NaturaGene-Ai

Precision Without Toxicity

TEST REPORT

Ms. ABC

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DATAR CANCER GENETICS

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PATIENT DETAILS

Name	: Ms. ABC
Birth Date	: 15-Dec-1975
Gender	: Female
Address	: —
Referring Doctor	: Dr. XYZ

SPECIMEN DETAILS

Tumor Type	: Rectal carcinoma
Specimen Type	: Blood
Draw Date	: 02-Apr-2025
Accession Date	: 03-Apr-2025
Report Date	: 15-Apr-2025

Specimen Analysis Summary

Blood

cf Total Nucleic Acids	: 52 Gene (SNAs | Indels | CNAs | Fusion Transcript)
mRNA	: 20802 Genes
Chemosensitivity Analysis	: 37 Drugs
Total Drugs Analysed	**: 100 Drugs (Please Refer Annexure)**

REPORT HIGHLIGHTS

Biomarkers	Drugs with Benefits
MMP Overexpression	☑ Berberine, Cannabidiol, Doxycycline, Lycopene, Pantoprazole, Scutellaria baicalensis, Ursolic Acid
VEGFA Overexpression	☑ Angiostop, Astaxanthin, Avemar, Fisetin, Ganoderma lucidum, Panax Ginseng
BCL2 Overexpression	☑ Asimina triloba, Menaquinone, Propolis
PTGS2 (COX2) Overexpression	☑ Ellagic Acid, Nigella sativa, Rubus occidentalis
WNT Overexpression	☑ Beta-Carotene, Capsaicin, Niclosamide, Salinomycin Sodium Salt
TP53 p.A88V, TP53 p.R213*	☑ Fenbendazole, Valproic acid, α-Tocopherol
KRAS p.G12D	☑ D-Limonene, Hydroxychloroquine, Statins, Vitamin C
VEGFA Overexpression KRAS p.G12D	☑ Allium sativum
MAPK Overexpression KRAS p.G12D	☑ Atorvastatin, Metformin, Annona muricata
BCL2 Overexpression MAPK Overexpression	☑ Annona muricata
VEGFA Overexpression TP53 p.A88V, TP53 p.R213*	☑ Apigenin, Aspirin
MMP Overexpression PTGS2 (COX2) Overexpression	☑ Bromelain, Melatonin
MMP Overexpression VEGFA Overexpression	☑ Iscador P, Iscador Qu, Proanthocyanidins, Salvia miltiorrhiza

Biomarkers	Drugs with Benefits
BCL2 Overexpression PTGS2 (COX2) Overexpression	☑ Moringa oleifera
WNT Overexpression PTGS2 (COX2) Overexpression	☑ NSAIDs (Ibuprofen Sulindac)
BCL2 Overexpression TP53 p.A88V, TP53 p.R213*	☑ Selenomethionine, Withania somnifera
MAPK Overexpression MMP Overexpression KRAS p.G12D	☑ Atorvastatin
BCL2 Overexpression MMP Overexpression PTGS2 (COX2) Overexpression	☑ Boswellia serrata
BCL2 Overexpression MMP Overexpression VEGFA Overexpression	☑ Curcumin
MAPK Overexpression MMP Overexpression VEGFA Overexpression	☑ Epigallocatechin gallate, Mebendazole
BCL2 Overexpression MAPK Overexpression WNT Overexpression	☑ Genistein
MAPK Overexpression MMP Overexpression BCL2 Overexpression KRAS p.G12D	☑ Metformin
FZD Overexpression MAPK Overexpression WNT Overexpression APC p.Q1367*, APC p.R564*	☑ Quercetin
WNT Overexpression MMP Overexpression BCL2 Overexpression PTGS2 (COX2) Overexpression	☑ Resveratrol
FZD Overexpression MMP Overexpression WNT Overexpression BCL2 Overexpression TP53 p.A88V, TP53 p.R213*	☑ Artesunate
FZD Overexpression MAPK Overexpression WNT Overexpression PTGS2 (COX2) Overexpression APC p.Q1367*, APC p.R564*	☑ Celecoxib

Longitudinal Monitoring Biomarkers

Biomarker	Result
Highest mutant allele frequency (HMAF)	7.07%

Disease Relevant Findings

Biomarker	Result
KRAS p.G12D	Mutation detected
BRAF	No mutations detected
RET	No fusions detected

Biomarker	Result
NRAS	No mutations detected
ERBB2/HER2	No alterations detected
NTRK1/3	No fusions detected

Summary of Other Genomic Alterations

Gene	Alteration Type (SNAs / Indels / CNAs/Fusion)	Variant Classification	Oncogenic Effect#	Therapeutic / Clinica l Significance
APC	p.R564* (MAF 2.4%) p.Q1367*(MAF 7.07%)	Pathogenic	Likely oncogenic	Refer to pageno. 5
TP53	p.R213*(MAF 5.4%)	Pathogenic	Likely oncogenic	Refer to pageno. 6
GNAS	p.R201C (MAF 0.19%)	Pathogenic	Oncogenic	Refer to pageno. 6
TP53	p.A88V (MAF 0.25%)	VUS	Unknown oncogenic effect	---

SNA: Single Nucleotide Alteration; CNA: Copy Number Alteration; INDELS: Insertion / Deletion; VUS: Variant of unknown/uncertain signifi-cance

Oncogenic effect annotation is based on OncoKB.

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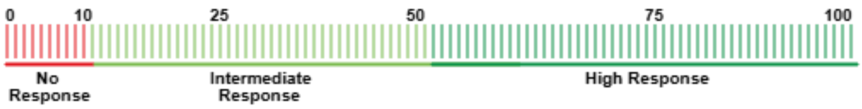
Response to Repurposed Drugs

Chemosensitivity

Drug Names	% Cell Death	Drug Response
Atorvastatin	67	
Chloroquine	63	
Aspirin	62	
Quercetin	62	
Celecoxib	62	
Fenbendazole	62	
Curcumin	60	
Diflunisal	58	
Dihydroberberine	57	
Resveratrol	54	
Doxycycline	54	
Epigallocatechin gallate	52	
Indol-3-carbinol	52	
Cannabidiol	52	
Genistein	50	
Bromelain	45	
Helixor M	41	
Helixor P	41	
Artesunate	40	
Ivermectin	40	
Helixor A	40	
Astaxanthin	37	
Iscador P	36	
Iscador Qu	34	
Metformin	28	
Mebendazole	27	
Vitamin C	25	
Melatonin	25	
DMSO	25	
Papain	25	
Niclosamide	21	
Salinomycin Sodium Salt	20	
Propranolol	15	
Valproic acid	11	
Chymotrypsin	10	
Dichloroacetate	10	
Calcitriol	< 10	
Glibenclamide	< 10	
Hydroxy Itraconazole	< 10	
Pantoprazole	< 10	
L-Citrulline	< 10	
Gymnema	< 10	

SCALE



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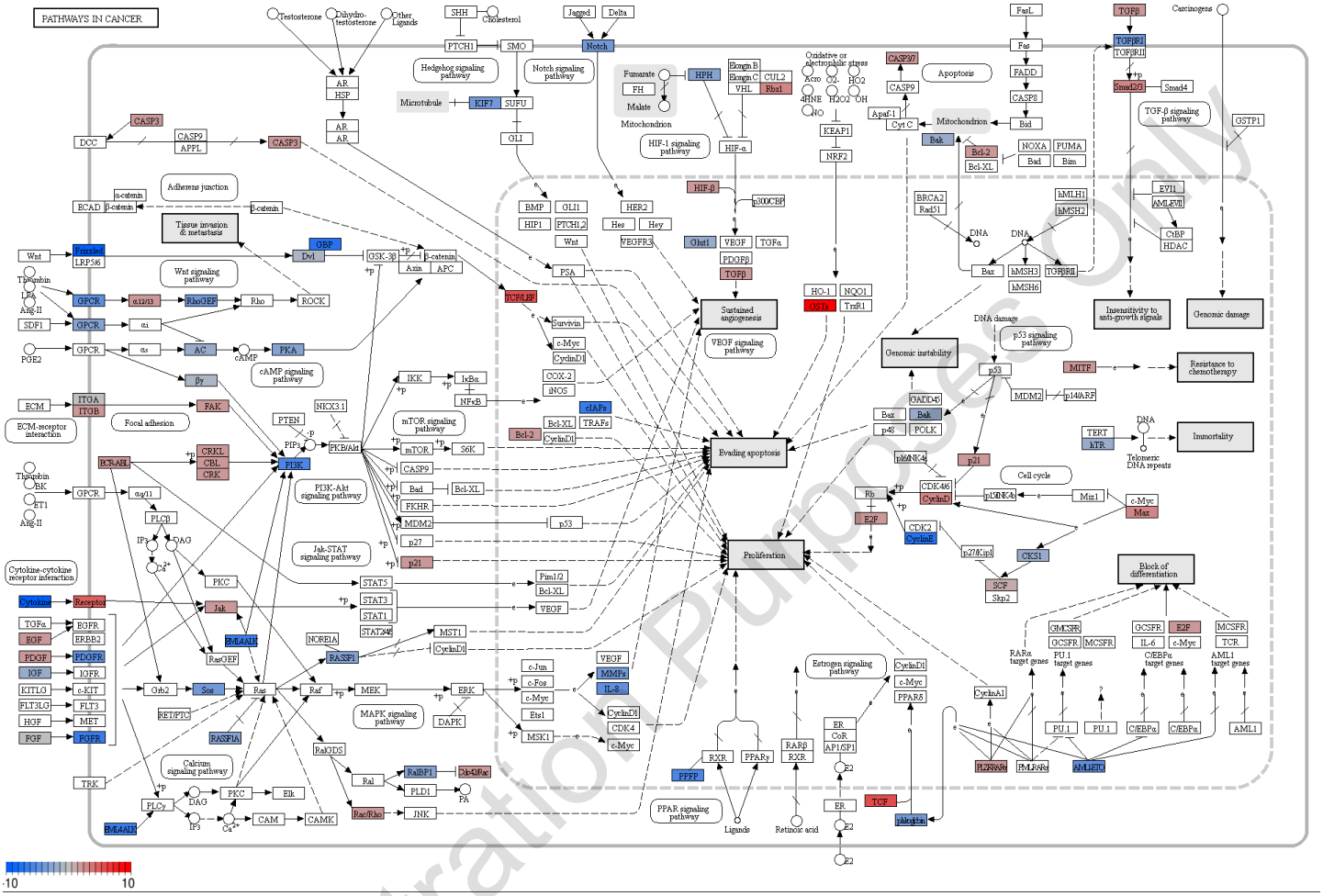
KEGG Pathway: 20802 Genes Analysis

KEGG Pathway

Comprehensive Pathway Perturbation in Primary Tumor



DATAR
CANCER GENETICS

KEGG Pathway: 20802 Genes Analysis

KEGG Pathway

Outof 20802 proteincoding genesanalyzed in the bloodsample, 7620 genes were expressed in the analyzedblood sample. 3604 genes were found to bedifferentially regulated in the blood sample.

Gene/s	Result (Fold change)	Drugs With Benefit
BCL2	▲ +2.93 FC	☑ Artesunate ☑ Curcumin ☑ Metformin ☑ Resveratrol ☑ Genistein ☑ Propolis ☑ Withania somnifera ☑ Boswellia serrata ☑ Annona muricata ☑ Moringa oleifera ☑ Asimina triloba ☑ Selenomethionine ☑ Menaquinone

Interpretation: In pre-clinical studies, Artesunate demonstrated anticancer activity by inducing apoptosis through downregulation of BCL2 gene (Wang et al., 2002; Yang et al., 2019).

In multiple tumor types, Curcumin induced autophagy, apoptosis and cell cycle arrest by downregulating BCL2 expression (Zhu and Bu, 2017; Yu et al., 2011; Rao et al., 2011; Yang et al., 2015).

Metformin induces apoptosis in cancer cells by downregulating BCL2 (Patel et al., 2015; Rangkuti et al., 2019).

Resveratrol is reported to exhibit anticancer activity by suppressing BCL2 expression in several cancer types (Cai et al., 2015; Varoni et al., 2016; Zadi Heydarabad et al., 2018).

Genistein is reported to exhibit anticancer activity by enhancing apoptosis in BCL2-overexpressing neuroblastoma cells, indicating its action is modulated by BCL2 expression levels (George et al., 2010).

Withania somnifera is reported to exhibit anticancer activity by modulating the SIRT1–BCL2/BAX pathway and inducing apoptosis in breast cancer models, even in the presence of BCL2 overexpression (Maarouf et al., 2023).

Boswellia serrata is reported to exhibit anticancer activity by altering the Bax/BCL2 ratio and promoting apoptosis in colon cancer cells (Trivedi et al., 2023).

Annona muricata is reported to exhibit anticancer activity by increasing the Bax/BCL2 ratio and inducing mitochondrial-mediated apoptosis in lung and breast cancer cells (Qazi et al., 2018).

Moringa oleifera is reported to exhibit anticancer activity by downregulating BCL2 expression and upregulating pro-apoptotic markers, leading to apoptosis (Kumar et al., 2023).

Asimina triloba is reported to exhibit anticancer activity by suppressing BCL2 expression and inducing apoptosis in gastric and cervical cancer cells (Nam et al.,2021).

Propolis is reported to exhibit cytotoxic activity in cancer cells; however, it showed no significant effect on BCL2 expression in HepG2 and 5637 cell lines (Sadeghi et al., 2015).

Selenomethionine is reported to protect cells from oxidative stress-induced apoptosis by preserving BCL2 expression and reducing ROS levels in trophoblast cell models (Khera et al., 2017).

Menaquinone is reported to exhibit anticancer activity by enhancing cytotoxicity in hepatocellular carcinoma cells when combined with BCL2 silencing, suggesting its potential in overcoming BCL2-mediated resistance (Yao et al., 2012).

Gene/s	Result (Fold change)	Drugs With Benefit
HMGB1	▲ +5.81 FC	☑ Chloroquine

Interpretation: In pre-clinical study, Chloroquine is reported to inhibit HMGB1-induced Iκ-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).

Gene/s	Result (Fold change)	Drugs With Benefit
MAP3K5 MAP4K2	▲ +2.88 FC +2.31 FC	☑ Atorvastatin ☑ Celecoxib ☑ Metformin ☑ Annona muricata ☑ Epigallocatechin gallate ☑ Quercetin ☑ Genistein ☑ Mebendazole

Interpretation: Atorvastatin induces apoptosis in multiple cancers by inhibiting MAPK-Bcl-2 signaling pathway (Reddy et al., 2006; Fromigue et al., 2006; Xiao et al., 2008; Bjarnadottir et al., 2013; Jones et al., 2018; Xu et al., 2018).

Several pre-clinical evidence demonstrates that Atorvastatin and Celecoxib and/or in combination, were more effective, than when given individually at higher doses. Inhibition of carcinogenesis by these agents is associated with the inhibition of cell proliferation and increase in apoptosis in tumor cells (Reddy et al, 2006; Xiao et al, 2008; Mármol et al, 2017; Huang et al., 2017; Li et al., 2018; Beckwitt et al., 2018; Ma et al., 2019).

Several studies have shown that Epigallocatechin-gallate (EGCG) demonstrated anti-tumor effect by suppressing MAPK pathway (Singh et al., 2011; Negri et al., 2018).

Pre-clinical studies have demonstrated that Mebendazole inhibits the growth of various cancer cells by targeting the MAPK pathway (Simbulan et al., 2017; Younis et al., 2019; Guerini et al., 2019).

Metformin exhibits anti-tumor activity in cancer cells by inhibiting the MAPK pathway (Lei et al., 2017).

Quercetin is reported to exhibit anticancer activity by inhibiting the expression of cyclin D1, P21, and Twist in gastric cancer cells, particularly through suppression of the P38MAPK pathway and reduction of P38MAPK phosphorylation (Zhang et al., 2017; Xie et al., 2025).

Acetogenins such as Annosquacin B and desacetyl uvaricin derived from Annona species have been reported to exhibit anticancer activity by modulating MAPK signaling pathways, including suppression of phosphorylation and inactivation of pathway components, leading to apoptosis and inhibition of tumor growth in multidrug-resistant breast and colorectal cancer cells (Zorofchian et al., 2015; Moghadamtousi et al., 2014; Niu et al., 2017; Qazi et al., 2018).

Genistein is reported to exhibit anticancer activity by modulating MAPK signaling through stabilization of its activation and phosphorylation via the RAS/RAF pathway, leading to cell cycle arrest and apoptosis in various cancer cell types (Banerjee et al., 2008; Kanzaki et al., 2008; Li et al., 2017; Javed et al., 2021).

Gene/s	Result (Fold change)	Drugs With Benefit
MMP	▲ +7.32 FC	☑ Atorvastatin ☑ Curcumin ☑ Resveratrol ☑ Doxycycline ☑ Cannabidiol ☑ Bromelain ☑ Artesunate ☑ Iscador P ☑ Iscador Qu ☑ Metformin ☑ Mebendazole ☑ Melatonin ☑ Berberine ☑ Lycopene ☑ Chymotrypsin ☑ Epigallocatechin gallate ☑ Boswellia serrata ☑ Scutellaria baicalensis ☑ Cordyceps sinensis ☑ Proanthocyanidins ☑ Ursolic Acid ☑ Salvia miltiorrhiza ☑ Pantoprazole

Interpretation: Mebendazole is found to inhibit invasion and migration of cancer cells by suppressing MMP activity (Pinto et al., 2015).

Metformin has been reported to block migration and invasion of tumor cells by inhibition of matrix metalloproteinase-9 (Hwang and Jeong, 2010).

Epigallocatechin-gallate (EGCG) is found to inhibit epithelial-mesenchimal transition (EMT) as well as cellular invasion in cancer cells by directly binding and downregulating collagenase activity of MMPs (Negri et al., 2018).

Artesunate inhibits invasion and metastasis in cancer cells through downregulating expression of MMPs (Rasheed et al., 2010; Wang et al., 2016; Ma et al., 2019).

Curcumin exerts antitumor activity in cancer cells through downregulating MMP activity (Hong et al., 2006; Kumar et al., 2012; Hassan and Daghestani, 2012; Cao et al., 2014; Bachmeier et al., 2018).

Cannabidiol showed anti-migratory and anti-invasive effects by inhibiting MMPs which in turn degraded the extra-cellular matrix (ECM), thus affecting metastasis of cancer to the distant organs (Chakravarti et al., 2014; Elbaz et al., 2015; Sharafi et al., 2019).

Multiple studies have shown that Resveratrol suppresses invasion and growth of cancer cells by inhibiting expression of MMPs (Yu et al., 2008; Weng et al., 2010; Ko et al., 2017).

Numerous studies have shown that Berberine and its derivatives demonstrate important anti-tumor effects. Berberine appears to exert its anticancer properties by inducing ROS production and prevention of cell migration via inhibition of the gene expression of MMP in various cancers (McCubrey et al, 2017; Li et al, 2018; Hu et al, 2019; Zhang et al, 2020).

The antibiotic agent, Doxycycline, non-selectively inhibits MMP activation and expression, and has been shown to suppress MMP activities in human cancer cells (Tang et al., 2013; Cathcart et al., 2015).

6-Shogaol is reported to inhibit cancer cell invasion by reducing MMP9 expression (Ling et al., 2010; Weng et al., 2010).

Bromelain is reported to reduce MMP9 expression significantly in acute ischemic stroke patients, suggesting its potential role in mitigating MMP9-mediated tissue damage (Sinurat et al., 2018).

Iscador P, a mistletoe extract with lower ML content, is under investigation for its potential to modulate MMP expression and inhibit cancer cell invasion. While ML-rich extracts like Iscador Qu downregulate MMP-2/-14, Iscador P's role remains of interest in ongoing metastasis-related research (Schotterl et al., 2017).

Iscador Qu, a mistletoe extract rich in mistletoe lectins, was shown to downregulate MMP2 and MMP14 expression in glioma cells, reducing tumor cell motility and invasion potential (Schotterl et al., 2017).

Melatonin demonstrated anti-metastatic effects in renal cell carcinoma by downregulating MMP-9 expression via inhibition of NF-κB signaling and modulation of Akt-JNK/ERK pathways, thereby suppressing tumor cell migration and invasion (Lin et al., 2016).

Pantoprazole has been shown to downregulate MMP-9 expression, suggesting potential anti-metastatic effects through inhibition of matrix degradation and cancer cell invasion pathways (Sayed et al., 2024).

Chymotrypsin-like serine proteases have been reported to activate pro-MMP-9, enhancing extracellular MMP-9 activity and potentially contributing to tumor invasion and metastasis via matrix remodeling (Yabluchanskiy et al., 2013).

Baicalein has been shown to downregulate MMP-2 and MMP-9 expression in lipopolysaccharide-induced cardiac injury models, suggesting its potential role in suppressing matrix degradation and inflammation-mediated tissue damage, mechanisms also relevant in cancer metastasis (Chen et al., 2014).

Boswellia serrata extract has been reported to suppress MMP-2 and MMP-9 expression in colon cancer cells, indicating its potential to inhibit tumor invasion and metastasis by targeting matrix degradation pathways (Trivedi et al., 2023).

Cordyceps sinensis-derived polysaccharide CME-1 has been shown to inhibit MMP-1 expression in melanoma cells by suppressing NF-κB and ERK/p38 MAPK signaling, thereby reducing cancer cell migration and metastatic potential (Jayakumar et al., 2014).

Lycopene has been shown to inhibit cigarette smoke-induced MMP-9 overexpression in macrophages and fibroblasts by blocking Ras prenylation and suppressing the MEK/ERK and NF- κB signaling pathways, suggesting potential anticancer and anti-inflammatory applications (Palozza et al., 2012).

Proanthocyanidins have shown significant potential in inhibiting matrix metalloproteinases (MMPs), which are enzymes involved in cancer metastasis, through various mechanisms including the suppression of MAPK and NF-κB signaling pathways. Grape Seed Proanthocyanidins have been found to inhibit the expression of MMP-2 and MMP-9 in human prostate carcinoma cells, which is associated with the inhibition of activation of MAPK and NFκB pathways (Yang et al, 2021). In tongue squamous cell carcinoma cells, GSPs inhibit migration and invasion by reversing epithelial-mesenchymal transition (EMT) through suppression of the TGF-β signaling pathway (Yang et al, 2017).

Salvia miltiorrhiza has shown potential in inhibiting matrix metalloproteinase-9 (MMP-9) expression and cancer cell invasion, particularly in breast cancer. Studies have demonstrated that Salvia miltiorrhiza extract (SME) can suppress TPA-induced MMP-9 expression and MCF-7 cell invasion by blocking the transcriptional activation of AP-1, a dimeric transcription factor involved in cancer progression (Jung et al, 2020). This effect is mediated through the MAPK/AP-1 signaling pathway, where SME reduces the phosphorylation of MAPKs such as ERK, JNK, and p38, and down-regulates phospho-c-Jun expression (Kim et al; 2017). In non-small cell lung cancer, methanol extract of Salvia miltiorrhiza inhibited cancer growth through the mitochondrial apoptotic pathway and PTEN-mediated inhibition of the PI3K/Akt pathway (Tian et al, 2021; Kim et al; 2017).

Ursolic acid has shown significant potential in targeting matrix metalloproteinases (MMPs) in various types of cancer, which are enzymes involved in the degradation of the extracellular matrix and play a critical role in cancer metastasis. Studies have demonstrated that ursolic acid can downregulate the expression and activity of MMP-2 and MMP-9, which are associated with cancer cell invasion and migration (Zong et al, 2022; Piet et al, 2022). Additionally, ursolic acid has been found to inhibit the uPA/uPAR-dependent MMPs pathway, further suppressing the migratory capacity of cancer cells. Ursolic acid targets multiple signaling pathways, including the Erk-VEGF/MMP-9 signaling pathways and polyamine metabolism, to exert its anti-metastatic effects (Zafar et al, 2022).

Gene/s	Result (Fold change)	Drugs With Benefit
FZD (+7.45FC)	▲ (+7.45FC) (+8.34 FC)	☑ Quercetin ☑ Celecoxib ☑ Artesunate

Interpretation: Quercetin inhibits cancer growth through inhibition of Wnt/β-catenin signalling pathway (Shan et al., 2009; Amado et al., 2011).

Celecoxib is one of the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs), which have chemo-preventive activity against cancers. It acts by down-regulating the Wnt pathway activity (Gong et al., 2012; Huang et al., 2017).

Artesunate reduces growth, migration and invasion through inhibiting activated Wnt pathway in multiple tumor cells (Li et al., 2007; Chen et al., 2017; Zheng and Pan, 2018).

Gene/s	Result (Fold change)	Drugs With Benefit
VEGFA	▲ (+3.12 FC)	☑ Aspirin ☑ Curcumin ☑ Astaxanthin ☑ Iscador P ☑ Iscador Qu ☑ Mebendazole ☑ Apigenin ☑ Fisetin ☑ Avemar ☑ Angiostop ☑ Ganoderma lucidum ☑ Panax Ginseng ☑ Proanthocyanidins ☑ Allium sativum ☑ Salvia miltiorrhiza ☑ Epigallocatechin gallate

Interpretation: Aspirin has been shown to affect vascular endothelial growth factor (VEGF) in various cancer models, potentially inhibiting tumor growth and metastasis. In clinical settings, aspirin has been associated with reduced circulating VEGF levels in tamoxifen-treated women, suggesting a potential benefit in modulating VEGF levels in breast cancer patients (Holmes et al, 2010). In addition, aspirin has been found to inhibit VEGF release from tumor cells, which is associated with suppressed angiogenesis. The mechanism involves the direct binding of aspirin to heparanase, an enzyme involved in cancer metastasis and angiogenesis, thereby inhibiting its enzymatic activity. This heparanase-dependent inhibition of VEGF release and angiogenesis suggests a potential therapeutic role for aspirin in cancer treatment (Dai et al, 2017; Zhang et al., 2019).

Curcumin has been shown to target vascular endothelial growth factor (VEGF) in various cancer models, demonstrating anti-angiogenic and anti-tumor effects. In hepatocellular carcinoma (HCC), curcumin inhibits tumor growth by reducing VEGF expression and the PI3K/AKT signaling pathway (Fu et al, 2015). In a VEGF over-expressing tumor model, curcumin inhibited tumor growth in a dose-dependent manner and improved anemia and extramedullary hematopoiesis in livers and spleens of tumor-bearing mice induced by tumor-derived VEGF (Pan et al, 2018). Curcumin's ability to target VEGF and its signaling pathways makes it a promising agent for cancer treatment, particularly in modulating the tumor microenvironment and improving therapeutic outcomes (Binion et al., 2008).

Epigallocatechin gallate (EGCG) has shown significant potential in targeting vascular endothelial growth factor (VEGF) in various cancers, including gastric and hepatocellular carcinoma. Studies indicate that EGCG inhibits cancer growth by suppressing VEGF production and angiogenesis, making it a promising candidate for anti-angiogenic cancer therapy. EGCG reduces VEGF production and angiogenesis by inhibiting the activation of signal transducer and activator of transcription 3 (Stat3) and modulating pathways such as MAPK/ERK1/2 and PI3K/AKT/HIF-1α/VEGF (Liao et al, 2020). Pre-clinical studies have demonstrated EGCG's potential in chemoprevention and therapy of HCC, with effects on oxidative stress, proliferation, invasion, migration, angiogenesis, apoptosis, and tumor metabolism (Li et al, 2023; Yu et al., 2025).

Astaxanthin has shown significant potential in targeting VEGF (vascular endothelial growth factor) in various cancer models, demonstrating anti-angiogenic and anti-tumor effects. Studies indicate that astaxanthin modulates VEGF expression and related pathways, which are critical for tumor growth and metastasis. For instance, in oral cancer models, astaxanthin significantly reduced VEGF and VEGFR2 expression, as well as HIF-1α nuclear translocation, leading to decreased tumor vessel formation (Kowshik et al, 2014). Similarly, in hepatocellular carcinoma, astaxanthin enhanced the efficacy of sorafenib by inhibiting the JAK2/STAT3 signaling pathway and reducing tumor hypoxia (Janani et al., 2021; Ren et al, 2023).

Iscador is known for its immunomodulating properties and has been used in anthroposophic medicine as a complementary cancer therapy. Clinical trials and systematic reviews suggest that Iscador may improve survival times in cancer patients, with some studies indicating a clinically relevant prolongation of survival. Additionally, some studies suggest that Iscador may enhance the body's self-regulation, potentially contributing to improved patient outcomes (Ostermann et al, 2009). While the specific impact of Iscador on VEGF is not detailed in the provided context, research has shown that mistletoe extracts, including Iscador, can induce apoptosis, stimulate immunocompetent cells, and protect DNA, which may indirectly affect VEGF-related pathways (G. Schaefermeyer and H. Schaefermeyer, 1998; Wode et al., 2020).

Iscador Qu, a mistletoe extract, has been studied for its potential antitumor effects in various cancer cell lines, including breast cancer. While specific information about its direct effect on VEGF (vascular endothelial growth factor) in cancer is not explicitly mentioned in the provided context, Iscador Qu has been shown to interfere with tumor angiogenesis, which is closely related to VEGF's role in promoting blood vessel formation in tumors (Srdic-Rajic et al, 2017). Additionally, Iscador Qu has been found to inhibit doxorubicin-induced senescence in MCF7 breast cancer cells, suggesting its potential to modulate cancer cell behavior and possibly influence factors like VEGF that contribute to tumor progression (Podlech et al., 2012; Robev et al, 2023).

Mebendazole has shown significant potential in targeting VEGF in various cancer models, demonstrating anti-angiogenic effects that inhibit tumor growth. Mebendazole inhibits VEGF expression and disrupts endothelial cell migration, impairing tumor vasculature (Elayapillai et al, 2022). In glioblastoma, mebendazole reduces microvessel density, creating a hypoxic environment that sensitizes cancer cells to apoptosis. A phase 2 randomized study evaluated the addition of mebendazole to lomustine (CCNU) or temozolomide (TMZ) in patients with recurrent GBM. The study found that the 9-month overall survival was 36.6% in the TMZ-MBZ arm and 45% in the CCNU-MBZ arm. However, the pre-set benchmark of 55%, 9-month OS was not achieved, possibly due to the inclusion of patients with poor performance status. (Elayapillai et al, 2022; Menon et al, 2022). Mebendazole significantly decreases VEGF levels, contributing to improved progression-free survival when combined with standard therapies in colorectal cancer (Sung et al., 2019; Hegazy et al, 2022).

Apigenin has been shown to inhibit the expression of vascular endothelial growth factor (VEGF) in various cancer cells, which plays a critical role in tumor angiogenesis and progression. Studies have demonstrated that apigenin reduces VEGF expression and secretion in lung, ovarian, breast, and other types of cancer cells (Liu et al, 2005; Fang et al, 2007; Shankar et al, 2017; Yan et al., 2017). In vivo studies have shown that apigenin significantly inhibited tumor growth and VEGF expression in tumor tissues, suggesting its potential as an anti-angiogenic agent (Liu et al, 2005; Yam et al, 2017; Wang et al., 2019; Naponelli et al., 2014).

Fisetin is a small phytochemical molecule with antitumor activity in multiple cancers. It significantly inhibited the proliferation of Y79 cells in a time- and dose-dependent manner. Fisetin also inhibited the migration and invasion of Y79 cells in a dose-dependent manner. Furthermore, Fisetin inhibited the expression of VEGFR in Y79 cells in a dose-dependent manner and tumor angiogenesis in vitro. Thus, Fisetin was found to inhibit angiogenesis via inhibition of the VEGF/VEGFR signaling pathway, and could be used as a candidate drug to inhibit angiogenesis in cancer cells (Wang et al., 2020; Zhou et al., 2023; Kim et al., 2023).

Ganoderma lucidum significantly inhibits the proliferation of human ovarian cancer cells by downregulating VEGF expression and upregulating connexin 43 (Cx43). Knockdown of Cx43 reverses its antiproliferative effect, highlighting its VEGF-Cx43-mediated mechanism in ovarian cancer (Dai et al., 2014).

Fermented ginseng (GFPL), enriched with anti-angiogenic ginsenosides RG3, RH1, and RH2, demonstrated significant downregulation of VEGF expression and tumor growth inhibition in lung cancer models, suggesting potent anti-angiogenic and anti-cancer effects via VEGF pathway suppression. Additionally, compounds like ginsenoside Rb1 and Rg1 from Panax ginseng have shown regulatory effects on VEGF/VEGFR signaling, supporting ginseng's role in modulating angiogenesis in cancer and ischemic conditions (Xiong et al., 2022; Song et al., 2023).

Grape seed proanthocyanidins (GSPs) have been shown to inhibit colon tumor growth and angiogenesis by suppressing VEGF and Ang1 expression in tumor cells and blocking endothelial cell migration, without causing toxicity. This effect is primarily mediated via ROS scavenging, leading to downregulation of the ROS/HIF-1α/VEGF-Ang1 axis, thereby interfering with both angiogenesis initiation and blood vessel maturation. These findings support the potential use of GSPs as a local, non-toxic antiangiogenic agent in colon cancer therapy (Huang et al., 2012).

Allium sativum (Garlic-derived extracts), including thiosulfinate-enriched (TASE) and stem extract (ASE), have been shown to downregulate VEGF expression by modulating the HIF-1α pathway in septic monocytes and suppressing VEGF mRNA in melanoma cells, indicating their anti-angiogenic and anti-cancer potential (Gam et al., 2022). Additionally, garlic-derived small extracellular vesicles (SEVs) significantly reduced VEGF protein levels in lung and kidney carcinoma cells, supporting garlic's role in inhibiting tumor angiogenesis across multiple models (Ozkan et al., 2021; Avendano-Ortiz et al., 2023).

Salvia miltiorrhiza (Danshen), particularly its active compound tanshinone IIA, suppresses VEGF and VEGFR2 expression, thereby inhibiting angiogenesis and proliferation in A549 lung cancer cells. It also induces apoptosis and S-phase cell cycle arrest. Additionally, Danshen extracts (ESM, DSS, Sal B) reduce VEGF-mediated endothelial permeability by modulating ERK signaling, highlighting its dual anti-angiogenic and anti-inflammatory potential in cancer therapy (Ding et al., 2005; Xie et al., 2015).

AVEMAR (Fermented Wheat Germ Extract) demonstrated anti-angiogenic activity by inhibiting VEGF and COX-2 gene expression in various cancer cell lines (NCI-N87, PC3, HeLa, and A549), thereby reducing angiogenesis and potentially limiting tumor metastasis. This mechanism aligns with known anti-angiogenic effects of polyphenol-rich compounds observed in both in vitro and in vivo models (Imir et al., 2018, Zhurakivska et al., 2018).

Philinopside A, a sulfated saponin from sea cucumber, exhibited potent anti-angiogenic and anti-tumor effects by inhibiting endothelial proliferation, migration, and tube formation in vitro and in vivo. These effects were mediated through broad inhibition of angiogenesis-related receptor tyrosine kinases, including VEGFR, FGFR1, PDGFR-β, and EGFR, contributing to tumor suppression via endothelial and tumor cell apoptosis (Tong et al., 2005).

Gene/s	Result (Fold change)	Drugs With Benefit
WNT	▲ +7.45 FC	☑ Artesunate ☑ Celecoxib ☑ Resveratrol ☑ Genistein ☑ Niclosamide ☑ Beta-Carotene ☑ Capsaicin ☑ Quercetin ☑ Salinomycin Sodium Salt ☑ NSAIDs (Ibuprofen/ Sulindac)

Interpretation: Artesunate reduces growth, migration and invasion through inhibiting activated Wnt pathway in multiple tumor cells (Li et al., 2007; Chen et al., 2017; Zheng and Pan, 2018).

Celecoxib is one of the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs), which have chemo-preventive activity against cancers. It acts by down-regulating the Wnt pathway activity (Gong et al., 2012; Huang et al., 2017).

Resveratrol exerts antitumor effects in Wnt-overexpressing cancers by disrupting the β-catenin/TCF4 transcriptional complex, downregulating Wnt target genes such as cyclin D1, and suppressing cancer stem cell renewal and proliferation. These effects have been demonstrated in colorectal and breast cancer models, highlighting its potential as a therapeutic agent targeting aberrant Wnt/β-catenin signaling (Fu et al., 2015; Liu et al., 2017).

Genistein suppresses aberrant Wnt/β-catenin activation in colorectal and renal cancer models by demethylating Wnt antagonist genes (such as sFRP2) and downregulating oncogenic miR-1260b, leading to reduced nuclear β-catenin levels, decreased expression of targets like cyclin D1/c-Myc, and inhibition of proliferation and invasion (Zhang et al., 2011).

Niclosamide has shown potential as a therapeutic agent for solid tumors with Wnt overexpression by targeting the Wnt/β-catenin signaling pathway. Studies have demonstrated that niclosamide inhibits Wnt/β-catenin signaling in various cancer types, including colorectal, ovarian, breast, and retinoblastoma, by suppressing the expression of Wnt pathway receptors like LRP6 and by promoting the degradation of β-catenin (Osada et al, 2011; Arend et al, 2018; Jiang et al, 2022). In colorectal cancer, Niclosamide has been shown to inhibit Wnt/β-catenin pathway activation, regardless of APC mutations, and exert antiproliferative effects in both cell lines and xenograft models (Osada et al, 2011). Similarly, in ovarian cancer, niclosamide and its analogs have been found to inhibit Wnt/β-catenin, mTOR, and STAT3 signaling, targeting chemoresistant cells and cancer stem cells (CSCs) (Osada et al, 2011).

Salinomycin sodium salt is a potent inhibitor of Wnt/β-catenin signaling, which is particularly relevant in the context of Wnt overexpression in solid tumors. It acts on the Wnt/Fzd/LRP complex, blocking Wnt-induced LRP6 phosphorylation and causing degradation of the LRP6 protein. In studies involving gastric cancer, Salinomycin has been shown to inhibit the proliferation of CD44+Oct4+ CSC subpopulations by suppressing Wnt1 and β-catenin expression. This inhibition was observed in vivo, where Salinomycin significantly reduced the tumor volume caused by Wnt1-overexpressing cell lines (Mao et al, 2014). Similarly, in colorectal cancer, salinomycin has been found to interfere with Wnt/β-catenin signaling, leading to reduced expression of Wnt target genes such as Fibronectin and Lgr5, which are involved in tumor growth and metastasis (Klose et al, 2016).

In a preclinical study, beta-carotene (BC) treatment inhibited Wnt/β-catenin signaling and reduced cancer stem cell (CSC) markers such as CD44, CD133, and ALDH1A1 in colon cancer cell lines and xenograft models and also suppressed tumor formation, delayed onset, highlighting its potential in targeting Wnt-driven colon cancer stemness (Lee et al., 2022).

In a clinical study, treatment of Ibuprofen and Sulindac inhibited Wnt/β-catenin pathway activation by reducing nuclear β-catenin accumulation and promoting its phosphorylation in colon adenoma cells. This suppression of Wnt overexpression led to decreased expression of downstream oncogenic targets like cyclin D1, highlighting the potential of these NSAIDs in mitigating Wnt-driven tumorigenesis in colorectal cancer (Greenspan et al., 2011).

Capsaicin suppresses Wnt/β-catenin signaling by reducing β-catenin mRNA and protein levels, enhancing its proteasomal degradation, and disrupting β-catenin/TCF-1 complex formation, leading to downregulation of oncogenic targets like c-Myc and cyclin D1 (Lee et al., 2012; Pramanik et al., 2015).

Quercetin inhibits cancer growth through inhibition of Wnt/β-catenin signalling pathway (Shan et al., 2009; Amado et al., 2011).

Gene/s	Result (Fold change)	Drugs With Benefit
PTGS2 (COX2)	▲ +3.81 FC	☑ Aspirin ☑ Bromelain ☑ Melatonin ☑ Diflunisal ☑ Boswellia serrata ☑ Moringa oleifera ☑ Nigella sativa ☑ Rubus occidentalis ☑ NSAIDs (Ibuprofen/ Sulindac) ☑ Celecoxib ☑ Resveratrol ☑ Ellagic Acid

Interpretation: Several clinical and pre-clinical studies, treatment of Aspirin showed improves clinical outcome and significant tumor reduction in cancer cells in COX-2 expression (Chan et al., 2007; Morgan et a., 2009; Ramzy et al., 2010; Langley et al., 2011; Ng et al., 2015; Patrignani et al., 2015). Abundant data show that low-dose aspirin therapy after a diagnosis of CRC decreases the risk of recurrence and death (Bains et al., 2016). Daily aspirin intake is recommended in colorectal cancer survivors for secondary prevention as per NCCN colon and rectal cancer guidelines (NCCN guidelines, 2025).

Pre-clinical studies suggest that low doses of Celecoxib and/or in combination with several regimens or chemotherapy show minimal additional toxicity and may enhance the effects of chemotherapy (Arun et al, 2004; Chow et al, 2005; Liu et al, 2011; De Cremoux et al, 2018).

Pre-clinical studies reported that, Bromelain inhibits COX-2 expression and enhances the anti-tumor effects of chemotherapy (Bhui et al., 2009; Mohamad et al., 2019).

Preclinical studies showed that, Resveratrol inhibit carcinogenesis in tumors by targeting COX-2 expression (Sexton et al., 2006; Zykova et al., 2008).

In preclinical studies, melatonin was shown to suppress COX-2 expression and enhance apoptosis in hepatocellular carcinoma models, thereby promoting tumor regression and boosting the efficacy of cisplatin (Nabih et al., 2023). Additionally, melatonin enhanced the antitumor effect of curcumin by inhibiting the IKK β/NF-κB/COX-2 signaling pathway (Shrestha et al., 2017).

In preclinical models, acetyl 11 keto β boswellic acid (AKBA), derived from Boswellia serrata, significantly downregulated COX 2 expression and inhibited PGE_2 synthesis, thereby suppressing tumor growth, inflammation, and metastasis in colorectal and gastric cancer models. These antineoplastic effects were linked to modulation of PI3K/Akt/COX 2 and NF κB signaling pathways and induction of apoptosis across multiple cancer cell types (Yadav wt al., 2012; Sun et al., 2020).

NSAIDs like sulindac and ibuprofen exhibit antitumor activity primarily via COX-2 inhibition, reducing prostaglandin-driven inflammation, proliferation, and angiogenesis. However, their long-term use is limited by COX-2–associated toxicities (Gurpinar et al., 2013).

Moringa oleifera exhibits potent anticancer activity by suppressing COX 2 overexpression and its downstream Wnt/β catenin and NF κB signaling pathways, leading to reduced proliferation, migration, and enhanced apoptosis in prostate and pancreatic cancer models. Its combined use with ionizing radiation further enhances tumor suppression, supporting its potential as a COX 2-targeted therapeutic strategy (Hagoel et al., 2019; Xie et al., 2021).

Nigella sativa, particularly its active compound thymoquinone (TQ), has been shown to inhibit COX-2 overexpression, a pro-inflammatory enzyme commonly upregulated in various cancers. By suppressing COX-2 expression, N. sativa reduces inflammation, oxidative stress, and tumor-promoting signaling pathways. This anti-inflammatory and antioxidant effect contributes to its potential anticancer activity, particularly in cancers where COX-2 drives proliferation, angiogenesis, and resistance to apoptosis (Al Wafai et al., 2013).

In a preclinical study, Rubus occidentalis also known as Black Raspberry Extract (BRE) significantly suppressed COX-2 expression, NF-κB activation, and PGE2 production in TNF-α/IL-1β-stimulated esophageal endothelial cells, thereby reducing inflammation and angiogenesis associated with esophageal cancer (Medda et al., 2014).

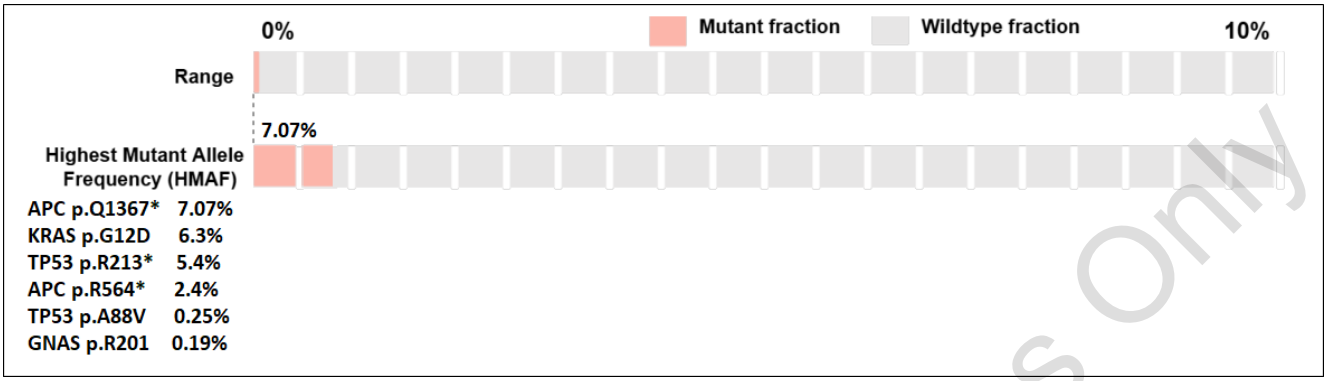
In a preclinical study, ellagic acid (EA), a bioactive compound from Nigella sativa, suppressed COX-2, COX-1, and oncogenic markers including c-Myc, Snail, and Twist1, leading to reduced acidity-enhanced migration and invasion of gastric cancer cells (Lim et al., 2019; Smyth et al., 2020). These results suggest EA's therapeutic potential in targeting inflammation-associated gastric cancer progression.

In this pre-clinical study, novel Diflunisal-based thiosemicarbazide and triazole compounds were tested for anticancer effects across multiple cancer cell lines. Compounds 15 and 16 showed selective activity against COX-2–overexpressing breast (T47D) and prostate (PC-3) cancer cells, with minimal toxicity in normal kidney cells (HEK-293). Molecular docking revealed strong COX-2 binding affinity, suggesting these compounds may act as selective COX-2 inhibitors with potential anticancer properties (Coskun et al., 2018).

Cell Free Nucleic Acids: Somatic Genome Alterations

Genomic Findings

Highest Mutant Allele Frequency



1. Highest mutant allele frequency of 7.07% was detected in the cell free nucleic acids isolated from patient's plasma.
2. Activating KRAS p.G12D mutation is suggestive of resistance to single agent anti-EGFR antibody therapies, Cetuximab, Panitumumab, Necitumumab and potential benefit from MEK inhibitors, Trametinib, Cobimetinib, Binimetinib as well as nonconventional drugs Atorvastatin, Hydroxychloroquine and Metformin.
3. APC loss-of-function mutations are suggestive of potential benefit from non-conventional drugs, Quercetin and Celecoxib.
4. Mutations in APC and TP53 genesare indicativeof an adverseprognosis in rectal cancer.
5. The clinical significance of GNAS p.R201C and TP53 p.A88V variants in rectal cancer is not yet known, as per available literature.

Genomic Findings

Single Nucleotide Alterations / Indels / Copy Number Alterations / Fusion

Markers (Transcript ID)	Variant	Category:
KRAS (NM_033360.4)	c.35G>A, p.G12D; [p.(Gly12Asp)]	Tier I (Level A)

Interpretation: Mutations in KRAS gene, mostly found in codons 12 and 13 are reported in approximately 45% of colorectal tumors (Neumann et al, 2009; Zocche et al, 2015; Modest et al, 2016; Li et al., 2020; Rahman et al., 2021). These mutations are associated with an adverse prognosis in colorectal cancer patients (Zocche et al, 2015; Andreatos et al, 2016; Jones et al, 2017; Li et al., 2020).

Studies suggest that tumors harboring mutations in KRAS exons 2, 3, or 4, predict resistance to single agent anti-EGFR antibody therapies, Cetuximab, Panitumumab and Necitumumab as well as lack of response to anti-EGFR tyrosine kinase inhibitors (De Roock et al., 2010; Wheeler et al., 2010; Janakiraman et al., 2010; Douillard et al., 2013; Ciardiello et al., 2014; Peeters et al., 2014; Tejpar et al., 2014; Stintzing et al., 2014; Stewart et al., 2015; Schirripa et al., 2015; Karthaus et al., 2016; Zhao et al., 2017). Also, mutations in KRAS gene are suggestive of less responsiveness to HER2-directed monotherapies Trastuzumab, Pertuzumab, Lapatinib, Neratinib and Tucatinib in HER2 positive tumors (Shinozaki et al., 2016; Patra et al., 2017; Siena et al., 2018).

A clinical study has reported that treatment with Oxaliplatin based therapies in KRAS mutated colorectal cancer patients resulted in longer progression free survival (PFS) as compared to KRAS wild type patients (Lin et al, 2013). However, in another study longer PFS was observed in KRAS wild type patients treated with Oxaliplatin based therapies (Soeda et al., 2014). Therefore, benefit from Oxaliplatin, based on KRAS mutation status cannot be conclusively determined.

Few reports suggest beneficial activity of Bevacizumab combined with chemotherapy in RAS-mutated colorectal cancer (Yeatman et al., 2018; Yone et al., 2019). However, few studies indicate less response for Bevacizumab treatment in RAS mutant colorectal cancer (Kubackova et al., 2015; Zhou et al., 2016; Sun et al., 2017). Therefore, benefit from Bevacizumab, based on KRAS mutation status cannot be conclusively determined.

Mutant KRAS is found to activate PI3K/PDK1/AKT as well as RAS/RAF/MAPK pathways and therefore is suggestive of potential therapeutic benefit from MEK inhibitors, Trametinib, Binimetinib, Cobimetinib, Avutometinib + Defactinib and Selumetinib (Ascierto et al., 2013; Blumenschein et al., 2015; Wu and Park, 2015; Iriana et al., 2016; Zeitouni et al., 2016; Dummer et al., 2017; Lemstrova et al., 2017; Han et al., 2018; Grisham et al., 2019).

MEK inhibitors such as Trametinib, Cobimetinib, Binimetinib and Selumetinib, are standard of care drugs for histiocytic neoplasms harboring MAP kinase pathway gene (BRAF, ARAF, NRAS, KRAS, MAP2K1/2) mutations as per NCCN guidelines (Histiocytic Neoplasms- NCCN guidelines, 2025).

The USFDA grants accelerated approval to the combination of Avutometinib and Defactinib for KRAS-mutated recurrent low-grade serous ovarian cancer.
In a pre-clinical, Avutometinib,in combination with the anti-EGFR antibody Cetuximab showed anti-tumor activity in colorectal cancer patient-derived xenograft (PDX) models harboring KRAS mutations (Chongkai et al., 2023).

Trametinib, used alone or with Dabrafenib is USFDA approved for the treatment of BRAF V600E positive anaplastic thyroid and non-small cell lung cancer as well as BRAF V600E or V600K positive unresectable or metastatic melanoma.
In a study of Cetuximab in combination with Trametinib in patients with KRAS mutant tumors (n=9) including colorectal cancer, the combination showed significantly longer progression-free survival as compared to previous lines of treatments in KRAS exon 2 mutation positive patients (Ledys et al., 2019).

Cobimetinib is a USFDA approved kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with Vemurafenib.
In a study, treatment of Cobimetinib and Atezolizumab in 22 KRAS mutant and 1 KRAS wild type colorectal cancer patients was well tolerated and showed overall response rate of 17% (Bendell et al., 2016).

Binimetinib in combination with Encorafenib is USFDA approved for the treatment of BRAF V600E or V600K positive unresectable or metastatic melanoma and non-small cell lung cancer.
In a case study, treatment of Binimetinib, Hydroxychloroquine and Bevacizumab demonstrated 17% reduction in the size of tumor lumps in a patient with KRAS p.G12D-mutated colorectal cancer (Orlov et al., 2020).

Selumetinib is USFDA approved for the treatment of neurofibromatosis type 1 pediatric patients with symptomatic, inoperable plexiform neurofibromas.
In a phase II study, Selumetinib plus Irinotecan as second-line therapy in patients with exon 2 KRAS mutated colorectal cancer, demonstrated partial response in 3 and stable disease for >4 weeks, (including three >1 year) in 16 of 31 evaluable patients (Hochster et al., 2015). However, in view of limited benefit offered by Selumetinib, the efficacy of Selumetinib in KRAS mutated colorectal cancer can not be conclusively determined.

The USFDA has granted accelerated approval to Sotorasib and Adagrasib as the first targeted therapy for patients with colorectal and non-small cell lung cancer whose tumors express a KRAS G12C mutation and who have received at least 1 prior therapy for their disease.
However, Sotorasib and Adagrasib are specific KRAS G12C inhibitor resulting in apoptosis only in KRAS G12C tumor cells.

A high-affinity therapeutic antisense oligonucleotide inhibitor of KRAS, AZD4785 is reported to selectively deplete cellular KRAS mRNA and protein, resulting in inhibition of downstream effector pathways and antiproliferative effects selectively in KRAS mutant cells (Ross et al., 2017).

The USFDA has granted a Fast Track Designation to Onvansertib for the second-line treatment of patients with KRAS-mutant metastatic colorectal cancer (mCRC) in combination with FOLFIRI (5-Fluorouracil, Leucovorin, and Irinotecan) and Bevacizumab (Avastin).
In a phase Ib/II study of the polo-like kinase 1 (PLK1) inhibitor, Onvansertib, in combination with FOLFIRI and Bevacizumab for second line treatment of KRAS-mutated metastatic colorectal cancer, the drug demonstrated partial response in 4 and stable disease with 4 of 9 evaluable patients with a median progression-free survival of >6 months (Ahn et al., 2020).
In a phase 1b/2 trial of the PLK1 inhibitor Onvansertib in combination with FOLFIRI-bev in second line treatment of KRAS- mutated (mKRAS) metastatic colorectal carcinoma (n=44) showed overall survival rate of 36% (Lenz et al., 2022).

Activating KRAS mutation is suggestive of potential benefit from investigational drug, RMC-6236. It is an orally available, smallmolecular inhibitor of RAS.

In a mouse clinical trial of RMC-6236 with KRAS G12X-mutant models of non-small cell lung cancer (n=15), pancreatic ductal adenocarcinoma (n=18) and colorectal cancer (n=18), the objective response rate was 53% (8/15), 61% (11/18) and 44% (8/18), respectively (Koltun et al., 2022).
A multicenter open-label study of RMC-6236 in patients with advanced solid tumors harboring specific mutations in RAS, is currently recruiting participants (NCT05379985).

MRTX-1133 is an orally available, small-molecule inhibitor of KRAS G12D.
In vivo studies with KRAS p.G12D-mutant pancreatic ductal adenocarcinoma mouse xenograft models demonstrated antitumor activity to MRTX-1133 as measured by complete or near-complete remissions following treatment (Kemp et al., 2023).

Escape of RAS/RAF-mutated tumors from MEK inhibition is mediated by autophagy. The use of Hydroxychloroquine, a known pharmacological downregulator of autophagy, is reported to potentiate antitumor activity of MEK inhibitors in pre-clinical as well as clinical studies with KRAS-mutated tumors (Wolpin et al., 2014; Amaravadi et al., 2016; Kinsey et al., 2019; Xavier et al., 2020).

KRAS mutations result in activation of the MAPK pathway and are thereby associated with potential benefit from non-conventional drug, Atorvastatin (Mohammed et al., 2012; Hymowitz and Malek, 2018) and Metformin (Iglesias et al., 2013; Chen et al., 2017; Xie et al., 2020).

Several studies have reported that KRAS mutated tumors are associated with better outcomes from immune checkpoint inhibitors (ICIs) (Torralvo et al., 2019; Herbst et al., 2019; Mazieres et al., 2020; Brueckl et al., 2020; Amanam et al., 2020; Fu et al., 2021).
A clinical trial on pooled mutant KRAS-targeted long peptide vaccine combined with Nivolumab and Ipilimumab for patients with resected MMR-p colorectal cancer, is currently recruiting participants (NCT04117087).

KRAS p.G12D is an oncogenic (ClinVar, OncoKB), gain-of-function mutation (OncoKB). It lies within a GTP binding region of the KRAS protein. This mutation results in decreased KRAS GTPase activity and increased activation of downstream signaling in cell culture (Modest et al., 2013). In silico analysis also predicts this variant to be a pathogenic, gain-of-function mutation.

The KRAS gene provides instructions for making a protein called K-RAS that is involved primarily in regulating cell division. As part of a signaling pathway known as the RAS/MAPK pathway, the protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide or to mature and take on specialized functions, like differentiation. It belongs to a class of genes known as oncogenes.

Markers (Transcript ID)	Variant	Category:
APC (NM_000038.6)	c.1690C>T, p.R564*; [p.(Arg564Ter)] c.4099C>T, p.Q1367*; [p.(Gln1367Ter)]	Tier I (Level B)

Interpretation: Inactivating APC mutations are reported frequently in rectal cancer and associated with an adverse prognosis (Aoki and Taketo, 2007; Kwong and Dove, 2009; Van den Broek et al., 2016; Zhang and Shay, 2017; Liu et al., 2018; Aghabozorgi et al., 2019). APC loss stabilizes beta-catenin and constitutively activates the Wnt pathway even in the absence of a WNT signal and therefore it is suggestive of potential benefit from non-conventional drugs, Quercetin and Celecoxib (Rubinfeld et al, 1997; Hankey et al, 2018; Neamtu et al., 2022).

Pre-clinical studies reported that Quercetin inhibits cancer growth through inhibition of Wnt/beta-catenin signalling pathway (Shan et al., 2009; Amado et al., 2011).

Celecoxib is one of the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs), which has chemo-preventive activity against cancers. It acts by down-regulating the Wnt pathway activity (Gong et al., 2012; Egashira et al., 2017; Huang et al., 2017).

APC p.R564* results in a premature truncation of the APC protein at amino acid 564 of 2843. It is predicted to result in a loss of APC protein function like other truncation mutations downstream of R564 (Smits et al., 1999; Azzopardi et al., 2008). APC p.Q1367* results in a premature truncation of the APC protein at amino acid 1367 of 2843 (Reinhart et al., 2016; Hochman et al., 2017). In silico analysis predicts this variant to be a loss-of-function mutation. APC p.R564* is reported in tumors of large intestine, small intestine, thyroid and skin. APC p.Q1367* is reported in tumors of large intestine and lung.

This gene encodes a tumor suppressor protein that acts as an antagonist of the WNT signaling pathway. It is also involved in other processes including cell migration and adhesion, transcriptional activation, and apoptosis. This protein also helps ensure that the number of chromosomes in a cell is correct following cell division.

Markers (Transcript ID)	Variant	Category:
TP53 (NM_000546.5)	c.637C>T, p.R213*; [p.(Arg213Ter)]	Tier I (Level B)

Interpretation: Approximately half of all colorectal cancers show TP53 gene mutations, with higher frequencies observed in distal colon and rectal tumors and lower frequencies in proximal tumors and those with the microsatellite instability or methylator phenotypes (Iacopetta, 2003; Sakai et al., 2016; Michel et al., 2021). Dysregulation of TP53 tumor suppressor gene is one of the most frequent events contributing to the transformation of colorectal cancer (CRC), as well as the aggressive and metastatic features of CRC. Also, CRC patients with mutant TP53 appear to be more chemo resistant than those with wild type TP53 (Li et al., 2015; Chow et al., 2016).

TP53 p.R213* is a likely oncogenic, loss-of-function mutation (OncoKB). Truncating mutations of TP53 occur throughout the gene and lead to the production of several C-terminally truncated protein forms. These alterations are predicted to be inactivating and are associated with poor prognosis (Bullock et al., 2001; Di Giammarino et al., 2002; Kawaguchi et al., 2005; Holstege et al., 2009; Lindenbergh-van et al., 2011). It results in a premature truncation of the TP53 protein at amino acid 213 of 393. It results in increased proliferation, migration, invasion, and TP53 protein stability in culture (Feng et al., 2023), and due to the effects of truncation mutations downstream of R213 (Kharaziha et al., 2019; Tong et al., 2021), is predicted to lead to a loss of TP53 protein function. In silico analysis also predicts this variants to be loss-of-function mutations.

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".

Markers (Transcript ID)	Variant	Category:
GNAS (NM_000516.7)	c.601C>T, p.R201C; [p.(Arg201Cys)]	Tier II (Level D)

Interpretation: GNAS mutations are reported in colorectal cancer (Zauber et al., 2016; Domingo et al., 2018). Activating GNAS mutations result in elevated cAMP and ERK/MAPK activation. Activation of MAPK pathway is suggestive of potential benefit from MEK inhibitors Trametinib, Cobimetinib, Selumetinib and Binimetinib (Wilson et al., 2010; Komatsu et al., 2014; Ang et al., 2017). However, efficacy of Cobimetinib, Selumetinib and Binimetinib in GNAS mutated tumors is not well evaluated.

Kindly refer to USFDA labels and/or studies of Trametinib mentioned earlier.

Trametinib in a patient with appendiceal adenocarcinoma with a GNAS p.R201C mutation showed clinical benefit including an improvement in quality of life (Ang et al., 2017).

However, efficacy of Trametinib in GNAS p.R201C mutated colorectal cancer is not well evaluated..

GNAS gain-of-function variants result in elevated cAMP and ERK/MAPK activation (Wilson et al., 2010). Aberrant activation of MAPK signaling, is known to confer clinical resistance to anti-EGFR-based therapy, Cetuximab, Panitumumab and Necitumumab (Ozawa et al., 2017; Miyamoto et al., 2017).

GNAS p.R201C is an oncogenic, gain-of-function mutation (OncoKB), located in the switch I domain of the protein. Expression of this mutation in a transgenic mouse model for intestinal cancer demonstrated that it is activating as measured by increased intestinal adenoma formation compared to wildtype (Wilson et al., 2010). In silico analysis also predicts this variant to be a gain-of-function mutation.

The GNAS gene provides instructions for making one component, the stimulatory alpha subunit, of a protein complex called a guanine nucleotide-binding protein (G protein). The G protein made with the subunit produced from the GNAS gene helps stimulate the activity of an enzyme called adenylate cyclase.

Blood Based Analysis

Variant Allele Fraction and Coverage

Variant (Transcript ID)	Genomic co-ordinates	Allele fraction	Coverage (X)
APC (NM_000038.6) c.1690C>T, p.R564*	chr5: 112164616C>T	2.4	1016
APC (NM_000038.6) c.4099C>T, p.Q1367*	chr5: 112175390C>T	7.07	53744
TP53 (NM_000546.5) c.637C>T, p.R213*	chr17: 7578212G>A	5.4	2561
GNAS (NM_000516.7) c.601C>T, p.R201C	chr20: 57484420C>T	0.19	1719
TP53 (NM_000546.6) c.263C>T, p.A88V	chr17: 7579424G>A	0.25	57788
KRAS (NM_033360.4) c.35G>A, p.G12D	chr12: 25398284C>T	6.3	1719

Criteria for Classification of Somatic Variants

Analysis Criteria

The criteria/guidance used in this report is in accordance with the guidelines provided by the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists (AMP/ASCO/CAP) 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).

The 'oncogenic effect' categories in this report are derived from OncoKB and reflect each variant's predicted role in cancer as oncogenic, likely oncogenic, likely neutral, or inconclusive/unknown.

Tier I: Variants/biomarkers with strong clinical significance (therapeutic, prognostic and/or diagnostic) Level A evidence: FDA approved therapies or standard guidelines fora 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 consensusamongdifferent 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.

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Drugs List

Drug List

Atorvastatin, Chloroquine, Aspirin, Quercetin, Celecoxib, Fenbendazole, Curcumin, Diflunisal, Dihydroberberine, Resveratrol, Doxycycline, Epigallocatechin gallate, Indol-3-carbinol, Cannabidiol, Genistein, Bromelain, Helixor M, Helixor P, Artesunate, Ivermectin, Helixor A, Astaxanthin, Iscador P, Iscador Qu, Metformin, Mebendazole, Vitamin C, Melatonin, DMSO, Papain, Niclosamide, Salinomycin Sodium Salt, Propranolol, Valproic acid, Beta-Carotene, Berberine (Goldenseal/Berberis), Boswellia serrata (Frankincense), Apigenin, NSAIDs (Ibuprofen, Sulindac), Fisetin, Propolis (Bee Resin), Ganoderma lucidum (Reishi), Selenomethionine (Selenium), Statins, Withania somnifera (Ashwagandha), Scutellaria baicalensis (Baicalein), Capsaicin (Chili Pepper), Cordyceps sinensis, Annona muricata (Graviola), Moringa oleifera, Nigella sativa (Black Seed), Panax Ginseng, Asimina triloba (Pawpaw Extract), Proanthocyanidins (Grape Seed Extract), Ursolic Acid (Apple Peel), α-Tocopherol (Vitamin E), Menaquinone (Vitamin K2), Hydroxychloroquine, Allium sativum (Garlic), Lycopene, Salvia miltiorrhiza (Danshen), Avemar (Fermented Wheat Germ Extract), Rubus occidentalis (Anthocyanins), D-Limonene, Ellagic Acid (Pomegranate Extract), Angiostop, Chymotrypsin, Dichloroacetate, Calcitriol, Glibenclamide, Hydroxy Itraconazole, Pantoprazole, L-Citrulline, Gymnema, AHCC (Active Hexose Correlated Compound), Apitoxin (Bee Venom), L-Arginine, Lentinan (Shiitake Extract), Polygonum cuspidatum (Polydatin), Coriolus versicolor PSP (Polysaccharide-Peptide), Sulforaphane (Broccoli Sprouts), Calciferol (Vitamin D), Saccharomyces cerevisiae (Yeast β-Glucan), Astragalus membranaceus (Huangqi), Cimicifuga racemosa (Black Cohosh), Glutamine, Honokiol (Magnolia Bark), Inositol Hexaphosphate (IP6), N-Acetylcysteine (NAC), Nicotinamide (Vitamin B3), Hypericin, Calcium, Cimetidine (Tagamet), Folate (Folic Acid), Zingiber officinale (Ginger), Low-Dose Naltrexone (LDN), Milk Thistle (Silymarin), Modified Citrus Pectin, Polysaccharide-K, Salvestrol

Exosomal Gene Expression Analysis

Exosomal Gene Expression Analysis

Exosomal RNA: 20802 mRNA

Genes Analyzed in Cell Free Nucleic Acids Analysis

Gene List

SNV Genes:

AKT1	ALK	APC	AR	ARAF	BRAF	CHEK2	CTNNB1	DDR2	EGFR
ERBB2	ERBB3	ESR1	FBXW7	FGFR1	FGFR2	FGFR3	FGFR4	FLT3	GNA11
GNAQ	GNAS	HRAS	IDH1	IDH2	KIT	KRAS	MAP2K1	MAP2K2	MET
MTOR	NRAS	NTRK1	NTRK3	PDGFRA	PIK3CA	PTEN	RAF1	RET	ROS1
SF3B1	SMAD4	SMO	TP53						

Fusion Genes:

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

CNV Genes:

CCND1	CCND2	CCND3	CDK4	CDK6	EGFR	ERBB2	FGFR1	FGFR2	FGFR3
MET	MYC								

Methods and Limitations

Methods

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 repurposed 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.

Exosomal mRNA analysis:

Blood was analyzed for mRNA expression analysis using semiconductor based Next Generation Sequencing method. High quality Exo somal 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. Analytical validation of this assay shown a sensitivity of 100% and specificity of 100%.

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 Oncomine™ Pan-Cancer Cell-Free panel (see gene list in the 'Genes analysed' section). Enriched DNA sequences were ligated with platform specific adaptor molecules and were sequenced on using semiconductor chip. The minimum average depth was 17000x for gene panel analyzed. High quality sequencing data (proportion Q20 bases ≥75%) was analyzed using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline v11.14 designed to accurately detect the rare somatic variants.

The lower limit of detection of the mutations targeted is 0.1% and variants present below 0.1% may not be detectable with this assay, whereas analytical sensitivity is 97.14% and specificity is 93.75% for SNV, CNV and Fusion. Actionable variant(s) observed below Limit of Detection are confirmed by Droplet Digital PCR.

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.

Information for Patients:

The Patient Analysis raw data may be shared on written request by the individual patient.

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 particu lar 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 bebased 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 useor 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

Authorized Signatory

Authorized Signatory

ANNEXURE - 01

NaturaGene Ai

Precision Without Toxicity

Ms. ABC

NaturaGene-Ai
Precision Without Toxicity

PATIENT DETAILS

Name	: Ms. ABC
Birth Date	: 15-Dec-1975
Gender	: Female
Address	: —
Referring Doctor	: Dr. XYZ

SPECIMEN DETAILS

Tumor Type	: Rectal carcinoma
Specimen Type	: Blood
Draw Date	: 02-Apr-2025
Accession Date	: 03-Apr-2025
Report Date	: 15-Apr-2025

REPORT HIGHLIGHTS

Drugs / Supplements	Response Biomarkers - Detected			Response Biomarkers - Not Detected		
	Chemosensitivity	Gene Overexpression	DNA Alterations	Chemosensitivity	Gene Overexpression	DNA Alterations
1. Atorvastatin	67% CD	▲ MAPK, MMP	KRAS p.G12D	-	⊟ HMGCR, CCND1, MYC, CD36, FABP4	-
2. Chloroquine	63% CD	▲ HMGB1	-	-	⊟ MAP1LC3B, BECN1	-
3. Aspirin	62% CD	▲ PTGS2 (COX2), VEGFA	TP53 p.R213* TP53 p.A88V	-	⊟ CCND1, MYC	PIK3CA
4. Quercetin	62% CD	▲ MAPK, FZD, WNT	APC p.R564* APC p.Q1367*	-	-	PIK3CA, AKT1, AKT2, MTOR
5. Celecoxib	62% CD	▲ MAPK, FZD, WNT PTGS2 (COX2)	APC p.R564* APC p.Q1367*	-	-	PIK3CA, AKT1, AKT2, MTOR
6. Fenbendazole	62% CD	-	TP53 p.R213* TP53 p.A88V	-	⊟ TUBB, GLUT1, HK2	-
7. Curcumin	60% CD	▲ BCL2, VEGFA, MMP	-	-	⊟ EGFR	PIK3CA, CDKN2A
8. Diflunisal	58% CD	▲ PTGS2 (COX2)	-	-	-	-
9. Dihydroberberine	57% CD	-	-	-	⊟ NFKB1	-
10 Resveratrol	54% CD	MMP, ▲ BCL2, WNT PTGS2 (COX2)	-	-	⊟ EGFR, SIRT1, NFKB1	PIK3CA, AKT1, AKT2, MTOR
11. Doxycycline	54% CD	▲ MMP	-	-	-	-
12. Epigallocatechin gallate	52% CD	▲ MAPK, VEGFA, MMP	-	-	⊟ EGFR	PIK3CA

Drugs / Supplements	Response Biomarkers - Detected			Response Biomarkers - Not Detected		
	Chemosensitivity	Gene Overexpression	DNA Alterations	Chemosensitivity	Gene Overexpression	DNA Alterations
13. Indol-3-carbinol	52% CD	-	-	-	⊟ ER, AR, CYP1A1, CYP1B1	ESR1
14. Cannabidiol	52% CD	▲ MMP	-	-	-	-
15. Genistein	50% CD	▲ BCL2, MAPK, WNT	TP53 p.R213* TP53 p.A88V	-	⊟ EGFR, JAK, STAT, CASP, ERK1/ ERK2	AKT1, AKT2
16. Bromelain	45% CD	▲ MMP, PTGS2 (COX2)	APC p.R564* APC p.Q1367*	-	⊟ CCND1	-
17 .Helixor M	41% CD	-	-	-	-	-
18 .Helixor P	41% CD	-		-	-	-
19. Artesunate	40% CD	▲ BCL2, MMP, FZD, WNT	TP53 p.R213* TP53 p.A88V	-	⊟ JAK2, CTNNB1	-
20. Ivermectin	40% CD	-	-	-	⊟ PAK1, CTNNB1, STAT, LRP6	AKT1, AKT2
21 .Helixor A	40% CD	-	-	-	-	-
22. Astaxanthin	37% CD	▲ VEGFA	-	-	⊟ NFKB1, STAT3, NFE2L2	-
23. Iscador P	36% CD	▲ MMP, VEGFA	-	-	-	-
24. Iscador Qu	34% CD	▲ MMP, VEGFA	-	-	-	-
25. Metformin	28% CD	▲ BCL2, MAPK, MMP	KRAS p.G12D	-	⊟ SIRT1, IGF1R, AMPK (PRKAA1)	mTOR, ERBB2
26. Mebendazole	27% CD	▲ MAPK, MMP, VEGFA	-	-	⊟ XIAP, TUBB	-
27. Vitamin C	25% CD	-	KRAS p.G12D	-	⊟ SLC2A1 (GLUT1), MYC, HIF1A, GLUT3	-

Drugs / Supplements	Response Biomarkers - Detected			Response Biomarkers - Not Detected		
	Chemosensitivity	Gene Overexpression	DNA Alterations	Chemosensitivity	Gene Overexpression	DNA Alterations
28. Melatonin	25% CD	▲ MMP, PTGS2 (COX2)	-	-	-	-
29. DMSO	25% CD	-	-	-	-	-
30. Papain	25% CD	-	-	-	-	-
31. Niclosamide	21% CD	▲ WNT	-	-	⊟ NFKB1, STAT3	NOTCH1
32. Salinomycin Sodium Salt	20% CD	▲ WNT	-	-	⊟ NANOG, Cd44, ALDH1	-
33. Propranolol	15% CD	▲ VEGFA	-	-	⊟ ADRB2	-
34. Valproic acid	11% CD	-	TP53 p.R213* TP53 p.A88V	-	⊟ HDAC1, HDAC2	PTEN, AKT1, AKT2, NOTCH1
35 Beta-Carotene	-	▲ WNT	-	-	⊟ RAR, RXR, CASP, Cd44, CD133, SKP2	-
36. Berberine (Goldenseal/ Berberis)	-	▲ MMP	-	-	⊟ NFKB1, EGFR, STAT3	AKT1, AKT2
37. Boswellia serrata (Frankincense)	-	▲ BCL2, MMP, PTGS2 (COX2)	-	-	⊟ PCNA, STAT3	-
38. Apigenin	-	▲ VEGFA	TP53 p.R213* TP53 p.A88V	-	⊟ STAT3	AKT1, AKT2
39. NSAIDs (Ibuprofen, Sulindac)	-	▲ PTGS2 (COX2), WNT	-	-	⊟ CTNNB1, EGFR, NFKB1	-
40. Fisetin	-	▲ VEGFA	-	-	⊟ EGFR, CTNNB1	PIK3CA
41. Propolis (Bee Resin)	-	▲ BCL2	-	-	⊟ TLR, CASP, NFKB1	-
42. Ganoderma lucidum (Reishi)	-	▲ VEGFA	-	-	⊟ TLR	AKT1, AKT2, PIK3CA

Drugs / Supplements	Response Biomarkers - Detected			Response Biomarkers - Not Detected		
	Chemosensitivity	Gene Overexpression	DNA Alterations	Chemosensitivity	Gene Overexpression	DNA Alterations
43. Selenomethionine (Selenium)	-	▲ BCL2	TP53 p.R213* TP53 p.A88V	-	⊟ GPX1	-
44. Statins	-	-	KRAS p.G12D	-	⊟ MYC, HMGCR, YAP1	-
45. Withania somnifera (Ashwagandha)	-	▲ BCL2	TP53 p.R213* TP53 p.A88V	-	-	-
46. Scutellaria baicalensis (Baicalein)	-	▲ MMP	-	-	⊟ CASP, EZH2	-
47. Capsaicin (Chili Pepper)	-	▲ WNT	-	-	⊟ CASP, CTNNB1	-
48. Cordyceps sinensis	-	▲ MMP	-	-	⊟ VEGFR2 (KDR)	PIK3CA
49. Annona muricata (Graviola)	-	▲ BCL2, MAPK	-	-	⊟ HIF1A	-
50. Moringa oleifera	-	▲ BCL2, PTGS2 (COX2)	-	-	⊟ NFKB1	-
51. Nigella sativa (Black Seed)	-	▲ PTGS2 (COX2)	-	-	⊟ NFKB1, STAT3	-
52 .Panax Ginseng	-	▲ VEGFA	-	-	⊟ Il6, TNF	-
53. Asimina triloba (Pawpaw Extract)	-	▲ BCL2	-	-	⊟ NFKB1, ATP1A1	-
54. Proanthocyanidins (Grape Seed Extract)	-	▲ MMP, VEGFA	-	-	-	PIK3CA
55. Ursolic Acid (Apple Peel)	-	▲ MMP	-	-	⊟ NFKB1, STAT3	-
56. α-Tocopherol (Vitamin E)	-	-	TP53 p.R213* TP53 p.A88V	-	⊟ NFKB1	-
57. Menaquinone (Vitamin K2)	-	▲ BCL2	-	-	⊟ NFKB1	AKT1, AKT2

Drugs / Supplements	Response Biomarkers - Detected			Response Biomarkers - Not Detected		
	Chemosensitivity	Gene Overexpression	DNA Alterations	Chemosensitivity	Gene Overexpression	DNA Alterations
58. Hydroxychloroquine	-	-	KRAS p.G12D	-	⊟ MAP1LC3B	PIK3CA
59. Allium sativum (Garlic)	-	▲ VEGFA	KRAS p.G12D	-	-	-
60. Lycopene	-	▲ MMP	-	-	⊟ IGF1R	-
61. Salvia miltiorrhiza (Danshen)	-	▲ MMP, VEGFA	-	-	-	-
62. Avemar (Fermented Wheat Germ Extract)	-	▲ VEGFA	-	-	-	-
63. Rubus occidentalis (Anthocyanins)	-	▲ PTGS2 (COX2)	-	-	-	-
64. D-Limonene	-	-	KRAS p.G12D	-	-	-
65. Ellagic Acid (Pomegranate Extract)	-	▲ PTGS2 (COX2)	-	-	-	-
66. Angiostop	-	▲ VEGFA	-	-	-	-
67. Chymotrypsin	-	▲ MMP	-	10% CD	-	-
68. Dichloroacetate	-	-	-	10% CD	⊟ PDK1	-
69. Calcitriol	-	-	-	9% CD	-	-
70. Glibenclamide	-	-	-	8% CD	⊟ ABCC, KCNJ	-
71. Hydroxy Itraconazole	-	-	-	8% CD	⊟ SMO, VEGFR2, PDGFR	-
72. Pantoprazole	-	-	-	7% CD	⊟ ATP6V1	-

Drugs / Supplements	Response Biomarkers - Detected			Response Biomarkers - Not Detected		
	Chemosensitivity	Gene Overexpression	DNA Alterations	Chemosensitivity	Gene Overexpression	DNA Alterations
73. L-Citrulline	-	-	-	7% CD	ANXA5, CASP	-
74. Gymnema	-	-	-	5% CD	TNF	-
75. AHCC (Active Hexose Correlated Compound)	-	-		-	STAT3, SOX2, CASP	-
76. Apitoxin (Bee Venom)	-	-	-	-	KCNJ6 (GIRK2), DR4/DR5	-
77. L-Arginine	-	-	-	-	ARG1, ARG2, NOS2	-
78. Lentinan (Shiitake Extract)	-	-	-	-	TNF, IL2, IFNG	-
79. Polygonum cuspidatum (Polydatin)	-	-	-	-	SIRT1, NRF2, BAX	-
80. Coriolus versicolor PSP (Polysaccharide-Peptide)	-	-	-	-	TNF, IL2, IL6	-
81. Sulforaphane (Broccoli Sprouts)	-	-	-	-	KEAP1, HDAC, NFE2L2 (Nrf2)	-
82. Calciferol (Vitamin D)	-	-	-	-	VDR, CYP27B1, CDKN1A	-
83. Saccharomyces cerevisiae (Yeast β-Glucan)	-	-	-	-	TLR, IL12, TNF	-
84. Astragalus membranaceus (Huangqi)	-	-	-	-	TERT, TLR	-
85. Cimicifuga racemosa (Black Cohosh)	-	-	-	-	ER, CYP19A1	-
86. Glutamine	-	-	-	-	GLS, MYC	-
87. Honokiol (Magnolia Bark)	-	-	-	-	EGFR, STAT3	-

Drugs / Supplements	Response Biomarkers - Detected			Response Biomarkers - Not Detected		
	Chemosensitivity	Gene Overexpression	DNA Alterations	Chemosensitivity	Gene Overexpression	DNA Alterations
88. Inositol Hexaphosphate (IP6)	-	-	-	-	-	AKT1, AKT2, PIK3CA
89. N-Acetylcysteine (NAC)	-	-	-	-	KEAP1, NFE2L2 (Nrf2)	-
90. Nicotinamide (Vitamin B3)	-	-	-	-	SIRT1, PARP1	-
91. Hypericin	-	-	-	-	NFKB1	-
92. Calcium	-	-	-	-	CASR	-
93. Cimetidine (Tagamet)	-	-	-	-	EGFR	-
94. Folate (Folic Acid)	-	-	-	-	MTHFR	-
95. Zingiber officinale (Ginger)	-	-	-	-	STAT3	-
96. Low-Dose Naltrexone (LDN)	-	-	-	-	TLR	-
97. Milk Thistle (Silymarin)	-	-	-	-	CYP3A4	-
98. Modified Citrus Pectin	-	-	-	-	GAL3	-
99. Polysaccharide-K	-	-	-	-	TLR	-
100. Salvestrol	-	-	-	-	CYP1B1	-