Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™
PRECISION MEDICINE

Order ID :	40002
Clinical ID :	DEF5660
Indication :	Non-Small Cell Lung Cancer(NSCLC)
Physician :	Dr. Brown
Patient Age :	32
Patient Gender :	Male
Patient Status :	Refractory
Biopsy Date :	2020-02-15
Sample Type :	FFPE
Genomic Input :	Whole Exome Sequence
Additional Input :	NA

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

1. Personalized Therapy Recommendation(s)

Drug Combination(s)
MITOMYCIN-C and REGORAFENIB
MITOMYCIN-C and TRAMETINIB
MITOXANTRONE and TRAMETINIB

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

2. Patient Disease Characteristics: Key Biomarker(s)

CHEK1	CSNK2A1
PARP1	HIF1A
CHEK2	
PLK1	
FOXM1	

*For more details on selected biomarker(s) and its impact on patient's disease profile, please check this link.

3. Biomarker Impact Score

Therapies of Interest	Patient Biomarker Characteristics						
	CHEK1	PARP1	CHEK2	PLK1	FOXM1	CSNK2A1	HIF1A
MITOMYCIN-C+REGORAFENIB	✓	✓	✓	✓	✓	✓	✓
MITOMYCIN-C+TRAMETINIB	✓		✓	✓	✓		
MITOXANTRONE+TRAMETINIB	✓	✓	✓	✓	✓	✓	✓

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

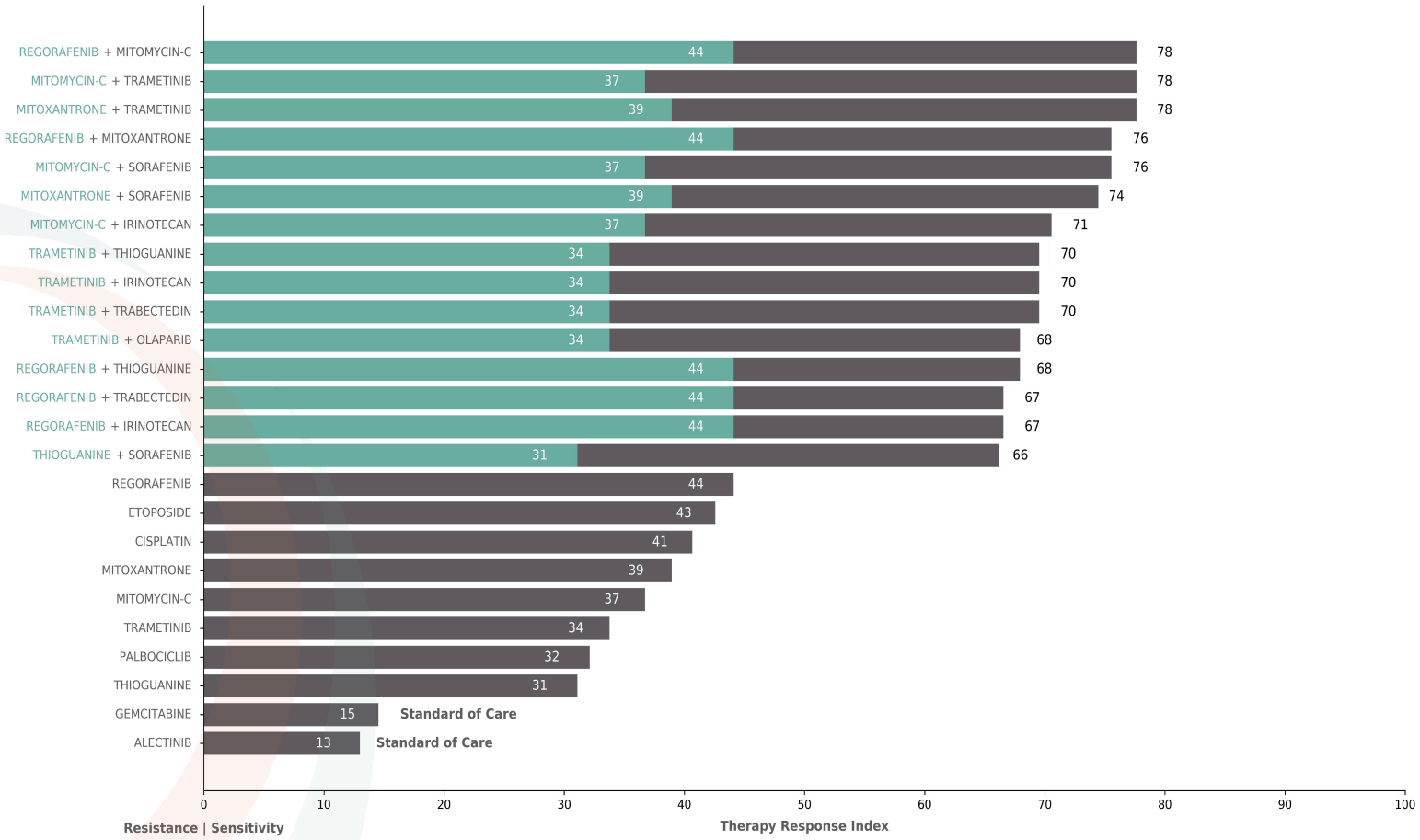
Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

4. Biosimulation of Therapy Response Index (TRI)

4.1 Top Combinations and Standard of Care Treatments



Therapy Response Index Value Color
White – Most efficacious monotherapy within combination
Black – Total Therapy Response Index

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 | **Cellworks ID:** 40002 | **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 | **Gender/Age:** Male / 32 | **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

5. Summary of Patient Genomic Profile

Input Data Type	Mutations and CNV
Genetic Mutation(s)	14
Copy Number Variation(s)	2
Gene(s) Methylated	0

5.1 Detailed Information of Genomic Aberration(s) Modeled

5.1.1 Gene Mutation(s) with Gain of Function

BRIP1	NFE2L2	NRAS	PTPRD

5.1.2 Gene Mutation(s) with Loss of Function

BMPR1A	BRCA1	KMT2D	NOTCH2	SETD2	SMARCA4	SMO	TSC1

5.1.3 Gene Mutations(s) with Switch of Function

KRAS	TP53

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

CDKN2A	CDKN2B

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

6. 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

MITOMYCIN-C				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
BRCA1	LOF	S	**MITOMYCIN-C** → **ICL** → **DSB** → **DNA DAMAGE** BRCA1 → DNA REPAIR (HR) ⊣ DNA DAMAGE	18483318 12181741 11406561
SETD2	LOF	S	**MITOMYCIN-C** → **ICL** → **DSB** → **DNA DAMAGE** SETD2 → H3K36 METHYLATION → BRCA1 → DNA REPAIR (HR) ⊣ DNA DAMAGE	24931610 12181741

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

MITOXANTRONE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
BRCA1	LOF	S	**MITOXANTRONE** → **TOP2CC** → **DSB** → **DNA DAMAGE** BRCA1 → DNA REPAIR (HR) ⊣ DNA DAMAGE	9665145 20824055 26880199 24130054 24244429

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

REGORAFENIB				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
KRAS	SOF	S	**REGORAFENIB** ⊣ **RAF1** KRAS → RAF1 → MAP2K1/2 → MAPK1/3 → FOXM1 → CANCER PROGRESSION	21170960 25213161 25838391 29279709
NRAS	GOF	S	**REGORAFENIB** ⊣ **RAF1** NRAS → RAF1 → MAP2K1/2 → MAPK1/3 → FOXM1 → CANCER PROGRESSION	21170960 25213161 25838391 29279709

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

TRAMETINIB				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
KRAS	SOF	S	**TRAMETINIB** ⊣ **MAP2K1/2** KRAS → RAF → MAP2K1/2 → MAPK1/3 → FOXM1 → CANCER PROGRESSION	21523318 10969079 25199829 21858223 25722381
NRAS	GOF	S	**TRAMETINIB** ⊣ **MAP2K1/2** NRAS → RAF → MAP2K1/2 → MAPK1/3 → MYC → FOXM1 → CANCER PROGRESSION	26347206 12835716 11773061 21858223 22507781

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

7. 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)
FOXM1	CDKN2A → ATRIP → BRCA1 ⊣ PLK1 → FOXM1	10373534 15775976 19737929 23404835 24067368
	KMT2D → CDKN1A ⊣ CCNA2_CDK2 → FOXM1	18285455
	BRCA1 ⊣ PLK1 → FOXM1	19737929 23404835 24067368
	NRAS → RALGDS → RALA → EXOC2 → TBK1 → PLK1 → FOXM1	11322487 17018283 19737929 20118982 20200357 23404835 24056301
	SETD2 → CDKN1A ⊣ CCNB1_CDK1 → FOXM1	18585004
	KRAS → RALGDS → RALA → EXOC2 → TBK1 → PLK1 → FOXM1	11322487 17018283 19737929 23404835 24056301

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
HIF1A	CDKN2A → ATRIP → BRCA1 → CDKN1A ⊣ CSNK2A1 → AKT → CALM1_NOS3 → HIF1A	10373534 10542266 11255227 11696579 12897144 14641020 15775976 16567799 19223555
	KMT2D → CDKN1A ⊣ CSNK2A1 → AKT → CALM1_NOS3 → HIF1A	11255227 11696579 12897144 14641020
	BRCA1 → CDKN1A ⊣ CSNK2A1 → AKT → CALM1_NOS3 → HIF1A	11255227 11696579 12897144 14641020 16567799
	NRAS → RALGDS → RALA → EXOC2 → TBK1 → AKT → CALM1_NOS3 → HIF1A	11322487 11696579 12897144 14641020 17018283 20118982 20200357 21106850 21329883 24056301 9188503
	SETD2 → CDKN1A ⊣ CSNK2A1 → AKT → CALM1_NOS3 → HIF1A	11255227 11696579 12897144 14641020 18585004 19622798
	KRAS → PIK3CA → PDPK1 → AKT → CALM1_NOS3 → HIF1A	10698680 11696579 12897144 14641020 22247021

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

KINASE**:

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
CSNK2A1	CDKN2A → ATRIP → BRCA1 → CDKN1A ⊣ CSNK2A1	10373534 11255227 15775976
	KMT2D → CDKN1A ⊣ CSNK2A1	11255227
	BRCA1 → CDKN1A ⊣ CSNK2A1	11255227
	NRAS → BRAF ⊣ BAD ⊣ BCL2 ⊣ BRCA1 → CDKN1A ⊣ CSNK2A1	11255227 15694340 15990872 17322918 19667065 21444675 27034005
	SETD2 → CDKN1A ⊣ CSNK2A1	11255227 18585004
	KRAS → RAF1 ⊣ BAD ⊣ BCL2 ⊣ BRCA1 → CDKN1A ⊣ CSNK2A1	11255227 15694340 15990872 17322918 19667065 21444675
PLK1	CDKN2A → ATRIP → BRCA1 ⊣ PLK1	10373534 15775976 24067368
	KMT2D → BRCA1 ⊣ PLK1	24067368
	BRCA1 ⊣ PLK1	24067368
	NRAS → RALGDS → RALA → EXOC2 → TBK1 → PLK1	11322487 17018283 20118982 20200357 24056301
	TSC1 → TSC1_TSC2 ⊣ RHEB → RPS6KB1 ⊣ BAD ⊣ BCL2 ⊣ BRCA1 ⊣ PLK1	11493700 12869586 15694340 15990872 17322918 21444675 24067368
	SETD2 → BRCA1 ⊣ PLK1	24067368
	KRAS → RALGDS → RALA → EXOC2 → TBK1 → PLK1	11322487 17018283 24056301

** Assayable key kinase biomarkers identified for this patient.

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 | **Cellworks ID:** 40002 | **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 | **Gender/Age:** Male / 32 | **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

8. Ventura™ Assessment sections

1. Personalized Therapy Recommendation(s)

This section provides the combination(s), from FDA-approved drugs that are predicted to provide best clinical response for an individual patient. As a first step to the process of identifying these combinations, drugs in the Cellworks Digital Drug Library are simulated individually on the patient's profile. The drugs that are most efficacious as monotherapy are then combinatorially simulated. The three combinations that are most efficacious are listed in this table.

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 (' ') 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 6 for a more thorough explanation.

4. Predicted Drug Sensitivity or Resistance (Histogram)

Drug Efficacy Score: This score includes Simulation Score and Biological Evidence Score for single and combination drugs. Simulation Score is the effect of the drug on the identified disease-specific biomarker(s) and phenotype(s). Biological Evidence Score is based on an algorithm that accounts for genes responsible for drug response and prioritization of indication-specific drug class.

4.1 Single Drug Efficacy Prediction

This histogram shows single drug efficacy for the patient's profile. The numbers on the Y-axis reflect the percentage of effectiveness of the drug on the patient's disease. Drugs are arranged in descending order - from the most efficacious drug that the patient profile is predicted to be sensitive to, to the least efficacious drug, that the patient profile is predicted to be resistant to.

4.2 Drug Combination Efficacy Prediction

This histogram shows drug combinations to which the patient is predicted to respond, in order of efficacy. The single drugs found to show positive impact on the patient profile, are combinatorically simulated on the patient profile to provide this output. A maximum of 20 drug combinations will be included in this section. The numbers on the Y-axis reflect the percentage of effectiveness of the drug combinations on the patient's disease

VENTURA™ PRECISION MEDICINE

Clinical ID: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

5. 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.

5.1 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.

6. 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.

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

7. 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: DEF5660 **Cellworks ID:** 40002 **Ref Physician:** Dr.Brown

Biopsy Sequence: 1 **Gender/Age:** Male / 32 **Date of Report:** May 18, 2020

Indication: Non-Small Cell Lung Cancer(NSCLC)

9. 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.

Intended Use

Cellworks is not an entity licensed to practice medicine or clinical activity and the Test Report generated by Cellworks does not amount to, or substitute, qualified professional medical advice. THIS REPORT IS PREPARED AS ADJUNCTIVE INFORMATION TO ASSIST HEALTH CARE PROVIDERS TO EVALUATE THEIR PATIENTS. CELLWORKS IS NOT RESPONSIBLE FOR ANY USE OF THIS TEST REPORT OR DATA BY ANY UNQUALIFIED PERSON. Decisions on patient care and treatment, including safety and security of treatments based on this Test Report must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition and the treatment should not solely be based on this Test Report. Cellworks provides no guarantee of the accuracy, relevance, exhaustiveness or appropriateness of any of the medical information referenced through this Test Report.

CELLWORKS DISCLAIMS ALL WARRANTIES, INCLUDING WITHOUT LIMITATION ANY IMPLIED WARRANTIES OF TITLE, NON- INFRINGEMENT, MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, IN RELATION TO INTERFACE, ITS SERVICES AND THE TEST REPORT. CELLWORKS PROVIDES NO ASSURANCE OR GUARANTEE THAT A HEALTHCARE PROVIDER, INSURER OR ANY OTHER THIRD PARTY PAYOR, WHETHER GOVERNMENTAL OR PRIVATE, WILL REIMBURSE A PATIENT FOR THE COST OF GENERATING TEST REPORT.

This is an automatically generated report. No signature is required.
--END OF THE REPORT--