

**ABOUT THE TEST** FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

<b>PATIENT</b>	<b>DISEASE</b> Ovary clear cell carcinoma	<b>PHYSICIAN</b>	<b>ORDERING PHYSICIAN</b> Yeh, Yi-Chen	<b>SPECIMEN</b>	<b>SPECIMEN SITE</b> Ovary
	<b>NAME</b> Han, I Fu		<b>MEDICAL FACILITY</b> Taipei Veterans General Hospital		<b>SPECIMEN ID</b> S111-68476K (PF23001)
	<b>DATE OF BIRTH</b> 07 February 1985		<b>ADDITIONAL RECIPIENT</b> None		<b>SPECIMEN TYPE</b> Slide Deck
	<b>SEX</b> Female		<b>MEDICAL FACILITY ID</b> 205872		<b>DATE OF COLLECTION</b> 28 September 2022
	<b>MEDICAL RECORD #</b> 41872371		<b>PATHOLOGIST</b> Not Provided		<b>SPECIMEN RECEIVED</b> 05 January 2023

## Biomarker Findings

**Homologous Recombination status** - HRD Not Detected

**Loss of Heterozygosity score** - 11.9%

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - 4 Muts/Mb

## Genomic Findings

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

**ARID1A** Y447fs\*172, K1819fs\*63

**PIK3CA** Q546R - subclonal<sup>†</sup>

**TET2** E1151\*

2 Disease relevant genes with no reportable alterations: **BRCA1**, **BRCA2**

<sup>†</sup> See About the Test in appendix for details.

## Report Highlights

- Evidence-matched clinical trial options based on this patient's genomic findings: (p. [7](#))
- Variants that may represent clonal hematopoiesis and may originate from non-tumor sources: **TET2** E1151\* (p. [6](#))

### BIOMARKER FINDINGS

**Homologous Recombination status** - HRD Not Detected

**Loss of Heterozygosity score** - 11.9%

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - 4 Muts/Mb

### GENOMIC FINDINGS

**ARID1A** - Y447fs\*172, K1819fs\*63

10 Trials [see p. 7](#)

**PIK3CA** - Q546R - subclonal

10 Trials [see p. 9](#)

### THERAPY AND CLINICAL TRIAL IMPLICATIONS

HRD Not Detected defined as absence of deleterious **BRCA1/2** alteration and LOH score < 16% or Cannot Be Determined (Coleman et al., 2017; 28916367).

No therapies or clinical trials. See Biomarker Findings section

No therapies or clinical trials. See Biomarker Findings section

No therapies or clinical trials. See Biomarker Findings section

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
none	none
none	none

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
 Foundation Medicine, Inc. | [www.rochefoundationmedicine.com](http://www.rochefoundationmedicine.com)

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

## 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.

**TET2 - E1151\*** ..... [p. 6](#)

## GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

**TET2 - E1151\*** ..... [p. 6](#)

**NOTE** Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents 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 exhaustive. 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. 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.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
 Foundation Medicine, Inc. | [www.rochefoundationmedicine.com](http://www.rochefoundationmedicine.com)

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

ORDERED TEST # ORD-1537951-01

BIOMARKER FINDINGS

BIOMARKER

## Loss of Heterozygosity score

RESULT  
11.9%

### POTENTIAL TREATMENT STRATEGIES

#### — Targeted Therapies —

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors<sup>1,2</sup>. In platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma, rucaparib elicited significantly longer median PFS (7.2 vs. 5.0 months, HR=0.51) and improved ORR (33.3% vs. 9.6%, p=0.0003) for patients with LOH score ≥ 16%<sup>2</sup>. In the maintenance setting in platinum-sensitive, BRCA1/2 wild-type patients, rucaparib was superior to placebo in both the LOH score ≥ 16% (median PFS, 9.7 vs. 5.4 months; HR=0.44) and LOH score < 16% (median PFS, 6.7 vs. 5.4 months; HR=0.58) cohorts<sup>1</sup>. Similar results have been reported for maintenance treatment with niraparib in ovarian cancer<sup>3</sup> when using a different measure

of HRD that includes genomic LOH<sup>4-5</sup>. Increased LOH has also been associated with improved sensitivity to platinum-containing chemotherapy regimens in patients with ovarian or breast cancer<sup>6-8</sup>.

### FREQUENCY & PROGNOSIS

In a study of more than 4,000 ovarian, Fallopian tube, or peritoneal cancer samples, genomic LOH score ≥ 16% was identified in 24.2% of BRCA1/2 wild-type cases, deleterious BRCA1/2 mutation was identified in an additional 17.2% of cases, and the remaining 58.7% of cases had LOH score < 16% and were BRCA1/2 wild-type<sup>9</sup>. Among the histological subtypes, LOH score ≥ 16% or BRCA1/2 mutation was reported in 42.4% of serous carcinomas, 37.6% of endometrioid carcinomas, 23.5% of carcinosarcomas, 20.6% of neuroendocrine carcinomas, 13.6% of clear cell carcinomas, and 8.1% of mucinous carcinomas; in BRCA1/2 wild-type samples, the median LOH score was significantly higher in serous as compared with non-serous cases<sup>9</sup>. In ovarian carcinoma, the median LOH score is significantly higher for BRCA1/2-mutated cases than BRCA1/2 wild-type cases (22.2% vs. 9.8%)<sup>9</sup>, and mutation or methylation of BRCA1, BRCA2, or RAD51C has been reported to be enriched in cases with

increased genomic LOH<sup>6,10</sup>. One study reported no association between LOH and either tumor stage or grade in ovarian serous carcinoma<sup>11</sup>. In patients with high-grade serous ovarian carcinoma, the frequency of LOH has been reported to increase significantly with age<sup>12</sup>.

### FINDING SUMMARY

The loss of heterozygosity (LOH) score is a profile of the percentage of the tumor genome that is under focal loss of one allele<sup>2</sup>; focal LOH events accumulate as genomic "scars" as a result of incorrect DNA double-strand break repair when the homologous recombination pathway is deficient (HRD)<sup>6,10,13-14</sup>. HRD and consequent genomic LOH occur as a result of genetic or epigenetic inactivation of one or more of the homologous recombination pathway proteins, including BRCA1, BRCA2, RAD51C, ATM, PALB2, and BRIP1<sup>13-16</sup>. This sample harbors a genomic LOH score below levels that have been associated with improved rates of clinical benefit from treatment with the PARP inhibitor rucaparib in patients with platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma<sup>2</sup>. However, patients with lower genomic LOH have also responded to rucaparib, and this type of LOH score does not preclude benefit from PARP inhibitors<sup>1,2</sup>.

BIOMARKER

## Microsatellite status

RESULT  
MS-Stable

### POTENTIAL TREATMENT STRATEGIES

#### — Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors<sup>17-19</sup>, including approved therapies nivolumab and pembrolizumab<sup>20</sup>. In a retrospective analysis of 361 patients with solid tumors treated

with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)<sup>21</sup>.

### FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported in 1.6-19.7% of ovarian cancer samples<sup>22-23</sup>, including 3.8% (1/26) of ovarian endometrioid adenocarcinomas<sup>24</sup>, and 10.0% (3/30) of ovarian clear cell carcinomas (CCOCs)<sup>25</sup>. No association of MSI-H with stage or survival was found in patients with ovarian cancer<sup>22,26</sup>.

### FINDING SUMMARY

Microsatellite instability (MSI) is a condition of

genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor<sup>27</sup>. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2<sup>27-29</sup>. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers<sup>30-32</sup>. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins<sup>27,29,31-32</sup>.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1537951-01

## BIOMARKER FINDINGS

## BIOMARKER

# Tumor Mutational Burden

## RESULT

4 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1<sup>33-35</sup>, anti-PD-1 therapies<sup>33-36</sup>, and combination nivolumab and ipilimumab<sup>37-42</sup>. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors<sup>33-36,43-47</sup>. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB  $\geq 10$  Muts/Mb (as measured by this assay) compared with those with TMB  $< 10$  Muts/Mb in a large cohort that included multiple tumor types<sup>43</sup>; similar findings were observed in the KEYNOTE 028 and 012 trials<sup>36</sup>. At

the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores  $\geq 10$  Muts/Mb were associated with prolonged time to treatment failure compared with scores  $< 10$  Muts/Mb (HR=0.68)<sup>47</sup>. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB  $\geq 10$  Muts/Mb independent of blood TMB at any cutpoint in matched samples<sup>48</sup>. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB  $\geq 16$  Muts/Mb than those with TMB  $\geq 10$  and  $< 16$  Muts/Mb<sup>46</sup>. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as  $\geq 16$ -20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy<sup>49</sup> or those with lower TMB treated with PD-1 or PD-L1-targeting agents<sup>34</sup>.

## FREQUENCY & PROGNOSIS

Ovarian clear cell carcinoma harbors a median TMB of 2.7 mutations per megabase (mut/Mb),

and 1.7% of cases have high TMB ( $> 20$  muts/Mb)<sup>50</sup>. In a study of high grade serous ovarian cancer, homologous recombination (HR)-deficient tumors, which comprised ~50% of all samples, harbored a higher neoantigen load compared to HR-proficient tumors; higher neoantigen load was associated with longer OS but not disease free survival<sup>51</sup>.

## FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma<sup>52-53</sup> and cigarette smoke in lung cancer<sup>54-55</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>56-57</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>58-62</sup>, and microsatellite instability (MSI)<sup>58,61-62</sup>. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types<sup>34-35,43</sup>.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1537951-01

GENOMIC FINDINGS

GENE

**ARID1A**

ALTERATION

Y447fs\*172, K1819fs\*63

TRANSCRIPT ID

NM\_006015.4, NM\_006015.4

CODING SEQUENCE EFFECT

1339\_1340TA>C, 5454\_5457delGAAG

VARIANT CHROMOSOMAL POSITION

chr1:27056343-27056344, chr1:27105842-27105846

VARIANT ALLELE FREQUENCY (% VAF)

15.0%, 15.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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 and ceralasertib<sup>63</sup>. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no

responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib<sup>64</sup>. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan<sup>65</sup>. In a Phase 1 trial, a patient with metastatic colorectal cancer harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months<sup>66</sup>. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to EZH2 inhibitors<sup>67-68</sup>, which are under investigation in clinical trials. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway<sup>69-71</sup>. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy<sup>72</sup>. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma<sup>73-74</sup> and to 5-fluorouracil in colorectal cancer cell lines<sup>75</sup>.

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, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2023)<sup>76-84</sup>. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas<sup>24,72,85-87</sup>, CRC<sup>72,88-90</sup>, and gastric cancer<sup>72,91-95</sup>. Several studies have reported no correlation between ARID1A loss and clinicopathological parameters in ovarian clear cell or endometrioid carcinomas or other endometrial cancers<sup>96-99</sup>, whereas others suggest that ARID1A loss is a negative prognostic factor<sup>74,100</sup>.

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<sup>80,94,101-107</sup>. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss<sup>80,92,102-103,108</sup>, whereas ARID1A missense mutations are mostly uncharacterized.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1537951-01

GENOMIC FINDINGS

GENE

PIK3CA

ALTERATION

Q546R - subclonal

TRANSCRIPT ID

NM\_006218.2

CODING SEQUENCE EFFECT

1637A>G

VARIANT CHROMOSOMAL POSITION

chr3:178936095

VARIANT ALLELE FREQUENCY (% VAF)

2.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K<sup>109-116</sup>, AKT<sup>117-118</sup>, or mTOR<sup>119-126</sup>. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate<sup>116</sup>. However, the Phase 2 study of copanlisib for patients with

endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)<sup>115</sup>. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations<sup>113-114</sup>. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study<sup>127</sup>. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)<sup>128</sup>. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)<sup>129</sup>. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)<sup>130</sup>, but has shown limited activity as monotherapy for PIK3CA-mutated solid tumors with a Phase 1a study reporting an ORR of 6.0% (8/134) and a DCR of 58% (78/134)<sup>110</sup>.

FREQUENCY & PROGNOSIS

PIK3CA mutation frequency is variable among different subtypes of ovarian cancer. Mutations

were detected in 33% (32/97) of clear cell carcinomas and in 12% of advanced epithelial ovarian carcinomas; however, PIK3CA mutations were detected in 3% of high-grade serous ovarian cancers and in fewer than 1% of tumors in the TCGA ovarian serous cystadenocarcinoma dataset<sup>15,131-133</sup>. A study of ovarian clear cell carcinomas reported an association of coexistent alterations in ARID1A and PIK3CA with poor prognosis<sup>134</sup>. There are differing reports on the impact of PIK3CA alteration on prognosis in patients with ovarian carcinoma; PIK3CA mutation or overexpression was associated with favorable survival in patients with ovarian clear cell carcinoma<sup>135-136</sup>, whereas PIK3CA amplification has been associated with higher grade ovarian tumors<sup>137-139</sup> and with shorter survival in patients with ovarian cancer in general<sup>140-143</sup>.

FINDING SUMMARY

PIK3CA encodes p110-α, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival<sup>144-145</sup>. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic<sup>146-167</sup>.

GENE

TET2

ALTERATION

E1151\*

TRANSCRIPT ID

NM\_017628.4

CODING SEQUENCE EFFECT

3451G>T

VARIANT CHROMOSOMAL POSITION

chr4:106158550

VARIANT ALLELE FREQUENCY (% VAF)

50.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address

genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies<sup>168</sup>. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2023).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation<sup>169-170</sup>. Alterations such as seen here may disrupt TET2 function or expression<sup>171-175</sup>.

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<sup>176-181</sup>. 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<sup>176-177</sup>. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease<sup>182</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH<sup>180,183-184</sup>. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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



**ORDERED TEST #** ORD-1537951-01

**CLINICAL TRIALS**

**NOTE** 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. 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 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](https://clinicaltrials.gov). Or, visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

**GENE**
**ARID1A**
**ALTERATION**

Y447fs\*172, K1819fs\*63

**RATIONALE**

ARID1A loss or inactivation may predict sensitivity to ATR inhibitors. On the basis of preclinical evidence, ARID1A loss or inactivation

may predict sensitivity to EZH2 and BET/BRD inhibitors.

**NCT02264678**
**PHASE 1/2**

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

**TARGETS**  
ATR, PARP, PD-L1

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

**NCT05252390**
**PHASE 1/2**

NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors

**TARGETS**  
BRD4, PARP, AR

**LOCATIONS:** California, Arizona, Michigan, Texas, Tennessee, Maryland, Virginia, North Carolina

**NCT05053971**
**PHASE 1/2**

Testing A New Anti-cancer Drug Combination, Entinostat and ZEN003694, for Advanced and Refractory Solid Tumors and Lymphomas

**TARGETS**  
BRD3, BRD4, BRD2, BRDT, HDAC

**LOCATIONS:** Oklahoma, Connecticut, Florida

**NCT04104776**
**PHASE 1/2**

A Study of CPI-0209 in Patients With Advanced Solid Tumors

**TARGETS**  
EZH2, TOP1

**LOCATIONS:** Washington, Salamanca (Spain), Michigan, Illinois, Ohio, Massachusetts, New Jersey, New York

**NCT04657068**
**PHASE 1/2**

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

**TARGETS**  
ATR

**LOCATIONS:** London (United Kingdom), Colorado, Oklahoma, Texas, Pennsylvania, Tennessee, Florida

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | [www.rochefoundationmedicine.com](http://www.rochefoundationmedicine.com)

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

**ORDERED TEST #** ORD-1537951-01

**CLINICAL TRIALS**
**NCT04491942**
**PHASE 1**

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to the Usual Chemotherapy Treatment (Cisplatin, or Cisplatin and Gemcitabine) for Advanced Solid Tumors With Emphasis on Urothelial Cancer

**TARGETS**  
ATR

**LOCATIONS:** California, Wisconsin, Ohio, Pennsylvania, New York, Maryland

**NCT04514497**
**PHASE 1**

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

**TARGETS**  
ATR, TOP1

**LOCATIONS:** Arizona, Minnesota, Oklahoma, Missouri, Pennsylvania, Connecticut, Florida

**NCT05327010**
**PHASE 2**

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

**TARGETS**  
PARP, BRD4, BRDT, BRD2, BRD3

**LOCATIONS:** Illinois, Texas, Georgia

**NCT04840589**
**PHASE 1**

Testing the Combination of ZEN003694 and Nivolumab With or Without Ipilimumab in Solid Tumors

**TARGETS**  
PD-1, CTLA-4, BRD4, BRDT, BRD2, BRD3

**LOCATIONS:** Ohio, Pennsylvania, New York, Maryland

**NCT05071937**
**PHASE 2**

ZEN003694 Combined With Talazoparib in Patients With Recurrent Ovarian Cancer

**TARGETS**  
BRD4, BRDT, BRD2, BRD3, PARP

**LOCATIONS:** Pennsylvania

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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



**ORDERED TEST #** ORD-1537951-01

**CLINICAL TRIALS**
**GENE**
**PIK3CA**
**ALTERATION**

Q546R - subclonal

**RATIONALE**

PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of

this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

**NCT04589845**
**PHASE 2**

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

**TARGETS**

TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha, RAFs, NRAS

**LOCATIONS:** Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China)

**NCT03239015**
**PHASE 2**

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

**TARGETS**

EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

**LOCATIONS:** Shanghai (China)

**NCT04337463**
**PHASE NULL**

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

**TARGETS**

mTORC1, mTORC2, PD-1

**LOCATIONS:** Chongqing (China), Chengdu (China)

**NCT04931342**
**PHASE 2**

A Study Evaluating the Efficacy and Safety of Biomarker-Driven Therapies in Patients With Persistent or Recurrent Rare Epithelial Ovarian Tumors

**TARGETS**

AKTs, MEK, ERBB2, PD-L1, VEGFA

**LOCATIONS:** Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Moskva (Russian Federation), Malvern (Australia), Ankara (Turkey), Istanbul (Turkey), Brno (Czechia), Dresden (Germany), Prague (Czechia), Muenchen (Germany)

**NCT04803318**
**PHASE 2**

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

**TARGETS**

mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

**LOCATIONS:** Guangzhou (China)

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

**ORDERED TEST #** ORD-1537951-01

**CLINICAL TRIALS**
**NCT04526470**
**PHASE 1/2**

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

**TARGETS**  
PI3K-alpha

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

**NCT05125523**
**PHASE 1**

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

**TARGETS**  
mTOR

**LOCATIONS:** Tianjin (China)

**NCT03772561**
**PHASE 1**

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

**TARGETS**  
PARP, AKTs, PD-L1

**LOCATIONS:** Singapore (Singapore)

**NCT04801966**
**PHASE NULL**

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

**TARGETS**  
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

**LOCATIONS:** Melbourne (Australia)

**NCT04551521**
**PHASE 2**

CRAFT: The NCT-PMO-1602 Phase II Trial

**TARGETS**  
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

**LOCATIONS:** Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
 Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1537951-01

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

**ARID1A**  
Q1334\_R1335insQ

**CDKN2A/B**  
R109H

**DAXX**  
P627S

**EGFR**  
L698T

**FANCA**  
S645F

**FGF10**  
amplification

**JAK2**  
I724T

**NOTCH2**  
G1016S

**PARP1**  
C908fs\*9

**RICTOR**  
amplification

**SDHA**  
amplification

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1537951-01

**APPENDIX**

Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include 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 324 genes as well as introns of 36 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	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B or WTX)	
APC	AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2
BCL6	BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1
BTG2	BTK	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	CDH1
CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R	CTCF
CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1	DDR2
DIS3	DNMT3A	DOT1L	EED	EGFR	EMSY (C11orf30)	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNA13	GNAS	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNFA1	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11 (MRE11A)	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD2 (WHSC1 or MMSET)	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	NTRK3
P2RY8	PALB2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCC1 (PD-1)	PDCC1LG2 (PD-L2)
PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1
PMS2	POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI
PRKN (PARK2)	PTCH1	PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51
RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10
REL	RET	RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC
SDHD	SETD2	SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO
SNCAIP	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)	TET2	TET2	TGFB2
TIPARP	TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA
VHL	WT1	XPO1	XRCC2	ZNF217	ZNF703			

**DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS**

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV4
ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT	KMT2A (MLL)
MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSP02	SDC4	SLC34A2	TERC*	TERT**	TPRSS2

\*TERC is an NCRNA

\*\*Promoter region of TERT is interrogated

**ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS**


Homologous Recombination status  
Loss of Heterozygosity (LOH) score  
Microsatellite (MS) status  
Tumor Mutational Burden (TMB)

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

ORDERED TEST # ORD-1537951-01

## APPENDIX

## About FoundationOne®CDx

FoundationOne 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, Ciplstraat 3, 2440 Geel, Belgium. 

### ABOUT FOUNDATIONONE CDx

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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:  
[www.rochefoundationmedicine.com/f1cdxtech](http://www.rochefoundationmedicine.com/f1cdxtech).

### INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx 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 solid malignant neoplasms.

### TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes

detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture-selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

### 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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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.

#### Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the 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 CDx 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 CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx 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 CDx analytical

methodology has identified as being present in <10% of the assayed tumor DNA.

### Ranking of Therapies and Clinical Trials

#### Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

#### Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

### 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](http://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. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to [NCCN.org](http://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.

### Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | [www.rochefoundationmedicine.com](http://www.rochefoundationmedicine.com)

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

ORDERED TEST # ORD-1537951-01

## APPENDIX

## About FoundationOne®CDx

- analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
- TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation [https://www.accessdata.fda.gov/cdrh\\_docs/pdf17/P170019B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf). The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
  - Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score  $\geq 16$  will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
  - The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and

extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

- Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
- Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
- Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in <https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/> report the frequency of *HER2* overexpression as 20% in breast cancer. Based on the F1CDx *HER2* CDx concordance study, approximately 10% of *HER2* amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

### REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal

hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

### VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	%CV*
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

\*Interquartile Range = 1st Quartile to 3rd Quartile

### 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 >10%, 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

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. | [www.rochefoundationmedicine.com](http://www.rochefoundationmedicine.com)

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



ORDERED TEST # ORD-1537951-01

**APPENDIX**

About FoundationOne®CDx

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*, *CBL*, *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.

**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 CDx.

**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. FoundationOne CDx is performed using DNA derived from tumor, 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
mut/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

**REFERENCE SEQUENCE INFORMATION**

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.4.0

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of the data. The median exon coverage for this sample is 911x. Foundation Medicine Inc. does not guarantee the suitability of use.

**ORDERED TEST #**    **ORD-1537951-01**
**APPENDIX    References**

1. Coleman RL, et al. Lancet (2017) PMID: 28916367
2. Swisher EM, et al. Lancet Oncol. (2017) PMID: 27908594
3. Mirza MR, et al. N. Engl. J. Med. (2016) PMID: 27717299
4. Telli ML, et al. Clin. Cancer Res. (2016) PMID: 26957554
5. Timms KM, et al. Breast Cancer Res. (2014) PMID: 25475740
6. Wang ZC, et al. Clin. Cancer Res. (2012) PMID: 22912389
7. Telli ML, et al. J. Clin. Oncol. (2015) PMID: 25847929
8. Isakoff SJ, et al. J. Clin. Oncol. (2015) PMID: 25847936
9. Elvin et al., 2017; ASCO Abstract 5512
10. Abkevich V, et al. Br. J. Cancer (2012) PMID: 23047548
11. Marquard AM, et al. Biomark Res (2015) PMID: 26015868
12. Pedersen BS, et al. Genes Chromosomes Cancer (2013) PMID: 23716468
13. Watkins JA, et al. Breast Cancer Res. (2014) PMID: 25093514
14. Vanderstichele A, et al. Eur. J. Cancer (2017) PMID: 28950147
15. Nature (2011) PMID: 21720365
16. N. Engl. J. Med. (2003) PMID: 12736286
17. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) PMID: 25392179
18. Kroemer G, et al. Oncoimmunology (2015) PMID: 26140250
19. Lal N, et al. Oncoimmunology (2015) PMID: 25949894
20. Le DT, et al. N. Engl. J. Med. (2015) PMID: 26028255
21. Ayers et al., 2016; ASCO-SITC Abstract P60
22. Segev Y, et al. Eur. J. Gynaecol. Oncol. (2015) PMID: 26775351
23. Plisiecka-Hałas J, et al. Anticancer Res. (2015) PMID: 18507046
24. Huang HN, et al. Histopathology (2015) PMID: 25195947
25. Strickland et al., 2016; ASCO Abstract 5514
26. Aysal A, et al. Am. J. Surg. Pathol. (2012) PMID: 22189970
27. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) PMID: 26337942
28. You JF, et al. Br. J. Cancer (2010) PMID: 21081928
29. Bairwa NK, et al. Methods Mol. Biol. (2014) PMID: 24623249
30. Boland CR, et al. Cancer Res. (1998) PMID: 9823339
31. Pawlik TM, et al. Dis. Markers (2004) PMID: 15528785
32. Boland CR, et al. Gastroenterology (2010) PMID: 20420947
33. Samstein RM, et al. Nat. Genet. (2019) PMID: 30643254
34. Goodman AM, et al. Mol. Cancer Ther. (2017) PMID: 28835386
35. Goodman AM, et al. Cancer Immunol Res (2019) PMID: 31405947
36. Cristescu R, et al. Science (2018) PMID: 30309915
37. Ready N, et al. J. Clin. Oncol. (2019) PMID: 30785829
38. Hellmann MD, et al. N. Engl. J. Med. (2018) PMID: 29658845
39. Hellmann MD, et al. Cancer Cell (2018) PMID: 29657128
40. Hellmann MD, et al. Cancer Cell (2018) PMID: 29731394
41. Rozeman EA, et al. Nat Med (2021) PMID: 33558721
42. Sharma P, et al. Cancer Cell (2020) PMID: 32916128
43. Marabelle A, et al. Lancet Oncol. (2020) PMID: 32919526
44. Ott PA, et al. J. Clin. Oncol. (2019) PMID: 30557521
45. Cristescu R, et al. J Immunother Cancer (2022) PMID: 35101941
46. Friedman CF, et al. Cancer Discov (2022) PMID: 34876409
47. Sturgill EG, et al. Oncologist (2022) PMID: 35274716
48. Schenker et al., 2022; AACR Abstract 7845
49. Legrand et al., 2018; ASCO Abstract 12000
50. Chalmers ZR, et al. Genome Med (2017) PMID: 28420421
51. Strickland KC, et al. Oncotarget (2016) PMID: 26871470
52. Pfeifer GP, et al. Mutat. Res. (2005) PMID: 15748635
53. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) PMID: 23875803
54. Pfeifer GP, et al. Oncogene (2002) PMID: 12379884
55. Rizvi NA, et al. Science (2015) PMID: 25765070
56. Johnson BE, et al. Science (2014) PMID: 24336570
57. Choi S, et al. Neuro-oncology (2018) PMID: 29452419
58. Cancer Genome Atlas Research Network, et al. Nature (2013) PMID: 23636398
59. Briggs S, et al. J. Pathol. (2013) PMID: 23447401
60. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) PMID: 24583393
61. Nature (2012) PMID: 22810696
62. Roberts SA, et al. Nat. Rev. Cancer (2014) PMID: 25568919
63. Williamson CT, et al. Nat Commun (2016) PMID: 27958275
64. Aggarwal et al., 2021; ESMO Abstract 5120
65. Thomas A, et al. J. Clin. Oncol. (2018) PMID: 29252124
66. Yap TA, et al. J Clin Oncol (2020) PMID: 32568634
67. Bitler BG, et al. Nat. Med. (2015) PMID: 25686104
68. Kim KH, et al. Nat. Med. (2015) PMID: 26552009
69. Wiegand KC, et al. BMC Cancer (2014) PMID: 24559118
70. Huang HN, et al. Mod. Pathol. (2014) PMID: 24336158
71. Samartzis EP, et al. Oncotarget (2014) PMID: 24979463
72. Okamura R, et al. J Immunother Cancer (2020) PMID: 32111729
73. Yokoyama Y, et al. J Gynecol Oncol (2014) PMID: 24459582
74. Katagiri A, et al. Mod. Pathol. (2012) PMID: 22101352
75. Xie C, et al. Tumour Biol. (2014) PMID: 24833095
76. Tate JG, et al. Nucleic Acids Res. (2019) PMID: 30371878
77. Cerami E, et al. Cancer Discov (2012) PMID: 22588877
78. Gao J, et al. Sci Signal (2013) PMID: 23550210
79. Wu RC, et al. Cancer Biol. Ther. (2014) PMID: 24618703
80. Jones S, et al. Hum. Mutat. (2012) PMID: 22009941
81. Dulak AM, et al. Nat. Genet. (2013) PMID: 23525077
82. Streppel MM, et al. Oncogene (2014) PMID: 23318448
83. Jiao Y, et al. J. Pathol. (2014) PMID: 24293293
84. Ross JS, et al. Oncologist (2014) PMID: 24563076
85. Hussein YR, et al. Mod. Pathol. (2015) PMID: 25394778
86. Bosse T, et al. Mod. Pathol. (2013) PMID: 23702729
87. Allo G, et al. Mod. Pathol. (2014) PMID: 23887303
88. Chou A, et al. Hum. Pathol. (2014) PMID: 24925223
89. Ye J, et al. Hum. Pathol. (2014) PMID: 25311944
90. Wei XL, et al. World J. Gastroenterol. (2014) PMID: 25561809
91. Chen K, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) PMID: 25583476
92. Wang K, et al. Nat. Genet. (2011) PMID: 22037554
93. Abe H, et al. Virchows Arch. (2012) PMID: 22915242
94. Wang DD, et al. PLoS ONE (2012) PMID: 22808142
95. Wiegand KC, et al. Hum. Pathol. (2014) PMID: 24767857
96. Rahman M, et al. Hum. Pathol. (2013) PMID: 22939958
97. Maeda D, et al. Int J Mol Sci (2010) PMID: 21614196
98. Lowery WJ, et al. Int. J. Gynecol. Cancer (2012) PMID: 22193641
99. Fadare O, et al. Mod. Pathol. (2013) PMID: 23524907
100. Mao TL, et al. Am. J. Surg. Pathol. (2013) PMID: 24076775
101. Guan B, et al. Cancer Res. (2011) PMID: 21900401
102. Wiegand KC, et al. N. Engl. J. Med. (2010) PMID: 20942669
103. Jones S, et al. Science (2010) PMID: 20826764
104. Yan HB, et al. Carcinogenesis (2014) PMID: 24293408
105. Huang J, et al. Nat. Genet. (2012) PMID: 22922871
106. Chan-On W, et al. Nat. Genet. (2013) PMID: 24185513
107. Mamo A, et al. Oncogene (2012) PMID: 21892209
108. Zang ZJ, et al. Nat. Genet. (2012) PMID: 22484628
109. Fritsch C, et al. Mol. Cancer Ther. (2014) PMID: 24608574
110. Juric D, et al. J. Clin. Oncol. (2018) PMID: 29401002
111. Gallant JN, et al. NPJ Precis Oncol (2019) PMID: 30793038
112. Delestre F, et al. Sci Transl Med (2021) PMID: 34613809
113. Morschhauser F, et al. Mol Cancer Ther (2020) PMID: 31619463
114. Patnaik A, et al. Ann. Oncol. (2016) PMID: 27672108
115. Santin AD, et al. Gynecol Oncol Rep (2020) PMID: 31934607
116. Damodaran S, et al. J Clin Oncol (2022) PMID: 35133871
117. André F, et al. N. Engl. J. Med. (2019) PMID: 31091374
118. Smyth LM, et al. NPJ Breast Cancer (2021) PMID: 33863913
119. Varnier R, et al. Eur J Cancer (2019) PMID: 31351267
120. Basse C, et al. JCO Precis Oncol (2018) PMID: 32914004
121. Sultova E, et al. Arch Gynecol Obstet (2021) PMID: 33277683
122. Mackay HJ, et al. Cancer (2014) PMID: 24166148
123. Myers AP, et al. Gynecol. Oncol. (2016) PMID: 27016228
124. Dhama J, et al. Cold Spring Harb Mol Case Stud (2018) PMID: 29588307
125. Harris EJ, et al. Front Oncol (2019) PMID: 30863722
126. Hanna GJ, et al. Clin Cancer Res (2018) PMID: 29301825
127. Krop et al., 2018; ASCO Abstract 101
128. Pascual J, et al. Cancer Discov (2021) PMID: 32958578
129. Dolly SO, et al. Clin. Cancer Res. (2016) PMID: 26787751
130. Canaud et al., 2021; ESMO Abstract LBA23
131. Kuo KT, et al. Am. J. Pathol. (2009) PMID: 19349352
132. Levine DA, et al. Clin. Cancer Res. (2005) PMID: 15837735
133. Matulonis UA, et al. PLoS ONE (2011) PMID: 21931712
134. Uehara Y, et al. PLoS ONE (2015) PMID: 26043110
135. Rahman M, et al. Hum. Pathol. (2012) PMID: 22705003
136. Abe A, et al. Hum. Pathol. (2013) PMID: 22955107
137. Carden CP, et al. Mol. Cancer Ther. (2012) PMID: 22556379
138. Kolasa JK, et al. Cancer Biol. Ther. (2009) PMID: 19029838
139. Nakayama K, et al. Int. J. Cancer (2007) PMID: 17351921
140. Kato S, et al. Int. J. Cancer (2007) PMID: 17590872
141. Woenckhaus J, et al. Virchows Arch. (2007) PMID: 17377809
142. Niskakoski A, et al. Int. J. Cancer (2013) PMID: 23716351
143. Huang J, et al. Genes Chromosomes Cancer (2011) PMID: 21563232
144. Samuels Y, et al. Cancer Cell (2005) PMID: 15950905
145. Nat. Rev. Cancer (2009) PMID: 19629070
146. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) PMID: 15647370
147. Ikenoue T, et al. Cancer Res. (2005) PMID: 15930273
148. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) PMID: 17376864
149. Horn S, et al. Oncogene (2008) PMID: 18317450
150. Rudd ML, et al. Clin. Cancer Res. (2011) PMID: 21266528
151. Hon WC, et al. Oncogene (2012) PMID: 22120714
152. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) PMID: 22120714

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

ORDERED TEST # ORD-1537951-01

**APPENDIX**
**References**

- 22949682
153. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) PMID: 19915146
154. Laurenti R, et al. Rev Saude Publica (1990) PMID: 2103068
155. Dan S, et al. Cancer Res. (2010) PMID: 20530683
156. Oda K, et al. Cancer Res. (2008) PMID: 18829572
157. Zhao L, et al. Oncogene (2008) PMID: 18794883
158. Lui VW, et al. Cancer Discov (2013) PMID: 23619167
159. Ross RL, et al. Oncogene (2013) PMID: 22430209
160. Rivière JB, et al. Nat. Genet. (2012) PMID: 22729224
161. Shibata T, et al. Cancer Lett. (2009) PMID: 19394761
162. Dogruluk T, et al. Cancer Res. (2015) PMID: 26627007
163. Croessmann S, et al. Clin. Cancer Res. (2018) PMID: 29284706
164. Ng PK, et al. Cancer Cell (2018) PMID: 29533785
165. Spangle JM, et al. (2020) PMID: 32929011
166. Chen L, et al. Nat Commun (2018) PMID: 29636477
167. Jin N, et al. J Clin Invest (2021) PMID: 34779417
168. Zehir A, et al. Nat. Med. (2017) PMID: 28481359
169. Ito S, et al. Nature (2010) PMID: 20639862
170. Guo JU, et al. Cell (2011) PMID: 21496894
171. Iyer LM, et al. Cell Cycle (2009) PMID: 19411852
172. Ko M, et al. Nature (2010) PMID: 21057493
173. Yang H, et al. Oncogene (2013) PMID: 22391558
174. Hu L, et al. Cell (2013) PMID: 24315485
175. Wang Y, et al. Mol. Cell (2015) PMID: 25601757
176. Jaiswal S, et al. N. Engl. J. Med. (2014) PMID: 25426837
177. Genovese G, et al. N. Engl. J. Med. (2014) PMID: 25426838
178. Xie M, et al. Nat. Med. (2014) PMID: 25326804
179. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) PMID: 28669404
180. Severson EA, et al. Blood (2018) PMID: 29678827
181. Fuster JJ, et al. Circ. Res. (2018) PMID: 29420212
182. Hematology Am Soc Hematol Educ Program (2018) PMID: 30504320
183. Chabon JJ, et al. Nature (2020) PMID: 32269342
184. Razavi P, et al. Nat. Med. (2019) PMID: 31768066

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Erik Williams, M.D. | 12 January 2023  
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
 Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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