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PRECISION INDIVIDUALIZED MEDICINE

Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens, Greece,
G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name:		**Date Sp. Extracted:**	-
Medical ID:		**Req. Physician:**	LAMPROPOULOS STEFANOS
Date Of Birth:	-	**Report No:**	2400xxx
Material #1:	PLASMA	**Date Received:**	00/00/2024
Material #2:	WHOLE PERIPHERAL BLOOD	**Date Of Report:**	00/00/2024
Sample #1 ID:		**Tumor type:**	Breast Cancer

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1. Report Summary

1021	Unique Genes (**38** Fusions) analyzed	**4**	Clinically significant biomarkers identified
7	Biomarker related approved therapies for indication	**6**	Biomarker related therapies with potential benefit
1	Biomarker related therapies with potential resistance	**34**	Biomarker related Clinical Trials

2. Clinically Significant Biomarkers*

Biomarker	Result	Approved therapies for indication	Therapies with potential benefit	Therapies with potential resistance/toxicity	Clinical Trials
BRCA1 Germline Pathogenic Variant	Exon 19 c.5266_5267insC(p.Q1756Pfs*74)	Talazoparib (1A.1) Olaparib (1A.1)	Rucaparib (2C.1) Niraparib (2C.1)	-	Yes
BRCA1	Exon 10 c.3455delA (p.D1152Afs*3)	Talazoparib (1A.1) Olaparib (1A.1)	Rucaparib (2C.1) Niraparib (2C.1)	-	Yes
PIK3CA	Exon 10 c.1633G>A (p.E545K)	Capivasertib+Fulvestrant (1A.1) Alpelisib+Fulvestrant (1A.1)	Everolimus (2C.1)	-	Yes
ESR1	Exon 9 c.1613A>G (p.D538G)	Elacestrant (1A.1)	Fulvestrant (2C.1)	Exemestane (2D)	Yes
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-
Tumor Mutational Burden (TMB)	7.68 Muts/MB	-	-	-	-

*Note: Variants' Level of Evidence (LoE) (e.g. 1A.1, 2C.1, 1B etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1

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2b. Germline variants

Gene	Finding	Clinical Significance	Zygosity
BRCA1	** c.5266_5267insC(p.Q1756Pfs*74) exon 19	Pathogenic-Clinically significant variant	Heterozygosity

** The BRCA1 gene is involved in the homologous recombination complex (HR), with pathogenic/likely pathogenic variants strongly associated with autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome. HBOC syndrome is characterized by an increased lifetime risk for breast cancer and contralateral breast cancer in females (>60%) and males (1.2%) and ovarian cancer (39%-58%). Pathogenic/likely pathogenic variants are also moderately associated with pancreatic ((PMID: 31429902, 12237281, 23628597, 28632866, 31378807, 26700119). The risk for contralateral breast cancer 20 years after the initial breast cancer diagnosis is 40% in these individuals (PMID: 28632866). Clinical management guidelines for HBOC syndrome can be found at www.nccn.org. The patient must be referred for genetic counseling for adequate interpretation of the study and post-genetic support. Relatives of this individual have up to 50% risk of having the same mutation. Predictive testing of this mutation should be offered to all at-risk adult relatives after receiving genetic counseling. Patients with germline mutations in HR genes may benefit from platinum-based therapies (PMID: 20406929) and treatment with PARP inhibitors (PMID: 31218365).

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3. Important biomarkers findings

Gene	Detected Range	Finding (VAF/Copy Number/Germline Mutation)
EGFR	Exon 18	Not detected
	Exon 19	Not detected
	Exon 20(including T790M)	Not detected
	Exon 21	Not detected
ERBB2(HER2)	Copy number gain	Not detected
	Mutation	Not detected
ESR1	Mutation	**p.D538G (0.3%)**
ALK	Rearrangement	Not detected
ROS1	Rearrangement	Not detected
MET	Copy number gain	Not detected
	Exon 14 skipping	Not detected
RET	Rearrangement	Not detected
BRAF	Codon 600 mutation	Not detected
KIT	Exon 9	Not detected
	Exon 11	Not detected
	Exon 13	Not detected
	Exon 17	Not detected
PDGFRA	Exon 12	Not detected
	Exon 18	Not detected
BRCA1	Mutation	**p.D1152Afs*3(0.7%)p.Q1756Pfs*74(Germline mutation)**
BRCA2	Mutation	Not detected
KRAS	Codon 12/13/59/61/117/146 mutation	Not detected
	Other mutations except codon 12/13/59/61/117/146	Not detected
NRAS	Codon 12/13/59/61/117/146 mutation	Not detected
	Other mutations except codon 12/13/59/61/117/146	Not detected
PIK3CA	Mutation	**p.E545K(0.3%)**
FGFR2	Rearrangement	Not detected
	Mutation	Not detected
FGFR3	Rearrangement	Not detected
	Mutation	Not detected
NTRK1	Rearrangement	Not detected
NTRK2	Rearrangement	Not detected
NTRK3	Rearrangement	Not detected
IDH1	Mutation	Not detected

Note:

1. 'Not detected/-' indicates the corresponding variations were not detected in this tested individual.
2. The genetic variations listed above are covered, but not limited to this list.
3. For a detailed information about listed variants, please refer to the Report Summary and the respective Interpretations sections.

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4. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant		Result	Clinical Interpretation
Biomarkers for predicting efficacy			
Tumor mutation burden (TMB)		TMB-L 7.68	-
Microsatellite instability (MSI)		Stable (MSS)	-
Affect the treatment effect - positive correlation			
PD-L1 amplification		Not detected	-
PBRM1 inactivating mutation Renal clear cell carcinoma)		Not detected	-
MLH1 suspected germline deleterious mutation		Not detected	-
MSH2 suspected germline deleterious mutation		Not detected	-
MSH6 suspected germline deleterious mutation		Not detected	-
PMS2 suspected germline deleterious mutation		Not detected	-
POLE mutation (driver)		Not detected	-
POLD1 mutation (driver)		Not detected	-
Other DNA damage repair (DDR) pathway genes	*ATM* mutation	Not detected	-
	ATR mutation	Not detected	-
	BAP1 mutation	Not detected	-
	BLM mutation	Not detected	-
	BRCA1 mutation	**Detected**	May increase the benefit rate of PD-1/PD-L1 inhibitors
	BRCA2 mutation	Not detected	-
	BRIP1 mutation	Not detected	-
	CHEK1 mutation	Not detected	-
	CHEK2 mutation	Not detected	-
	ERCC3 mutation	Not detected	-
	ERCC4 mutation	Not detected	-
	ERCC5 mutation	Not detected	-
	FANCA mutation	Not detected	-
	FANCC mutation	Not detected	-
	MRE11A mutation	Not detected	-
	NBN mutation	Not detected	-
	RAD50 mutation	Not detected	-
	RAD51 mutation	Not detected	-
	RAD51B mutation	Not detected	-
	RAD51D mutation	Not detected	-
	RAD54L mutation	Not detected	-
TP53 mutation		Not detected	-

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KRAS mutation	Not detected	-
Biomarker/Variant	**Result**	**Clinical Interpretation**
Affect the treatment effect - negative correlation		
PTEN inactivating mutation	Not detected	-
JAK1 inactivating mutation	Not detected	-
JAK2 inactivating mutation	Not detected	-
B2M inactivating mutation	Not detected	-
EGFR mutation （L858R/EX19del）	Not detected	-
ALK rearrangement	Not detected	-
STK11 inactivating mutation	Not detected	-
KEAP1 inactivating mutation	Not detected	-
11q13 amplification	Not detected	-
MDM2 amplification	Not detected	-
MDM4 amplification	Not detected	-
DNMT3A inactivating mutation	Not detected	-
Indicator affecting prognosis of immune checkpoint inhibitor therapy		
HLA-I Zygosity (At least one of type A, B, C is homozygous)	Not detected	-

Note:

1. Not detected/- indicates the corresponding variation were not detected in this tested individual.
2. The interpretation of the detection results of *PBRM1* inactivating mutations is only applicable to renal clear cell carcinoma.
3. The indicators/gene clinical interpretations listed above are for reference only, and the specific decisions need to refer to professional physician instructions.
4. For a detailed interpretation, showed in Interpretation for biomarker of checkpoint inhibitor.
5. *POLE* and *POLD1* mutations are restricted to currently reported mutations that may lead to hypermutation in tumor, resulting in tumor mutation burden increase.
6. HLA-I results analyzed by the phenotypes of HLA-A, HLA-B and HLA-C loci detected from tumor samples. Due to the lack of control samples, HLA-I typing cannot be accurately analyzed and it is possible that show homozygosity because of the occurrence of HLA-LOH in the tumor tissue.

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5. Interpretations for targeted therapies

Genetic Variation:	*NM_007294.3(BRCA1):c.5266_5267insC(p.Q1756Pfs*74)*	VAF: 49%	OncoKB

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with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy. Approval was based upon data from the international Phase 3 ENGOT-OV16/NOVA trial, a double-blind, placebo-controlled study. Niraparib significantly increased PFS in patients with and without germline BRCA mutations as compared to control. Treatment with Niraparib reduced the risk of disease progression or death by 74% in patients with germline BRCA mutations (HR 0.26) and by 55% in patients without germline BRCA mutations (HR 0.45). The magnitude of benefit was similar for patients entering the trial with a partial response or a complete response. For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Approval was based on the PRIMA study (NCT02655016). The PRIMA study significantly improved PFS for patients treated with Niraparib, regardless of biomarker status. In the HRd population, Niraparib resulted in a 57% reduction in the risk of disease progression or death vs. placebo(PMID: 21605559). Niraparib is being examined in several clinical trials as therapy for BRCA-mutated locally advanced/metastatic breast cancer (PMID: 23810788). Niraparib has shown some activity in BRCA carriers with breast cancer on the BRAVO study and is being studied in different combinations (PMID: 34301749). Rucaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. FDA approval was based on the results of ARIEL3 (NCT01968213), a double-blind, multicenter clinical trial. ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to Rucaparib as compared with placebo in all patients, and in the HRD and tBRCA subgroups. For the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Approval was based on two multicenter, single-arm, open-label clinical trials, Study 10 (NCT01482715) and ARIEL2 (NCT01891344). For the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial. The confirmed ORR was 44% (95% CI: 31, 57). Median DOR was not evaluable (NE; 95% CI: 6.4, NE). The use of Rucaparib in breast cancer patients has being examined in several clinical trials (PMID: 27002934).

Talazoparib DrugBank

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inhibition of PARP enzymatic activity and increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death. Olaparib is available as oral tablets marketed under the brand name Lynparza. It is indicated for the following conditions:

Ovarian cancer

- For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
- In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability.
- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- For the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

Breast cancer

- For the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Latest research supports the use of adjuvant olaparib in patients with high-risk early-stage HER2-negative breast cancer and germline BRCA mutations (PMID: 34081848).

Pancreatic cancer

- For the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

Prostate cancer

- For the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.

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There are three main types of ovarian cancer: epithelial (90%), germ cell (5%) and sex cord stromal cell (5%). Epithelial ovarian, being the most common, fifth leading cause of cancer-related deaths in women in the United States. Advanced ovarian cancer particularly poses challenges due to reduced therapeutic response rates from standard platinum-based chemotherapy and overall survival rates. Rucaparib has shown to induce cytotoxicity in tumor cell lines with deficiencies in BRCA1/2 and other DNA repair genes . Of all the BRCA1/2 mutations in ovarian cancer, most are due to germline mutations (18%), and approximately 7% represent somatic mutations acquired within the tumor . The indication of rucaparib as an oral monotherapy in patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer was granted accelerated approval in 2016 for selected patients who have previously received greater than two lines of platinum-based therapy. It is currently marketed in the US under the brand name Rubraca that contains rucaparib camsylate as the active ingredient. It is indicated for:

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- for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies.

Prostate cancer

- for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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Genetic Variation:	*NM_006218.2(PIK3CA):c.1633G>A(p.E545K)*	VAF: 0.3%	OncoKB

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the SOLAR-1 study (NCT02437318), a randomized, double-blind, placebo-controlled trial of alpelisib plus fulvestrant versus placebo plus fulvestrant. Among a subset of patients with PIK3CA mutations, the median PFS by local assessment was 11.0 months (95% CI, 7.5-14.5) for those who received the alpelisib combination compared with 5.7 months (95% CI, 3.7-7.4) for those who received placebo plus fulvestrant. Those results, assessed after a median follow-up of 20 months, translated into a 35% reduction in the risk of progression or death, with a hazard ratio of 0.65 in favor of alpelisib. There was no advantage to alpelisib on median PFS in patients without a PIK3CA mutation. Activating mutations in PIK3CA may also confer resistance to anti-HER2 therapies. PIK3CA activating mutations or amplification may predict sensitivity to inhibitors of the PI3K-AKTmTOR pathway. The mTOR inhibitor everolimus is FDA approved, in combination with the aromatase inhibitor exemestane, to treat postmenopausal women with hormonereceptor- positive, HER2-negative advanced breast cancer. These therapies and other mTOR inhibitors are in clinical trials in breast cancer and other solid tumor types. Inhibitors of PI3K and AKT, alone or in combination with other therapies are also in clinical trials in solid tumors.

Capivasertib DrugBank

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
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confirmed via FDA-approved diagnostic tests. Studies evaluating the therapeutic effectiveness of alpelisib in other cancers, such as ovarian cancer and colorectal cancer, are under ongoing investigations. Alpelisib was granted FDA approval on 24 May 2019. Alpelisib is indicated in combination with fulvestrant to treat postmenopausal women, and men, with advanced or metastatic breast cancer. This cancer must be hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, and PIK3CA mutated. The cancer must be detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Fulvestrant DrugBank

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Scientific Director: George Nasioulas PhD

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prior duration and setting of endocrine therapy. Approximately 20-40% of patients who have received aromatase inhibition (AI) for metastatic breast cancer (MBC) have ESR1 mutations, with prevalence varying by sites of metastatic disease (PMID: 33526469, 27986707). In contrast, ESR1 mutation prevalence is only 4-5% in recurrent breast cancer after prior adjuvant AI (including recurrence while on adjuvant AI), 1.5-7% after neoadjuvant AI, and less than 1% in ET-naive MBC (PMID: 26560360). Thus, ESR1 mutations in HR- positive breast cancer occur almost exclusively after AI in the metastatic setting. ESR1 mutations alone, however, only partly account for endocrine resistance in MBC. About 50% of endocrine resistance cases are associated with an ESR1 mutation; other mechanisms, increasingly uncovered, include alterations in the PI3K-AKT-mTORC1, RAS-MAPK, and CDK4/6-RB-E2F pathways, and ESR1 loss, amplification, and translocation (PMID: 30205045). In addition, ESR1 mutations usually occur with several concurrent genomic alterations, and together, these confer a globally worse prognosis (PMID: 27532364, 33526469). Furthermore, current treatments include endocrine therapy partnered with additional targeted therapy, such as inhibition of CDK4/6, PI3K, or mTORC1. In these situations, a general theme is that ESR1 mutation alone is insufficient for full resistance, although this remains to be modelled and studied experimentally.

Variant Description

The ESR1 p.Asp538Gly (D538G) mutation is known to be oncogenic (OncoKB). This mutation has been associated with resistance to endocrine treatment. In a study of patients with breast cancer with liver metastasis, five of the patients who developed resistance to hormonal therapy, exhibited a mutation of A to G at position 1,613 of ERÎ±, resulting in a substitution of aspartic acid at position 538 to glycine (D538G). Importantly, the mutation was not detected in the primary tumors obtained prior to endocrine treatment. Structural modeling indicated that D538G substitution leads to a conformational change in the ligand-binding domain, which mimics the conformation of activated ligand-bound receptor and alters binding of tamoxifen. Indeed, experiments in breast cancer cells indicated constitutive, ligand-independent transcriptional activity of the D538G receptor, and overexpression of it enhanced proliferation and conferred resistance to tamoxifen. These data indicate a novel mechanism of acquired endocrine resistance in breast cancer. Further studies are needed to assess the frequency of D538G-ERÎ± among patients with breast cancer and explore ways to inhibit its activity and restore endocrine sensitivity (PMID: 24217577).

Targeted Drug Interpretation

The FDA has granted an accelerated approval to elacestrant for the treatment of patients with estrogen receptor œpositive, HER2-negative advanced or metastatic breast cancer following at least 1 prior lines of endocrine therapy. The approval is supported by data from the phase 3 EMERALD study (NCT03778931). The investigational oral selective estrogen receptor degrader (SERD) was evaluated among patients with ESR1-mutant disease (n = 115) vs standard-of-care (SOC) endocrine therapy (n = 113) of either fulvestrant or an aromatase inhibitor. The median progression-free survival was 3.8 months (95% CI, 2.2-7.3) vs 1.9 months (95% CI, 1.9-2.1) with the SERD and SOC, respectively (HR, 0.55; 95% CI, 0.39-0.77; P = .0005). The overall survival outcomes were not statically significant (HR, 0.90; 95% CI, 0.63-1.30). Results presented during the 2022 SABCS showed that the duration of prior CDK4/6 inhibition played a role for patients who received elacestrant. Among those with ESR1-mutant disease who received at least 12 months of CDK4/6 inhibition (n = 78), the median PFS was 8.61 months vs 1.91 months with SOC (n = 81; HR, 0.410; 95% CI, 0.262-0.634). The 6-, 12-, and 18-month PFS rates were 55.81%, 35.81%, and 28.49% with elacestrant vs 22.66%, 8.39%, and 0% with SOC. Fulvestrant has been approved for women with breast cancer: as a standalone treatment for postmenopausal women with HR-positive metastatic breast cancer whose disease progressed after treatment with other antiestrogen therapy, in combination with the CDK4/6 inhibitor Palbociclib for the treatment of women with advanced or metastatic HR-positive, HER2-negative breast cancer that has progressed after endocrine therapy and as a standalone treatment, or monotherapy, for postmenopausal women with advanced hormone receptor (HR)-positive, HER2-negative breast cancer who have not undergone endocrine therapy previously. Turner et al (2020) have shown that the detection of ESR1 mutations in baseline ctDNA is

Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

associated with inferior progression free survival (PFS) and overall survival (OS) in patients treated with exemestane versus fulvestrant (PMID: 32546646).

Elacestrant DrugBank

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info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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6. Interpretation for polymorphism variants related with chemotherapy drugs

Drug Classes	Test Content	Drug name	Gene	dbSNP	Patient's Genotype	Patient's Variant-Drug Phenotype Annotation	Evidence Level
5-Fluorouracil (5-Fu), Fluoropyrimidines	Drug efficacy	5-Fu + Oxaliplatin	*GSTP1*	rs1695	AG	Associated with moderate response to treatment	2A
5-Fluorouracil (5-Fu), Fluoropyrimidines	Drug toxicity	5-Fu or Capecitabine	*DPYD*	rs2297595	TT	Associated with decreased risk of drug toxicity	2A
5-Fluorouracil (5-Fu), Fluoropyrimidines	Drug toxicity	5-Fu or Capecitabine	*MTHFR*	rs1801133	AG	Associated with moderate risk of drug toxicity	2A
5-Fluorouracil (5-Fu), Fluoropyrimidines	Drug toxicity	5-Fu + Leucovorin or Tegafur + Leucovorin	*UMPS*	rs1801019	GG	Associated with decreased risk of drug toxicity	2B
5-Fluorouracil (5-Fu), Fluoropyrimidines	Drug toxicity	Fluoropyrimidine-based therapy	*DPYD*	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
5-Fluorouracil (5-Fu), Fluoropyrimidines	Drug toxicity	Fluoropyrimidine-based therapy	*DPYD*	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
5-Fluorouracil (5-Fu), Fluoropyrimidines	Drug toxicity	Fluoropyrimidine-based therapy	*DPYD*	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Anthracyclines	Drug toxicity	Anthracyclines	*CBR3*	rs1056892	AG	Associated with increased risk of drug toxicity	2B
Anthracyclines	Drug toxicity	Epirubicin	*GSTP1*	rs1695	AG	Associated with decreased risk of drug toxicity	2A
Anthracyclines	Drug efficacy	Epirubicin	*GSTP1*	rs1695	AG	Associated with better response to treatment	2A
Aromatase inhibitors	Drug efficacy	Letrozole, Anastrozole	*CYP19A1*	rs4646	AC	Associated with better response to treatment	3
Aromatase inhibitors	Drug efficacy	Anastrozole	*ABCB1*	rs2032582	CC	Associated with poorer response to treatment	3
Aromatase inhibitors	Drug toxicity	Anastrozole	*ABCB1*	rs1045642	GG	Associated with increased risk of drug toxicity	3
Capecitabine	Drug toxicity	Capecitabine-Based Chemotherapy	*MTHFR*	rs1801131	GT	Associated with increased risk of drug toxicity	2A
Capecitabine	Drug toxicity	Capecitabine-Based Chemotherapy	*DPYD*	rs2297595	TT	Associated with decreased risk of drug toxicity	2A
Capecitabine	Drug toxicity	5-Fu or Capecitabine	*MTHFR*	rs1801133	AG	Associated with moderate risk of drug toxicity	2A
Capecitabine	Drug toxicity	Capecitabine	*DPYD*	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
Capecitabine	Drug toxicity	Capecitabine	*DPYD*	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
Capecitabine	Drug toxicity	Capecitabine	*DPYD*	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Cyclophosphamide	Drug toxicity	Cyclophosphamide	*XRCC1*	rs25487	CC	Associated with increased risk of drug toxicity	3
Cyclophosphamide	Drug toxicity	Cyclophosphamide	*MTHFR*	rs1801133	AG	Associated with decreased risk of drug toxicity	2A
Cyclophosphamide	Drug toxicity	Cyclophosphamide + Epirubicin	*GSTP1*	rs1695	AG	Associated with decreased risk of drug toxicity	2A
Cyclophosphamide	Drug efficacy	Cyclophosphamide	*XRCC1*	rs25487	CC	Associated with better response to treatment	3
Cyclophosphamide	Drug efficacy	Cyclophosphamide	*SOD2*	rs4880	AG	Associated with moderate response to treatment	2B
Cyclophosphamide	Drug efficacy	Cyclophosphamide + Epirubicin	*GSTP1*	rs1695	AG	Associated with better response to treatment	2A

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
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Cyclophosphamide	Drug efficacy	Cyclophosphamide + Doxorubicin	*ABCB1*	rs2032582	CC	Associated with better response to treatment	3
Etoposide	Drug toxicity	Etoposide	*SLIT1*	rs2784917	GG	Associated with decreased risk of drug toxicity	4
Etoposide	Drug toxicity	Etoposide	*ABCB1*	rs1045642	GG	Associated with decreased risk of drug toxicity	3
Gemcitabine	Drug toxicity	Gemcitabine	*RRM1*	rs9937	GG	Associated with decreased risk of drug toxicity	4
Gemcitabine	Drug toxicity	Gemcitabine	*CDA*	rs60369023	GG	Associated with decreased risk of drug toxicity	3
Gemcitabine	Drug toxicity	Gemcitabine	*CDA*	rs2072671	CC	Associated with increased risk of gastrointestinal toxicity and neutropenia, decreased risk of hematologic toxicity	2B
Irinotecan	Drug toxicity	Irinotecan	*UGT1A1*	rs8175347	6TA/7TA	Associated with moderate risk of drug toxicity	2A
Irinotecan	Drug toxicity	Irinotecan	*UGT1A1*	rs4148323	GG	Associated with decreased risk of drug toxicity	2A
Irinotecan	Drug toxicity	Irinotecan	*C8orf34*	rs1517114	CG	Associated with increased risk of drug toxicity	2B
Methotrexate	Drug toxicity	Methotrexate	*MTHFR*	rs1801133	AG	Associated with decreased risk of drug toxicity	3
Methotrexate	Drug toxicity	Methotrexate	*MTRR*	rs1801394	GG	Associated with increased risk of drug toxicity	2B
Methotrexate	Drug toxicity	Methotrexate	*ABCB1*	rs1045642	GG	Associated with decreased risk of drug toxicity	2A
Methotrexate	Drug efficacy	Methotrexate	*ATIC*	rs4673993	TT	Associated with poorer response to treatment	2B
Pemetrexed	Drug efficacy	Pemetrexed	*MTHFR*	rs1801133	AG	Associated with poorer response to treatment	3
Platinum-Based Chemotherapy	Drug toxicity	Cisplatin	*XPC*	rs2228001	GG	Associated with increased risk of drug toxicity	1B
Platinum-Based Chemotherapy	Drug toxicity	Platinum compounds	*GSTP1*	rs1695	AG	Associated with increased risk of drug toxicity	2A
Platinum-Based Chemotherapy	Drug toxicity	Cisplatin, Platinum, Platinum compounds	*ERCC1*	rs3212986	CC	Associated with increased risk of drug toxicity	2B
Platinum-Based Chemotherapy	Drug toxicity	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*ERCC1*	rs11615	AA	Associated with increased risk of drug toxicity	2B
Platinum-Based Chemotherapy	Drug toxicity	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*XRCC1*	rs25487	CC	Associated with increased risk of drug toxicity	2B
Platinum-Based Chemotherapy	Drug efficacy	Carboplatin	*MTHFR*	rs1801133	AG	Associated with poorer response to treatment	2A
Platinum-Based Chemotherapy	Drug efficacy	Platinum compounds	*XRCC1*	rs1799782	GG	Associated with poorer response to treatment	NA
Platinum-Based Chemotherapy	Drug efficacy	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*ERCC1*	rs11615	AA	Associated with poorer response to treatment	2B
Platinum-Based Chemotherapy	Drug efficacy	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*XRCC1*	rs25487	CC	Associated with better response to treatment	2B
Tamoxifen	Drug efficacy	Tamoxifen	*CYP19A1*	rs4646	AC	Associated with poorer response to treatment of Pre-menopausal women with	2B

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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						breast cancer, Associated with better response to treatment of Post-menopausal women with breast cancer	
Tamoxifen	Drug efficacy	Tamoxifen	*ABCB1*	rs1045642	GG	Associated with better response to treatment	3
Tamoxifen	Recurrent risk	Tamoxifen	*CYP2D6*	rs3892097	CC	Aassociated with decreased risk of recurrence, increased risk of hot flashes	2A
Tamoxifen	Recurrent risk	Tamoxifen	*CYP2D6*	rs1065852	AG	Aassociated with increased risk of recurrence	3
Taxanes	Drug toxicity	Paclitaxel	*ABCB1*	rs1045642	GG	Associated with decreased risk of drug toxicity	3
Taxanes	Drug toxicity	Paclitaxel	*SOD2*	rs4880	AG	Associated with decreased risk of drug toxicity	3
Taxanes	Drug toxicity	docetaxel	*ERCC1*	rs3212986	CC	Associated with increased risk of drug toxicity	3
Taxanes	Drug toxicity	docetaxel	*ERCC1*	rs11615	AA	Associated with increased risk of drug toxicity	3
Taxanes	Drug toxicity	Taxanes	*ABCB1*	rs2032582	CC	Associated with decreased risk of drug toxicity	3
Taxanes	Drug efficacy	Paclitaxel + Cisplatin	*TP53*	rs1042522	CC	Associated with better response to treatment	2B
Taxanes	Drug efficacy	Paclitaxel	*ABCB1*	rs2032582	CC	Associated with poorer response to treatment	3
Vinca alkaloids	Drug efficacy	Vincristine	*ABCB1*	rs1045642	GG	Associated with better response to treatment	3

Note:

1. The level of variant-drug associations evidence is based on PharmGKB website, for more detailed information please see http://www.pharmgkb.org/page/clinAnnLevels.

Level 1A: Annotation for a variant-drug combination in a CPIC- or medical society-endorsed pharmacogenomics guideline, or implemented at a PGRN site, or in another major health system;

Level 1B: Annotation for a variant-drug combination in which the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant P-values, and, preferably with a strong effect size;

Level 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely;

Level 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small;

Level 3: Annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association;

Level 4: Annotation based on a case report, non-significant study, or in vitro, molecular, or functional assay evidence only.

2. The variant-drug correlation relationship derived from multiple independent studies, therefore, the interpretations of the same class of drug for the tested individual may be inconsistent. The final drug instruction needs to combine with the specific clinical situation.

3. The detection results are only based on the analysis of tumor samples and lack of control, the results of some loci may be specific to tumor tissues due to factors such as loss of heterozygosity.

Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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7. Other Genomic findings*

***Note**: In this section, damaging variants in genes without clinical actionability or without convincing evidence of cancer association are reported.

Genetic Variation:	*NM_004380.2(CREBBP):c.5486A>C(p.H1829P)*	VAF: 0.8%	OncoKB

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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		TOP2A,p.R1318W, is identified in this case. Algorithms developed to predict the effect of missense changes on protein structure and function suggest that this variant is likely to be deleterious, but this prediction has not been confirmed by published functional studies.
RBM10	c.424G>C (p.E142Q)	RBM10 encodes a nuclear protein that belongs to a family of proteins with RNA-binding motif. RBM10 is located on the X chromosome and therefore subject to X-inactivation whereby the remaining active allele is widely expressed in human cell lines and tissues (PMID: 15514923). Mutations that result in a truncated RBM10 protein are identified as the causes of TARP (Talipes equinovarus, Atrial septal defect, Robin sequence, and Persistent left superior vena cava) syndrome, which has been reported to cause pre- or postnatal death in affected males (PMID: 24000153). RBM10 was discovered to be among the most frequently mutated genes in lung adenocarcinoma samples (PMID: 25079552); mutations in this gene have also been observed in breast, colon, ovary, pancreas and prostate cancers (PMID: 16959974). RBM10 has been characterized as an RNA-binding protein both in vitro and in vivo, and identified as an important regulator of alternative splicing (PMID: 24332178). Recently, RBM10 has been shown to regulate alternative splicing of FAS and Bcl-X, two genes involved in apoptosis (PMID: 24530524). A missense alteration in RBM10,p.E142Q, is identified in this case.
IKZF1	c.1126C>G (p.L376V)	IKZF1 (IKAROS Family Zinc Finger 1) encodes a transcription factor that belongs to the family of zinc-finger DNA-binding proteins associated with chromatin remodeling. This protein regulates hematopoietic differentiation and immune system development, and functions as a tumor suppressor (PMID: 24659638, 22150303). Mutations in IKZF1 are associated with acute lymphoblastic leukemia (PMID: 24659638, PMID: 22150303) and IKZF1 deletions have been observed in pediatric precursor B-cell ALL (PMID: 31076445) (PMID: 31076445).A missense alteration in IKZF1,p.L376V, is identified in this case. Algorithms developed to predict the effect of missense changes on protein structure and function suggest that this variant is likely to be tolerated, but this prediction has not been confirmed by published functional studies.
GRM3	c.1873T>A (p.S625T)	GRM3 (Glutamate Metabotropic Receptor 3) is a Group II G-coupled glutamate receptor that functions in regulation of glutamatergic signaling (PMID: 16417579, 22564439). A missense alteration in GRM3,p.S625T, is identified in this case. Algorithms developed to predict the effect of missense changes on protein structure and function suggest that this variant is likely to be tolerated, but this prediction has not been confirmed by published functional studies.

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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9. Germline variants

Gene	Transcript	Exon	c.HGVS	p.HGVS	Zygosity	Classification
BRCA1	**NM_007294.3**	**EX19**	**c.5266_5267insC**	**p.Q1756Pfs*74**	**Heterozygosity**	**Pathogenic**

Note:

1. - indicates no relevant variations were detected in this test.
2. When detected, pathogenic or likely pathogenic variants are reported. Variants of uncertain significance or variants that are benign or likely benign are not reported.
3. The somatic or germline origin of the alteration identified cannot be verified due to the absence of control sample analysis (blood or saliva).
4. Variant classification interpretation is based on ACMG (American College of Medical Genetics and Genomics) guidelines for the interpretation of germline sequence variants (PMID:25741868).

10. HLA-I Polymorphism variation

Somatic HLA-I Zygosity

The anti-tumor activity of immune checkpoint inhibitor therapy is related to CD8+ T cells. The recognition of cancer cells by CD8+ T cells is achieved by HLA-I (human leukocyte antigen class I) molecules presenting tumor antigens.

HLA alleles have the characteristics of polymorphism and codominance. HLA-I loci subdivided into HLA-A, HLA-B and HLA-C. When a patient's HLA-I is homozygous at least one locus, this patient is expected to present less and less diverse tumor neoantigens to T cells compared to patients who are heterozygous at all three loci. In two cohorts, patients with heterozygous HLA-I showed longer OS than those with homozygous alleles, cohort1: HR=1.4 (1.02-1.9), P-value=0.036; cohort2: HR=1.31 (1.03- 1.7), P-value=0.028; among 32 patients with heterozygous HLA-I but at least one locus with LOH (loss of heterozygosity), patients with HLA-I LOH have a higher survival risk (P = 0.05, HR = 1.60, 95% CI 1.03-2.43), and these patients mainly with low mutation burden (P = 0.0006, HR = 3.68, 95% CI 1.64-8.23) (PMID:29217585).

Gene	Test Content	Result
HLA-A	Zygosity	Heterozygosity
HLA-B	Zygosity	Heterozygosity
HLA-C	Zygosity	Heterozygosity

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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11. Clinical Trials to consider

PIK3CA associated clinical trials

NCT05501886

Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

Title	First-in-Human Study of Mutant-selective PI3KÎ± Inhibitor, RLY-2608, as a Single Agent in Advanced Solid Tumor Patients and in Combination With Fulvestrant in Patients With Advanced Breast Cancer
Treatment	RLY-2608| Fulvestrant| Palbociclib 125mg| Ribociclib 400mg| Ribociclib 600mg
Location	United States

NCT05341570

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

Treatment	BET Bromodomain Inhibitor ZEN-3694| Biopsy| Biospecimen Collection| Diagnostic Imaging| Talazoparib
Location	United States

NCT05340413

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

Title	Evaluation of Talazoparib, a PARP Inhibitor, in Patients With Somatic BRCA Mutant Metastatic Breast Cancer: Genotyping Based Clinical Trial
Treatment	Talazoparib
Location	United States

NCT05097599

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

Title	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)
Treatment	Olaparib| Dasatinib| Nivolumab plus Ipilimumab| Axitinib| Bosutinib| Crizotinib| Palbociclib| Sunitinib| Temsirolimus| Erlotinib| Trastuzumab plus Pertuzumab| Vemurafenib plus Cobimetinib| Vismodegib| Tucatinib
Location	Canada

NCT06065059

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

Title	Combination Therapy in Cancers With Mutations in DNA Repair Genes
Treatment	Niraparib| Irinotecan
Location	United States

NCT06022029

Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

Treatment	Giredestrant| Fulvestrant| Abemaciclib| Palbociclib| Ribociclib| LHRH Agonist| FoundationOne Liquid CDx Assay (F1LCDx)
Location	United States,Argentina

NCT05306340

Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

12. Appendix

12.a. Immune checkpoint inhibitors predictive biomarkers

Tumor Mutation Burden (TMB)

bTMB (blood-based tumor mutational burden) usually refers to the number of somatic nonsynonymous mutations or all mutations per megabase in the gene region examined by whole exome sequencing or targeted sequencing in a tumor peripheral blood sample. bTMB is derived from DNA released into blood circulation by tumor cells (circulating tumor - ctDNA). Tissue TMB (tTMB) is approved as a tumor agnostic biomarker for immunotherapy in patients with metastatic solid tumors. bTMB is positively correlated with tTMB, which can reflect the level of TMB in tumor tissues to some extent. Studies have shown that bTMB is not correlated with the expression of PD-L1 in tumor tissues (PMID: 30082870).

A retrospective analysis confirmed correlation between tTMB and bTMB in patients with NSCLC included in the OAK (NCT02008227, n=850) and Poplar (NCT01903993, n=287) clinical trials of Atezolizumab in second-line treatment for advanced non-small cell lung cancer. High TMB was associated with response to immunotherapy in both trials. A different study successfully correlated blood and tissue TMB results on 2000 NSCLC samples from Geneplus database. The correlation of bTMB with outcomes after front line treatment with Pembrolizumab and Pembrolizumab plus Chemotherapy was also evaluated, at a cutoff of ≥16 mut/Mb, in 66 pts with mNSCLC. Early results suggested that bTMB may predict therapeutic outcomes after first line Pembrolizumab based therapy in mNSCLC. However, the prospective phase III BFAST trial concluded that bTMB at a cut-off of ≥16 mut/Mb was not a predictive biomarker for clinical outcomes with atezolizumab in patients with previously untreated metastatic NSCLC, although the 18-month PFS and OS both numerically favored atezolizumab in this bTMB group (PMID: 35995953).

Evaluation of tissue- and plasma-derived TMB from the CheckMate 848 clinical trial, showed that at the prespecified cutoff of 10 mut/Mb, 15.8% and 20.7% of samples had high tTMB and bTMB, respectively; the positive (PPA), negative and overall percentage agreements between assays were 60%, 88%, and 84%, respectively. TMB correlation (Spearman's r, 0.54; P < 0.0001) and PPA (66%) were improved among 806 (79.3%) sample pairs with plasma maximum somatic allele frequency ≥ 1% (https://doi.org/10.1158/1538-7445.AM2022-2139).

Plasma samples with high bTMB values are highly correspondent with tTMB, whereas bTMB low results may also be the result of low tumor burden at earlier stages of disease as well as poorly shedding tumors (PMID: 35217576). Typically, bTMB reports higher than tTMB, as reported in Drusbosky et al, who analyzed 5610 blood specimens with the 80th percentile bTMB being ≥16 mut/Mb tissue equivalency (PMID: 35274716).

At present, there is no consensus on the application of bTMB in clinical cancer treatment.

Table S1. TMB interpretation and cut-offs.

Tumour Type	Immunotherapy agent	Study/Trial	TMB high cut-off	Type of benefit
NSCLC	Anti PD-L1	B1FIRST [1]	**≥16 Muts/Mb**	ORR
NSCLC	Anti PD-L1	BFAST Cohort C [2]	**≥16 Muts/Mb**	-
NSCLC	Anti PD-L1	MYSTIC [3]	**≥20 Muts/Mb**	OS
NSCLC	Anti PD-L1	OAK [4]	**≥16 Muts/Mb**	PFS
NSCLC	Anti PD-L1	POPLAR [4]	**≥16 Muts/Mb**	PFS

Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

1. Mok, Tony & Gadgeel, S. & Kim, et al. Blood first line ready screening trial (B-F1RST) and blood first assay screening trial (BFAST) enable clinical development of novel blood-based biomarker assays for tumor mutational burden (TMB) and somatic mutations in 1L advanced or metastatic NSCLC. 2017. Annals of Oncology. 28. 10.1093/annonc/mdx380.084.| **2**. Peters S, et al. Atezolizumab versus chemotherapy in advanced or metastatic NSCLC with high blood-based tumor mutational burden: primary analysis of BFAST cohort C randomized phase 3 trial. Nat Med. 2022 Sep;28(9):1831-1839. | **3**. Rizvi NA, et al. MYSTIC Investigators. Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020 May 1;6(5):661-674. doi: 10.1001/jamaoncol.2020.0237. | **4.** Gandara DR, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nat Med. 2018 Sep;24(9):1441-1448. doi: 10.1038/s41591-018-0134-3.

Microsatellite Instability (MSI)

MSI (microsatellite instability, MSI) refers to the phenomenon that the sequence of microsatellites increases or decreases. Microsatellite (MS), also called Short Tandem Repeats (STRs) or Simple Sequence Repeat (SSRs), consists of repeated sequences of 1-6 nucleotides. This report uses NGS panel detection and is based on the 1021 Panel platform. The results of MSI are divided into three types: MSI-H, which means microsatellites are highly unstable; MSS, which means microsatellites are stable; MSI-U, which means that the sample does not meet the MSI evaluation conditions (tissues or pleural fluid samples may not have passed the MSI indicator calculation quality control due to the low DNA and/or content of tumor cells).

FDA approved pembrolizumab for solid tumors with MSI-H or dMMR (highly unstable microsatellites or MMR defects) and approved for MSI-H or dMMR colorectal cancer as the first-line treatment (PMID: 35680043, 33264544). FDA approved nivolumab for the treatment of children or adults who have progressed after 5-FU/oxaliplatin/irinotecan treatment with MSI-H or dMMR metastatic colorectal cancer. The NCCN clinical practice guidelines for colorectal cancer indicate that pembrolizumab/nivolumab can be used for the treatment of patients with dMMR/MSI-H colorectal cancer (PMID: 28734759).

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

12.c. Methodology

ctDNA analysis was performed using plasma-extracted cfDNA, in combination with DNA extracted from leukocytes as a control to avoid the detection of false positive results due to clonal hematopoiesis mutations. The MagMAX Cell-Free DNA Isolation Kit (Thermofischer Scientific) and the MagCore Genomic DNA Whole Blood Kit (RBC Bioscience) were used for cfDNA and genomic DNA extraction respectively. A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology Multi-Gene Variant Assay (GenePlus) which is a qualitative test that detects variants in 1021 tumor-related genes and gene rearrangements / fusions in 38 genes. Sequencing was carried out on an MGI sequencing platform (DNBSEQ-G400). The analysis includes the entire exon regions of 312 genes, introns/promoters/fusion breakpoint regions of 38 genes and partial coding exons of 709 genes. The test also reports 30+ immune response biomarkers, including Tumor Mutational Burden (TMB) score and Microsatellite Instability (MSI) status.

Sequencing data are analyzed through bioinformatics pipeline for variant calling and interpretation using the Gene+Box data analysis and management system.

Sensitivity: Positive reference standards are tested with the assay, all corresponding mutation sites can be accurately detected, and the positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs) assessed was 100%. Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 100%.

Limit of Detection (LoD): The limit of detection (LoD) of this assay is listed in the table below. The LoD is based on as low as 30 ng of gDNA input for library preparation.

Variant Type	Limit of Detection
Single nucleotide variations (SNV)	VAF ≥0.3%
Insertions/deletions (Indel)	VAF ≥0.3%
Fusion (or rearrangement)	VAF ≥0.5%

Disclaimer

1. This test is mainly used to assist clinical decision-making and the result does not represent clinical decision.
2. The test should be interpreted by combining the actual patient context. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.
3. The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: https://clinicaltrials.gov/.
4. As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
5. Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follows guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).

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Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens,
Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

6. Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phaseIII-ucsc), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (2013-12-06), Clinvar (2018-8) and Cosmic(V80).

Limitations

1. The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
2. Limited cell free tumor DNA (ctDNA) amount could result in false negative results.
3. Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
4. Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
6. Fraction of base quality ≥ Q30: The proportion of base quality in sequencing data that reaches or exceeds Q30, indicating that the probability of base recognition accuracy rate exceeds 99.9%.
7. Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.

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52, Spaton Ave., 15344,Gerakas, Athens,
Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

12.d. Quality Control Results

Quality Control Index		Result	Criterion
Sequencing Quality Assessment	Average effective sequencing depth[1]	2889	≥ 1000
	Fraction of target covered with ≥ 50x[2]	100%	≥99%
	Fraction of base quality ≥ Q30[3]	93%	≥80%
Overall Assessment[4]		PASS	

Note :

1. Average effective sequencing depth : Average sequencing depth on target without duplicated reads.
2. Fraction of target covered with ≥ 50x : The proportion of bases that sequencing depth reach or above 50x on target, this index reflecting the coverage uniformity of sequencing.
3. Fraction of base quality ≥ Q30 : The proportion of base quality in sequencing data that reach or above Q30, that is the probability of base recognition accuracy rate exceeds 99.9%.
4. Overall Assessment : The quality control overall assessment results are divided into two levels: "PASS" and "RISK". When the overall quality assessment result is "RISK", 94-96% of coverage was achieved in the genes analysed, hence there is a small range where clinical actionable variations could be undetected.

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

12.e. Genes Analyzed

312 genes including all exon regions and available for detecting SNV / Indel / CNV									
ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	APC	AR	ARAF	ARID1A
ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2
AXL	B2M	BAP1	BARD1	BCL2	BCL2L1	BCOR	BLM	BMPR1A	BRAF
BRCA1	BRCA2	BRD4	BRIP1	BTK	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD274	CDC73	CDH1	CDK12	CDK4	CDK6	CDK8
CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP
CRKL	CSF1R	CTCF	CTNNA1	CTNNB1	CUL3	CYLD	DAXX	DDR1	DDR2
DICER1	DNMT3A	DOT1L	EGFR	EIF1AX	EMSY	EP300	EPAS1	EPCAM	EPHA2
EPHA3	EPHA5	EPHB1	EPHB6	ERBB2	ERBB3	ERBB4	ERCC1	ERCC3	ERCC4
ERCC5	ERG	ERRFI1	ESR1	EXT1	EXT2	EZH2	FAM123B	FAM175A	FANCA
FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FANCM	FAS	FAT1	FAT2
FBXW7	FGF19	FGF3	FGF4	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN
FLT1	FLT3	FLT4	FOXA1	FOXL2	FOXP1	FUBP1	GALNT12	GATA3	GNA11
GNAQ	GNAS	GRIN2A	GRM3	HDAC1	HGF	HNF1A	HOXB13	HRAS	IDH1
IDH2	IFNG	IFNGR1	IGF1R	IKBKE	IKZF1	IL7R	INPP4B	IRF2	IRS2
JAK1	JAK2	JAK3	JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT
KRAS	LRP1B	MAF	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAPK1	MAX	MCL1
MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MLH3	MLL
MLL2	MLL3	MPL	MRE11A	MS4A1	MSH2	MSH3	MSH6	MST1R	MTOR
MUTYH	MYC	MYCL1	MYCN	MYD88	NBN	NCOR1	NF1	NF2	NFE2L2
NFKB1A	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NSD1	NTHL1	NTRK1
NTRK2	NTRK3	PALB2	PARK2	PARP1	PAX5	PBRM1	PCK1	PDCD1	PDCD1LG2
PDGFRA	PDGFRB	PDK1	PIK3CA	PIK3CB	PIK3CG	PIK3R1	PIK3R2	PMS1	PMS2
POLD1	POLE	POT1	PPP2R1A	PRDM1	PRKAR1A	PTCH1	PTCH2	PTEN	PTPN11
PTPRD	RAC1	RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1
RARA	RB1	RBM10	RECQL	RECQL4	RET	RHOA	RICTOR	RINT1	RNF43
ROS1	RPTOR	RUNX1	SDHA	SDHAF2	SDHB	SDHC	SDHD	SERPINB3	SERPINB4
SETD2	SF3B1	SLX4	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1
SOX2	SOX9	SPOP	SRC	STAG2	STAT3	STK11	SUFU	SYK	TBX3
TCF7L2	TERC	TET2	TGFBR2	TMEM127	TMPRSS2	TNFAIP3	TNFRSF14	TOP1	TOP2A
TP53	TSC1	TSC2	TSHR	U2AF1	VEGFA	VHL	WRN	WT1	XPO1
XRCC2	ZMAT3								

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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38 genes including specific intron, promoter and fusion breakpoint regions and available for detecting gene rearrangement or fusion									
ALK	BCL2L11	BRAF	BRCA1	BRD4	CD74	EGFR	EML4	ERG	ETV6
EZR	FGFR1	FGFR2	FGFR3	KIF5B	KIT	MAML2	MET	MSH2	MYC
MYCL1	NCOA4	NOTCH2	NTRK1	NTRK2	NTRK3	PDGFRA	RAF1	RET	ROS1
RSPO2	SDC4	SLC34A2	TERT	TFE3	TMPRSS2	TPM3	PMS2		
709 genes including partial exon regions and available for detecting SNV / Indel									
ABCA13	ABCB1	ABCC1	ABCC11	ABCC2	ABCG2	ABL2	ACACA	ACIN1	ACTB
ACTG1	ACTG2	ACVR2A	ACVRL1	ADAM29	ADAMTS5	ADCY1	AFF1	AFF2	AFF3
AHNAK	AKAP9	ALB	AMOT	ANGPT1	ANK3	ANKRD11	ANKRD30A	ANKRD30B	APEX1
APOBEC3B	ARAP3	ARFGEF1	ARFGEF2	ARHGAP29	ARHGAP35	ARID4B	ARID5B	ARNT	ASCL4
ASH1L	ASMTL	ASPM	ASTN1	ASXL2	ATIC	ATP11B	ATP12A	ATP1A1	ATP2B3
BAZ2B	BBC3	BBS9	BCAS1	BCL10	BCL11A	BCL11B	BCL2A1	BCL2L11	BCL3
BCL6	BCL9	BCORL1	BCR	BIRC3	BMPR2	BNC2	BPTF	BRD2	BRD3
BRSK1	BRWD1	BTLA	BUB1	C15orf23	C15orf55	C1QA	C1S	C3orf70	C7orf53
C8orf34	CACNA1E	CADM2	CALR	CAMTA1	CASP1	CASQ2	CBLB	CBR1	CBR3
CCDC168	CCNA1	CCNB3	CCT3	CCT5	CCT6B	CD22	CD33	CD5L	CD74
CDA	CDH11	CDH18	CDH23	CDK13	CHD1	CHD1L	CHD4	CHD6	CHD8
CHD9	CHFR	CHI3L1	CHN1	CIITA	CLDN18	CLP1	CLSPN	CLTC	CNOT3
CNOT4	CNTN1	CNTN5	CNTNAP1	CNTNAP5	COL1A1	COL2A1	COL5A1	COL5A2	COL5A3
COPS2	CPS1	CRIPAK	CRLF2	CRNKL1	CRTC1	CSF1	CSF3R	CSMD1	CSMD3
CSNK1A1	CSNK1G3	CTLA4	CTNNA2	CTNND1	CUX1	CXCR4	CYBA	CYP19A1	CYP1A1
CYP1B1	CYP2A13	CYP2C8	CYP2D6	CYP3A4	CYP3A5	DCC	DDX3X	DDX5	DEK
DHX35	DHX9	DIAPH1	DIS3L2	DLC1	DMD	DNAH6	DNAJB1	DNM2	DNMT1
DNMT3B	DOCK2	DOCK7	DPYD	DRGX	DTX1	DUSP22	DYSF	E2F3	EBF1
ECT2L	EED	EEF1A1	EGFL7	EGR3	EIF2AK3	EIF2C3	EIF3A	EIF4A2	EIF4G3
ELAC2	ELF1	ELF3	ELMO1	ELN	EME2	EMID2	EML4	EPC1	EPHA1
EPHA4	EPHA7	EPHB2	EPHB4	EPOR	EPPK1	EPS15	ERBB2IP	ERCC2	ESR2
ETS1	ETV1	ETV5	ETV6	EWSR1	EZR	F8	FAM131B	FAM135B	FAM157B
FAM46C	FAM5C	FAP	FASLG	FAT3	FAT4	FCGR1A	FCGR2A	FCGR2B	FCGR3A
FCRL4	FGF10	FGF12	FGF14	FGF23	FGF6	FLG	FLI1	FLNC	FMN2
FN1	FNDC4	FOXA2	FOXO1	FOXO3	FOXQ1	FRMPD4	FUS	FXR1	FYN
FZD1	G3BP1	G3BP2	GAB2	GABRA6	GATA1	GATA2	GFRAL	GIGYF1	GKN2
GLB1L3	GLI1	GLI2	GLI3	GMPS	GNA13	GNG2	GPC3	GPR124	GPS2

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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GPX1	GRB7	GSK3B	GSTM5	GSTP1	GUSB	H3F3A	H3F3B	H3F3C	HCLS1
HCN1	HDAC4	HDAC9	HECW1	HEY1	HIST1H1C	HIST1H1D	HIST1H1E	HIST1H2AC	HIST1H2AG
HIST1H2AL	HIST1H2AM	HIST1H2BC	HIST1H2BD	HIST1H2BJ	HIST1H2BK	HIST1H2BO	HIST1H3B	HIST1H3C	HIST1H3D
HIST1H3F	HIST1H3G	HIST1H3H	HIST1H3I	HIST1H4I	HIST3H3	HLA-A	HLA-B	HLA-C	HLF
HMCN1	HNF1B	HNRPDL	HOXA11	HOXA13	HOXA3	HOXA9	HOXC13	HOXD11	HOXD13
HSD3B1	HSP90AA1	HSP90AB1	HSPA8	HSPD1	HSPH1	ICK	ICOSLG	ID3	IFITM3
IGF1	IGF2	IGF2R	IGLL5	IKZF2	IKZF3	IL10	IL1RAPL1	IL21R	IL6
IL6ST	IMPG1	ING1	INHBA	INPP4A	INPPL1	INSR	IRF4	IRF6	IRS1
ITGB3	ITK	ITSN1	JARID2	KALRN	KAT6A	KAT6B	KCNJ5	KCNQ2	KDM2B
KEL	KIF5B	KLF4	KLHL6	KLK1	KRTAP5-5	L3MBTL1	LAMA2	LATS1	LATS2
LCP1	LEF1	LGALS8	LIFR	LPHN2	LPP	LRP2	LRP4	LRP5	LRP6
LRRC7	LRRK2	LYN	LZTS1	MACF1	MAD1L1	MAGI2	MAML2	MAML3	MAP3K13
MAPK3	MCC	MCM3	MDC1	MECOM	MEF2C	MGA	MIB1	MIOS	MKL1
MLL4	MLLT3	MMP11	MMP2	MN1	MNDA	MNX1	MSH4	MSN	MSR1
MTHFR	MTRR	MUC5B	MYH11	MYH14	MYH9	MYO3A	MYOD1	NAP1L1	NAV3
NCAM2	NCF2	NCF4	NCK1	NCOA3	NCOA4	NCOR2	NCSTN	NDUFA13	NFATC4
NFE2L3	NKX3-1	NLRC3	NOD1	NOS3	NOTCH4	NQO1	NR1I2	NR2F2	NR4A2
NRG1	NRP2	NRXN1	NTM	NUMA1	NUP107	NUP210	NUP93	NUP98	OBSCN
OGDH	OMD	OPCML	OR11G2	OR2T4	OR4A15	OR4C6	OR5L2	OR6F1	P2RY8
P4HB	PABPC1	PABPC3	PAG1	PAK1	PAK3	PASK	PAX3	PAX7	PC
PCDH18	PCSK6	PCSK7	PDCD11	PDE4DIP	PDGFB	PDILT	PER1	PGR	PHF1
PHF6	PIK3C2A	PIK3C2B	PIK3C2G	PIK3C3	PIM1	PKD1L2	PKHD1	PLAG1	PLCB1
PLCG1	PLCG2	PLK1	PLXNA1	PLXNB2	PNRC1	POLQ	POM121	POM121L12	POU2AF1
PPM1D	PPP1R17	PPP6C	PRDM16	PREX2	PRF1	PRKAA1	PRKCB	PRKCI	PRKDC
PRRX1	PRX	PSG2	PSIP1	PSMB1	PSMB5	PTGS1	PTGS2	PTPN13	PTPN2
PTPRB	PTPRK	PTPRO	PTPRS	PTPRT	PTPRU	RAB35	RAC2	RAD21	RAD54B
RANBP2	RASA1	RASGRP1	RBL1	REL	RELN	RFC1	RGS3	RHEB	RHOH
RHOT1	RIT1	RNASEL	ROBO1	ROBO2	ROBO3	ROCK1	RPGR	RPS6KB1	RPS6KB2
RSPO2	RSPO3	RUNX1T1	RUNX2	RXRA	RYR1	RYR2	SBDS	SCUBE2	SDC4
SEC31A	SEMA3A	SEMA3E	SEMA6A	SERPINA7	SETBP1	SETDB1	SF1	SF3A1	SFPQ
SGCZ	SGK1	SH2B3	SH2D1A	SH3PXD2A	SHH	SI	SIN3A	SLC16A1	SLC1A2
SLC22A16	SLC22A18	SLC22A2	SLC22A3	SLC34A2	SLCO1B3	SLIT1	SLIT2	SMARCD1	SMARCE1
SMC1A	SMC1B	SNCAIP	SNTG1	SNX29	SOD2	SOS1	SOX10	SOX17	SPEN
SPRR3	SPSB4	SPTA1	SRD5A2	SRGAP1	SRGAP3	SRSF2	SRSF7	STAG1	STAT1
SUCLG1	SUCLG2	SULT1A1	SUZ12	SVEP1	SYNCRIP	SYNE1	TAF1	TAF15	TAF1L
TAL1	TBL1XR1	TBX15	TBX22	TCEB1	TCF12	TCF3	TCF4	TCL1A	TEC

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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TENM3	TERT	TET1	TFDP1	TFDP2	TFE3	TGFBR1	THBS2	TJP1	TLE1
TLL2	TLR4	TLX3	TMEM132D	TNFSF11	TNN	TP53BP1	TP63	TP73	TPM3
TPR	TRAF2	TRAF7	TRIM24	TRIM58	TRIO	TRPC5	TRRAP	TSHZ2	TSHZ3
TTF1	TUBA3C	TUBB3	TUSC3	TXNIP	TYMS	TYR	UBE2D2	UBR5	UGT1A1
UMPS	UPF3B	USH2A	USP6	USP8	VEZF1	VIM	VTCN1	WASF3	WDR90
WDTC1	WHSC1	WHSC1L1	WIPF1	WNK1	WNT5A	WSCD2	WWOX	WWP1	WWP2
XIAP	XPC	XRCC1	XRCC3	YAP1	YY1AP1	ZBTB16	ZC3H11A	ZFHX3	ZFP36L1
ZFP36L2	ZFPM2	ZIC3	ZNF217	ZNF384	ZNF521	ZNF638	ZNF750	ZNF804B	

Genes analyzed for germline mutations

APC	ATM *1	ATR *1	AXIN2	BAP1 *1	BARD1 *1	BLM *1	BMPR1A	BRCA1*1*2	BRCA2*1*2
BRIP1 *1	CDH1	CDK4	CDKN2A	CHEK2*1*2	EPCAM*2	FAM175A*1	FANCA *1	FANCL*1	FANCM *1
GALNT12	HOXB13	MEN1	MITF	MLH1	MRE11 *1	MSH2*2	MSH3	MSH6*2	MUTYH*2
NBN *1	NF1	NTHL1	PALB2*1*2	PMS2	POLD1	POLE	PTEN	RAD50*1*2	RAD51B*1
RAD51C*1*2	RAD51D*1*2	RET	RNF43	SMAD4	SMARCA4	STK11	TP53*2	VHL	

*1 Genes of the homologous recombination (HR) complex
*2 Unless otherwise noted analysis of large rearrangement was performed on the following genes: BRCA1, BRCA2, CHEK2, EPCAM (Exons 8, 9), MLH1, MSH2, MSH6, MUTYH, PALB2, RAD50 (Exons 1, 2, 4, 10, 14, 21, 23 and 25), RAD51C, RAD51D, and TP53.

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Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens,
Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

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Genekor Medical S.A.
52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
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12.f. Levels of Evidence for Genomic Biomarkers

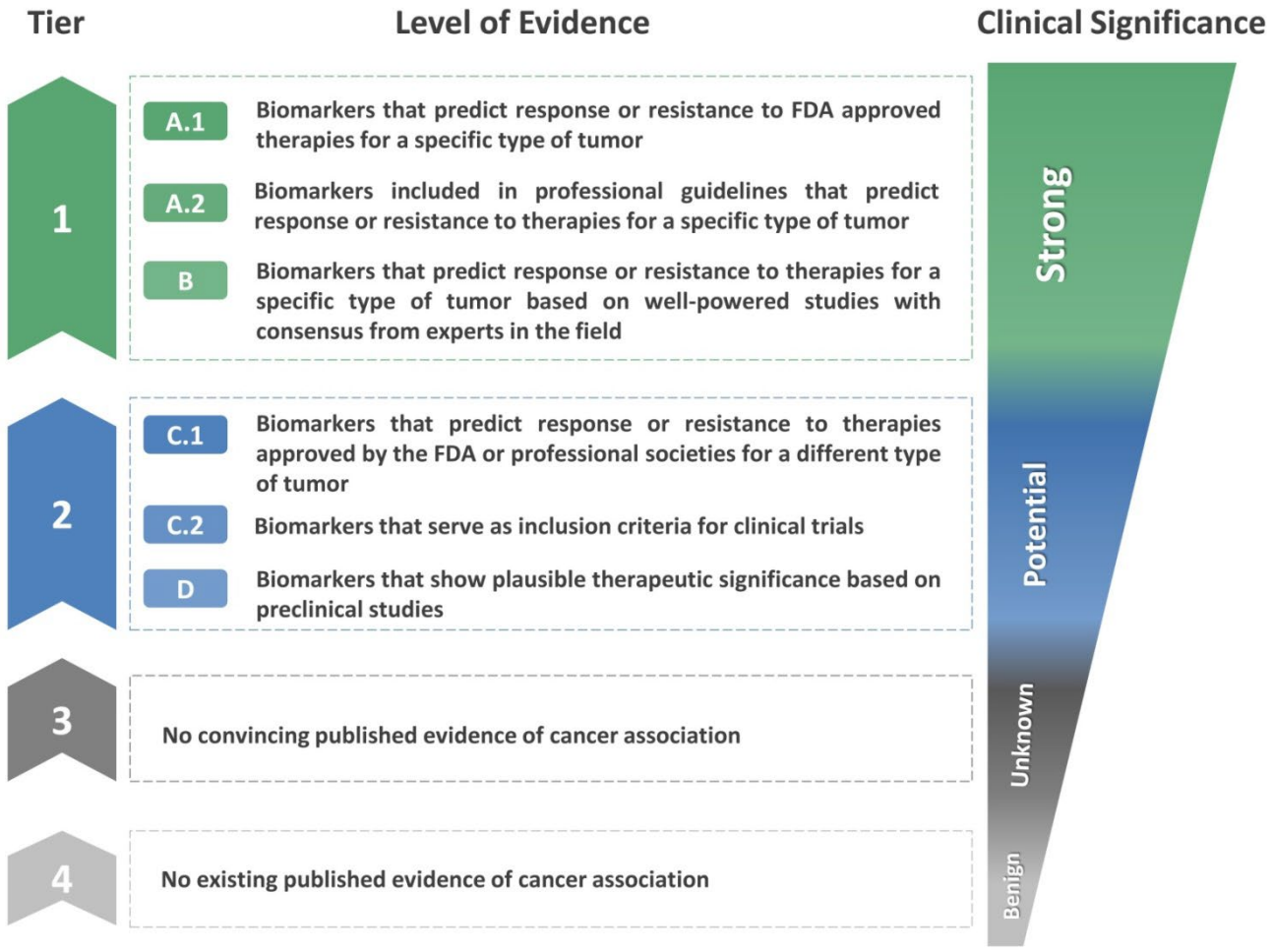

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
info@genekor.com www.genekor.com
Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

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52, Spaton Ave., 15344,Gerakas, Athens, Greece, G.E.MI. nr: 0007856001000
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Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: Report No:

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