Endometrial Cancer gene panel (SNVs, InDels & Fusions) **

Clinical Summary:

High grade endometroid carcinoma of endometrium, FIGO Grade 3, pT1bN0Mx FIGO Stage II C .

TEST RESULT SUMMARY

Next Generation Sequencing (NGS) Test Result

Result - POSITIVE
CLINICALLY RELEVANT VARIANT/S DETECTED

AMP Classification ^	CDS variant details	Interpretation	Treatment Recommendations	$Treatment Response
***TP53* p.Arg273Cys (MISSENSE)** Variant Allele Frequency - 32.65%				
Tier II	c.817C>T (ENST00000269305.9)	Likely Oncogenic	NA	Prognostic
***TP53* p.Arg196Ter (NONSENSE)** Variant Allele Frequency - 5.31%				
Tier II	c.586C>T (ENST00000269305.9)	Oncogenic	NA	Prognostic
***MSH6* p.Cys579ValfsTer7 (FRAMESHIFT-DEL)** Variant Allele Frequency - 9.62%				
Tier II	c.1735del (ENST00000234420.11)	Oncogenic	NA	Diagnostic
***MSH6* p.Asp1031AlafsTer21 (FRAMESHIFT-DEL)** Variant Allele Frequency - 5.85%				
Tier II	c.3092del (ENST00000234420.11)	Oncogenic	NA	Diagnostic
***PIK3CA* p.Arg38Cys (MISSENSE)** Variant Allele Frequency - 18%				
Tier II	c.112C>T (ENST00000263967.4)	Likely Oncogenic	NA	Prognostic
***PIK3CA* p.Arg108His (MISSENSE)** Variant Allele Frequency - 5.85%				

AMP Classification ^	CDS variant details	Interpretation	Treatment Recommendations	$Treatment Response
Tier II	c.323G>A (ENST00000263967.4)	Oncogenic	NA	Prognostic
***PTEN* p.Arg130Gln (MISSENSE)** Variant Allele Frequency - 18.3%				
Tier II	c.389G>A (ENST00000371953.8)	Oncogenic	NA	Prognostic
***PTEN* p.Arg173Cys (MISSENSE)** Variant Allele Frequency - 12.24%				
Tier II	c.517C>T (ENST00000371953.8)	Oncogenic	NA	Prognostic
***ARID1A* p.Arg1276Ter (NONSENSE)** Variant Allele Frequency - 10.46%				
Tier II	c.3826C>T (ENST00000324856.13)	Oncogenic	NA	Prognostic
***FBXW7* p.Arg465His (MISSENSE)** Variant Allele Frequency - 11.48%				
Tier II	c.1394G>A (ENST00000281708.10)	Likely oncogenic	NA	NA

NOTE: No clinically significant mutation has been detected in *POLE* gene in this sample.

No clinically significant fusion has been detected in this sample

^Refer to Glossary section for the classification criteria details.

$Drug Approvals are based on US-FDA Guidelines. Kindly refer to local guidelines if required.

ADDITIONAL BIOMARKERS DETECTED

This section provides information about variants that do not have any therapeutic value. However, these variants may or may not have a likely oncogenic effect.

Gene	Exon	Nucleotide change	Protein change	Alternate allele Depth (x)	Allele Burden (%)	Functional predictions	Population MAF (%)
BRAF	12	ENST00000646891 .1 c.1330C>T chr7:g.140781678G>A	p.Arg444Trp	169x	11.86%	D(SIFT); D(LRT); BN(Polyphen2)	0 (1000G); 0 (gnomAD)
AKT1	10	ENST00000649815 .2 c.808G>A chr14:g.104773475C>T	p.Val270Met	68x	7.68%	D(SIFT); D(LRT); PoD(Polyphen2)	0 (1000G); 0 (gnomAD)
ARID1A	20	ENST00000324856 .13 c.6259G>A chr1:g.26780157G>A	p.Gly2087Arg	85x	16.04%	D(SIFT); N(LRT); PrD(Polyphen2)	0 (1000G); 0 (gnomAD)
PIK3CA	6	ENST00000263967 .4 c.1070G>A chr3:g.179204513G>A	p.Arg357Gln	24x	8.51%	T(SIFT); D(LRT); PoD(Polyphen2)	0 (1000G); 0 (gnomAD)

ACTIONABLE BIOMARKER DETAILS

_TP53_ (p.Arg273Cys) - MISSENSE

Gene: *TP53*	**Exon:** 8	**Variant Allele Frequency:** 32.65%
Nucleotide change: chr17:g.7673803G>A	**Protein change:** p.Arg273Cys	**Population MAF:** NA (1000G);0(gnomAD);
cDNA change: c.817C>T	**Variant Type:** MISSENSE	**In-silico Predictions:** D(SIFT); D(LRT); PrD(Polyphen2)
Transcript ID: ENST00000269305.9	**Variant Allele Depth/Total depth:** 921/2821x	**Gene Function:** Tumor Suppressor Gene

Gene Summary: *TP53* encodes the p53 tumor suppressor protein, a transcription factor that responds to cellular stresses, including DNA damage and oncogenic activation, by inducing downstream anti-tumor responses such as DNA repair and apoptosis [PMID: 11099028]. *TP53* is the most commonly mutated gene in human cancers, and germline mutations occur in the cancer predisposition syndrome Li-Fraumeni [PMID: 21765642].

Clinical and Therapeutic Relevance: In the TCGA (The Cancer Genome Atlas) dataset of 373 endometrial carcinomas, the frequency of *TP53* mutations was found to be 25 % [PMID: 23636398]. In a study of 125 cases of grades 1 and 2, stage 1 and II endometrioid carcinomas, 9% of cases harboring *TP53* mutations have been shown to be associated with worse recurrence-free survival on multivariate analysis. **This suggests that having a *TP53* mutation in a low stage and low-grade endometrioid carcinoma is of adverse prognostic significance [PMID: 28281553].**

PubMed References: 23636398, 28281553

TP53 (p.Arg196Ter) - NONSENSE

Gene: *TP53*	**Exon:** 6	**Variant Allele Frequency:** 5.31%
Nucleotide change: chr17:g.7674945G>A	**Protein change:** p.Arg196Ter	**Population MAF:** NA (1000G);NA(gnomAD);
cDNA change: c.586C>T	**Variant Type:** NONSENSE	**In-silico Predictions:** NA(SIFT); NA(LRT); NA(Polyphen2)
Transcript ID: ENST00000269305.9	**Variant Allele Depth/Total depth:** 19/358x	**Gene Function:** Tumor Suppressor Gene

Gene Summary: *TP53* encodes the p53 tumor suppressor protein, a transcription factor that responds to cellular stresses, including DNA damage and oncogenic activation, by inducing downstream anti-tumor responses such as DNA repair and apoptosis [PMID: 11099028]. *TP53* is the most commonly mutated gene in human cancers, and germline mutations occur in the cancer predisposition syndrome Li-Fraumeni [PMID: 21765642].

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PubMed References: 23636398, 28281553

MSH6 (p.Cys579ValfsTer7) - FRAMESHIFT-DEL

Gene: *MSH6*	**Exon:** 4	**Variant Allele Frequency:** 9.62%
Nucleotide change: chr2:g.47799718del	**Protein change:** p.Cys579ValfsTer7	**Population MAF:** NA (1000G);NA(gnomAD);
cDNA change: c.1735del	**Variant Type:** FRAMESHIFT-DEL	**In-silico Predictions:** NA(SIFT); NA(LRT); NA(Polyphen2)
Transcript ID: ENST00000234420.11	**Variant Allele Depth/Total depth:** 130/1352x	**Gene Function:** Tumor Suppressor Gene

Gene Summary: *MSH6* is a tumor suppressor involved in post-replication DNA mismatch repair. Select mutations of *MSH6* are associated with Lynch syndrome and can lead to genomic instability via microsatellite instability in tumors. *MSH6* and other MMR genes are most notably implicated in hereditary non-polyposis colon cancer (HNPCC), also known as Lynch syndrome (PMID: 1648437). Loss of function mutations or epigenetic silencing both in the germline and somatic context lead to an increased mutation rate that drives carcinogenesis as well as microsatellite instability (MSI). Although most commonly seen in colon cancer, *MSH6* mutations have also been reported in a wide range of other cancer types and syndromes, including endometrial and uterine cancers (PMID: 16106253).

Clinical and Therapeutic Relevance: Women with *MSH6* mutations, Bonadona et al.2 report a lifetime endometrial cancer risk by age 80 of 17% (95% CI 8% to 47%), while Baglietto et al.4 found a lifetime endometrial cancer risk by age 80 of 44% (95% CI 30% to 58%) in a multinational study population [PMID: 23765559]. In a case study it has shown a partial response and a long-term remission from the frontline single-agent pembrolizumab in a woman with metastatic uterine serous carcinoma and Lynch syndrome due to a germline MSH6 gene mutation [https://doi.org/10.1002/onco.13832]. **Pathogenic mutations in this gene maybe associated with dMMR phenotype. dMMR tumors have a particular sensitivity to immune checkpoint inhibitors, including antiprogram death 1 (anti-PD-1), anti-program death ligand 1 (anti-PDL1), and anti-cytotoxic T-lymphocyteassociated protein 4 (anti-CTLA4). Specifically, in endometrial cancer, several phase II trials carried out in patients pretreated with chemotherapy have found response rates with immunotherapy ranging from 27 to 57% while they are less than 10% for pMMR tumors [PMID: 34069845]. The FDA has approved pembrolizumab [https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-endometrial-carcinoma] and dostarlimab-gxly [https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-dostarlimab-gxly-chemotherapy-endometrial-cancer, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-dostarlimab-gxly-dmmr-endometrial-cancer] for endometrial cancer (EC) that is mismatch repair deficient (dMMR), or microsatellite instability-high (MSI-H).**

PubMed References: 23765559, 34069845

MSH6 (p.Asp1031AlafsTer21) - FRAMESHIFT-DEL

Gene: *MSH6*	**Exon:** 4	**Variant Allele Frequency:** 5.85%
Nucleotide change: chr2:g.47801075del	**Protein change:** p.Asp1031AlafsTer21	**Population MAF:** NA (1000G);NA(gnomAD);
cDNA change: c.3092del	**Variant Type:** FRAMESHIFT-DEL	**In-silico Predictions:** NA(SIFT); NA(LRT); NA(Polyphen2)
Transcript ID: ENST00000234420.11	**Variant Allele Depth/Total depth:** 58/991x	**Gene Function:** Tumor Suppressor Gene

MSH6 (p.Asp1031AlafsTer21) - FRAMESHIFT-DEL

Gene Summary: *MSH6* is a tumor suppressor involved in post-replication DNA mismatch repair. Select mutations of *MSH6* are associated with Lynch syndrome and can lead to genomic instability via microsatellite instability in tumors. *MSH6* and other MMR genes are most notably implicated in hereditary non-polyposis colon cancer (HNPCC), also known as Lynch syndrome (PMID: 1648437). Loss of function mutations or epigenetic silencing both in the germline and somatic context lead to an increased mutation rate that drives carcinogenesis as well as microsatellite instability (MSI). Although most commonly seen in colon cancer, *MSH6* mutations have also been reported in a wide range of other cancer types and syndromes, including endometrial and uterine cancers (PMID: 16106253).

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PubMed References: 23765559, 34069845

PIK3CA (p.Arg38Cys) - MISSENSE

Gene: *PIK3CA*	**Exon:** 2	**Variant Allele Frequency:** 18%
Nucleotide change: chr3:g.179198937C>T	**Protein change:** p.Arg38Cys	**Population MAF:** NA (1000G);NA(gnomAD);
cDNA change: c.112C>T	**Variant Type:** MISSENSE	**In-silico Predictions:** D(SIFT); D(LRT); PrD(Polyphen2)
Transcript ID: ENST00000263967.4	**Variant Allele Depth/Total depth:** 180/1000x	**Gene Function:** Oncogene

Gene Summary: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) encodes p110 alpha catalytic subunit of phosphatidylinositol 3-kinase (PI3K) protein. It is involved in diverse cell functions such as cell survival, proliferation, degranulation, cell migration and trafficking. It is frequently mutated in a diverse range of cancers including breast, endometrial and cervical cancers. Gain-of-function missense mutations are mainly found in this gene and few hotspot codons (420, 542, 545, 546, 1047) are actionable in breast cancer.

PIK3CA (p.Arg38Cys) - MISSENSE

Clinical and Therapeutic Relevance: The clinical and genomic data of 307 patients with endometrioid endometrial adenocarcinoma (EEC) were obtained from TCGA project that includes 90 patients in the copy-number low-EEC (CNL-EEC) subgroup. In CNL-EEC subgroup patients, somatic *PIK3CA* mutations (48/90 cases) were associated with significantly improved overall survival compared with that of wild-type *PIK3CA* (P=0.018). Furthermore, this improved survival was specific to the CNL-EEC subgroup and was not observed in other TCGA molecular subgroups. The majority of CNL-EEC cases were low-stage (stage I) and low-to-intermediate grade (grades 1– 2) endometrioid tumors. Overall, in the TCGA cohort, PIK3CA mutations had a favourable effect on the survival of patients with EEC, and this effect was dependent on tumoral molecular sub-stratification [PMID: 26722235].

PubMed References: 26722235

PIK3CA (p.Arg108His) - MISSENSE

Gene: *PIK3CA*	**Exon:** 2	**Variant Allele Frequency:** 5.85%
Nucleotide change: chr3:g.179199148G>A	**Protein change:** p.Arg108His	**Population MAF:** NA (1000G);0.000657(gnomAD);
cDNA change: c.323G>A	**Variant Type:** MISSENSE	**In-silico Predictions:** D(SIFT); D(LRT); PrD(Polyphen2)
Transcript ID: ENST00000263967.4	**Variant Allele Depth/Total depth:** 20/342x	**Gene Function:** Oncogene

Gene Summary: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) encodes p110 alpha catalytic subunit of phosphatidylinositol 3-kinase (PI3K) protein. It is involved in diverse cell functions such as cell survival, proliferation, degranulation, cell migration and trafficking. It is frequently mutated in a diverse range of cancers including breast, endometrial and cervical cancers. Gain-of-function missense mutations are mainly found in this gene and few hotspot codons (420, 542, 545, 546, 1047) are actionable in breast cancer.

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PubMed References: 26722235

PTEN (p.Arg130Gln) - MISSENSE		
Gene: *PTEN*	**Exon:** 5	**Variant Allele Frequency:** 18.3%
Nucleotide change: chr10:g.87933148G>A	**Protein change:** p.Arg130Gln	**Population MAF:** NA (1000G);NA(gnomAD);
cDNA change: c.389G>A	**Variant Type:** MISSENSE	**In-silico Predictions:** D(SIFT); D(LRT); PrD(Polyphen2)

PTEN (p.Arg130Gln) - MISSENSE		
Transcript ID: ENST00000371953.8	**Variant Allele Depth/Total depth:** 672/3672x	**Gene Function:** Tumor Suppressor Gene

Gene Summary: This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded by this gene is a phosphatidylinositol-3,4,5-trisphosphate 3 phosphatase. *PTEN* is a multi-functional tumor suppressor that is very commonly lost in human cancer. Observed in prostate cancer, glioblastoma, endometrial, lung, and breast cancer to varying degrees. Up to 70% of prostate cancer patients have been observed to have loss of expression of the gene. It is a part of the PI3K/AKT/mTOR pathway and mTOR inhibitors have been relatively ineffective in treating patients with *PTEN* loss.

Clinical and Therapeutic Relevance: In a clinical study involving 221 primary endometrial carcinoma patients, mutational analysis of *PTEN* gene was done along with immuno-histochemical analysis. Expression of *PTEN* was lost in 56 patients (25%), and *PIK3CA* was overexpressed in 159 patients (72%). Overexpression of *PIK3CA* was associated with p-Akt overexpression (P<0.001), which was in turn associated with loss of nuclear p27 expression (P=0.028). Loss of *PTEN* expression was found to be associated with endometrioid histology (P=0.03) and was inversely associated with the presence of lymphovascular space invasion (P=0.03). Univariate and multivariate survival analyses revealed that factors of *PTEN* loss, age <70, histological grade 1,early International Federation of Gynecology and Obstetrics (FIGO) stage, and absence of lymphovascular invasion were independent prognostic indicators for better overall survival (P=0.03, 0.04, 0.01, <0.001, and 0.03,respectively). The subset analysis showed a stronger tendency of *PTEN* loss towards favourable survival in advanced-stage (III and IV) disease than in early-stage (I and II) disease (P=0.05 vs 0.14). Moreover, this mutational analysis demonstrated that *PTEN* expression loss was associated with *PTEN* - truncating mutations (P=0.03). Thus, loss of *PTEN* expression is a significant and independent prognostic factor for favourable survival in the disease [PMID: 23949151].

PubMed References: 23949151

PTEN (p.Arg173Cys) - MISSENSE

Gene: *PTEN*	**Exon:** 6	**Variant Allele Frequency:** 12.24%
Nucleotide change: chr10:g.87952142C>T	**Protein change:** p.Arg173Cys	**Population MAF:** NA (1000G);0.000658(gnomAD);
cDNA change: c.517C>T	**Variant Type:** MISSENSE	**In-silico Predictions:** D(SIFT); D(LRT); PrD(Polyphen2)
Transcript ID: ENST00000371953.8	**Variant Allele Depth/Total depth:** 142/1160x	**Gene Function:** Tumor Suppressor Gene

Gene Summary: This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded by this gene is a phosphatidylinositol-3,4,5-trisphosphate 3 phosphatase. *PTEN* is a multi-functional tumor suppressor that is very commonly lost in human cancer. Observed in prostate cancer, glioblastoma, endometrial, lung, and breast cancer to varying degrees. Up to 70% of prostate cancer patients have been observed to have loss of expression of the gene. It is a part of the PI3K/AKT/mTOR pathway and mTOR inhibitors have been relatively ineffective in treating patients with *PTEN* loss.

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PubMed References: 23949151

ARID1A (p.Arg1276Ter) - NONSENSE

Gene: *ARID1A*	**Exon:** 15	**Variant Allele Frequency:** 10.46%
Nucleotide change: chr1:g.26773456C>T	**Protein change:** p.Arg1276Ter	**Population MAF:** NA (1000G);NA(gnomAD);
cDNA change: c.3826C>T	**Variant Type:** NONSENSE	**In-silico Predictions:** NA(SIFT); NA(LRT); NA(Polyphen2)
Transcript ID: ENST00000324856.13	**Variant Allele Depth/Total depth:** 149/1424x	**Gene Function:** Tumor Suppressor Gene

Gene Summary: The *ARID1A* gene provides instructions for making a protein that forms one piece (subunit) of several different SWI/SNF protein complexes. SWI/SNF complexes regulate gene activity (expression) by a process known as chromatin remodeling. Variants in the *ARID1A* gene have been found in many types of cancer, including cancers of the ovaries and lining of the uterus (endometrium) in women and cancers of the kidney, stomach, bladder, lung, breast, and brain.

ARID1A (p.Arg1276Ter) - NONSENSE

Clinical and Therapeutic Relevance: *ARID1A* mutations were found in 57% of ovarian clear-cell carcinomas [PMID: 28055103], 40% of uterine endometrioid carcinomas [PMID: 16495918], and between 20% and 36% of uterine carcinosarcomas [PMID: 19592079]. A study investigating the ARID1A loss in patients with endometrioid carcinoma reported that no *ARID1A* loss was seen in complex atypical hyperplasia, with loss increasing to 25% and 44% of patients with low-grade and high-grade endometrioid carcinomas, respectively [PMID: 24076775]. *ARID1A* has also been used as a prognostic marker in endometrial cancer. A significant association of reduced *ARID1A* expression has been found with shorter progression-free survival in patients with endometrium-related cancer and ovarian clear-cell carcinoma, as well as with higher FIGO stage of both endometrial and ovarian cancer [PMID: 28466574]. A total of 67 patients with pathologically confirmed grade 3 endometrioid endometrial carcinoma (G3EEC) were included in the study. The recurrence-free survival (RFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared with a log-rank test. A recurrence was observed in 9 (13%) of the 67 patients with early stage G3EEC. The respective 5-years RFS and OS rates were 87.7% and 93.7%, and 68.6% and 85.7%, respectively for stages I and II. Multivariate analysis showed significantly longer RFS among patients with *ARID1A* loss (hazard ratio = 8.7; 95% CI, 1.09–69.6, p = 0.04). No significant differences were observed in RFS and OS of patients according to p53 and MMR expression status.ARID1A expression status was a prognosticator for patients with early stage G3EEC without adjuvant therapy, whereas p53 and MMR expression status showed no impact on survival outcomes. *ARID1A* may become a useful biomarker for stratification of adjuvant treatment for early stage G3EEC patients [PMID: 34257552].

PubMed References: 28055103, 16495918, 19592079, 24076775, 28466574, 34257552

FBXW7 (p.Arg465His) - MISSENSE

Gene: *FBXW7*	**Exon:** 11	**Variant Allele Frequency:** 11.48%
Nucleotide change: chr4:g.152328232C>T	**Protein change:** p.Arg465His	**Population MAF:** NA (1000G);NA(gnomAD);
cDNA change: c.1394G>A	**Variant Type:** MISSENSE	**In-silico Predictions:** D(SIFT); D(LRT); PrD(Polyphen2)
Transcript ID: ENST00000281708.10	**Variant Allele Depth/Total depth:** 100/871x	**Gene Function:** Tumor Suppressor Gene

Gene Summary: The *FBXW7* gene encodes an F-box protein subunit involved in substrate recognition by an SCF (Skp1-Cul1-F-box protein)-type ubiquitin ligase complex. Upon substrate identification, this complex modifies the substrate such that it is targeted for protein degradation. Substrates of *FBXW7* include the proteins c-MYC, mTOR (PMID: 18787170), NOTCH1, cyclin-E, and JUN, which are instrumental in the regulation of cell division, differentiation and growth, and which are often inappropriately activated in cancer. Since *FBXW7* substrates are proto-oncogenes that are processed for degradation by the SCF complex, *FBXW7* functions as a tumor suppressor. Inactivation of *FBXW7* by mutation or copy number loss results in aberrant accumulation of oncoproteins, which subsequently contributes to malignant transformation (PMID: 27399335). Most mutations in *FBXW7* are point mutations that disrupt substrate binding, while <10% are small deletions or insertions (PMID: 17909001).

Clinical and Therapeutic Relevance: *FBXW7* is frequently somatically mutated in 6%–18% grade 3 endometrioid endometrial cancers (G3EECs) and 15%–29% serous endometrial cancers (SECs), high-risk cancers associated with poor prognosis.[https://doi.org/10.1016/j.ctarc.2021.100502]. *FBXW7* mutations lead to increased Cyclin E1, steroid receptor coactivator 3 (SRC-3), c-MYC, Rictor, glycogen synthase kinase 3 (GSK3), P70S6 kinase, and protein kinase B (AKT) phosphorylated protein levels in serous EC cells which demonstrate that CRISPR-edited *FBXW7*-mutant ARK1 serous EC cells exhibit increased sensitivity to SI-2 (a SRC inhibitor) and dinaciclib (a cyclin dependent kinase (CDK) inhibitor) compared to parental ARK1 cells that reveal biochemical effects of *FBXW7* mutations in the context of EC and provide in vitro evidence of sensitivity to targeted inhibitors [PMID: 29963728].

FBXW7 (p.Arg465His) - MISSENSE

PubMed References: 29963728

AMP-ASCO-CAP CLASSIFICATION CRITERIA

Genetic test results are reported based on the somatic variant classification recommendations of College of American Pathologists (CAP) /American society for Clinical Oncology (ASCO)/Association of Molecular Pathologists (AMP) [PMID: 27993330] as described in the table below:

Tier	Criteria
Tier I	Variants of strong clinical significance.
Tier II	Variants of potential clinical significance.
Tier III	Variants of unknown clinical significance
Tier IV	Benign or likely benign variants

DISCLAIMER

- **Decisions regarding treatment action plan should not be solely based on these test results. These findings are highly recommended to be correlated with the patient's clinical, pathological, radiological and family history for decisions on diagnosis, prognosis, or therapeutics.**
- The therapy information provided in this report is based on FDA approved drugs data, NCCN guidelines, peer-reviewed published literature, standard clinical databases, and strength of biomarker results. These therapies may or may not be suitable/beneficial to a particular patient. This clinical report summarizes potentially effective medications, potentially ineffective medications, and medications that may pose a higher risk of adverse reactions by mapping the patient's genetic alterations to the biomedical reference information. The report may also provide prognostic and diagnostic biomarkers detected or shown for the given disease context.The treatment recommendations for the variants classified in Tier II are not provided.
- The clinical trials information provided in this report is compiled from www.clinicaltrials.gov as per currently available data, however completeness of information provided herein cannot be guaranteed. This information should only be used as a guide and specific eligibility criteria should be reviewed thoroughly for the concerned patient. Labs does not guarantee or promise an enrolment in any clinical trials.
- The identification of a genomic biomarker does not necessarily imply pharmacological effectiveness or ineffectiveness. The medications identified by the treating physician may or may not be suitable for use on a particular patient. Thus, the clinical report does not guarantee that any particular agent will be effective in the treatment of any particular condition. Also, the absence of a treatment option does not determine the effectiveness or predict an ineffective or safety-relevant effect of a medication selected by the treating physician.
- The classification and clinically relevant information for the reported variants is based on peer-reviewed publications, public clinical databases, medical guidelines (WHO, NCCN, ASCO, AMP) or other publicly available information and it has been ensured that the information provided is up to date at the time of report generated, however continuous updates may happen in public domains. Also, the classification of variants can change based on the updated literature evidence. Re-analysis of the results can be requested at additional cost.
- This test is performed on the patient's tumor sample without a paired blood sample; therefore, it may include variations which may be of germline origin. However, this test is designed and validated for the detection and reporting of somatic genomic variants only and does not discriminate between germline and somatic variants. If clinically warranted, appropriate germline testing and genetic counselling for the patient should be considered for further evaluation.

- **Due to poor quality of FFPE tissue blocks, the QC parameters for extracted RNA may not pass to proceed further with the testing, therefore there is a possibility of assay failure at various steps (RNA QC, Library QC, Bioinformatics QC) or compromised results that include low gene coverage and low variant depth.**However, sample status in such scenarios shall be sent through mail to the ordering clinician.
- The limit of detection (LOD) of allele fraction for SNVs and Indels is ≥5% and for fusions is ≥10 spanning reads. However, the report may include, at the discretion of laboratory director, the variants with lower alleleburden (3-5%) having strong or potential clinical significance or those have been reported earlier in the patient. Variants with <1% allele fraction and variants of uncertain significance with <5% allele fraction are not routinely reported. However, possibility of false negative or false positive below the limit of detection of this assay cannot be ruled out.
- Large deletions and deep intronic variations are not detected in this assay.
- **Additional case specific disclaimer : Although the panel coverage is >95%, the average depth of *NTRK1*, *RET*, and *FGFR3* genes are below the reporting criteria. Hence, possibility of false negative result cannot be ruled out. Please correlate clinically.**

TEST DESCRIPTION

The Laboratory's Endometrial cancer panel is a high throughput next-generation sequencing based single assay that may provide treatment benefit to the patients. This panel covers a total of 32 key endometrial cancer genes for the assessment of various SNVs, InDels, and Fusions (in RNA).

TEST METHODOLOGY

Sample type: FFPE Specimen; A histopathologic review is performed to determine the tumor content in the FFPE block/curls.

Extraction and Library Preparation: Tumor nucleic acid is extracted from FFPE (Formalin fixed) tissue block and used to perform targeted gene capture using a custom hybrid capture kit.

Sequencing: The QC passed libraries are sequenced to a minimum depth of 250X on validated Illumina sequencing platform.

Data Analysis: The sequences are processed using a customized and validated analysis pipeline designed to accurately detect all classes of genomic alterations (SNVs, InDels and Fusions).

Variant Annotation and Reporting: The variants are annotated using our in-house annotation pipeline. Reportable genomic alterations are prioritized, classified, and reported based on AMP-ASCO-CAP guidelines [PMID:27993330] and NCCN guidelines.

Limit of Detection (LOD): The LOD for SNVs and InDels is 5% Variant allele Frequency (VAF) and for Fusions is >10 spanning reads.

The transcript used for clinical reporting generally represents the canonical transcript (according to Ensembl release 99 human gene model), which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported. Variants annotated on incomplete, and nonsense mediated decay transcripts are not reported.

GENES ANALYSED

SNVs/InDels							
AKT1	*ARID1A*	*BRCA1*	*BRCA2*	*BRAF*	*CHEK2*	*CTNNB1*	*EPCAM*
ERBB2	*FBXW7*	*FGFR1*	*FGFR2*	*FGFR3*	*KRAS*	*MLH1*	*MSH2*
MSH3	*MSH6*	*MUTYH*	*NTRK1*	*NTRK2*	*NTRK3*	*PIK3CA*	*PIK3R1*
PMS2	*POLD1*	*POLE*	*PTEN*	*RET*	*SMARCA4*	*STK11*	*TP53*

FUSIONS						
FGFR1	*FGFR2*	*FGFR3*	*NTRK1*	*NTRK2*	*NTRK3*	*RET*

CLINICAL TRIALS

The following trials are potentially best suited for your patient's indication, considering all reported treatment recommendations. See https://clinicaltrials.gov (clinical trials from NCT) or https://trialsearch.who.int (clinical trials from other registries) for more information.

Clinical trials in total : 0 **Trial countries :** IN-India, US-United States

S.No	Title	Phase and ID	Intervention	Disease	Age & Sex
No Clinical Trials.					

END OF REPORT