Companion Diagnostic (CDx) Associated Findings

**GENOMIC FINDINGS DETECTED**

<table>
<thead>
<tr>
<th>GENOMIC FINDING</th>
<th>FDA-APPROVED THERAPEUTIC OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA2</strong></td>
<td>LYNPARZA® (olaparib)</td>
</tr>
<tr>
<td>BRCA2(NM_000059)-ZNF18(NM_144680) fusion (B15*; Z4*)</td>
<td>RUBRACA® (rucaparib)</td>
</tr>
<tr>
<td>Q2157fs*18</td>
<td>LYNPARZA® (olaparib)</td>
</tr>
<tr>
<td></td>
<td>RUBRACA® (rucaparib)</td>
</tr>
</tbody>
</table>

**OTHER SHORT VARIANTS AND SELECT REARRANGEMENTS AND COPY NUMBER ALTERATIONS IDENTIFIED**

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See professional services section for information on the alterations listed in this section as well as any additional detected copy number alterations, gene rearrangements, or biomarkers.

**OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE**

- **ALK** ALK(NM_004304) deletion exon 14 - intron 15
- **DNMT3A** V441fs*210 #
- **DNMT3A** K420fs*229 #
- **MLL2** P4261fs*71 #
- **MUTYH** G382D
- **RB1** E282fs*3
- **TET2** Q591fs*10 #

# Variants in this gene may be derived from a nontumor source such as clonal hematopoiesis (CH). The efficacy of targeting such nontumor somatic alterations (e.g., CH) is unknown. Refer to the appendix for additional details.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).
**Biomarker Findings**

**Blood Tumor Mutational Burden** - 14 Muts/Mb

**Microsatellite status** - MSI-High Not Detected

**Tumor Fraction** - 48%

**Genomic Findings**

For a complete list of the genes assayed, please refer to the Appendix.

- **ALK** deletion exons 14-15
- **BRCA2** Q2157fs*18, complex rearrangement exon 15
- **RADS18** rearrangement intron 8
- **DNMT3A** V441fs*210, K420fs*229
- **MLL2** P4261f*210, K420fs*229
- **MUTYH** G382D
- **RB1** E282fs*3
- **TET2** Q591fs*10

**Therapies with Clinical Benefit**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>VAF %</th>
<th>NCCN Category</th>
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</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>2A</td>
<td>2A</td>
</tr>
<tr>
<td>Niraparib</td>
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<td></td>
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<tr>
<td>Talazoparib</td>
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</table>

**Therapies with Lack of Response**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>NCCN Category</th>
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</table>

**Tumor Fraction** is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.

**Sample Preparation (in Patient’s Tumor Type)**

- Olaparib
- Rucaparib

**Sample Analysis (in Other Tumor Type)**

- Niraparib
- Talazoparib
GENOMIC FINDINGS

RAD51B - rearrangement intron 8 11.9%

10 Trials see p. 23

ALK - deletion exons 14-15 14.5%

9 Trials see p. 19

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT’S TUMOR TYPE)

- Olaparib
- Rucaparib
- Niraparib
- Talazoparib

THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)

- Entrectinib
- Alectinib
- Brigatinib
- Ceritinib
- Crizotinib
- Lorlatinib

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >30%. See appendix for details.

**MUTYH - G382D**

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

**DNMT3A - V441fs*210, K420fs*229**

**MLL2 - P4261fs*71**

**MUTYH - G382D**

**RB1 - E282fs*3**

**TET2 - Q591fs*10**

**IMPORTANT NOTE** Genomic alterations detected may be associated with activity of certain FDA-approved drugs, however, the agents listed in this report may have varied clinical evidence in the patient’s tumor type. Neither the therapeutic agents nor the clinical trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient’s tumor type. In the appropriate clinical context, germline testing of APC, BRCA1, BRCA2, BRIP1, MEN1, MLH1, MSH2, MSH6, MUTYH, NF2, PALB2, PMS2, PTEN, RAD51C, RAD51D, RB1, RET, SDHB, SDHC, SDHD, SMAD4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL, and WT1 is recommended.

Variant Allele Frequency is not applicable for copy number alterations.
<table>
<thead>
<tr>
<th>Variant Allele Frequency Percentage (VAF%)</th>
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</thead>
<tbody>
<tr>
<td>20% increments</td>
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<tr>
<td>0.5% increments</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HISTORIC PATIENT FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Tumor Mutational Burden</strong></td>
</tr>
<tr>
<td>14 Muts/Mb</td>
</tr>
<tr>
<td><strong>Microsatellite status</strong></td>
</tr>
<tr>
<td>MSI-High Not Detected</td>
</tr>
<tr>
<td><strong>Tumor Fraction</strong></td>
</tr>
<tr>
<td>48%</td>
</tr>
<tr>
<td><strong>ALK</strong></td>
</tr>
<tr>
<td>deletion exons 14-15</td>
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<tr>
<td>14.5%</td>
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<tr>
<td><strong>BRCA2</strong></td>
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<tr>
<td>Q2157fs*18 complex rearrangement exon 15</td>
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<tr>
<td>29.3%</td>
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<tr>
<td><strong>RAD51B</strong></td>
</tr>
<tr>
<td>rearrangement intron 8</td>
</tr>
<tr>
<td>11.9%</td>
</tr>
<tr>
<td><strong>DNMT3A</strong></td>
</tr>
<tr>
<td>V441fs*210</td>
</tr>
<tr>
<td>K420fs*229</td>
</tr>
<tr>
<td>0.64%</td>
</tr>
<tr>
<td><strong>MLL2</strong></td>
</tr>
<tr>
<td>P426fs*71</td>
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<tr>
<td>31.9%</td>
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<tr>
<td><strong>MUTYH</strong></td>
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<tr>
<td>G382D</td>
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<tr>
<td>38.4%</td>
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<tr>
<td><strong>RB1</strong></td>
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<tr>
<td>E282fs*3</td>
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<tr>
<td>45.5%</td>
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</table>
This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene
Not Detected = baited but not detected on test
Detected = present (VAF% is not applicable)
VAF% = variant allele frequency percentage
Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

HISTORIC PATIENT FINDINGS

| TET2 | Q591fs*10 | 7.9% |

**IMPORTANT NOTE**

This content is for professional use only. For information on how to report this to a clinician, please refer to the FoundationOne Liquid CDx Patient Education Brochure.
from immune checkpoint inhibitors following patients with higher bTMB derive clinical benefit in NSCLC, multiple clinical trials have shown including anti-PD-L1 greater sensitivity to immunotherapeutic agents, HSNSCC, increased bTMB may be associated with on the basis of clinical evidence in NSCLC and HSNSCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1 and anti-PD-1 therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutoffs ranging from 6 to 16 Muts/Mb. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor.

**Potential Treatment Strategies**

On the basis of clinical evidence in NSCLC and HSNSCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1 and anti-PD-1 therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutoffs ranging from 6 to 16 Muts/Mb. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor.

**Frequency & Prognosis**

Average FTMB levels in solid tumors other than NSCLC have not been evaluated (COSiPoRTal, COSMIC, PubMed, Mar 2021)5-7. The effects of hypermutation on prognosis and clinical features in prostate cancer have not been extensively investigated (PubMed, Feb 2021).

**Finding Summary**

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma5,8 and cigarette smoke in lung cancer9-10, treatment with immunosuppressive-based chemotherapy in glioma11-12, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes13-15, and microsatellite instability (MSI)16-17. This sample harbors a BTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents1-3.

**Finding Summary**

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDs uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content12, the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy14-15.
ALK mutations or rearrangements may confer sensitivity to ALK TKIs such as crizotinib, ceritinib, brigatinib, alectinib, lorlatinib, and entrectinib. An ongoing Phase 2 study of lorlatinib for patients with ALK-positive NSCLC previously treated with second-generation TKIs reported an intracranial ORR of 54% and an extracranial ORR of 37%. Lorlatinib also elicited significant clinical activity for patients with NSCLC and intracranial or intrathecal metastases and against resistance mutations associated with progression on first- and second-generation ALK TKIs such as G1202R. Crizotinib, ceritinib, and lorlatinib further displayed antitumor activity against ALK+ inflammatory myofibroblastic tumors (IMTs) in Phase 1/2 trials. Phase 1 studies of the ALK/ROS1/TRK inhibitor entrectinib have reported responses for 4 of 7 (57%) kinase inhibitor-naive patients with ALK-rearranged solid tumors, including patients with NSCLC, renal cell carcinoma, and colorectal cancer, but in none of the other patients with ALK non-fusion alterations. A Phase 1/1B trial of entrectinib for children and adolescents with recurrent or refractory solid tumors reported responses in patients with infantile fibrosarcoma (IFS; 1 CR) or inflammatory myofibroblastic tumor (IMT; 1 PR) harboring ALK fusions. A Phase 2 trial of the HSP90 inhibitor ganetespib reported PRs for a small number of patients with ALK-rearranged NSCLC. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

**FREQUENCY & PROGNOSIS**

ALK fusions have not been widely reported in the context of prostate cancer (PubMed, Mar 2021). Published data investigating the prognostic implications of ALK alterations in prostate carcinoma are limited (PubMed, Feb 2021).

**FINDING SUMMARY**

ALK encodes a receptor tyrosine kinase, a member of the insulin receptor superfamily, whose activation induces the downstream pathways associated with cell survival, angiogenesis, and cell proliferation. Although this specific alteration has not been functionally characterized, internal deletions of either exons 4-11 or exons 2-3 of ALK have been demonstrated to be activating and oncogenic. In addition, a truncated variant of ALK expressed from an alternative transcription site prior to the kinase domain, and lacking the transmembrane and extracellular regions (encoded by exons 1-19), has been shown to be oncogenic. Therefore, the ALK deletion variant detected here is likely to be activating, although this has not been directly demonstrated.
GENE
BRCA2

ALTERATION
Q2157fs*18, complex rearrangement exon 15

TRANSFFER ID
NM_000059

CODING SEQUENCE EFFECT
6468_6469delTC

PO POTENTIAL TREATATIONAL STRATEGIES
Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors19-91 or to ATR inhibitors77,78. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations60,65,68,75-76 and for patients with platinum-resistant or -refractory disease69,74,75. In a case study, a patient with therapy-induced neuroendocrine prostate cancer and an inactivating BRCA2 rearrangement experienced a CR ongoing for 20 months to the ATR inhibitor berzosertib79. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)79, ovarian carcinoma80, and triple-negative breast cancer (TNBC)81 showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA2-deficient cells to ATR inhibitors. The Phase 3 PROfound study for patients with metastatic castration-resistant prostate cancer (mCRPC) who had progressed on a new hormonal agent reported improved radiographic PFS with olaparib compared with physician’s choice of abiraterone/prednisone or enzalutamide for patients with BRCA1/2 or ATM alterations (7.4 vs. 3.6 mo., HR=0.34)82. Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as trabectedin, lurbinitedir, and the platinum chemotherapies cisplatin and carboplatin83-93.

FREQUENCY & PROGNOSIS
BRCA2 mutations have been identified in 3-6% of primary and 6-7% of metastatic prostate cancer specimens84-94, with deleterious germline BRCA2 mutations present in 3% of men with metastatic prostate cancer95. BRCA2 homozygous deletion has been reported in 3-6% of prostate adenocarcinoma cases96-100. The positive predictive value of prostate specific antigen (PSA) levels was found to be higher in patients with BRCA1/2 mutations than in the general population101. BRCA2 germline mutations have been associated with attributes of aggressive prostate cancer at diagnosis, including high Gleason score, nodal involvement, advanced tumor stage, and metastatic spread102. Germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers103. Following radical conventional treatment for localized prostate cancer, patients with germline BRCA1/2 mutations experienced significantly shorter metastasis-free survival (HR=2.56) and CSS (HR=2.17) than noncarriers104. For patients with metastatic castration-resistant prostate cancer (mCRC), germline BRCA2 mutations were an independent marker of poor prognosis (CSS 17.4 vs. 33.2 months, HR=2.11) in 1 study105. Germline BRCA2 mutations in mCRC were associated with relative benefit from first-line abiraterone or enzalutamide compared with taxanes (CSS 24.0 vs. 17.0 months, PFS on the second systemic therapy 18.6 vs. 8.6 months) in a large prospective cohort study106. Three patients with non-neuroendocrine prostate cancer harboring BRCA2 mutations derived clinical benefit from treatment with platinum-based chemotherapy107-109.

FINDING SUMMARY
The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage107. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis108. Alterations such as seen here may disrupt BRCA2 function or expression107-109,110.

POTENTIAL GERMLINE IMPLICATIONS
One or more of the BRCA2 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Sep 2020)111. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer112-117, and the lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers has been estimated to be as high as >80% and 25%, respectively118. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%119. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population120-124. In the appropriate clinical context, germline testing of BRCA2 is recommended.
**GENE**

RAD51B

**ALTERATION**
rearrangement intron 8

**FREQUENCY & PROGNOSIS**
In the TCGA datasets, RAD51B mutation or deletion was most frequently observed in uterine corpus endometrial carcinoma (4.4%), bladder urothelial carcinoma (4.4%), sarcoma (2.7%), uterine carcinosarcoma (1.8%), stomach adenocarcinoma (1.6%), lung squamous cell carcinoma (2.5%), and ovarian serous cystadenocarcinoma (1.2%)(cBioPortal, 2021). Cases of germline nonsense and splice site RAD51B mutations have been reported in ovarian and breast cancer and melanoma, correlating with reduced RAD51B expression. Polymorphisms at the RAD51B locus have been associated with an increased risk of breast cancer. In gastric cancer, increased RAD51B expression was associated with advanced stage and worse overall survival.

**FINDING SUMMARY**
RAD51B, also known as RAD51L1, is involved in homologous recombination-mediated DNA repair. RAD51B alterations that remove or disrupt domains required for its homologous recombination activity, as observed here, are predicted to be inactivating.

**GENE**

DNMT3A

**ALTERATION**
V441fs*210, K420fs*229

**TRANSCRIPT ID**
NM_022552, NM_022552

**CODING SEQUENCE EFFECT**
1321delG, 1257_1263delTAAGGGC

**FREQUENCY & PROGNOSIS**
DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021). Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021). Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

**FINDING SUMMARY**
The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor. Alterations such as seen here may disrupt DNMT3A function or expression.
MLL2

Alteration: P4261fs*71

Coding Sequence Effect: 12781_12785delCCTCA

Gene Symbol: MLL2

Protein Coding Sequence Effect: NM_003482

Protein Alteration: P4261fs*71

FINDING SUMMARY
MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role.

MUTYH

Alteration: G382D

Coding Sequence Effect: NM_001048171

Gene Symbol: MUTYH

Protein Coding Sequence Effect: NM_001048171

Protein Alteration: G382D

FINDING SUMMARY
MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C). Numerous other MUTYH mutations have also been shown to result in loss of function. Mutations were found to be significantly associated with MAP in patients with MUTYH-mutant CRC. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (ClinVar, Sep 2020). Therefore, in the appropriate clinical context, genel testing of MUTYH is recommended.

FREQUENCY & PROGNOSIS
In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2021). Monoallelic MUTYH mutation occurs in 1-2% of the general population. MUTYH-associated polyposis or MAP is a distinct and phenotypically heterogeneous autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC). MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established. Estimates for the prevalence of MAP in the general population range from 1:5,000–1:10,000. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.