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Patient Name: 정구선
Gender: F
Sample ID: N25-222

Primary Tumor Site: ovary
Collection Date: 2025.09.01

Sample Cancer Type: Ovarian Cancer

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Relevant Ovarian Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
BRCA1	None detected	NTRK2	None detected
BRCA2	***BRCA2 p.(Q2157Ifs*18) c.6468_6469delTC***	NTRK3	None detected
ERBB2	None detected	RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***5.7 Mut/Mb measured***
Genomic Instability	***GIM 23 (High)***

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

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*BRCA2 p.(Q2157Ifs*18) c.6468_6469delTC* BRCA2, DNA repair associated Allele Frequency: 56.74% Locus: chr13:32914953 Transcript: NM_000059.4	**bevacizumab + olaparib** 1, 2 / II+ **olaparib** 1, 2 / II+ **rucaparib** 1 / II+ bevacizumab + niraparib II+ niraparib II+	**abiraterone + niraparib** 1, 2 / II+ **olaparib** 1, 2 / II+ **rucaparib** 1 / II+ **talazoparib + hormone therapy** 1 / II+ niraparib II+ olaparib + hormone therapy II+ talazoparib II+	28
IA	*Genomic Instability* GIM 23 (High)	**bevacizumab + olaparib** 1, 2 / II+ niraparib II+	None*	17

*** 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	*TP53 p.(R248Q) c.743G>A* tumor protein p53 Allele Frequency: 55.47% Locus: chr17:7577538 Transcript: NM_000546.6	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

*BRCA2 p.(Q2157Ifs*18) c.6468_6469delTC*	**pidnarulex** [1]
Genomic Instability	**pidnarulex** [1]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

*ERCC2 p.(M677I) c.2031G>A, FAT1 p.(T2369Rfs*2) c.7105delA, MAPK1 amplification, MLH1 p.(V384D) c.1151T>A, MPL p.(P70L) c.209C>T, Microsatellite stable, PPP2R2A deletion, YAP1 amplification, TPMT amplification, MEN1 deletion, EMSY amplification, CBL amplification, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRCA2	p.(Q2157Ifs*18)	c.6468_6469delTC	.	chr13:32914953	56.74%	NM_000059.4	frameshift Deletion
TP53	p.(R248Q)	c.743G>A	COSM10662	chr17:7577538	55.47%	NM_000546.6	missense
ERCC2	p.(M677I)	c.2031G>A	.	chr19:45855779	51.06%	NM_000400.4	missense
FAT1	p.(T2369Rfs*2)	c.7105delA	.	chr4:187540634	64.07%	NM_005245.4	frameshift Deletion
MLH1	p.(V384D)	c.1151T>A	.	chr3:37067240	77.40%	NM_000249.4	missense
MPL	p.(P70L)	c.209C>T	.	chr1:43803899	50.00%	NM_005373.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	69.75%	NM_000903.3	missense
GATA2	p.(G292R)	c.874G>C	.	chr3:128202846	27.22%	NM_032638.5	missense
ARHGEF38	p.(T455M)	c.1364C>T	.	chr4:106580341	24.22%	NM_001242729.2	missense
MSH3	p.(A57_A62del)	c.162_179delTGCAGCGGCCGCAGCGGC	.	chr5:79950707	75.09%	NM_002439.5	nonframeshift Deletion
OR5A1	p.([C182=;D183N])	c.546_547delCGinsTA	.	chr11:59211187	2.06%	NM_001004728.2	synonymous, missense
POLE	p.(I603V)	c.1807A>G	.	chr12:133245513	54.38%	NM_006231.4	missense
ARHGAP35	p.(P45Q)	c.134C>A	.	chr19:47422066	44.27%	NM_004491.5	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
GUCY2F	p.(P294H)	c.881C>A	.	chrX:108708522	77.59%	NM_001522.3	missense
GUCY2F	p.(K291R)	c.872A>G	.	chrX:108708531	49.76%	NM_001522.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MAPK1	chr22:22123473	6.35	2.11
PPP2R2A	chr8:26149298	0.65	0.66
YAP1	chr11:101981594	4.94	1.75
TPMT	chr6:18130879	5.45	1.88
MEN1	chr11:64571785	0.73	0.68
EMSY	chr11:76157926	5.57	1.91
CBL	chr11:119103202	5.14	1.8
DPYD	chr1:97544504	5.59	1.92
NOTCH2	chr1:120457903	5.86	1.99
EPCAM	chr2:47596575	5.8	1.97
MSH6	chr2:48010318	5.27	1.83
APC	chr5:112043374	5.51	1.9
RAD50	chr5:131892978	4.47	1.63
ABL1	chr9:133738250	0.82	0.7
MRE11	chr11:94153270	5.27	1.83
SDHD	chr11:111957573	5.1	1.79
KMT2A	chr11:118307146	4.27	1.58
CYLD	chr16:50783549	4.45	1.63
BCL2	chr18:60795830	0.73	0.68
SMARCB1	chr22:24129273	4.86	1.73
NF2	chr22:29999923	5.31	1.85

Biomarker Descriptions

BRCA2 p.(Q2157Ifs*18) c.6468_6469delTC, Genomic Instability

BRCA2, DNA repair associated

Background: Homologous recombination repair (HRR) is a DNA repair mechanism that targets double stranded breaks (DSBs) and interstrand cross-links (ICL) in DNA[114]. Homologous recombination deficiency (HRD) is characterized by the cell's inability to repair these DSBs[114,115]. HRD is caused by genetic or epigenetic alterations in the HRR pathway genes, most notably BRCA1 and BRCA2 along with other genes such as ATM and PALB2[116,117,118,119]. A consequence of HRD due to the failure to repair DSBs is genomic instability[120,121]. Genomic instability is an increased tendency towards acquiring genomic alterations during cell

Biomarker Descriptions (continued)

division[122,123,124,125,126,127]. These alterations include small structural variations (i.e., single nucleotide variants (SNVs), insertions, and deletions) as well as significant structural variations (i.e., loss or gain of large chromosome fragments)[123,128,129]. Variations of genomic instability include chromosomal instability, intrachromosomal instability, microsatellite instability, and epigenetic instability[122]. Importantly, while the impact of frame-shift mutations in specific HRR genes can be mitigated by secondary mutations that restore the correct reading frame and thereby alleviate HRD, the effects of genomic instability are permanent and not reversible[130,131,132]. For this reason, the alterations characteristic of genomic instability are referred to as genomic scars[133,134]. Some of the genomic scar signatures that are characteristic of the HRD phenotype include loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transition (LST)[114,135]. Current methods for HRD detection are heterogeneous and the definition for HRD positive tumors varies depending on the cancer type[114]. Generally, these methods detect the causes of HRD (i.e., alterations in HRR genes) and/or the consequences (i.e., signatures of genomic instability/genomic scarring)[114,120,136,137].

Alterations and prevalence: In a pan-cancer analysis of HRR gene mutations and genomic scar signatures in 8847 tumors across 33 cancer types, 17.5% of tumors were HRD-positive and 4% of tumors were positive for the BRCA1/2 mutation[138]. Specifically, HRD-positive status was observed in over 50% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 35-45% of esophageal carcinoma, uterine carcinosarcoma, sarcoma, and lung adenocarcinoma, 20-30% of stomach adenocarcinoma, bladder urothelial carcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma, 5-15% of endometrial cancer, mesothelioma, cervical cancer, pancreatic adenocarcinoma, cutaneous melanoma, hepatocellular carcinoma, diffuse large B-cell lymphoma, and adrenocortical carcinoma, and 1-4% of rectum adenocarcinoma, prostate adenocarcinoma, colon adenocarcinoma, testicular germ cell tumors, kidney chromophobe, glioblastoma multiforme, low grade glioma, and renal clear cell carcinoma[138]. 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[139,140,141,142,143,144,145,146]. 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[6,7]. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme[6,7].

Potential relevance: HRD status is an important biomarker in advanced ovarian and prostate cancer because it predicts response to certain treatments including poly-ADP ribose polymerase (PARP) inhibitors and platinum chemotherapies[147,148,149]. Disruption of HRR or inhibition of PARP, are tolerated by cells through the utilization of complementary DNA repair pathways. However, presence of HRD and subsequent treatment with PARP inhibitors block DNA repair, causing accumulation of DNA damage and cell death through synthetic lethality[114,150,151,152]. Several PARP inhibitors are approved by the FDA for various cancers associated with markers of HRD. Olaparib[153] was the first PARP inhibitor originally approved in 2014 for ovarian cancer with germline mutations in BRCA1/2 (gBRCAm). The utility of olaparib has since expanded to include genomic instability markers and mutations in other HRR genes. Specifically, olaparib as monotherapy is now indicated for gBRCAm and somatic BRCA1/2 mutated (sBRCAm) ovarian cancer and in combination with bevacizumab for BRCA1/2 mutated or genomic instability positive ovarian cancer[153]. In addition, olaparib is approved in prostate cancer with germline or somatic mutations in HRR genes including ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L[117,153,154]. Olaparib is also approved for gBRCAm HER2 negative breast cancer and as maintenance therapies for gBRCAm pancreatic cancers[153]. Other PARP inhibitors that are FDA approved for BRCA mutated cancers include rucaparib[155] (2016) that is indicated for gBRCAm or sBRCAm ovarian and prostate cancers, niraparib[156] (2017) that is indicated for gBRCAm ovarian cancer, and talazoparib[56] (2018) that is indicated for gBRCAm HER2-negative metastatic breast cancer. Niraparib is also recommended for the treatment of HRD-positive ovarian cancer, defined by BRCA1/2 mutations and/or genomic instability[157]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA1/2 mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], for BRCA1/2, PALB2, or other HRR gene mutations in breast and ovarian cancers. Like PARP inhibitors, pidnarulex[14] causes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. Despite tolerability and efficacy, acquired resistance to PARP inhibitors such as olaparib has been clinically reported[158]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[159]. Other potential mechanisms of resistance to PARP inhibitors include restoration of HRR activity, stabilization of the replication forks, inhibition of PARP trapping, increased drug efflux mediated by P-glycoprotein, and cell cycle control alterations[159,160,161,162].

TP53 p.(R248Q) c.743G>A

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[66]. Alterations in TP53 are required

Biomarker Descriptions (continued)

for oncogenesis as they result in loss of protein function and gain of transforming potential[67]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[68,69].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[6,7,70,71,72,73]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282[6,7]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[74,75,76,77]. Alterations in TP53 are also observed in pediatric cancers[6,7]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[6,7]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[6,7].

Potential relevance: The small molecule p53 reactivator, PC14586[78] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[79], (2019) and breakthrough designation[80] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[81,82]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[83]. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)[24,37,84,85,86,87]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[88]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[89].

ERCC2 p.(M677I) c.2031G>A

ERCC excision repair 2, TFIIH core complex helicase subunit

Background: The ERCC2 gene encodes ERCC excision repair 2, TFIIH core complex helicase subunit, also known as XPD[1]. ERCC2 is a protein involved in the nucleotide excision repair (NER) pathway responsible for repairing bulky DNA lesions caused by UV radiation, environmental mutagens, chemical agents, and cyclopurines generated by reactive oxygen species[62]. ERCC2 functions as a helicase along with ERCC3/XPB in the TFIIH core complex[62]. During repair of bulky lesions by NER, the TFIIH core complex binds to the lesion, followed by DNA damage verification by ERCC2, which is essential for NER[62]. Following lesion binding and verification, ERCC2 unwinds DNA in the 5'-3' direction[62]. Mutations in ERCC2 lead to stalled RNA polymerase, resulting in persistent block of transcription[62]. Germline ERCC2 mutations can lead to hereditary disorders including: Cockayne syndrome, characterized by skin cancer susceptibility and neurodegerneration; xeroderma pigmentosum (XP), characterized by neurodegeneration and developmental defects; and trichothiodystrophy (TTD), characterized by brittle hair due to sulfur deficiency as well as other developmental defects[62,63].

Alterations and prevalence: Somatic mutations in ERCC2 are predominantly missense and occur in 9% of bladder urothelial carcinoma, 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and cholangiocarcinoma, and 2% of lung squamous cell carcinoma[6,7]. The missense mutation, N238S, is observed to be recurrent in bladder urothelial carcinoma and is predicted to result in ERCC2 loss of function[6,7,64]. Biallelic loss of ERCC2 is observed in 2% of brain lower grade glioma and diffuse large B-cell lymphoma, as well as 1% of sarcoma and ovarian serous cystadenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for ERCC2 aberrations. In one study, ERCC2 mutations correlated with enhanced response to cisplatin based chemotherapy compared to wild-type ERCC2 in patients with muscle-invasive urothelial carcinoma[65].

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

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[1,33]. 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[33]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[33]. 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[33]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[33].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[6,7]. 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[6,7]. 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[6,7].

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

MAPK1 amplification

mitogen-activated protein kinase 1

Background: The MAPK1 gene encodes the mitogen-activated protein kinase 1, also known as ERK2[1]. MAPK1 is involved in the ERK1/2 signaling pathway along with MAPK3, MAP2K2, MAP2K4, BRAF, and RAF1[90,91]. Activation of MAPK proteins occurs through a kinase signaling cascade[91,92,93]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[91,92,93]. 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[91,92,93]. MAPK1 activation leads to homodimerization and phosphorylation of downstream targets including transcription factors RSK, MSK, and MYC, cytoskeletal molecules, and nucleoporins[94]. MAPK1 mutations have been observed to confer gain of function and promote MAPK pathway signaling, supporting an oncogenic role for MAPK1[95,96].

Alterations and prevalence: Somatic mutations in MAPK1 are observed in up to 4% of cervical squamous cell carcinoma, and up to 2% of head and neck squamous cell and uterine corpus endometrial carcinomas[6,7]. The most common missense mutations occur at codon 322[6,7]. Amplifications in MAPK1 are observed in up to 4% of sarcoma, and 3% of bladder carcinoma, lung squamous carcinoma, and ovarian cancer[6,7].

Potential relevance: Currently, no therapies are approved for MAPK1 aberrations.

MLH1 p.(V384D) c.1151T>A

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[41]. 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[41,42]. 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[43,44]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[41]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[41]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[45]. 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[46,47,48]. 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[46,49]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[47,49,50,51]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[52,53,54,55].

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[6,7]. Alterations in MLH1 are observed in pediatric cancers[6,7]. 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)[6,7].

Potential relevance: The PARP inhibitor, talazoparib[56] 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[57]. 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[58,59]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[60,61].

Biomarker Descriptions (continued)

MPL p.(P70L) c.209C>T

MPL proto-oncogene, thrombopoietin receptor

Background: The MPL gene encodes the MPL proto-oncogene, a transmembrane thrombopoietin receptor. Binding of the cytokine thrombopoietin to MPL leads to JAK2 activation and subsequent signaling that regulates stem cell homeostasis, cell survival, and proliferation[34]. Mutations in MPL typically disrupt normal auto-inhibitory functions and result in subsequent ligand-independent thrombopoietin receptor activation[34]. Gain-of-function mutations in MPL are associated with myeloproliferative neoplasms (MPN) and hereditary thrombocytosis. Loss-of-function mutations are linked to bone marrow failure syndromes, due to the regulation of thrombopoiesis by thrombopoietin[35].

Alterations and prevalence: Somatic mutations in MPL are present in 3-5% of primary myelofibrosis (PMF)[34,36]. Specifically, MPL W515L/K mutations are reported in 5-8% of myelofibrosis (MF) and 1-4% of essential thrombocythemia (ET)[37]. Other observed MPL mutations include V501A, Y252H, and S204P[34].

Potential relevance: MPL W515K/L mutations confer intermediate prognosis in MPN[37].

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[97]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[47,49]. 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[48]. 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[98]. 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)[98]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[50,99,100,101,102]. 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[49]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[47,49,50,51].

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[47,49,103,104]. 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[103,104].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[57] (2014) and nivolumab[58] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[57] 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[57]. Dostarlimab[105] (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[100,106]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[59] (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[100,107,108]. 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[108]. 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[109,110]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[109,110].

PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)[9,10]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[11]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[9].

Biomarker Descriptions (continued)

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer[9,10,12,13]. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma[6].

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib[9]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[15].

YAP1 amplification

Yes associated protein 1

Background: The YAP1 gene encodes the Yes1 associated transcriptional regulator[1]. YAP1 functions as a transcriptional coactivator for TEAD transcription factors and is an important effector of the Hippo signaling pathway[2]. The Hippo pathway is considered a tumor suppressor pathway due to its involvement in various cellular processes including cell proliferation, apoptosis, stem cell expansion, and negative regulation of YAP1[2,3]. Aberrations in YAP1, including upregulation, have been associated with tumorigenesis and shorter survival[3,4]. Germline mutations, specifically R331W, have been associated with an increased risk for lung adenocarcinoma[5].

Alterations and prevalence: Somatic mutations in YAP1 are observed in 3% of uterine corpus endometrial carcinoma, 2% of skin cutaneous melanoma, esophageal adenocarcinoma, kidney chromophobe, and 1% of uveal melanoma, kidney renal papillary cell carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and colorectal adenocarcinoma[6,7]. Amplification of YAP1 is observed in 10% of cervical squamous cell carcinoma, 5% of head and neck squamous cell carcinoma and ovarian cystadenocarcinoma, and 3% of bladder urothelial carcinoma, sarcoma, and esophageal adenocarcinoma[6,7]. YAP1 fusions are observed in 1% of sarcoma, esophageal adenocarcinoma, cervical squamous cell carcinoma, skin cutaneous melanoma, and head and neck squamous cell carcinoma[6,7].

Potential relevance: Currently, no therapies are approved for YAP1 aberrations. YAP1::TFE3 fusion is considered an ancillary diagnostic marker for epithelioid hemangioendothelioma[8]. Overexpression of YAP1 is a poor prognostic marker in hepatocellular carcinoma, gastric cancer, colorectal cancer, non-small cell lung cancer, and small cell lung cancer[2].

TPMT amplification

thiopurine S-methyltransferase

Background: The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines[1,111,112]. 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[111,112,113]. 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[111,113].

Alterations and prevalence: Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma[6,7]. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma[6,7]. 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[6,7].

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

MEN1 deletion

menin 1

Background: The MEN1 gene encodes the menin 1 protein[1]. MEN1 is a tumor suppressor that functions as a scaffold protein and is known to play a role in histone modification and epigenetic gene regulation through alteration of chromatin structure[1,38]. MEN1 also interacts with several proteins involved in transcription, signaling pathways, and cell division, including JUND, NF-κB, SMAD3, and estrogen receptor α[38,39,40]. Germline mutations in MEN1 result in multiple endocrine neoplasia type 1 (also referred to as MEN1),

Biomarker Descriptions (continued)

which is an inherited familial cancer syndrome that causes a predisposition to endocrine tumors, including pituitary, parathyroid, and pancreatic cancer[39,40].

Alterations and prevalence: Somatic mutations in MEN1 are observed in 8% of adrenocortical carcinoma, 5% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and skin cutaneous melanoma[6,7]. Biallelic deletion of MEN1 is observed in 1% of adrenocortical carcinoma and esophageal adenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for MEN1 aberrations.

EMSY amplification

EMSY transcriptional repressor, BRCA2 interacting

Background: The EMSY gene encodes the EMSY transcriptional repressor, BRCA2 interacting[1]. EMSY is a nuclear protein that interacts with the transactivation domain of BRCA2, resulting in the suppression of BRCA2 transcriptional activity.[16,17]. EMSY colocalizes with γ-H2AX at DNA damage sites, regulates chromatin remodeling, and suppresses interferon-stimulated genes in a BRCA2 dependent manner[16,18]. Overexpression of EMSY inactivates BRCA2 leading to chromosomal instability and tumorigenesis[16,18].

Alterations and prevalence: Somatic mutations in EMSY are observed in 7% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, colorectal adenocarcinoma, and 2% of lung adenocarcinoma, uterine carcinosarcoma, and stomach adenocarcinoma[6,7]. Amplification of EMSY is observed in 8% of ovarian serous cystadenocarcinoma, 6% of breast invasive carcinoma and esophageal adenocarcinoma, and 4% of head and neck squamous cell carcinoma and skin cutaneous melanoma[6,7].

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

CBL amplification

Cbl proto-oncogene

Background: The CBL gene encodes the casitas B-lineage lymphoma (CBL) ubiquitin ligase, a member of the ubiquitin ligase (E3) protein family that also includes CBL-b and CBL-c[19]. CBL proteins are characterized by their highly conserved N-terminal tyrosine kinase binding (TKB) domain and RING finger (RF) catalytic domain which are directly involved in the regulation of receptor tyrosine kinase (RTK) signaling[19,20]. Upon recognition of an activated RTK via its TKB domain, CBL mediates the transfer of ubiquitin from the ubiquitin-conjugating enzyme (E2) via its RF domain, consequently targeting the RTK for proteasome degradation. CBL can also function as an adaptor protein via recruitment of signaling molecules to active RTKs[20]. CBL is the target of genetic aberrations, including missense mutations and translocations, which can lead to oncogenic transformation in hematological malignancies as well as solid tumors[20,21,22,23]. Mutations in CBL often result in a loss of E3 ligase activity, thereby preventing proteasome-mediated RTK degradation, which supports the role of CBL as a tumor suppressor gene[21]. However, CBL mutants often maintain their adapter function, contributing to their transforming potential and suggesting a simultaneous oncogenic role for CBL in cancer[20]. Hereditary mutations in CBL lead to constitutive activation of RAS and MAPK pathways resulting in genetic disorders known as RASopathies which can lead to increased cancer risk[24].

Alterations and prevalence: Genetic alterations in CBL were first recognized in acute myeloid leukemia (AML) as a result of an interstitial deletion leading to MLL::CBL fusion[25,26]. However, fusions involving CBL are relatively rare. Aberrations in CBL most often involve missense mutations which commonly cluster in the linker region or RF domain corresponding to exons 8 and 9[20,21]. Such mutations lead to disruption of E3 ligase activity and have been reported in systemic mastocytosis (SM), 1-3% of de novo AML, 10% of secondary AML, 8% of atypical AML, and 10-15% of juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML)[6,20,27,28,29,30,31]. Mutations in CBL have also been reported in 1-6% of melanomas, lung, stomach, colorectal, esophageal, and uterine cancers[6,23].

Potential relevance: Mutations in CBL confer adverse prognosis in SM and have been shown to be independently predictive of inferior survival[28,32].

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.

BRCA2 p.(Q2157Ifs*18) c.6468_6469delTC

pidnarulex

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

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

Reference:

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

Genomic Instability

pidnarulex

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

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

Reference:

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC,

Genes Assayed (continued)

Genes Assayed for the Detection of Copy Number Variations (continued)

CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

Genes Assayed with Full Exon Coverage

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

BRCA2 p.(Q2157Ifs*18) c.6468_6469delTC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	◑	◑	◑	◑	● (IV)
rucaparib	◑	◑	✖	◑	✖
bevacizumab + olaparib	●	●	●	●	✖

* 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

BRCA2 p.(Q2157Ifs*18) c.6468_6469delTC (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abiraterone + niraparib	○	○	○	✖	✖
talazoparib + enzalutamide	○	○	✖	✖	✖
niraparib	✖	◑	✖	●	● (II)
bevacizumab + niraparib	✖	●	✖	✖	✖
olaparib + abiraterone acetate	✖	○	✖	✖	✖
talazoparib	✖	✖	✖	○	● (II)
olaparib, bevacizumab	✖	✖	✖	✖	● (IV)
GEN-1, chemotherapy, olaparib, niraparib	✖	✖	✖	✖	● (III)
fluzoparib	✖	✖	✖	✖	● (II)
niraparib, dostarlimab	✖	✖	✖	✖	● (II)
olaparib, talazoparib, atezolizumab + talazoparib	✖	✖	✖	✖	● (II)
tuvusertib, lartesertib, niraparib	✖	✖	✖	✖	● (II)
ZEN-3694, talazoparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
AZD-9574	✖	✖	✖	✖	● (I/II)
IDB-476	✖	✖	✖	✖	● (I/II)
niraparib, GSK-101	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/II)
ATX-559	✖	✖	✖	✖	● (I)
HS-10502	✖	✖	✖	✖	● (I)
MOMA-313, olaparib	✖	✖	✖	✖	● (I)
niraparib, chemotherapy	✖	✖	✖	✖	● (I)
novobiocin	✖	✖	✖	✖	● (I)
olaparib, chemotherapy	✖	✖	✖	✖	● (I)
pidnarulex	✖	✖	✖	✖	● (I)
SIM-0501	✖	✖	✖	✖	● (I)
XL-309, olaparib	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

Genomic Instability

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + olaparib	●	✖	●	●	✖
niraparib	✖	●	✖	●	● (II)
olaparib	✖	✖	✖	✖	● (IV)
olaparib, bevacizumab	✖	✖	✖	✖	● (IV)
GEN-1, chemotherapy, olaparib, niraparib	✖	✖	✖	✖	● (III)
atezolizumab + talazoparib	✖	✖	✖	✖	● (II)
fluzoparib	✖	✖	✖	✖	● (II)
tuvusertib, lartesertib, niraparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
niraparib, GSK-101	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/II)
HS-10502	✖	✖	✖	✖	● (I)
MOMA-313, olaparib	✖	✖	✖	✖	● (I)
pidnarulex	✖	✖	✖	✖	● (I)
SIM-0501	✖	✖	✖	✖	● (I)
XL-309, olaparib	✖	✖	✖	✖	● (I)

TP53 p.(R248Q) c.743G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TP53-EphA-2-CAR-DC, anti-PD-1	✖	✖	✖	✖	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***36.2%***
BRCA1	***LOH, 17q21.31(41197602-41276231)x3***
BRCA2	***LOH, 13q13.1(32890491-32972932)x2***
CDK12	***LOH, 17q12(37618286-37687611)x3***
RAD51D	***LOH, 17q12(33427950-33446720)x3***

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. Shibata et al. A time for YAP1: Tumorigenesis, immunosuppression and targeted therapy. Int J Cancer. 2018 Nov 1;143(9):2133-2144. PMID: 29696628
3. Fernandez-L et al. YAP1 is amplified and up-regulated in hedgehog-associated medulloblastomas and mediates Sonic hedgehog-driven neural precursor proliferation. Genes Dev. 2009 Dec 1;23(23):2729-41. PMID: 19952108
4. Liu et al. Clinical significance of yes-associated protein overexpression in cervical carcinoma: the differential effects based on histotypes. Int J Gynecol Cancer. 2013 May;23(4):735-42. PMID: 23502453
5. Chen et al. R331W Missense Mutation of Oncogene YAP1 Is a Germline Risk Allele for Lung Adenocarcinoma With Medical Actionability. J Clin Oncol. 2015 Jul 10;33(20):2303-10. PMID: 26056182
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
7. 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
8. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 5.2024]
9. Kalev et al. Loss of PPP2R2A inhibits homologous recombination DNA repair and predicts tumor sensitivity to PARP inhibition. Cancer Res. 2012 Dec 15;72(24):6414-24. PMID: 23087057
10. Álvarez-Fernández et al. Therapeutic relevance of the PP2A-B55 inhibitory kinase MASTL/Greatwall in breast cancer. Cell Death Differ. 2018 May;25(5):828-840. PMID: 29229993
11. Perrotti et al. Protein phosphatase 2A: a target for anticancer therapy. Lancet Oncol. 2013 May;14(6):e229-38. PMID: 23639323
12. Beca et al. Altered PPP2R2A and Cyclin D1 Expression Defines a Subgroup of Aggressive Luminal-Like Breast Cancer. BMC Cancer. 2015 Apr 15;15:285. doi: 10.1186/s12885-015-1266-1. PMID: 25879784
13. Curtis et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012 Apr 18;486(7403):346-52. PMID: 22522925
14. https://www.senhwabio.com//en/news/20220125
15. NCCN Guidelines® - NCCN-Prostate Cancer [Version 2.2025]
16. Dansonka-Mieszkowska et al. Clinical importance of the EMSY gene expression and polymorphisms in ovarian cancer. Oncotarget. 2018 Apr 3;9(25):17735-17755. PMID: 29707144
17. Hughes-Davies et al. EMSY links the BRCA2 pathway to sporadic breast and ovarian cancer. Cell. 2003 Nov 26;115(5):523-35. PMID: 14651845
18. Kondrashova et al. Clarifying the role of EMSY in DNA repair in ovarian cancer. Cancer. 2019 Aug 15;125(16):2720-2724. PMID: 31154666
19. Ryan et al. The N terminus of Cbl-c regulates ubiquitin ligase activity by modulating affinity for the ubiquitin-conjugating enzyme. J. Biol. Chem. 2010 Jul 30;285(31):23687-98. PMID: 20525694
20. Liyasova et al. Molecular pathways: cbl proteins in tumorigenesis and antitumor immunity-opportunities for cancer treatment. Clin. Cancer Res. 2015 Apr 15;21(8):1789-94. PMID: 25477533
21. Katzav et al. Mutations of c-Cbl in myeloid malignancies. Oncotarget. 2015 May 10;6(13):10689-96. PMID: 26028666
22. Kales et al. Cbl and human myeloid neoplasms: the Cbl oncogene comes of age. Cancer Res. 2010 Jun 15;70(12):4789-94. PMID: 20501843
23. Tan et al. CBL is frequently altered in lung cancers: its relationship to mutations in MET and EGFR tyrosine kinases. PLoS ONE. 2010 Jan 29;5(1):e8972. PMID: 20126411
24. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
25. Tefferi. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. Leukemia. 2010 Jun;24(6):1128-38. PMID: 20428194
26. Fu et al. Identification of CBL, a proto-oncogene at 11q23.3, as a novel MLL fusion partner in a patient with de novo acute myeloid leukemia. Genes Chromosomes Cancer. 2003 Jun;37(2):214-9. PMID: 12696071
27. Traina et al. Single nucleotide polymorphism array lesions, TET2, DNMT3A, ASXL1 and CBL mutations are present in systemic mastocytosis. PLoS ONE. 2012;7(8):e43090. PMID: 22905207
28. Pardanani et al. ASXL1 and CBL mutations are independently predictive of inferior survival in advanced systemic mastocytosis. Br. J. Haematol. 2016 Nov;175(3):534-536. PMID: 26628266
29. Loh et al. Mutations in CBL occur frequently in juvenile myelomonocytic leukemia. Blood. 2009 Aug 27;114(9):1859-63. PMID: 19571318

References (continued)

30. Jankowska et al. Mutational spectrum analysis of chronic myelomonocytic leukemia includes genes associated with epigenetic regulation: UTX, EZH2, and DNMT3A. Blood. 2011 Oct 6;118(14):3932-41. PMID: 21828135
31. Itzykson et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J. Clin. Oncol. 2013 Jul 1;31(19):2428-36. PMID: 23690417
32. NCCN Guidelines® - NCCN-Systemic Mastocytosis [Version 1.2020]
33. Peng et al. Role of FAT1 in health and disease. Oncol Lett. 2021 May;21(5):398. PMID: 33777221
34. Kim et al. CALR, JAK2, and MPL mutation profiles in patients with four different subtypes of myeloproliferative neoplasms: primary myelofibrosis, essential thrombocythemia, polycythemia vera, and myeloproliferative neoplasm, unclassifiable. Am. J. Clin. Pathol. 2015 May;143(5):635-44. PMID: 25873496
35. Cleyrat et al. Gene editing rescue of a novel MPL mutant associated with congenital amegakaryocytic thrombocytopenia. Blood Adv. 2017 Sep 26;1(21):1815-1826. PMID: 29296828
36. Rozovski et al. An accurate, simple prognostic model consisting of age, JAK2, CALR, and MPL mutation status for patients with primary myelofibrosis. Haematologica. 2017 Jan;102(1):79-84. PMID: 27686378
37. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 1.2025]
38. Nelakurti et al. Comprehensive Analysis of MEN1 Mutations and Their Role in Cancer. Cancers (Basel). 2020 Sep 14;12(9). PMID: 32937789
39. Tsukada et al. MEN1 gene and its mutations: basic and clinical implications. Cancer Sci. 2009 Feb;100(2):209-15. PMID: 19068082
40. Matkar et al. Menin: a scaffold protein that controls gene expression and cell signaling. Trends Biochem Sci. 2013 Aug;38(8):394-402. PMID: 23850066
41. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
42. 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
43. 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
44. 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
45. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. Clin Cancer Res. 2010 Nov 1;16(21):5107-13. PMID: 20823149
46. 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
47. 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
48. 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
49. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
50. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
51. 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
52. 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
53. 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
54. 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
55. 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
56. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf
57. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
58. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf

References (continued)

59. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
60. 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
61. 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
62. Marteijn et al. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 2014 Jul;15(7):465-81. PMID: 24954209
63. Cleaver et al. Disorders of nucleotide excision repair: the genetic and molecular basis of heterogeneity. Nat Rev Genet. 2009 Nov;10(11):756-68. PMID: 19809470
64. Hirotsu et al. Genomic Profiling Identified ERCC2 E606Q Mutation in Helicase Domain Respond to Platinum-Based Neoadjuvant Therapy in Urothelial Bladder Cancer. Front Oncol. 2020;10:1643. PMID: 32984035
65. Van et al. Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. Cancer Discov. 2014 Oct;4(10):1140-53. PMID: 25096233
66. Nag et al. The MDM2-p53 pathway revisited. J Biomed Res. 2013 Jul;27(4):254-71. PMID: 23885265
67. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012
68. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010 Jan;2(1):a001008. PMID: 20182602
69. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
70. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
71. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
72. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. Nat. Genet. 2016 Jun;48(6):607-16. PMID: 27158780
73. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
74. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. Hum. Mutat. 2002 Jun;19(6):607-14. PMID: 12007217
75. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. Genes Cancer. 2011 Apr;2(4):466-74. PMID: 21779514
76. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene. 2007 Apr 2;26(15):2157-65. PMID: 17401424
77. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. Hum. Mutat. 2014 Jun;35(6):766-78. PMID: 24729566
78. https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html
79. https://ir.aprea.com//news-releases/news-release-details/aprea-therapeutics-receives-fda-fast-track-designation
80. http://vp280.alertir.com/en/pressreleases/karolinska-development%27s-portfolio-company-aprea-therapeutics-receives-fda-breakthrough-therapy-designation-1769167
81. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. Front Oncol. 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
82. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165
83. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251. PMID: 34185076
84. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2025]
85. 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
86. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 3.2025]

References (continued)

87. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 3.2024]
88. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 2.2025]
89. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat. Med. 2020 Aug 3. PMID: 32747829
90. 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
91. 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
92. 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
93. 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
94. Roskoski. ERK1/2 MAP kinases: structure, function, and regulation. Pharmacol. Res. 2012 Aug;66(2):105-43. PMID: 22569528
95. Roskoski. MEK1/2 dual-specificity protein kinases: structure and regulation. Biochem. Biophys. Res. Commun. 2012 Jan 6;417(1):5-10. PMID: 22177953
96. Marampon et al. Biological Rationale for Targeting MEK/ERK Pathways in Anti-Cancer Therapy and to Potentiate Tumour Responses to Radiation. Int J Mol Sci. 2019 May 23;20(10). PMID: 31126017
97. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
98. 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
99. 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
100. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
101. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
102. 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
103. 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
104. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
105. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
106. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
107. 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
108. 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
109. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
110. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
111. Katara et al. TPMT Polymorphism: When Shield Becomes Weakness. Interdiscip Sci. 2016 Jun;8(2):150-155. PMID: 26297310
112. Yong et al. The role of pharmacogenetics in cancer therapeutics. Br J Clin Pharmacol. 2006 Jul;62(1):35-46. PMID: 16842377
113. 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
114. Stewart et al. Homologous Recombination Deficiency: Concepts, Definitions, and Assays. Oncologist. 2022 Mar 11;27(3):167-174. PMID: 35274707
115. Creeden et al. Homologous recombination proficiency in ovarian and breast cancer patients. BMC Cancer. 2021 Oct 28;21(1):1154. PMID: 34711195
116. Sokol et al. Pan-Cancer Analysis of BRCA1 and BRCA2 Genomic Alterations and Their Association With Genomic Instability as Measured by Genome-Wide Loss of Heterozygosity. JCO Precis Oncol. 2020;4:442-465. PMID: 32903788

References (continued)

117. Heeke et al. Prevalence of Homologous Recombination-Related Gene Mutations Across Multiple Cancer Types. JCO Precis Oncol. 2018;2018. PMID: 30234181
118. 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
119. Kondrashova et al. Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma. Nat Commun. 2018 Sep 28;9(1):3970. PMID: 30266954
120. Hoppe et al. Biomarkers for Homologous Recombination Deficiency in Cancer. J. Natl. Cancer Inst. 2018 Jul 1;110(7):704-713. PMID: 29788099
121. Wagener-Ryczek et al. Biomarkers for Homologous Recombination Deficiency in Cancer. J Pers Med. 2021 Jun 28;11(7). PMID: 34203281
122. Negrini et al. Genomic instability--an evolving hallmark of cancer. Nat Rev Mol Cell Biol. 2010 Mar;11(3):220-8. PMID: 20177397
123. Yao et al. Genomic Instability and Cancer. J Carcinog Mutagen. 2014;5. PMID: 25541596
124. Chen et al. GSA: an independent development algorithm for calling copy number and detecting homologous recombination deficiency (HRD) from target capture sequencing. BMC Bioinformatics. 2021 Nov 23;22(1):562. PMID: 34814825
125. Popova et al. Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation. Cancer Res. 2012 Nov 1;72(21):5454-62. PMID: 22933060
126. Timms et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. Breast Cancer Res. 2014 Dec 5;16(6):475. PMID: 25475740
127. Birkbak et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. Cancer Discov. 2012 Apr;2(4):366-375. PMID: 22576213
128. Duijf et al. Mechanisms of Genomic Instability in Breast Cancer. Trends Mol Med. 2019 Jul;25(7):595-611. PMID: 31078431
129. Stoler et al. The onset and extent of genomic instability in sporadic colorectal tumor progression. Proc Natl Acad Sci U S A. 1999 Dec 21;96(26):15121-6. PMID: 10611348
130. Sakai et al. Functional restoration of BRCA2 protein by secondary BRCA2 mutations in BRCA2-mutated ovarian carcinoma. Cancer Res. 2009 Aug 15;69(16):6381-6. PMID: 19654294
131. Sakai et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature. 2008 Feb 28;451(7182):1116-20. PMID: 18264087
132. Swisher et al. Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. Cancer Res. 2008 Apr 15;68(8):2581-6. PMID: 18413725
133. Watkins et al. Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers. Breast Cancer Res. 2014 Jun 3;16(3):211. PMID: 25093514
134. Marquard et al. Pan-cancer analysis of genomic scar signatures associated with homologous recombination deficiency suggests novel indications for existing cancer drugs. Biomark Res. 2015;3:9. PMID: 26015868
135. Chao et al. Genomic scar signatures associated with homologous recombination deficiency predict adverse clinical outcomes in patients with ovarian clear cell carcinoma. J Mol Med (Berl). 2018 Jun;96(6):527-536. PMID: 29725737
136. Doig et al. Homologous Recombination Repair Deficiency: An Overview for Pathologists. Mod Pathol. 2023 Mar;36(3):100049. PMID: 36788098
137. Nguyen et al. Pan-cancer landscape of homologous recombination deficiency. Nat Commun. 2020 Nov 4;11(1):5584. PMID: 33149131
138. Rempel et al. Pan-cancer analysis of genomic scar patterns caused by homologous repair deficiency (HRD). NPJ Precis Oncol. 2022 Jun 9;6(1):36. PMID: 35681079
139. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
140. 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
141. 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
142. 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
143. 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

References (continued)

144. 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
145. 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
146. 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
147. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823
148. Ferrone et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009 Jan 20;27(3):433-8. PMID: 19064968
149. Cavanagh et al. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hered Cancer Clin Pract. 2015;13(1):16. PMID: 26236408
150. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019 Jul 1;25(13):3759-3771. PMID: 30760478
151. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
152. Iglehart et al. Synthetic lethality--a new direction in cancer-drug development. N Engl J Med. 2009 Jul 9;361(2):189-91. PMID: 19553640
153. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
154. de et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020 May 28;382(22):2091-2102. PMID: 32343890
155. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
156. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214876s000lbl.pdf
157. NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2025]
158. 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
159. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
160. Dias et al. Understanding and overcoming resistance to PARP inhibitors in cancer therapy. Nat Rev Clin Oncol. 2021 Dec;18(12):773-791. PMID: 34285417
161. Giudice et al. PARP Inhibitors Resistance: Mechanisms and Perspectives. Cancers (Basel). 2022 Mar 10;14(6). PMID: 35326571
162. Kim et al. Alternate therapeutic pathways for PARP inhibitors and potential mechanisms of resistance. Exp Mol Med. 2021 Jan;53(1):42-51. PMID: 33487630