[5,6]. Biallelic deletion of SMARCA4 is observed in 2% of esophageal adenocarcinoma and diffuse large B-cell lymphoma[5,6]. Alterations in SMARCA4 are also observed in pediatric cancers[6]. Somatic mutations in SMARCA4 are observed in 47% of non-Hodgkin lymphoma (8 in 17 cases), 5% of Hodgkin lymphoma (3 in 61 cases) and T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 4% of embryonal tumors (13 in 332 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of bone cancer (5 in 327 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and glioma (1 in 297 cases)[6]. Biallelic deletion of SMARCA4 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for SMARCA4 aberrations. SMARCA4 mutations and deletions are considered a diagnostic marker for the SMARCA4-deficient uterine sarcoma (SDUS) subtype[215].

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, a cell cycle checkpoint regulator[1]. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[145]. CHEK2 also stabilizes p53, leading to cell-cycle arrest in G1 phase, and is capable of phosphorylating BRCA1 and promoting DNA repair including homologous recombination repair (HRR)[146,147,148]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[149,150,151]. Reduced expression of CHEK2 is associated with several cancers including breast cancer, colorectal cancer, and prostate cancer, supporting its role as a tumor suppressor[150].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations[152]. Somatic mutations in CHEK2 are observed in 7% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, 3% of cholangiocarcinoma, and 2% of diffuse large B-cell lymphoma, adrenocortical carcinoma, stomach adenocarcinoma, lung adenocarcinoma, colorectal adenocarcinoma, and kidney chromophobe[5,6]. Deletion of CHEK2 is observed in 3% of adrenocortical carcinoma and thymoma, and 2% of bladder urothelial carcinoma,[5,6]. Alterations in CHEK2 are also observed in pediatric cancers[6]. Somatic mutations in CHEK2 are observed in less than 1% of bone cancer (2 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and peripheral nervous system cancers (1 in 1158 cancers)[6]. Deletion of CHEK2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[6].

Potential relevance: The PARP inhibitor, olaparib[28] (2020) is approved for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes, including CHEK2. Additionally, talazoparib[30](2023) in combination with enzalutamide is approved for mCRPC with mutations in HRR genes, including CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[93], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FANCA deletion

Fanconi anemia complementation group A

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, 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[59,60]. 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[59]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[61,62]. Loss of function mutations in the FA family and HRR pathway, including FANCA, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[63,64]. 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[65,66]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[60,66,67,68,69].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in FANCA are observed in 4-8% of uterine, colorectal, and bladder cancers and about 6% of melanoma[5]. Biallelic loss is also reported in 2-5% of uveal melanoma, invasive breast carcinoma, ovarian cancer, and prostate cancer[5].

Potential relevance: The PARP inhibitor, talazoparib[30] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes FANCA. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCA are shown to confer enhanced sensitivity in vitro to DNA damaging agents, including cisplatin, as well as PARP inhibitors such as olaparib[70,71]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[69].

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[104]. 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[105,106,107]. 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[105,106,107,108]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[104,106,107]. 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[104,106,107].

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.

SMAD4 deletion

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[98,99]. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression[99,247,248]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[98,99]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[98]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[6,248,249]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[5,6,250].

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[99,248,251,252,253]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[254,255]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[255]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[256].

Biomarker Descriptions (continued)

ERCC2 deletion

ERCC excision repair 2, TFIIH core complex helicase subunit

Background: The ERCC2 gene encodes ERCC excision repair 2, TFIIH core complex helicase subunit, also known as XPD[1]. ERCC2 is a protein involved in the nucleotide excision repair (NER) pathway responsible for repairing bulky DNA lesions caused by UV radiation, environmental mutagens, chemical agents, and cyclopurines generated by reactive oxygen species[94]. ERCC2 functions as a helicase along with ERCC3/XPB in the TFIIH core complex[94]. During repair of bulky lesions by NER, the TFIIH core complex binds to the lesion, followed by DNA damage verification by ERCC2, which is essential for NER[94]. Following lesion binding and verification, ERCC2 unwinds DNA in the 5'-3' direction[94]. Mutations in ERCC2 lead to stalled RNA polymerase, resulting in persistent block of transcription[94]. Germline ERCC2 mutations can lead to hereditary disorders including: Cockayne syndrome, characterized by skin cancer susceptibility and neurodegerneration; xeroderma pigmentosum (XP), characterized by neurodegeneration and developmental defects; and trichothiodystrophy (TTD), characterized by brittle hair due to sulfur deficiency as well as other developmental defects[94,95].

Alterations and prevalence: Somatic mutations in ERCC2 are predominantly missense and occur in 9% of bladder urothelial carcinoma, 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and cholangiocarcinoma, and 2% of lung squamous cell carcinoma[5,6]. The missense mutation, N238S, is observed to be recurrent in bladder urothelial carcinoma and is predicted to result in ERCC2 loss of function[5,6,96]. Biallelic loss of ERCC2 is observed in 2% of brain lower grade glioma and diffuse large B-cell lymphoma, as well as 1% of sarcoma and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ERCC2 aberrations. In one study, ERCC2 mutations correlated with enhanced response to cisplatin based chemotherapy compared to wild-type ERCC2 in patients with muscle-invasive urothelial carcinoma[97].

JAK3 deletion

Janus kinase 3

Background: The JAK3 gene encodes Janus kinase 3, a non-receptor protein tyrosine kinase (PTK)[1,7]. JAK3 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[7]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[8]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[8,9,10].

Alterations and prevalence: Recurrent somatic mutations in JAK3 have been observed in T-cell lymphomas and acute lymphoblastic leukemia (ALL)[11,12]. Mutations in the pseudokinase domain (M511I, A573V, R657W), and kinase domain (L857Q) activate the JAK/STAT pathway and transform hematopoietic cells in vitro[11]. These variants are infrequently observed in solid cancers[5]. Somatic mutations in JAK3 are observed in 8% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma and uterine carcinosarcoma, 3% of adrenocortical carcinoma, stomach adenocarcinoma, and colorectal adenocarcinoma, and 2% of lung squamous cell carcinoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma, cervical squamous cell carcinoma, liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and esophageal adenocarcinoma[5,6]. JAK3 is amplified in 6% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of mesothelioma and esophageal adenocarcinoma[5,6]. Alterations in JAK3 are rare in pediatric cancers[5,6]. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases), and 1% of leukemia (4 in 354 cases), and less than 1% of glioma (2 in 297 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), bone cancer (1 in 327 cases), embryonal tumors (1 in 332 cases), and peripheral nervous system tumors (1 in 1158 cases)[5,6]. Amplification of JAK3 is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[5,6].

Potential relevance: Currently, no therapies are approved for JAK3 aberrations. Tofacitinib (2012), a JAK3 inhibitor, is FDA approved for rheumatoid and psoriatic arthritis[13]. Activating mutations in JAK3, including the germline variant V722I, promoted increased expression of PD-L1 in lung cancer and were associated with durable benefit from tofacitinib PD-L1 blockade[14]. JAK3 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia in adults and children[15,16,17].

KMT2B deletion

lysine methyltransferase 2B

Background: The KMT2B gene encodes the lysine methyltransferase 2B protein, a transcriptional coactivator and histone H3 lysine K (H3K4) methyltransferase[1]. KMT2B belongs to the SET domain protein methyltransferase superfamily[203]. Specifically, KMT2B along with KDM6A promotes the transcription of the oncogene MYC by H3K4 methylation[204].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in KMT2B are observed in 22% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 11% colorectal adenocarcinoma, 10% of stomach adenocarcinoma, 7% of adrenocortical carcinoma, and 5% of bladder urothelial carcinoma and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KMT2B aberrations.

MAP2K4 deletion

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4[1]. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[81]. Activation of MAPK proteins occurs through a kinase signaling cascade[81,82,83]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[81,82,83]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[81,82,83]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[84].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[5,6]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[5,6]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[85,86].

Potential relevance: Currently, no therapies are approved for MA2PK4 aberrations.

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7[1]. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10[81,83,205]. Activation of MAPK proteins occurs through a kinase signaling cascade[81,82,83]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[81,82,83]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[81,82,83].

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

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

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[119]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[120,121]. 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[122]. 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[123]. 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)[123]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[124,125,126,127,128]. 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[121]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[120,121,125,129].

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[120,121,130,131]. 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[130,131].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[132] (2014) and nivolumab[133] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[132] is also approved

Biomarker Descriptions (continued)

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[132]. Dostarlimab[134] (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[126,135]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[136] (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[126,137,138]. 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[138]. 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[139,140]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[139,140].

PARP1 deletion

poly(ADP-ribose) polymerase 1

Background: The PARP1 gene encodes the poly(ADP-ribose) polymerase 1 protein[1]. PARP1 belongs to the large PARP protein family that also includes PARP2, PARP3, and PARP4[22]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[22,23]. PARP enzymes are involved in several DNA repair pathways[22,23]. In base excision repair (BER), PARP1 recognizes DNA single-strand breaks and is capable of auto-PARylation (self-PARylation) which promotes the recruitment of additional BER enzymes[23,24]. PARP1 is also responsible for sensing DNA double-strand breaks (DSBs) and assists in end resection during homologous recombination repair (HRR) through the recruitment MRE11 to DSBs[24]. PARylation of histones H1, H2A, and H2B by PARP1 promotes an open chromatin conformation, which allows DNA repair machinery access to sites of DNA damage[25].

Alterations and prevalence: Somatic mutations in PARP1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of adrenocortical carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for PARP1 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[26,27]. Although not indicated for specific alterations in PARP1, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[28] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[28] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[29] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[30] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[31] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

RAD54L deletion

RAD54 like (S. cerevisiae)

Background: The RAD54L gene encodes the RAD54-like protein and is a member of the Snf2 family of Superfamily 2 (SF2) helicase-like proteins, which also includes its homolog RAD54B[87]. The Snf2 family are a group of DNA translocases that use ATP-hydrolysis to remodel chromatin structure and therefore regulate genome integrity by controlling transcriptional regulation, chromosome stability, and DNA repair[87,88,89]. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases[87,90]. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination[91]. RAD54L is a tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss[92].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in RAD54L are observed in up to 5% of uterine cancer[5,6].

Potential relevance: The PARP inhibitor, olaparib[28] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[93], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RNASEH2A deletion

ribonuclease H2 subunit A

Background: The RNASEH2A gene encodes the ribonuclease H2 subunit A protein[1]. RNASEH2A functions as the catalytic subunit of the RNase H2 holoenzyme along with the auxiliary RNASEH2B and RNASEH2C subunits[173,174]. RNase H2 removes ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[173]. Specifically, RNase H2 interacts with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[173]. Although deregulation of RNASEH2A expression has been observed in multiple cancer types, its role in oncogenesis is unclear[175].

Alterations and prevalence: Somatic mutations in RNASEH2A are observed in 2% of uterine corpus endometrial carcinoma, skin cutaneous melanoma, and kidney chromophobe[5,6].

Potential relevance: Currently, no therapies are approved for RNASEH2A aberrations.

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1[1]. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)[197]. RPA is involved in multiple DNA repair processes including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)[197]. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair[197].

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma[5,6]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for RPA1 aberrations.

SDHB deletion

succinate dehydrogenase complex iron sulfur subunit B

Background: The SDHB gene encodes succinate dehydrogenase complex iron sulfur subunit B, a subunit of the succinate dehydrogenase (SDH) enzyme complex[1]. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD[55,56]. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain[55,56]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[57]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[55,56]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,58].

Alterations and prevalence: Somatic mutations in SDHB are observed in 1% cervical squamous cell carcinoma, uterine corpus endometrial carcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, stomach adenocarcinoma, thymoma, lung squamous cell carcinoma, and kidney renal clear cell carcinoma[5,6]. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[5,6].

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

Biomarker Descriptions (continued)

STK11 deletion

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression[153]. STK11 preserves hematopoietic stem cell homeostasis, and its loss drives metabolic dysfunction and promotes leukemic progression in myeloproliferative neoplasms via ROS and HIF-1α activation[154,155]. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development[156,157].

Alterations and prevalence: Somatic mutations in STK11 are observed in 13% of lung adenocarcinoma, 4% of cervical squamous cell carcinoma, 3% of cholangiocarcinoma and uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, pancreatic adenocarcinoma, adrenocortical carcinoma, and esophageal adenocarcinoma[5,6,158,159]. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer[5,6]. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others[5,6,156,159,160]. Biallelic loss of STK11 is observed in 3% of sarcoma, cervical squamous cell carcinoma, and ovarian serous cystadenocarcinoma[5,6]. Alterations in STK11 are also observed in pediatric cancers[161]. Biallelic loss of STK11 is observed in 6% of B-lymphoblastic leukemia/lymphoma (45 in 731 cases), 2% of leukemia (4 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)[161]. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and glioma (1 in 297 cases)[161].

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription), TNG-260[162] in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors[163]. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)[164].

TP53 deletion

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[257]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[258]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[259,260].

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%)[5,6,158,261,262,263]. 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[264,265,266,267]. 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[268] (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[269,270]. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[271]. 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)[15,51,52,53,272]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[273]. 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[274].

Biomarker Descriptions (continued)

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[1,176]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[176,177]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[178].

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[178].

SPEN deletion

spen family transcriptional repressor

Background: SPEN encodes spen family transcriptional repressor[1]. SPEN plays a role in chromosome X inactivation and regulation of transcription[222,223,224]. As a transcriptional repressor, SPEN sequesters transcriptional activators and interacts with other repressors and chromatin remodeling complexes, such as histone deacetylases (HDACs) and the NuRD complex[222,224]. In ERα-positive breast cancers, SPEN binds ERα in a ligand-independent manner and negatively regulates the transcription of ERα targets, acting as a tumor suppressor gene to regulate cell proliferation, tumor growth, and survival[225,226].

Alterations and prevalence: Somatic mutations in SPEN are observed in 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 10% of stomach adenocarcinoma, 7% of diffuse large B-cell lymphoma, bladder urothelial carcinoma, and colorectal adenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of head and neck squamous cell carcinoma and lung adenocarcinoma, 4% of lung squamous cell carcinoma and ovarian serous cystadenocarcinoma, 3% of kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, breast invasive carcinoma, glioblastoma multiforme, and acute myeloid leukemia, and 2% of pancreatic adenocarcinoma, adrenocortical carcinoma, liver hepatocellular carcinoma, uterine carcinosarcoma, and esophageal adenocarcinoma[5,6]. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[5,6].

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

EPHA2 deletion

EPH receptor A2

Background: The EPHA2 gene encodes the EPH receptor A2[1]. EPHA2 is a member of the erythropoietin-producing hepatocellular carcinoma (Eph) receptors, a group of receptor tyrosine kinases divided into EPHA (EphA1-10) and EPHB (EphB1-6) classes of proteins[72,73]. Like classical tyrosine kinase receptors, Eph activation is initiated by ligand binding resulting downstream signaling involved in various cellular processes including cell growth, differentiation, and apoptosis[73]. Specifically, Eph-EphrinA ligand interaction regulates pathways critical for malignant transformation and key downstream target proteins including PI3K, SRC, Rho and Rac1 GTPases, MAPK, and integrins[72,73].

Alterations and prevalence: Somatic mutations in EPHA2 are observed in 11% of cholangiocarcinoma, 7% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and skin cutaneous melanoma, 6% of bladder urothelial carcinoma, and 5% of diffuse large B-cell lymphoma (DLBCL) and cervical squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for EPHA2 aberrations.

ACVR2A deletion

activin A receptor type 2A

Background: The ACVR2A gene encodes the activin A type 2A receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenic protein (BMP)/transforming growth factor-beta (TGFβ) receptor family[1,18]. ACVR2A is a type II receptor that forms heterotetrametric complex with at least two type I receptors (ACVR1 and ACVR1B) and two type II receptors (including BMPR2 and ACVR2B)[18,19]. When ligands, such as activin A or BMPs, dimerize and bind to the heterotetrametric complex, type II receptors transphosphorylate and activate type I receptors leading to phosphorylation of SMAD proteins and downstream

Biomarker Descriptions (continued)

signaling[18,19]. Downregulation of ACVR2A has been associated with increased cell migration, tumor progression, and metastases in colon cancer[20].

Alterations and prevalence: Somatic mutations of ACVR2A are observed in 11% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 7% of colorectal adenocarcinoma, 3% of liver hepatocellular carcinoma, skin cutaneous melanoma, and cholangiocarcinoma, 2% of cervical squamous cell carcinoma, and 1% of kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, and glioblastoma multiforme, and esophageal adenocarcinoma[5,6]. Biallelic deletion of ACVR2A is observed in 4% of prostate adenocarcinoma, 2% of liver hepatocellular carcinoma, and 1% of stomach adenocarcinoma, thymoma, testicular germ cell tumors, esophageal adenocarcinoma, and colorectal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ACVR2A aberrations.

FAT1 p.(T2369Rfs*2) c.7105delA

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[1,21]. 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[21]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[21]. 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[21]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[21].

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.

PRDM1 deletion

PR/SET domain 1

Background: The PRDM1 gene encodes the PR/SET domain 1 protein, also known as BLIMP1[1]. PRDM1 is a transcriptional repressor that regulates B- and T-cell differentiation[141,142,143]. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs[144]. PRDM1, along with other transcription factors, also regulates the expression of IL-2, IL-21, and IL-10 in effector T-cells, resulting in T-cell mediated immunosuppression through IL repression[143]. Dysregulation of B-cell terminal differentiation, as a result of PRDM1 mutations, has been observed to contribute to lymphoma development, supporting a tumor suppressor role for PRDM1[144].

Alterations and prevalence: Somatic mutations in PRDM1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 5% diffuse large B-cell lymphoma (DLBCL), and 3% of cholangiocarcinoma[5,6]. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)[144]. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma[5,6].

Potential relevance: Currently, no therapies are approved for PRDM1 aberrations.

CSMD3 deletion

CUB and Sushi multiple domains 3

Background: CSMD3 encodes the CUB and Sushi multiple domains 3 protein, a member of the CSMD family, which includes CSMD1 and CSMD2[1,2]. Proteins containing CUB and Sushi domains are known to mediate protein-protein interactions between the transmembrane and extracellular proteins[2,3]. CSMD family proteins have 14 CUB and 26–28 Sushi domains, which are reported to regulate dendrite growth, neuronal migration, and synapse formation[2,3]. In cancer, mutation of CMSD3 has been associated with greater tumor mutational burden (TMB)[2,4].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations of CSMD3 are observed in 43% of lung squamous cell carcinoma, 40% of lung adenocarcinoma, 37% of skin cutaneous melanoma, 25% of stomach adenocarcinoma, 24% of uterine corpus endometrial carcinoma, 19% of esophageal adenocarcinoma and head and neck squamous cell carcinoma, 17% of colorectal adenocarcinoma, 14% of bladder urothelial carcinoma, 10% of diffuse large B-cell lymphoma, 8% of liver hepatocellular carcinoma and cervical squamous cell carcinoma, 7% of ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma, and 4% of adrenocortical carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, prostate adenocarcinoma and, uveal melanoma[5,6]. Amplification of CSMD3 is observed in 20% of ovarian serous cystadenocarcinoma, 12% of breast invasive carcinoma, 11% of uterine carcinosarcoma, 10% of liver hepatocellular carcinoma, and esophageal adenocarcinoma, 8% of prostate adenocarcinoma, 7% of pancreatic adenocarcinoma, 6% of uveal melanoma and head and neck squamous cell carcinoma, and 5% of bladder urothelial carcinoma and stomach adenocarcinoma[5,6]. Biallelic loss of CSMD3 is observed in 2% of mesothelioma and prostate adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CSMD3 aberrations.

RECQL4 deletion

RecQ like helicase 4

Background: RECQL4 encodes RecQ like helicase 4 and is member of the RecQ family of DNA helicases, which also includes RECQL1, WRN, BLM, and RECQL5[1,227,228]. RECQL4 plays an important role in DNA replication, telomere maintenance, homologous recombination, and genomic stability[228,229,230]. Mutations in RECQL4 can lead to several developmental syndromes including, Rothmund-Thomson syndrome (RTS), Baller-Gerold syndrome (BGS), and RAPADILINO syndrome, which confer predisposition to the development of several cancer types including skin cancer, osteosarcoma, lymphoma, and leukemia[231,232,233]. Although widely considered a tumor suppressor gene, amplification and overexpression of RECQL4 has been observed to promote tumor growth in some cancer types[234,235,236].

Alterations and prevalence: Somatic mutations in RECQL4 are observed in 5% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma and skin cutaneous melanoma, and 2% of lung squamous cell carcinoma, cervical squamous cell carcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, liver hepatocellular carcinoma, esophageal adenocarcinoma, and head and neck squamous cell carcinoma[5,6]. Amplification of RECQL4 is observed in 27% of ovarian serous cystadenocarcinoma, 11% of breast invasive carcinoma, 10% of esophageal adenocarcinoma and liver hepatocellular carcinoma, 9% of pancreatic adenocarcinoma and uterine carcinosarcoma, 8% of head and neck squamous cell carcinoma, 6% of prostate adenocarcinoma, 5% of lung adenocarcinoma, stomach adenocarcinoma, and lung squamous cell carcinoma, 4% of skin cutaneous melanoma and brain lower grade glioma, 3% of uterine corpus endometrial carcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, and uveal melanoma, and 2% of sarcoma and diffuse large B-cell lymphoma[5,6]. Biallelic loss of RECQL4 is observed in 4% of diffuse large B-cell lymphoma and 2% of brain lower grade glioma[5,6].

Potential relevance: Currently, no therapies are approved for RECQL4 aberrations.

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,109,110]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[110,111]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[112,113,114,115,116]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[112,115,117,118].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[5,6]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

Biomarker Descriptions (continued)

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[216]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[216,217]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[218,219,220].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[5,6]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[5,6]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[5,6,221]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[221].

Potential relevance: Currently, no therapies are approved for GPS2 aberrations.

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,179,180]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[179,180,181,182]. NCOR1 has been shown to exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[180]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types, including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[180,183].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[5,6]. Biallelic loss of NCOR1 is observed in 3% of liver hepatocellular carcinoma and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[5,6]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[5,6]. Alterations in NCOR1 are also observed in pediatric cancer[6]. Somatic mutations in NCOR1 are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of leukemia (6 in 354 cases), Hodgkin lymphoma (1 in 61 cases), B-lymphoblastic leukemia/lymphoma (4 in 252 cases), bone cancer (5 in 327 cases), and embryonal cancer (5 in 332 cases), and less than 1% of glioma (2 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)[6]. Biallelic deletion of NCOR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases) and leukemia (2 in 250 cases)[6].

Potential relevance: Currently, no therapies are approved for NCOR1 aberrations.

DSC3 deletion

desmocollin 3

Background: The DSC3 gene encodes desmocollin 3, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC1 and DSC2[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[165]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[166]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC3 in tumorigenesis[165,167,168,169].

Alterations and prevalence: Somatic mutations in DSC3 are observed in 19% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, and 3% of bladder urothelial carcinoma[5,6]. Biallelic deletion of DSC3 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for DSC3 aberrations.

Biomarker Descriptions (continued)

DSC1 deletion

desmocollin 1

Background: The DSC1 gene encodes desmocollin 1, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC2 and DSC3[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[165]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[166]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC1 in tumorigenesis[165,167,168,169].

Alterations and prevalence: Somatic mutations in DSC1 are observed in 17% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, and 3% of lung adenocarcinoma, lung squamous cell carcinoma, and colorectal adenocarcinoma[5,6]. Biallelic deletion of DSC1 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for DSC1 aberrations.

SMAD2 deletion

SMAD family member 2

Background: The SMAD2 gene encodes the SMAD family member 2, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes[1,98,99]. SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class while SMAD4 belongs to the common mediator SMAD (co-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[98,99]. As part of the R-SMAD class, SMAD2 functions by mediating signal transmission in the transforming growth factor beta (TGF-β) signaling pathway, a pathway critical in cell growth, differentiation, and tumor development[99]. Following activation of type I TGF-β receptors, SMAD2 and SMAD3 are activated via phosphorylation and form a complex with SMAD4, leading to nuclear translocation and activation or repression of target genes[100,101]. Deregulation of SMAD2, including mutation and loss of expression, has been observed in cancer leading to disruption of SMAD2/3/4 complex formation and tumorigenesis, supporting a tumor suppressor role for SMAD2[101,102].

Alterations and prevalence: Somatic mutations in SMAD2 are observed in 5% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma, 3% of skin cutaneous melanoma, and 2% of stomach adenocarcinoma and lung adenocarcinoma[5,6]. The nonsense, truncating mutation, p.S464*, is the most commonly observed alteration and is recurrent[5,6,101]. Two recurrent hotspot mutations R321 and P305 occur in the mad homology 2 (MH2) domain leading to the disruption of the heterotrimeric SMAD2/SMAD3-SMAD4 complex[5,6,103]. SMAD2 deletion is observed in 4% of esophageal adenocarcinoma and 3% of pancreatic adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for SMAD2 aberrations.

KEAP1 deletion

kelch like ECH associated protein 1

Background: The KEAP1 gene encodes the kelch like ECH associated protein 1, a tumor suppressor and a member of the KEAP1-CUL3-RBX1 E3 ubiquitin ligase complex[1,237]. KEAP1 helps facilitate the negative regulation of the proto-oncogene NFE2L2 (NRF2) through ubiquitination, which leads to proteasomal degradation of NFE2L2[238]. Aberrations in KEAP1 can result in loss of function leading to accumulation of NFE2L2, thereby altering the transcription genes involved in antioxidant response, drug metabolism, DNA repair, autophagy, cell survival, and proliferation[238,239,240].

Alterations and prevalence: Somatic mutations in KEAP1 are observed in 18% of lung adenocarcinoma, 10% of lung squamous cell carcinoma, 6% of cholangiocarcinoma, 5% of liver hepatocellular carcinoma, 4% of uterine corpus endometrial carcinoma and head and neck squamous cell carcinoma, 3% of esophageal adenocarcinoma, and 2% of stomach adenocarcinoma, skin cutaneous melanoma, adrenocortical carcinoma, and bladder cancer[6]. Alterations in KEAP1 are also observed in pediatric cancers[6]. Somatic mutations in KEAP1 are observed in less than 1% of 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 embryonal tumors (1 in 332 cases)[6]. Biallelic deletion of KEAP1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for KEAP1 aberrations.

Biomarker Descriptions (continued)

NOTCH3 deletion

notch 3

Background: The NOTCH3 gene encodes the notch receptor 3 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, 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[206]. 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[207,208]. 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[209,210,211,212].

Alterations and prevalence: Somatic mutations observed in NOTCH3 are primarily missense or truncating and are found in about 12% of melanoma and uterine cancer, as well as 3-6% of diffuse large B-cell lymphoma (DLBCL), adrenocortical carcinoma, esophageal, colorectal, cervical, squamous lung, bladder, and head and neck cancers[5].

Potential relevance: Currently, no therapies are approved for NOTCH3 aberrations.

CIC deletion

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily[1,170]. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes[1,170]. CIC interacts with the HDAC complex and SWI/SNF to transcriptionally repress target genes, which include members of the E-Twenty Six (ETS) oncogene family ETV1, ETV4 and ETV5[170]. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC[170].

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma[5,6]. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)[5,6]. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma[170,171].

Potential relevance: Currently, no therapies are approved for CIC aberrations. CIC fusions, including CIC::DUX4 fusion, t(10;19)(q26;q13) and t(4;19)(q35;q13), are ancillary diagnostic markers for CIC-Rearranged Sarcoma[80,172].

ARHGAP35 deletion

Rho GTPase activating protein 35

Background: ARHGAP35 encodes Rho GTPase activating protein 35, human glucocorticoid receptor DNA binding factor. ARHGAP35 functions as a repressor of glucocorticoid receptor transcription[1]. Rho GTPases regulate various cellular processes such as cell adhesion, cell migration and play a critical role in metastasis through the negative regulation of RhoA which is localized to the cell membrane[198,199]. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis[200,201].

Alterations and prevalence: Somatic mutations of AHGAP35 are observed in 20% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 6% of skin cutaneous melanoma, bladder urothelial carcinoma, and lung squamous cell carcinoma, 5% of colorectal adenocarcinoma, and 4% of stomach adenocarcinoma and lung adenocarcinoma[5,6]. In endometrial cancer, R997* has been observed to be recurrent and has been observed to confer loss of RhoGAP activity due to protein truncation and loss of its RhoGAP domain[202]. Amplification of AHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma[5,6]. Biallelic loss of AHGAP35 has been observed in 2% of sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for ARHGAP35 aberrations.

ASXL1 deletion

additional sex combs like 1, transcriptional regulator

Background: The ASXL1 gene encodes the ASXL transcriptional regulator 1 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation[1,32]. ASXL1 belongs to the ASXL gene family, which also includes ASXL2 and ASXL3[32]. ASXL proteins contain a conserved c-terminal plant homeodomain (PHD) which facilitates interaction with DNA and

Biomarker Descriptions (continued)

histones[32,33]. ASXL1 influences chromatin remodeling and transcription through interaction with BAP1 and polycomb repressive complex (PRC) proteins, as well as other transcriptional activators and repressors[32,34]. In cancer, ASXL1 is the target of somatic mutations which often result in a truncated ASXL1 protein and loss of its PHD[35,36,37]. Such mutations can lead to impaired protein function and consequent upregulation of HOXA gene expression, supporting a tumor suppressor role for ASXL1[38].

Alterations and prevalence: Missense, nonsense, and frameshift mutations in ASXL1 are reported in 3-6% of de novo acute myeloid leukemia (AML), up to 36% of secondary AML, approximately 15% of myelodysplastic syndromes (MDS), up to 23% of myeloproliferative neoplasms (MPN), up to 30% of systemic mastocytosis (SM), and approximately 45% of chronic myelomonocytic leukemia (CMML)[5,34,39,40,41,42,43,44,45]. The ASXL1 G646Wfs*12 mutation accounts for over 50% of ASXL1 mutated cases in myeloid malignancies[36,41,46]. This mutation results from a single nucleotide expansion that occurs within an eight base pair guanine repeat that extends from c.1927 to c.1934. It is proposed that the high prevalence of the G646Wfs*12 variant is due to replication slippage which can occur in areas of repetitive sequence[47]. As a consequence, detection of G646Wfs*12 may result as an artifact of PCR and/or sequencing[48]. However, multiple studies observe an increase in the frequency of G646Wfs*12 in myeloid cancer relative to normal suggesting that G646Wfs*12 is a bona fide somatic mutation[39,47,49].

Potential relevance: The majority of frameshift and nonsense mutations in ASXL1 that result in protein truncation and removal of the PHD domain are considered pathogenic[50]. Mutations in ASXL1 confer poor/adverse risk in AML[45,51]. Additionally, ASXL1 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and CMML[52]. Moreover, ASXL1 mutations are independently associated with inferior overall survival (OS) in patients with MPN or SM[53,54].

TOP1 deletion

topoisomerase (DNA) I

Background: The TOP1 gene encodes DNA topoisomerase I, a member of the type I topoisomerase subfamily which also includes TOP3A and TOP3B[1,184]. Topoisomerases function as enzymes that create breaks in the backbone of DNA to relieve the negative supercoiling of DNA that occurs during replication or transcription[185,186]. Topoisomerases also function in DNA repair[186]. Specifically, TOP1 is responsible for catalyzing single-strand breaks followed by the re-ligation of DNA strands after unwinding[185]. In normal transcription, TOP1 activity maintains genomic stability by preventing the formation of RNA:DNA hybrid R-loops, which can interfere with the transcription and replication processes[185]. TOP1 amplification and overexpression have been observed in several cancer types and are believed to contribute to cancer growth and progression[185,187,188,189].

Alterations and prevalence: TOP1 amplification is observed in 7% of colorectal adenocarcinoma, 5% of uterine carcinosarcoma, 4% of adrenocortical carcinoma and stomach cancer, and 2% of esophageal cancer[5,6]. Somatic mutations in TOP1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and adrenocortical carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for TOP1 aberrations. TOP1 inhibitors including irinotecan (1996) for colon or rectal cancer as well as topotecan (1996) for small cell lung and cervical cancers are FDA approved, although not indicated for specific alterations. Mutations in TOP1 may confer resistance to topoisomerase inhibitors including irinotecan[190,191,192]. Additionally, amplification of TOP1 in melanoma and colorectal cancer as well as overexpression in liver and ovarian cancers have been shown to be associated with poor prognosis[193,194,195,196].

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[241,242]. 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[243,244]. Along with transcriptional coactivation, EP300 also functions in the formation of the transcription pre-initiation complex[243]. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[245].

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[246].

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

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 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,

Genes Assayed (continued)

Genes Assayed with Full Exon Coverage (continued)

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

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)

SMARCA4 deletion

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

CHEK2 deletion

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

FANCA deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (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.

Relevant Therapy Summary (continued)

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

SMAD4 deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***14.54%***
CHEK2	***CNV, CN:1.0***
CHEK2	***LOH, 22q12.1(29083868-29130729)x1***
RAD54L	***CNV, CN:1.0***
RAD54L	***LOH, 1p34.1(46714017-46743911)x1***

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

Thermo Fisher Scientific's Ion Torrent 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. Lu et al. CSMD3 is Associated with Tumor Mutation Burden and Immune Infiltration in Ovarian Cancer Patients. Int J Gen Med. 2021;14:7647-7657. PMID: 34764678
3. Lau et al. Identification of two new members of the CSMD gene family. Genomics. 2003 Sep;82(3):412-5. PMID: 12906867
4. Cai et al. Epigenetic alterations are associated with tumor mutation burden in non-small cell lung cancer. J Immunother Cancer. 2019 Jul 26;7(1):198. PMID: 31349879
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. Eshaq et al. Non-Receptor Tyrosine Kinases: Their Structure and Mechanistic Role in Tumor Progression and Resistance. Cancers (Basel). 2024 Aug 2;16(15). PMID: 39123481
8. Babon et al. The molecular regulation of Janus kinase (JAK) activation. Biochem. J. 2014 Aug 15;462(1):1-13. PMID: 25057888
9. Müller et al. The protein tyrosine kinase JAK1 complements defects in interferon-alpha/beta and -gamma signal transduction. Nature. 1993 Nov 11;366(6451):129-35. PMID: 8232552
10. Ren et al. JAK1 truncating mutations in gynecologic cancer define new role of cancer-associated protein tyrosine kinase aberrations. Sci Rep. 2013 Oct 24;3:3042. PMID: 24154688
11. Degryse et al. JAK3 mutants transform hematopoietic cells through JAK1 activation, causing T-cell acute lymphoblastic leukemia in a mouse model. Blood. 2014 Nov 13;124(20):3092-100. PMID: 25193870
12. Song et al. Oncogenic activation of the STAT3 pathway drives PD-L1 expression in natural killer/T-cell lymphoma. Blood. 2018 Sep 13;132(11):1146-1158. PMID: 30054295
13. Harrington et al. Janus Kinase Inhibitors in Rheumatoid Arthritis: An Update on the Efficacy and Safety of Tofacitinib, Baricitinib and Upadacitinib. J Clin Med. 2023 Oct 23;12(20). PMID: 37892827
14. Van Allen et al. Long-term Benefit of PD-L1 Blockade in Lung Cancer Associated with JAK3 Activation. Cancer Immunol Res. 2015 Aug;3(8):855-63. PMID: 26014096
15. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
16. NCCN Guidelines® - NCCN-Pediatric Acute Lymphoblastic Leukemia [Version 1.2026]
17. Mullighan et al. JAK mutations in high-risk childhood acute lymphoblastic leukemia. Proc. Natl. Acad. Sci. U.S.A. 2009 Jun 9;106(23):9414-8. PMID: 19470474
18. Valer et al. ACVR1 Function in Health and Disease. Cells. 2019 Oct 31;8(11). PMID: 31683698
19. Haupt et al. Variable signaling activity by FOP ACVR1 mutations. Bone. 2018 Apr;109:232-240. PMID: 29097342
20. Zhuo et al. Downregulation of Activin A Receptor Type 2A Is Associated with Metastatic Potential and Poor Prognosis of Colon Cancer. J Cancer. 2018;9(19):3626-3633. PMID: 30310521
21. Peng et al. Role of FAT1 in health and disease. Oncol Lett. 2021 May;21(5):398. PMID: 33777221
22. Amé et al. The PARP superfamily. Bioessays. 2004 Aug;26(8):882-93. PMID: 15273990
23. Morales et al. Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. Crit Rev Eukaryot Gene Expr. 2014;24(1):15-28. PMID: 24579667
24. Ray Chaudhuri et al. The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nat Rev Mol Cell Biol. 2017 Oct;18(10):610-621. PMID: 28676700
25. Schreiber et al. Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol. 2006 Jul;7(7):517-28. PMID: 16829982
26. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019 Jul 1;25(13):3759-3771. PMID: 30760478
27. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
28. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
29. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
30. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf
31. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214876s003s004lbl.pdf
32. Katoh. Functional and cancer genomics of ASXL family members. Br. J. Cancer. 2013 Jul 23;109(2):299-306. PMID: 23736028

References (continued)

33. Gelsi-Boyer et al. Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. Br. J. Haematol. 2009 Jun;145(6):788-800. PMID: 19388938
34. Gelsi-Boyer et al. Mutations in ASXL1 are associated with poor prognosis across the spectrum of malignant myeloid diseases. J Hematol Oncol. 2012 Mar 21;5:12. doi: 10.1186/1756-8722-5-12. PMID: 22436456
35. Larsson et al. The changing mutational landscape of acute myeloid leukemia and myelodysplastic syndrome. Mol. Cancer Res. 2013 Aug;11(8):815-27. PMID: 23645565
36. Alvarez Argote et al. ASXL1 mutations in myeloid neoplasms: pathogenetic considerations, impact on clinical outcomes and survival. Curr Med Res Opin. 2018 May;34(5):757-763. PMID: 28027687
37. Yang et al. Gain of function of ASXL1 truncating protein in the pathogenesis of myeloid malignancies. Blood. 2018 Jan 18;131(3):328-341. PMID: 29113963
38. Abdel-Wahab et al. ASXL1 mutations promote myeloid transformation through loss of PRC2-mediated gene repression. Cancer Cell. 2012 Aug 14;22(2):180-93. PMID: 22897849
39. Alberti et al. Discriminating a common somatic ASXL1 mutation (c.1934dup; p.G646Wfs*12) from artifact in myeloid malignancies using NGS. Leukemia. 2018 Aug;32(8):1874-1878. PMID: 29959414
40. Kakosaiou et al. ASXL1 mutations in AML are associated with specific clinical and cytogenetic characteristics. Leuk. Lymphoma. 2018 Oct;59(10):2439-2446. PMID: 29411666
41. Paschka et al. ASXL1 mutations in younger adult patients with acute myeloid leukemia: a study by the German-Austrian Acute Myeloid Leukemia Study Group. Haematologica. 2015 Mar;100(3):324-30. PMID: 25596267
42. Jawhar et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. Haematologica. 2017 Jun;102(6):1035-1043. PMID: 28255023
43. Jawhar et al. KIT D816 mutated/CBF-negative acute myeloid leukemia: a poor-risk subtype associated with systemic mastocytosis. Leukemia. 2019 May;33(5):1124-1134. PMID: 30635631
44. Damaj et al. ASXL1 but not TET2 mutations adversely impact overall survival of patients suffering systemic mastocytosis with associated clonal hematologic non-mast-cell diseases. PLoS ONE. 2014;9(1):e85362. PMID: 24465546
45. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2026]
46. Boultwood et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. Leukemia. 2010 May;24(5):1062-5. doi: 10.1038/leu.2010.20. Epub 2010 Feb 25. PMID: 20182461
47. Yannakou et al. ASXL1 c.1934dup;p.Gly646Trpfs*12-a true somatic alteration requiring a new approach. Blood Cancer J. 2017 Dec 15;7(12):656. doi: 10.1038/s41408-017-0025-8. PMID: 29242575
48. Abdel-Wahab et al. The most commonly reported variant in ASXL1 (c.1934dupG;p.Gly646TrpfsX12) is not a somatic alteration. Leukemia. 2010 Sep;24(9):1656-7. doi: 10.1038/leu.2010.144. Epub 2010 Jul 1. PMID: 20596031
49. Montes-Moreno et al. Clinical molecular testing for ASXL1 c.1934dupG p.Gly646fs mutation in hematologic neoplasms in the NGS era. PLoS ONE. 2018;13(9):e0204218. PMID: 30222780
50. Landrum et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018 Jan 4;46(D1):D1062-D1067. PMID: 29165669
51. 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
52. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
53. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
54. NCCN Guidelines® - NCCN-Systemic Mastocytosis [Version 1.2020]
55. Renkema et al. SDHA mutations causing a multisystem mitochondrial disease: novel mutations and genetic overlap with hereditary tumors. Eur J Hum Genet. 2015 Feb;23(2):202-9. PMID: 24781757
56. Burnichon et al. SDHA is a tumor suppressor gene causing paraganglioma. Hum Mol Genet. 2010 Aug 1;19(15):3011-20. PMID: 20484225
57. Saxena et al. SDHB-Deficient Cancers: The Role of Mutations That Impair Iron Sulfur Cluster Delivery. J Natl Cancer Inst. 2016 Jan;108(1). PMID: 26719882
58. Ricketts et al. Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD. Hum Mutat. 2010 Jan;31(1):41-51. PMID: 19802898
59. Niraj et al. The Fanconi Anemia Pathway in Cancer. Annu Rev Cancer Biol. 2019 Mar;3:457-478. PMID: 30882047
60. Rodríguez et al. Fanconi anemia pathway. Curr Biol. 2017 Sep 25;27(18):R986-R988. PMID: 28950089

References (continued)

61. 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
62. 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
63. Lord et al. BRCAness revisited. Nat. Rev. Cancer. 2016 Feb;16(2):110-20. PMID: 26775620
64. Byrum et al. Defining and Modulating 'BRCAness'. Trends Cell Biol. 2019 Sep;29(9):740-751. PMID: 31362850
65. 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
66. 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
67. Levran et al. Sequence variation in the Fanconi anemia gene FAA. Proc. Natl. Acad. Sci. U.S.A. 1997 Nov 25;94(24):13051-6. PMID: 9371798
68. Antonio Casado et al. A comprehensive strategy for the subtyping of patients with Fanconi anaemia: conclusions from the Spanish Fanconi Anemia Research Network. J. Med. Genet. 2007 Apr;44(4):241-9. PMID: 17105750
69. Tischkowitz et al. Deletion and reduced expression of the Fanconi anemia FANCA gene in sporadic acute myeloid leukemia. Leukemia. 2004 Mar;18(3):420-5. PMID: 14749703
70. McCabe et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res. 2006 Aug 15;66(16):8109-15. PMID: 16912188
71. Wilkes et al. A germline FANCA alteration that is associated with increased sensitivity to DNA damaging agents. Cold Spring Harb Mol Case Stud. 2017 Sep;3(5). PMID: 28864460
72. Tan et al. EPHA2 mutations with oncogenic characteristics in squamous cell lung cancer and malignant pleural mesothelioma. Oncogenesis. 2019 Sep 4;8(9):49. PMID: 31484920
73. Tandon et al. Emerging strategies for EphA2 receptor targeting for cancer therapeutics. Expert Opin Ther Targets. 2011 Jan;15(1):31-51. PMID: 21142802
74. Wilson et al. SWI/SNF nucleosome remodellers and cancer. Nat. Rev. Cancer. 2011 Jun 9;11(7):481-92. PMID: 21654818
75. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. Nat Commun. 8;14648. PMID: 28262751
76. Weissmiller et al. Inhibition of MYC by the SMARCB1 Tumor Suppressor. Nat Commun. 10 (1). PMID: 31043611
77. 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
78. Fitzhugh. Rhabdoid Tumor Predisposition Syndrome and Pleuropulmonary Blastoma Syndrome. J Pediatr Genet. 2016 Jun;5(2):124-8. PMID: 27617153
79. 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
80. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
81. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. Clin. Cancer Res. 2013 May 1;19(9):2301-9. PMID: 23406774
82. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. Int J Mol Sci. 2020 Feb 7;21(3). PMID: 32046099
83. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. Br J Pharmacol. 2014 Jan;171(1):24-37. PMID: 24117156
84. Ahn et al. Map2k4 functions as a tumor suppressor in lung adenocarcinoma and inhibits tumor cell invasion by decreasing peroxisome proliferator-activated receptor γ2 expression. Mol. Cell. Biol. 2011 Nov;31(21):4270-85. PMID: 21896780
85. Robinson et al. Mitogen-activated protein kinase kinase 4/c-Jun NH2-terminal kinase kinase 1 protein expression is subject to translational regulation in prostate cancer cell lines. Mol. Cancer Res. 2008 Mar;6(3):501-8. PMID: 18337456
86. Xue et al. MAP3K1 and MAP2K4 mutations are associated with sensitivity to MEK inhibitors in multiple cancer models. Cell Res. 2018 Jul;28(7):719-729. PMID: 29795445
87. Heyer et al. Rad54: the Swiss Army knife of homologous recombination?. Nucleic Acids Res. 2006;34(15):4115-25. PMID: 16935872
88. Ryan et al. Snf2-family proteins: chromatin remodellers for any occasion. Curr Opin Chem Biol. 2011 Oct;15(5):649-56. PMID: 21862382

References (continued)

89. Matsuda et al. Mutations in the RAD54 recombination gene in primary cancers. Oncogene. 1999 Jun 3;18(22):3427-30. PMID: 10362365
90. Bugreev et al. Rad54 protein promotes branch migration of Holliday junctions. Nature. 2006 Aug 3;442(7102):590-3. PMID: 16862129
91. Mason et al. RAD54 family translocases counter genotoxic effects of RAD51 in human tumor cells. Nucleic Acids Res. 2015 Mar 31;43(6):3180-96. PMID: 25765654
92. 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
93. https://www.senhwabio.com//en/news/20220125
94. Marteijn et al. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 2014 Jul;15(7):465-81. PMID: 24954209
95. Cleaver et al. Disorders of nucleotide excision repair: the genetic and molecular basis of heterogeneity. Nat Rev Genet. 2009 Nov;10(11):756-68. PMID: 19809470
96. Hirotsu et al. Genomic Profiling Identified ERCC2 E606Q Mutation in Helicase Domain Respond to Platinum-Based Neoadjuvant Therapy in Urothelial Bladder Cancer. Front Oncol. 2020;10:1643. PMID: 32984035
97. Van Allen et al. Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. Cancer Discov. 2014 Oct;4(10):1140-53. PMID: 25096233
98. Ahmed et al. The TGF-β/Smad4 Signaling Pathway in Pancreatic Carcinogenesis and Its Clinical Significance. J Clin Med. 2017 Jan 5;6(1). PMID: 28067794
99. Zhao et al. The role of TGF-β/SMAD4 signaling in cancer. Int. J. Biol. Sci. 2018;14(2):111-123. PMID: 29483830
100. Massagué et al. Smad transcription factors. Genes Dev. 2005 Dec 1;19(23):2783-810. PMID: 16322555
101. Fleming et al. SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer. Cancer Res. 2013 Jan 15;73(2):725-35. PMID: 23139211
102. Fukuchi et al. Lack of activated Smad2 in transforming growth factor-beta signaling is an unfavorable prognostic factor in patients with esophageal squamous cell carcinoma. J Surg Oncol. 2006 Jul 1;94(1):51-6. PMID: 16788944
103. Galka-Marciniak et al. A pan-cancer atlas of somatic mutations in miRNA biogenesis genes. Nucleic Acids Res. 2021 Jan 25;49(2):601-620. PMID: 33406242
104. 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
105. 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
106. Petrilli et al. Role of Merlin/NF2 inactivation in tumor biology. Oncogene. 2016 Feb 4;35(5):537-48. PMID: 25893302
107. 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
108. 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
109. Zhao et al. Zinc Finger Homeodomain Factor Zfhx3 Is Essential for Mammary Lactogenic Differentiation by Maintaining Prolactin Signaling Activity. J Biol Chem. 2016 Jun 10;291(24):12809-12820. PMID: 27129249
110. Miura et al. Cloning and characterization of an ATBF1 isoform that expresses in a neuronal differentiation-dependent manner. J Biol Chem. 1995 Nov 10;270(45):26840-8. PMID: 7592926
111. Berry et al. Positive and negative regulation of myogenic differentiation of C2C12 cells by isoforms of the multiple homeodomain zinc finger transcription factor ATBF1. J Biol Chem. 2001 Jul 6;276(27):25057-65. PMID: 11312261
112. Kataoka et al. Alpha-fetoprotein producing gastric cancer lacks transcription factor ATBF1. Oncogene. 2001 Feb 15;20(7):869-73. PMID: 11314020
113. Ninomiya et al. Regulation of the alpha-fetoprotein gene by the isoforms of ATBF1 transcription factor in human hepatoma. Hepatology. 2002 Jan;35(1):82-7. PMID: 11786962
114. Kaspar et al. Myb-interacting protein, ATBF1, represses transcriptional activity of Myb oncoprotein. J Biol Chem. 1999 May 14;274(20):14422-8. PMID: 10318867
115. Sun et al. Frequent somatic mutations of the transcription factor ATBF1 in human prostate cancer. Nat Genet. 2005 Apr;37(4):407-12. PMID: 15750593

References (continued)

116. Mabuchi et al. Tumor suppressor, AT motif binding factor 1 (ATBF1), translocates to the nucleus with runt domain transcription factor 3 (RUNX3) in response to TGF-beta signal transduction. Biochem Biophys Res Commun. 2010 Jul 23;398(2):321-5. PMID: 20599712
117. Sun et al. Deletion of atbf1/zfhx3 in mouse prostate causes neoplastic lesions, likely by attenuation of membrane and secretory proteins and multiple signaling pathways. Neoplasia. 2014 May;16(5):377-89. PMID: 24934715
118. Kawaguchi et al. A diagnostic marker for superficial urothelial bladder carcinoma: lack of nuclear ATBF1 (ZFHX3) by immunohistochemistry suggests malignant progression. BMC Cancer. 2016 Oct 18;16(1):805. PMID: 27756245
119. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
120. 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
121. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
122. 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
123. 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
124. 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
125. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
126. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
127. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
128. 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
129. 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
130. 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
131. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
132. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
133. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
134. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
135. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
136. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
137. 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
138. 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
139. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
140. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
141. Martins et al. Transcriptional repressor Blimp-1 regulates T cell homeostasis and function. Nat Immunol. 2006 May;7(5):457-65. PMID: 16565721
142. Nutt et al. BLIMP1 guides the fate of effector B and T cells. Nat Rev Immunol. 2007 Dec;7(12):923-7. PMID: 17965637
143. Fu et al. New insights into Blimp-1 in T lymphocytes: a divergent regulator of cell destiny and effector function. J Biomed Sci. 2017 Jul 21;24(1):49. PMID: 28732506
144. Kallies et al. Terminal differentiation of lymphocytes depends on Blimp-1. Curr Opin Immunol. 2007 Apr;19(2):156-62. PMID: 17291741
145. Matsuoka et al. Linkage of ATM to cell cycle regulation by the Chk2 protein kinase. Science. 1998 Dec 4;282(5395):1893-7. PMID: 9836640

References (continued)

146. Cai et al. Structure and activation mechanism of the CHK2 DNA damage checkpoint kinase. Mol. Cell. 2009 Sep 24;35(6):818-29. PMID: 19782031
147. Zhang et al. Chk2 phosphorylation of BRCA1 regulates DNA double-strand break repair. Mol. Cell. Biol. 2004 Jan;24(2):708-18. PMID: 14701743
148. Huang et al. Chk1 and Chk2 are differentially involved in homologous recombination repair and cell cycle arrest in response to DNA double-strand breaks induced by camptothecins. Mol. Cancer Ther. 2008 Jun;7(6):1440-9. PMID: 18566216
149. Apostolou et al. Current perspectives on CHEK2 mutations in breast cancer. Breast Cancer (Dove Med Press). 2017;9:331-335. PMID: 28553140
150. Nevanlinna et al. The CHEK2 gene and inherited breast cancer susceptibility. Oncogene. 2006 Sep 25;25(43):5912-9. PMID: 16998506
151. Näslund-Koch et al. Increased Risk for Other Cancers in Addition to Breast Cancer for CHEK2*1100delC Heterozygotes Estimated From the Copenhagen General Population Study. J. Clin. Oncol. 2016 Apr 10;34(11):1208-16. PMID: 26884562
152. Cybulski et al. CHEK2 is a multiorgan cancer susceptibility gene. Am J Hum Genet. 2004 Dec;75(6):1131-5. PMID: 15492928
153. Li et al. Role of the LKB1/AMPK pathway in tumor invasion and metastasis of cancer cells (Review). Oncol. Rep. 2015 Dec;34(6):2821-6. PMID: 26398719
154. Gan et al. Lkb1 regulates quiescence and metabolic homeostasis of haematopoietic stem cells. Nature. 2010 Dec 2;468(7324):701-4. PMID: 21124456
155. Marinaccio et al. LKB1/ STK11 Is a Tumor Suppressor in the Progression of Myeloproliferative Neoplasms. Cancer Discov. 2021 Jun;11(6):1398-1410. PMID: 33579786
156. Zhou et al. LKB1 Tumor Suppressor: Therapeutic Opportunities Knock when LKB1 Is Inactivated. Genes Dis. 2014 Sep 1;1(1):64-74. PMID: 25679014
157. Hemminki et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature. 1998 Jan 8;391(6663):184-7. PMID: 9428765
158. 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
159. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
160. Sanchez-Cespedes et al. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. Cancer Res. 2002 Jul 1;62(13):3659-62. PMID: 12097271
161. De Braekeleer et al. ETV6 fusion genes in hematological malignancies: a review. Leuk. Res. 2012 Aug;36(8):945-61. PMID: 22578774
162. https://ir.tangotx.com//news-releases/news-release-details/tango-therapeutics-announces-first-patient-dosed-tng260-phase-12
163. Koyama et al. STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment. Cancer Res. 2016 Mar 1;76(5):999-1008. PMID: 26833127
164. Skoulidis et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. Cancer Discov. 2018 Jul;8(7):822-835. PMID: 29773717
165. Chidgey et al. Desmosomes: a role in cancer?. Br J Cancer. 2007 Jun 18;96(12):1783-7. PMID: 17519903
166. Dubash et al. Desmosomes. Curr Biol. 2011 Jul 26;21(14):R529-31. PMID: 21783027
167. Hardman et al. Desmosomal cadherin misexpression alters beta-catenin stability and epidermal differentiation. Mol Cell Biol. 2005 Feb;25(3):969-78. PMID: 15657425
168. Wang et al. Lower DSC1 expression is related to the poor differentiation and prognosis of head and neck squamous cell carcinoma (HNSCC). J Cancer Res Clin Oncol. 2016 Dec;142(12):2461-2468. PMID: 27601166
169. Oshiro et al. Epigenetic silencing of DSC3 is a common event in human breast cancer. Breast Cancer Res. 2005;7(5):R669-80. PMID: 16168112
170. Wong et al. Making heads or tails - the emergence of capicua (CIC) as an important multifunctional tumour suppressor. J Pathol. 2020 Apr;250(5):532-540. PMID: 32073140
171. Huang et al. Recurrent CIC Gene Abnormalities in Angiosarcomas: A Molecular Study of 120 Cases With Concurrent Investigation of PLCG1, KDR, MYC, and FLT4 Gene Alterations. Am J Surg Pathol. 2016 May;40(5):645-55. PMID: 26735859
172. NCCN Guidelines® - NCCN-Bone Cancer [Version 1.2026]
173. 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

References (continued)

174. 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
175. Yang et al. Prognostic Value of RNASEH2A-, CDK1-, and CD151-Related Pathway Gene Profiling for Kidney Cancers. Int J Mol Sci. 2018 May 28;19(6). PMID: 29843367
176. 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
177. 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
178. 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
179. Geiger et al. Role of the Nuclear Receptor Corepressor 1 (NCOR1) in Atherosclerosis and Associated Immunometabolic Diseases. Front Immunol. 2020;11:569358. PMID: 33117357
180. Martínez-Iglesias et al. Tumor suppressive actions of the nuclear receptor corepressor 1. Pharmacol Res. 2016 Jun;108:75-79. PMID: 27149915
181. Bhaskara et al. Hdac3 is essential for the maintenance of chromatin structure and genome stability. Cancer Cell. 2010 Nov 16;18(5):436-47. PMID: 21075309
182. Mottis et al. Emerging roles of the corepressors NCoR1 and SMRT in homeostasis. Genes Dev. 2013 Apr 15;27(8):819-35. PMID: 23630073
183. Noblejas-López et al. Evaluation of transcriptionally regulated genes identifies NCOR1 in hormone receptor negative breast tumors and lung adenocarcinomas as a potential tumor suppressor gene. PLoS One. 2018;13(11):e0207776. PMID: 30485330
184. Hevener et al. Recent developments in topoisomerase-targeted cancer chemotherapy. Acta Pharm Sin B. 2018 Oct;8(6):844-861. PMID: 30505655
185. Kim et al. The Top1 paradox: Friend and foe of the eukaryotic genome. DNA Repair (Amst.). 2017 Aug;56:33-41. PMID: 28641942
186. Thomas et al. Targeting Topoisomerase I in the Era of Precision Medicine. Clin. Cancer Res. 2019 Nov 15;25(22):6581-6589. PMID: 31227499
187. Kümler et al. Topoisomerase-1 gene copy aberrations are frequent in patients with breast cancer. Int. J. Cancer. 2015 Oct 15;137(8):2000-6. PMID: 25855483
188. Grunnet et al. TOP1 gene copy numbers are increased in cancers of the bile duct and pancreas. Scand. J. Gastroenterol. 2015 Apr;50(4):485-94. PMID: 25615400
189. Lee et al. Targeting of Topoisomerase I for Prognoses and Therapeutics of Camptothecin-Resistant Ovarian Cancer. PLoS ONE. 2015;10(7):e0132579. PMID: 26207989
190. Gongora et al. New Topoisomerase I mutations are associated with resistance to camptothecin. Mol. Cancer. 2011 May 27;10:64. PMID: 21619602
191. Arakawa et al. Three missense mutations of DNA topoisomerase I in highly camptothecin-resistant colon cancer cell sublines. Oncol. Rep. 2013 Sep;30(3):1053-8. PMID: 23836376
192. Rasheed et al. Mechanisms of resistance to topoisomerase I-targeting drugs. Oncogene. 2003 Oct 20;22(47):7296-304. PMID: 14576839
193. Ryan et al. Topoisomerase I amplification in melanoma is associated with more advanced tumours and poor prognosis. Pigment Cell Melanoma Res. 2010 Aug;23(4):542-53. PMID: 20465595
194. Rømer et al. Topoisomerase 1(TOP1) gene copy number in stage III colorectal cancer patients and its relation to prognosis. Mol Oncol. 2013 Feb;7(1):101-11. PMID: 23110915
195. Liu et al. DNA topoisomerase 1 and 2A function as oncogenes in liver cancer and may be direct targets of nitidine chloride. Int. J. Oncol. 2018 Nov;53(5):1897-1912. PMID: 30132517
196. Bai et al. Targeting of topoisomerases for prognosis and drug resistance in ovarian cancer. J Ovarian Res. 2016 Jun 18;9(1):35. PMID: 27315793
197. Binz et al. Replication Protein A phosphorylation and the cellular response to DNA damage. DNA Repair, 01 Aug 2004, 3(8-9):1015-1024. PMID: 15279788
198. Croft et al. Regulating the conversion between rounded and elongated modes of cancer cell movement. Cancer Cell. 2008 Nov 4;14(5):349-51. PMID: 18977323
199. Garrett et al. Reoperative median sternotomy. Ann Thorac Surg. 1989 Aug;48(2):305. PMID: 2764627
200. Héraud et al. Cells. 2019 Apr 12;8(4). PMID: 31013840

References (continued)

201. Zhao et al. Glucocorticoid receptor DNA binding factor 1 expression and osteosarcoma prognosis. Tumour Biol. 2014 Dec;35(12):12449-58. PMID: 25185653
202. Jonsson et al. Fresh gas flow in coaxial Mapleson A and D circuits during spontaneous breathing. Acta Anaesthesiol Scand. 1986 Oct;30(7):588-93. PMID: 3101384
203. Froimchuk et al. Histone H3 lysine 4 methyltransferase KMT2D. Gene. 2017 Sep 5;627:337-342. PMID: 28669924
204. Leng et al. Histone 3 lysine-27 demethylase KDM6A coordinates with KMT2B to play an oncogenic role in NSCLC by regulating H3K4me3. Oncogene. 2020 Oct;39(41):6468-6479. PMID: 32879445
205. Cargnello et al. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev. 2011 Mar;75(1):50-83. PMID: 21372320
206. 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
207. Bray. Notch signalling in context. Nat. Rev. Mol. Cell Biol. 2016 Nov;17(11):722-735. PMID: 27507209
208. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. Cell. 2009 Apr 17;137(2):216-33. PMID: 19379690
209. 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
210. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. Nat Rev Urol. 2018 Jun;15(6):345-357. PMID: 29643502
211. 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
212. 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
213. Jelinic et al. Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. Nat. Genet. 2014 May;46(5):424-6. PMID: 24658004
214. Hasselblatt et al. SMARCA4-mutated atypical teratoid/rhabdoid tumors are associated with inherited germline alterations and poor prognosis. Acta Neuropathol. 2014 Sep;128(3):453-6. PMID: 25060813
215. NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 3.2025]
216. Cheng et al. G protein pathway suppressor 2 (GPS2) is a transcriptional corepressor important for estrogen receptor alpha-mediated transcriptional regulation. J Biol Chem. 2009 Dec 25;284(52):36395-36404. PMID: 19858209
217. Si et al. G protein pathway suppressor 2 suppresses gastric cancer by destabilizing epidermal growth factor receptor. Cancer Sci. 2021 Dec;112(12):4867-4882. PMID: 34609770
218. Bien-Willner et al. Mutation and expression analysis in medulloblastoma yields prognostic variants and a putative mechanism of disease for i17q tumors. Acta Neuropathol Commun. 2014 Jul 17;2:74. PMID: 25030029
219. Huang et al. G protein pathway suppressor 2 (GPS2) acts as a tumor suppressor in liposarcoma. Tumour Biol. 2016 Oct;37(10):13333-13343. PMID: 27460081
220. Chan et al. Loss of G-Protein Pathway Suppressor 2 Promotes Tumor Growth Through Activation of AKT Signaling. Front Cell Dev Biol. 2020;8:608044. PMID: 33490071
221. O'Meara et al. Identification of an MLL4-GPS2 fusion as an oncogenic driver of undifferentiated spindle cell sarcoma in a child. Genes Chromosomes Cancer. 2014 Dec;53(12):991-8. PMID: 25139254
222. Dossin et al. SPEN integrates transcriptional and epigenetic control of X-inactivation. Nature. 2020 Feb;578(7795):455-460. PMID: 32025035
223. Li et al. SPEN induces miR-4652-3p to target HIPK2 in nasopharyngeal carcinoma. Cell Death Dis. 2020 Jul 2;11(7):509. PMID: 32641685
224. Radio et al. SPEN haploinsufficiency causes a neurodevelopmental disorder overlapping proximal 1p36 deletion syndrome with an episignature of X chromosomes in females. Am J Hum Genet. 2021 Mar 4;108(3):502-516. PMID: 33596411
225. Légaré et al. The Estrogen Receptor Cofactor SPEN Functions as a Tumor Suppressor and Candidate Biomarker of Drug Responsiveness in Hormone-Dependent Breast Cancers. Cancer Res. 2015 Oct 15;75(20):4351-63. PMID: 26297734
226. Légaré et al. SPEN, a new player in primary cilia formation and cell migration in breast cancer. Breast Cancer Res. 2017 Sep 6;19(1):104. PMID: 28877752
227. Croteau et al. RECQL4 in genomic instability and aging. Trends Genet. 2012 Dec;28(12):624-31. PMID: 22940096
228. Arora et al. RECQL4 helicase has oncogenic potential in sporadic breast cancers. J Pathol. 2016 Mar;238(4):495-501. PMID: 26690729

References (continued)

229. Chi et al. RecQL4 cytoplasmic localization: implications in mitochondrial DNA oxidative damage repair. Int J Biochem Cell Biol. 2012 Nov;44(11):1942-51. PMID: 22824301
230. Singh et al. The human RecQ helicases BLM and RECQL4 cooperate to preserve genome stability. Nucleic Acids Res. 2012 Aug;40(14):6632-48. PMID: 22544709
231. Guo et al. RECQL4, Negatively Regulated by miR-10a-5p, Facilitates Cell Proliferation and Invasion via MAFB in Ovarian Cancer. Front Oncol. 2020;10:524128. PMID: 33014878
232. Lu et al. RECQ DNA Helicases and Osteosarcoma. Adv Exp Med Biol. 2020;1258:37-54. PMID: 32767233
233. Balajee. Human RecQL4 as a Novel Molecular Target for Cancer Therapy. Cytogenet Genome Res. 2021;161(6-7):305-327. PMID: 34474412
234. Fang et al. RecQL4 helicase amplification is involved in human breast tumorigenesis. PLoS One. 2013;8(7):e69600. PMID: 23894508
235. Su et al. Human RecQL4 helicase plays critical roles in prostate carcinogenesis. Cancer Res. 2010 Nov 15;70(22):9207-17. PMID: 21045146
236. Chen et al. Overexpression of RECQL4 is associated with poor prognosis in patients with gastric cancer. Oncol Lett. 2018 Oct;16(4):5419-5425. PMID: 30250613
237. Baird et al. The Molecular Mechanisms Regulating the KEAP1-NRF2 Pathway. Mol Cell Biol. 2020 Jun 15;40(13). PMID: 32284348
238. Suzuki et al. Toward clinical application of the Keap1-Nrf2 pathway. Trends Pharmacol. Sci. 2013 Jun;34(6):340-6. PMID: 23664668
239. Ohta et al. Loss of Keap1 function activates Nrf2 and provides advantages for lung cancer cell growth. Cancer Res. 2008 Mar 1;68(5):1303-9. PMID: 18316592
240. Rojo de la Vega et al. NRF2 and the Hallmarks of Cancer. Cancer Cell. 2018 Jul 9;34(1):21-43. PMID: 29731393
241. 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
242. 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
243. Attar et al. Exploitation of EP300 and CREBBP Lysine Acetyltransferases by Cancer. Cold Spring Harb Perspect Med. 2017 Mar 1;7(3). PMID: 27881443
244. 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
245. Schorry et al. Genotype-phenotype correlations in Rubinstein-Taybi syndrome. Am. J. Med. Genet. A. 2008 Oct 1;146A(19):2512-9. PMID: 18792986
246. Pasqualucci et al. Inactivating mutations of acetyltransferase genes in B-cell lymphoma. Nature. 2011 Mar 10;471(7337):189-95. PMID: 21390126
247. Cicenas et al. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 Mutations in Pancreatic Cancer. Cancers (Basel). 2017 Apr 28;9(5). PMID: 28452926
248. Miyaki et al. Role of Smad4 (DPC4) inactivation in human cancer. Biochem. Biophys. Res. Commun. 2003 Jul 11;306(4):799-804. PMID: 12821112
249. Mehrvarz Sarshekeh et al. Association of SMAD4 mutation with patient demographics, tumor characteristics, and clinical outcomes in colorectal cancer. PLoS ONE. 2017;12(3):e0173345. PMID: 28267766
250. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
251. Yan et al. Reduced Expression of SMAD4 Is Associated with Poor Survival in Colon Cancer. Clin. Cancer Res. 2016 Jun 15;22(12):3037-47. PMID: 26861460
252. Voorneveld et al. A Meta-Analysis of SMAD4 Immunohistochemistry as a Prognostic Marker in Colorectal Cancer. Transl Oncol. 2015 Feb;8(1):18-24. PMID: 25749173
253. Shugang et al. Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis. Transl Oncol. 2016 Feb;9(1):1-7. PMID: 26947875
254. Boulay et al. SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer. Br. J. Cancer. 2002 Sep 9;87(6):630-4. PMID: 12237773
255. Kozak et al. Smad4 inactivation predicts for worse prognosis and response to fluorouracil-based treatment in colorectal cancer. J. Clin. Pathol. 2015 May;68(5):341-5. PMID: 25681512

References (continued)

256. Ozawa et al. SMAD4 Loss Is Associated with Cetuximab Resistance and Induction of MAPK/JNK Activation in Head and Neck Cancer Cells. Clin. Cancer Res. 2017 Sep 1;23(17):5162-5175. PMID: 28522603
257. Nag et al. The MDM2-p53 pathway revisited. J Biomed Res. 2013 Jul;27(4):254-71. PMID: 23885265
258. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012
259. 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
260. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
261. Peter S et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
262. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
263. 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
264. 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
265. 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
266. 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
267. 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
268. 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
269. 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
270. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165
271. 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
272. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2026]
273. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]
274. 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