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

Patient Name: 이수열
Gender: M
Sample ID: N25-173

Primary Tumor Site: unknown
Collection Date: 2025.03.25

Sample Cancer Type: Melanoma

Table of Contents	Page
Variant Details	4
Biomarker Descriptions	8
Alert Details	38
Relevant Therapy Summary	40

Report Highlights
23 Relevant Biomarkers
25 Therapies Available
51 Clinical Trials

Relevant Melanoma Findings

Gene	Finding	Gene	Finding
BRAF	***BRAF p.(V600E) c.1799T>A***	NTRK2	None detected
KIT	None detected	NTRK3	None detected
NRAS	None detected	RET	None detected
NTRK1	None detected	ROS1	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***6.68 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*BRAF p.(V600E) c.1799T>A* B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 55.84% Locus: chr7:140453136 Transcript: NM_004333.6	**binimetinib + encorafenib** [1, 2 / I, II+] **cobimetinib + vemurafenib** [1, 2 / I, II+] **dabrafenib** [1, 2 / I, II+] **dabrafenib + trametinib** [1, 2 / I, II+] **vemurafenib** [1, 2 / I, II+] **atezolizumab + cobimetinib + vemurafenib** [1 / II+] **trametinib** [1, 2] encorafenib [I, II+] ipilimumab + nivolumab [I, II+] anti-PD-1 [II+] dabrafenib + pembrolizumab + trametinib [II+] ipilimumab [II+] nivolumab [II+] nivolumab + relatlimab [II+] pembrolizumab [II+]	**binimetinib + encorafenib** [1, 2 / I, II+] **cetuximab + encorafenib** [1, 2 / I, II+] **cetuximab + encorafenib + chemotherapy** [1 / I, II+] **dabrafenib + trametinib** [1, 2 / I, II+] encorafenib + panitumumab [I, II+] encorafenib + panitumumab + chemotherapy [I, II+] bevacizumab + chemotherapy [I] dabrafenib [I] vemurafenib [I] cobimetinib + vemurafenib [II+] dabrafenib + MEK inhibitor selumetinib	28

*** 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	*SMARCB1 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 Locus: chr22:24129273	None*	cabozantinib pazopanib sunitinib	4
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	9
IIC	*CDK4 amplification* cyclin dependent kinase 4 Locus: chr12:58142242	None*	None*	5
IIC	*BRCA1 deletion* BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	3
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	*BAP1 deletion* BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	2
IIC	*BARD1 deletion* BRCA1 associated RING domain 1 Locus: chr2:215593375	None*	None*	2
IIC	*BRIP1 deletion* BRCA1 interacting protein C-terminal helicase 1 Locus: chr17:59760627	None*	None*	2
IIC	*CHEK2 deletion* checkpoint kinase 2 Locus: chr22:29083868	None*	None*	2
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	2
IIC	*RAD50 deletion* RAD50 double strand break repair protein Locus: chr5:131892978	None*	None*	2
IIC	*ARID1B deletion* AT-rich interaction domain 1B Locus: chr6:157099057	None*	None*	1
IIC	*ARID2 deletion* AT-rich interaction domain 2 Locus: chr12:46123536	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	*CDK12 deletion* cyclin dependent kinase 12 Locus: chr17:37618286	None*	None*	1
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
IIC	*ERBB3 amplification* erb-b2 receptor tyrosine kinase 3 Locus: chr12:56477596	None*	None*	1
IIC	*FANCD2 deletion* Fanconi anemia complementation group D2 Locus: chr3:10070306	None*	None*	1
IIC	*FANCG deletion* Fanconi anemia complementation group G Locus: chr9:35074046	None*	None*	1
IIC	*FANCL deletion* Fanconi anemia complementation group L Locus: chr2:58386886	None*	None*	1
IIC	*LATS1 deletion* large tumor suppressor kinase 1 Locus: chr6:149982844	None*	None*	1
IIC	*RAD51C deletion* RAD51 paralog C Locus: chr17:56769933	None*	None*	1
IIC	*RAD51D deletion* RAD51 paralog D Locus: chr17:33427950	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

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

BRAF p.(V600E) c.1799T>A	**plixorafenib** [1]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

APC deletion, AXIN2 deletion, FANCC deletion, MLH1 deletion, MLH3 deletion, MSH3 deletion, Microsatellite stable, NF1 deletion, PARP3 deletion, PIK3R1 deletion, POLE deletion, RAD51B deletion, SDHB deletion, SETD2 deletion, TCF7L2 deletion, XRCC2 deletion, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, PGD deletion, SPEN deletion, EPHA2 deletion, FUBP1 deletion, DPYD deletion, UGT1A1 p.(G71R) c.211G>A, VHL deletion, TGFBR2 deletion, DOCK3 deletion, PBRM1 deletion, INPP4B deletion, FAT1 deletion, SDHA deletion, CDH10 deletion, ADAMTS12 deletion, MAP3K1 deletion, RASA1 deletion, ERAP1 deletion, ADAMTS2 deletion, TPMT p.(Y240C) c.719A>G, HLA-B deletion, PRDM1 deletion, HDAC2 deletion, TNFAIP3 deletion, MAP3K4 deletion, POT1 deletion, EZH2 deletion, KMT2C deletion, JAK2 deletion, PTCH1 deletion, PPP6C deletion, LARP4B deletion, GATA3 deletion, MAPK8 deletion, ARID5B deletion, CYP2C9 deletion, SUFU deletion, KMT2D deletion, ACVR1B deletion, STAT6 amplification, CBFB deletion, NQO1 p.(P187S) c.559C>T, SPOP deletion, RNF43 deletion, PPM1D deletion, PRKAR1A deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRAF	p.(V600E)	c.1799T>A	COSM476	chr7:140453136	55.84%	NM_004333.6	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	60.31%	NM_000463.3	missense
TPMT	p.(Y240C)	c.719A>G	COSM4986703	chr6:18130918	50.36%	NM_000367.5	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	39.02%	NM_000903.3	missense
FAM178B	p.(D72E)	c.216C>A	.	chr2:97637986	59.52%	NM_001122646.3	missense
CTNNB1	p.(S60F)	c.179C>T	.	chr3:41266182	21.34%	NM_001904.4	missense
PARP9	p.(L505P)	c.1514T>C	.	chr3:122259570	3.56%	NM_001146103.2	missense
C6	p.(A2D)	c.5C>A	.	chr5:41203328	55.52%	NM_000065.5	missense
APC	p.(R399G)	c.1195A>G	.	chr5:112154924	5.20%	NM_000038.6	missense
RAD50	p.(S738R)	c.2214C>A	.	chr5:131938998	76.83%	NM_005732.4	missense
MLN	p.([V15A;A16T])	c.44_46delTAGinsCAA	.	chr6:33768895	2.90%	NM_002418.3	missense, missense
CCND3	p.(E224K)	c.670G>A	.	chr6:41904338	50.73%	NM_001760.5	missense
OR4C15	p.(I247V)	c.739A>G	.	chr11:55322683	4.75%	NM_001001920.2	missense
KMT2A	p.(H581D)	c.1741C>G	.	chr11:118343615	4.00%	NM_001197104.2	missense
DIS3	p.(N603Y)	c.1807A>T	.	chr13:73342999	35.54%	NM_014953.5	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
SMARCB1	chr22:24129273	1.05	0.64
MTAP	chr9:21802646	0.58	0.46
CDK4	chr12:58142242	9.3	3.81
BRCA1	chr17:41197602	1	0.67
CDKN2A	chr9:21968178	0.27	0.33
BAP1	chr3:52436290	0.99	0.61
BARD1	chr2:215593375	1	0.86
BRIP1	chr17:59760627	1	0.7
CHEK2	chr22:29083868	1	0.67
NF2	chr22:29999923	1.04	0.63
RAD50	chr5:131892978	1.06	0.64
ARID1B	chr6:157099057	0.88	0.57
ARID2	chr12:46123536	1.14	0.67
CDK12	chr17:37618286	1	0.59
CDKN2B	chr9:22005728	0.52	0.43

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
ERBB3	chr12:56477596	5.29	2.27
FANCD2	chr3:10070306	1.16	0.67
FANCG	chr9:35074046	0.96	0.6
FANCL	chr2:58386886	1	0.84
LATS1	chr6:149982844	1.09	0.65
RAD51C	chr17:56769933	1	0.71
RAD51D	chr17:33427950	1	0.59
APC	chr5:112043374	1.13	0.67
AXIN2	chr17:63526027	1.05	0.63
FANCC	chr9:97863909	1.1	0.65
MLH1	chr3:37034957	1.04	0.63
MLH3	chr14:75483761	1.17	0.68
MSH3	chr5:79950540	1.12	0.66
NF1	chr17:29422233	1.08	0.64
PARP3	chr3:51976651	0.83	0.55
PIK3R1	chr5:67522468	0.88	0.57
POLE	chr12:133201214	0.94	0.59
RAD51B	chr14:68290164	1	0.65
SDHB	chr1:17345303	1.1	0.66
SETD2	chr3:47058542	1.06	0.64
TCF7L2	chr10:114710485	0.91	0.58
XRCC2	chr7:152345702	1.04	0.63
TNFRSF14	chr1:2488070	0.99	0.61
ERRFI1	chr1:8073246	1.05	0.63
ENO1	chr1:8921399	1.08	0.64
PGD	chr1:10459132	0.96	0.6
SPEN	chr1:16174516	0.96	0.6
EPHA2	chr1:16451707	1.03	0.62
FUBP1	chr1:78414385	1.01	0.62
DPYD	chr1:97544504	1.14	0.67
VHL	chr3:10183418	1.05	0.63
TGFBR2	chr3:30648337	1.06	0.64
DOCK3	chr3:51101879	0.87	0.57
PBRM1	chr3:52582040	1.12	0.66

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
INPP4B	chr4:142949914	1.21	0.69
FAT1	chr4:187509708	1.19	0.69
SDHA	chr5:218412	0.87	0.57
CDH10	chr5:24487706	1.04	0.63
ADAMTS12	chr5:33527235	0.94	0.59
MAP3K1	chr5:56111388	1.09	0.65
RASA1	chr5:86564256	1.1	0.65
ERAP1	chr5:96112128	1.03	0.62
ADAMTS2	chr5:178549645	0.94	0.59
HLA-B	chr6:31322252	1.21	0.7
PRDM1	chr6:106534408	0.88	0.57
HDAC2	chr6:114262171	0.91	0.58
TNFAIP3	chr6:138192315	1.03	0.63
MAP3K4	chr6:161412931	1.06	0.64
POT1	chr7:124464001	1.03	0.63
EZH2	chr7:148506391	0.99	0.61
KMT2C	chr7:151833866	0.96	0.6
JAK2	chr9:5021954	0.71	0.5
PTCH1	chr9:98209140	0.94	0.59
PPP6C	chr9:127911878	1.03	0.63
LARP4B	chr10:858847	1.04	0.63
GATA3	chr10:8097519	0.84	0.56
MAPK8	chr10:49609682	1	0.61
ARID5B	chr10:63661463	0.83	0.55
CYP2C9	chr10:96698378	0.81	0.54
SUFU	chr10:104263903	0.97	0.61
KMT2D	chr12:49415529	0.83	0.55
ACVR1B	chr12:52345528	0.84	0.56
STAT6	chr12:57490294	7.18	2.99
CBFB	chr16:67063242	1.17	0.68
SPOP	chr17:47677716	1.06	0.64
RNF43	chr17:56432226	0.92	0.59
PPM1D	chr17:58677747	1.12	0.66
PRKAR1A	chr17:66511464	1.1	0.65

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
RAF1	chr3:12625930	1.06	0.64
MYD88	chr3:38180156	0.99	0.61
GATA2	chr3:128200046	0.83	0.55
TERT	chr5:1253783	0.92	0.59
CTNND2	chr5:10988230	0.91	0.58
PRDM9	chr5:23509577	0.68	0.49
IL7R	chr5:35857035	1.17	0.68
PDGFRB	chr5:149497160	0.84	0.56
FGFR4	chr5:176517731	0.99	0.61
FLT4	chr5:180030092	1.06	0.64
FYN	chr6:111982890	0.96	0.6
ROS1	chr6:117622071	1.14	0.67
ESR1	chr6:152163831	0.73	0.51
ABCB1	chr7:87145849	0.86	0.56
CDK6	chr7:92244380	0.9	0.57
MET	chr7:116339789	1.21	0.69
SMO	chr7:128845103	0.99	0.61
BRAF	chr7:140434479	1.17	0.68
RHEB	chr7:151164183	1.14	0.67
FGFR1	chr8:38271452	0.92	0.58
IKBKB	chr8:42129602	0.99	0.61
CD274	chr9:5456050	0.56	0.44
PDCD1LG2	chr9:5522530	0.75	0.52
NTRK2	chr9:87549097	0.91	0.58
ABL1	chr9:133738250	0.96	0.6
RET	chr10:43609070	0.94	0.59
FGFR2	chr10:123239426	1.05	0.63
HRAS	chr11:532637	1	0.62
TBX3	chr12:115109599	4.57	1.99
MAX	chr14:65472833	1.01	0.62
ERBB2	chr17:37863255	0.95	0.6
RARA	chr17:38487425	0.96	0.6
STAT5B	chr17:40354722	0.86	0.56
STAT3	chr17:40467740	0.88	0.57

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
RPS6KB1	chr17:57970507	1.05	0.64
GNA13	chr17:63010302	1.06	0.64
SOX9	chr17:70117435	0.97	0.6
H3-3B	chr17:73772413	1	0.62
RPTOR	chr17:78519448	1.08	0.64
ZNF217	chr20:52188253	0.55	0.44

Biomarker Descriptions

BRAF p.(V600E) c.1799T>A

B-Raf proto-oncogene, serine/threonine kinase

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1(CRAF)[347]. BRAF is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival[348,349]. BRAF mutations are categorized into three distinct functional classes, namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway[350]. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF[350]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[350,351,352].

Alterations and prevalence: Somatic mutations in BRAF are observed in 59% of thyroid carcinoma, 53% of skin cutaneous melanoma, 12% of colorectal adenocarcinoma, 8% of lung adenocarcinoma, 5% of uterine corpus endometrial carcinoma, and 2-3% of bladder urothelial carcinoma, lung squamous cell carcinoma, stomach adenocarcinoma, cholangiocarcinoma, diffuse large B-cell lymphoma, glioblastoma multiforme, uterine carcinosarcoma, and head and neck squamous cell carcinoma[4,5]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[351,353]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R, G464V/E, and BRAF fusions[351]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[351]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancers, and prevalent in histiocytic neoplasms[354,355,356]. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11, as well as additional codons flanking V600 in the activation loop[353]. BRAF amplification is observed in 8% of ovarian serous cystadenocarcinoma, 4% of skin cutaneous melanoma, and 2% of sarcoma, uterine carcinosarcoma, and glioblastoma multiforme[4,5]. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[357,358,359,360,361]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain, leading to constitutive kinase activation[352,357,359]. Alterations in BRAF are rare in pediatric cancers, with the most predominant being the V600E mutation and the BRAF::KIAA1549 fusion, both of which are observed in low-grade gliomas[362]. Somatic mutations are observed in 6% of glioma and less than 1% of bone cancer (2 in 327 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[4,5]. Amplification of BRAF is observed in 1% or less of Wilms tumor (2 in 136 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[4,5].

Potential relevance: Vemurafenib[363] (2011) is the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation, and it is also approved for BRAF V600E-positive Erdheim-Chester Disease (2017). BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[351]. BRAF kinase inhibitors including dabrafenib[364] (2013) and encorafenib[365] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[365] is approved in combination with cetuximab[366] (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations[351]. The MEK inhibitors, trametinib[367] (2013) and binimetinib[368] (2018), were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC[369]. The combinations of dabrafenib/trametinib[367](2015) and vemurafenib/cobimetinib[370] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017), children with low-grade gliomas, and children and adults with solid tumors (2022) harboring a BRAF V600E mutation[364]. The PD-L1 antibody, atezolizumab[371], has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. The FDA has granted fast track designation (2023) to ABM-1310[372] for BRAF V600E-mutated

Biomarker Descriptions (continued)

glioblastoma (GBM) patients. In 2018, binimetinib[373] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib[374] was granted fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787[375], for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. The FDA also granted fast track designation (2023) to the BRAF inhibitor, plixorafenib (PLX-8394)[376], for BRAF Class I (V600) and Class II (including fusions) altered cancer patients who have already undergone previous treatments. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[377]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification, alternative splice transcripts, as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[378,379,380,381,382,383,384]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[361].

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[109]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[109,116]. 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[117]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[118,119].

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[116]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[117]. Somatic mutations in SMARCB1 are observed in 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and kidney chromophobe[4,5]. Alterations in SMARCB1 are also observed in pediatric cancers[4,5]. 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)[4,5]. Biallelic deletion of SMARCB1 is observed in 22% of embryonal tumors and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[4,5].

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[120,121].

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[324,325]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[325].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[325,326]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[4,5]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[4,5].

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

CDK4 amplification

cyclin dependent kinase 4

Background: The CDK4 gene encodes the cyclin-dependent kinase 4 protein, a homologue of CDK6. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle[276,277]. CDK4 kinase is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma

Biomarker Descriptions (continued)

protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression[278]. Germline mutations in CDK4 are associated with familial melanoma[279,280,281].

Alterations and prevalence: Recurrent somatic mutations of CDK4 codon K22 and R24 are observed in melanoma (1-2%) and lung cancer (approximately 0.1%). Codons K22 and R24 are necessary for binding and inhibition by p16/CDKN2A[282,283,284]. CDK4 is recurrently amplified in several cancer types, most notably in sarcomas (15-20%), glioma (10-15%), adrenocortical carcinoma (5%), lung adenocarcinoma (5%), and melanoma (3%)[4,5,285,286].

Potential relevance: Currently, no therapies are approved for CDK4 aberrations. Amplification of region 12q14-15, which includes CDK4, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/welldifferentiated liposarcoma (ALT/WDLS)[121]. Small molecule inhibitors targeting CDK4/6 including palbociclib (2015), abemaciclib (2017), and ribociclib (2017), are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

BRCA1 deletion

BRCA1, DNA repair associated

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[58,59]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[58,59]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[60,61,62]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[60,63].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[64,65,66,67,68,69,70,71]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[4,5].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[72]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[73,74]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[40] (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[40] 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[75] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[76] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[76] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[77] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[78] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[79]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[80]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348[81], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

Biomarker Descriptions (continued)

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[220]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[221,222,223]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[224]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[1,224,225]. CDKN2A aberrations commonly co-occur with CDKN2B[220]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[226]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[227,228].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[229]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[4,5]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[4,5]. Alterations in CDKN2A are also observed in pediatric cancers[5]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[5]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[5].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[121,230,231]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[232]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[233,234,235]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[236]. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[237,238,239,240].

BAP1 deletion

BRCA1 associated protein 1

Background: The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes[1]. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation[255]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[255]. Germline mutations in BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma[256,257,258,259,260,261].

Alterations and prevalence: Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma[4,5]. BAP1 biallelic deletions are observed in 11% of mesothelioma[4,5].

Potential relevance: Currently, no therapies are approved for BAP1 aberrations.

BARD1 deletion

BRCA1 associated RING domain 1

Background: The BARD1 gene encodes the BRCA1 associated RING domain 1 protein which binds to BRCA1 and contributes to the in vitro E3 ligase activity that is required for the tumor suppressor function of the BRCA1 gene[1,161]. The cysteine-rich N-terminal RING finger domains of BARD1 and BRCA1 heterodimerize to regulate a diverse range of cellular pathways, such as ubiquitination, transcriptional regulation, and homologous recombination repair (HRR) of double-stranded DNA damage[1,161,162,163]. Mutual stability between BARD1 and BRCA1 is essential in maintaining HRR functionality. Genetic alterations in either BARD1 or BRCA1 can disrupt

Biomarker Descriptions (continued)

the BARD1/BRCA1 interaction[1,162,164,165]. BARD1 is a tumor suppressor and loss of function (LOF) mutations are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[165,166]. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility[164]. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53[167]. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer[167,168].

Alterations and prevalence: Somatic mutations in BARD1 are found in 5% of uterine cancer, 3% of stomach cancer as well as melanoma, and 2% of bladder cancer as well as lung adenocarcinoma[4,5]. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[40] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BARD1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

BRIP1 deletion

BRCA1 interacting protein C-terminal helicase 1

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA[155]. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control[156]. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[36,150]. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)[157]. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer[157,158]. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer[155,159].

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

Potential relevance: The PARP inhibitor, olaparib[40] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy[150,160]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[391]. 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)[392,393,394]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[395,396,397].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations. Somatic mutations in CHEK2 are common (2-6%) in uterine carcinoma, bladder carcinoma, and lung adenocarcinoma[4,5]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[40] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib[76] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

NF2 deletion

neurofibromin 2

Background: The NF2 gene encodes the cytoskeletal Merlin (Moesin-ezrin-radixin-like) protein. NF2 is also known as Schwannomin due to its prevalence in neuronal Schwann cells. NF2 is structurally and functionally related to the Ezrin, Radixin, Moesin (ERM) family

Biomarker Descriptions (continued)

which is known to control plasma membrane function, thereby influencing cell shape, adhesion, and growth[169,170,171]. 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[169,170,171,172]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[170,171,173]. 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[170,171,173].

Alterations and prevalence: Somatic mutations in NF2 are predominantly misssense or truncating and are observed in about 23% of mesothelioma, 5% of cholangiocarcinoma and uterine cancer, and about 3% of papillary renal cell carcinoma (pRCC), bladder, and cervical cancers[4]. Biallelic loss of NF2 is also observed in approximately 8% of mesothelioma cases[4].

Potential relevance: Currently, no therapies are approved for NF2 aberrations. However, the FDA granted Fast Track designation (2022) to the novel TEAD inhibitor, IK-930, for unresectable NF2-deficient malignant pleural mesothelioma (MPM)[174].

RAD50 deletion

RAD50 double strand break repair protein

Background: The RAD50 gene encodes the RAD50 double-strand break repair protein and belongs to the adenosine triphosphate (ATP) binding cassette (ABC) transporter family of ATPases[430,431]. RAD50 is an important structural maintenance of chromosome (SMC) protein and mutations in this gene are associated with genomic instability[431,432]. RAD50 is a tumor suppressor gene and part of the multisubunit MRE11/RAD50/NBN (MRN) complex[432,433]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[432,433]. RAD50 contains long coiled-coil regions that link the ATPase domain, as well as a zinc hook domain that interacts with MRE11 and bridges DNA ends together during the DNA damage response[432,434]. RAD50 is a tumor suppressor gene. Loss of function mutations in RAD50 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[36,150]. The presence of germline mutations in RAD50 is associated with unfavorable recurrence free-survival in BRCA1/2 negative breast cancer patients, although there is no association with increased risk of breast cancer[435].

Alterations and prevalence: Somatic mutations in RAD50 are observed in up to 8% of uterine cancer, 5% of melanoma, and 4% of colorectal cancer[4,5]. Lack of MRN complex proteins are observed in 41% (55/134) of epithelial ovarian cancer patients[436].

Potential relevance: Currently, no therapies are approved for RAD50 aberrations. RAD50 expression is a predictor of clinical outcomes in patients who receive postoperative radiotherapy[437]. Specifically, tissue microarray (TMA) analysis of tumors from 127 NSCLC patients demonstrated that patients with low RAD50 expression had better clinical outcomes including overall survival (OS), distant-metastasis free survival (DMFS), disease-free survival (DFS), and local-regional recurrence-free survival (LRRFS) in comparison to patients with high RAD50 expression[437]. Another study identified RAD50 copy number deletion as a candidate marker for survival and response to PARP inhibitors in BRCA wild-type ovarian cancer with the BRCAness phenotype[438].

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein[1]. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A[1,470]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[109,470].The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[109]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[109,116]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[470].

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[116]. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ARID1B aberrations. Mutations in chromatin modifying genes, including ARID1B, are considered to be characteristic genetic features of hepatosplenic T-cell lymphoma (HSTL), as they have been observed in up to 62% of cases[452,471].

Biomarker Descriptions (continued)

ARID2 deletion

AT-rich interaction domain 2

Background: The ARID2 gene encodes the AT-rich interaction domain 2 protein[1]. ARID2, also known as BAF200, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID5B[124]. ARID2 is an essential member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[110,124]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[109,110]. ARID2 may alter the expression of IFN responsive genes, which suppress cell proliferation[124]. Loss of function mutations in ARID2 may promote cell proliferation, suggesting a tumor suppressor role of ARID2[124].

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[116]. Somatic mutations in ARID2 are observed in 17% of skin cutaneous melanoma, 11% of uterine corpus endometrial carcinoma, 8% of bladder urothelial carcinoma and stomach adenocarcinoma, 7% of colorectal adenocarcinoma, and 5% of liver hepatocellular carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma[4,5]. ARID2 biallelic deletions are observed in 2% of mesothelioma[4,5].

Potential relevance: Currently, no therapies are approved for ARID2 aberrations.

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[251,252,253]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[36,251,252,253,254]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[36,253]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[254]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[254].

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma[1,4]. CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma[1,4].

Potential relevance: The PARP inhibitor, olaparib[40] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib[76] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP inhibitors[36,254]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression[1,220]. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[220]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[221,222,223]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[220]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,245,246].

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous cell carcinoma, 25% of diffuse large B -cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[4,5]. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma[4,5]. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14%

Biomarker Descriptions (continued)

of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers[4,5]. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)[4,5].

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma[232].

ERBB3 amplification

erb-b2 receptor tyrosine kinase 3

Background: The ERBB3 gene encodes the erb-b2 receptor tyrosine kinase 3, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB3/HER3, EGFR/ERBB1/HER1, ERBB2/HER2, and ERBB4/HER4 make up the HER protein family[290]. ERBB3/HER3 binds to extracellular factors, such as neuregulins, but has an impaired kinase domain[291]. Upon ligand binding, ERBB3 forms hetero-dimers with other ERBB/HER family members, including ERBB2/HER2 resulting in activation of tyrosine kinase activity primarily through its dimerization partner.

Alterations and prevalence: ERBB3 gene amplification leading to an increase in expression occurs at low frequency (1-5%) in several cancer types including bladder, esophagus, lung adenocarcinoma, ovarian, pancreas, sarcoma, stomach, and uterine cancers[4,5,202,285,292,293,294]. ERBB3 is also the target of relatively frequent (5-10%) and recurrent somatic mutations in diverse cancer types including bladder, cervical, colorectal, and stomach cancers[4,5,202,292,295]. Recurrent ERBB3 mutations such as V104L/M, occur primarily in the extracellular domain.

Potential relevance: Currently, no therapies are approved for ERBB3 aberrations. Overexpression and activation of ERBB3/HER3 is one mechanism of acquired resistance to therapies targeting EGFR and ERBB2/HER2[296,297]. Preclinical and translational research studies have characterized the oncogenic potential of recurrent ERBB3 mutations and their sensitivity to anti-ERBB antibodies and small molecule inhibitors[298,299,300,301]. A phase I study exhibited progression-free survival (PFS) of 2.5 months and overall survival (OS) of 9 months in 25 patients with ERBB3 mutations treated by anti-ERBB antibodies or molecular-targeted agents[302].

FANCD2 deletion

Fanconi anemia complementation group D2

Background: The FANCD2 gene encodes the FA complementation group D2 protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), 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[32,33]. 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[32]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[34,35]. Loss of function mutations in the FA family and HRR pathway, including FANCD2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[36,37]. 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[38,39].

Alterations and prevalence: Somatic mutations in FANCD2 are observed in 4-8% of diffuse large B-cell lymphoma (DLBCL), melanoma, bladder, and uterine cancer[4].

Potential relevance: Currently, no therapies are approved for FANCD2 aberrations. Consistent with other genes that contribute to the BRCAness phenotype, FANCD2 deficiency or loss of function has been shown to confer enhanced sensitivity to PARP inhibitors in vitro[82,83,84].

FANCG deletion

Fanconi anemia complementation group G

Background: The FANCG gene encodes the FA complementation group G protein, a member of Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[32,33]. 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[32]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[34,35]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1

Biomarker Descriptions (continued)

or BRCA2 loss[36,37]. 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[38,39].

Alterations and prevalence: Somatic mutations in FANCG are observed in 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma[4,5].

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

FANCL deletion

Fanconi anemia complementation group L

Background: The FANCL gene encodes the FA complementation group L protein, a member of Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), 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[32,33]. 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[32]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[34,35]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[36,37]. 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[38,39].

Alterations and prevalence: Somatic mutations in FANCL are observed in 2% of diffuse large B-cell lymphoma (DLBCL), uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma, and 1% of skin cutaneous melanoma, uveal melanoma, lung squamous cell carcinoma, bladder urothelial carcinoma and stomach adenocarcinoma[4,5].

Potential relevance: The PARP inhibitor, olaparib[40] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes, including FANCL. Inhibitors targeting PARP induce synthetic lethality in HRR deficient cells[41]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

LATS1 deletion

large tumor suppressor kinase 1

Background: The LATS1 gene encodes the large tumor suppressor kinase 1[1]. LATS1 is a serine/threonine protein kinase and, along with LATS2, is a member of the AGC kinase family comprised of more than 60 members[320,321]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[322]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[322]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[323].

Alterations and prevalence: Somatic mutations in LATS1 are observed in 9% of uterine corpus endometrial carcinoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, and skin cutaneous melanoma, and 3% of stomach adenocarcinoma and lung adenocarcinoma[4,5]. Biallelic deletion of LATS1 is observed in 8% of uveal melanoma, 6% of diffuse large B-cell lymphoma, and 2% liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and thymoma[4,5].

Potential relevance: Currently, no therapies are approved for LATS1 aberrations.

RAD51C deletion

RAD51 paralog C

Background: The RAD51C gene encodes the RAD51 paralog C protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs[144]. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)[145]. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)[146]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing[147]. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity[148,149]. RAD51C is a

Biomarker Descriptions (continued)

tumor suppressor gene and loss of function mutations in RAD51C are implicated in the BRCAness phenotype, characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[36,150].

Alterations and prevalence: Somatic mutations in RAD51C are observed in 1-3% of adrenocortical carcinoma, melanoma, squamous lung, bladder, and uterine cancers[4].

Potential relevance: The PARP inhibitor, olaparib[40] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51C. Additionally, talazoparib[76] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes RAD51C. In one study, RAD51C underexpression was observed in olaparib-sensitive gastric cancer cell lines, and olaparib treatment sensitized cells to irradiation[151]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD51D deletion

RAD51 paralog D

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[145]. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[146]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[147]. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[36,150]. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer[152].

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer[4].

Potential relevance: The PARP inhibitor, olaparib[40] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors[150]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

APC deletion

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[197]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[198,199]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[197,200]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[201].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[4,5,202]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[203,204].

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

AXIN2 deletion

axin 2

Background: The AXIN2 gene encodes the axis inhibition protein 2, a cytoplasmic protein that contains a regulation of G-protein signaling (RGS) domain and a disheveled and axin (DIX) domain, which are responsible for a variety of protein-protein interactions and signaling regulation[1,175,176,177]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[178,179]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[179]. AXIN2 has been observed to be involved the regulation of the cell cycle through its involvement in WNT signaling and has been suggested to promote mitochondrial-associated apoptosis[180,181]. Loss of AXIN2 expression has been observed to contribute to the development of gastric cancer[182].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations of AXIN2 are observed in 7% of uterine corpus endometrial carcinoma, 5% of colorectal adenocarcinoma, 4% of bladder urothelial carcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma and skin cutaneous melanoma[4,5]. Biallelic deletion of AXIN2 is observed in 4% of diffuse large B-cell lymphoma[4,5].

Potential relevance: Currently, no therapies are approved for AXIN2 aberrations.

FANCC deletion

Fanconi anemia complementation group C

Background: The FANCC gene encodes the FA complementation group C protein, a member of the Fanconi anemia (FA) family, which also includes FANCA, FANCB, 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[32,33]. 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[32]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[34,35]. Loss of function mutations in the FA family and HRR pathway, including FANCC, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[36,37]. 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[38,39].

Alterations and prevalence: Somatic mutations in FANCC are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, 2% of colorectal adenocarcinoma, stomach adenocarcinoma and uterine carcinosarcoma, and 1% of bladder urothelial carcinoma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for FANCC aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCC are shown to confer enhanced sensitivity in vitro to PARP inhibitors such as olaparib[82].

MLH1 deletion

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[50]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[50,125]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[126,127]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[50]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[50]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[128]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[129,130,131]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[129,132]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[130,132,133,134]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[135,136,137,138].

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma[4,5]. Alterations in MLH1 are observed in pediatric cancers[4,5]. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)[4,5].

Potential relevance: The PARP inhibitor, talazoparib[76] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[139]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[140,141]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[142,143].

MLH3 deletion

mutL homolog 3

Background: The MLH3 gene encodes the mutL homolog 3 protein[1]. MLH3 heterodimerizes with MLH1 to form the MutLγ complex which functions as an endonuclease during meiosis, specifically in meiotic recombination[50]. MLH3 is considered a mismatch repair

Biomarker Descriptions (continued)

(MMR) gene due to its functional role in yeast, however, its exact MMR role in humans is less clear[50,51,52]. Low expression of MMR genes, including MLH3, have been associated with high levels of microsatellite instability (MSI-H) in colorectal cancer[53].

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

Potential relevance: Currently, no therapies are approved for MLH3 aberrations.

MSH3 deletion

mutS homolog 3

Background: The MSH3 gene encodes the mutS homolog 3 protein[1]. MSH3 heterodimerizes with MSH2 to form the MutSβ complex, an ATPase which functions in mismatch repair (MMR) by recognizing mismatches and initiating repair[50,54]. MSH3 is capable of interacting with proliferating cellular nuclear antigen (PCNA), which may facilitate MutSβ localization to DNA mispairs[50,54]. Mutations in MSH3 have been observed to be associated with microsatellite instability (MSI) in colon cancer[55].

Alterations and prevalence: Somatic mutations in MSH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma, and 3% of skin cutaneous melanoma[4,5]. Biallelic deletion of MSH3 are observed in 3% of ovarian serous cystadenocarcinoma and 2% of prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MSH3 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[183]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[130,132]. 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[131]. 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[184]. 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)[184]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[133,185,186,187,188]. 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[132]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[130,132,133,134].

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[130,132,189,190]. 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[189,190].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[139] (2014) and nivolumab[140] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[139] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[139]. Dostarlimab[191] (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[186,192]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[141] (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[186,193,194]. 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[194]. 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[195,196]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[195,196].

Biomarker Descriptions (continued)

NF1 deletion

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[315]. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state[315,316]. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival[315]. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)[96,315,317].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[315]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[315,318]. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)[96,315].

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)[121].

PARP3 deletion

poly(ADP-ribose) polymerase family member 3

Background: The PARP3 gene encodes the poly(ADP-ribose) polymerase 3 protein[1]. PARP3 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP4[102]. 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[102,103]. PARP enzymes are involved in several DNA repair pathways[102,103]. Although the functional role of PARP3 is not well understood, PARP3 may serve a role in double-strand break (DSB) repair by facilitating selection for either non-homologous end joining (NHEJ) or homologous recombination repair (HRR)[104,105]. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs[104].

Alterations and prevalence: Somatic mutations in PARP3 are observed in 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, lung adenocarcinoma, and stomach adenocarcinoma[4,5]. Biallelic deletions in PARP3 are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, 2% of esophageal adenocarcinoma and sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for PARP3 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[41,106]. Although not indicated for specific alterations in PARP3, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[40] (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[40] 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[75] (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[76] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[77] (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.

PIK3R1 deletion

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[267]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[267]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[267]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[268,269]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[268,269,270,271]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[272]. Loss of function mutations in

Biomarker Descriptions (continued)

PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[267].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine cancer, 10% of uterine carcinosarcoma and glioblastoma, 6% of colorectal cancer, and 3-4% of melanoma, low grade glioma (LGG), stomach, and cervical cancers[4]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[4].

Potential relevance: Currently, no therapies are approved for PIK3R1 aberrations.

POLE deletion

DNA polymerase epsilon, catalytic subunit

Background: The POLE gene encodes the DNA polymerase epsilon, catalytic subunit protein[1]. POLE is one of the four-subunits in the DNA polymerase epsilon complex that also includes POLE2, POLE3, and POLE4[457,458]. The DNA polymerase epsilon complex mediates DNA repair, chromosomal replication, and genomic stability[457,458]. Specifically, POLE is the largest subunit in the complex and contains the catalytic and proofreading exonuclease active sites proposed to function in leading strand synthesis during homologous recombination repair (HRR)[458,459]. Mutations in POLE lead to increased mutation rates and subsequent tumor formation thereby impacting genomic stability[458,459]. Somatic POLE mutations are characterized by a hypermutated phenotype due to the increase in single-nucleotide substitutions[460]. Monoallelic POLE variants have also been associated with adenomatous polyposis and may confer an increased risk in colorectal cancer (CRC)[461,462,463,464,465]. Germline mutations in POLE exonuclease domains are associated with a predisposition to polymerase proofreading-associated polyposis[460].

Alterations and prevalence: Recurrent somatic mutations occur in 15% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of colorectal adenocarcinoma, stomach adenocarcinoma, and bladder urothelial carcinoma, as well as 5% of lung squamous cell carcinoma and lung adenocarcinoma[4,5]. Specifically, mutations in the proofreading domain of POLE occur in 7-12% of endometrial cancer and 1-2% of colorectal cancer[458,460]. POLE mutations are associated with high tumor mutational burden (TMB)[458,460,466].

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

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[145]. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[146]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[147]. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[36,150]. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents[153]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[154].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[4,5]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[154].

Potential relevance: The PARP inhibitor, olaparib[40] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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[85,86]. 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[85,86]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[87]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and

Biomarker Descriptions (continued)

tumorigenesis[85,86]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,88].

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[4,5]. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

SETD2 deletion

SET domain containing 2

Background: The SETD2 gene encodes the SET domain containing 2 histone lysine methyltransferase, a protein responsible for the trimethylation of lysine-36 on histone H3 (H3K36)[444,445]. Methylation of H3K36 is a hallmark of active transcription and can be either mono-, di-, or tri-methylated where di- and tri-methylation are thought to be responsible for transcriptional regulation[446]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[447,448]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[445]. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR deficiency (dMMR) and consequent microsatellite instability (MSI)[449]. Both copy number deletion and mutations resulting in SETD2 loss of function have been observed in a variety of cancers, suggesting a tumor suppressor role for SETD2[445,450].

Alterations and prevalence: Inactivating somatic mutations in SETD2 were first described in clear cell renal cell carcinoma (ccRCC) and are observed to be predominantly missense or truncating[4,450,451]. Mutations at codon R1625 are observed to be the most recurrent with R1625C having been identified to result in loss of SETD2 H3K36 trimethylase activity[4,444]. SETD2 mutation is observed in about 14% of uterine cancer, 12% of ccRCC, 9% of mesothelioma, and 6-7% of melanoma, lung adenocarcinoma, papillary renal cell carcinoma (pRCC), colorectal and bladder cancers[444]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[444].

Potential relevance: Currently, no therapies are approved for SETD2 aberrations. Mutations in SETD2 can be used to support diagnosis of hepatosplenic T-cell lymphoma (HSTCL)[452].

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[1,388]. Through its interaction with β-catenin, TCF7L2 functions as a central transcriptional regulator of the WNT pathway by modulating the expression of several genes involved in epithelial to mesenchymal transdifferentiation (EMT) and cancer progression, including MYC[388,389,390]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[388]. Loss of TCF7L2 function is commonly observed in colorectal cancer due to mutations or copy number loss which has been correlated with increased tumor invasion and metastasis, supporting a tumor suppressor role for TCF7L2[388].

Alterations and prevalence: Somatic mutations of TCF7L2 are observed in 11% colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, and 2% of skin cutaneous melanoma and uterine carcinosarcoma[4,5]. Biallelic deletion of TCF7L2 is observed in 2% diffuse large B-cell lymphoma, brain lower grade glioma, and colorectal adenocarcinoma, and 1% of bladder urothelial carcinoma, mesothelioma, stomach adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for TCF7L2 aberrations.

XRCC2 deletion

X-ray repair cross complementing 2

Background: The XRCC2 gene encodes the X-ray repair cross complementing 2 protein, also known as FANCU, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC3 paralogs[1,166,334]. XRCC2 forms the BCDX2 complex with other RAD51 paralogs, RAD51B, RAD51C, and RAD51D[166,334]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[147]. XRCC2 regulates the assembly of RAD51 filaments to assist in strand-exchange activity during homologous recombination repair (HRR)[166,334]. XRCC2 germline biallelic mutations result in Fanconi Anemia (FA) complementation group U, an atypical form of FA associated with defects in HRR[335].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in XRCC2 are observed in 3% of uterine corpus endometrial carcinoma and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma[4,5]. Biallelic deletions in XRCC2 are observed in 2% of acute myeloid leukemia (AML), sarcoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for XRCC2 aberrations. Pre-clinical evidence suggests that XRCC2 biallelic mutations may demonstrate sensitivity to the PARP inhibitor olaparib[336].

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14[1]. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines[262]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[262]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[262,263]. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival[262]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[263].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[4,5]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[264]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[265,266].

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,472]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[472,473]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[472,474]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[472,475,476,477,478]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[472,475,476,479,480].

Alterations and prevalence: Somatic mutations in ERRFI1 are observed in 4% of uterine corpus endometrial carcinoma and 2% of skin cutaneous melanoma, uterine carcinosarcoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of ERRFI1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma and diffuse large B-cell lymphoma, and 2% of liver hepatocellular carcinoma, pheochromocytoma and paraganglioma, and glioblastoma multiforme[4,5].

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

ENO1 deletion

enolase 1

Background: The ENO1 gene encodes enolase 1 and its alternatively spliced protein isoform, c-MYC promoter binding protein 1 (MBP1)[1,398]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[398]. In addition to its role in glycolysis, ENO1 acts as a cell surface plasminogen receptor and is involved in cytoskeleton reorganization, stabilization of the mitochondrial membrane, and modulation of several oncogenic pathways, including PI3K/AKT, AMPK/mTOR and Wnt/β-catenin[398,399,400]. ENO1 has been found to be overexpressed in various cancers contributing to upregulation of glycolysis, cancer cell survival and proliferation, chemoresistance, extracellular matrix degradation, migration, invasion, and metastases[398,399,401]. In contrast, MBP1 is known to repress c-MYC transcription under cellular stress and low glucose conditions, leading to suppression of cellular proliferation, migration, and invasion[398,399].

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

Biomarker Descriptions (continued)

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

PGD deletion

phosphogluconate dehydrogenase

Background: The PGD gene encodes phosphogluconate dehydrogenase, an essential enzyme of the pentose phosphate pathway (PPP) that catalyzes oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate and reduction of NADP+ to NADPH[1,241]. PPP mediated generation of pentose phosphates and NADPH is essential for nucleic acid synthesis and fatty acid synthesis, respectively, making it a crucial metabolic pathway for cancer cell survival and proliferation[242,243]. Although biallelic deletion appears to be more common than amplification across cancer types, post-translational modifications and overexpression of PGD in cancer have also been observed to result in elevated PPP activity, which is associated with cancer cell proliferation[241,244].

Alterations and prevalence: Somatic mutations in PGD have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, and bladder urothelial carcinoma[4,5]. Biallelic loss of PGD has been observed in 4% of adrenocortical carcinoma, 3% of cholangiocarcinoma, and 2% of pheochromocytoma and paraganglioma and diffuse large B-cell lymphoma[4,5]. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma[4,5].

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

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[439,440,441]. 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[439,441]. 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[442,443].

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[4,5]. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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[107,108]. 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[108]. 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[107,108].

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[4,5].

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

Biomarker Descriptions (continued)

FUBP1 deletion

far upstream element binding protein 1

Background: The FUBP1 gene encodes the far upstream element binding protein 1, a DNA/RNA binding protein implicated in a variety of cellular functions[1,219]. Specifically, FUBP1 is observed to bind single-stranded DNA (ssDNA) and RNA resulting in the regulation of transcription, translation, and splicing[219]. FUBP1 activates the transcription of targets including the oncogene MYC which functions in cell cycle regulation, metabolism, and apoptosis[219]. FUBP1 is also observed to repress the transcription of targets including the tumor suppressors CDKN1A, CDKN2B, and CDKN1B, which function in cell cycle regulation[219].

Alterations and prevalence: Somatic mutations in FUBP1 are observed in 9% of brain lower grade glioma, 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of colorectal adenocarcinoma[4,5]. Mutations typically result in inactivation of FUBP1 through alteration of splicing sites, introduction of stop codons, or out-of-frame insertions or deletions[219]. Biallelic loss of FUBP1 is observed in 3% of pheochromocytoma and paraganglioma[4,5]. Co-deletion of 1p and 19q is frequently observed in oligodendrogliomas, which results in the monoallelic loss of FUBP1 and CIC on 19q[219].

Potential relevance: Currently, no therapies are approved for FUBP1 aberrations.

DPYD deletion

dihydropyrimidine dehydrogenase

Background: The DPYD gene (also known as DPD) encodes dihydropyrimidine dehydrogenase, the initial and rate-limiting enzyme that catalyzes the reduction of uracil and thymidine in the pyrimidine catabolism pathway[1,2]. DPYD is responsible for the inactivation and liver clearance of fluoropyrimidines (fluorouracil, capecitabine, and other analogs), which are the core chemotherapies used in the treatment of solid tumors, such as colorectal, pancreatic, gastric, breast, and head and neck cancers[3]. Inherited DPYD polymorphisms, including DPYD*2A, DPYD*13, DPYD c.2846A>T, and DPYD c.1129-5923T>G, can result in DPD deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to fluoropyrimidine drugs due to an increase in systemic drug exposure[3].

Alterations and prevalence: Somatic mutations in DPYD have been observed in 20% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 6% of stomach adenocarcinoma, 5% of diffuse large B-cell lymphoma and colorectal adenocarcinoma, 4% of lung adenocarcinoma, 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of adrenocortical carcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and sarcoma[4,5]. Biallelic loss of DPYD has been observed in 4% of pheochromocytoma and paraganglioma and 2% of esophageal adenocarcinoma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for DPYD.

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,327]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[327,328]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[329]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[329,330,331,332]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[333].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

Biomarker Descriptions (continued)

VHL deletion

von Hippel-Lindau tumor suppressor

Background: The VHL gene encodes the von Hippel-Lindau tumor suppressor protein[1]. VHL possesses ubiquitin ligase activity and forms a ternary complex with transcription elongation factors C and B to make up the VCB complex, which is critical for VHL function[1,56]. VHL is involved in hypoxia-inducible-factor (HIF) regulation through ubiquitination, thereby targeting HIFs, including HIF1α, for proteasomal degradation[56]. Mutations in VHL lead to a destabilized VCB complex that is rapidly degraded by the proteasome, resulting in defective HIF regulation and tumorigenesis[56]. Germline mutations in VHL cause the Von Hippel-Lindau hereditary cancer syndrome, which confers predisposition to several cancer types including clear cell renal carcinoma, central nervous system, and retinal hemangioblastomas, pheochromocytoma, and pancreatic neuroendocrine tumors[56]. Belzutifan is considered for the treatment of progressive pancreatic neuroendocrine tumor harboring VHL germline aberrations[57].

Alterations and prevalence: Somatic mutations in VHL are predominantly truncating followed by missense mutations and are collectively observed in 41% of kidney renal clear cell carcinoma, and 2% of pheochromocytoma and paraganglioma, thymoma and kidney chromophobe[4,5]. Biallelic deletions are observed in 3% of kidney renal clear cell carcinoma and 2% of prostate adenocarcinoma[4,5].

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

TGFBR2 deletion

transforming growth factor beta receptor 2

Background: TGFBR2 encodes transforming growth factor beta receptor 2[1]. Along with TGFBR1 and TGFBR3, TGFBR2 is a member of the TGF-beta receptor family[45]. Both TGFBR1 and TGFBR2 function as serine/threonine and tyrosine kinases, whereas TGFBR3 does not possess any kinase activity[45]. TGFBR1 heterodimerizes with TGFBR2 and activates ligand binding of TGF-beta cytokines namely TGFB1, TGFB2, and TGFB3[45]. Heterodimerization with TGFBR2 enables TGFBR1 to phosphorylate downstream SMAD2/3, which leads to activation of SMAD4[46]. This process regulates various signaling pathways implicated in cancer initiation and progression, including epithelial to mesenchymal transition (EMT) and apoptosis[47,48,49].

Alterations and prevalence: Somatic mutations in TGFBR2 are observed in 5% of esophageal adenocarcinoma, and head and neck squamous cell carcinoma, 4% of pancreatic adenocarcinoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cholangiocarcinoma[4,5]. Biallelic deletion of TGFRB2 is observed in 3% of kidney renal clear cell carcinoma and 2% of stomach adenocarcinoma and head and neck squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TGFBR2 aberrations.

DOCK3 deletion

dedicator of cytokinesis 3

Background: The DOCK3 gene encodes dedicator of cytokinesis 3, a member of the DOCK (dedicator of cytokinesis) family of guanine nucleotide exchange factors (GEFs)[1]. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling[490]. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion[1,491,492]. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of β-catenin/WNT signaling[493,494]. Additionally knockdown of DOCK3 has been observed to inhibit tumor cell adhesion, migration, and invasion in non-small cell lung cancer cell lines, further supporting a tumor suppressive role for DOCK3[492].

Alterations and prevalence: Somatic mutations in DOCK3 are observed in 21% of skin cutaneous melanoma, 16% of uterine corpus endometrial carcinoma, 12% of stomach adenocarcinoma, 9% of colorectal adenocarcinoma, 6% of esophageal adenocarcinoma, 4% of sarcoma, and lung adenocarcinoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and kidney chromophobe[4,5]. Biallelic loss of DOCK3 is observed in 4% of diffuse large B-cell lymphoma, 3% of esophageal adenocarcinoma and kidney renal clear cell carcinoma, and 2% of sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for DOCK3 aberrations.

Biomarker Descriptions (continued)

PBRM1 deletion

polybromo 1

Background: The PBRM1 gene encodes polybromo 1 protein[1]. PBRM1, also known as BAF180, is a member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[109]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[109,110]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[109,111]. PBRM1 also promotes centromere cohesion in order to maintain genomic stability and prevent aneuploidy by silencing transcription near double-stranded DNA breaks (DSBs), supporting a tumor suppressor role for PBRM1[112,113].

Alterations and prevalence: Somatic mutations in PBRM1 are observed in 38% of kidney renal clear cell carcinoma, 22% of cholangiocarcinoma, 10% of uterine corpus endometrial carcinoma, and 8% of skin cutaneous melanoma[4,5]. Biallelic deletion of PBRM1 is observed in 5% of mesothelioma, 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, and 2% of esophageal adenocarcinoma, uterine carcinosarcoma, stomach adenocarcinoma, and sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for PBRM1 aberrations.

INPP4B deletion

inositol polyphosphate-4-phosphatase type II B

Background: INPP4B encodes inositol polyphosphate 4-phosphatase type II, a member of the inositol polyphosphate 4-phosphatase family which also includes INPP4A[1,495]. INPP4B, along with PTEN and PIPP, is a phosphoinositide phosphatase that modulates the PI3K/AKT signaling pathway by hydrolyzing phosphatidylinositol 3,4-bisphosphate to generate phosphatidylinositol 3-phosphate, thereby suppressing the PI3K/AKT signaling cascade[496]. Although overexpression of INPP4B has been observed in several tumor types and is suggested to be associated with poor outcomes and response to therapy, alterations including mutations leading to loss of INPP4B function have been observed to result in enhanced AKT signaling, cell proliferation, and decreased survival in other tumor types, supporting a tumor suppressor role for INPP4B[497,498].

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

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

FAT1 deletion

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[1,319]. 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[319]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[319]. 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[319]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[319].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[4,5]. 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[4,5]. 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[4,5].

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

Biomarker Descriptions (continued)

SDHA deletion

succinate dehydrogenase complex flavoprotein subunit A

Background: The SDHA gene encodes succinate dehydrogenase complex flavoprotein subunit A, a major catalytic subunit of the succinate dehydrogenase (SDH) enzyme complex[1,86]. 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[85,86]. 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[85,86]. SDHA is involved in the oxidation of succinate with a coupled reduction of the cofactor FAD[85,86]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[85,86]. Inherited pathogenic mutations in SDHA are known to confer increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[85,86,122,123].

Alterations and prevalence: Somatic mutations in SDHA are observed in 4% of uterine corpus endometrial carcinoma, 3% of colorectal adenocarcinoma, kidney chromophobe, and skin cutaneous melanoma, and 2% of cervical squamous cell carcinoma, stomach adenocarcinoma, uterine carcinosarcoma, bladder urothelial carcinoma, and lung squamous cell carcinoma[4,5]. Biallelic loss of SDHA is observed in 2% of uterine carcinosarcoma[4,5].

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

CDH10 deletion

cadherin 10

Background: The CDH10 gene encodes cadherin 10, a type II classical cadherin and member of the cadherin superfamily[1]. Cadherins are important in calcium-dependent cell-cell adhesion, and are known to mediate cell recognition, cell movement, and maintain structural and functional cell and tissue polarity[6]. CDH10 is classified as an atypical type II cadherin due to its lack of a histidine-alanine-valine (HAV) cell adhesion recognition motif, a hallmark characteristic to type I cadherins[1,6]. Abnormal expression of cadherins results in increased tumor cell invasion, which precedes metastasis of tumors[7,8].

Alterations and prevalence: Somatic mutations of CDH10 are observed in 20% of lung squamous cell carcinoma, 16% of lung adenocarcinoma, 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 8% of stomach adenocarcinoma, and colorectal adenocarcinoma, 6% of head and neck squamous cell carcinoma, 4% of bladder urothelial carcinoma and esophageal adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of pancreatic adenocarcinoma, ovarian serous cystadenocarcinoma, uterine carcinosarcoma, and sarcoma[4,5]. Amplification of CDH10 is observed in 10% of lung squamous cell carcinoma, 7% of lung adenocarcinoma and esophageal adenocarcinoma, 6% of bladder urothelial carcinoma, 5% of ovarian serous cystadenocarcinoma and cervical squamous cell carcinoma, 4% of sarcoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% uterine corpus endometrial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CDH10 aberrations.

MAP3K1 deletion

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1[1]. Activation of MAPK proteins occurs through a kinase signaling cascade[303,304,306]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[303,304,306]. 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[303,304,306]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[406]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[406]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[406].

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma[4,5]. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[406]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MAP3K1 aberrations.

Biomarker Descriptions (continued)

RASA1 deletion

RAS p21 protein activator 1

Background: The RASA1 gene encodes the Ras p21 protein activator 1[1]. RASA1 is a member of the RasGAP family, which includes RASA2[114,115]. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form[114]. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis[114]. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways[114]. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types[114].

Alterations and prevalence: Somatic mutations in RASA1 are observed in 11% of uterine corpus endometrial carcinoma, 6% of lung squamous cell carcinoma, 5% of stomach adenocarcinoma and of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, head and neck squamous cell carcinoma, colorectal carcinoma, and uterine carcinosarcoma, and 3% of esophageal adenocarcinoma[4,5]. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for RASA1 aberrations.

ERAP1 deletion

endoplasmic reticulum aminopeptidase 1

Background: The ERAP1 gene encodes the endoplasmic reticulum aminopeptidase 1 protein[1]. ERAP1, and structurally related ERAP2, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[407,408]. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules[407,409]. ERAP1 has also been shown to be involved in the shedding of cytokine receptors (including TNFR1, IL6-Ra, and type II IL-II receptor) and is observed to be secreted by macrophages, which is believed to enhance phagocytosis[407,410,411]. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma[407,412].

Alterations and prevalence: Somatic mutations in ERAP1 are observed in 7% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and stomach adenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[4,5]. Biallelic deletions are observed in 2% of ovarian serous cystadenocarcinoma and prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, stomach adenocarcinoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ERAP1 aberrations.

TPMT p.(Y240C) c.719A>G

thiopurine S-methyltransferase

Background: The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines[1,385,386]. TPMT is the major enzyme responsible for the metabolic inactivation of thiopurine chemotherapeutic drugs used in the treatment of acute lymphoblastic leukemia (ALL), including, 6-mercaptopurine, 6-thioguanine, and azathioprine[385,386,387]. Inherited TPMT polymorphisms, including TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, and TPMT*8, can result in TPMT deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to thiopurine drugs due to an increase in systemic drug exposure[385,387].

Alterations and prevalence: Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma[4,5]. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma[4,5]. Amplification of TPMT is observed in 7% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma, 4% of diffuse large B-cell lymphoma, uveal melanoma, uterine carcinosarcoma, and skin cutaneous melanoma, 3% of cholangiocarcinoma, and 2% of breast invasive carcinoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma[4,5].

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[337]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[338]. The classical MHC class I

Biomarker Descriptions (continued)

genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[339,340,341]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[342].

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[4,5]. Biallelic loss of HLA-B is observed in 5% of DLBCL[4,5].

Potential relevance: Currently, no therapies are approved for HLA-B 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[205,206,207]. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs[208]. 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[207]. 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[208].

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[4,5]. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)[208]. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma[4,5].

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

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein[1]. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[413]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[413]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[413,414]. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes[413]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[413]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[413,415].

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[4,5]. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma[4,5].

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies[416]. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy[417]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[418]. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens[419].

TNFAIP3 deletion

TNF alpha induced protein 3

Background: The TNFAIP3 gene encodes the TNF alpha induced protein 3[1]. TNFAIP3, also known as A20, is a ubiquitin modifying protein that possesses deubiquitination, E3 ligase, and ubiquitin binding activity[273]. TNFAIP3 is known to negatively regulate the NF-κB pathway by means of its ubiquitin modifying ability, thus impacting inflammatory and immune responses[273,274]. Specifically, TNFAIP3 is known to function as a cysteine protease with deubiquitination (DUB) capability and possesses seven zinc finger motifs that mediate binding to K63- and M1- polyubiquitin chains, thereby altering protein degradation and other protein-protein interactions[273]. TNFAIP3

Biomarker Descriptions (continued)

deficient cells are observed to promote aberrant NF-κB signaling, deregulation of which is proposed to contribute to lymphoma pathogenesis[273,275].

Alterations and prevalence: Somatic mutations in TNFAIP3 are observed in 12% of diffuse large B-cell lymphoma (DLBCL), 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and bladder urothelial carcinoma[4,5]. Biallelic loss of TNFAIP3 is observed in 30% of human B-cell lymphoma, 12% of DLBCL and 8% of uveal melanoma[4,5,273].

Potential relevance: Currently, no therapies are approved for TNFAIP3 aberrations.

MAP3K4 deletion

mitogen-activated protein kinase kinase kinase 4

Background: The MAP3K4 gene encodes the mitogen-activated protein kinase kinase kinase 4, also known as MEKK4[1]. MAP3K4 is involved in the JNK signaling pathway along with MAP3K12, MAP2K4, MAP2K7, MAPK8, MAPK9, and MAPK10[303]. Activation of MAPK proteins occurs through a kinase signaling cascade[303,304,306]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[303,304,306]. 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[303,304,306]. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4[420].

Alterations and prevalence: Somatic mutations in MAP3K4 are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 7% of uterine carcinosarcoma, and 6% of colorectal adenocarcinoma[4,5]. Biallelic deletions are observed in 6% of uveal melanoma, 3% of ovarian serous cystadenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL)[4,5].

Potential relevance: Currently, no therapies are approved for MAP3K4 aberrations.

POT1 deletion

protection of telomeres 1

Background: The POT1 gene encodes the protection of telomeres 1 protein, a nuclear protein and member of the Shelterin complex along with TERF1, TERF2, TPP1, TINF2, and TERF2IP[467]. The Shelterin complex is responsible for the protection and maintenance telomeres[1,467,468]. POT1 mediates the association of the Shelterin complex with single-stranded telomeric DNA, resulting in the prevention of telomerase binding and subsequent telomere elongation[467,469]. POT1 also inhibits inappropriate DNA damage response at telomeres by preventing the binding of RPA and inhibiting recruitment of ATR, thereby protecting telomeres from erroneous repair[468]. Loss of function POT1 germline mutations have been observed in melanoma, chronic lymphocytic leukemia (CLL), angiosarcoma, and glioma[468].

Alterations and prevalence: Somatic mutations in POT1 are observed in 5% of uterine corpus endometrial carcinoma, 3% of bladder urothelial carcinoma, 2% of lung adenocarcinoma, skin cutaneous melanoma, stomach adenocarcinoma, and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for POT1 aberrations.

EZH2 deletion

enhancer of zeste 2 polycomb repressive complex 2 subunit

Background: The EZH2 gene encodes the enhancer of zeste homolog 2 protein, a histone methyltransferase that functions as both a transcriptional suppressor and co-activator[89]. EZH2 mediates methylation of histone H3 at Lys 27 (H3K27me3) and promotes tumor growth and metastasis through regulation of the cell cycle[89,90]. Since EZH2 loss-of-function is associated with the development of cancer, it is considered a tumor suppressor. EZH2 is overexpressed in various cancer types, consequently, it can also function as an oncogene[89].

Alterations and prevalence: Diverse EZH2 alterations including missense, nonsense, frameshift mutations, and inactivating deletions are observed in 18-25% of T-cell acute lymphocytic leukemia (T-ALL), 3-13% of myeloproliferative neoplasms (MPN), 8-12% of myelodysplastic/myeloproliferative neoplasms overlap disorders (MDS/MPN), and 6% of diverse MDS[90,91]. Heterozygous gain-of-function mutations at tyrosine 641 (Y641) are observed in 22% of germinal center B-cell (GBC) and diffuse large B-cell lymphoma (DLBCL), and 7-17% of follicular lymphoma (FL)[90,92]. In solid tumors, EZH2 mutations are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 3% of cholangiocarcinoma[4,5]. Amplifications are observed in up to 7%

Biomarker Descriptions (continued)

of ovarian carcinoma[4,5]. Increased EZH2 copy number corresponds with enhanced protein expression and is observed in over 50% of hormone-refractory prostate cancers[93].

Potential relevance: The methyltransferase inhibitor tazemetostat[94] was FDA approved (2020) for EZH2 mutated relapsed or refractory follicular lymphoma after at least 2 prior systemic therapies. Tazemetostat was also granted FDA fast track designation in 2016 for DLBCL harboring EZH2 activating mutations[95]. Somatic mutation in EZH2 is one of the possible molecular abnormality requirements for the diagnosis of myelodysplasia-related AML (AML-MR)[26]. EZH2 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and MDS/MPN[96]. EZH2 mutations also confer poor prognosis in essential thrombocythemia (ET), primary myelofibrosis (PMF), and AML[25,97,98]. EZH2 overexpression correlates with malignancy, poor prognosis, and poor survival, and has been detected in MDS and acute myeloid leukemia (AML)[89,99]. Several studies have shown that EZH2 overexpression enhances chemoresistance in solid tumor types[100,101].

KMT2C deletion

lysine methyltransferase 2C

Background: The KMT2C gene encodes the lysine methyltransferase 2C protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2C belongs to the SET domain protein methyltransferase superfamily[247]. KMT2C is capable of di- and tri-methylation of histone 3 lysine 4 (H3K4) at select transcriptional enhancers depending on the cell type[248]. KMT2C is also found to interact with BAP1 to control ubiquitin-mediated gene silencing of H2A by Polycomb group (PcG) complexes[249,250]. Specifically, KMT2C interaction with BAP1 promotes KMT2C histone recruitment/methyltransferase activity and, along with BAP1 deubiquitination of H2A, facilitates transcription of target genes[249,250]. Mutations that occur within the SET domain of KMT2C are frequently observed in cancer and alter the methylation activity and target methylation states, thereby impacting gene regulation[248].

Alterations and prevalence: Somatic mutations in KMT2C are observed in 20% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, 19% of skin cutaneous melanoma and cervical squamous cell carcinoma, 15% of lung squamous cell carcinoma, 14% of stomach adenocarcinoma and lung adenocarcinoma, and 11% of cholangiocarcinoma[4,5]. Biallelic deletion of KMT2C is observed in 3% of sarcoma, stomach adenocarcinoma, 2% of esophageal adenocarcinoma, acute myeloid leukemia, uterine carcinosarcoma, and head and neck squamous cell carcinoma[4,5].

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

JAK2 deletion

Janus kinase 2

Background: The JAK2 gene encodes Janus kinase 2, a non-receptor protein tyrosine kinase (PTK)[1,9]. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[9]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[10]. 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[10,11,12]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion[13,14].

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) is associated with loss of heterozygosity on chromosome 9p and subsequently the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2[15,16]. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)[17,18]. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL[19,20]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR[21,22,23,24]. JAK2 fusions are infrequently observed in solid tumors[4]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[4]. JAK2 is amplified in 4% of sarcoma, diffuse large B-cell lymphoma, and head and neck squamous cell carcinoma, 3% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[4,5]. Alterations in JAK2 are also observed in pediatric cancers[4,5]. Somatic mutations are observed in 6% of B-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of leukemia (3 in 354 cases), bone cancer (2 in 327 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)[4,5]. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[4,5]. JAK2 is amplified in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[4,5].

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of polycythemia vera (PV)[25,26]. Ruxolitinib[27] (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[28]. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were

Biomarker Descriptions (continued)

associated with loss of function mutations in JAK1/2[29]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[21,22,23,24].

PTCH1 deletion

patched 1

Background: The PTCH1 gene encodes the patched 1 protein, a transmembrane protein that along with PTCH2, belongs to the patched gene family[1]. PTCH1 is involved in the Hedgehog (Hh) signaling pathway that plays a significant role in embryonic development, cell proliferation, and cell differentiation[487,488]. PTCH1 is a tumor suppressor gene that inhibits the transmembrane receptor Smoothened (SMO) and prevents downstream Hh signaling pathway activation[487,488]. The Hh pathway is activated when one of the Hh ligands including Sonic hedgehog (SHh), Indian hedgehog (IHh), or Desert Hedgehog (DHh) bind to PTCH1 and disrupt SMO inhibition[488]. Inactivating mutations in PTCH1 lead to ligand-independent signaling of Hh, as PTCH1 no longer prevents SMO activity[488]. Germline mutations in PTCH1 are associated with basal cell nevus syndrome (BCNS) or Gorlin Syndrome with a predisposition to non-cancerous and cancerous tumors including basal cell carcinoma[488,489].

Alterations and prevalence: Inactivating mutations in PTCH1 are observed in 85% of sporadic basal cell carcinomas[489]. Somatic mutations in PTCH1 are also observed in 11% of uterine corpus endometrial carcinoma and 4-5% of stomach adenocarcinoma, skin cutaneous melanoma, cholangiocarcinoma, esophagus adenocarcinoma, colorectal adenocarcinoma, and mesothelioma[4,5].

Potential relevance: Currently, no therapies are approved for PTCH1 aberrations.

PPP6C deletion

protein phosphatase 6 catalytic subunit

Background: PPP6C encodes protein phosphatase 6 catalytic subunit and is a member of the serine/threonine protein phosphatase family[1,287]. As the catalytic subunit of the heterotrimeric phosphoprotein phosphatase 6 (PP6) holoenzyme, PPP6C is involved in diverse processes such as cell cycle regulation, DNA damage response, autophagy, miRNA processing, inflammatory signaling, and lymphocyte development[287,288]. Loss of PPP6C results in hyperphosphorylation of Aurora A kinase, which results in defects in mitotic spindle assembly and subsequent genomic instability[288]. Overexpression of PPP6C has been observed to result in decreased colony formation of human endometrial carcinoma cells in vitro, supporting a possible tumor suppressor role for PPP6C[289].

Alterations and prevalence: Somatic mutations in PPP6C are observed in 7% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of colorectal adenocarcinoma[4,5]. Biallelic loss of PPP6C is observed in 1% of thyroid carcinoma, pancreatic adenocarcinoma, and skin cutaneous melanoma[4,5]. Amplification of PPP6C is observed in 2% kidney chromophobe[4,5].

Potential relevance: Currently, no therapies are approved for PPP6C aberrations.

LARP4B deletion

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein[1]. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7[43]. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs[43]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[44].

Alterations and prevalence: Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[4,5]. Biallelic deletions in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for LARP4B aberrations.

GATA3 deletion

GATA binding protein 3

Background: The GATA3 gene encodes GATA binding protein 3, a member of the GATA family of zinc-finger transcription factors, which also includes GATA1, GATA2, and GATA4-6[1,214,215]. The GATA family regulates transcription of many genes by binding to the

Biomarker Descriptions (continued)

DNA consensus sequence T/A(GATA)A/G[215]. GATA3 functions in the differentiation of immune cells and tissue development[216,217]. As GATA3 also functions in luminal cell development and cell function, it is a common marker of the gene expression profile in luminal breast cancer[216].

Alterations and prevalence: Somatic mutations in GATA3 are observed in 12% of breast invasive carcinoma, 4% of uterine corpus endometrial carcinoma and stomach adenocarcinoma, and 3% of colorectal adenocarcinoma and skin cutaneous melanoma[4,5]. Biallelic loss of GATA3 is observed in 2% of diffuse large B-cell lymphoma (DLBCL)[4,5]. Alterations in GATA3 are also observed in the pediatric population[5]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and Hodgkin lymphoma (1 in 61 cases), and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), and leukemia (1 in 311 cases)[5]. Biallelic deletion is observed in 1% of peripheral nervous system cancers (1 in 91 cases), less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[5].

Potential relevance: Currently, no therapies are approved for GATA3 aberrations. Low GATA3 expression is associated with invasion and poor prognosis in breast cancer[216,218].

MAPK8 deletion

mitogen-activated protein kinase 8

Background: The MAPK8 gene encodes the mitogen-activated protein kinase 8, also known as JNK1[1]. MAPK8 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAP2K7, MAPK9, and MAPK10[303,304,305]. Activation of MAPK proteins occurs through a kinase signaling cascade[303,304,306]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[303,304,306]. 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[303,304,306].

Alterations and prevalence: Somatic mutations in MAPK8 are observed in 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma[4,5]. Biallelic deletions are observed in 1% of bladder urothelial carcinoma, esophageal adenocarcinoma, adrenocortical carcinoma, and skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for MAPK8 aberrations.

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein[1]. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2[30,31]. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes[31]. ARID5B is known to be essential for the development of hematopoietic cells[31]. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)[31].

Alterations and prevalence: Somatic mutations in ARID5B are observed in 15% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 5% of diffuse large B-cell lymphoma, 4% of stomach adenocarcinoma[4,5]. Biallelic loss of ARID5B is observed in 1% of kidney chromophobe, lung squamous cell carcinoma, and skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for ARID5B aberrations.

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins[1]. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids[1,307]. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents[308,309]. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro[308,309,310]. CYPC29 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis[307,308,309,310]. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors[308]. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease[308].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in CYP2C9 are observed in 12% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of cervical squamous cell carcinoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[4,5]. Biallelic loss of CYP2C9 is observed in 2% diffuse large B-cell lymphoma and prostate adenocarcinoma[4,5]. Amplification of CYP2C9 is observed in 1% of pheochromocytoma, paraganglioma, and ovarian serous cystadenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CYP2C9.

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling[1]. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation[209]. SUFU is capable of interacting and complexing with GLI1 and GLI2, thereby regulating transactivation of GLI1 and GLI2 target genes and inhibiting hedgehog pathway signaling[210,211]. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU[212]. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and is observed almost exclusively in children less than 3 years of age[213].

Alterations and prevalence: Somatic mutations are observed in 4% endometrial carcinoma, 2% esophageal adenocarcinoma, and stomach adenocarcinoma[5]. Biallelic deletion of SUFU is observed in 2% of mesothelioma, diffuse large cell B-cell lymphoma, and prostate adenocarcinoma[5].

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

KMT2D deletion

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2D belongs to the SET domain protein methyltransferase superfamily[247]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[247]. Mutations or deletions in the enzymatic SET domain of KMT2D are believed to result in loss of function and may contribute to defective enhancer regulation and altered gene expression[247].

Alterations and prevalence: Somatic mutations in KMT2D are predominantly missense or truncating and are observed in 29% of diffuse large B-cell lymphoma (DLBCL), 28% of bladder urothelial carcinoma, 27% of uterine corpus endometrial carcinoma, 22% of lung squamous cell carcinoma, 21% of skin cutaneous melanoma, 17% of stomach adenocarcinoma, 15% of head and neck squamous cell carcinoma, and 14% of cervical squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for KMT2D aberrations.

ACVR1B deletion

activin A receptor type 1B

Background: The ACVR1B gene encodes the activin A type 1B receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenic protein (BMP)/transforming growth factor-beta (TGFβ) receptor family[1,311]. ACVR1B is a type I receptor that forms a heterotetrametric complex with at least two type I receptors (including ACVR1) and two type II receptors (including BMPR2, ACVR2A, and ACVR2B)[311,312]. 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 signaling[311,312]. Loss of function mutations and homozygous deletion in ACVR1B has been observed in pancreatic cancer and is associated with increased cell growth, colony formation, and tumorigenicity[313,314].

Alterations and prevalence: Somatic mutations of ACVR1B are observed in 5% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, 3% of stomach adenocarcinoma, 2% of lung adenocarcinoma, skin cutaneous melanoma, lung squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and kidney chromophobe, and 1% of head and neck squamous cell carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, brain lower grade glioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma, and acute myeloid leukemia[4,5]. Biallelic deletion of ACRV1B is observed in 1% of stomach adenocarcinoma, brain lower grade glioma, and pancreatic adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ACVR1B aberrations.

Biomarker Descriptions (continued)

STAT6 amplification

signal transducer and activator of transcription 6

Background: The STAT6 gene encodes the signal transducer and activator of transcription 6. STAT6, a transcription factor, is a member of a highly conserved signal transducer and activator of transcription (STAT) family which also includes STAT1-4, STAT5A, and STAT5B[421]. Inactive STAT transcription factors in the cytoplasm are activated by tyrosine phosphorylation, resulting in STAT dimerization and nuclear translocation[421]. Following translocation to the nucleus, STAT dimers interact with specific enhancers and promote transcriptional initiation of target genes[421]. Specifically, STAT6 activation is facilitated by IL-3 or IL-13 mediated cytokine receptor stimulation resulting in Th2 mediated immune responses, eosinophil recruitment during allergic inflammation, and immunoglobulin class switching to IgE[422]. Abnormal STAT6 activation contributes to oncogenesis by increasing the expression of proteins involved in proliferation, migration, and invasion, supporting an oncogenic role for STAT6[422].

Alterations and prevalence: Amplifications in STAT6 are observed in 3% of sarcoma and 2% of lung adenocarcinoma and cholangiocarcinoma[4,5]. Somatic mutations in STAT6 are observed in 9% of diffuse large B-cell lymphoma (DLBCL), 5% of uterine cancer, and 4% of melanoma[4,5].

Potential relevance: Currently, no therapies are approved for STAT6 aberrations.

CBFB deletion

core-binding factor beta subunit

Background: The CBFB gene encodes the core-binding factor subunit beta, a member of the PEBP2/CBF transcription factor family[1]. CBFB is capable of heterodimerization with the RUNX protein family (RUNX1, RUNX2, and RUNX3) which results in the formation of the core binding factor (CFB) complex, a transcription factor complex responsible for the regulation of many critical functions in hematopoiesis and osteogenesis[402,403,404]. Although possessing no DNA-binding activity, CBFB has been observed to enhance stability and transcriptional activity of RUNX proteins, thereby exhibiting a critical role in RUNX mediated transcriptional regulation[403,404]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[404]

Alterations and prevalence: Somatic mutations in CBFB are observed in 2% of diffuse large B-cell lymphoma, breast invasive carcinoma, and uterine corpus endometrial carcinoma[4]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[4]. Translocations including inv(16) and t(16;16) have been observed to be recurrent in de novo AML, occurring in 7-10% of patients, and have been associated with the AML M4 with bone barrow eosinophilia (M4Eo) subtype[405]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[405].

Potential relevance: Currently, no therapies are approved for CBFB aberrations. In AML, CBFB translocations, including inv(16) and t(16;16) which result in CBFB::MYH11 fusion, are associated with favorable prognosis and define a distinct molecular subtype of AML according to the World Health Organization (WHO)[26,97,98].

SPOP deletion

speckle type BTB/POZ protein

Background: The SPOP gene encodes the speckle type BTB/POZ protein[1]. SPOP is an E3 ligase substrate adaptor, with specificity for cullin3-RING ubiquitin ligase (CRL3), which recruits substrates for ubiquitination[343]. Substrates recruited by SPOP include proteins involved in epigenetic modification, hormone signaling effectors, and cascade effectors, such as androgen receptor (AR), estrogen receptor (ER), CCNE1, MYC, and PTEN[343]. Mutations in SPOP meprin and TRAF-C homology (MATH) domains have been implicated to have loss of function as well as gain of function roles that are cancer-type dependent and are based on SPOP's specificity for its various substrates[343,344,345,346]. In prostate cancer, mutations in the SPOP substrate-binding cleft of the MATH domain, involving residues F133, F102, W131 and Y87, lead to increased levels of AR. In endometrial cancer, mutations in the SPOP substrate-binding face of the MATH domain, involving residues M117, E47, R121 and E50, lead to decreased levels of estrogen and progesterone receptors[343,344,345,346]. Moreover, improved overall survival has been observed from hormonal therapies in patients with SPOP mutated prostate cancer[346].

Alterations and prevalence: Somatic mutations in SPOP are observed in 11% of prostate adenocarcinoma, 10% of uterine corpus endometrial carcinoma, 7% of uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma[4,5]. Amplification of SPOP is observed in 6% of breast invasive carcinoma, 5% of mesothelioma, and 2% of esophageal adenocarcinoma and pancreatic adenocarcinoma[4,5].

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

Biomarker Descriptions (continued)

RNF43 deletion

ring finger protein 43

Background: The RNF43 gene encodes the ring finger protein 43[1]. RNF43 is a transmembrane E3 ubiquitin ligase and a negative regulator of the Wnt signaling pathway[453,454]. Wnt signaling leads to the expression of genes that control cell proliferation, migration, and cell polarity formation[453]. RNF43 functions as a tumor suppressor and inhibits the Wnt pathway by ubiquitination and degradation of the Wnt receptor frizzled (FZD)[453,454].

Alterations and prevalence: Somatic mutations in RNF43 are observed in 14% endometrial carcinoma, 8% gastroesophageal junction cancer and colorectal adenocarcinoma, and 6% pancreatic adenocarcinoma[4,5]. Somatic frameshift mutations in RNF43 including R117fs and G659fs are frequently observed in colorectal and endometrial cancers with microsatellite instability[453,455,456].

Potential relevance: Currently, no therapies are approved for RNF43 aberrations.

PPM1D deletion

protein phosphatase, Mg2+/Mn2+ dependent 1D

Background: The PPM1D gene encodes the protein phosphatase, Mg2+/Mn2+ dependent 1D, also known as wild-type p53-induced phosphatase 1 (WIP1) or protein phosphatase 2C delta (PP2Cδ)[423]. PPM1D is a member of the PP2C family of Ser/Thr protein phosphatases[1]. PPM1D negatively regulates several key tumor suppressor pathways including ATM, CHK2, P38 MARK and P53, which are involved in cell stress, cell cycle regulation, DNA damage repair and tumor cell metabolism[423,424]. PPM1D amplification/overexpression and/or mutations occur in various solid cancers, including breast cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, ovarian carcinoma and neuroblastoma[424]. Truncating mutations in the last exon of PPM1D lead to the production of a stable, enzymatically active protein and are commonly associated with clonal hematopoiesis, a condition that has been shown to be present in patients with therapy-related myeloid neoplasm such as therapy-related acute myeloid leukemia (t-AML) or therapy-related myelodysplastic syndrome (t-MDS)[425,426].

Alterations and prevalence: Somatic mutations in PPM1D are predominantly truncating or missense and are observed in 6% of uterine corpus endometrial carcinoma, 2% of stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[4,5]. Amplification of PPM1D is observed in 8% of breast invasive carcinoma, 5% of mesothelioma, 4% of liver hepatocellular carcinoma, 3% of bladder urothelial carcinoma and stomach adenocarcinoma, and 2% of adrenocortical carcinoma, skin cutaneous melanoma, ovarian serous cystadenocarcinoma, pheochromocytoma and paraganglioma, esophageal adenocarcinoma, pancreatic adenocarcinoma, thymoma, sarcoma, and lung adenocarcinoma[4,5]. Alterations in PPM1D are also observed in pediatric cancers[5]. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma and glioma, and less than 1% of leukemia (1 in 311 cases), embryonal tumor (1 in 332 cases), and peripheral nervous system cancers (3 in 1158 cases)[5]. PPM1D amplification is observed in 2% of peripheral nervous system cancers, and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[5].

Potential relevance: Currently, no therapies are approved for PPM1D aberrations. Overexpression of PPM1D has been associated with tumor progression and poor prognosis in non-small cell lung cancer, nasopharyngeal carcinoma and prostate cancer[427,428,429].

PRKAR1A deletion

protein kinase cAMP-dependent type I regulatory subunit alpha

Background: The PRKAR1A gene encodes the protein kinase cAMP-dependent type I regulatory subunit alpha of protein kinase A (PKA), an inactive tetrameric holoenzyme with two regulatory (R) subunits and two catalytic (C) subunits (namely PRKACA and PRKACB)[1,481]. PKA is a cAMP-dependent protein kinase involved in the phosphorylation of several downstream targets and an essential regulator of several cell signaling pathways involved in differentiation, proliferation, and apoptosis[1,482,483]. PKA is activated when the R subunits bind cAMP, which results in the dissociation of active monomeric C subunits and the subsequent phosphorylation of target proteins[1,482]. Mutations in PRKAR1A lead to increased availability of free catalytical subunits and increased PKA activity[484,485]. Loss of PRKAR1A has been shown to promote tumor cell proliferation and migration in lung cancer cell lines suggesting a tumor suppressor role in cancer[486].

Alterations and prevalence: Somatic mutations in PRKAR1A are observed in 5% of adrenocortical carcinoma, 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma and uterine carcinosarcoma[4,5]. Biallelic loss of PRKAR1A is observed in 4% of adrenocortical carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for PRKAR1A aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-05-14. For the most up-to-date information, search www.fda.gov.

BRAF p.(V600E) c.1799T>A

binimetinib + cetuximab + encorafenib

Cancer type: Colorectal Cancer

Variant class: BRAF V600E mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to the MEK inhibitor, binimetinib, in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer.

Reference:

https://markets.businessinsider.com/news/stocks/array-biopharma-receives-fda-breakthrough-therapy-designation-for-braftovi-in-combination-with-mektovi-and-cetuximab-for-brafv600e-mutant-metastatic-colorectal-cancer-1027437791

plixorafenib

Cancer type: Solid Tumor

Variant class: BRAF V600 mutation

Supporting Statement:
The FDA has granted Fast Track designation to a novel small molecule inhibitor, plixorafenib (PLX-8394), for the treatment of patients with cancers harboring BRAF Class 1 (V600) and Class 2 (including fusions) alterations who have exhausted prior therapies.

Reference:

https://fore.bio/fore-biotherapeutics-announces-fast-track-designation-granted-by-fda-to-fore8394-for-the-treatment-of-cancers-harboring-braf-class-1-and-class-2-alterations/

ABM-1310

Cancer type: Glioblastoma IDH-wildtype (Grade 4)

Variant class: BRAF V600E mutation

Supporting Statement:
The FDA has granted Fast Track designation to ABM-1310 for the treatment of glioblastoma (GBM) patients with BRAF V600E mutation.

Reference:

https://www.prnewswire.com/news-releases/abm-therapeutics-abm-1310-granted-fast-track-designation-by-the-fda-following-orphan-drug-designation-301937168.html

NF2 deletion

IK-930

Cancer type: Mesothelioma **Variant class:** NF2 deletion

Supporting Statement:

The FDA has granted Fast Track designation for IK-930, a novel TEAD inhibitor targeting the Hippo signaling pathway, for unresectable NF2-deficient malignant pleural mesothelioma (MPM).

Reference:

https://ir.ikenaoncology.com//news-releases/news-release-details/ikena-oncology-receives-fda-fast-track-designation-novel-tead

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 (continued)

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

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

BRAF p.(V600E) c.1799T>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
dabrafenib + trametinib	◑	◑	◑	◑	✖
binimetinib + encorafenib	◑	◑	◑	●	✖
cobimetinib + vemurafenib	●	◑	●	●	● (II/III)
dabrafenib	●	◑	●	✖	● (II)
vemurafenib	●	◑	●	✖	✖
atezolizumab + cobimetinib + vemurafenib	●	●	✖	✖	✖
trametinib	●	✖	●	✖	✖
cetuximab + encorafenib	○	○	○	○	✖
cetuximab + encorafenib + FOLFOX	○	○	✖	✖	✖
encorafenib	✖	●	✖	●	✖
dabrafenib + pembrolizumab + trametinib	✖	●	✖	✖	✖
encorafenib + panitumumab	✖	○	✖	✖	✖
encorafenib + panitumumab + FOLFOX	✖	○	✖	✖	✖
selumetinib	✖	○	✖	✖	✖
anti-PD-1	✖	✖	✖	●	✖
ipilimumab	✖	✖	✖	●	✖
ipilimumab + nivolumab	✖	✖	✖	●	✖

* 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

BRAF p.(V600E) c.1799T>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nivolumab	✖	✖	✖	●	✖
nivolumab + relatlimab	✖	✖	✖	●	✖
pembrolizumab	✖	✖	✖	●	✖
bevacizumab + CAPOX	✖	✖	✖	○	✖
bevacizumab + FOLFOX	✖	✖	✖	○	✖
bevacizumab + FOLFOXIRI	✖	✖	✖	○	✖
dabrafenib + MEK inhibitor	✖	✖	✖	○	✖
binimetinib, encorafenib	✖	✖	✖	✖	● (II)
dabrafenib, camrelizumab	✖	✖	✖	✖	● (II)
encorafenib, binimetinib	✖	✖	✖	✖	● (II)
encorafenib, binimetinib, nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
regorafenib, dabrafenib, trametinib, encorafenib, binimetinib	✖	✖	✖	✖	● (II)
RX208	✖	✖	✖	✖	● (II)
tunlametinib, vemurafenib	✖	✖	✖	✖	● (II)
defactinib, avutometinib, encorafenib	✖	✖	✖	✖	● (I/II)
encorafenib, binimetinib, palbociclib	✖	✖	✖	✖	● (I/II)
nivolumab, tumor infiltrating lymphocytes, aldesleukin	✖	✖	✖	✖	● (I/II)
RX208, serplulimab	✖	✖	✖	✖	● (I/II)
RX208, trametinib	✖	✖	✖	✖	● (I/II)
tazemetostat, trametinib, dabrafenib	✖	✖	✖	✖	● (I/II)
vemurafenib, metformin hydrochloride	✖	✖	✖	✖	● (I/II)
binimetinib, nivolumab, encorafenib	✖	✖	✖	✖	● (I)
exarafenib, binimetinib	✖	✖	✖	✖	● (I)
HSK42360	✖	✖	✖	✖	● (I)
IK-595	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
nilotinib, dabrafenib, trametinib, encorafenib, binimetinib	✖	✖	✖	✖	● (I)
PF-07799544, PF-07799933	✖	✖	✖	✖	● (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

BRAF p.(V600E) c.1799T>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
PF-07799933, binimetinib	✖	✖	✖	✖	● (I)
RO-7276389, cobimetinib	✖	✖	✖	✖	● (I)

SMARCB1 deletion

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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (I/II)
TNG-462	✖	✖	✖	✖	● (I/II)
GTA-182	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
MRTX-1719	✖	✖	✖	✖	● (I)
PH020-803	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

CDK4 amplification

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

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

Relevant Therapy Summary (continued)

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

CDK4 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
PF-07220060, midazolam	✖	✖	✖	✖	● (I/II)

BRCA1 deletion

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

CDKN2A deletion

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

BAP1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	✖	✖	✖	● (II)
olaparib, pembrolizumab	✖	✖	✖	✖	● (II)

BARD1 deletion

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

BRIP1 deletion

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

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

Relevant Therapy Summary (continued)

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

CHEK2 deletion

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

NF2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BPI-460372	✖	✖	✖	✖	● (I)
IAG-933	✖	✖	✖	✖	● (I)

RAD50 deletion

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

ARID1B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib, pembrolizumab	✖	✖	✖	✖	● (II)

ARID2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib, pembrolizumab	✖	✖	✖	✖	● (II)

CDK12 deletion

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

CDKN2B deletion

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

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

Relevant Therapy Summary (continued)

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

ERBB3 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
HMBD001	✖	✖	✖	✖	● (I/II)

FANCD2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib, pembrolizumab	✖	✖	✖	✖	● (II)

FANCG deletion

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

FANCL deletion

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

LATS1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IAG-933	✖	✖	✖	✖	● (I)

RAD51C deletion

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

RAD51D deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***56.93%***
BRCA1	***CNV, CN:1.0***
BRCA1	***LOH, 17q21.31(41197602-41276123)x1***
BARD1	***CNV, CN:1.0***
BARD1	***LOH, 2q35(215593375-215674382)x1***
BRIP1	***CNV, CN:1.0***
BRIP1	***LOH, 17q23.2(59760627-59938976)x1***
CDK12	***CNV, CN:1.0***
CDK12	***LOH, 17q12(37618286-37687611)x1***
CHEK2	***CNV, CN:1.0***
CHEK2	***LOH, 22q12.1(29083868-29130625)x1***
FANCL	***CNV, CN:1.0***
FANCL	***LOH, 2p16.1(58386886-58468467)x1***
RAD51B	***CNV, CN:1.0***
RAD51B	***LOH, 14q24.1(68290164-69061406)x1***
RAD51C	***CNV, CN:1.0***
RAD51C	***LOH, 17q22(56769933-56811619)x1***
RAD51D	***CNV, CN:1.0***
RAD51D	***LOH, 17q12(33427950-33446720)x1***

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

Thermo Fisher Scientific's Ion Torrent 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 (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. 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. Lohkamp et al. Insights into the mechanism of dihydropyrimidine dehydrogenase from site-directed mutagenesis targeting the active site loop and redox cofactor coordination. Biochim Biophys Acta. 2010 Dec;1804(12):2198-206. PMID: 20831907
3. Innocenti et al. All You Need to Know About DPYD Genetic Testing for Patients Treated With Fluorouracil and Capecitabine: A Practitioner-Friendly Guide. JCO Oncol Pract. 2020 Dec;16(12):793-798. PMID: 33197222
4. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
5. 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
6. Jinawath et al. Alterations of type II classical cadherin, cadherin-10 (CDH10), is associated with pancreatic ductal adenocarcinomas. Genes Chromosomes Cancer. 2017 May;56(5):427-435. PMID: 28124395
7. Paredes et al. Epithelial E- and P-cadherins: role and clinical significance in cancer. Biochim Biophys Acta. 2012 Dec;1826(2):297-311. PMID: 22613680
8. Cavallaro et al. Cell adhesion and signalling by cadherins and Ig-CAMs in cancer. Nat Rev Cancer. 2004 Feb;4(2):118-32. PMID: 14964308
9. 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
10. Babon et al. The molecular regulation of Janus kinase (JAK) activation. Biochem. J. 2014 Aug 15;462(1):1-13. PMID: 25057888
11. 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
12. 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
13. Zaretsky et al. Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma. N. Engl. J. Med. 2016 Sep 1;375(9):819-29. PMID: 27433843
14. Garcia-Diaz et al. Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. Cell Rep. 2017 May 9;19(6):1189-1201. PMID: 28494868
15. Baxter et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005 Mar 19-25;365(9464):1054-61. PMID: 15781101
16. Kralovics et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N. Engl. J. Med. 2005 Apr 28;352(17):1779-90. PMID: 15858187
17. Hidalgo-López et al. Morphologic and Molecular Characteristics of De Novo AML With JAK2 V617F Mutation. J Natl Compr Canc Netw. 2017 Jun;15(6):790-796. PMID: 28596259
18. Aynardi et al. JAK2 V617F-positive acute myeloid leukaemia (AML): a comparison between de novo AML and secondary AML transformed from an underlying myeloproliferative neoplasm. A study from the Bone Marrow Pathology Group. Br. J. Haematol. 2018 Jul;182(1):78-85. PMID: 29767839
19. 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
20. Scott. Lymphoid malignancies: Another face to the Janus kinases. Blood Rev. 2013 Mar;27(2):63-70. PMID: 23340138
21. Chase et al. Ruxolitinib as potential targeted therapy for patients with JAK2 rearrangements. Haematologica. 2013 Mar;98(3):404-8. PMID: 22875628
22. Rumi et al. Efficacy of ruxolitinib in chronic eosinophilic leukemia associated with a PCM1-JAK2 fusion gene. J. Clin. Oncol. 2013 Jun 10;31(17):e269-71. PMID: 23630205
23. Schwaab et al. Limited duration of complete remission on ruxolitinib in myeloid neoplasms with PCM1-JAK2 and BCR-JAK2 fusion genes. Ann. Hematol. 2015 Feb;94(2):233-8. PMID: 25260694
24. Rumi et al. Efficacy of ruxolitinib in myeloid neoplasms with PCM1-JAK2 fusion gene. Ann. Hematol. 2015 Nov;94(11):1927-8. PMID: 26202607
25. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 1.2025]
26. Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719. PMID: 35732831
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202192s028lbl.pdf
28. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 3.2024]

References (continued)

29. Shin et al. Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations. Cancer Discov. 2017 Feb;7(2):188-201. PMID: 27903500
30. Patsialou et al. DNA-binding properties of ARID family proteins. Nucleic Acids Res. 2005;33(1):66-80. PMID: 15640446
31. Wang et al. The Role of ARID5B in Acute Lymphoblastic Leukemia and Beyond. Front Genet. 2020;11:598. PMID: 32595701
32. Niraj et al. The Fanconi Anemia Pathway in Cancer. Annu Rev Cancer Biol. 2019 Mar;3:457-478. PMID: 30882047
33. Rodríguez et al. Fanconi anemia pathway. Curr Biol. 2017 Sep 25;27(18):R986-R988. PMID: 28950089
34. 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
35. 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
36. Lord et al. BRCAness revisited. Nat. Rev. Cancer. 2016 Feb;16(2):110-20. PMID: 26775620
37. Byrum et al. Defining and Modulating 'BRCAness'. Trends Cell Biol. 2019 Sep;29(9):740-751. PMID: 31362850
38. 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
39. 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
40. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
41. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019 Jul 1;25(13):3759-3771. PMID: 30760478
42. https://www.senhwabio.com//en/news/20220125
43. Seetharaman et al. The RNA-binding protein LARP4 regulates cancer cell migration and invasion. Cytoskeleton (Hoboken). 2016 Nov;73(11):680-690. PMID: 27615744
44. Koso et al. Identification of RNA-Binding Protein LARP4B as a Tumor Suppressor in Glioma. Cancer Res. 2016 Apr 15;76(8):2254-64. PMID: 26933087
45. Vander et al. TGF-β receptors: In and beyond TGF-β signaling. Cell Signal. 2018 Dec;52:112-120. PMID: 30184463
46. Shi et al. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell. 2003 Jun 13;113(6):685-700. PMID: 12809600
47. Heldin et al. Role of Smads in TGFβ signaling. Cell Tissue Res. 2012 Jan;347(1):21-36. PMID: 21643690
48. Sorrentino et al. The type I TGF-beta receptor engages TRAF6 to activate TAK1 in a receptor kinase-independent manner. Nat Cell Biol. 2008 Oct;10(10):1199-207. PMID: 18758450
49. Ioannou et al. Smad4 and epithelial-mesenchymal transition proteins in colorectal carcinoma: an immunohistochemical study. J Mol Histol. 2018 Jun;49(3):235-244. PMID: 29468299
50. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
51. Kadyrova et al. Human MutLγ, the MLH1-MLH3 heterodimer, is an endonuclease that promotes DNA expansion. Proc Natl Acad Sci U S A. 2020 Feb 18;117(7):3535-3542. PMID: 32015124
52. Al-Sweel et al. mlh3 mutations in baker's yeast alter meiotic recombination outcomes by increasing noncrossover events genome-wide. PLoS Genet. 2017 Aug;13(8):e1006974. PMID: 28827832
53. Narayanan et al. Tumor Infiltrating Lymphocytes and Macrophages Improve Survival in Microsatellite Unstable Colorectal Cancer. Sci Rep. 2019 Sep 17;9(1):13455. PMID: 31530839
54. Tamura et al. Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. Int J Clin Oncol. 2019 Sep;24(9):999-1011. PMID: 31273487
55. Ikeda et al. Close correlation between mutations of E2F4 and hMSH3 genes in colorectal cancers with microsatellite instability. Cancer Res. 1998 Feb 15;58(4):594-8. PMID: 9485005
56. Gossage et al. VHL, the story of a tumour suppressor gene. Nat Rev Cancer. 2015 Jan;15(1):55-64. PMID: 25533676
57. NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 1.2025]
58. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. Breast Cancer Res. 2002;4(1):9-13. PMID: 11879553
59. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. Oncogene. 2002 Dec 16;21(58):8981-93. PMID: 12483514

References (continued)

60. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 Jun 20;317(23):2402-2416. PMID: 28632866
61. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J. Natl. Cancer Inst. 2007 Dec 5;99(23):1811-4. PMID: 18042939
62. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823
63. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis . JNCI Cancer Spectr. 2020 Aug;4(4):pkaa029. PMID: 32676552
64. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
65. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. Mayo Clin. Proc. 2010 Dec;85(12):1111-20. PMID: 21123638
66. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc. Natl. Acad. Sci. U.S.A. 2011 Nov 1;108(44):18032-7. PMID: 22006311
67. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J. Clin. Oncol. 2012 Jul 20;30(21):2654-63. PMID: 22711857
68. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiol. Biomarkers Prev. 2004 Dec;13(12):2078-83. PMID: 15598764
69. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643-6. PMID: 14576434
70. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br. J. Cancer. 2000 Nov;83(10):1301-8. PMID: 11044354
71. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. Environ Mol Mutagen. 2022 Jul;63(6):308-316. PMID: 36054589
72. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. Br. J. Cancer. 2018 Nov;119(11):1401-1409. PMID: 30353044
73. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005 Apr 14;434(7035):913-7. PMID: 15829966
74. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917-21. PMID: 15829967
75. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
76. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf
77. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214876s000lbl.pdf
78. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
79. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. J. Pathol. 2013 Feb;229(3):422-9. PMID: 23165508
80. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
81. https://ir.tangotx.com//news-releases/news-release-details/tango-therapeutics-reports-third-quarter-2023-financial-results
82. 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
83. Duan et al. Fanconi anemia repair pathway dysfunction, a potential therapeutic target in lung cancer. Front Oncol. 2014 Dec 19;4:368. doi: 10.3389/fonc.2014.00368. eCollection 2014. PMID: 25566506
84. Murata et al. Predictors and Modulators of Synthetic Lethality: An Update on PARP Inhibitors and Personalized Medicine. Biomed Res Int. 2016;2016:2346585. doi: 10.1155/2016/2346585. Epub 2016 Aug 24. PMID: 27642590
85. 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
86. Burnichon et al. SDHA is a tumor suppressor gene causing paraganglioma. Hum Mol Genet. 2010 Aug 1;19(15):3011-20. PMID: 20484225
87. 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

References (continued)

88. 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
89. Gan et al. Epigenetic regulation of cancer progression by EZH2: from biological insights to therapeutic potential. 6:10. PMID: 29556394
90. Yamagishi et al. Targeting EZH2 in cancer therapy. Curr Opin Oncol. 2017 Sep;29(5):375-381. PMID: 28665819
91. Li. EZH2: novel therapeutic target for human cancer. 4:1. PMID: 25520914
92. Morin et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. Nat. Genet. 2010 Feb;42(2):181-5. PMID: 20081860
93. Saramäki et al. The gene for polycomb group protein enhancer of zeste homolog 2 (EZH2) is amplified in late-stage prostate cancer. Genes Chromosomes Cancer. 2006 Jul;45(7):639-45. PMID: 16575874
94. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/211723s005lbl.pdf
95. https://ashpublications.org/ashclinicalnews/news/2804/FDA-Grants-Fast-Track-Designation-to-Tazemetostat
96. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
97. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2025]
98. 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
99. Sauvageau et al. Polycomb group proteins: multi-faceted regulators of somatic stem cells and cancer. Cell Stem Cell. 2010 Sep 3;7(3):299-313. PMID: 20804967
100. Gardner et al. Chemosensitive Relapse in Small Cell Lung Cancer Proceeds through an EZH2-SLFN11 Axis. Cancer Cell. 2017 Feb 13;31(2):286-299. PMID: 28196596
101. Fan et al. Inhibition of EZH2 reverses chemotherapeutic drug TMZ chemosensitivity in glioblastoma. Int J Clin Exp Pathol. 2014;7(10):6662-70. PMID: 25400745
102. Amé et al. The PARP superfamily. Bioessays. 2004 Aug;26(8):882-93. PMID: 15273990
103. 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
104. Rulten et al. PARP-3 and APLF function together to accelerate nonhomologous end-joining. Mol Cell. 2011 Jan 7;41(1):33-45. PMID: 21211721
105. Beck et al. PARP3 affects the relative contribution of homologous recombination and nonhomologous end-joining pathways. Nucleic Acids Res. 2014 May;42(9):5616-32. PMID: 24598253
106. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
107. 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
108. Tandon et al. Emerging strategies for EphA2 receptor targeting for cancer therapeutics. Expert Opin Ther Targets. 2011 Jan;15(1):31-51. PMID: 21142802
109. Wilson et al. SWI/SNF nucleosome remodellers and cancer. Nat. Rev. Cancer. 2011 Jun 9;11(7):481-92. PMID: 21654818
110. Hodges et al. The Many Roles of BAF (mSWI/SNF) and PBAF Complexes in Cancer. Cold Spring Harb Perspect Med. 2016 Aug 1;6(8). PMID: 27413115
111. Thompson. Polybromo-1: the chromatin targeting subunit of the PBAF complex. Biochimie. 2009 Mar;91(3):309-19. PMID: 19084573
112. Hopson et al. BAF180: Its Roles in DNA Repair and Consequences in Cancer. ACS Chem Biol. 2017 Oct 20;12(10):2482-2490. PMID: 28921948
113. Carril-Ajuria et al. Cancers (Basel). 2019 Dec 19;12(1). PMID: 31861590
114. Zhang et al. Role of RASA1 in cancer: A review and update (Review). Oncol Rep. 2020 Dec;44(6):2386-2396. PMID: 33125148
115. King et al. Nonredundant functions for Ras GTPase-activating proteins in tissue homeostasis. Sci Signal. 2013 Feb 26;6(264):re1. PMID: 23443682
116. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. Nat Commun. 8;14648. PMID: 28262751
117. Weissmiller et al. Inhibition of MYC by the SMARCB1 Tumor Suppressor. Nat Commun. 10 (1). PMID: 31043611
118. 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

References (continued)

119. Fitzhugh. Rhabdoid Tumor Predisposition Syndrome and Pleuropulmonary Blastoma Syndrome. J Pediatr Genet. 2016 Jun;5(2):124-8. PMID: 27617153
120. 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
121. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 5.2024]
122. Pantaleo et al. Front Oncol. 2021;11:778461. PMID: 35059314
123. Oudijk et al. SDHA mutations in adult and pediatric wild-type gastrointestinal stromal tumors. Mod Pathol. 2013 Mar;26(3):456-63. PMID: 23174939
124. Zhao et al. ARID2: a new tumor suppressor gene in hepatocellular carcinoma. Oncotarget. 2011 Nov;2(11):886-91. PMID: 22095441
125. Zhao et al. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for anti-PD-1/PD-L1 Immunotherapy Efficacy. J Hematol Oncol. 12(1),54. PMID: 31151482
126. Berends et al. MLH1 and MSH2 protein expression as a pre-screening marker in hereditary and non-hereditary endometrial hyperplasia and cancer. Int. J. Cancer. 2001 May 1;92(3):398-403. PMID: 11291077
127. Gausachs et al. MLH1 promoter hypermethylation in the analytical algorithm of Lynch syndrome: a cost-effectiveness study. Eur. J. Hum. Genet. 2012 Jul;20(7):762-8. PMID: 22274583
128. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. Clin Cancer Res. 2010 Nov 1;16(21):5107-13. PMID: 20823149
129. Lynch et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. 2009 Jul;76(1):1-18. PMID: 19659756
130. 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
131. 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
132. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
133. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
134. 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
135. Bonadona et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011 Jun 8;305(22):2304-10. PMID: 21642682
136. Engel et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012 Dec 10;30(35):4409-15. PMID: 23091106
137. Grant et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015 Mar;148(3):556-64. PMID: 25479140
138. Hu et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. 2018 Jun 19;319(23):2401-2409. PMID: 29922827
139. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
140. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf
141. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
142. Buccoliero et al. Pediatric High Grade Glioma Classification Criteria and Molecular Features of a Case Series. Genes (Basel). 2022 Mar 31;13(4). PMID: 35456430
143. Friker et al. MSH2, MSH6, MLH1, and PMS2 immunohistochemistry as highly sensitive screening method for DNA mismatch repair deficiency syndromes in pediatric high-grade glioma. Acta Neuropathol. 2025 Feb 2;149(1):11. PMID: 39894875
144. Somyajit et al. RAD51C: a novel cancer susceptibility gene is linked to Fanconi anemia and breast cancer. Carcinogenesis. 2010 Dec;31(12):2031-8. PMID: 20952512
145. Sullivan et al. RAD-ical New Insights into RAD51 Regulation. Genes (Basel). 2018 Dec 13;9(12). PMID: 30551670
146. Suwaki et al. RAD51 paralogs: roles in DNA damage signalling, recombinational repair and tumorigenesis. Semin. Cell Dev. Biol. 2011 Oct;22(8):898-905. PMID: 21821141
147. Chun et al. Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. Mol. Cell. Biol. 2013 Jan;33(2):387-95. PMID: 23149936

References (continued)

148. Badie et al. RAD51C facilitates checkpoint signaling by promoting CHK2 phosphorylation. J. Cell Biol. 2009 May 18;185(4):587-600. PMID: 19451272
149. Renglin et al. RAD51C (RAD51L2) is involved in maintaining centrosome number in mitosis. Cytogenet. Genome Res. 2007;116(1-2):38-45. PMID: 17268176
150. 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
151. Min et al. RAD51C-deficient cancer cells are highly sensitive to the PARP inhibitor olaparib. Mol. Cancer Ther. 2013 Jun;12(6):865-77. PMID: 23512992
152. Godin et al. Novel insights into RAD51 activity and regulation during homologous recombination and DNA replication. Biochem. Cell Biol. 2016 Oct;94(5):407-418. PMID: 27224545
153. Date et al. Haploinsufficiency of RAD51B causes centrosome fragmentation and aneuploidy in human cells. Cancer Res. 2006 Jun 15;66(12):6018-24. PMID: 16778173
154. Pelttari et al. RAD51B in Familial Breast Cancer. PLoS ONE. 2016;11(5):e0153788. PMID: 27149063
155. Ali et al. BRIP-1 germline mutation and its role in colon cancer: presentation of two case reports and review of literature. BMC Med Genet. 2019 May 7;20(1):75. PMID: 31064327
156. Daino et al. Loss of the BRCA1-interacting helicase BRIP1 results in abnormal mammary acinar morphogenesis. PLoS ONE. 2013;8(9):e74013. PMID: 24040146
157. Taniguchi et al. Molecular pathogenesis of Fanconi anemia: recent progress. Blood. 2006 Jun 1;107(11):4223-33. PMID: 16493006
158. Weber-Lassalle et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. Breast Cancer Res. 2018 Jan 24;20(1):7. PMID: 29368626
159. Ramus et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J. Natl. Cancer Inst. 2015 Nov;107(11). PMID: 26315354
160. Pennington et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin. Cancer Res. 2014 Feb 1;20(3):764-75. PMID: 24240112
161. Morris et al. BRCA1 : BARD1 induces the formation of conjugated ubiquitin structures, dependent on K6 of ubiquitin, in cells during DNA replication and repair. Hum. Mol. Genet. 2004 Apr 15;13(8):807-17. PMID: 14976165
162. Baer et al. The BRCA1/BARD1 heterodimer, a tumor suppressor complex with ubiquitin E3 ligase activity. Curr. Opin. Genet. Dev. 2002 Feb;12(1):86-91. PMID: 11790560
163. Zhao et al. BRCA1-BARD1 promotes RAD51-mediated homologous DNA pairing. Nature. 2017 Oct 19;550(7676):360-365. PMID: 28976962
164. Cimmino et al. Dualistic Role of BARD1 in Cancer. Genes (Basel). 2017 Dec 8;8(12). PMID: 29292755
165. De et al. BRCAness: a deeper insight into basal-like breast tumors. Ann. Oncol. 2013 Nov;24 Suppl 8:viii13-viii21. PMID: 24131964
166. 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
167. Irminger-Finger et al. Identification of BARD1 as mediator between proapoptotic stress and p53-dependent apoptosis. Mol. Cell. 2001 Dec;8(6):1255-66. PMID: 11779501
168. Thai et al. Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian and uterine cancers. Hum. Mol. Genet. 1998 Feb;7(2):195-202. PMID: 9425226
169. 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
170. Petrilli et al. Role of Merlin/NF2 inactivation in tumor biology. Oncogene. 2016 Feb 4;35(5):537-48. PMID: 25893302
171. 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
172. 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
173. 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
174. https://ir.ikenaoncology.com//news-releases/news-release-details/ikena-oncology-receives-fda-fast-track-designation-novel-tead
175. Qiao et al. Hepatology. 2019 Dec;70(6):2003-2017. PMID: 30737831
176. Tuteja. Signaling through G protein coupled receptors. Plant Signal Behav. 2009 Oct;4(10):942-7. PMID: 19826234

References (continued)

177. Kishida et al. DIX domains of Dvl and axin are necessary for protein interactions and their ability to regulate beta-catenin stability. Mol Cell Biol. 1999 Jun;19(6):4414-22. PMID: 10330181
178. Komiya et al. Wnt signal transduction pathways. Organogenesis. 2008 Apr;4(2):68-75. PMID: 19279717
179. Zhang et al. J Hematol Oncol. 2020 Dec 4;13(1):165. PMID: 33276800
180. Fu et al. Eur Rev Med Pharmacol Sci. 2020 Jan;24(1):418-427. PMID: 31957856
181. Hadjihannas et al. EMBO Rep. 2012 Apr;13(4):347-54. PMID: 22322943
182. Cai et al. Mol Med Rep. 2012 May;5(5):1191-6. PMID: 22367735
183. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
184. 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
185. 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
186. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
187. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
188. 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
189. 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
190. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
191. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
192. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
193. 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
194. 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
195. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
196. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
197. Wang et al. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. Cell. Physiol. Biochem. 2018;51(6):2647-2693. PMID: 30562755
198. Stamos et al. The β-catenin destruction complex. Cold Spring Harb Perspect Biol. 2013 Jan 1;5(1):a007898. PMID: 23169527
199. Minde et al. Messing up disorder: how do missense mutations in the tumor suppressor protein APC lead to cancer?. Mol Cancer. 2011 Aug 22;10:101. doi: 10.1186/1476-4598-10-101. PMID: 21859464
200. Aoki et al. Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. J. Cell. Sci. 2007 Oct 1;120(Pt 19):3327-35. PMID: 17881494
201. Miyoshi et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. Hum. Mol. Genet. 1992 Jul;1(4):229-33. PMID: 1338904
202. 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
203. Rowan et al. APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". Proc. Natl. Acad. Sci. U.S.A. 2000 Mar 28;97(7):3352-7. PMID: 10737795
204. Laurent-Puig et al. APC gene: database of germline and somatic mutations in human tumors and cell lines. Nucleic Acids Res. 1998 Jan 1;26(1):269-70. PMID: 9399850
205. Martins et al. Transcriptional repressor Blimp-1 regulates T cell homeostasis and function. Nat Immunol. 2006 May;7(5):457-65. PMID: 16565721
206. Nutt et al. BLIMP1 guides the fate of effector B and T cells. Nat Rev Immunol. 2007 Dec;7(12):923-7. PMID: 17965637
207. 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

References (continued)

208. Kallies et al. Terminal differentiation of lymphocytes depends on Blimp-1. Curr Opin Immunol. 2007 Apr;19(2):156-62. PMID: 17291741
209. Merchant et al. Suppressor of fused regulates Gli activity through a dual binding mechanism. Mol Cell Biol. 2004 Oct;24(19):8627-41. PMID: 15367681
210. Zhang et al. Structural insight into the mutual recognition and regulation between Suppressor of Fused and Gli/Ci. Nat Commun. 2013;4:2608. PMID: 24217340
211. Cherry et al. Structural basis of SUFU-GLI interaction in human Hedgehog signalling regulation. Acta Crystallogr D Biol Crystallogr. 2013 Dec;69(Pt 12):2563-79. PMID: 24311597
212. Doheny et al. Hedgehog Signaling and Truncated GLI1 in Cancer. Cells. 2020 Sep 17;9(9). PMID: 32957513
213. Guerrini-Rousseau et al. Germline SUFU mutation carriers and medulloblastoma: clinical characteristics, cancer risk, and prognosis. Neuro Oncol. 2018 Jul 5;20(8):1122-1132. PMID: 29186568
214. Katsumura et al. The GATA factor revolution in hematology. Blood. 2017 Apr 13;129(15):2092-2102. PMID: 28179282
215. Orkin. GATA-binding transcription factors in hematopoietic cells. Blood. 1992 Aug 1;80(3):575-81. PMID: 1638017
216. Takaku et al. GATA3 in Breast Cancer: Tumor Suppressor or Oncogene?. Gene Expr. 2015;16(4):163-8. PMID: 26637396
217. Chou et al. GATA3 in development and cancer differentiation: cells GATA have it!. J Cell Physiol. 2010 Jan;222(1):42-9. PMID: 19798694
218. Mehra et al. Identification of GATA3 as a breast cancer prognostic marker by global gene expression meta-analysis. Cancer Res. 2005 Dec 15;65(24):11259-64. PMID: 16357129
219. Debaize et al. The master regulator FUBP1: its emerging role in normal cell function and malignant development. Cell Mol Life Sci. 2019 Jan;76(2):259-281. PMID: 30343319
220. Xia et al. Dominant role of CDKN2B/p15INK4B of 9p21.3 tumor suppressor hub in inhibition of cell-cycle and glycolysis. Nat Commun. 2021 Apr 6;12(1):2047. PMID: 33824349
221. Scruggs et al. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. Am. J. Respir. Cell Mol. Biol. 2018 Aug;59(2):200-214. PMID: 29420051
222. Roussel. The INK4 family of cell cycle inhibitors in cancer. Oncogene. 1999 Sep 20;18(38):5311-7. PMID: 10498883
223. Aytac et al. Rb independent inhibition of cell growth by p15(INK4B). Biochem. Biophys. Res. Commun. 1999 Aug 27;262(2):534-8. PMID: 10462509
224. Hill et al. The genetics of melanoma: recent advances. Annu Rev Genomics Hum Genet. 2013;14:257-79. PMID: 23875803
225. Kim et al. The regulation of INK4/ARF in cancer and aging. Cell. 2006 Oct 20;127(2):265-75. PMID: 17055429
226. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. Mayo Clin. Proc. 2008 Jul;83(7):825-46. PMID: 18613999
227. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. J. Invest. Dermatol. 2007 May;127(5):1234-43. PMID: 17218939
228. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. Ann. Surg. 2002 Dec;236(6):730-7. PMID: 12454511
229. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. Clin Cancer Res. 2021 Jul 15;27(14):4025-4035. PMID: 34074656
230. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2025]
231. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2025]
232. Louis et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol. 2020 Jul;30(4):844-856. PMID: 32307792
233. Longwen et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. J Transl Med. 2019 Jul 29;17(1):245. PMID: 31358010
234. Logan et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. Anticancer Res. 2013 Aug;33(8):2997-3004. PMID: 23898052
235. von et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmocological Inhibitors of the CDK4/6 Cell-Cycle Pathway. Cancer Res. 2015 Sep 15;75(18):3823-31. PMID: 26183925
236. Cen et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. Neuro-oncology. 2012 Jul;14(7):870-81. PMID: 22711607
237. Vitzthum et al. The role of p16 as a biomarker in nonoropharyngeal head and neck cancer. Oncotarget. 2018 Sep 7;9(70):33247-33248. PMID: 30279955

References (continued)

238. Chung et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J. Clin. Oncol. 2014 Dec 10;32(35):3930-8. PMID: 25267748
239. Bryant et al. Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer. J. Natl. Cancer Inst. 2018 Dec 1;110(12):1393-1399. PMID: 29878161
240. Stephen et al. Significance of p16 in Site-specific HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma. Cancer Clin Oncol. 2013;2(1):51-61. PMID: 23935769
241. Liu et al. Tyrosine phosphorylation activates 6-phosphogluconate dehydrogenase and promotes tumor growth and radiation resistance. Nat Commun. 2019 Mar 1;10(1):991. PMID: 30824700
242. Patra et al. The pentose phosphate pathway and cancer. Trends Biochem Sci. 2014 Aug;39(8):347-54. PMID: 25037503
243. Kowalik et al. Emerging Role of the Pentose Phosphate Pathway in Hepatocellular Carcinoma. Front Oncol. 2017;7:87. PMID: 28553614
244. Rao et al. O-GlcNAcylation of G6PD promotes the pentose phosphate pathway and tumor growth. Nat Commun. 2015 Sep 24;6:8468. PMID: 26399441
245. Jafri et al. Germline Mutations in the CDKN2B Tumor Suppressor Gene Predispose to Renal Cell Carcinoma. . Cancer Discov.2015 Jul;5(7):723-9. PMID: 25873077
246. Tu et al. CDKN2B deletion is essential for pancreatic cancer development instead of unmeaningful co-deletion due to juxtaposition to CDKN2A. Oncogene. 2018 Jan 4;37(1):128-138. PMID: 28892048
247. Froimchuk et al. Histone H3 lysine 4 methyltransferase KMT2D. Gene. 2017 Sep 5;627:337-342. PMID: 28669924
248. Fagan et al. COMPASS Ascending: Emerging clues regarding the roles of MLL3/KMT2C and MLL2/KMT2D proteins in cancer. Cancer Lett. 2019 Aug 28;458:56-65. PMID: 31128216
249. Wang et al. Resetting the epigenetic balance of Polycomb and COMPASS function at enhancers for cancer therapy. Nat Med. 2018 Jun;24(6):758-769. PMID: 29785026
250. Masclef et al. Roles and mechanisms of BAP1 deubiquitinase in tumor suppression. Cell Death Differ. 2021 Feb;28(2):606-625. PMID: 33462414
251. Malgorzata et al. CDK12 loss in cancer cells affects DNA damage response genes through premature cleavage and polyadenylation. Nat Commun . 2019 Apr 15;10(1):1757. PMID: 30988284
252. Joshi et al. Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. J. Biol. Chem. 2014 Mar 28;289(13):9247-53. PMID: 24554720
253. Blazek et al. The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. Genes Dev. 2011 Oct 15;25(20):2158-72. PMID: 22012619
254. Paculová et al. The emerging roles of CDK12 in tumorigenesis. . doi: 10.1186/s13008-017-0033-x. eCollection 2017. PMID: 29090014
255. Murali et al. Tumours associated with BAP1 mutations. Pathology. 2013 Feb;45(2):116-26. PMID: 23277170
256. Wiesner et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat. Genet. 2011 Aug 28;43(10):1018-21. PMID: 21874003
257. Wadt et al. A cryptic BAP1 splice mutation in a family with uveal and cutaneous melanoma, and paraganglioma. Pigment Cell Melanoma Res. 2012 Nov;25(6):815-8. PMID: 22889334
258. Cheung et al. Further evidence for germline BAP1 mutations predisposing to melanoma and malignant mesothelioma. Cancer Genet. 2013 May;206(5):206-10. PMID: 23849051
259. Njauw et al. Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families. PLoS ONE. 2012;7(4):e35295. PMID: 22545102
260. Pilarski et al. Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases. Genes Chromosomes Cancer. 2014 Feb;53(2):177-82. PMID: 24243779
261. Popova et al. Germline BAP1 mutations predispose to renal cell carcinomas. Am. J. Hum. Genet. 2013 Jun 6;92(6):974-80. PMID: 23684012
262. So et al. The TNF-TNFR Family of Co-signal Molecules. Adv Exp Med Biol. 2019;1189:53-84. PMID: 31758531
263. Costello et al. Stimulation of non-Hodgkin's lymphoma via HVEM: an alternate and safe way to increase Fas-induced apoptosis and improve tumor immunogenicity. Leukemia. 2003 Dec;17(12):2500-7. PMID: 14562115
264. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 2.2025]

References (continued)

265. Launay et al. High rate of TNFRSF14 gene alterations related to 1p36 region in de novo follicular lymphoma and impact on prognosis. Leukemia. 2012 Mar;26(3):559-62. PMID: 21941365
266. Cheung et al. Acquired TNFRSF14 mutations in follicular lymphoma are associated with worse prognosis. Cancer Res. 2010 Nov 15;70(22):9166-74. PMID: 20884631
267. Cheung et al. Targeting therapeutic liabilities engendered by PIK3R1 mutations for cancer treatment. Pharmacogenomics. 2016 Feb;17(3):297-307. PMID: 26807692
268. Cantley. The phosphoinositide 3-kinase pathway. Science. 2002 May 31;296(5573):1655-7. PMID: 12040186
269. Fruman et al. The PI3K Pathway in Human Disease. Cell. 2017 Aug 10;170(4):605-635. PMID: 28802037
270. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat. Rev. Genet. 2006 Aug;7(8):606-19. PMID: 16847462
271. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. Nat. Rev. Mol. Cell Biol. 2012 Feb 23;13(3):195-203. PMID: 22358332
272. Chagpar et al. Direct positive regulation of PTEN by the p85 subunit of phosphatidylinositol 3-kinase. Proc. Natl. Acad. Sci. U.S.A. 2010 Mar 23;107(12):5471-6. PMID: 20212113
273. Malynn et al. A20: A multifunctional tool for regulating immunity and preventing disease. Cell Immunol. 2019 Jun;340:103914. PMID: 31030956
274. Giordano et al. The tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20) imposes a brake on antitumor activity of CD8 T cells. Proc Natl Acad Sci U S A. 2014 Jul 29;111(30):11115-20. PMID: 25024217
275. Küppers. The biology of Hodgkin's lymphoma. Nat Rev Cancer. 2009 Jan;9(1):15-27. PMID: 19078975
276. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
277. Sherr et al. Targeting CDK4 and CDK6: From Discovery to Therapy. Cancer Discov. 2016 Apr;6(4):353-67. PMID: 26658964
278. Weinberg. The retinoblastoma protein and cell cycle control. Cell. 1995 May 5;81(3):323-30. PMID: 7736585
279. Rane et al. Germ line transmission of the Cdk4(R24C) mutation facilitates tumorigenesis and escape from cellular senescence. Mol. Cell. Biol. 2002 Jan;22(2):644-56. PMID: 11756559
280. Zuo et al. Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. Nat. Genet. 1996 Jan;12(1):97-9. PMID: 8528263
281. Molven et al. A large Norwegian family with inherited malignant melanoma, multiple atypical nevi, and CDK4 mutation. Genes Chromosomes Cancer. 2005 Sep;44(1):10-8. PMID: 15880589
282. Ceha et al. Several noncontiguous domains of CDK4 are involved in binding to the P16 tumor suppressor protein. Biochem. Biophys. Res. Commun. 1998 Aug 19;249(2):550-5. PMID: 9712735
283. Tsao et al. Novel mutations in the p16/CDKN2A binding region of the cyclin-dependent kinase-4 gene. Cancer Res. 1998 Jan 1;58(1):109-13. PMID: 9426066
284. Sotillo et al. Invasive melanoma in Cdk4-targeted mice. Proc. Natl. Acad. Sci. U.S.A. 2001 Nov 6;98(23):13312-7. PMID: 11606789
285. 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
286. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
287. Maskin et al. PPP6C, a serine-threonine phosphatase, regulates melanocyte differentiation and contributes to melanoma tumorigenesis through modulation of MITF activity. Sci Rep. 2022 Apr 2;12(1):5573. PMID: 35368039
288. Cho et al. PPP6C negatively regulates oncogenic ERK signaling through dephosphorylation of MEK. Cell Rep. 2021 Mar 30;34(13):108928. PMID: 33789117
289. Wandzioch et al. PME-1 modulates protein phosphatase 2A activity to promote the malignant phenotype of endometrial cancer cells. Cancer Res. 2014 Aug 15;74(16):4295-305. PMID: 24928782
290. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science. 1985 Sep 6;229(4717):974-6. PMID: 2992089
291. Knighton et al. Structural features that specify tyrosine kinase activity deduced from homology modeling of the epidermal growth factor receptor. Proc. Natl. Acad. Sci. U.S.A. 1993 Jun 1;90(11):5001-5. PMID: 8389462
292. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
293. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011 Jun 29;474(7353):609-15. PMID: 21720365

References (continued)

294. Cancer et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73. PMID: 23636398
295. Donna et al. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7. PMID: 22810696
296. Mujoo et al. Regulation of ERBB3/HER3 signaling in cancer. Oncotarget. 2014 Nov 15;5(21):10222-36. PMID: 25400118
297. Gaborit et al. Emerging anti-cancer antibodies and combination therapies targeting HER3/ERBB3. Hum Vaccin Immunother. 2016 Mar 3;12(3):576-92. PMID: 26529100
298. Mishra et al. Genomic alterations of ERBB receptors in cancer: clinical implications. Oncotarget. 2017 Dec 26;8(69):114371-114392. PMID: 29371993
299. Jaiswal et al. Oncogenic ERBB3 mutations in human cancers. Cancer Cell. 2013 May 13;23(5):603-17. PMID: 23680147
300. Zhang et al. HER3/ErbB3, an emerging cancer therapeutic target. Acta Biochim. Biophys. Sin. (Shanghai). 2016 Jan;48(1):39-48. PMID: 26496898
301. Ross et al. Targeting HER2 in colorectal cancer: The landscape of amplification and short variant mutations in ERBB2 and ERBB3. Cancer. 2018 Apr 1;124(7):1358-1373. PMID: 29338072
302. Verlingue et al. Human epidermal receptor family inhibitors in patients with ERBB3 mutated cancers: Entering the back door. Eur. J. Cancer. 2018 Mar;92:1-10. PMID: 29413684
303. 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
304. 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
305. 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
306. 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
307. Schmelzle et al. Esophageal cancer proliferation is mediated by cytochrome P450 2C9 (CYP2C9). Prostaglandins Other Lipid Mediat. 2011 Feb;94(1-2):25-33. PMID: 21167292
308. Sausville et al. The Cytochrome P450 Slow Metabolizers CYP2C9*2 and CYP2C9*3 Directly Regulate Tumorigenesis via Reduced Epoxyeicosatrienoic Acid Production. Cancer Res. 2018 Sep 1;78(17):4865-4877. PMID: 30012669
309. Wei et al. Elevated 14,15- epoxyeicosatrienoic acid by increasing of cytochrome P450 2C8, 2C9 and 2J2 and decreasing of soluble epoxide hydrolase associated with aggressiveness of human breast cancer. BMC Cancer. 2014 Nov 18;14:841. PMID: 25406731
310. Jernström et al. CYP2C8 and CYP2C9 polymorphisms in relation to tumour characteristics and early breast cancer related events among 652 breast cancer patients. Br J Cancer. 2009 Dec 1;101(11):1817-23. PMID: 19935798
311. Valer et al. ACVR1 Function in Health and Disease. Cells. 2019 Oct 31;8(11). PMID: 31683698
312. Haupt et al. Variable signaling activity by FOP ACVR1 mutations. Bone. 2018 Apr;109:232-240. PMID: 29097342
313. Su et al. ACVR1B (ALK4, activin receptor type 1B) gene mutations in pancreatic carcinoma. Proc Natl Acad Sci U S A. 2001 Mar 13;98(6):3254-7. PMID: 11248065
314. Togashi et al. Homozygous deletion of the activin A receptor, type IB gene is associated with an aggressive cancer phenotype in pancreatic cancer. Mol Cancer. 2014 May 27;13:126. PMID: 24886203
315. Philpott et al. The NF1 somatic mutational landscape in sporadic human cancers. 2017 Jun 21;11(1):13. doi: 10.1186/s40246-017-0109-3. PMID: 28637487
316. Scheffzek et al. The Ras-RasGAP complex: structural basis for GTPase activation and its loss in oncogenic Ras mutants. Science. 1997 Jul 18;277(5324):333-8. PMID: 9219684
317. Fioretos et al. Isochromosome 17q in blast crisis of chronic myeloid leukemia and in other hematologic malignancies is the result of clustered breakpoints in 17p11 and is not associated with coding TP53 mutations. Blood. 1999 Jul 1;94(1):225-32. PMID: 10381517
318. Brems et al. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. Lancet Oncol. 2009 May;10(5):508-15. PMID: 19410195
319. Peng et al. Role of FAT1 in health and disease. Oncol Lett. 2021 May;21(5):398. PMID: 33777221
320. Furth et al. The LATS1 and LATS2 tumor suppressors: beyond the Hippo pathway. Cell Death Differ. 2017 Sep;24(9):1488-1501. PMID: 28644436

References (continued)

321. Leroux et al. AGC kinases, mechanisms of regulation #and innovative drug development. Semin Cancer Biol. 2018 Feb;48:1-17. PMID: 28591657
322. Meng et al. Mechanisms of Hippo pathway regulation. Genes Dev. 2016 Jan 1;30(1):1-17. PMID: 26728553
323. Yu et al. Mutation analysis of large tumor suppressor genes LATS1 and LATS2 supports a tumor suppressor role in human cancer. Protein Cell. 2015 Jan;6(1):6-11. PMID: 25482410
324. Harasawa et al. Chemotherapy targeting methylthioadenosine phosphorylase (MTAP) deficiency in adult T cell leukemia (ATL). Leukemia. 2002 Sep;16(9):1799-807. PMID: 12200696
325. Bertino et al. Targeting tumors that lack methylthioadenosine phosphorylase (MTAP) activity: current strategies. Cancer Biol Ther. 2011 Apr 1;11(7):627-32. PMID: 21301207
326. Katya et al. Cancer Dependencies: PRMT5 and MAT2A in MTAP/p16-Deleted Cancers. 10.1146/annurev-cancerbio-030419-033444
327. Ouzzine et al. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. Front Cell Neurosci. 2014;8:349. PMID: 25389387
328. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. Oncogene. 2006 Mar 13;25(11):1659-72. PMID: 16550166
329. Allain et al. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. Br J Cancer. 2020 Apr;122(9):1277-1287. PMID: 32047295
330. Izumi et al. Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. Mol Carcinog. 2014 Apr;53(4):314-24. PMID: 23143693
331. Sundararaghavan et al. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas?. Oncotarget. 2017 Jan 10;8(2):3640-3648. PMID: 27690298
332. Lu et al. Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. PLoS One. 2015;10(5):e0127524. PMID: 26010150
333. Karas et al. JCO Oncol Pract. 2021 Dec 3:OP2100624. PMID: 34860573
334. Andreassen et al. XRCC2 (X-ray repair cross complementing 2). Atlas Genet Cytogenet Oncol Haematol. 2019 Jan;23(1):1-7. PMID: 31275435
335. Shamseldin et al. Exome sequencing reveals a novel Fanconi group defined by XRCC2 mutation. J Med Genet. 2012 Mar;49(3):184-6. PMID: 22232082
336. Park et al. Complementation of hypersensitivity to DNA interstrand crosslinking agents demonstrates that XRCC2 is a Fanconi anaemia gene. J Med Genet. 2016 Oct;53(10):672-680. PMID: 27208205
337. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
338. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. Annu Rev Immunol. 2013;31:529-61. PMID: 23298204
339. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
340. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
341. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
342. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. Cancers (Basel). 2020 Jul 2;12(7). PMID: 32630675
343. Cuneo et al. The ubiquitin ligase adaptor SPOP in cancer. FEBS Journal. PMID: 31495053
344. Clark et al. SPOP and cancer: a systematic review. Am J Cancer Res. 2020;10(3):704-726. PMID: 32266086
345. Janouskova et al. Opposing effects of cancer-type-specific SPOP mutants on BET protein degradation and sensitivity to BET inhibitors. Nat Med. 2017 Sep;23(9):1046-1054. PMID: 28805821
346. Ludimila. Opposing Roles of SPOP Mutations in Human Prostate and Endometrial Cancers. JCO Precis Oncol . 2023 Sep:7:e2300088. . PMID: 37677121
347. Yuryev et al. The RAF family: an expanding network of post-translational controls and protein-protein interactions. Cell Res. 1998 Jun;8(2):81-98. PMID: 9669024
348. Cheng et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. Mod. Pathol. 2018 Jan;31(1):24-38. PMID: 29148538

References (continued)

349. Alrabadi et al. Detection of driver mutations in BRAF can aid in diagnosis and early treatment of dedifferentiated metastatic melanoma. Mod. Pathol. 2019 Mar;32(3):330-337. PMID: 30315274
350. Quan et al. The association between BRAF mutation class and clinical features in BRAF-mutant Chinese non-small cell lung cancer patients. Journal of Translational Medicine, 29 Aug 2019, 17(1):298. PMID: 31470866
351. Yao et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. Nature. 2017 Aug 10;548(7666):234-238. PMID: 28783719
352. Bracht et al. BRAF Mutations Classes I, II, and III in NSCLC Patients Included in the SLLIP Trial: The Need for a New Pre-Clinical Treatment Rationale. Cancers (Basel). 2019 Sep 17;11(9). PMID: 31533235
353. Wan et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell. 2004 Mar 19;116(6):855-67. PMID: 15035987
354. Tiacci et al. BRAF mutations in hairy-cell leukemia. N. Engl. J. Med. 2011 Jun 16;364(24):2305-15. PMID: 21663470
355. Diamond et al. Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. Cancer Discov. 2016 Feb;6(2):154-65. doi: 10.1158/2159-8290.CD-15-0913. Epub 2015 Nov 13. PMID: 26566875
356. Imielinski et al. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. J Clin Invest. 2014 Apr;124(4):1582-6. doi: 10.1172/JCI72763. Epub 2014 Feb 24. PMID: 24569458
357. Ciampi et al. Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. J. Clin. Invest. 2005 Jan;115(1):94-101. PMID: 15630448
358. Palanisamy et al. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. Nat. Med. 2010 Jul;16(7):793-8. PMID: 20526349
359. Jones et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res. 2008 Nov 1;68(21):8673-7. PMID: 18974108
360. Cin et al. Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. Acta Neuropathol. 2011 Jun;121(6):763-74. doi: 10.1007/s00401-011-0817-z. Epub 2011 Mar 20. PMID: 21424530
361. Ross et al. The distribution of BRAF gene fusions in solid tumors and response to targeted therapy. Int. J. Cancer. 2016 Feb 15;138(4):881-90. PMID: 26314551
362. Tan et al. Paediatric Gliomas: BRAF and Histone H3 as Biomarkers, Therapy and Perspective of Liquid Biopsies. Cancers (Basel). 2021 Feb 4;13(4). PMID: 33557011
363. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf
364. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/202806s038,217514s009lbl.pdf
365. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210496s018lbl.pdf
366. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
367. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204114s038,217513s009lbl.pdf
368. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210498s011lbl.pdf
369. Subbiah et al. Clinical Development of BRAF plus MEK Inhibitor Combinations. Trends Cancer. 2020 Sep;6(9):797-810. PMID: 32540454
370. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206192s006lbl.pdf
371. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761034s053lbl.pdf
372. https://www.prnewswire.com/news-releases/abm-therapeutics-abm-1310-granted-fast-track-designation-by-the-fda-following-orphan-drug-designation-301937168.html
373. https://markets.businessinsider.com/news/stocks/array-biopharma-receives-fda-breakthrough-therapy-designation-for-braftovi-in-combination-with-mektovi-and-cetuximab-for-brafv600e-mutant-metastatic-colorectal-cancer-1027437791
374. https://biomed-valley.com/news/#press-releases
375. https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food
376. https://fore.bio/fore-biotherapeutics-announces-fast-track-designation-granted-by-fda-to-fore8394-for-the-treatment-of-cancers-harboring-braf-class-1-and-class-2-alterations/
377. Kulkarni et al. BRAF Fusion as a Novel Mechanism of Acquired Resistance to Vemurafenib in BRAFV600E Mutant Melanoma. Clin. Cancer Res. 2017 Sep 15;23(18):5631-5638. PMID: 28539463
378. Johnson et al. Acquired BRAF inhibitor resistance: A multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. Eur. J. Cancer. 2015 Dec;51(18):2792-9. PMID: 26608120

References (continued)

379. Nazarian et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature. 2010 Dec 16;468(7326):973-7. doi: 10.1038/nature09626. Epub 2010 Nov 24. PMID: 21107323
380. Rizos et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin. Cancer Res. 2014 Apr 1;20(7):1965-77. PMID: 24463458
381. Shi et al. A novel AKT1 mutant amplifies an adaptive melanoma response to BRAF inhibition. Cancer Discov. 2014 Jan;4(1):69-79. PMID: 24265152
382. Van et al. The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. Cancer Discov. 2014 Jan;4(1):94-109. doi: 10.1158/2159-8290.CD-13-0617. Epub 2013 Nov 21. PMID: 24265153
383. Villanueva et al. Concurrent MEK2 mutation and BRAF amplification confer resistance to BRAF and MEK inhibitors in melanoma. Cell Rep. 2013 Sep 26;4(6):1090-9. PMID: 24055054
384. Shi et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. Cancer Discov. 2014 Jan;4(1):80-93. PMID: 24265155
385. Katara et al. TPMT Polymorphism: When Shield Becomes Weakness. Interdiscip Sci. 2016 Jun;8(2):150-155. PMID: 26297310
386. Yong et al. The role of pharmacogenetics in cancer therapeutics. Br J Clin Pharmacol. 2006 Jul;62(1):35-46. PMID: 16842377
387. McLeod et al. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. Leukemia. 2000 Apr;14(4):567-72. PMID: 10764140
388. Wenzel et al. Loss of the nuclear Wnt pathway effector TCF7L2 promotes migration and invasion of human colorectal cancer cells. Oncogene. 2020 May;39(19):3893-3909. PMID: 32203164
389. Hong et al. MAD2B, a novel TCF4-binding protein, modulates TCF4-mediated epithelial-mesenchymal transdifferentiation. J Biol Chem. 2009 Jul 17;284(29):19613-22. PMID: 19443654
390. He et al. Identification of c-MYC as a target of the APC pathway. Science. 1998 Sep 4;281(5382):1509-12. PMID: 9727977
391. 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
392. 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
393. Zhang et al. Chk2 phosphorylation of BRCA1 regulates DNA double-strand break repair. Mol. Cell. Biol. 2004 Jan;24(2):708-18. PMID: 14701743
394. 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
395. Apostolou et al. Current perspectives on CHEK2 mutations in breast cancer. Breast Cancer (Dove Med Press). 2017;9:331-335. PMID: 28553140
396. Nevanlinna et al. The CHEK2 gene and inherited breast cancer susceptibility. Oncogene. 2006 Sep 25;25(43):5912-9. PMID: 16998506
397. 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
398. Huang et al. ENO1 and Cancer. Mol Ther Oncolytics. 2022 Mar 17;24:288-298. PMID: 35434271
399. Almaguel et al. Alpha-Enolase: Emerging Tumor-Associated Antigen, Cancer Biomarker, and Oncotherapeutic Target. Front Genet. 2020;11:614726. PMID: 33584813
400. Qiao et al. Enolase 1, a Moonlighting Protein, as a Potential Target for Cancer Treatment. Int J Biol Sci. 2021;17(14):3981-3992. PMID: 34671213
401. Xu et al. Enolase 1 Correlated With Cancer Progression and Immune-Infiltrating in Multiple Cancer Types: A Pan-Cancer Analysis. Front Oncol. 2020;10:593706. PMID: 33643901
402. Link et al. Core binding factor at the crossroads: determining the fate of the HSC. J Cell Physiol. 2010 Jan;222(1):50-6. PMID: 19813271
403. Qin et al. Cbfb regulates bone development by stabilizing Runx family proteins. J Bone Miner Res. 2015 Apr;30(4):706-14. PMID: 25262822
404. Malik et al. The transcription factor CBFB suppresses breast cancer through orchestrating translation and transcription. Nat Commun. 2019 May 6;10(1):2071. PMID: 31061501
405. Lesser et al. Tables of power for the F-test for comparing two exponential survival distributions. J Chronic Dis. 1981;34(11):533-44. PMID: 17287858

References (continued)

406. Pham et al. MAP3K1: Genomic Alterations in Cancer and Function in Promoting Cell Survival or Apoptosis. Genes Cancer. 2013 Nov;4(11-12):419-26. PMID: 24386504
407. Stratikos et al. A role for naturally occurring alleles of endoplasmic reticulum aminopeptidases in tumor immunity and cancer predisposition. Front Oncol. 2014;4:363. PMID: 25566501
408. López. How ERAP1 and ERAP2 Shape the Peptidomes of Disease-Associated MHC-I Proteins. Front Immunol. 2018;9:2463. PMID: 30425713
409. Serwold et al. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. Nature. 2002 Oct 3;419(6906):480-3. PMID: 12368856
410. Cui et al. Identification of ARTS-1 as a novel TNFR1-binding protein that promotes TNFR1 ectodomain shedding. J Clin Invest. 2002 Aug;110(4):515-26. PMID: 12189246
411. Cui et al. Shedding of the type II IL-1 decoy receptor requires a multifunctional aminopeptidase, aminopeptidase regulator of TNF receptor type 1 shedding. J Immunol. 2003 Dec 15;171(12):6814-9. PMID: 14662887
412. Mehta et al. Genetic variation of antigen processing machinery components and association with cervical carcinoma. Genes Chromosomes Cancer. 2007 Jun;46(6):577-86. PMID: 17366619
413. Falkenberg et al. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014 Sep;13(9):673-91. PMID: 25131830
414. Li et al. HDAC2 promotes the migration and invasion of non-small cell lung cancer cells via upregulation of fibronectin. Biomed Pharmacother. 2016 Dec;84:284-290. PMID: 27665474
415. Li et al. HDACs and HDAC Inhibitors in Cancer Development and Therapy. Cold Spring Harb Perspect Med. 2016 Oct 3;6(10). PMID: 27599530
416. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021991s009lbl.pdf
417. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022393s017lbl.pdf
418. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206256Orig1s006lbl.pdf
419. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf
420. Yang et al. Mitogen-activated protein kinase kinase kinase 4 deficiency in intrahepatic cholangiocarcinoma leads to invasive growth and epithelial-mesenchymal transition. Hepatology. 2015 Dec;62(6):1804-16. PMID: 26340507
421. Kamran et al. Role of STAT3 in cancer metastasis and translational advances. Biomed Res Int. 2013;2013:421821. PMID: 24199193
422. Delgado-Ramirez et al. Signal transducer and activator of transcription 6 as a target in colon cancer therapy. Oncol Lett. 2020 Jul;20(1):455-464. PMID: 32565970
423. Deng et al. The role of PPM1D in cancer and advances in studies of its inhibitors. Biomed Pharmacother. 2020 May;125:109956. PMID: 32006900
424. Le et al. WIP1 phosphatase at the crossroads of cancer and aging. Trends Biochem Sci. 2010 Feb;35(2):109-14. PMID: 19879149
425. Hsu et al. PPM1D Mutations Drive Clonal Hematopoiesis in Response to Cytotoxic Chemotherapy. Cell Stem Cell. 2018 Nov 1;23(5):700-713.e6. PMID: 30388424
426. Miller et al. PPM1D modulates hematopoietic cell fitness and response to DNA damage and is a therapeutic target in myeloid malignancy. Blood. 2023 Dec 14;142(24):2079-2091. PMID: 37595362
427. Yang et al. PPM1D overexpression predicts poor prognosis in non-small cell lung cancer. Tumour Biol. 2015 Mar;36(3):2179-84. PMID: 25412952
428. Sun et al. Overexpression of Wild-Type p53-Induced Phosphatase 1 Confers Poor Prognosis of Patients with Nasopharyngeal Carcinoma. Pathol Oncol Res. 2015 Apr;21(2):283-91. PMID: 25060857
429. Wu et al. PPM1D exerts its oncogenic properties in human pancreatic cancer through multiple mechanisms. Apoptosis. 2016 Mar;21(3):365-78. PMID: 26714478
430. Deshpande et al. Rad50 ATPase activity is regulated by DNA ends and requires coordination of both active sites. Nucleic Acids Res. 2017 May 19;45(9):5255-5268. PMID: 28369545
431. Kinoshita et al. RAD50, an SMC family member with multiple roles in DNA break repair: how does ATP affect function?. Chromosome Res. 2009;17(2):277-88. PMID: 19308707
432. Rupnik et al. The MRN complex. Curr. Biol. 2008 Jun 3;18(11):R455-7. PMID: 18522810
433. Assenmacher et al. MRE11/RAD50/NBS1: complex activities. Chromosoma. 2004 Oct;113(4):157-66. PMID: 15309560
434. Hopfner et al. The Rad50 zinc-hook is a structure joining Mre11 complexes in DNA recombination and repair. Nature. 2002 Aug 1;418(6897):562-6. PMID: 12152085

References (continued)

435. Fan et al. RAD50 germline mutations are associated with poor survival in BRCA1/2-negative breast cancer patients. Int. J. Cancer. 2018 Oct 15;143(8):1935-1942. PMID: 29726012
436. Brandt et al. Lack of MRE11-RAD50-NBS1 (MRN) complex detection occurs frequently in low-grade epithelial ovarian cancer. BMC Cancer. 2017 Jan 10;17(1):44. PMID: 28073364
437. Wang et al. RAD50 Expression Is Associated with Poor Clinical Outcomes after Radiotherapy for Resected Non-small Cell Lung Cancer. Clin. Cancer Res. 2018 Jan 15;24(2):341-350. PMID: 29030353
438. Zhang et al. Copy number deletion of RAD50 as predictive marker of BRCAness and PARP inhibitor response in BRCA wild type ovarian cancer. Gynecol. Oncol. 2016 Apr;141(1):57-64. PMID: 27016230
439. Dossin et al. SPEN integrates transcriptional and epigenetic control of X-inactivation. Nature. 2020 Feb;578(7795):455-460. PMID: 32025035
440. 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
441. 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
442. 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
443. 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
444. Hacker et al. Structure/Function Analysis of Recurrent Mutations in SETD2 Protein Reveals a Critical and Conserved Role for a SET Domain Residue in Maintaining Protein Stability and Histone H3 Lys-36 Trimethylation. J. Biol. Chem. 2016 Sep 30;291(40):21283-21295. PMID: 27528607
445. Fahey et al. SETting the Stage for Cancer Development: SETD2 and the Consequences of Lost Methylation. Cold Spring Harb Perspect Med. 2017 May 1;7(5). PMID: 28159833
446. Zaghi et al. H3K36 Methylation in Neural Development and Associated Diseases. Front Genet. 2020 Jan 9;10:1291. doi: 10.3389/fgene.2019.01291. eCollection 2019. PMID: 31998360
447. Suzuki et al. H3K36 methylation state and associated silencing mechanisms. Transcription. 2017 Jan;8(1):26-31. PMID: 27723431
448. Sun et al. H3K36me3, Message From Chromatin to DNA Damage Repair. Cell Biosci . 2020 Jan 31;10:9. doi: 10.1186/s13578-020-0374-z. eCollection 2020. PMID: 32021684
449. Li et al. The Histone Mark H3K36me3 Regulates Human DNA Mismatch Repair Through Its Interaction With MutSα. Cell. 2013 Apr 25;153(3):590-600. PMID: 23622243
450. Duns et al. Histone methyltransferase gene SETD2 is a novel tumor suppressor gene in clear cell renal cell carcinoma. Cancer Res. 2010 Jun 1;70(11):4287-91. PMID: 20501857
451. Dalgliesh et al. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. Nature. 2010 Jan 21;463(7279):360-3. PMID: 20054297
452. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 1.2025]
453. Hao et al. Control of Wnt Receptor Turnover by R-spondin-ZNRF3/RNF43 Signaling Module and Its Dysregulation in Cancer. Cancers (Basel). 2016 Jun 8;8(6). PMID: 27338477
454. Tsukiyama et al. Molecular Role of RNF43 in Canonical and Noncanonical Wnt Signaling. Mol. Cell. Biol. 2015 Jun 1;35(11):2007-23. PMID: 25825523
455. Fennell et al. RNF43 is mutated less frequently in Lynch Syndrome compared with sporadic microsatellite unstable colorectal cancers. Fam. Cancer. 2018 Jan;17(1):63-69. PMID: 28573495
456. Giannakis et al. RNF43 is frequently mutated in colorectal and endometrial cancers. Nat. Genet. 2014 Dec;46(12):1264-6. PMID: 25344691
457. Bellelli et al. Mol. Cell. 2018 May 17;70(4):707-721.e7. PMID: 29754823
458. Rayner et al. A panoply of errors: polymerase proofreading domain mutations in cancer. Nat. Rev. Cancer. 2016 Feb;16(2):71-81. PMID: 26822575
459. Yao et al. Comprehensive Analysis of POLE and POLD1 Gene Variations Identifies Cancer Patients Potentially Benefit From Immunotherapy in Chinese Population. Sci Rep. 2019 Oct 31;9(1):15767. PMID: 31673068
460. Nebot-Bral et al. Hypermutated tumours in the era of immunotherapy: The paradigm of personalised medicine. Eur. J. Cancer. 2017 Oct;84:290-303. PMID: 28846956
461. Bellido et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet Med. 2016 Apr;18(4):325-32. PMID: 26133394

References (continued)

462. Esteban-Jurado et al. POLE and POLD1 screening in 155 patients with multiple polyps and early-onset colorectal cancer. Oncotarget. 2017 Apr 18;8(16):26732-26743. PMID: 28423643
463. Palles et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013 Feb;45(2):136-44. PMID: 23263490
464. Valle et al. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. Hum Mol Genet. 2014 Jul 1;23(13):3506-12. PMID: 24501277
465. Elsayed et al. Germline variants in POLE are associated with early onset mismatch repair deficient colorectal cancer. Eur J Hum Genet. 2015 Aug;23(8):1080-4. PMID: 25370038
466. Chalmers et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. 9:34. PMID: 28420421
467. Schmutz et al. Shelterin. Curr Biol. 2016 May 23;26(10):R397-9. PMID: 27218840
468. Wu et al. Role of POT1 in Human Cancer. Cancers (Basel). 2020 Sep 24;12(10). PMID: 32987645
469. Liu et al. PTOP interacts with POT1 and regulates its localization to telomeres. Nat Cell Biol. 2004 Jul;6(7):673-80. PMID: 15181449
470. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. Cancer Discov. 2013 Jan;3(1):35-43. PMID: 23208470
471. McKinney et al. The Genetic Basis of Hepatosplenic T-cell Lymphoma. Cancer Discov. 2017 Apr;7(4):369-379. PMID: 28122867
472. Cui et al. ERRFI1 induces apoptosis of hepatocellular carcinoma cells in response to tryptophan deficiency. Cell Death Discov. 2021 Oct 4;7(1):274. PMID: 34608122
473. Hackel et al. Mig-6 is a negative regulator of the epidermal growth factor receptor signal. Biol Chem. 2001 Dec;382(12):1649-62. PMID: 11843178
474. Frosi et al. A two-tiered mechanism of EGFR inhibition by RALT/MIG6 via kinase suppression and receptor degradation. J Cell Biol. 2010 May 3;189(3):557-71. PMID: 20421427
475. Wendt et al. The antitumorigenic function of EGFR in metastatic breast cancer is regulated by expression of Mig6. Neoplasia. 2015 Jan;17(1):124-33. PMID: 25622905
476. Lin et al. Mitogen-inducible gene-6 is a multifunctional adaptor protein with tumor suppressor-like activity in papillary thyroid cancer. J Clin Endocrinol Metab. 2011 Mar;96(3):E554-65. PMID: 21190978
477. Xu et al. Upregulation of mitogen-inducible gene 6 triggers antitumor effect and attenuates progesterone resistance in endometrial carcinoma cells. Cancer Gene Ther. 2015 Nov;22(11):536-41. PMID: 26450625
478. Li et al. Low expression of Mig-6 is associated with poor survival outcome in NSCLC and inhibits cell apoptosis via ERK-mediated upregulation of Bcl-2. Oncol Rep. 2014 Apr;31(4):1707-14. PMID: 24573418
479. Li et al. Downregulation of Mig-6 in nonsmall-cell lung cancer is associated with EGFR signaling. Mol Carcinog. 2012 Jul;51(7):522-34. PMID: 21739478
480. Ferby et al. Mig6 is a negative regulator of EGF receptor-mediated skin morphogenesis and tumor formation. Nat Med. 2006 May;12(5):568-73. PMID: 16648858
481. Chen et al. PRKACB is downregulated in non-small cell lung cancer and exogenous PRKACB inhibits proliferation and invasion of LTEP-A2 cells. Oncol Lett. 2013 Jun;5(6):1803-1808. PMID: 23833645
482. Turnham et al. Protein kinase A catalytic subunit isoform PRKACA; History, function and physiology. Gene. 2016 Feb 15;577(2):101-8. PMID: 26687711
483. Cheadle et al. Regulatory subunits of PKA define an axis of cellular proliferation/differentiation in ovarian cancer cells. BMC Med Genomics. 2008 Sep 26;1:43. PMID: 18822129
484. Meoli et al. Protein kinase A effects of an expressed PRKAR1A mutation associated with aggressive tumors. Cancer Res. 2008 May 1;68(9):3133-41. PMID: 18451138
485. Bossis et al. Minireview: PRKAR1A: normal and abnormal functions. Endocrinology. 2004 Dec;145(12):5452-8. PMID: 15331577
486. Wang et al. PRKAR1A is a functional tumor suppressor inhibiting ERK/Snail/E-cadherin pathway in lung adenocarcinoma. Sci Rep. 2016 Dec 20;6:39630. PMID: 27995993
487. Pasca et al. Hedgehog signalling in cancer formation and maintenance. Nat. Rev. Cancer. 2003 Dec;3(12):903-11. PMID: 14737121
488. Skoda et al. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. Bosn J Basic Med Sci. 2018 Feb 20;18(1):8-20. PMID: 29274272

References (continued)

489. Johnson et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. Science. 1996 Jun 14;272(5268):1668-71. PMID: 8658145
490. Namekata et al. MOCA induces membrane spreading by activating Rac1. J Biol Chem. 2004 Apr 2;279(14):14331-7. PMID: 14718541
491. Laurin et al. Insights into the biological functions of Dock family guanine nucleotide exchange factors. Genes Dev. 2014 Mar 15;28(6):533-47. PMID: 24637113
492. Zhu et al. Inhibition of RAC1-GEF DOCK3 by miR-512-3p contributes to suppression of metastasis in non-small cell lung cancer. Int J Biochem Cell Biol. 2015 Apr;61:103-14. PMID: 25687035
493. Caspi et al. A novel functional screen in human cells identifies MOCA as a negative regulator of Wnt signaling. Mol Biol Cell. 2008 Nov;19(11):4660-74. PMID: 18716063
494. Cui et al. Oncotarget. 2016 Feb 2;7(5):5613-29. PMID: 26716413
495. Rodgers et al. Regulation of PI3K effector signalling in cancer by the phosphoinositide phosphatases. Biosci Rep. 2017 Feb 28;37(1). PMID: 28082369
496. Wang et al. Inositol Polyphosphate 4-Phosphatase Type II Is a Tumor Suppressor in Multiple Myeloma. Front Oncol. 2021;11:785297. PMID: 35070988
497. Yang et al. INPP4B exerts a dual function in the stemness of colorectal cancer stem-like cells through regulating Sox2 and Nanog expression. Carcinogenesis. 2020 Mar 13;41(1):78-90. PMID: 31179504
498. Woolley et al. Phosphoinositide signaling in cancer: INPP4B Akt(s) out. Trends Mol Med. 2015 Sep;21(9):530-2. PMID: 26150301