FOUNDATION MEDICINE®

Take Note of Changes to Your Report

Tumor Mutational Burden (TMB) is now reported for both FoundationOne® and FoundationOne® Heme.
Microsatellite Instability (MSI) status is now reported for FoundationOne® only.

These measures are associated with improved outcomes for immunotherapies and can help identify patients most likely to benefit from immune checkpoint inhibitors.[6-14] The information will be displayed as follows.

THERAPEUTIC IMPLICATIONS

GENOMIC FINDINGS	FDA-APPROVED THERAPIES	FDA-APPROVED THERAPIES (In Another Tumor Type)	POTENTIAL CLINICAL TRIALS
Tumor Mutation Burden TMB-Status; XX Muts/Mb	Therapy 1	Therapy 3 Therapy 4	Yes | See section
Microsatellite Status MSI-Status	Therapy 1 Therapy 2	Therapy 3 Therapy 4	Yes | See section

TMB is a quantitative genomic biomarker associated with response to immune checkpoint inhibitors[1-7]

- For solid and hematologic malignancies, TMB-High (≥20 Mutations/Mb of genome) is on the front page of the report
- For colorectal cancer, non-small cell lung cancer, melanoma, urothelial and endometrial carcinomas, all TMB statuses (High, Intermediate, Low, or Unknown) are on the front page of the report
- In all other diseases, any TMB status other than High is in the Variants of Unknown Significance (VUS) section in the appendix

MSI is a biomarker that offers prognostic and predictive insights in colorectal and endometrial cancers[6-14]

- For solid tumors, MSI-High is on the front page of the report
- For colorectal and endometrial cancers, all MSI statuses (High, Ambiguous, Stable, or Unknown) are on the front page of the report
- In all other diseases, any MSI status other than High is reported in the Variants of Unknown Significance (VUS) section in the appendix

FOUNDATIONICE PATIENTMATCH

219 providers have seen patients with similar tumor types and alterations.

You can use FoundationICE to request information on how those patients responded to targeted therapies via PatientMatch.

Similar Patients by Alteration

ERBB2 | S310F
41 similar patients including UC San Diego Moores Cancer Cen..

ASXL1 | E705*
12 similar patients including NYU Medical Center, and City of ...

Additional alterations and their matches may be available. Log in to foundationice.com for details.

ASK AN EXPERT ABOUT YOUR CASE OR SUBMIT A PATIENTMATCH REQUEST
https://foundationice.com/patient-report/TRF152366

1. Rosenberg JE, et al. Lancet. 2016;387(10031):1909-20. 2. Spigel DR, et al. J Clin Oncol. 2015;33(suppl; abstr 8009). 3. Hodi FS, et al. N Engl J Med. 2010;363(13):1290. 4. Johnson DB, et al. J Clin Oncol. 2016;34(suppl; abstr). 5. Rivzi NA, et al. Science. 2015;348(6230):124-128. 6. Lochhead P, et al. J Natl Cancer Inst. 2013. doi: 10.1093/jnci/djt173. 7. Tafe LJ, et al. Mol Diagn. 2015 Sep;17(5):472-82. 8. Kocarnik JM, et al. Gastroenterol Rep. 2015;4:269-76. 9. Salipante SJ, et al. Clin Chem. 2014;60(9):1192-9. 10. You J-F, et al. Br J Cancer. 2010;103:1840-1845. 11. Bairwa NK, et al. Methods Mol Biol. 2014;1105:497-509. 12. Goldstein J, et al. Annals of Oncology. 2014;8:1643-9. 13. Lipson EJ, et al. Clin Cancer Res. 2013;19(2):462-8. 14. Le DT, et al. N Engl J Med. 2015;372:2509-20.

FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Kumar, Ashwini	**18 May 2016**	**Kidney urothelial carcinoma**

Date of Birth	01 August 1941	**Medical Facility**	Max Healthcare	**Specimen Received**	06 May 2016
Sex	Male	**Ordering Physician**	Verma, Amit	**Specimen Site**	Kidney
FMI Case #	TRF152366	**Additional Recipient**	Not Given	**Date of Collection**	05 March 2016
Medical Record #	Not Given	**Medical Facility ID #**	201107	**Specimen Type**	Block
Specimen ID	S-4489/16C	**Pathologist**	Not Provided		

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS[‖]

7 genomic alterations

5 therapies associated with potential clinical benefit

0 therapies associated with lack of response

4 clinical trials

[‖] Reduced sensitivity due to sample quality – See Appendix: Performance Specifications for details.

TUMOR TYPE: KIDNEY UROTHELIAL CARCINOMA

Genomic Alterations Identified[†]

ERBB2 S310F
ASXL1 E705* – subclonal[#]
EP300 E1334*
RB1 I532fs*18
TERT promoter -124C>T
TET2 E10Q
TP53 E285K

[†] For a complete list of the genes assayed and performance specifications, please refer to the Appendix
[#] See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
ERBB2 S310F	None	Ado-trastuzumab emtansine Afatinib Lapatinib Pertuzumab Trastuzumab	Yes, see clinical trials section
ASXL1 E705* - subclonal	None	None	None
EP300 E1334*	None	None	None
RB1 I532fs*18	None	None	None
TERT promoter -124C>T	None	None	None
TET2 E10Q	None	None	None

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Genomic Alterations Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
TP53 E285K	None	None	None

Note: Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have little or no evidence in the patient's tumor type. Neither the therapeutic agents 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.

GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
ERBB2 S310F	**Gene and Alteration:** ERBB2 (also known as HER2) encodes the receptor tyrosine kinase HER2, which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation [1]. S310 is located in the HER2 extracellular domain and mutations at this position, including S310F and S310Y, have been reported to be activating[2,3]. In clinical studies, patients with the ERBB2 S310F mutation have benefited from ERBB2-targeted therapies including trastuzumab, pertuzumab, and lapatinib[4,5]. **Frequency and Prognosis:** ERBB2 mutations have been reported in 9-10% of bladder urothelial carcinomas[6,7]. One study has reported enrichment for ERBB2 mutations in micropapillary urothelial carcinoma (40% of MPUC samples), as compared with non-MPUC urothelial carcinomas (9% of samples)[8]; all of the mutations reported in MPUC were found in the extracellular domain of Her2 and 5/6 mutations were found at S310[8]. A case report of an inflammatory breast cancer patient with both ERBB2 V777L and S310F point mutations demonstrated clinical benefit following treatment with lapatinib in combination with trastuzumab and capecitabine[5]. ERBB2 S310F mutation has also been reported in one case of HER2-negative EMPD; a sustained partial response to lapatinib in combination with capecitabine was observed in this patient, and the response continued with lapatinib therapy alone[9]. **Potential Treatment Strategies:** On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[4,10,11,12,13,14], pertuzumab in combination with trastuzumab[4,15,16], and ado-trastuzumab emtansine (T-DM1)[17], as well as dual EGFR/HER2 kinase inhibitors such as lapatinib[5,18,19,20], afatinib[14,21,22,23,24], neratinib[25,26], and dacomitinib[27]. A patient with breast cancer and ERBB2 S310F had 12 months of clinical benefit from the combination of trastuzumab, pertuzumab, and fulvestrant[4], and a patient with inflammatory breast cancer and ERBB2 V777L and S310F activating mutations experienced tumor shrinkage in response to combined treatment with lapatinib and trastuzumab[5]. In patients with breast cancer, concurrent PIK3CA or PTEN alterations that activate the PI3K pathway have been associated with resistance to therapies that target HER2, including trastuzumab and lapatinib[28,29,30,31,32]. However, other studies have reported conflicting results, with one study suggesting that neither PIK3CA nor PTEN alterations is associated with trastuzumab resistance[33] and another study reporting a correlation between PIK3CA mutation and increased clinical response to the combination of letrozole and lapatinib[34]. Clinical trials of agents aimed at preventing or overcoming resistance to anti-HER2 therapies are under way, including agents targeting the PI3K-AKT pathway or HSP90[35,36].
ASXL1 E705* - subclonal	**Gene and Alteration:** ASXL1 (additional sex combs-like 1) encodes a chromatin-binding protein involved in transcriptional regulation through interaction with the polycomb complex proteins and various other transcriptional regulators [37,38]. Germline inactivating mutations affecting ASXL1 underlie the very rare developmental disorder Bohring-Opitz syndrome[39]. ASXL1 alterations that remove the PHD domain (amino acids 1491-1541), including truncating mutations and deletions, lead to aberrant epigenetic regulation[38,40,41].

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GENE ALTERATION	INTERPRETATION
	Frequency and Prognosis: ASXL1 mutations have been reported in various solid tumors, including 4% of colorectal cancers [42], 3% of breast cancers[43], 2% of hepatocellular carcinomas[44], 2% (1/61) of prostate cancers[45], and 1.4% (1/74) head and neck squamous cell carcinomas[46]. ASXL1 amplification has also been reported in 5.1% of cervical cancers[47]. ASXL1 mutations have mainly been studied and reported in the context of hematological malignancies, where they have been correlated with poor prognosis in myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML), and myeloproliferative neoplasms (MPN)[37,40,48]. **Potential Treatment Strategies:** There are no targeted therapies available to address genomic alterations in ASXL1.
● ***EP300*** E1334*	**Gene and Alteration:** EP300 encodes p300, a multifunctional regulatory protein with transcriptional coactivation and acetyltransferase activities. P300 is structurally similar to CREBBP and has been implicated in the control of a diverse array of cellular processes, including interferon-mediated transcriptional response to viral infection [49], astrocyte differentiation[50], and DNA repair[51]. P300 cooperates with MDM2 to regulate turnover of the tumor suppressor p53[52]. **Frequency and Prognosis:** Gene fusions conjoining EP300 with MLL have been identified in acute myeloid leukemia (AML) with t(11; 22)(q23; q13) chromosomal rearrangements [53], and infrequent somatic mutations of EP300 have been documented in several cancer types, including B-cell lymphoma[54], colorectal cancer[55], bladder cancer[56], esophageal squamous cell carcinoma[57], and cervical squamous cell carcinoma[58]. High tumor tissue expression of p300 has been linked with unfavorable outcomes in breast[59,60], colorectal[61], prostate[62], laryngeal[63], nasopharyngeal[64], non-small cell lung[65], small cell lung[66], hepatocellular[67], and esophageal squamous cell[68] carcinomas. A study of 327 patients with melanoma found a correlation between high expression of BRAF and cytoplasmic p300 and disease progression[69]. **Potential Treatment Strategies:** There are no targeted therapies available to address genomic alterations in EP300, but the use of histone deacetylase inhibitors is being investigated in clinical trials recruiting patients with either lymphoma or urothelial carcinoma harboring EP300 alterations.
● ***RB1*** I532fs*18	**Gene and Alteration:** RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle [70,71]. RB1 alterations that disrupt or remove the pocket domain (aa 373-771) and/or the C-terminal domain (aa 773-928), such as observed here, are predicted to be inactivating[72,73,74,75,76,77,78]. Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[79]. Germline mutations in RB1 account for approximately 40% of RB tumors[80] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[81,82]. In the appropriate clinical context, germline testing of RB1 is recommended. **Frequency and Prognosis:** RB1 mutations have been reported in 10-23% of bladder urothelial carcinoma cases [6,7,83,84,85]. Expression of RB has been reported in 47-52% of bladder urothelial carcinomas in one study, and was found to correlate with RB1 alteration[86]. Loss of RB expression has been suggested to play a role in the progression of urothelial cancers, and has been associated with advanced tumor stage and poor patient survival[87,88,89].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: Preclinical studies are investigating possible therapies to address Rb inactivation, exploring avenues such as Aurora kinase inhibitors, BCL-2 family inhibitors, and Notch pathway activation [90,91,92]. Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in preclinical studies as well as in patients with bladder or breast cancer[71,93]. Rb loss or inactivation predicts resistance to CDK4/6 inhibitors, such as palbociclib, abemaciclib, or ribociclib, which act upstream of Rb[94,95,96,97,98].
● ***TERT*** promoter -124C>T	**Gene and Alteration:** Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length [99]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[100,101,102]. 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)[103,104,105], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[103]. **Frequency and Prognosis:** TERT promoter mutations have been observed in melanoma, glioma, thyroid, and bladder cancers [104,105,106,107,108,109,110,111,112]. TERT promoter mutations were detected in 60% (3/5) and 11% (1/9) of upper tract urothelial carcinomas of the renal pelvis and ureter, respectively[113]. Urothelial carcinomas have been reported to have the highest frequency of TERT promoter mutations among various urogenital tumors[114]. One study reported TERT promoter mutations in 67% (14/21) and 56% (34/61) of high grade and low grade bladder carcinomas, respectively[105], while another study demonstrated that 85% (44/52) of all bladder cancer samples and 88% (7/8) of bladder cancer cell lines exhibited TERT promoter alteration[111]. TERT promoter mutations correlated with increased TERT mRNA expression in urothelial cancer cells[115]. In patients with bladder urothelial carcinoma, both TERT promoter mutations and increased TERT expression associate with poor prognosis, although carrying an additional germline alteration at -245 (rs2853669) may confer a better prognosis[107,115,116]. **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.
● ***TET2*** E10Q	**Gene and Alteration:** TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation [117,118]. Although this alteration has not been fully characterized and its effect on TET2 function is unclear, it has been previously reported in the context of cancer, which may indicate biological relevance. **Frequency and Prognosis:** TET2 mutation is rare in urothelial carcinomas, detected in only 2% of samples analyzed (COSMIC, Dec 2015). TET2 mutation has not been extensively studied in urothelial carcinomas in the scientific literature (PubMed, Dec 2015). Decreased expression and activity of TET proteins have been observed in solid tumors when compared to surrounding normal tissues [119]. **Potential Treatment Strategies:** TET2 mutations may lead to increased DNA methylation and may predict sensitivity to DNA methyltransferase (DNMT) inhibitors such as the FDA approved therapies azacitidine and decitabine. TET2 mutation status in patients with myelodysplastic syndrome (MDS) was significantly associated with better response rate to the DNMT inhibitors azacitidine and/or decitabine[120,121,122], and a patient with TET2-mutated angioimmunoblastic T-cell lymphoma (AITL) achieved a complete response to azacitidine[123]. However, as the alteration in this tumor has not been functionally characterized, it is not known whether these therapeutic approaches would be relevant.

GENE ALTERATION	INTERPRETATION
● ***TP53*** E285K	**Gene and Alteration:** Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers [124]. Mutations affecting the DNA binding domain (aa 100-292), the tetramerization domain (aa 325-356), or the C-terminal regulatory domain (aa 356-393), such as observed here, are thought to disrupt the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[125,126,127,128]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[129,130,131,132,133,134]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[135] to 1:20,000[134], and in the appropriate clinical context, germline testing of TP53 is recommended. **Frequency and Prognosis:** TP53 mutations are frequent in cancers of the urinary tract and have been reported in 42% of urothelial carcinoma (UC) cases (COSMIC, Apr 2016), specifically in 33% of renal pelvis UC[136], 49–54% of bladder UC[6,83], and 25% (22/71) of ureter UC samples[137]. Expression of p53 has been correlated with TP53 mutation, and reported in 52–84% of bladder cancers[85,86,138,139,140,141], 36–53% of upper urinary tract UCs (UTUC)[142,143,144], and in 4/4 urethral clear cell carcinomas[145]. TP53 mutations in both bladder and renal pelvis UC are more common in invasive tumors[85,136,146,147], and have been associated with inferior survival in patients with UC of the renal pelvis[136] or UTUC[148]. Alterations to the p53 pathway are correlated with aggressive disease and poor prognosis in bladder cancer[149,150,151], and p53 overexpression has been linked to poor progression-free survival in UTUC[148,152], disease progression in UC of the renal pelvis and ureter[153], and higher tumor grade in bladder squamous cell carcinoma[154,155,156]. A wild type p53-like gene expression signature, but not TP53 mutation status, has been reported to be associated with resistance to neoadjuvant chemotherapy in patients with muscle invasive bladder cancer[157,158]. **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 AZD1775[159,160,161,162], therapies that reactivate mutant p53 such as APR-246[163], or p53 gene therapy and immunotherapeutics such as SGT-53[164,165,166,167] and ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer (Oza et al., 2015; ASCO Abstract 5506). Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel (Leijen et al., 2015; ASCO Abstract 2507). In a Phase 1 clinical trial, 8 of 11 evaluable patients receiving SGT-53 as a single agent exhibited stable disease[168]. Clinical trials of SGT-53 in combination with chemotherapy are underway. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model[169]. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53 (Kumar et al., 2012; AACR Abstract 2874). Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

THERAPIES

There are no therapies FDA-approved in this patient's tumor type that are specific to the reported genomic alterations.

ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Ado-trastuzumab emtansine	**Approved Indications:** Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein HER2 on the cell surface, inhibiting HER2 signaling [170,171]; it also releases the cytotoxic therapy DM1 into cells, leading to cell death[171,172]. T-DM1 is FDA approved for the treatment of HER2-positive (HER2+), metastatic breast cancer. **Gene Association:** Activating mutations in ERBB2 or amplification of ERBB2 may predict sensitivity to T-DM1. **Supporting Data:** The vast majority of data on the therapeutic use of TDM-1 has been collected in the context of breast cancer. A Phase 3 clinical trial in Her2-positive breast cancer has reported that T-DM1 brought about significantly longer overall survival and progression-free survival, as compared with lapatinib plus capecitabine, in patients previously treated with trastuzumab/taxane [17].
Afatinib	**Approved Indications:** Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the treatment of metastatic non-small cell lung cancer (NSCLC) in patients with EGFR exon 19 deletions or exon 21 (L858R) missense mutations. **Gene Association:** ERBB2 activating mutations or amplification may predict sensitivity to afatinib. **Supporting Data:** A Phase 2 trial of afatinib in patients with either EGFR or ERBB2 amplification and esophagogastric, biliary tract, urothelial tract, or gynecologic cancer has reported a 5% (1/20) objective response, with one complete response achieved and stable disease achieved in 8 patients. The authors concluded that afatinib activity as a single agent was encouraging [173]. A Phase 1 trial of afatinib in advanced cancer reported disease stabilization in 14/31 patients[174]. A Phase 1 study of afatinib combined with pemetrexed in patients with advanced solid tumors has reported confirmed partial response in 3% (1/30) of patients and stable disease in 33% (10/30) of patients (Chu et al., 2013; ASCO Abstract 2523). A Phase 1 trial of volasertib and afatinib in patients with advanced solid tumors has reported partial response in 7% (2/29) of patients (Peeters et al., 2013; ASCO Abstract 2521). Outcomes of partial response and/or stable disease have been reported in various clinical trials involving multiple cancer types, including HER2-positive breast cancer, non-small cell lung cancer (NSCLC), colorectal cancer, and esophageal cancer[23,175,176,177,178].
Lapatinib	**Approved Indications:** Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2 (HER2/NEU), and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer. **Gene Association:** ERBB2 amplification or activating mutations may confer sensitivity to lapatinib. A case report of an inflammatory breast cancer patient with both ERBB2 V777L and S310F point mutations demonstrated clinical benefit following treatment with lapatinib in combination with trastuzumab and capecitabine [5]. ERBB2 S310F mutation has also been reported in one case of HER2-negative EMPD; a sustained partial response to lapatinib in combination with capecitabine was observed in this patient, and the response continued with lapatinib therapy alone[9].

	Supporting Data: A Phase 2 study of single agent lapatinib in patients with urothelial (transitional cell) carcinoma did not meet its primary endpoint of objective response rate, but clinical benefit was observed, particularly in patients with EGFR or ERBB2 amplification [179]. A small study of 6 metastatic transitional cell carcinoma patients treated with paclitaxel and lapatinib reported negative side effects; most patients discontinued therapy[180].
Pertuzumab	**Approved Indications:** Pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. It is FDA approved in combination with trastuzumab and docetaxel to treat a subset of patients with HER2-positive (HER2+) breast cancer [15]. **Gene Association:** ERBB2 amplification or activating mutations may predict sensitivity to pertuzumab. Pertuzumab is under clinical investigation in multiple tumor types. **Supporting Data:** Published clinical studies have not evaluated pertuzumab specifically for the treatment of bladder or urothelial carcinomas (PubMed, Dec 2015). Pertuzumab received FDA approval based on a Phase 3 randomized study that demonstrated significant improvement in progression-free survival (PFS), with a trend toward improvement in overall survival (OS), for the combination of pertuzumab, trastuzumab, and docetaxel, as compared to treatment with trastuzumab and docetaxel alone, for patients with HER2-positive breast cancer [15,181]. In a Phase 1 study of pertuzumab in advanced cancer, partial responses were observed in 1 patient with ovarian cancer and another patient with pancreatic islet cell carcinoma; stable disease was observed in 3 patients with prostate cancer and 1 patient each with lung, colon, or ovarian cancer[182]. Three additional Phase 1 studies of pertuzumab alone or in combination with capecitabine or docetaxel in advanced solid tumors did not report any responses in a total of 52 patients; however, stable disease was reported in a subset of patients with breast, rectal, lung, ovarian, or hormone-refractory prostate cancer[183,184,185].
Trastuzumab	**Approved Indications:** Trastuzumab is a monoclonal antibody that targets the protein HER2/neu (encoded by ERBB2). It is FDA approved for the treatment of breast cancers or metastatic gastric or gastroesophageal adenocarcinomas that overexpress HER2. **Gene Association:** ERBB2 amplification or activating mutations may confer sensitivity to trastuzumab. A case report of an inflammatory breast cancer patient with both ERBB2 V777L and S310F point mutations demonstrated clinical benefit following treatment with lapatinib in combination with trastuzumab and capecitabine [5]. **Supporting Data:** The majority of data investigating the therapeutic use of trastuzumab has been in the context of breast cancer. Trastuzumab has been reported to show activity in combination with chemotherapy in HER2-positive urothelial carcinoma, but the relative benefit is difficult to ascertain without Phase 3 data [186,187]. Trastuzumab was approved for breast cancer on the basis of a Phase 3 randomized clinical trial comparing treatment with trastuzumab and chemotherapy to treatment with chemotherapy alone. The addition of trastuzumab was associated with significant improvements in time to progression, objective response rate, response duration, and overall survival[10].

Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have little or no evidence in the patient's tumor type.

CLINICAL TRIALS TO CONSIDER

IMPORTANT: 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 meant to be a complete list of available trials. In order to conduct a more thorough search, please go to www.clinicaltrials.gov and use the search terms provided below. For more information about a specific clinical trial, type the NCT ID of the trial indicated below into the search bar.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***ERBB2*** S310F	ERBB2 amplification and mutations that promote HER2 activation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of chemotherapy or other targeted therapies, such as HSP90 inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "Her2", "trastuzumab", "lapatinib", pertuzumab", "ado-trastuzumab emtansine", "afatinib", "urothelial carcinoma", and/or "solid tumor".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
An Open-label, Multicenter, Multinational, Phase 2 Study Exploring the Efficacy and Safety of Neratinib Therapy in Patients With Solid Tumors With Activating HER2, HER3 or EGFR Mutations or With EGFR Gene Amplification.	Phase 2	EGFR, ERBB2, ERBB4	California, Massachusetts, Missouri, New Jersey, New York, Tennessee, Texas, Barcelona (Spain), Cremona (Italy), Helsinki (Finland), Madrid (Spain), Petch Tiqwa (Israel), Rehovot (Israel), Torino (Italy), Valencia (Spain), Victoria (Australia)	NCT01953926
My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents	Phase 2	SMO, BRAF, EGFR, ERBB2	Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Maryland, Minnesota, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Virginia, Washington	NCT02091141
Phase I/IB Multi-center Study of Irreversible EGFR/HER2 Tyrosine Kinase Inhibitor Afatinib (BIBW 2992) in Combination With Capecitabine for Advanced Solid Tumors and Pancretico-Biliary Cancers	Phase 1	EGFR, ERBB2, ERBB4	Washington	NCT02451553
Phase I Active Immunotherapy Trial With a Combination of Two Chimeric (Trastuzumab-like and Pertuzumab-like)Human Epidermal Growth Factor Receptor 2 (HER-2) B Cell Peptide Vaccine Emulsified in ISA 720 and Nor-MDP Adjuvant in Patients With Advanced Solid Tumors	Phase 1	ERBB2	Ohio	NCT01376505

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APPENDIX

VARIANTS OF UNKNOWN SIGNIFICANCE

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 make their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ARID1B R1842T	***ASXL1*** S1168T	***ATM*** S978P	***BRCA1*** E908K	***BRCA2*** D2312V	***BRIP1*** N1028K
C11orf30 D73N	***CTNNA1*** A80V	***ERBB2*** E1021K	***FAT1*** I4051M	***GLI1*** K658N	***MLL3*** splice site 9518-1G>A
PRKDC R913*	***RUNX1T1*** R255K	***SPEN*** M1173I	***STK11*** F354L	***TSC1*** E931Q,Q573K	***WISP3*** S10L

APPENDIX

GENES ASSAYED IN FOUNDATIONONE

FoundationOne is designed to include all genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 315 genes as well as introns of 28 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA Gene List: Entire Coding Sequence for the Detection of Base Substitutions, Insertion/Deletions, and Copy Number Alterations

ABL1	*ABL2*	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B)*	*APC*	*AR*
ARAF	*ARFRP1*	*ARID1A*	*ARID1B*	*ARID2*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*	*BCOR*
BCORL1	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTK*	*C11orf30 (EMSY)*
CARD11	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CD274*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHD2*	*CHD4*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CRLF2*
CSF1R	*CTCF*	*CTNNA1*	*CTNNB1*	*CUL3*	*CYLD*	*DAXX*	*DDR2*	*DICER1*	*DNMT3A*
DOT1L	*EGFR*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*
ERG	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*
FANCG	*FANCL*	*FAS*	*FAT1*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*	*FLCN*	*FLT1*	*FLT3*
FLT4	*FOXL2*	*FOXP1*	*FRS2*	*FUBP1*	*GABRA6*	*GATA1*	*GATA2*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GLI1*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GRM3*
GSK3B	*H3F3A*	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*HSP90AA1*	*IDH1*	*IDH2*	*IGF1R*
IGF2	*IKBKE*	*IKZF1*	*IL7R*	*INHBA*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*
JAK2	*JAK3*	*JUN*	*KAT6A (MYST3)*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*
KIT	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LMO1*	*LRP1B*	*LYN*	*LZTR1*
MAGI2	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*
MEN1	*MET*	*MITF*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH6*	*MTOR*	*MUTYH*
MYC	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*
NOTCH2	*NOTCH3*	*NPM1*	*NRAS*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*	*PAK3*
PALB2	*PARK2*	*PAX5*	*PBRM1*	*PDCD1LG2*	*PDGFRA*	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3CA*
PIK3CB	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PLCG2*	*PMS2*	*POLD1*	*POLE*	*PPP2R1A*	*PRDM1*
PREX2	*PRKAR1A*	*PRKCI*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*	*QKI*	*RAC1*
RAD50	*RAD51*	*RAF1*	*RANBP2*	*RARA*	*RB1*	*RBM10*	*RET*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*RUNX1T1*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SLIT2	*SMAD2*	*SMAD3*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX10*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SPTA1*	*SRC*	*STAG2*	*STAT3*	*STAT4*	*STK11*
SUFU	*SYK*	*TAF1*	*TBX3*	*TERC*	*TERT (promoter only)*	*TET2*	*TGFBR2*	*TNFAIP3*	*TNFRSF14*
TOP1	*TOP2A*	*TP53*	*TSC1*	*TSC2*	*TSHR*	*U2AF1*	*VEGFA*	*VHL*	*WISP3*
WT1	*XPO1*	*ZBTB2*	*ZNF217*	*ZNF703*					

DNA Gene List: For the Detection Select Rearrangements

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*EGFR*	*ETV1*	*ETV4*
ETV5	*ETV6*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*MSH2*	*MYB*	*MYC*	*NOTCH2*
NTRK1	*NTRK2*	*PDGFRA*	*RAF1*	*RARA*	*RET*	*ROS1*	*TMPRSS2*		

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APPENDIX

FOUNDATIONONE PERFORMANCE SPECIFICATIONS

ACCURACY		
Sensitivity: Base Substitutions	At Mutant Allele Frequency ≥10%	>99.9% (CI* 99.6%-100%)
	At Mutant Allele Frequency 5-10%	99.3% (CI* 98.3%-99.8%)
Sensitivity: Insertions/Deletions (1-40 bp)	At Mutant Allele Frequency ≥20%	97.9% (CI* 92.5%-99.7%)
	At Mutant Allele Frequency 10-20%	97.3% (CI* 90.5%-99.7%)
Sensitivity: Copy Number Alterations—Amplifications (ploidy <4, Amplification with Copy Number ≥8)	At ≥30% tumor nuclei	>99.0% (CI* 93.6%-100%)
	At 20% tumor nuclei	92.6% (CI* 66.1%-99.8%)
Sensitivity: Copy Number Alterations—Deletions (ploidy <4, Homozygous Deletions)	At ≥30% tumor nuclei	97.2% (CI* 85.5%-99.9%)
	At 20% tumor nuclei	88.9% (CI* 51.8%-99.7%)
Sensitivity: Rearrangements (selected rearrangements in specimens with ≥20% tumor nuclei)**		>90.0% [1] >99.0% for ALK fusion[2] (CI* 89.1%-100%)
Specificity of all variant types	Positive Predictive Value (PPV)	>99.0%
REPRODUCIBILITY (average concordance between replicates)		96.4% inter-batch precision 98.9% intra-batch precision

*95% Confidence Interval

** Performance for gene fusions within targeted introns only. Sensitivity for gene fusions occurring outside targeted introns or in highly repetitive intronic sequence contexts is reduced.

[1] Based on analysis of coverage and re-arrangement structure in the COSMIC database for the solid tumor fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.

[2] Based on ALK re-arrangement concordance analysis vs. a standard clinical FISH assay described in: Yelensky, R. et al. Analytical validation of solid tumor fusion gene detection in a comprehensive NGS-based clinical cancer genomic test, In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 4699

Assay specifications were determined for typical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne, please refer to the article, Frampton, GM. et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, Nat Biotechnol (2013 Oct. 20).

For additional information specific to the performance of this specimen, please contact Foundation Medicine, Inc. at 1-888-988-3639.

[II] Reduced Sensitivity: Although we can definitively confirm the presence of the genomic alterations detailed in this report, the data obtained may have been insufficient for comprehensive detection of genomic alterations. Reduced sensitivity may be due to poor sample quality or, in rare cases, to patient transplant history.

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ABOUT FOUNDATIONONE™

FoundationOne™: FoundationOne was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

Diagnostic Significance: FoundationOne identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal): An alteration denoted as "amplification – equivocal" implies that the FoundationOne assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne analytical methodology has identified as being present in <10% of the assayed tumor DNA.

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.

Alterations and Drugs Not Presented in Ranked Order: In this Report, neither any biomarker alteration, nor any drug associated with potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

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.

Treatment Decisions are 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 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 or variant characteristics may result in reduced sensitivity. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne is performed using DNA derived from tumor, and as such germline events may not be reported. The following targets typically have low coverage resulting in a reduction in sensitivity: *SDHD* exon 6 and *TP53* exon 1.

FoundationOne complies with all European Union (EU) requirements of the IVD Directive 98/79EC. As such, the FoundationOne Assay has been registered for CE mark by our EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

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