



Order ID: 118877

Clinical ID: NOP4455

Indication: Non-Small Cell Lung Cancer(NSCLC)

Physician: Dr. White

Patient Age: 70

Patient Gender: Female

Patient Status: Newly Diagnosed

Biopsy Date: 2019-09-20

Sample Type: FFPE

Genomic Input: Whole Exome Sequence

Additional Input: NA

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1. Drug Response Prediction

Therapies of Interest	Patient Predicted Response				
CABOZANTINIB	Responder				
CARBOPLATIN_ETOPOSIDE	Responder				
CARBOPLATIN_GEMCITABINE	Responder				
CARBOPLATIN_PACLITAXEL	Responder				
CARBOPLATIN_PACLITAXEL_RADIATION	Responder				
CARBOPLATIN_PEMETREXED	Responder				
CARBOPLATIN_PEMETREXED_RADIATION	Responder				
CISPLATIN_ETOPOSIDE	Responder				
CISPLATIN_ETOPOSIDE_RADIATION	Responder				
CISPLATIN_GEMCITABINE	Responder				
CISPLATIN_PACLITAXEL	Responder				
CISPLATIN_PEMETREXED	Responder				
CISPLATIN_PEMETREXED_RADIATION	Responder				
RADIATION	Responder				
AFATINIB	Non-Responder				
ALECTINIB	Non-Responder				
BRIGATINIB	Non-Responder				
CERITINIB	Non-Responder				

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Therapies of Interest	Patient Predicted Response			
CRIZOTINIB	Non-Responder			
DABRAFENIB	Non-Responder			
DABRAFENIB_TRAMETINIB	Non-Responder			
ERLOTINIB	Non-Responder			
GEFITINIB	Non-Responder			
GEMCITABINE	Non-Responder			
METHOTREXATE	Non-Responder			
OSIMERTINIB	Non-Responder			
PACLITAXEL	Non-Responder			
PEMETREXED	Non-Responder			
VANDETANIB	Non-Responder			
VEMURAFENIB	Non-Responder			

^{*}For more details of actionable molecular target(s) and pathway(s), please check this link.





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2. Patient Disease Characteristics: Key Biomarker(s)

DDIT3	PFKM
CHEK2	PIK3CA
H2AFX	PRKCE
IKBKB	PTK2
PARP1	ROCK1

^{*}For more details on selected biomarker(s) and its impact on patient's disease profile, please check this <u>link</u>.

3. Biomarker Impact Score

Theresis of leteres	Patient Biomarker Characteristics									
Therapies of Interest	DDIT3	CHEK2	H2AFX	IKBKB	PARP1	PFKM	PIK3CA	PRKCE	PTK2	ROCK1
CABOZANTINIB				~		~	~	~	~	~
CARBOPL <mark>ATIN_</mark> ETOPOSIDE	~	~	~	✓	~	~	~	~	~	~
CARBOPLAT <mark>IN_GE</mark> MCITABINE	~	~	~	✓	~	~	~	~	~	~
CARBOPLAT <mark>IN_PA</mark> CLITAXEL	~	~	~	~	~	~		~	~	~
CARBOPLATIN_PA <mark>CLITAX</mark> EL_RADIATION	~	~	~	✓	~	~		~	~	~
CARBOPLA <mark>TIN_PE</mark> METREXED	~	~	~	~	~	~	~	~	~	~
carboplatin_ <mark>pemetr</mark> exed_radiation	~	~	~	✓	~	~	~	~	~	~
CISPLATIN_ETOPOSIDE	~	~	~	✓	~	~	~	~	~	~
cisp <mark>latin_etop</mark> oside_radiation	~	~	~	~	~	~	~	~	~	~

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Th				Patient	Biomarke	er Charac	teristics			
Therapies of Interest	DDIT3	CHEK2	H2AFX	IKBKB	PARP1	PFKM	PIK3CA	PRKCE	PTK2	ROCK1
CISPLATIN_GEMCITABINE	~	~	~	~	~	~	~	~	~	~
CISPLATIN_PACLITAXEL	~	~	~	~	~	~		~	~	~
CISPLATIN_PEMETREXED	~	~	~	~	~	~	~	~	~	~
cisplatin_pemetrexed_radiation	~	~	~	~	~	~	~	~	~	~
RADIATION	~	~	~	~	~	~	~	~	~	
AFATINIB				~		~	~			
ALECTINIB				~		~	~	~	~	~
BRIGATINIB				~		~	~	~	~	~
CERITINIB				~		~	~		~	
C <mark>rizoti</mark> nib				~		~	~		~	~
DA <mark>BRAFEN</mark> IB										
dabrafen <mark>ib_tra</mark> metinib				~		~		~		~
ERLOTINIB										
G <mark>EFITINIB</mark>										
GEMCITABINE				~		~		~		~
METHOTREXATE				~		~	~			~
OSIMERTINIB										
PACLITAXEL				~	~	~		~	~	~

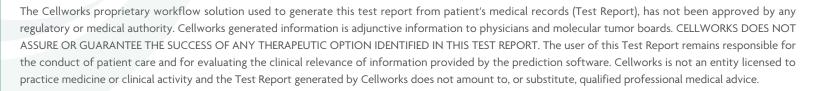




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Therapies of Interest PEMETREXED	Patient Biomarker Characteristics									
	DDIT3	CHEK2	H2AFX	IKBKB	PARP1	PFKM	PIK3CA	PRKCE	PTK2	ROCK1
			~	~	~	~		~		~
VANDETANIB				~		~	~	~	~	~
VEMURAFENIB										







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4. Summary of Patient Genomic Profile

Input Data Type Targeted Nucleotide Sequencing

Genetic Mutation(s) 51
Copy Number Variation(s) 59
Gene(s) Methylated 0

4.1 Detailed Information of Genomic Aberration(s) Modeled

4.1.1 Gene Mutation(s) with Gain of Function

ABCB1	CSF2RB	E2F4	FN1	KMT2A	MAP3K4	MYLK	NCOR1
POLM	PSPH	PTGS2	PTP4A3	PTPRG	SALL4	YBX3	

4.1.2 Gene Mutation(s) with Loss of Function

ABCB5	ALOX5AP	ARHGEF15	ASH2L	BAK1	CERS6	CES1	CHD4
DHX16	ESRRA	FOXM1	FOXO3	HSP90AA1	KAT6A	MKI67	MMP8
NOTCHI	NOTCH2	NOXO1	PIK3CG	RAD51C	RGS2	RIPK4	SETD2
SFRP1	SGPP1	SOX11	TBK1	TCF7L2	TDG	TF	TIMP2
WNK1	wwox		•	•			

4.1.3 Gene Mutations(s) with Switch of Function

IDH2	TP53
	1177

4.1.4 Gene(s) with Increase in Copy Number Variation [CNV]

AGAP2	AMPD1	ARHGEF25	B4GALNT1	CDKN3	COPS6	CUL1	EIF3K
ЕРНВ6	GPD1	GSTK1	HOXC6	ITGA5	LGALS7	MCM7	MIR25





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MIR29A	MIR29B1	MIR365A	MIR371A	MIR372	MIR373	MIR519B	MIRLET7I
NABP2	NFE2	NT5C1A	OS9	PIP4K2C	PLCG1	PRSS1	PSMA3
RYR1	SH2B2	SMARCC2	SMARCD1	TFPI2	TOP1	VASN	WDR77

4.1.5 Gene(s) with Decrease in Copy Number Variation [CNV]

ATP10A	CTSD	IGF2	INS	KLF13	MUC2	MUC5AC	NDN
NOP10	PTEN	RASA4	RASGRP1	ROS1	SEC23A	THBS1	TJP1
TOLLIP	UBE3A	ZNF91					

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5. Therapy Rationale(s)

Rationales provided in this section highlight the pathways connected to drug sensitivity and resistance and include references to supporting published literature.

Species in red denote drug impact points. Species highlighted in blue are the key biomarkers.

STATUS: **GOF:** Gain of Function Mutations; **LOF:** Loss of Function Mutations; **SOF:** Switch of Function Mutations; **AMP:** CNV Over-expression; **DEL:** CNV Knock-down:

TYPE: R: Resistant Gene/Loop for the Drug; S: Sensitive Gene/Loop for the Drug

	AFATINIB					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)		
PTEN	DEL	R	PTEN → PIKFYVE → PIKFYVE → PIKFYVE	23757022 27902463 21779440 9895304 20361045		

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	CABOZANTINIB					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)		
PTEN	DEL	S	PTEN PI345P3 PDPKI AKT TSC1_TSC2 RHEB MTOR HIFIA KDR CANCER PROGRESSION	21779440 24756794 25534569 19143635 16612574		

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	CARBOPLATIN					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)		
TP53	SOF	R	CARBOPLATIN → ICL → DSB → DNA DAMAGE Mut_TP53 → ABCB1 ← CARBOPLATIN	22296372 11483599		
RAD51C	LOF	S	CARBOPLATIN — ICL — DSB — DNA DAMAGE RAD51C — DNA REPAIR (HR) — DNA DAMAGE	28646019 3512077		





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	CISPLATIN				
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
IDH2	SOF	S	CISPLATIN — ICL — DSB — DNA DAMAGE IDH2 — TET2 — CPGMET — BRCA1/2 — DNA REPAIR (HR) — DNA DAMAGE	21130701 21203981 15546503 11536045 29367755 21870267	
TP53	SOF	R	CISPLATIN — ICL — DSB — DNA DAMAGE Mut_TP53 — ABCB1 — CISPLATIN	22296372 11483599	
RAD51C	LOF	S	CISPLATIN — ICL — DSB — DNA DAMAGE RAD51C — DNA REPAIR (HR) — DNA DAMAGE	28646019 25058905	





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DABRAFENIB					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
PTEN DEL	R	DABRAFENIB RAFI	8413257 25700356 21858223 21725359		
	K	PTEN → PI345P3 → PDPK1 → AKT → RAFI	12048182 29607117 21779440 23251089		





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ERLOTINIB					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
PTEN	DEL	R	PTEN → PIKFYVE → PIKFYVE → EGFR	27734950 19351834 22133747 19884556 19806185	





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	ETOPOSIDE					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)		
TP53	SOF	R	ETOPOSIDE → TOP2CC → DSB → DNA DAMAGE Mut_TP53 → TDP2 → TOP2CC	24766193 22508727		
RAD51C	LOF	S	ETOPOSIDE → TOP2CC → DSB → DNA DAMAGE RAD51C → DNA REPAIR (HR) → DNA DAMAGE	19377506 20824055		





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GEFITINIB					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
PTEN	DEL	R	PTEN PI345P3 → PDPK1 → AKT → PIKFYVE EGFR	14555504 15695376	





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	GEMCITABINE				
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
ABCB1	GOF	R	GEMCITABINE → dFdCTP → DNA DAMAGE ABCB1 ← GEMCITABINE	10340887 19598259 25564970 18765824	
NT5C1A	AMP	R	GEMCITABINE	28077438 10340887	
TP53	SOF	R	GEMCITABINE	27048304 11802204 21804948 19010910 1406603 26067754	





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METHOTREXATE					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
TP53	SOF	R	METHOTREXATE DHFR Mut_TP53 DHFR (High level of DHFR expression confers reduced sensitivity to Methotrexate)	12359872 9649296	





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OSIMERTINIB					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
PTEN	DEL	R	OSIMERTINIB — EGFR PTEN — PI345P3 — PDPK1 — AKT — PIKFYVE EGFR	23757022 28565936 21779440 26473643 19351834	





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	PACLITAXEL					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)		
PTEN	DEL	R	PACLITAXEL SPINDLE POISON ANAPC1_CDC26_CDC20 CCNB1_CDK1 MITOTIC_CATASTROPHE MITOTIC_SLIPPAGE APOPTOSIS PTEN PI345P3 PDPK1 AKT AKTIS1 MTOR HIFIA TUBB3 PACLITAXEL	18466115 17386266 18515545 18178340 17502379 23364970 19143635 15094766 14673156 22354785 21779440 20361045 19143636		





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PEMETREXED					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
TP53	SOF	R	PEMETREXED TYMS DNA DAMAGE Mut_TP53 MYC TYMS (Increased levels of TYMS diminish the effective levels of PEMETREXED)	26502926 20628382 16107691 24040222	





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RADIATION					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
SETD2	LOF	S	RADIATION → DSB → DNA DAMAGE SETD2 → H3K36 METHYLATION → BRCA1 → DNA REPAIR (HR) → DNA DAMAGE	24931610 25988165 12947386 17629934 24003211	
PTEN	DEL	R	PTEN AKT PRKDC DNA REPAIR (NHEJ) DNA DAMAGE	18644989 17513297 19404218 17431403 21779440	
TP53	SOF	R	RADIATION — DSB — DNA DAMAGE Mut_TP53 — KMT2A — H3K4 METHYLATION — BRCA1 DNA REPAIR (HR) — DSB	21670155 29343972 29662640 26331536 10373498 28375985 23849504	
RAD51C	LOF	S	RADIATION → DSB → DNA DAMAGE RAD51C → DNA REPAIR (HR) → DNA DAMAGE	28646019 20490962 28076755	





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TRAMETINIB					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
PTEN	DEL	R	TRAMETINIB ■ MAP2K1/2 PTEN ■ PI345P3 ■ PDPK1 ■ AKT ■ RAF MAP2K1/2 ■ MAP2K1/2 ■ RAF ■ RAF<	12087097 15023437 23453810 21523318 24811175	





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VANDETANIB					
Gene	Gene Status Type Gene Status Drug Action Pathway(s)				
PTEN	DEL	R	VANDETANIB ──■ EGFR PTEN ──■ PI345P3 ── PDPK1 ── AKT ── PIKFYVE ■■ EGFR	19491268 14555504	





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VEMURAFENIB					
Gene	Status	Туре	Gene Status Drug Action Pathway(s)	Supporting PMID(s)	
PTEN DEL		VEMURAFENIB ——— RAFI	8413257 25700356 21858223 21725359		
	DEL	R	PTEN → PDPK1 → AKT ← RAFI	12048182 23116250 29607117 21779440	





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6. Genomic Aberration to Key Biomarker Pathway(s)

This section provides a snapshot of paths connecting the most significant gene aberrations with patient biomarkers and references to published research supporting these pathways.

RED: Gain of Function/Switch of Function Mutation(s) or Amplified Gene(s)

BLUE: Loss of Function Mutation(s) or Deleted Gene(s)

TRANSCRIPTION FACTORS:

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)		
	EIF3K — EIF3E — EIF4E — MCL1 — BECN1 — MAP3K7 — MAP2K3 — MAPK14 — DDIT3	15273249	20978232	9430721
DDIT3	SETD2 — BBC3 — BCL2 — MAP3K7 — MAP2K3 — MAPK14 — DDIT3	10748100 17322918 9430721	15273249 18585004	15694340 20978232
	COPS6 → MAP3K1 → MAP2K3 → MAPK14 → DDIT3	15273249 9430721	20978232	26237449
	PTEN BBC3 BCL2 MAP3K7 MAP2K3 MAP2K3 DDIT3	10748100 17322918 9430721	15273249 20978232	15694340 21873427
	FOXO3 → BECN1 → MAP3K7 → MAP2K3 → MAPK14	15273249 9430721	18054311	20978232
	AGAP2 → PRKAA1 → MAPK14 → DDIT3	16179588		

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KINASE**:

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
PFKM	AGAP2 PRKAA1 PFKM	21258367
	SMARCC2 PRDM1 IL2 IL2RB_JAK1 JAK3 PLCG1 PRKCE	15039446 8026467 8598449
PRKCE	PLCG1 → PRKCE	24692553
	AGAP2 PRKAA1 PRKCE	26797128
PTK2	SMARCC2 → MMP9 → IGFBP2 → ITGA5_ITGB1 → PTK2	16569642 19889638 20514406 8649427
	PLCGI → PRKCA → VCL → ITGA1_ITGB1 → PTK2	11741957 12138200 19889638 8649427
	AGAP2 → PRKAA1 → PRKCA → VCL → ITGA1_ITGB1	11741957 12138200 19889638 8649427
	SMARCC2 PROM1 IL2 IL2RB_JAK1 JAK3 PLCG1 PRKCA IKBKB	10022904 15039446 8026467 8598449
IKBKB	PLCG1 → PRKCA → IKBKB	10022904
	AGAP2 → PRKAA1 → PRKCA → IKBKB	10022904
ROCKI	SMARCC2 PRDM1 IL2 IL2RB_JAK1 JAK3 PLCG1 PRKCE RHOA ROCK1	15039446 8026467 8598449
	PLCG1 → PRKCE → RHOA → ROCK1	23828571
	TJP1 → TJP1_TJP2 → RHOA → ROCK1	23828571
	AGAP2 → PRKAA1 → PRKCE → RHOA → ROCK1	23828571





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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)			
	SMARCC2 → MMP9 → IGFBP2 → ITGA5_ITGB1 → PTK2 → PIK3CA	11114741 18039660 8649427	15539082 19889638	16569642 20514406	
	PLCG1 → PRKCA → EZR → PIK3CA	10377409			
PIK3CA	TJP1 → TJP1_TJP2 → ROCK1 → EZR → PIK3CA	23828571			
	FOXO3 → SIRTI → SH2B2 → CBL → AXL → PIK3CA	11406619 15031295 22219356 9687507	11425860 15958209 8995358 9989826	11997497 16129412 9233773	
	AGAP2 → PIK3CA PIK3CA	11438544	18281483	19230867	

^{**} Assayable key kinase biomarkers identified for this patient.





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7. Singula™ Assessment sections

1. Drug Response Prediction

This section illustrates predicted response to Standard Care therapy or any specific therapy of interest for an indication. The response is indicated as an easily interpretable, 'Responder' or 'Non-Responder'.

2. Patient Disease Characteristics: Key Biomarker(s)

Using biosimulation modeling, Cellworks determines key biomarkers in the patient's genomic profile. They are points of convergence of the pathways impacted by the mutations in the patient's profile. These key biomarkers are tumor promoter/suppressor genes that the drug needs to impact in order for the patient to repsond to treatment.

3. Biomarker Impact

This table shows the impact that the therapies of interest have on the 'Key Biomarkers' identified for the patient profile. The check symbol (' \checkmark ') implies that the therapy is predicted to be successful in impacting the biomarker. Not all therapies impact key biomarkers equally. Please see the therapy rationale in Section 5 for a more thorough explanation.

4. Summary of Patient Genomic Profile

This section provides an aggregated overview of the patient genomics used for therapy assessment. It shows the type of input received from the next generation sequencing data (NGS) with the number of genetic mutations, copy number variations (CNVs) and any epigenetic data that is reported.

4.1 Detailed Information of Genomic Aberration(s) Modeled

This section lists all the mutations, CNVs and epigenetic data which are modelled via the Cellworks biosimulation for the patient. This information forms the patient-specific input on which a Cellworks assessment is based.

5. Therapy Rationales

A therapy rationale illustrates the role of key mutations in causing sensitivity or resistance to drugs. A drug will have a therapy rationale for every mutation that contributes significantly to its sensitivity or resistance.

The first illustration in the rationale defines the mechanism of action of the drug.

The second illustration articulates the signalling or metabolic pathway by which the mutation of interest contributes to drug sensitivity or resistance including the point of intersection (if any) with the drug's mechanism of action.

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Clinical ID: NOP4455 Cellworks ID: 118877 Ref Physician: Dr.White

Biopsy Sequence: 1 Gender/Age: Female / 70 Date of Report: Dec 19, 2019

Indication: Non-Small Cell Lung Cancer(NSCLC)

The description is accompanied by relevant PMIDs that were used to determine the interaction.

6. Genomic Aberration to Key Biomarker Pathway(s)

This section illustrates moelecular biochemical pathways from a genomic aberration in the patient profile to critical biomarkers identified by Cellworks biosimulation. The description is accompanied by relevant PMIDs that were used to determine the interaction

Regarding Toxicity

The current assessment assumes that the drugs are faithfully delivered to the site of action. Cellworks considers all molecular interactions once delivered to the site of action (Pharmacodynamics of the drug compound). Cellworks does not account for absorption, distribution, metabolism & excretion (ADME) properties of the drug that determine how the drug is delivered to the site of action. Any toxicity in the delivery process, or pharmacokinetics, is not considered.





Clinical ID: NOP4455 Cellworks ID: 118877 Ref Physician: Dr. White

Biopsy Sequence: 1 **Gender/Age:** Female / 70 **Date of Report:** Dec 19, 2019

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8. Terms of Usage

Cellworks Therapeutic Solutions

The Cellworks proprietary workflow solution used to generate this test report from patient's medical records (Test Report), has not been approved by any regulatory or medical authority. Cellworks generated information is adjunctive information to physicians and molecular tumor boards. CELLWORKS DOES NOT ASSURE OR GUARANTEE THE SUCCESS OF ANY THERAPEUTIC OPTION IDENTIFIED IN THIS TEST REPORT. The therapeutic options provided in the Test Report are not ranked in order of efficacy, safety or cost-effectiveness and are sorted based on our model's analysis of the input data. All individual drugs included in therapy options identified in the Test Report have been cleared and approved by the United States Food and Drug Administration (FDA) for other indications. At the specific request of the patient or treating physician, the Test Report may identify drugs or therapy options that are also in an advanced stage of clinical trials and yet to be approved. This will provide adjunctive information to the physicians for selecting a clinical trial for the patient.

Therapeutic agents associated with potential benefit or lack of benefit, as indicated in the Test Report are based on biomarker results provided in the report and on published evidence with PMID references. This evidence in some cases may have been obtained from studies performed in the cancer type present in the tested patient's sample.

No Guarantee of Clinical Benefit

The finding of a biomarker expression does not necessarily indicate pharmacologic effectiveness or lack thereof. The agents identified may or may not be suitable for use with a particular patient and the Test Report does not guarantee or suggest that any particular agent will be effective with the treatment of any particular condition. The user of this Test Report remains responsible for the conduct of patient care and for evaluating the clinical relevance of information provided by the prediction software.

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