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PATIENT: **XXXXXXXXXXXXX**			TEST REF: **GNL-NL-XXXXX**
TEST NUMBER: G-NL-XXXXX	COLLECTED: 00-XXX-2023		PRACTITIONER: **XXXXXXXXXXXX**
GENDER: XXXXXX	RECEIVED: 00-XXX-2023		
AGE: XX	TESTED: 00-XXX-2023		XXXXXXXXXXXXXXXXXXXX

TEST NAME: exacta® - Including drug and natural agents

Report Highlights

Indications	USFDA Approved* / NCCN recommended*	Off Label Therapy*
VEGFA ICC Positive	☑ Bevacizumab	☑ Ziv-Aflibercept
mTOR ICC Positive	☐ None	☑ Everolimus ☑ Temsirolimus
EGFR ICC Positive	☐ None	☑ Panitumumab ☑ Cetuximab ☑ Necitumumab

☑ SOC Drugs with Benefit ☑ Off Label Drugs with Benefit ☒ Drugs without Clinical Benefit / with Potential Resistance

ICC: Immunocytochemistry; CTC: Circulating Tumor Cells; SOC: Standard of Care; NCCN: National Comprehensive Cancer Network - Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer.

* The USFDA approval or NCCN recommendation may not be for the detected biomarker or alteration. The association of the detected biomarker or alteration and the drug may be based only on the literature evidence.

Biomarkers for Immune Checkpoint Inhibitors

Biomarker	Result
Blood based - tumor mutation burden (bTMB)	1 Mutation/Mb
MLH1, MLH3, MSH2, MSH6, PMS2 pathogenic/ likely pathogenic mutations	Negative

Longitudinal Monitoring Biomarkers

Biomarker	Result
Highest mutant allele frequency (HMAF)	1.57%
Number of CTCs detected	2 CTCs/ml

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Report Highlights

Cytotoxic Drugs

Chemosensitivity Analysis : % Cell Death (CD) ± Molecular biomarker

USFDA Approved / NCCN recommended		Off Label Therapy	
Drugs	Result	Drugs	Result
☑ Cisplatin	75% CD	☑ Vinblastine	51% CD
☑ Oxaliplatin	74% CD	☑ Trabectedin	44% CD
☑ Cyclophosphamide	73% CD	☑ Eribulin	33% CD
☑ Docetaxel	72% CD	☑ Bleomycin	28% CD
☑ Pemetrexed	70% CD; TYMS (-2.45 FC)	☒ Cabazitaxel	<25% CD
☑ Gemcitabine	67% CD	☒ Dacarbazine	<25% CD
☑ Irinotecan	66% CD	☒ Dactinomycin	<25% CD
☑ Vinorelbine	66% CD	☒ Epirubicin	<25% CD
☑ Ifosfamide	64% CD	☒ Methotrexate	<25% CD
☑ Doxorubicin	53% CD	☒ Mitomycin	<25% CD
☒ 5-Fluorouracil/Capecitabine	<25% CD	☒ Mitoxantrone	<25% CD
☒ Carboplatin	<25% CD	☒ Temozolomide	<25% CD
☒ Etoposide	<25% CD	☒ Vincristine	<25% CD
☒ Melphalan	<25% CD		
☒ Paclitaxel	<25% CD		
☒ Topotecan	<25% CD		

FC: Fold Change

☑ SOC Drugs with Benefit ☑ Off Label Drugs with Benefit ☒ Drugs without Clinical Benefit / with Potential Resistance

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Report Highlights

Additional Report Highlights

Indications for Non-Oncology Drugs

Drug	Indication
☑ Epigallocatechin gallate	53% CD
☑ Hypericin	52% CD
☑ Melatonin	52% CD
☑ Diflunisal	51% CD
☑ Doxycycline	47% CD
☑ Glutathione	41% CD
☑ Iscador Qu	37% CD
☑ Dichloroacetate	30% CD
☑ Artesunate	25% CD
☑ Iscador P	25% CD
☑ Helixor P	23% CD
☑ Quercetin	22% CD
☑ Resveratrol	21% CD
☑ Curcumin	20% CD
☑ Indol-3-carbinol	19% CD
☑ Helixor M	18% CD
☑ DMSO	17% CD
☑ Helixor A	17% CD
☑ Cannabidiol	16% CD
☑ Atorvastatin	16% CD
☑ Chloroquine	15% CD; HMGB1 (+4.97 FC) overexpression
☑ Metformin	14% CD
☑ Celecoxib	12% CD
☑ Pantoprazole	11% CD

☑ Drugs with Benefit

Disease Relevant Findings

Biomarker	Result	Biomarker	Result
BRCA1/2	No pathogenic/ likely pathogenic germline alterations detected	BRAF	No mutations detected
RET	No fusions detected	NTRK1/3	No fusions detected

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Pharmacogenetics : Drugs with Contraindications

Drug	Indication
⊟ None	⊟ None

Pharmacogenetics - Drugs with Increased Risk of Toxicity

Drug	Indication	Drug	Indication
[!] Belinostat	UGT1A1	[!] Carboplatin	ERCC1, MTHFR
[!] Cisplatin	XPC, ERCC1	[!] Erlotinib	UGT1A1
[!] Gemcitabine	NT5C2	[!] Irinotecan	UGT1A1
[!] Methotrexate	ABCB1, MTHFR	[!] Nilotinib	UGT1A1
[!] Oxaliplatin	ERCC1	[!] Pazopanib	UGT1A1
[!] Regorafenib	UGT1A1	[!] Sacituzumab govitecan	UGT1A1

Pharmacogenetics - Drugs with Labeled Risk of Toxicity

Drug	Indication	Drug	Indication
☑ 5-Fluorouracil	DPYD	☑ Capecitabine	DPYD
☑ Dabrafenib	G6PD	☑ Erdafitinib	CYP2C9
☑ Gefitinib	CYP2D6	☑ Mercaptopurine	TPMT, NUDT15
☑ Rasburicase	G6PD	☑ Tegafur	DPYD
☑ Thioguanine	TPMT, NUDT15	☑ Trametinib	G6PD
☑ Vincristine	CEP72		

⊟ Not Applicable [!] Drugs with Increased Risk of Toxicity ☑ Drugs with Labeled Risk of Toxicity

Summary of Other Genomic Alterations

Gene	Alteration Type (SNAs / Indels / CNAs/ Fusion)	Variant Classification	Therapeutic / Clinical Significance
TP53	p.V197M (MAF 1.57% at 64985X) p.R181H (MAF 0.28% at 88536X)	Pathogenic	Refer to page no. 6

SNA: Single Nucleotide Alteration; CNA: Copy Number Alteration; INDELS: Insertion / Deletion; MAF: Mutant Allele Frequency

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Blood Based - Tumor Mutation Burden (bTMB)

Genomic Findings

Markers	Result	Interpretation	Category
Blood based - Tumor Mutation Burden (bTMB)	1 Mutation/Mb	Low bTMB	Tier III

Blood based - Tumor Mutation Burden (bTMB) is: 1 Mutation/Mb. bTMB was calculated based on the allelic fraction of the somatic mutations detected by Next Generation Sequencing analysis of 411 genes.

Tumor mutation burden (TMB), the total number of somatic coding mutations in a tumor, is a promising predictive biomarker for immunotherapy response in cancer patients (Chan et al., 2018; Fancello et al., 2019). The somatic mutations in tumor DNA can give rise to neoantigens, mutation-derived antigens that are recognized and targeted by the immune system, especially after treatment with agents that activate T cells. Therefore, more somatic mutations a tumor has, the more neoantigens it is likely to form, and TMB can represent a useful estimation of tumor neoantigenic load (Chan et al., 2018; Fancello et al., 2019). Tumor mutation burden (TMB) is, thus, an informative biomarker for predicting response to immune checkpoint inhibitors like Pembrolizumab, Nivolumab, Atezolizumab, Avelumab, Durvalumab and Ipilimumab.

Clinical studies have shown associations between elevated TMB and efficacy of immune checkpoint inhibitors, alone or in combination with other agents, in multiple solid tumors including, lung cancer, urothelial carcinoma, melanoma, colorectal cancer, head and neck squamous cell carcinoma and other cancer types (Johnson et al., 2016; Goodman et al., 2017; Carbone et al., 2017; Hellmann et al., 2018; Eroglu et al., 2018; Miao et al., 2018; Rizvi et al., 2018; Powles et al., 2018; Socinski et al., 2018; Legrand et al., 2018; Chae et al., 2019; Ott et al., 2019).

Analysis of tumor mutation burden (TMB) across more than 100,000 multiple solid cancer specimens suggests that patients with TMB >20 mutations/Mb may derive benefit from immune checkpoint inhibitors (Chalmers et al., 2017).

In various malignancies TMB >10 mutations/Mb have shown benefit from immune checkpoint inhibitors (Johnson et al., 2016; Legrand et al., 2018; Georges et al., 2019; Zhu et al., 2019; Rizvi et al., 2020; Gullapalli et al., 2020).

Pembrolizumab has been USFDA approved for the treatment of patients with tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors.

In a clinical trial of NSCLC patients with blood TMB (bTMB) of 6 or higher, anti-programmed cell death 1 (anti-PD-1) and anti-programmed cell death ligand 1 (anti-PD-L1) therapy showed objective response rate of 39.3% (Wang et al., 2019). Also, it is reported that, TMB measured from the blood is a predictive biomarker for PFS in patients receiving Atezolizumab monotherapy in NSCLC. Analyses of POPLAR and OAK trials demonstrate that, bTMB≥16 is a clinically meaningful and technically robust cut-point to determine clinical benefit from immune checkpoint inhibitors (Gandara et al., 2018).

The median tumor mutation burden (TMB) (n=2100) for ovarian serous carcinoma is reported to be 2.7 mutations/Mb, while the maximum TMB is 511.9 mutations/Mb (95% Confidence Interval, 0.2 - 0.7) (Chalmers et al., 2017).

High TMB (TMB-H) is indicative of potential benefit from immune checkpoint inhibitors. Blood based - Tumor mutation burden (bTMB) detected in the submitted sample is 1 mutation/Mb. Therefore in this case, there is no indication of immune checkpoint inhibitor therapy based on TMB.

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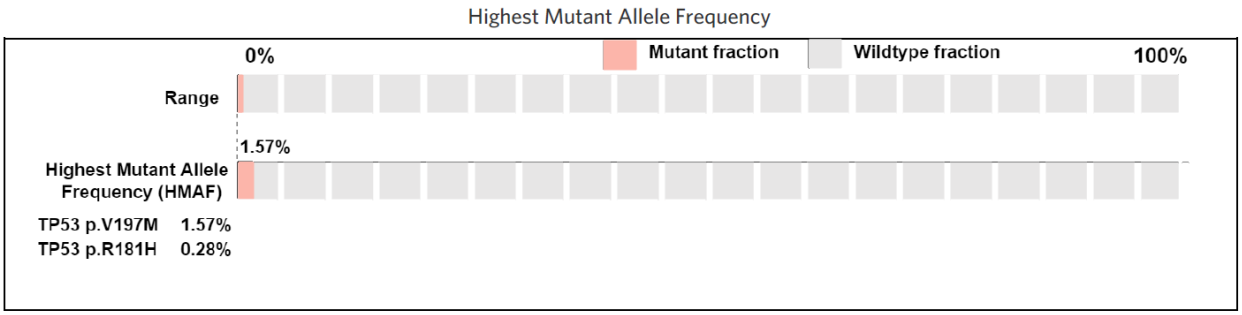
Cell Free Nucleic Acids: Somatic Genome Alterations

Genomic Findings



1. Highest mutant allele frequency of 1.57% was detected in the cell free nucleic acids isolated from patient's plasma.
2. Mutations in TP53 gene are indicative of an adverse prognosis in ovarian cancer.

Genomic Findings
Single Nucleotide Alterations / Indels / Copy Number Alterations / Fusion

Genomic Findings

Markers (Transcript ID)	Variant	Category:
TP53 (NM_000546.5)	c.589G>A, p.V197M; [p.(Val197Met)]	Tier I (Level B)
	c.542G>A, p.R181H; [p.(Arg181His)]	

Interpretation: Mutations in TP53 gene are reported in ovarian cancer and shown to be associated with an adverse prognosis (Cole et al., 2016; Zhang et al., 2017; Mandilaras et al., 2019).

TP53 p.V197M and p.R181H lie within the DNA-binding domain of the TP53 protein (Freed-Pastor and Prives, 2012). In vitro studies with various human cancer cell lines expressing TP53 p.V197M demonstrated this mutation is inactivating as measured by reduced growth suppression activity as compared to wildtype (Andrade et al., 2014, Barbosa et al., 2014; Mendelaar et al., 2022). In silico analysis also predicts TP53 p.V197M to be a loss-of-function mutation. It is reported in tumors of large intestine, pancreas, lung, urinary tract and upper aerodigestive tract. In biochemical assays, TP53 p.R181H mutant was found to have defective DNA binding activity compared to wildtype TP53 (Doffe et al; 2021). In silico analysis predicts TP53 p.R181H to be a gain-of-function mutation. It is reported in tumors of large intestine, endometrium, prostate, pancreas, haematopoietic and lymphoid system.

The TP53 gene provides instructions for making a protein called tumor protein p53 (or p53). This protein acts as a tumor suppressor, which means that it regulates cell division by keeping cells from growing and dividing too fast or in an uncontrolled way. Because p53 is essential for regulating cell division and preventing tumor formation, it has been nicknamed the "guardian of the genome".

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BRCA1/2 Mutation Analysis

Genomic Findings

No pathogenic/likely pathogenic germline mutations detected in BRCA1/BRCA2 genes in the submitted sample as evaluated by Next-Generation Sequencing (NGS).
No large genomic rearrangements (LGRs) (large deletions and duplications) detected in the BRCA1 /BRCA2 genes as evaluated by Multiplex Ligation-dependent Probe Amplification (MLPA).

Gene	Alterations	Drugs without Benefit
BRCA1, BRCA2	Not detected	☒ Olaparib ☒ Talazoparib ☒ Niraparib ☒ Rucaparib

Interpretation: Absence of pathogenic/likely pathogenic germline alterations in BRCA1/2 genes is suggestive of lack of benefit from Olaparib, Talazoparib, Niraparib and Rucaparib.

Olaparib is USFDA approved for breast, pancreatic, ovarian epithelial, fallopian tube, or primary peritoneal cancer patients with germline BRCA mutations. It is also USFDA approved for prostate cancer patients with germline or somatic mutations in the genes involved in the HRR pathway.

Talazoparib is USFDA approved for patients with germline BRCA-mutated HER2-negative metastatic breast cancer.

Niraparib is USFDA approved for ovarian epithelial, fallopian tube or primary peritoneal cancer with BRCA mutations.

Rucaparib is USFDA approved for prostate cancer and advanced ovarian epithelial, fallopian tube, or primary peritoneal cancer patients with germline BRCA mutations.

Mismatch Repair (MMR) Gene Mutations

Analysis of the mismatch repair (MMR) genes, MLH1, MLH3, MSH2, MSH6 and PMS2, did not detect any pathogenic or likely pathogenic germline mutations in the submitted sample.

It is reported that, immune checkpoint blockade therapy has a promising response in MMR- deficient (dMMR) cancers regardless of the tissue of origin (Viale et al., 2017; Zhang et al., 2018). Literature-based evidence suggests that loss of mismatch repair function via germline or somatic mutation confers the microsatellite instability (MSI) phenotype that is associated with high TMB and response to immune-checkpoint inhibitors (Richman, 2015; Lee et al., 2016; Viale et al., 2017; Mouw et al., 2017; Zhang et al., 2018). An average of 1782 somatic mutations per tumor and 578 potential neoantigens are found in mismatch repair deficient (dMMR) tumors, compared with 73 mutations and 21 neoantigens in mismatch repair proficient (pMMR) tumors by exome sequencing (P = 0.007). Higher numbers of somatic mutations and neoantigens are correlated with better responses and longer progression free survival (PFS). Furthermore, dMMR tumors have a dense infiltration of CD8+ TILs, which induces a better and more durable response (Le et al., 2015). Subsequently, USFDA approved Pembrolizumab and Dostarlimab-gxly for all dMMR/MSI-H solid tumors (Lemery et al., 2017; Chang et al., 2018; Zhao et al., 2019; Andre et al., 2021).

No germline pathogenic and likely pathogenic mutations indicative of dMMR status are detected in the MMR genes. Therefore in this case, there is no indication of immune checkpoint inhibitor therapy based on germline analysis of MMR genes.

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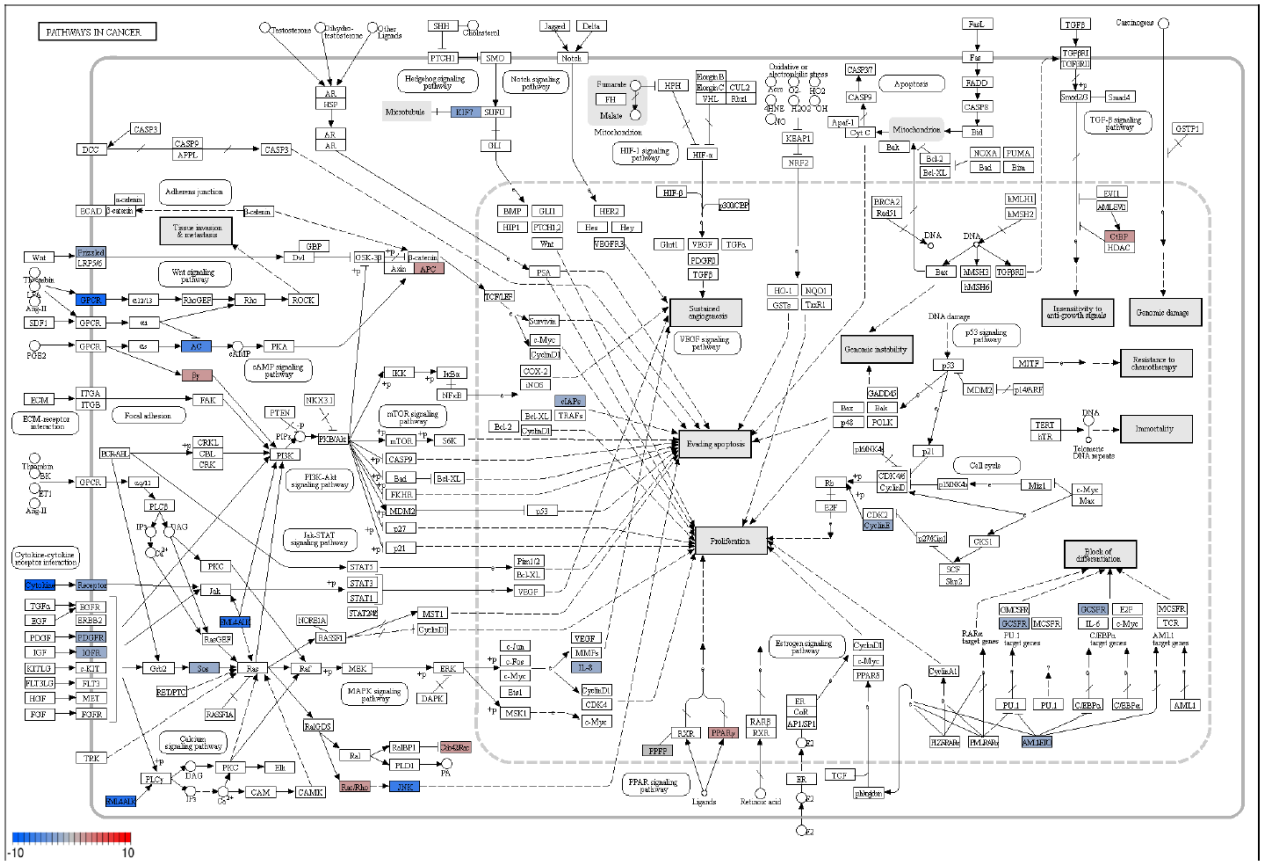
KEGG Pathway: 20802 Genes Analysis

KEGG Pathway

Comprehensive Pathway Perturbation in Primary Tumor



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Global Gene Expression Highlights

Gene Expression

Out of 20802 protein coding genes analyzed in the blood sample, **7700** genes were expressed in the analyzed blood sample.

1317 genes were found to be differentially regulated in the blood sample.

List of Oncology Drugs with Potential Benefit

Gene/s	Result (Fold change)	Drugs With Benefit
TYMS	▼ -2.45 FC	☑ 5-Fluorouracil ☑ Capecitabine ☑ Pemetrexed

Interpretation: Downregulation of TYMS is suggestive of potential benefit from 5-Fluorouracil, Capecitabine and Pemetrexed. Pemetrexed and its polyglutamated derivatives inhibit thymidylate synthase (TYMS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide transformylase (GART), all of which are involved in the denovo biosynthesis of thymidine and purine nucleotides. Antimetabolite agents including Pemetrexed, induce an imbalance in the cellular nucleotide pool and inhibit nucleic acid biosynthesis that results in arresting the proliferation of tumor cells and inducing cell death (Hazarika et al., 2005; Chattopadhyay et al., 2007; Obata et al., 2013; Abdallah et al., 2015; Ahn et al., 2015; Hamal et al., 2018).

5-Fluorouracil is USFDA approved for the treatment of breast, colorectal, gastric (stomach) and pancreatic cancer.
Capecitabine is USFDA approved for the treatment of breast and colorectal cancer.
Pemetrexed is USFDA approved for the treatment of non-squamous non-small cell lung cancer and malignant pleural mesothelioma.
5-Fluorouracil, Capecitabine and Pemetrexed are recommended as standard of care drugs for the treatment of epithelial ovarian/fallopian tube/ primary peritoneal cancer as per NCCN guidelines (NCCN guidelines, 2023).

Gene/s	Result (Fold change)	Drugs With Benefit
DHFR	▼ -3.62 FC	☑ Methotrexate

Interpretation: Downregulation of DHFR gene is suggestive of potential benefit from Methotrexate (Nakano et al., 2017).

Methotrexate is USFDA approved for the treatment of acute lymphoblastic leukemia, breast cancer, head and neck cancer, mycosis fungoides (a type of cutaneous T-cell lymphoma), non-Hodgkin lymphoma and osteosarcoma.
In a clinical study, the combination of Methotrexate and Cyclophosphamide for the treatment of recurrent ovarian cancer showed good tolerability and efficacy with overall clinical benefit rate of 54.54%. A partial response in 2 of 11 patients was reported (Scheusan et al., 2009).
In a clinical study, continuous low-dose oral Cyclophosphamide and Methotrexate therapy as arm A (maintenance arm) and arm B (observation arm) in patients with advanced ovarian carcinoma (n=30) after complete clinical response to platinum and Paclitaxel chemotherapy demonstrated median progression-free survival of 18 months in maintenance arm (A) and 15.5 months in observational arm (B) with median follow-up of 27 months (El-Husseiny et al., 2016).

List of Non-oncology Agents That May Provide Therapeutic Benefit

Gene/s	Result (Fold change)	Drugs With Benefit
HMGB1	▲ +4.97 FC	☑ Chloroquine

Interpretation: In pre-clinical study, Chloroquine is reported to inhibit HMGB1-induced IK-B degradation and NF-κB activation and thereby preventing cytokine-like activities of HMGB1 (Andersson and Tracey, 2011; Zhang et al., 2012; Fiuza et al., 2013). Chloroquine demonstrated anticancer activity by inducing apoptosis in several cancer types (Yang et al., 2013; Wu et al., 2015; Verbaanderd et al., 2017).

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List of Oncology Drugs Without Therapeutic Benefit

Markers	Result (Fold Change)	Drugs Without Benefit
	None Detected	

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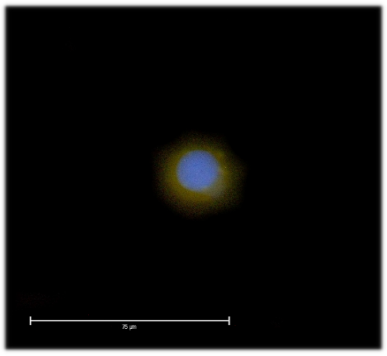
Circulating Tumor Cell Detection

CTCs

Circulating Tumor Cells (CTCs): **DETECTED**

Number of CTCs: **2 CTCs/ml peripheral blood**

CTCs are defined as EPCAM+ve, CK+ve, CD45-ve cells



Fluorescent microscopic image of CTC

Interpretation

2 CTCs/ml peripheral blood detected in the submitted sample.

Recommendation

Circulating tumor cell enumeration may be performed every 8 to 12 weeks to monitor disease status in consultation with the treating physician.

Immunocytochemistry (ICC) Analysis on Circulating Tumors and Associated Cells (CTCs)

ICC-CTCs

Markers	Result
VEGFA	Positive

Interpretation: Positive staining for VEGFA is indicative of potential benefit from Bevacizumab and Ziv-Aflibercept (Weickhardt et al., 2011; Tsai et al., 2015).

Bevacizumab is USFDA approved for the treatment of multiple tumor types, including ovarian epithelial, fallopian tube, or primary peritoneal cancer.
Bevacizumab is also recommended as a standard of care drug for the treatment of ovarian cancer as per NCCN guidelines (NCCN guidelines, 2023).

Ziv-Aflibercept is USFDA approved for the treatment of metastatic colorectal cancer.
In a case report, treatment with Aflibercept showed progression-free survival of 30 months and was well tolerated in a patient with relapsed ovarian cancer (Redondo et al., 2015).
In a phase 1–2 study, treatment of Docetaxel plus Aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer showed confirmed overall response rate of 54% in 46 evaluable patients (Coleman et al., 2011).

Markers	Result
mTOR	Positive

Interpretation: Positive staining for mTOR is indicative of potential benefit from Everolimus and Temsirolimus (Li et al., 2014; Rodriguez-Moreno et al., 2017; Du et al., 2018; Kuo et al., 2019).

Everolimus is USFDA approved for treatment of hormone receptor positive (HR+), HER2 negative (HER2-) breast cancer; neuroendocrine tumors of pancreatic, gastrointestinal, lung origin; renal cell carcinoma and subependymal giant cell astrocytoma.
In a phase II trial, combination of Everolimus and Letrozole in relapsed estrogen receptor positive high grade ovarian cancer showed an acceptable toxicity profile with 12 week progression-free survival rate of 47% in 19 evaluable patients (Colon-Otero et al., 2017).

Temsirolimus is USFDA approved for treatment of patients with advanced renal cell carcinoma.
In a phase II evaluation study, treatment with Carboplatin and Paclitaxel followed by Temsirolimus as first-line therapy in stage III-IV clear cell carcinoma of the ovary (n=90) was well tolerated with progression-free survival rate for >12 months in 54% of patients (Farley et al., 2016).

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Markers	Result
EGFR	Positive

Interpretation: Positive staining for EGFR is indicative of potential benefit from Panitumumab, Cetuximab and Necitumumab (Douillard et al., 2014; Trivedi et al., 2016; Thakur and Wozniak, 2017; Caratelli et al., 2020).

Panitumumab is USFDA approved for treatment of colorectal cancer.
In phase II nonrandomized multicenter study, combination of Panitumumab and pegylated liposomal Doxorubicin in KRAS wild-type platinum-resistant epithelial ovarian cancer (n=43) showed efficacy (response rate: 18.6%, progression-free survival: 2.7 months, overall survival: 8.1 months), but with considerable skin toxicity (Steffensen et al., 2013).

Cetuximab is USFDA approved for the treatment of head and neck and colorectal cancer.
In a phase II trial, combination of Cetuximab and Carboplatin in patients with relapsed platinum-sensitive ovarian or primary peritoneal carcinoma showed modest activity [objective response in 9 (3 complete response; 6 partial response); stable disease in 8 out of 26 patients] (Secord et al., 2008).

Necitumumab is USFDA approved for the treatment of squamous non-small cell lung cancer.
In a phase I pharmacologic study, treatment of Necitumumab in patients with advanced solid malignancies (including ovarian cancer), was well tolerated and showed antitumor activity (partial response in 2 and stable disease in 16 out of 60 patients) (Kuenen et al., 2010).

Markers	Result
VEGFR1/FLT1	Negative

Interpretation: No staining for VEGFR1/FLT1 is indicative of potential lack of benefit from Axitinib, Cabozantinib, Lenvatinib, Pazopanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib and Tivozanib (De Luca and Normanno, 2010; Paule et al., 2010; Chiang et al., 2012; Chu et al., 2013; Hepgur et al., 2013; Yamamoto et al., 2014; Daudigeos-Dubus et al., 2015; Kim et al., 2015; Tannir et al., 2017; Ortega et al., 2017; Schmidinger and Danesi, 2018; Morse et al., 2019; Jacob et al., 2020; Salgia et al., 2020).

Axitinib is USFDA approved for the treatment of advanced renal cell carcinoma (RCC).

Cabozantinib is USFDA approved for the treatment of hepatocellular carcinoma, advanced renal cell carcinoma (RCC) and thyroid cancer.

Lenvatinib is USFDA approved for the treatment of endometrial, hepatocellular carcinoma, advanced renal cell carcinoma and thyroid cancer.

Pazopanib is USFDA approved for treatment of advanced renal cell carcinoma and soft tissue sarcoma.

Ponatinib is USFDA approved for the treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia and/or acute lymphoblastic leukemia.

Regorafenib is USFDA approved for the treatment of colorectal, hepatocellular cancers and gastrointestinal stromal tumors (GIST).

Sorafenib is USFDA approved for the treatment of advanced renal cell, hepatocellular and thyroid carcinoma.

Sunitinib is USFDA approved for the treatment of advanced renal cell carcinoma, gastrointestinal stromal tumor and pancreatic neuroendocrine tumors.

Tivozanib is USFDA approved for the treatment of relapsed or refractory advanced renal cell carcinoma.

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Markers	Result
VEGFR2/KDR	Negative

Interpretation: No staining for VEGFR2/KDR is indicative of potential lack of benefit from Axitinib, Cabozantinib, Lenvatinib, Pazopanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib, Tivozanib, Ramucirumab and Vandetanib (De Luca and Normanno, 2010; Paule et al., 2010; Chiang et al., 2012; Chu et al., 2013; Hepgur et al., 2013; Yamamoto et al., 2014; Daudigeos-Dubus et al., 2015; Kim et al., 2015; Tannir et al., 2017; Ortega et al., 2017; Schmidinger and Danesi, 2018; Morse et al., 2019; Jacob et al., 2020; Salgia et al., 2020).

Ramucirumab is USFDA approved for the treatment of non-small cell lung cancer, stomach adenocarcinoma or gastroesophageal junction adenocarcinoma and colorectal cancer.

Vandetanib is USFDA approved for the treatment of medullary thyroid cancer.

Kindly refer to USFDA labels of Axitinib, Cabozantinib, Lenvatinib, Pazopanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib and Tivozanib mentioned earlier.

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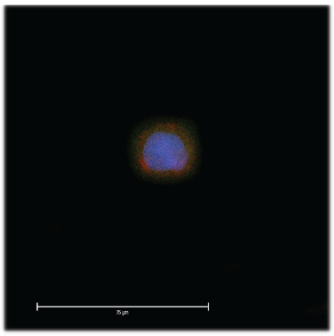
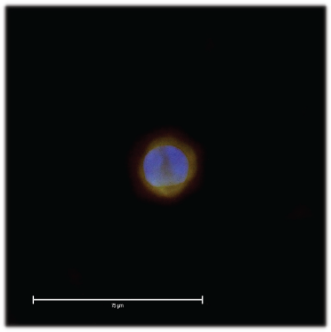
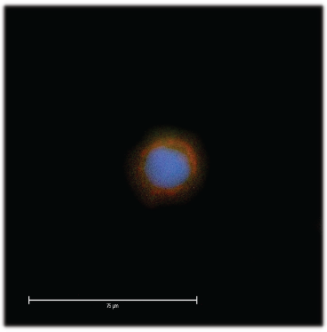
ICC-CTCs



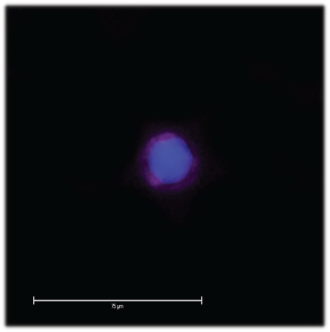
VEGFA ICC **Positive**



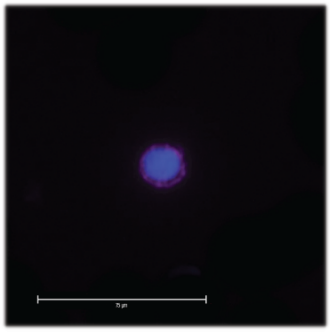
mTOR ICC **Positive**



EGFR ICC **Positive**



VEGFR1/FLT1 ICC **Negative**



VEGFR2/KDR ICC **Negative**

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PATIENT: XXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXX	COLLECTED: 00-XXX-2023		PRACTITIONER: XXXXXXXXXXXXX
GENDER: XXXXXX	RECEIVED: 00-XXX-2023		
AGE: XX	TESTED: 00-XXX-2023		XXXXXXXXXXXXXXXXXXXXX

TEST NAME: exacta® - Including drug and natural agents

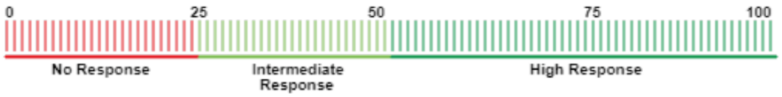
Chemosensitivity Analysis on CTCs

Chemosensitivity

Chemosensitivity assay performed on cultured circulating tumor and its associated cells indicates the effectiveness of chemotherapeutic drugs in descending order of efficacy.

Drug Names	% Cell Death	Drug Response
Cisplatin	75	
Oxaliplatin	74	
Cyclophosphamide	73	
Docetaxel	72	
Pemetrexed	70	
Gemcitabine	67	
Irinotecan	66	
Vinorelbine	66	
Ifosfamide	64	
Doxorubicin	53	
Vinblastine	51	
Trabectedin	44	
Eribulin	33	
Bleomycin	28	
5-Fluorouracil/Capecitabine	< 25	
Cabazitaxel	< 25	
Carboplatin	< 25	
Dacarbazine	< 25	
Dactinomycin	< 25	
Epirubicin	< 25	
Etoposide	< 25	
Melphalan	< 25	
Methotrexate	< 25	
Mitomycin	< 25	
Mitoxantrone	< 25	
Paclitaxel	< 25	
Temozolomide	< 25	
Topotecan	< 25	
Vincristine	< 25	

CHEMO SCALE



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PATIENT: XXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXX
GENDER: XXXXXX
AGE: XX

COLLECTED: 00-XXX-2023
RECEIVED: 00-XXX-2023
TESTED: 00-XXX-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER:
XXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXXXX

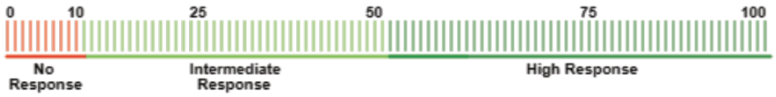
TEST NAME: exacta® - Including drug and natural agents

Response to Repurposed Drugs

Chemosensitivity

Drug Names	% Cell Death	Drug Response
Epigallocatechin gallate	53	
Hypericin	52	
Melatonin	52	
Diflunisal	51	
Doxycycline	47	
Glutathione	41	
Iscador Qu	37	
Dichloroacetate	30	
Artesunate	25	
Iscador P	25	
Helixor P	23	
Quercetin	22	
Resveratrol	21	
Curcumin	20	
Indol-3-carbinol	19	
Helixor M	18	
DMSO	17	
Helixor A	17	
Cannabidiol	16	
Atorvastatin	16	
Chloroquine	15	
Metformin	14	
Celecoxib	12	
Pantoprazole	11	
Bromelain	< 10	
Genistein	< 10	
Propranolol	< 10	
Vitamin C	< 10	
Aspirin	< 10	
Glibenclamide	< 10	

CHEMO SCALE



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Pharmacogenetic Analysis

Pharmacogenetics

Drug with Contraindication

- None

Drug with Increased Risk of Toxicity

- Belinostat
- Carboplatin
- Cisplatin
- Erlotinib
- Gemcitabine
- Irinotecan
- Methotrexate
- Nilotinib
- Oxaliplatin
- Pazopanib
- Regorafenib
- Sacituzumab govitecan

Drug with Labelled Toxicity

- 5-Fluorouracil
- Capecitabine
- Dabrafenib
- Erdafitinib
- Gefitinib
- Mercaptopurine
- Rasburicase
- Tegafur
- Thioguanine
- Trametinib
- Vincristine

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Analysis of Pharmacogenetics Markers for Oncology Drugs

Pharmacogenetics

Drug	Gene Analysis	Interpretation
Belinostat Evidence level : Level 1A	UGT1A1; *28/*28	The patient has a poor metabolizer status for UGT1A1 gene, leading to significantly reduced UGT1A1 activity. Patients with such genotype may have decreased clearance of Belinostat. Reduce the starting dose of Belinostat to 750 mg/m2 to minimize dose limiting toxicities (Belinostat FDA Label).
Carboplatin Evidence level : Level 2A,2B	ERCC1; rs11615 AA MTHFR; rs1801133 GG	The patient has an unfavorable genotype in the analysed ERCC1 gene variant. Patients with this genotype may have an increased risk of nephrotoxicity, when treated with Carboplatin (PatiÃ4o-GarcÃa et al., 2009; Khrunin et al., 2010; Tzvetkov et al., 2011).
Cisplatin Evidence level : Level 1B,2B	ERCC1; rs11615 AA XPC; rs2228001 GT	The patient has unfavorable genotypes in the analysed XPC and ERCC1 gene variants. Patients with such genotype may have an increased risk of toxicity including hearing loss, neutropenia and nephrotoxicity when treated with Cisplatin (Sakano et al., 2010; Khrunin et al., 2010; Tzvetkov et al., 2011).
Erlotinib Evidence level : Level 1A	UGT1A1; *28/*28	The patient has a poor metabolizer status for UGT1A1. Patients with this genotype who are treated with Erlotinib may have an increased risk of hyperbilirubinemia (Erlotinib EMA Label).
Gemcitabine Evidence level : Level 2B	NT5C2; rs11598702 TT	The patient has an unfavorable genotype in the analysed variant of NT5C2 gene. Patients with such genotype may have a decreased clearance of Gemcitabine and an increased risk of toxicity (Mitra et al., 2012).
Irinotecan Evidence level : Level 1A	UGT1A1; *28/*28	The patient has a poor metabolizer status for UGT1A1. Patients with this genotype who are treated with Irinotecan -based regimens may have an increased risk of neutropenia, diarrhea, or asthenia. When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of Irinotecan should be considered. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count. Rigorous clinical surveillance is recommended (Irinotecan FDA Label).
Methotrexate Evidence level : Level 2A	ABCB1; rs1045642 AA MTHFR; rs1801133 GG	The patient has an unfavorable genotype in the analysed ABCB1 gene variant. Patients with such genotype when treated with Methotrexate, may have an increased concentrations of the drug and an increased risk of toxicity (Suthandiram et al., 2014).

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Drug	Gene Analysis	Interpretation
Nilotinib Evidence level : Level 1A	UGT1A1; *28/*28	The patient has a poor metabolizer status for UGT1A1. Patients with this genotype who are treated with Nilotinib may have an increased risk of hyperbilirubinemia (Nilotinib FDA Label).
Oxaliplatin Evidence level : Level 2B	ERCC1; rs11615 AA	The patient has an unfavorable genotype in ERCC1 gene. Patients with such genotype when treated with Oxaliplatin may have an increased risk for nephrotoxicity (Khrunin et al., 2010; Tzvetkov et al., 2011).
Pazopanib Evidence level : Level 1A	UGT1A1; *28/*28	The patient has a poor metabolizer status for UGT1A1. Patients with this genotype who are treated with Pazopanib may have an increased risk of hyperbilirubinemia (Pazopanib FDA Label).
Regorafenib Evidence level : Level 1A	UGT1A1; *28/*28	The patient has a poor metabolizer status for UGT1A1. Patients with this genotype who are treated with Regorafenib may have an increased risk of hyperbilirubinemia (Regorafenib EMA Label).
Sacituzumab govitecan Evidence level : Level 1A	UGT1A1; *28/*28	The patient has a poor metabolizer status for UGT1A1 gene, leading to significantly reduced UGT1A1 activity. Patients with such genotype who are treated with Sacituzumab govitecan may have an increased risk of neutropenia and other adverse reactions. Closely monitor for severe neutropenia (Sacituzumab govitecan FDA Label).
5-Fluorouracil Evidence level : Level 1A	DPYD; *1/*5	The patient has a normal metabolizer status for DPYD gene leading to normal DPYD activity. Labelled risk for 5-Fluorouracil toxicity. Use as directed (Fluorouracil FDA Label).
Capecitabine Evidence level : Level 1A	DPYD; *1/*5	The patient has a normal metabolizer status for DPYD gene leading to normal DPYD activity. Labelled risk for Capecitabine toxicity. Use as directed (Capecitabine FDA Label).
Dabrafenib Evidence level : Level 1A	G6PD; wildtype/wildtype	The patient is not a carrier of G6PD deficient genotype. Patients with such genotype who are treated with Dabrafenib may have a reduced risk of hemolysis (Dabrafenib FDA Label).
Erdafitinib Evidence level : Level 1A	CYP2C9; *1/*1	The patient has a normal metabolizer status for CYP2C9 leading to an optimal enzyme activity. Patients with such genotype may have an optimal plasma concentration of Erdafitinib. Use as directed (Erdafitinib FDA Label).

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Drug	Gene Analysis	Interpretation
Gefitinib Evidence level : Level 1A	**CYP2D6; *1/*1**	The patient has a normal metabolizer status for CYP2D6. Patients with such genotype who are treated with Gefitinib may have normal metabolism of Gefitinib. Use as directed (Gefitinib FDA Label).
Mercaptopurine Evidence level : Level 1A	**NUDT15; *1/*1** **TPMT; *1/*1**	The patient is a normal metabolizer for TPMT and NUDT 15 genes. Patients with such metabolizer status who are treated with Mercaptopurine may have an increased inactivation of Mercaptopurine and a decreased risk of developing severe, life-threatening myelotoxicity. Use as directed. Start with normal starting dose and adjust doses of Mercaptopurine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment (Mercaptopurine FDA Label).
Rasburicase Evidence level : Level 1A	**G6PD; wildtype/wildtype**	The patient is not a carrier of G6PD deficient genotype. Patients with such genotype who are treated with Rasburicase may have a reduced risk of hemolysis (Rasburicase FDA Label).
Tamoxifen Evidence level : Level 1A	**CYP2D6; *1/*1**	The patient is a normal metabolizer for CYP2D6. Breast cancer patient with this metabolizer status and breast cancer show optimal metabolism of Tamoxifen resulting in optimal endoxifen concentrations, decreased likelihood of recurrence, increased event-free and recurrence-free survival, when treated with Tamoxifen in an adjuvant setting. Use as directed (CPIC Guideline for CYP2D6 and Tamoxifen Therapy).
Tegafur Evidence level : Level 1A	**DPYD; *1/*5**	The patient has a normal metabolizer status for DPYD gene leading to normal DPYD activity. Labelled risk for Tegafur toxicity. Use as directed (Fluorouracil FDA Label).
Thioguanine Evidence level : Level 1A	**NUDT15; *1/*1** **TPMT; *1/*1**	The patient is a normal metabolizer for TPMT and NUDT 15 genes. Patients with such metabolizer status who are treated with Thioguanine may have an increased inactivation of Thioguanine and a decreased risk of developing severe, life-threatening myelotoxicity. Use as directed. Start with normal starting dose and adjust doses of Thioguanine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment (Thioguanine FDA Label).
Trametinib Evidence level : Level 1A	**G6PD; wildtype/wildtype**	The patient is not a carrier of G6PD deficient genotype. Patients with such genotype who are treated with Trametinib may have a reduced risk of hemolysis (Trametinib FDA Label).

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Drug	Gene Analysis
Vincristine	CEP72; rs924607 CC
Evidence level : Level 2B	

Interpretation
The patient has a favorable genotype in the analysed variant of CEP72 gene.
Patients with such genotypes who are treated with Vincristine may have a decreased, but not absent, risk of peripheral nervous system diseases (Diouf et al., 2015).

Cell Free Nucleic Acids Analysis

Variant Allele Fraction and Coverage

Variant (Transcript ID)	Genomic co-ordinates	Allele fraction	Coverage (X)
TP53 (NM_000546.5) c.589G>A, p.V197M	chr17: 7578260C>T	1.57	64985
TP53 (NM_000546.5) c.542G>A, p.R181H	chr17: 7578388C>T	0.28	88536

Due to suboptimal coverage or no sequence, the presence or absence of variants contained within certain target regions of the genes listed below could not be meaningfully assessed.
FLT3, MET, NF2, PTEN

Criteria for Classification of Somatic Variants

Analysis Criteria

The criteria/guidance used in this report is in accordance with the guidelines provided by the American College of Medical Genetics and Genomics (ACMG) for the interpretation and reporting of sequence variants in cancer. Somatic sequence variations are categorized into four tiers based on their clinical significance (Li et al., 2017).

Tier I: Variants/biomarkers with strong clinical significance (therapeutic, prognostic and/or diagnostic)
Level A evidence: FDA approved therapies or standard guidelines for a specific tumor type.
Level B evidence: Statistically significant studies with consensus for specific tumor type.

Tier II: Biomarkers with potential clinical significance (therapeutic, prognostic and/or diagnostic)
Level C evidence: FDA approved therapies or standard guidelines for a different tumor type (off-label use of the drug). An inclusion criteria for clinical trials.
Level D evidence: No consensus among different studies.

Tier III: Biomarker whose association with cancer is not evident from available literature and is not frequently present in general population.

Tier IV: Biomarker whose association with cancer has not been reported till date and is frequently present in general population. This category of variants is not included in this report as per guidelines.

Criteria of Classification for Pharmacogenetic Analysis

Each variant-drug combination can be graded based on the measure of confidence in the association and the strength of prescribing recommendation.

Level 1: Evidence based on pharmacogenetics guidelines or well-established association studies

Level 2: Evidence of moderate variant-drug association from studies.

Level 3: Evidence suggests no consensus among different studies.

Drug Metabolizer Status Categories

Based on the different combination of haplotypes an individual inherits in each drug metabolizing gene, a drug metabolizer status can be predicted. There are 4 different drug metabolizer status types:

Poor Metabolizers (also called "PM"), Poor metabolizers have two non-functional alleles and therefore have little to no enzyme activity.

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Intermediate Metabolizers (also called "IM"), Intermediate metabolizers have one non-functional allele and one normally functioning allele, and therefore have decreased enzyme activity.

Normal Metabolizers (also called "NM") Normal metabolizers have 2 normally functioning alleles and therefore have normal enzyme activity.

Ultra-Rapid Metabolizers (also called "UM"). Ultra-rapid metabolizers have one or more alleles which result in increased enzyme activity compared to extensive metabolizers.
The impact of each metabolizer type on medication response depends on the role of the enzyme in the metabolism of the specific drug in question. For example, for a drug that is inactivated by the enzyme, an ultra-rapid metabolizer may need a higher dose of the drug to reach a therapeutic range while for another drug, that is activated by the enzyme; ultra-rapid metabolizer status may be associated with increased exposure to the drug and therefore an increased risk of adverse drug reactions.

Criteria for Classification of Germline Variants

The American College of Medical Genetics and Genomics (ACMG) developed guidance for the interpretation of sequence variants and recommended the use of following specific standard terminology to describe variants identified in genes that cause Mendelian disorders (Richards et al.,2015).

Pathogenic: Functional or expression evidence suggests deleterious effect on gene function.

Likely Pathogenic/Probably Deleterious: Limited or no functional evidence available, but overall biological expectations suggestive of deleterious effect.

Variants of unknown significance (VUS): Little or nothing has been reported on this variant or its effects.

Likely Benign: The variant has been seen in cases, but also in controls. Variant may be present in a high percentage of the population, and may be present in a non-conserved region.

Benign: Established in the literature as a variant that is not associated with Mendelian (single-gene inherited) disease, or known to have an allele frequency that is far too high to be compatible with the prevalence of disease, mode of inheritance and penetrance patterns known for that condition.

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Genes Analyzed

Gene List

SNV Genes:

ABL1	ABL2	ACVR2A	ADAMTS20	AFF1	AFF3	AKAP9	AKT1	AKT2	AKT3
ALK	APC	AR	ARAF	ARID1A	ARID2	ARNT	ASXL1	ATF1	ATM
ATR	ATRX	AURKA	AURKB	AURKC	AXL	BAI3	BAP1	BCL10	BCL11A
BCL11B	BCL2	BCL2L1	BCL2L2	BCL3	BCL6	BCL9	BCR	BIRC2	BIRC3
BIRC5	BLM	BLNK	BMPR1A	BRAF	BRD3	BRIP1	BTK	BUB1B	CARD11
CASC5	CBL	CCND1	CCND2	CCND3	CCNE1	CD79A	CD79B	CDC73	CDH1
CDH11	CDH2	CDH20	CDH5	CDK12	CDK4	CDK6	CDK8	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CKS1B	CMPK1	COL1A1	CRBN	CREB1
CREBBP	CRKL	CRTC1	CSF1R	CSMD3	CTNNA1	CTNNB1	CYLD	CYP2C19	CYP2D6
DAXX	DCC	DDB2	DDIT3	DDR2	DEK	DICER1	DNMT3A	DPYD	DST
EGFR	EML4	EP300	EP400	EPHA3	EPHA7	EPHB1	EPHB4	EPHB6	ERBB2
ERBB3	ERBB4	ERCC1	ERCC2	ERCC3	ERCC4	ERCC5	ERG	ESR1	ETS1
ETV1	ETV4	EXT1	EXT2	EZH2	FAM123B	FANCA	FANCC	FANCD2	FANCF
FANCG	FAS	FBXW7	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLI1
FLT1	FLT3	FLT4	FN1	FOXL2	FOXO1	FOXO3	FOXP1	FOXP4	FZR1
G6PD	GATA1	GATA2	GATA3	GDNF	GNA11	GNAQ	GNAS	GPR124	GRM8
GUCY1A2	HCAR1	HIF1A	HLF	HNF1A	HOOK3	HRAS	HSP1915AA1	HSP90AB1	ICK
IDH1	IDH2	IGF1R	IGF2	IGF2R	IKBKB	IKBKE	IKZF1	IL2	IL21R
IL6ST	IL7R	ING4	IRF4	IRS2	ITGA10	ITGA9	ITGB2	ITGB3	JAK1
JAK2	JAK3	JUN	KAT6A	KAT6B	KDM5C	KDM6A	KDR	KEAP1	KIT
KLF6	KRAS	LAMP1	LCK	LIFR	LPHN3	LPP	LRP1B	LTF	LTK
MAF	MAFB	MAGEA1	MAGI1	MALT1	MAML2	MAP2K1	MAP2K2	MAP2K4	MAP3K7
MAPK1	MAPK8	MARK1	MARK4	MBD1	MCL1	MDM2	MDM4	MEN1	MET
MITF	MLH1	MLL	MLL2	MLL3	MLLT10	MMP2	MN1	MPL	MRE11A
MSH2	MSH6	MTOR	MTR	MTRR	MUC1	MUTYH	MYB	MYC	MYCL1
MYCN	MYD88	MYH11	MYH9	NBN	NCOA1	NCOA2	NCOA4	NF1	NF2
NFE2L2	NFKB1	NFKB2	NIN	NKX2-1	NLRP1	NOTCH1	NOTCH2	NOTCH4	NPM1
NRAS	NSD1	NTRK1	NTRK3	NUMA1	NUP214	NUP98	PAK3	PALB2	PARP1
PAX3	PAX5	PAX7	PAX8	PBRM1	PBX1	PDE4DIP	PDGFB	PDGFRA	PDGFRB
PER1	PGAP3	PHOX2B	PIK3C2B	PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIK3R2
PIM1	PKHD1	PLAG1	PLCG1	PLEKHG5	PML	PMS1	PMS2	POT1	POU5F1
PPARG	PPP2R1A	PRDM1	PRKAR1A	PRKDC	PSIP1	PTCH1	PTEN	PTGS2	PTPN11
PTPRD	PTPRT	RAD50	RAF1	RALGDS	RARA	RB1	RECQL4	REL	RET
RHOH	RNASEL	RNF2	RNF213	ROS1	RPS6KA2	RRM1	RUNX1	RUNX1T1	SAMD9
SBDS	SDHA	SDHB	SDHC	SDHD	SEPT9	SETD2	SF3B1	SGK1	SH2D1A
SMAD2	SMAD4	SMARCA4	SMARCB1	SMO	SMUG1	SOCS1	SOX11	SOX2	SRC
SSX1	STK11	STK36	SUFU	SYK	SYNE1	TAF1	TAF1L	TAL1	TBX22
TCF12	TCF3	TCF7L1	TCF7L2	TCL1A	TET1	TET2	TFE3	TGFBR2	TGM7
THBS1	TIMP3	TLR4	TLX1	TNFAIP3	TNFRSF14	TNK2	TOP1	TP53	TPR
TRIM24	TRIM33	TRIP11	TRRAP	TSC1	TSC2	TSHR	UBR5	UGT1A1	USP9X
VHL	WAS	WHSC1	WRN	WT1	XPA	XPC	XPO1	XRCC2	ZNF384
ZNF521									

CNV Genes:

ABL1	ABL2	ACVR2A	ADAMTS20	AFF1	AFF3	AKAP9	AKT1	AKT2	AKT3
ALK	APC	AR	ARID1A	ARID2	ARNT	ASXL1	ATF1	ATM	ATR

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ATRX	AURKA	AURKB	AURKC	AXL	BAI3	BAP1	BCL10	BCL11A	BCL11B
BCL2	BCL2L1	BCL2L2	BCL3	BCL6	BCL9	BCR	BIRC2	BIRC3	BIRC5
BLM	BLNK	BMPR1A	BRAF	BRD3	BRIP1	BTK	BUB1B	CARD11	CASC5
CBL	CCND1	CCND2	CCND3	CCNE1	CD79A	CD79B	CDC73	CDH1	CDH11
CDH2	CDH20	CDH5	CDK12	CDK4	CDK6	CDK8	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CKS1B	CMPK1	COL1A1	CRBN	CREB1	CREBBP
CRKL	CRTC1	CSF1R	CSMD3	CTNNA1	CTNNB1	CYLD	CYP2C19	CYP2D6	DAXX
DCC	DDB2	DDIT3	DDR2	DEK	DICER1	DNMT3A	DPYD	DST	EGFR
EML4	EP300	EP400	EPHA3	EPHA7	EPHB1	EPHB4	EPHB6	ERBB2	ERBB3
ERBB4	ERCC1	ERCC2	ERCC3	ERCC4	ERCC5	ERG	ESR1	ETS1	ETV1
ETV4	EXT1	EXT2	EZH2	FAM123B	FANCA	FANCC	FANCD2	FANCF	FANCG
FAS	FBXW7	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLI1	FLT1
FLT3	FLT4	FN1	FOXL2	FOXO1	FOXO3	FOXP1	FOXP4	FZR1	G6PD
GATA1	GATA2	GATA3	GDNF	GNA11	GNAQ	GNAS	GPR124	GRM8	GUCY1A2
HCAR1	HIF1A	HLF	HNF1A	HOOK3	HRAS	HSP90AA1	HSP90AB1	ICK	IDH1
IDH2	IGF1R	IGF2	IGF2R	IKBKB	IKBKE	IKZF1	IL2	IL21R	IL6ST
IL7R	ING4	IRF4	IRS2	ITGA10	ITGA9	ITGB2	ITGB3	JAK1	JAK2
JAK3	JUN	KAT6A	KAT6B	KDM5C	KDM6A	KDR	KEAP1	KIT	KLF6
KRAS	LAMP1	LCK	LIFR	LPHN3	LPP	LRP1B	LTF	LTK	MAF
MAFB	MAGEA1	MAGI1	MALT1	MAML2	MAP2K1	MAP2K2	MAP2K4	MAP3K7	MAPK1
MAPK8	MARK1	MARK4	MBD1	MCL1	MDM2	MDM4	MEN1	MET	MITF
MLH1	MLL	MLL2	MLL3	MLLT10	MMP2	MN1	MPL	MRE11A	MSH2
MSH6	MTOR	MTR	MTRR	MUC1	MUTYH	MYB	MYC	MYCL1	MYCN
MYD88	MYH11	MYH9	NBN	NCOA1	NCOA2	NCOA4	NF1	NF2	NFE2L2
NFKB1	NFKB2	NIN	NKX2-1	NLRP1	NOTCH1	NOTCH2	NOTCH4	NPM1	NRAS
NSD1	NTRK1	NTRK3	NUMA1	NUP214	NUP98	PAK3	PALB2	PARP1	PAX3
PAX5	PAX7	PAX8	PBRM1	PBX1	PDE4DIP	PDGFB	PDGFRA	PDGFRB	PER1
PGAP3	PHOX2B	PIK3C2B	PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIK3R2	PIM1
PKHD1	PLAG1	PLCG1	PLEKHG5	PML	PMS1	PMS2	POT1	POU5F1	PPARG
PPP2R1A	PRDM1	PRKAR1A	PRKDC	PSIP1	PTCH1	PTEN	PTGS2	PTPN11	PTPRD
PTPRT	RAD50	RAF1	RALGDS	RARA	RB1	RECQL4	REL	RET	RHOH
RNASEL	RNF2	RNF213	ROS1	RPS6KA2	RRM1	RUNX1	RUNX1T1	SAMD9	SBDS
SDHA	SDHB	SDHC	SDHD	SEPT9	SETD2	SF3B1	SGK1	SH2D1A	SMAD2
SMAD4	SMARCA4	SMARCB1	SMO	SMUG1	SOCS1	SOX11	SOX2	SRC	SSX1
STK11	STK36	SUFU	SYK	SYNE1	TAF1	TAF1L	TAL1	TBX22	TCF12
TCF3	TCF7L1	TCF7L2	TCL1A	TET1	TET2	TFE3	TGFBR2	TGM7	THBS1
TIMP3	TLR4	TLX1	TNFAIP3	TNFRSF14	TNK2	TOP1	TP53	TPR	TRIM24
TRIM33	TRIP11	TRRAP	TSC1	TSC2	TSHR	UBR5	UGT1A1	USP9X	VHL
WAS	WHSC1	WRN	WT1	XPA	XPC	XPO1	XRCC2	ZNF384	ZNF521

Fusion Genes:

ALK	BRAF	ERG	ETV1	FGFR1	FGFR2	FGFR3	MET	NTRK1	NTRK3
RET	ROS1								

Exosomal Gene Expression Analysis

Exosomal RNA: 20802 mRNA

Biomarkers Analyzed for Mismatch Repair (MMR) Genes

MLH1	MLH3	MSH2	MSH6	PMS2

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BRCA1/2 Mutation Analysis

BRCA1 and BRCA2 genes sequencing; deletion & duplication (MLPA)

Genes Analyzed for Pharmacogenetics

Genes	Variants Analyzed
ABCB1	c.3435T>C
CEP72	n.366+1469G>A
CYP2C9	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *18, *35
CYP2D6	*1, *2, *3, *4, *6, *7, *8, *9, *10, *11, *12, *15, *17, *19, *20, *29, *35, *38, *41, *42, *44, *56 and *5, XN
DPYD	*1, *10, *11, *12, *13, *2A, *3, *4, *5, *6, *7, *8, *9A, *9B, c.1024G>A, c.1057C>T, c.1314T>G, c.1896T>C, c.2279C>T, c.2639G>T, c.2846A>T, c.2872A>G, c.2933A>G, c.496A>G, c.557A>G, c.61C>T, c.62G>A, c.1129-5923C>G (HapB3), c.1236G>A (HapB3)
ERCC1	c.354T>C
G6PD	Gaohe; Sunderland; Orissa; Murcia Oristano; Ube Konan; Vancouver; Santa Maria; G6PD A- 680T_376G; Mt Sinai; Sierra Leone; G6PD A- 968C_376G; Ananindeua; Taipei Chinese-3; Malaga; Mediterranean Haplotype; Mediterranean_Dallas_Panama_Sassari_Cagliari_ Birmingham; Coimbra Shunde; Sibari; Cincinnati; Minnesota_Marion_Gastonia_LeJeune; Nanning; Chinese-5; Ierapetra; Serres; Iowa_Walter Reed_Springfield; Guadalajara; Riverside; Asahi; Ludhiana; Pawnee; Surabaya; Japan_Shinagawa; Puerto Limon; Alhambra; Nashville_Anaheim_Portici; Beverly Hills_Genova_Iwate_Niigata_Yamaguchi; Tomah; Montpellier; Loma Linda; Mira d'Aire; Chatham; Rehevot; Kalyan-Kerala_Jamnaga_Rohini; Viangchan_Jammu; Seattle_Lodi_Modena_Ferrara II_Athens-like; Aveiro; Nilgiri; Nankang; Ilesha; Crispim; Sao Borja; Lagosanto; Namouru; A- 202A_376G; Hechi; Metaponto; Aures; Acrokorinthos; A; Vanua Lava; Mediterranean_Dallas_Panama_Sassari_Cagliari_Birmingham; wildtype; 202G>A_376A>G_1264C>G
MTHFR	c.665C>T
NT5C2	c.175+1178A>G
NUDT15	*1, *2, *3, *4, *5, *6
TPMT	*1, *2, *3A, *3B, *3C, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *20, *21, *23, *24, *25, *26, *29, *31, *32, *33, *34, *37
UGT1A1	*1, *28
XPC	c.2815C>A

Drugs Tested in Chemosensitivity Analysis

Drug List

5-Fluorouracil/Capecitabine, Artesunate, Aspirin, Atorvastatin, Bleomycin, Bromelain, Cabazitaxel, Cannabidiol, Carboplatin, Celecoxib, Chloroquine, Cisplatin, Curcumin, Cyclophosphamide, DMSO, Dacarbazine, Dactinomycin, Dichloroacetate, Diflunisal, Docetaxel, Doxorubicin, Doxycycline, Epigallocatechin gallate, Epirubicin, Eribulin, Etoposide, Gemcitabine, Genistein, Glibenclamide, Glutathione, Helixor A, Helixor M, Helixor P, Hypericin, Ifosfamide, Indol-3-carbinol, Irinotecan, Iscador P, Iscador Qu, Melatonin, Melphalan, Metformin, Methotrexate, Mitomycin, Mitoxantrone, Oxaliplatin, Paclitaxel, Pantoprazole, Pemetrexed, Propranolol, Quercetin, Resveratrol, Temozolomide, Topotecan, Trabectedin, Vinblastine, Vincristine, Vinorelbine, Vitamin C

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Antibody Details - Immunocytochemistry (ICC) Analysis

Antibody

Marker	Clone	Marker	Clone
EPCAM	REA831	CK	REA764
CD45	HI30	mTOR	Polyclonal
VEGFR1	REA569	VEGFR2	REA1116
VEGFA	JH121	EGFR	EP22

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Methods and Limitations

Methods

Cell free nucleic acids analysis:

Cell free nucleic acids were analyzed for mutation and fusion detection using semiconductor based Next Generation Sequencing technology. Cell free nucleic acids extracted from the plasma of submitted specimen was subjected to target enrichment by multiplex PCR amplification using Ion AmpliSeq Comprehensive Cancer panel targeting 409 as well as Oncomine Pan-Cancer Cell-Free Assay 52 (see gene list in the 'Genes analyzed section') oncogenes and tumor suppressor genes. Enriched DNA sequences were ligated with platform specific adaptor molecules and were sequenced using semiconductor chip. Sequenced data was aligned with the human genome (hg19), analyzed at 17000x minimum average depth for 52 gene panel and 1000x for 409 gene panel using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline vS11.11 and DCGL NGS Bioinformatics Pipeline vS7.13 designed to accurately detect the rare somatic variants.

Paired analysis was performed to differentiate between somatic and germline mutations. Lower limit of detection of the mutations targeted is 0.1% for underlined genes in genes analyzed section and 1% for other genes and variants present below LOD may not be detectable with this assay, whereas analytical sensitivity is 97.43% and specificity is 99.5%.

A negative test result does not exclude the possibility of mutations being present in the test sample probably due to the reads representing minor allele fraction is below the detectable limit of the assay or other limiting technical/analytical factors. The scope of copy number variations analysis includes copy number gain/amplification of the detected gene(s).

The clinical sensitivity of most assays for detection of alterations in cell free nucleic acids is limited as compared with tumor tissue-based testing. This may result from a high ratio of normal to tumor DNA or excess degradation of cell free nucleic acids or may simply reflect the biologic heterogeneity of solid tumors, some of which may shed abundant nucleic acid into the circulation and others that may not. Tumor type, size, disease stage, sites of metastasis, histologic grade, or other features may also affect levels, however, much remains to be elucidated.

Exosomal mRNA analysis:

Blood was analyzed for mRNA expression analysis using semiconductor based Next Generation Sequencing method. High quality Exosomal RNA was extracted from the submitted specimen. It was subjected to mRNA library preparation using a targeted Ion AmpliSeq Transcriptome Human Gene Expression panel. RNA sequencing was performed to achieve at least 4 million mappable high-quality reads for the paired analysis. Sequence reads were aligned to the hg19 transcriptome reference sequence in Torrent Suite Software using the Ion Torrent Mapping Alignment Program. Differential Gene Expression analysis was performed using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline vS5.10 designed to detect the Significantly expressed genes.

MMR gene analysis:

EDTA blood was analysed for mutation detection using semiconductor based Next Generation Sequencing technology. High quality genomic DNA was extracted from the submitted specimen and subjected to target enrichment by high multiplex PCR amplification using Ion AmpliSeq panel targeting mutation of genes mentioned above. Enriched DNA sequences were ligated with platform specific adaptor molecules and was sequenced on using semiconductor chip. Sequenced data was aligned with the human genome (hg19), analyzed at 500x minimum average depth using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline vS2.14, designed to accurately detect the germline variants.

Analytical Validation of this assay shown sensitivity of 100% and specificity 100%.

Pathogenic/likely pathogenic mutation if detected in the sample is confirmed by gold standard Sanger Sequencing method. Sanger sequencing data is analyzed using SeqScape Software ver 3.0.

BRCA1/2 gene analysis:

Genomic DNA was analyzed for deletion/duplication detection in BRCA1/2 genes using Ion Proton sequencer. High quality genomic DNA extracted from the submitted specimen was subjected to target enrichment by multiplex PCR amplification using panel targeting BRCA genes. Enriched DNA sequences were ligated with platform specific adaptor molecules and sequenced using semiconductor P1 chip. The minimum average depth was 1000x for gene panel analyzed. High quality sequencing data (proportion Q20 bases ≥ 75%) was analyzed using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline vP17.3, designed to accurately detect the rare variants.

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Multiplex Ligation-dependent Probe Amplification (MLPA) assay:

The simultaneous analysis was performed by the Multiplex Ligation-dependent Probe Amplification (MLPA) for BRCA1 and BRCA2 to rule out deletions and duplications. Genomic DNA was isolated from sample submitted. Using MLPA reagents from MRC-Holland B.V. (Amsterdam, the Netherlands) and the MLPA procedure was performed as recommended by the manufacturer.

Analytical Validation of this assay shown sensitivity of 100% and specificity 100%.

Pharmacogenetic analysis:

Blood was analyzed for genotyping using semiconductor based Next Generation Sequencing technology. High quality genomic DNA was extracted from the submitted specimen and subjected to target enrichment by high multiplex PCR amplification using Ion AmpliSeq panel. Enriched DNA sequences were ligated with platform specific adaptor molecules and was sequenced on using semiconductor P1 chip. The minimum average depth was 500x for panel of genes analyzed. High quality sequencing data (proportion of Q20 bases ≥75%) was analyzed using DCGL NGS Bioinformatics Pipeline vS14.6. This test does not detect polymorphisms other than those listed. Drug metabolism may be affected by non-genetic factors. DNA testing does not replace the need for clinical and therapeutic drug monitoring. Analytical Validation of this assay shown sensitivity of 100% and specificity 100%.

The performance of the assay specific reagents used in this assay has been established and its performance characteristics defined by Datar Cancer Genetics. This test may not detect all variants in non-coding regions that could affect copy number changes encompassing all or a large portion of the gene. Tumor mutation analysis panel testing is limited in detecting the following types of mutations (this might not be exhaustive): large rearrangements and deletion/ duplications, epigenetic factors, mutations in repetitive or high GC rich regions and mutations in gene with corresponding pseudo genes or other highly homologous sequences. Presence of PCR inhibitors in the sample may prevent DNA amplification for mutation analysis. Rare and novel mutations may be clinically uncharacterized.

Also note that the current knowledge on the genetic of the disease or pathogenic disorder or on the inheritance of the genes may be incomplete. If the test identifies the genetic cause of the disorder, it is possible that this knowledge may or may not help with the prognosis and management of the disease.

CTC Enumeration and ICC analysis:

Enriched CTCs from the submitted peripheral blood were labelled with EPCAM, Cytokeratin and CD45 antibodies and analyzed by High content imaging platform. Analytical Validation of this assay shown sensitivity of 99.99% and specificity 99.99%.

Circulating Tumor and its associated cells from the submitted peripheral blood were analyzed through Cell stabilization protocol using Cell Wizard System. Cells were labelled with mTOR, VEGFR1, VEGFR2, VEGF-A and EGFR antibodies and analyzed by Fluorescent microscopy for Immunocytochemistry (ICC).

Blood based Chemosensitivity analysis:

Circulating tumor and its associated cells were isolated from the submitted peripheral blood sample. The live cancer cells were tested against multiple chemotherapy agents. The number of drugs selected for testing depend on the number of circulating tumor associated cells isolated from the submitted sample.

A defined number of cells were incubated with different drugs with respective drug concentrations, mean peak plasma concentration and cell death events were measured. The extent of cell death was determined either using Varioskan LUX platform. Percent cell death was calculated to evaluate the response level of the drug. Appropriate positive and negative controls were tested and evaluated in a similar manner simultaneously with the test sample.

Analytical Validation of this assay shown sensitivity of 99.99% and specificity 99.99%.

Information to Patient:

This is a Laboratory developed test, and its performance characteristics were determined by Datar Cancer Genetics UK Private Limited, United Kingdom. It has not been cleared or approved by the U.S. Food and Drug Administration. This Laboratory is registered under the Clinical Laboratory Improvement Amendments (CLIA)-USA to perform high complexity clinical laboratory testing.

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The processing of samples for Molecular Genetics and Cell Culture analysis is carried out at our Laboratory - Datar Cancer Genetics UK Private Limited, United Kingdom.

The analysis of the generated data as well as the preparation of Reports is carried out by our partner laboratory - Datar Cancer Genetics Private Limited, Nasik, India.

This facility is certified by the College of American Pathologists (CAP) and under the Clinical Laboratory Improvement Amendments (CLIA)-USA as qualified to perform high complexity clinical laboratory testing. It is accredited under ISO 15189:2012 and ISO 27001:2013 for Information Security Management Systems.

Disclaimer

This report documents the genetic alterations detected in the submitted sample material. Information in this report is provided for information purpose only and should only 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 physicians, taking into consideration all applicable information concerning the patient's condition, such as personal and family history, physician's examination, information from other diagnostic test and patient references, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test or on the information contained in this report.

This information in this report does not constitute a treatment recommendation by Datar Cancer Genetics, either to use or not to use any specific therapeutic agent, and should not be interpreted as treatment advice. Decisions on patient care and treatment rest solely within the discretion of the patient's treating physician.

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End of Report

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TEST NAME: exacta® - Including drug and natural agents

Clinical Trials Relevant to Patient's Genomic Findings

Clinical Trials

TP53 mutation

NCT number: NCT04169841 **Phase: II** **Treatment:** Durvalumab, Tremelimumab, Olaparib **Cancer Type:** Ovarian Cancer	**Study Title:** Precision Medicine Phase II Study Evaluating the Efficacy of a Double Immunotherapy by Durvalumab and Tremelimumab Combined With Olaparib in Patients With Solid Cancers and Carriers of Homologous Recombination Repair Genes Mutation in Response or Stable After Olaparib Treatment **Variant Classification:** HRR mutation **Locations:** France
NCT number: NCT05002868 **Phase: I** **Treatment:** RP12146 **Cancer Type:** Ovarian Cancer	**Study Title:** A Multi-center, Open-label, Phase I/Ib Study to Assess the Safety, Pharmacokinetics and Anti-tumor Activity of RP12146, a Poly (ADP-ribose) Polymerase (PARP) Inhibitor, in Patients With Locally Advanced or Metastatic Solid Tumors. **Variant Classification:** HRR mutation **Locations:** Czech Republic, Poland
NCT number: NCT03188965 **Phase: I/II** **Treatment:** Elimusertib **Cancer Type:** Ovarian Cancer	**Study Title:** An Open-label, First-in-human, Dose-escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Maximum Tolerated Dose and / or Recommended Phase II Dose of the ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas **Variant Classification:** DNA repair pathway **Locations:** Canada, Japan, Singapore, Switzerland
NCT number: NCT04267939 **Phase: I** **Treatment:** Elimusertib, Niraparib **Cancer Type:** Ovarian Cancer	**Study Title:** An Open-label Phase Ib Study to Determine the Maximum Tolerated and/or Recommended Phase 2 Dose of the ATR Inhibitor Elimusertib (BAY 1895344) in Combination With PARP Inhibitor Niraparib, in Participants With Recurrent Advanced Solid Tumors and Ovarian Cancer **Variant Classification:** DNA repair pathway **Locations:** United States **Contacts:** Bayer Clinical Trials Contact [888-842-2937; clinical-trials-contact@bayer.com]

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TEST NAME: exacta® - Including drug and natural agents

NCT number:
NCT02029001

Phase: II

Treatment:
Olaparib

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients with Progressive Locally-advanced or Metastatic Solid Tumors.

Variant Classification:
HRR mutation

Locations:
France

NCT number:
NCT03415659

Phase: I

Treatment:
HWH-340

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Phase I, Open-label, Single-center, Single/Multiple-dose, Dose-escalation/Dose-expansion Clinical Study on Tolerance and Pharmacokinetics of HWH340 Tablet in Patients With Advanced Solid Tumors

Variant Classification:
HRR mutation

Locations:
China

NCT number:
NCT03767075

Phase: II

Treatment:
Atezolizumab

Cancer Type:
Unspecified Solid Tumor

Study Title:
Basket of Baskets: A Modular, Open-label, Phase II, Multicentre Study To Evaluate Targeted Agents in Molecularly Selected Populations With Advanced Solid Tumours

Variant Classification:
DNA repair mutation

Locations:
France, Germany, Netherlands, Spain, Sweden, United Kingdom

NCT number:
NCT04905914

Phase: I/II

Treatment:
ATRN-119

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Phase I/IIa, Open-Label, Safety, Pharmacokinetic, And Preliminary Efficacy Study Of Oral ATRN-119 In Patients With Advanced Solid Tumors

Variant Classification:
DNA repair mutation

Locations:
United States

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NCT number:
NCT04901702

Phase: I/II

Treatment:
Talazoparib, Chemotherapy

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Randomized Phase I/II Study of Talazoparib or Temozolomide in Combination With Onivyde in Children With Recurrent Solid Malignancies and Ewing Sarcoma

Variant Classification:
HRR pathway

Locations:
Canada, United States

Contacts:
Dr. Sara Federico [866-278-5833; referralinfo@stjude.org]

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TEST NAME: exacta® - Including drug and natural agents

NCT number:
NCT04992013

Phase: II

Treatment:
Niraparib

Cancer Type:
Unspecified Solid Tumor

Study Title:
Genomically Guided Phase II Study to Evaluate the Clinical Benefit of Niraparib in Tumors Metastatic to the CNS

Variant Classification:
DNA repair pathway

Locations:
United States

Contacts:
Dr. Priscilla Brastianos [617-643-1938; pbrastianos@mgh.harvard.edu]

NCT number:
NCT04693468

Phase: I

Treatment:
Talazoparib, Palbociclib, Axitinib, Crizotinib

Cancer Type:
Unspecified Solid Tumor

Study Title:
Modular Phase IB Hypothesis-Testing, Biomarker-Driven, Talazoparib Combination Trial (TalaCom)

Variant Classification:
DNA repair pathway

Locations:
United States

Contacts:
Timothy A. Yap [713-563-1784; tyap@mdanderson.org]

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