PATIENT
DISEASE Prostate cancer (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED		FDA-APPROVED THERAPEUTIC OPTIONS
BRCA2	BRCA2(NM_000059)-ZNF18(NM_144680) fusion (B15*; Z4*)	LYNPARZA® (olaparib) RUBRACA® (rucaparib)
	Q2157fs*18	LYNPARZA® (olaparib) RUBRACA® (rucaparib)

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).

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT

DISEASE Prostate cancer (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

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
RAD51B rearrangement intron 8
DNMT3A V441fs*210, K420fs*229
MLL2 P4261fs*71
MUTYH G382D
RB1 E282fs*3
TET2 Q591fs*10

10 Therapies with Clinical Benefit
0 Therapies with Lack of Response
31 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 14 Muts/Mb **10 Trials** see p. 17	None	None
Microsatellite status - MSI-High Not Detected	MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).	
Tumor Fraction - 48%	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.	

GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
BRCA2 -	Q2157fs*18	29.3%	Olaparib	1	Niraparib
	complex rearrangement exon 15	22.3%	Rucaparib	2A	Talazoparib
10 Trials see p. 21					

1 *NCCN category*

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
RAD51B -	rearrangement intron 8	11.9%	Olaparib [1]	Niraparib
			Rucaparib	Talazoparib
10 Trials see p. 23				
ALK -	deletion exons 14-15	14.5%	Entrectinib	Alectinib
				Brigatinib
				Ceritinib
				Crizotinib
				Lorlatinib
9 Trials see p. 19				

[ ] *NCCN category*

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 ..... p. 9

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

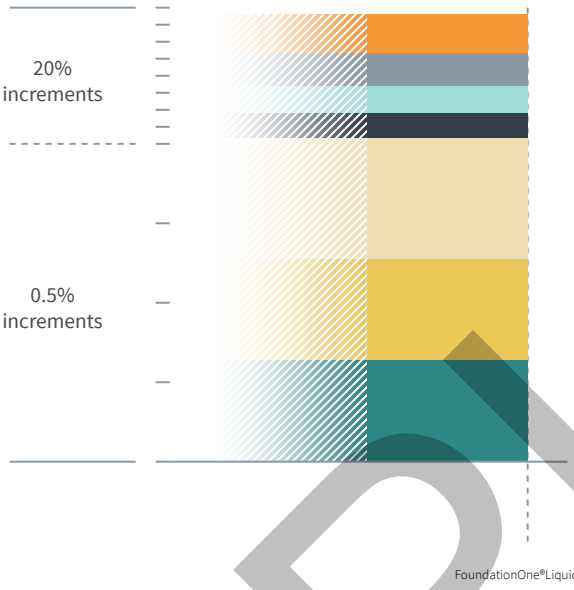
For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

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*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531



Variant Allele Frequency Percentage (VAF%)

HISTORIC PATIENT FINDINGS		
Blood Tumor Mutational Burden		14 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		48%
ALK	deletion exons 14-15	14.5%
BRCA2	Q2157fs*18	29.3%
	complex rearrangement exon 15	22.3%
RAD51B	rearrangement intron 8	11.9%
DNMT3A	V441fs*210	0.64%
	K420fs*229	0.64%
MLL2	P4261fs*71	31.9%
MUTYH	G382D	38.4%
RB1	E282fs*3	45.5%

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

HISTORIC PATIENT FINDINGS		
TET2	Q591fs*10	7.9%

IMPORTANT NOTE 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

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

BIOMARKER
Blood Tumor Mutational Burden

RESULT
14 Muts/Mb

POTENTIAL TREATMENT STRATEGIES
On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] 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 cutpoints ranging from 6 to 16 Muts/Mb[1]. 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[4].

FREQUENCY & PROGNOSIS
Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, 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 melanoma[8-9] and cigarette smoke in lung cancer[10-11], treatment with temozolomide-based chemotherapy in glioma[12-13], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[14-18], and microsatellite instability (MSI)[14,17-18]. 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 agents[1-3].

BIOMARKER
Tumor Fraction

RESULT
48%

POTENTIAL TREATMENT STRATEGIES
Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if tumor fraction is not detected as high, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[19-24].

FREQUENCY & PROGNOSIS
Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[25]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[26], Ewing sarcoma and osteosarcoma[27], prostate cancer[22], breast cancer[28], leiomyosarcoma[29], esophageal cancer[30], colorectal cancer[31], and gastrointestinal cancer[32].

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 CDx 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 content[33], 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 therapy[34-35].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
ALK

ALTERATION
deletion exons 14-15

POTENTIAL TREATMENT STRATEGIES

ALK mutations or rearrangements may confer sensitivity to ALK TKIs such as crizotinib[36-37], ceritinib[38], brigatinib[39-40], alectinib[41], lorlatinib[42], and entrectinib[43]. 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%[44]. Lorlatinib also elicited significant clinical activity for patients with NSCLC and intracranial[45] or intrathecal[46] metastases and against resistance mutations associated with progression on first- and second-generation ALK TKIs such as G1202R[47-48]. Crizotinib[49], ceritinib[50], and lorlatinib[51-52] 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 0 of 13 patients with ALK fusion-positive tumors previously treated with an ALK inhibitor and in none of the other patients with ALK non-fusion alterations[43]. 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; 1PR) harboring ALK fusions[53]. A Phase 2 trial of the HSP90 inhibitor ganetespib reported PRs for a small number of patients with ALK-rearranged NSCLC[54]. 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[55]. Although this specific alteration has not been functionally characterized, internal deletions of either exons 4-11[56] or exons 2-3[57] 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[58]. Therefore, the ALK deletion variant detected here is likely to be activating, although this has not been directly demonstrated.

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
BRCA2

ALTERATION
Q2157fs*18, complex rearrangement exon 15

TRANSCRIPT ID
NM_000059

CODING SEQUENCE EFFECT
6468_6469delTC

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[59-76] or to ATR inhibitors[77-78]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[60,65,68,75-76] and for patients with platinum-resistant or -refractory disease[59,64,71,74]. 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 berzosertib[78]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[79], ovarian carcinoma[80], 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 (CRPC) 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, lurbinectedin, and the platinum chemotherapies cisplatin and carboplatin[83-93].

FREQUENCY & PROGNOSIS

BRCA2 mutations have been identified in 3–6% of primary and 6–7% of metastatic prostate cancer specimens[94-96], with deleterious germline BRCA2 mutations present in 5% of men with metastatic prostate cancer[97]. BRCA2 homozygous deletion has been reported in 3–6% of prostate adenocarcinoma cases[98-100]. 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 population[101]. 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 spread[102]. Germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers[102]. Following radical conventional treatment for localized prostate cancer, patients with germline BRCA1/2 mutations experienced significantly shorter metastasis-free survival (HR=2.36) and CSS (HR=2.17) than noncarriers[103]. For patients with metastatic castration-resistant prostate cancer (mCRPC), germline BRCA2 mutations were an independent marker of poor prognosis (CSS 17.4 vs. 33.2 months, HR=2.11) in 1 study[104]. Germline BRCA2 mutations in mCRPC 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 18.9 vs. 8.6 months) in a large prospective cohort study[104]. Three patients with non-neuroendocrine prostate cancer harboring BRCA2 mutations derived clinical benefit from treatment with platinum-based chemotherapy[105-106].

FINDING SUMMARY

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[107]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[108]. Alterations such as seen here may disrupt BRCA2 function or expression[107,109-124].

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)[125]. 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 cancer[126-127], and the lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers has been estimated to be as high as >80% and 23%, respectively[128]. 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%[129]. 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 population[128,130-135]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
RAD51B

ALTERATION
rearrangement intron 8

POTENTIAL TREATMENT STRATEGIES
Clinical evidence in ovarian cancer[65] and prostate cancer[136-137] indicates that RAD51B inactivation may confer sensitivity to PARP inhibitors. Loss of functional RAD51B also sensitizes cells to DNA-damaging agents such as mitomycin C[138-140].

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)[5-6]. Cases of germline nonsense and splice site RAD51B mutations have been reported in ovarian and breast cancer and melanoma, correlating with reduced RAD51B expression[141-143]. Polymorphisms at the RAD51B locus have been associated with an increased risk of breast cancer[144-147]. In gastric cancer, increased RAD51B expression was associated with advanced stage and worse overall survival[148].

FINDING SUMMARY
RAD51B, also known as RAD51L1, is involved in homologous recombination-mediated DNA repair[138,140,149-150]. RAD51B alterations that remove or disrupt domains required for its homologous recombination activity[138,140,142,150-153], 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

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS
DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021)[5-6]. 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[154-159]. 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[154-155]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[160]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[158,161-162]. 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[163-164]. 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[165-170]. Alterations such as seen here may disrupt DNMT3A function or expression[171-174].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
MLL2

ALTERATION
P4261fs*71

TRANSCRIPT ID
NM_003482

CODING SEQUENCE EFFECT
12781_12785delCCTCA

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS
MLL2 alterations are observed in a number of solid tumor contexts (COSMIC, 2021)[7], and are especially prevalent in lung squamous cell carcinoma (SCC)[175] and small cell lung carcinoma (SCLC)[176]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[177]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[178]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[179]. 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[154-159]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[158,161-162]. 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
MLL2 encodes an H_3K_4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[180]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[181]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[182].

GENE
MUTYH

ALTERATION
G382D

TRANSCRIPT ID
NM_001048171

CODING SEQUENCE EFFECT
1145G>A

POTENTIAL TREATMENT STRATEGIES
There are no therapies or clinical trials available to address MUTYH alterations in cancer.

FREQUENCY & PROGNOSIS
In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2021)[7]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[183-184]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[185-187]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[188].

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[189]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[183-184,190-192]. Numerous other MUTYH mutations have also been shown to result in loss of function[190-193].

POTENTIAL GERMLINE IMPLICATIONS
One or more of the MUTYH 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 MUTYH-associated polyposis (ClinVar, Sep 2020)[125]. 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 (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[183,194-196]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[183]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[197-201]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[184]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531