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**Patient Name:** 장미숙
**Gender:** F
**Sample ID:** N25-156

**Primary Tumor Site:** Breast
**Collection Date:** 2024.03.15

## Sample Cancer Type: Breast Cancer



### Report Highlights
4 Relevant Biomarkers
3 Therapies Available
11 Clinical Trials

## Relevant Breast Cancer Findings

| Gene | Finding |
|---|---|
| BRCA1 | None detected |
| ERBB2 | None detected |

| Genomic Alteration | Finding |
|---|---|
| Tumor Mutational Burden | ***5.69 Mut/Mb measured*** |

## Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IIC | *BRCA2 deletion*<br>BRCA2, DNA repair associated<br>Locus: chr13:32890491 | None* | niraparib II+<br>olaparib II+<br>rucaparib II+ | 3 |
| IIC | *FGFR1 amplification*<br>fibroblast growth factor receptor 1<br>Locus: chr8:38271452 | None* | None* | 7 |
| IIC | *FANCA deletion*<br>Fanconi anemia complementation group A<br>Locus: chr16:89804984 | None* | None* | 1 |
| IIC | *RB1 deletion*<br>RB transcriptional corepressor 1<br>Locus: chr13:48877953 | None* | None* | 1 |

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

### Prevalent cancer biomarkers without relevant evidence based on included data sources

*Microsatellite stable, PIK3R1 deletion, PPP2R2A deletion, RB1 p.(S838*) c.2513C>A, RNASEH2B deletion, RNF43 p.(R117Tfs*41) c.349_350delCGinsA, RPA1 deletion, TP53 p.(D281E) c.843C>A, DNMT3A deletion, ASXL2 deletion, UGT1A1 p.(G71R) c.211G>A, MAP3K1 deletion, RASA1 deletion, HLA-A deletion, CYLD deletion, CBFB deletion, CTCF deletion, CDH1*

*deletion, NQO1 p.(P187S) c.559C>T, ZFHX3 deletion, GPS2 deletion, NCOR1 deletion, SOX9 p.(K242Nfs*9) c.723_724delCA, SOX9 p.(D244Rfs*8) c.729_730insC, TOP1 deletion, PTPRT deletion, Tumor Mutational Burden*

# Variant Details

## DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| RB1 | p.(S838*) | c.2513C>A | . | chr13:49047519 | 51.74% | NM_000321.3 | nonsense |
| RNF43 | p.(R117Tfs*41) | c.349_350delCGinsA | . | chr17:56448297 | 0.78% | NM_017763.6 | frameshift Block Substitution |
| TP53 | p.(D281E) | c.843C>A | COSM43906 | chr17:7577095 | 56.73% | NM_000546.6 | missense |
| UGT1A1 | p.(G71R) | c.211G>A | COSM4415616 | chr2:234669144 | 52.51% | NM_000463.3 | missense |
| NQO1 | p.(P187S) | c.559C>T | . | chr16:69745145 | 77.75% | NM_000903.3 | missense |
| SOX9 | p.(K242Nfs*9) | c.723_724delCA | . | chr17:70119720 | 3.52% | NM_000346.4 | frameshift Deletion |
| SOX9 | p.(D244Rfs*8) | c.729_730insC | . | chr17:70119725 | 96.48% | NM_000346.4 | frameshift Insertion |
| MSH3 | p.(A61_P63dup) | c.189_190insGCAGCGCCC | . | chr5:79950735 | 42.06% | NM_002439.5 | nonframeshift Insertion |
| JAK2 | p.(C644Y) | c.1931G>A | . | chr9:5077519 | 49.35% | NM_004972.4 | missense |
| LATS2 | p.(E943Q) | c.2827G>C | . | chr13:21549449 | 9.95% | NM_014572.3 | missense |
| PARP4 | p.(?) | c.3285_3285+5delinsAGT | . | chr13:25021149 | 100.00% | NM_006437.4 | unknown |

## Copy Number Variations

| Gene | Locus | Copy Number | CNV Ratio |
|---|---|---|---|
| BRCA2 | chr13:32890491 | 1 | 0.68 |
| FGFR1 | chr8:38271452 | 19.19 | 7.79 |
| FANCA | chr16:89804984 | 1.13 | 0.65 |
| RB1 | chr13:48877953 | 1.09 | 0.64 |
| PIK3R1 | chr5:67522468 | 1.16 | 0.67 |
| PPP2R2A | chr8:26149298 | 1.08 | 0.64 |
| RNASEH2B | chr13:51484145 | 0.96 | 0.59 |
| RPA1 | chr17:1733385 | 1.16 | 0.67 |
| DNMT3A | chr2:25457069 | 1.05 | 0.62 |
| ASXL2 | chr2:25964858 | 1.08 | 0.63 |
| MAP3K1 | chr5:56111388 | 1.1 | 0.65 |
| RASA1 | chr5:86564256 | 1.04 | 0.62 |
| HLA-A | chr6:29910229 | 0.96 | 0.59 |
| CYLD | chr16:50783549 | 1.13 | 0.65 |
| CBFB | chr16:67063242 | 0.92 | 0.57 |

# Variant Details (continued)

## Copy Number Variations (continued)

| Gene | Locus | Copy Number | CNV Ratio |
|---|---|---|---|
| CTCF | chr16:67644720 | 1.08 | 0.64 |
| CDH1 | chr16:68771249 | 1.11 | 0.65 |
| ZFHX3 | chr16:72820995 | 1.01 | 0.61 |
| GPS2 | chr17:7216071 | 0.97 | 0.6 |
| NCOR1 | chr17:15935586 | 1.19 | 0.68 |
| TOP1 | chr20:39690023 | 0.91 | 0.57 |
| PTPRT | chr20:40710527 | 1.01 | 0.61 |
| AKT3 | chr1:243663007 | 0.94 | 0.58 |
| ALK | chr2:29416263 | 1.13 | 0.65 |
| CUL3 | chr2:225338933 | 4.8 | 2.11 |
| PLCG1 | chr20:39766236 | 1.04 | 0.62 |

# Biomarker Descriptions

**BRCA2 deletion**

*BRCA2, DNA repair associated*

Background: The breast cancer early onset gene 2 (BRCA2) 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[38,39]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[38,39]. 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[40,41,42]. 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%[40,43].

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[44,45,46,47,48,49,50,51]. 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[7,8].

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)[52]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[53,54]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[55] (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[55] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib[56] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[57] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[57] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib[58] (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

## Biomarker Descriptions (continued)

in combination with abiraterone acetate[59] 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[60]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[61]. 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[18], 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[62], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

**FGFR1 amplification**

*fibroblast growth factor receptor 1*

Background: The FGFR1 gene encodes fibroblast growth receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 3, and 4[1]. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain[1]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLCγ/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[184,185,186].

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions[187]. Amplification of FGFR1 is observed in 17% of lung squamous cell carcinoma, 11% of breast invasive carcinoma, 8% of bladder urothelial carcinoma, 7% of uterine carcinosarcoma and head and neck squamous cell carcinoma, 6% of esophageal adenocarcinoma, 5% of sarcoma, 4% of colorectal adenocarcinoma and pancreatic adenocarcinoma, 3% of prostate adenocarcinoma, ovarian serous cystadenocarcinoma, and lung adenocarcinoma, and 2% of uterine corpus endometrial carcinoma[7,8,188,189,190]. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types[191]. Somatic mutations in FGFR1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma[7,8]. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but are less common in solid tumors[192,193,194]. Alterations in FGFR1 are rare in pediatric cancers[7,8]. Amplification of FGFR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases). Somatic mutations in FGFR1 are observed in 6% of non-Hodgkin Lymphoma, 3% of soft tissue sarcoma, 2% of glioma, and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), Wilms tumor (2 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[7,8].

Potential relevance: The FGFR kinase inhibitor, pemigatinib[195] (2022) is approved for the treatment of adults with relapsed/refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. Additionally, the FDA granted fast-track designation to Debio 1347[196] (2018) for solid tumors harboring aberrations in FGFR1, FGFR2, or FGFR3. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members[197]. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations[198,199,200,201,202,203,204]. In a phase II clinical trial, dovitinib, a multi-tyrosine kinase inhibitor (TKI), exhibited an overall response rate (ORR) of 11.5% and a disease control rate (DCR) of 50% in patients with advanced squamous cell lung cancer possessing FGFR1 amplification[205]. The patients had a median overall survival (OS) of 5 months and progression-free survival (PFS) of 2.9 months[205]. Likewise, in a phase Ib study testing the FGFR inhibitor AZD4547, the median OS was 4.9 months in patients with FGFR1-amplified advanced squamous cell lung cancer. One of 13 (8%) patients achieved a partial response, 4 (31%) exhibited stable disease, and 2 (13.3%) demonstrated PFS at 12 weeks[206]. Rearrangements in FGFR1 are associated with poor risk pediatric and adult acute lymphoblastic leukemia[207,208,209].

**FANCA deletion**

*Fanconi anemia complementation group A*

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[63,64]. 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[63]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[65,66]. Loss of function mutations in the FA family and HRR pathway, including FANCA, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[67,68]. 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[69,70]. Of those

## Biomarker Descriptions (continued)

diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[64,70,71,72,73].

Alterations and prevalence: Somatic mutations in FANCA are observed in 4-8% of uterine, colorectal, and bladder cancers and about 6% of melanoma[7]. Biallelic loss is also reported in 2-5% of uveal melanoma, invasive breast carcinoma, ovarian cancer, and prostate cancer[7].

Potential relevance: The PARP inhibitor, talazoparib[57] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes FANCA. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCA are shown to confer enhanced sensitivity in vitro to DNA damaging agents, including cisplatin, as well as PARP inhibitors such as olaparib[74,75]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[73].

**RB1 deletion, RB1 p.(S838*) c.2513C>A**

*RB transcriptional corepressor 1*

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[78,79]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[80]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[78,79,81]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[82].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[8]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[8]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[83,84,85].

Potential relevance: Currently, there are no therapies approved for RB1 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[114]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[115,116]. 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[117]. 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[118]. 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)[118]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[119,120,121,122,123]. 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[116]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[115,116,120,124].

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[115,116,125,126]. 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[125,126].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[127] (2014) and nivolumab[128] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[127] 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[127]. Dostarlimab[129] (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[121,130]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[131] (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[121,132,133]. 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[133]. The majority of patients with tumors

## Biomarker Descriptions (continued)

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[134,135]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[134,135].

**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[210]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[210]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[210]. 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[211,212]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[211,212,213,214]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[215]. Loss of function mutations in 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[210].

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[7]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[7].

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

**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)[13,14]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[15]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[13].

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[13,14,16,17]. 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[7].

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[18], 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[13]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[19].

**RNASEH2B deletion**

*ribonuclease H2 subunit B*

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[1]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[142,143]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[142]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[142].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[7,8]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[7,8].

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

## Biomarker Descriptions (continued)

**RNF43 p.(R117Tfs*41) c.349_350delCGinsA**

*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[173,174]. Wnt signaling leads to the expression of genes that control cell proliferation, migration, and cell polarity formation[173]. RNF43 functions as a tumor suppressor and inhibits the Wnt pathway by ubiquitination and degradation of the Wnt receptor frizzled (FZD)[173,174].

Alterations and prevalence: Somatic mutations in RNF43 are observed in 14% endometrial carcinoma, 8% gastroesophageal junction cancer and colorectal adenocarcinoma, and 6% pancreatic adenocarcinoma[7,8]. Somatic frameshift mutations in RNF43 including R117fs and G659fs are frequently observed in colorectal and endometrial cancers with microsatellite instability[173,175,176].

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

**RPA1 deletion**

*replication protein A1*

Background: The RPA1 gene encodes replication protein A1[1]. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)[162]. RPA is involved in multiple DNA repair processes including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)[162]. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair[162].

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma[7,8]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[7,8].

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

**TP53 p.(D281E) c.843C>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[216]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[217]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[218,219].

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%)[7,8,188,220,221,222]. 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[7,8]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[223,224,225,226]. Alterations in TP53 are also observed in pediatric cancers[7,8]. 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 )[7,8]. 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)[7,8].

Potential relevance: The small molecule p53 reactivator, PC14586[227] (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[228], (2019) and breakthrough designation[229] (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[230,231]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[232]. 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)[28,29,140,207,233,234]. In mantle cell lymphoma, TP53 mutations are associated with poor

## Biomarker Descriptions (continued)

prognosis when treated with conventional therapy including hematopoietic cell transplant[235]. 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[236].

**DNMT3A deletion**

*DNA methyltransferase 3 alpha*

Background: The DNMT3A gene encodes the DNA methyltransferase 3 alpha which functions as a de novo methyltransferase (DNMT) with equal methylation efficiency for unmethylated and hemimethylated DNA[20]. Methylation of DNA occurs at CpG islands, a region of DNA consisting of sequential cytosine/guanine dinucleotide pairs. CpG island methylation plays an important role in development as well as stem cell regulation. Alterations to global DNA methylation patterns are dependent on DNMTs, which are associated with cancer initiation and progression[21,22].

Alterations and prevalence: DNMT3A mutations are observed in approximately 25% of all acute myeloid leukemia (AML) including 29-34% of AML with normal karyotype (NK-AML)[7,23,24,25,26,27,28]. Mutations in DNMT3A are also reported in 12-18% of myelodysplastic syndromes (MDS) as well as 4-6% of melanoma, lung adenocarcinoma, and uterine cancer[7,29]. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported[7,23]. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations[30,31]. The R882 mutations occur at the dimer/tetramer interface within the catalytic domain, which leads to disruption of DNMT3A tetramerization and loss of CpG methylation[32,33]. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity[34].

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML[23,26,27,31]. DNMT3A mutations are a useful in the diagnosis of angioimmunoblastic T-cell lymphoma (AITCL) when trying to differentiate from other peripheral T-cell lymphomas (PTCL)[35].

**ASXL2 deletion**

*additional sex combs like 2, transcriptional regulator*

Background: The ASXL2 gene encodes the ASXL transcriptional regulator 2 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation[1,102]. ASXL2 belongs to the ASXL gene family, which also includes ASXL1 and ASXL3[102]. ASXL proteins contain a conserved C-terminal plant homeodomain (PHD), which facilitates interaction with DNA and histones[102]. ASXL2 influences chromatin remodeling and transcription through interaction with BAP1 as well as other transcriptional activators and repressors[102].

Alterations and prevalence: Somatic mutations in ASXL2 are observed in 8% of uterine corpus endometrial carcinoma and bladder urothelial carcinoma, 7% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and uterine carcinosarcoma[7,8]. ASXL2 mutations in acute myeloid leukemia (AML) are observed to co-occur with t(8;21)(q22;q22)/RUNX1::RUNX1T1[103]. ASXL2 deletions are observed in 4% diffuse large B-cell lymphoma (DLBCL) and 2% of uterine carcinosarcoma[7,8].

Potential relevance: Currently, no therapies are approved for ASXL2 aberrations. ASXL2 mutations have been shown to be associated with better prognosis in pediatric AML with t(8;21)[103].

**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[1,86]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[86,87]. 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[88]. 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[88,89,90,91]. 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[92].

## Biomarker Descriptions (continued)

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[7,8].

Potential relevance: Currently, no therapies are approved for UGT1A1 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[163,164,165]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[163,164,165]. 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[163,164,165]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[166]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[166]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[166].

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[7,8]. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[166]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[7,8].

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

**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[76,77]. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form[76]. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis[76]. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways[76]. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types[76].

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[7,8]. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma[7,8].

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

**HLA-A deletion**

*major histocompatibility complex, class I, A*

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[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[93]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[94]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[95,96,97]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[98].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[7,8]. Biallelic loss of HLA-A is observed in 4% of DLBCL[7,8].

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

## Biomarker Descriptions (continued)

**CYLD deletion**

*CYLD lysine 63 deubiquitinase*

Background: The CYLD gene encodes CYLD lysine 63 deubiquitinase, which is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) family of deubiquitinases[1,2]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[3]. CLYD contains a USP domain with a catalytic triad formed by Cys601, His871, and Asp889 that selectively hydrolyses K63-linked ubiquitin chains from signaling molecules and regulates cell survival, proliferation, and tumorigenesis[4,5]. CYLD plays a tumor suppressor role by negatively regulating NF-κB activation by deubiquitinating multiple NF-κB signaling components, including NEMO, Tak1, TRAF2, TRAF6, and RIP1[6]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin appendage tumors[5,6]. CYLD has also been found to be downregulated in melanoma, salivary gland tumors, head and neck cancer, colon and hepatocellular carcinoma, cervical cancer, lung cancer, and renal cell carcinoma[5].

Alterations and prevalence: Somatic mutations in CYLD have been observed in 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of thymoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[7,8]. Biallelic loss of CYLD has been observed in 2% of prostate adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, and uterine carcinosarcoma[7,8].

Potential relevance: Currently, no therapies are approved for CYLD 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[136,137,138]. 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[137,138]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[138]

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[7]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[7]. 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[139]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[139].

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)[28,140,141].

**CTCF deletion**

*CCCTC-binding factor*

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family[1]. CTCF promotes the formation of cohesion-mediated loops, the formation of which organizes chromatin into self-interacting topologically associated domains (TADs) and influences gene expression[99]. Additionally, CTCF has been observed to function as a transcription factor through the binding of transcriptional start sites (TSS), but may also play a role in transcriptional repression[99,100,101]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[99].

Alterations and prevalence: Somatic mutations in CTCF are observed in 25% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma and uterine carcinosarcoma, 4% of colorectal adenocarcinoma, and 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and cholangiocarcinoma[7,8].

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

## Biomarker Descriptions (continued)

**CDH1 deletion**

*cadherin 1*

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)[1,177]. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-dependent transmembrane glycoproteins expressed in epithelial cells[1]. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments[178]. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis[179,180]. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer[181].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[7,8,182,183]. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocelluar carcinomas[7,8]. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[7,8].

Potential relevance: Currently, no therapies are approved for CDH1 aberrations.

**ZFHX3 deletion**

*zinc finger homeobox 3*

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,104,105]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[105,106]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[107,108,109,110,111]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[107,110,112,113].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[7,8]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[7,8].

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

**GPS2 deletion**

*G protein pathway suppressor 2*

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[167]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[167,168]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[169,170,171].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[7,8]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[7,8]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[7,8,172]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[172].

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

## Biomarker Descriptions (continued)

**NCOR1 deletion**

*nuclear receptor corepressor 1*

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,144,145]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[144,145,146,147]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[145]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[145,148].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[7,8]. Biallelic loss of NCOR1 are observed in 3% of liver hepatocellular carcinoma, and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[7,8]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[7,8].

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

**SOX9 p.(K242Nfs*9) c.723_724delCA, SOX9 p.(D244Rfs*8) c.729_730insC**

*SRY-box 9*

Background: The SOX9 gene encodes the SRY-box transcription factor 9 protein[1]. SOX9 regulates developmental pathways including stemness, differentiation, and progenitor development[36]. SOX9 has been shown to regulate cell cycle progression and cell proliferation[36]. In cancer, SOX9 aberrations have been observed to confer both gain or loss of function depending on the cancer type, supporting both tumor suppressor and oncogenic roles for SOX9[37].

Alterations and prevalence: Somatic mutations in SOX9 are predominantly missense or truncating and are observed in 12% of colorectal adenocarcinoma, 4% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma[7,8]. Amplification of SOX9 is observed in 3% of sarcoma, breast invasive carcinoma, mesothelioma, esophageal adenocarcinoma, and liver hepatocellular carcinoma, 2% of stomach adenocarcinoma, bladder urothelial carcinoma, lung adenocarcinoma, skin cutaneous melanoma, lung squamous cell carcinoma, uterine carcinosarcoma, brain lower grade glioma, pancreatic adenocarcinoma, thymoma, and ovarian serous cystadenocarcinoma, and 1% of cervical squamous cell carcinoma, pheochromocytoma and paraganglioma, uterine corpus endometrial carcinoma and prostate adenocarcinoma[7,8]. Biallelic deletion is also observed in 1% of uveal melanoma, sarcoma, and stomach adenocarcinoma[7,8].

Potential relevance: Currently, no therapies are approved for SOX9 aberrations.

**TOP1 deletion**

*topoisomerase (DNA) I*

Background: The TOP1 gene encodes DNA topoisomerase I, a member of the type I topoisomerase subfamily which also includes TOP3A and TOP3B[1,149]. Topoisomerases function as enzymes that create breaks in the backbone of DNA to relieve the negative supercoiling of DNA that occurs during replication or transcription[150,151]. Topoisomerases also function in DNA repair[151]. Specifically, TOP1 is responsible for catalyzing single-strand breaks followed by the re-ligation of DNA strands after unwinding[150]. In normal transcription, TOP1 activity maintains genomic stability by preventing the formation of RNA:DNA hybrid R-loops, which can interfere with the transcription and replication processes[150]. TOP1 amplification and overexpression have been observed in several cancer types and are believed to contribute to cancer growth and progression[150,152,153,154].

Alterations and prevalence: TOP1 amplification is observed in 7% of colorectal adenocarcinoma, 5% of uterine carcinosarcoma, 4% of adrenocortical carcinoma and stomach cancer, and 2% of esophageal cancer[7,8]. Somatic mutations in TOP1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and adrenocortical carcinoma[7,8].

Potential relevance: Currently, no therapies are approved for TOP1 aberrations. TOP1 inhibitors including irinotecan (1996) for colon or rectal cancer as well as topotecan (1996) for small cell lung and cervical cancers are FDA approved, although not indicated for specific alterations. Mutations in TOP1 may confer resistance to topoisomerase inhibitors including irinotecan[155,156,157]. Additionally,

## Biomarker Descriptions (continued)

amplification of TOP1 in melanoma and colorectal cancer as well as overexpression in liver and ovarian cancers have been shown to be associated with poor prognosis[158,159,160,161].

**PTPRT deletion**

*protein tyrosine phosphatase, receptor type T*

Background: PTPRT encodes protein tyrosine phosphatase receptor type T, part of the protein tyrosine phosphatase (PTP) family which consists of 125 members[1,9,10]. PTPs are responsible for protein dephosphorylation of tyrosine residues and are involved in several cellular processes including proliferation, differentiation, adhesion, and survival[11,12]. Aberrant tyrosine phosphorylation resulting from PTP dysfunction has been linked to cancer progression[11,12].

Alterations and prevalence: Somatic mutations in PTPRT are observed in 29% of skin cutaneous melanoma, 12% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 10% of colorectal adenocarcinoma and lung adenocarcinoma, 7% of esophageal adenocarcinoma and lung squamous cell carcinoma, 5% of uterine carcinosarcoma and bladder urothelial carcinoma, 4% of head and neck squamous cell carcinoma and cervical squamous cell carcinoma, 3% of glioblastoma multiforme and liver hepatocellular carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, and ovarian serous cystadenocarcinoma[7,8]. Biallelic loss of PTPRT is observed in about 1% of mesothelioma, prostate adenocarcinoma, and acute myeloid leukemia.[7,8].

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

## Genes Assayed

### Genes Assayed for the Detection of DNA Sequence Variants

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

### Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2,

# Genes Assayed (continued)

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

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 deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| olaparib | ✖ | ○ | ✖ | ✖ | ● (II) |
| niraparib | ✖ | ○ | ✖ | ✖ | ✖ |
| rucaparib | ✖ | ○ | ✖ | ✖ | ✖ |
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |

## FGFR1 amplification

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| hormone therapy, catequentinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pemigatinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| regorafenib | ✖ | ✖ | ✖ | ✖ | ● (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

### FGFR1 amplification (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| sunitinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| BBI-355, futibatinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| ABSK-121 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### FANCA deletion

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

### RB1 deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| ARTS-021 | ✖ | ✖ | ✖ | ✖ | ● (I/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 | ***11.28%*** |
| BRCA2 | ***CNV, CN:1.0*** |
| BRCA2 | ***LOH, 13q13.1(32890491-32972932)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.

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