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

PATIENT

DISEASE Rectum adenocarcinoma (CRC)

DATE OF BIRTH 12 September 1939
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID CSCH 9/12/1939
SPECIMEN TYPE Blood
DATE OF COLLECTION 09 June 2021
SPECIMEN RECEIVED 14 June 2021

Biomarker Findings

Blood Tumor Mutational Burden - 16 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Cannot Be Determined

Genomic Findings

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

ATM S131*, R805*
ARID1A Q2207fs*17
FBXW7 R367*
APC R283*, E1397*
KDM5C M506I
PTPN11 D61Y
SDHA R75*
TERT promoter -146C>T, promoter -124C>T
TP53 R306*, C135Y

4 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 - 16 Muts/Mb **10 Trials** see p. 15	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 - Cannot Be Determined	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)
ATM -	S131*	2.9%	None	Niraparib
	R805*	0.24%		Olaparib
				Rucaparib
				Talazoparib
10 Trials see p. 18				
ARID1A -	Q2207fs*17	0.88%	None	None
5 Trials see p. 17				

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GENOMIC FINDINGS	VAF %
FBXW7 - R367*	0.48%
8 Trials see p. 20	

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
None	None

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.

SDHA - R75* 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.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

ATM - S131*, R805* p. 6

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.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the 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. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved by the US FDA or other national authorities; however, they might not have been approved in your respective country. 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.

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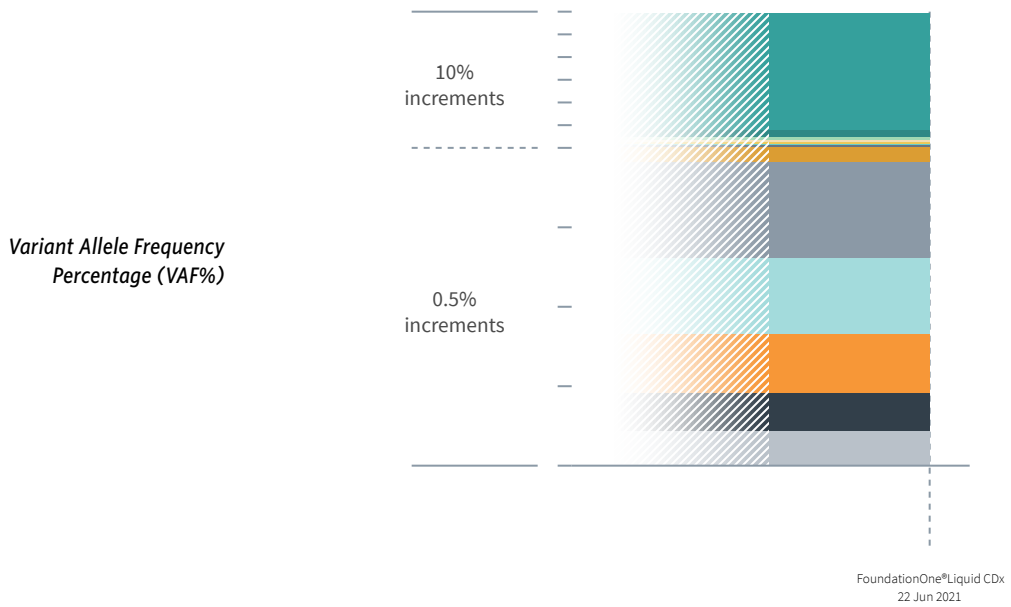

HISTORIC PATIENT FINDINGS		ORD-1118357-01 VAF%
Blood Tumor Mutational Burden		16 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Cannot Be Determined
ATM	R805*	0.24%
	S131*	2.9%
ARID1A	Q2207fs*17	0.88%
FBXW7	R367*	0.48%
APC	R283*	0.60%
	E1397*	0.37%
KDM5C	M506I	0.99%
PTPN11	D61Y	0.62%
SDHA	R75*	51.3%
TERT	promoter -146C>T	0.22%
	promoter	1.3%

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HISTORIC PATIENT FINDINGS		ORD-1118357-01 VAF%
	-124C>T	
TP53	R306*	0.66%
	C135Y	0.66%

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

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
16 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]. Although direct associations between blood or tissue TMB and prognosis of patients with CRC have not been reported, multiple studies have shown that MSI-H CRCs have a better prognosis than MSI-low (MSI-L) or microsatellite stable (MSS) tumors[8-15].

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[16-17] and cigarette smoke in lung cancer[18-19], treatment with temozolomide-based chemotherapy in glioma[20-21], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[22-26], and microsatellite instability (MSI)[22,25-26]. 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
Cannot Be Determined

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[27-32].

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)[33]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[34], Ewing sarcoma and osteosarcoma[35], prostate cancer[30], breast cancer[36], leiomyosarcoma[37], esophageal cancer[38], colorectal cancer[39], and gastrointestinal cancer[40].

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[41], 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[42-43]. However, the tumor fraction estimate in this sample could not be determined with confidence.

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GENE
ATM

ALTERATION
S131*, R805*

TRANSCRIPT ID
NM_000051, NM_000051

CODING SEQUENCE EFFECT
392C>G, 2413C>T

POTENTIAL TREATMENT STRATEGIES

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[44]. Clinical data in prostate cancer[45-47], gastric cancer[48], colorectal cancer[49], breast cancer[49], papillary renal cell carcinoma[50], and cholangiocarcinoma[51] indicate that loss or inactivation of ATM may confer sensitivity to PARP inhibitors[52-59]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with CRC who achieved a CR to berzosertib[60] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[61] harbored ATM inactivation or protein loss; preclinical studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[62-64] and hematologic malignancies[62,65] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[66].

FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, ATM mutations have been reported in 11% of cases[25]. Loss of heterozygosity (LOH) of ATM has been observed in 23-31% of distal colon cancers, but not in proximal colon tumors[67]. ATM expression or mutation has been associated with longer survival for patients with CRC[68-69].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[70]. Loss of functional ATM promotes tumorigenesis[71]. Alterations such as seen here may disrupt ATM function or expression[72-74].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the ATM 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) associated with ataxia-telangiectasia syndrome (ClinVar, Mar 2021)[75]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer[76]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[77]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[70,77]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[77]. In the appropriate clinical context, germline testing of ATM is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

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[78-83]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[82,84-85]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
ARID1A

ALTERATION
Q2207fs*17

TRANSCRIPT ID
NM_006015

CODING SEQUENCE EFFECT
6619_6620delCA

POTENTIAL TREATMENT STRATEGIES

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620; 1 patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[86-87]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to inhibitors of EZH2[88-89], which are under investigation in clinical trials. Other studies have reported that loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[90-92]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy in patients with ovarian clear cell carcinoma[93-94] and to 5-fluorouracil (5-FU) in CRC cell lines[95].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma (CRC), and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2021)[5-7,96-101]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[102-105], CRC[106-108], and gastric cancer[109-113]. ARID1A protein loss is reportedly more common in mismatch repair-deficient, BRAF V600E-mutated CRC tumors and is correlated with poor tumor staging and distant metastases, although data regarding an association between ARID1A protein loss and overall survival in CRC are mixed[106-108].

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[97,112,114-120]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[97,110,115-116,121], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
FBXW7

ALTERATION
R367*

TRANSCRIPT ID
NM_033632

CODING SEQUENCE EFFECT
1099C>T

POTENTIAL TREATMENT STRATEGIES

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[122-123]. Several case studies reported clinical benefit for patients with FBXW7-mutated cancers, including lung adenocarcinoma[124], renal cell carcinoma[50], and cervical squamous cell carcinoma[125]. Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat colorectal cancer (CRC), even for tumors that harbor alterations in PIK3CA, AKT, and/or PTEN[126-132]. One patient with CRC harboring an AKT1 E17K mutation experienced short-term stable disease on monotherapy treatment with the AKT inhibitor AZD5363[132]. Resistance to therapy may arise, at least in part, through activation of the RAS-MAPK pathway[127-129]. Combinations of therapies may be required to overcome this lack of response, as demonstrated by both clinical and preclinical studies evaluating the efficacy of PI3K-AKT-mTOR pathway inhibitors in combination with chemotherapy[133] or inhibitors of the VEGF signaling pathway[134-135]. FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[136].

FREQUENCY & PROGNOSIS

Mutations in FBXW7 have been identified in 9-21% of colorectal adenocarcinomas[25,137-138] and also in 4-7% of colorectal adenomas[139-140]. FBXW7 has been reported to be the fourth most commonly mutated gene in colorectal cancer, with mutations in 6-10% of cases in the scientific literature[139,141-142]. Low FBXW7 mRNA levels are associated with poor patient prognosis, and FBXW7 inactivation in colorectal cancer has been associated with chromosomal instability[139,143].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[144]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[144-145]. Alterations such as seen here may disrupt FBXW7 function or expression[145-152].

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GENE
APC

ALTERATION
R283*, E1397*

TRANSCRIPT ID
NM_000038, NM_000038

CODING SEQUENCE EFFECT
847C>T, 4189G>T

POTENTIAL TREATMENT STRATEGIES
There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[153]. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines[154-155]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[156].

FREQUENCY & PROGNOSIS
APC alterations have been found in 77% of tumors in the Colorectal Adenocarcinoma TCGA dataset[25]. Inactivation of APC leads to activation of the Wnt/beta-catenin pathway, which is thought to play a role in the adenoma-carcinoma transition in some cancers, including colorectal cancer (CRC)[157]. The prognostic significance of APC mutations in sporadic CRC remains unclear[158]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[159].

FINDING SUMMARY
APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[160]. Alterations such as seen here may disrupt APC function or expression[161-165].

POTENTIAL GERMLINE IMPLICATIONS
One or more of the APC 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) associated with familial adenomatous polyposis (ClinVar, Mar 2021)[75]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[166-168]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[169], and in the appropriate clinical context germline testing of APC is recommended.

GENE
KDM5C

ALTERATION
M506I

TRANSCRIPT ID
NM_004187

CODING SEQUENCE EFFECT
1518G>A

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in KDM5C.

FREQUENCY & PROGNOSIS
Somatic mutations of KDM5C have been observed in a number of solid tumors and infrequently in hematologic malignancies, and the role of KDM5C inactivation has been well characterized in clear cell renal cell carcinoma (ccRCC)[170-173]. However, KDM5C amplification and overexpression has been implicated in prostate cancer, where KDM5C has been associated with poor patient prognosis[174].

FINDING SUMMARY
KDM5C encodes a histone lysine demethylase that acts, along with related histone-modifying enzymes, to control gene expression in response to developmental and environmental cues[175]. In addition to its role as a histone-modifying demethylase, KDM5C has been suggested to play a role in regulation of the SMAD3 signal transduction response to TGF-beta, a role that would be consistent with function as a tumor suppressor[176]. Germline inactivating mutations in KDM5C cause an X-linked intellectual disability syndrome also characterized by short stature and hyperreflexia[177].

GENE
PTPN11

ALTERATION
D61Y

TRANSCRIPT ID
NM_002834

CODING SEQUENCE EFFECT
181G>T

POTENTIAL TREATMENT STRATEGIES
SHP-2 has been reported to activate the RAS-MEK-ERK, PI3K-AKT-mTOR, and SRC kinase pathways[178-181]. Based on a case study of a patient with histiocytic sarcoma harboring an activating PTPN11 mutation who experienced a PR to trametinib[182], as well as preclinical data[183-185], PTPN11 activation may predict sensitivity to MEK inhibitors in histiocytic neoplasms.

FREQUENCY & PROGNOSIS
In the Colorectal Adenocarcinoma TCGA dataset, PTPN11 mutation has been observed in 2% of cases[25]. Low to moderate SHP-2 expression has been reported in 30% of colorectal cancer samples and associated with improved patient survival[186-187].

FINDING SUMMARY
PTPN11 encodes the protein tyrosine-protein phosphatase non-receptor type 11, also known as SHP-2. PTPN11 plays a critical role in both embryonic development and cancer[188]. PTPN11 is also known to be somatically mutated in a variety of cancers, where both oncogenic and tumor suppressor roles for PTPN11 have been described[189-191]. The N-terminal SRC homology 2 (SH2) domain (aa 6-102) negatively regulates SHP-2 activity by binding to the active site of the SHP-2 protein tyrosine phosphatase (PTP) domain (aa 247-521)[192]. Alterations that disrupt this interaction or affect the specificity and structure of the SH2 and PTP domains, such as seen here, have been characterized as activating[180,189,193-205] and are predicted to be oncogenic[180,189,194-197,206-209].

POTENTIAL GERMLINE IMPLICATIONS
Germline mutations in PTPN11 have been found in the developmental disorder Noonan syndrome, which predisposes individuals to various cancers, including embryonal rhabdomyosarcoma, neuroblastoma, and juvenile myelomonocytic leukemia[195,210-214].

GENE
SDHA

ALTERATION
R75*

TRANSCRIPT ID
NM_004168

CODING SEQUENCE EFFECT
223C>T

POTENTIAL TREATMENT STRATEGIES
There are no therapies available to directly target the loss or inactivation of SDH genes. Preclinical studies have shown that succinate, which can accumulate as a result of SDH inactivation, promotes angiogenesis via VEGF upregulation[215-216]. Case studies have reported objective responses in patients with renal cell carcinoma harboring either SDHA or SDHC alterations treated with multikinase inhibitors that target VEGFR, including sunitinib and pazopanib[217]; however, these clinical data are limited. In a Phase 2 trial of vandetanib for children and adults with gastrointestinal stromal tumors (GISTs) with decreased SDH expression that were wild-type for KIT and PDGFRA, no partial or complete responses were observed and 2/9 patients experienced prolonged stable disease[218].

FREQUENCY & PROGNOSIS
Somatic mutations in SDHA are rare, and have been observed in fewer than 1% of tumors across all cancer types (COSMIC, 2021)[7]. Deficiency in succinate dehydrogenase activity has been associated with an aggressive subset of renal cell carcinoma with distinctive clinical and morphological features, affecting mostly younger patients[219-223].

FINDING SUMMARY
SDHA encodes the succinate dehydrogenase complex, subunit A, flavoprotein. This protein is involved in the mitochondrial respiratory chain. SDH deficiency due to germline inactivating mutations in SDH genes is associated with paraganglioma-pheochromocytoma syndrome, Leigh syndrome, and gastrointestinal stromal tumors (GIST), which typically do not harbor mutations in KIT or PDGFRA and are not sensitive to treatment with imatinib[224-227].

POTENTIAL GERMLINE IMPLICATIONS
One or more of the SDHA 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) associated with hereditary paraganglioma-pheochromocytoma syndrome and mitochondrial complex II deficiency (ClinVar, Mar 2021)[75]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. In the context of hereditary pheochromocytoma and paraganglioma, SDHA mutations are more rare and less penetrant than mutations in other SDH genes, and have been identified in 3 to 7% of patients with genetically unexplained disease[228-230]. In the appropriate clinical context, germline testing of SDHA is recommended.

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GENE
TERT

ALTERATION
promoter -146C>T, promoter -124C>T

TRANSCRIPT ID
NM_198253, NM_198253

CODING SEQUENCE EFFECT
-146C>T, -124C>T

POTENTIAL TREATMENT STRATEGIES

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches are under development, including immunotherapies utilizing TERT as a tumor-associated antigen, antisense oligonucleotide- or peptide-based therapies, and TERT promoter-directed cytotoxic molecules.

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported to occur at a low frequency in colorectal cancer[231]. Expression of hTERT and telomerase activity are associated with decreased overall survival in patients with colorectal cancer[232-234].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[235]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[236-238]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[239-241], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[239].

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GENE
TP53

ALTERATION
R306*, C135Y

TRANSCRIPT ID
NM_000546, NM_000546

CODING SEQUENCE EFFECT
916C>T, 404G>A

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[242-245], or p53 gene therapy and immunotherapeutics such as SGT-53[246-250] and ALT-801[251]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[252]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[253]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[254]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[255]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[256]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[257]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[250]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[258]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[259-261]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[262]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[65,263]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[264-265]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 60% of colorectal cancer cases[25,266-271]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[272]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[273].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[274]. Alterations such as seen here may disrupt TP53 function or expression[275-279].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 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) associated with Li-Fraumeni syndrome (ClinVar, Mar 2021)[75]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[280-282], including sarcomas[283-284]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[285] to 1:20,000[284]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[286]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

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[78-83]. 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[78-79]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[287]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[82,84-85]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Niraparib

Assay findings association

ATM
S131*, R805*

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[45-47,288] , colorectal cancer[49], breast cancer[49], gastric cancer[48], cholangiocarcinoma[51], and papillary renal cell carcinoma[50].

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of colorectal cancer are limited (PubMed, Feb 2021). Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[289]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[290]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[291].

Olaparib

Assay findings association

ATM
S131*, R805*

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[45-47,288] , colorectal cancer[49], breast cancer[49], gastric cancer[48], cholangiocarcinoma[51], and papillary renal cell carcinoma[50].

SUPPORTING DATA

A Phase 2 study reported olaparib monotherapy to be ineffective for patients with genomically unselected colorectal cancer and disease progression on prior standard systemic therapy, regardless of microsatellite status[292]. Olaparib has been studied primarily for the treatment of ovarian cancer and has resulted in significantly higher response rates for patients with BRCA1/2 mutations than for those without[293-294] . Olaparib treatment has also demonstrated clinical activity for patients with breast, prostate, or pancreatic cancer and BRCA1/2 mutations[293-297] .

Rucaparib

Assay findings association

ATM
S131*, R805*

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[45-47,288] , colorectal cancer[49], breast cancer[49], gastric cancer[48], cholangiocarcinoma[51], and papillary renal cell carcinoma[50].

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of colorectal cancer are limited (PubMed, Feb 2021). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[298]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[253]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[299]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[300]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[301]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[302]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[303]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[304].

Talazoparib

Assay findings association

ATM
S131*, R805*

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[45-47,288] , colorectal cancer[49], breast cancer[49], gastric cancer[48], cholangiocarcinoma[51], and papillary renal cell carcinoma[50].

SUPPORTING DATA

Clinical data on the efficacy of talazoparib for the treatment of colorectal cancer are limited (PubMed, Feb 2021). Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study[305-306] . In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration[49]. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer[307-310] .

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the

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listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

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ORDERED TEST # ORD-1118357-01

CLINICAL TRIALS

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

BIOMARKER

Blood Tumor Mutational Burden

RESULT

16 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

NCT03797326

PHASE 2

Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) in Previously Treated Participants With Select Solid Tumors (MK-7902-005/E7080-G000-224/LEAP-005)

TARGETS
PD-1, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Cali (Colombia), Bogota (Colombia), Pereira (Colombia), Medellin (Colombia), Florida, Tennessee, Texas, New Jersey, Pennsylvania, New York

NCT03110107

PHASE 1/2

First-In-Human Study of Monoclonal Antibody BMS-986218 by Itself and in Combination With Nivolumab in Patients With Advanced Solid Tumors

TARGETS
CTLA-4, PD-1

LOCATIONS: Vina del Mar (Chile), Santiago (Chile), Cordoba (Argentina), Rio Cuarto (Argentina), Cuiudad Autonoma De Buenos Aires (Argentina), Buenos Aires (Argentina), Ciudad Autónoma De Buenos Aires (Argentina), Georgia, Pennsylvania

NCT03179436

PHASE 1/2

Safety, Pharmacokinetics (PK), and Efficacy of MK-1308 in Combination With Pembrolizumab in Advanced Solid Tumors (MK-1308-001)

TARGETS
CTLA-4, PD-1

LOCATIONS: Santiago (Chile), Virginia, Toronto (Canada), Montreal (Canada), Sevilla (Spain), Valencia (Spain), San Sebastian (Spain), Cape Town (South Africa), Kraaifontein (South Africa), Bordeaux (France)

NCT03207867

PHASE 2

A Phase 2 Study of NIR178 in Combination With PDR001 in Patients With Solid Tumors and Non-Hodgkin Lymphoma

TARGETS
PD-1, ADORA2A

LOCATIONS: Caba (Argentina), Florida, Maryland, Ohio, Wisconsin, California, Barcelona (Spain), Marseille (France), Rotterdam (Netherlands), Liege (Belgium)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Pennsylvania, Indiana

NCT03767348

PHASE 2

Study of RP1 Monotherapy and RP1 in Combination With Nivolumab

TARGETS
PD-1

LOCATIONS: Florida, North Carolina, Tennessee, Kentucky, New York, New Jersey, Iowa, Arizona, Wisconsin

NCT03611868

PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Florida, Texas, Tennessee, Arkansas, Virginia, District of Columbia, Pennsylvania, Missouri

NCT04042116

PHASE 1/2

A Study to Evaluate Lucitanib in Combination With Nivolumab in Patients With a Solid Tumor

TARGETS
FGFRs, VEGFRs, PD-1

LOCATIONS: Florida, North Carolina, Tennessee, Oklahoma, Ohio, Pennsylvania, New York, Massachusetts, Colorado, California

NCT04122625

PHASE 1/2

Study to Assess Safety and Efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) Mimetic Debio 1143

TARGETS
PD-1, IAPs

LOCATIONS: Florida, Texas, Washington, Ohio, Missouri, Pennsylvania, New York, Massachusetts, Michigan

NCT03656718

PHASE 1/2

A Study of Subcutaneous Nivolumab Monotherapy With or Without Recombinant Human Hyaluronidase PH20 (rHuPH20)

TARGETS
PD-1

LOCATIONS: Santiago (Chile), Caba (Argentina), Sao Paulo (Brazil), Texas, Georgia, South Carolina, North Carolina

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GENE
ARID1A

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

ALTERATION
Q2207fs*17

NCT02595931

PHASE 1

ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
ATR

LOCATIONS: Florida, North Carolina, Tennessee, Missouri, Pennsylvania, Connecticut, Massachusetts, California

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: New York, Massachusetts, California, Saint Herblain (France), Withington (United Kingdom), Sutton (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Villejuif (France)

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT03641547

PHASE 1

M6620 Plus Standard Treatment in Oesophageal and Other Cancer

TARGETS
ATR

LOCATIONS: Cardiff (United Kingdom), Glasgow (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

GENE
ATM

ALTERATION
S131*, R805*

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors.

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Lima (Peru), Trujillo (Peru), Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Buenos Aires (Argentina), Ciudad de Buenos Aires (Argentina), Berazategui (Argentina)

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Lima (Peru), Bellavista (Peru), Cuzco (Peru), Arequipa (Peru), Cali (Colombia), Medellin (Colombia), Bucaramanga (Colombia), Barranquilla (Colombia), Buenos Aires (Argentina), Ciudad de Buenos Aires (Argentina)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Pennsylvania, Indiana

NCT03329001

PHASE 1

Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Compared to Niraparib Capsule

TARGETS
PARP

LOCATIONS: Florida, Georgia, Texas, Tennessee, Oklahoma, Connecticut, Michigan, Colorado, California

NCT03188965

PHASE 1

First-in-human Study of ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

TARGETS
ATR

LOCATIONS: Florida, Texas, Georgia, Virginia, Pennsylvania, New York, Ohio, Massachusetts

ORDERED TEST # ORD-1118357-01

CLINICAL TRIALS

NCT02595931

PHASE 1

ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
ATR

LOCATIONS: Florida, North Carolina, Tennessee, Missouri, Pennsylvania, Connecticut, Massachusetts, California

NCT02286687

PHASE 2

Phase II Study of BMN 673

TARGETS
PARP

LOCATIONS: Texas

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: Texas, Maryland, London (United Kingdom), Newcastle upon Tyne (United Kingdom)

NCT03337087

PHASE 1/2

Liposomal Irinotecan, Fluorouracil, Leucovorin Calcium, and Rucaparib in Treating Patients With Metastatic Pancreatic, Colorectal, Gastroesophageal, or Biliary Cancer

TARGETS
PARP, TOP1

LOCATIONS: Georgia, Arizona, Minnesota

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

GENE
FBXW7

ALTERATION
R367*

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors. Several clinical studies have shown that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit when used as a monotherapy in patients with colorectal cancer; combination therapies may be required to overcome this lack of response.

NCT03439462

PHASE 1/2

ABI-009 (Nab-rapamycin) in Combination With FOLFOX and Bevacizumab as First-line Therapy in Patients With Advanced or Metastatic Colorectal Cancer

TARGETS
mTOR, VEGFA

LOCATIONS: Louisiana, Texas, New Jersey, Arizona, Nevada, Washington

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

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NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

APC D1714N	***ARAF*** E578D	***ATM*** L1934Q and N504_L507del	***BARD1*** Y180H
BCOR A165V	***CEBPA*** V278M	***CREBBP*** R742S	***CTCF*** L209H
DDR2 R668H	***EPHB1*** A269T and I882T	***ERBB3*** S236P	***MDM4*** Q221R
MLL2 A4236V	***PDGFRA*** L420F and R479*	***PMS2*** T777S	***TSC1*** M322T

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APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***
ESR1 **Exons 4-8**	*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
HNF1A	***HRAS*** **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*
INPP4B	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)

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KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*
MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*MRE11A*	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*
MTAP	***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*
NF1	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**
NRAS **Exons 2, 3**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**
PDGFRB **Exons 12-21, 23**	*PDK1*	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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FoundationOne Liquid CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also detects select genomic rearrangements, select copy number alterations, tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. *Note:* A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

RANKING OF ALTERATIONS AND THERAPIES

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous 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%.
8. Tumor fraction is the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from observed aneuploid instability in the sample.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited

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to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. 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. Interpretation should be based on clinical context.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne Liquid CDx.

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test or the information contained in this report.

Certain sample of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
Muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

MR Suite Version 4.1.0

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