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VENTURA™
PRECISION MEDICINE

Order ID :	11420
Clinical ID :	PQR8888
Indication :	Acute Myeloid Leukemia(AML)
Physician :	Dr. White
Patient Age :	27
Patient Gender :	Female
Patient Status :	Active Cancer
Biopsy Date :	2020-03-10
Sample Type :	Whole Blood
Genomic Input :	Whole Exome Sequence
Additional Input :	NA

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1. Personalized Therapy Recommendation(s)

Drug Combination(s)
IRINOTECAN and MITOMYCIN-C
BUSULFAN and OLAPARIB
BUSULFAN and DOXORUBICIN *(PMID : 16986128, 1578910)*

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

2. Patient Disease Characteristics: Key Biomarker(s)

CHEK1	PRKCE
CSNK2A1	STAT3
H2AFX	TP53
MTOR	
PARP1	

*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	CSNK2A1	H2AFX	MTOR	PARP1	PRKCE	STAT3	TP53
IRINOTECAN+MITOMYCIN-C	✓	✓	✓		✓	✓	✓	✓
BUSULFAN+OLAPARIB	✓	✓	✓	✓	✓	✓	✓	✓
BUSULFAN+DOXORUBICIN	✓	✓	✓		✓			

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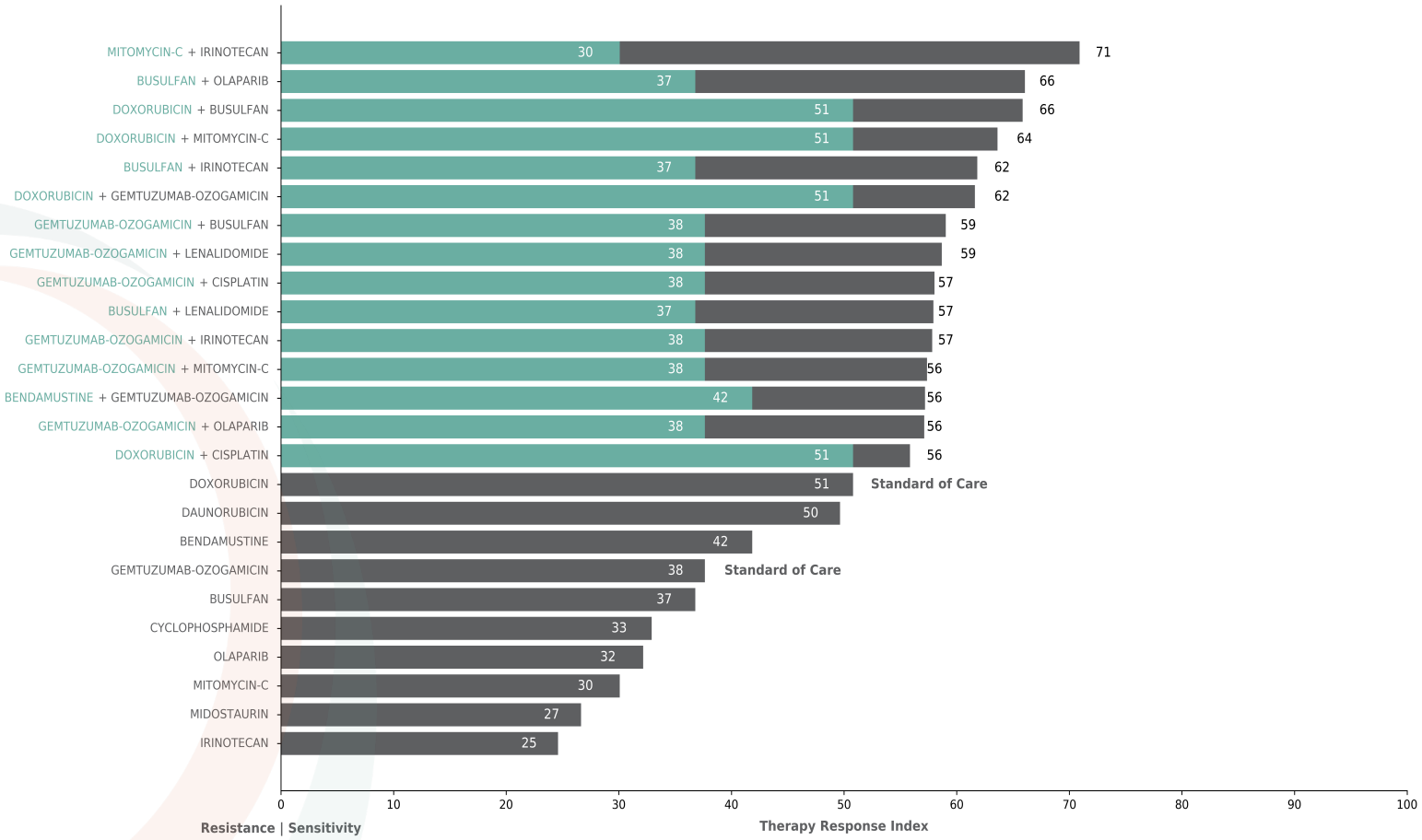
4. Biosimulation of Therapy Response Index (TRI)

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

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5. Summary of Patient Genomic Profile

Input Data Type	Mutations and CNV
Genetic Mutation(s)	21
Copy Number Variation(s)	263
Gene(s) Methylated	0

5.1 Detailed Information of Genomic Aberration(s) Modeled

5.1.1 Gene Mutation(s) with Gain of Function

ACTN4	CD34	CHPT1	E2F4	PHGDH	PSPH

5.1.2 Gene Mutation(s) with Loss of Function

ALOX5AP	ANK2	CD1D	CD1E	DPYD	ESRRA	FOXO3	LTBP2
MMP2	MUC4	NLRC5	NOTCH2	PTPRB	TET2	TP73	

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

ALDOA	CD19	E4F1	EIF3C	EME2	ITGAD	KCTD13	LAT
MAPK3	MIR365A	MLST8	MVP	NOXO1	NTHL1	NUPR1	PAGR1
PPP4C	SH2B1	TGFB1I1	TRAF7	TSC2	UBE2I	VASN	

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

A2M	ABCC4	ACAT2	ACSL6	ADRB2	AFDN	AICDA	ALG11
ALOX15	APTX	ARID1B	ARRB2	ATP2A3	ATP6V0E1	ATP7B	BAG1
BCAP31	BCL7A	BHLHE41	BORA	CA9	CAMKK1	CAST	CCND2
CCNG1	CCNH	CD27	CD274	CD4	CD72	CDKN1B	CDKN2A

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CDKN2B	CHD1	CHD4	CITED2	CLEC7A	CLIP1	CLTA	CNOT8
COPS7A	CREB3	CRK	CSF2	CSNK1A1	CXCL16	CYFIP2	DACH1
DERL2	DIABLO	DLL1	DNAJA1	DNAJC3	DOCK2	DPPA3	DUSP1
DUSP16	DUSP9	DYNLT1	EBF1	EDNRB	ELL2	ENO2	EPS8
ERAP1	ERC1	ESR1	ETV6	EZR	FANCG	FBXO5	FBXW11
FGF18	FLNA	FNIP1	FOXM1	G6PD	GABARAPL1	GAPDH	GLDC
GLRX	GNE	GPC6	GRIN2B	HCFC1	HIC1	HMMR	HTR4
IFNA1	IFNB1	IFNGR1	IGF2R	IKBKG	IL11RA	IL12B	IL20RA
IL22RA2	IL3	ING4	IRAK1	IRF1	ITGAE	ITK	ITPR2
JAK2	KDM4C	KDM5A	KLF5	KNTC1	KRAS	LATS1	LCP2
LDHB	LPA	LRP6	LTBR	MAGEA1	MAGEA10	MAGEA12	MAGEA2
MAGEA3	MAGEA4	MAGEA6	MAP3K4	MAP3K5	MAT2B	MECP2	MEF2C
MELK	MGP	MGST1	MINK1	MIR143	MIR145	MIR17	MIR20A
MIR22	MIS12	MLLT3	MLXIP	MNT	MTHFD1L	MYB	MYBBP1A
MYO1C	NAA10	NANOG	NLRP1	NOX3	NPM1	NPR2	NR2F1
NTF3	NUMB	OLFM4	P2RX1	P4HA2	PAX5	PDCD1LG2	PDCD2
PDE3A	PITPNA	PLAA	PLD2	PLG	PLXNB3	PPARGC1B	PPP2R2B
PRPF8	PSMB1	PSMB6	PSMD9	PTPN6	PTPRD	PTPRO	PTTG1
RAD50	RAD52	RASA1	RHOBTB3	RPA1	RPL10	RPS6	RPS6KA2
RRAGA	SERPINF1	SERPINF2	SETD1B	SH3PXD2B	SHPRH	SLC22A1	SLC22A2
SLC22A4	SLC22A5	SLC25A11	SLC27A6	SLC2A3	SLC43A2	SLCO1A2	SLCO1B1
SLCO1B3	SLU7	SMARCA2	SOD2	SPARC	SPDL1	SPRY2	SPSB2
ST8SIA1	STK10	TAB2	TAPBPL	TBC1D4	TEAD4	TEK	THBS2
TIGAR	TKTL1	TLN1	TLX3	TNFAIP3	TNFRSF1A	TPI1	UBE2G1
UBE2R2	UGGT2	ULBP1	ULBP2	ULBP3	USP5	USP6	UTRN

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VCP	VIP	WNK1	YBX3	YWHAE	ZBTB2	ZDHHC14	ZDHHC21

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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

BUSULFAN				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
FANCG	DEL	S	**BUSULFAN** → **ICL** → **DSB** → **DNA DAMAGE** FANCG → FA-COMPLEX → DNA REPAIR (HR) ⊣ DNA DAMAGE	20509860 26238431 26385482 25891850 12861027
RAD52	DEL	S	**BUSULFAN** → **ICL** → **DSB** → **DNA DAMAGE** RAD52 → DNA REPAIR (HR) ⊣ DNA DAMAGE	9889125 23966156 19200054 21113301

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DOXORUBICIN				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	S	**DOXORUBICIN** → **TOP2CC** → **DSB** → **DNA DAMAGE** TET2 ⊣ CPGMET ⊣ BRCA1/2 → DNA REPAIR(HR) ⊣ DNA DAMAGE	15546503 22395470 25886910 28569220 2049226
RAD50	DEL	S	**DOXORUBICIN** → **TOP2CC** → **DSB** → **DNA DAMAGE** RAD50 → MRE11A-NBN-RAD50 → DNA REPAIR(HR) ⊣ DNA DAMAGE	23213480 22056077 21087997 26880199 27912094
RAD52	DEL	S	**DOXORUBICIN** → **TOP2CC** → **DSB** → **DNA DAMAGE** RAD52 → DNA REPAIR (HR) ⊣ DNA DAMAGE	9889125 30944311

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IRINOTECAN				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
RAD50	DEL	S	**IRINOTECAN** → **SN-38** → **TOP1CC** → **SSB** → **DSB** → **DNA DAMAGE** RAD50 → MRE11A-NBN-RAD50 → DNA REPAIR (HR) ⊣ DNA DAMAGE	12397185 15834151 1651156 18941461 22039049 21060845

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MITOMYCIN-C				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
FANCG	DEL	S	**MITOMYCIN-C** → **ICL** → **DSB** → **DNA DAMAGE** FANCG → FA-COMPLEX → DNA REPAIR (HR) ⊣ DNA DAMAGE	18483318 20647419
RAD52	DEL	S	**MITOMYCIN-C** → **ICL** → **DSB** → **DNA DAMAGE** RAD52 → DNA REPAIR (HR) ⊣ DNA DAMAGE	18483318

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OLAPARIB				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
FANCG	DEL	S	**OLAPARIB** ⊣ **PARP1/2** ⊣ **DNA DAMAGE** FANCG → FA COMPLEX → DNA REPAIR (ICL) ⊣ DNA DAMAGE	23849504 12915460 18800822
RAD50	DEL	S	**OLAPARIB** ⊣ **PARP1/2** → **DNA REPAIR (HR)** ⊣ **DNA DAMAGE** RAD50 → MRE11A-NBN-RAD50 → DNA REPAIR (HR) ⊣ DNA DAMAGE	12972939 19593371 18800822

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PERSONALIZED THERAPY. TRANSPARENT DESIGN.

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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)
TP53	UBE2I → MDM2 → MDM2_MDM4 ⊣ TP53	10935507 11384992 11744695 14707141 15199139 15295102 15851483 16107876 23416275 9582019
	RAD50 → RAD51 ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ MDM4 → MDM2_MDM4 ⊣ TP53	10935507 10959836 11744695 14707141 14985505 15199139 15231735 15295102 15851483 16027121 16107876 20412774
	RAD52 → RAD51 ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ MDM4 → MDM2_MDM4 ⊣ TP53	10851248 10935507 11744695 14707141 14985505 15199139 15231735 15295102 15851483 16027121 16107876 20412774
	FANCG ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ MDM4 → MDM2_MDM4 ⊣ TP53	10935507 11744695 14707141 14985505 15199139 15231735 15295102 15851483 16027121 16107876 20412774 21159649

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VENTURA™ PRECISION MEDICINE

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Indication: Acute Myeloid Leukemia(AML)

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
STAT3	UBE2I → PTPN11 → STAT3	10918587 20671117 26775640 8962143
	RAD50 → RAD51 ⊣ AKT ⊣ BAD ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	10880354 10959836 11050396 11707444 12897128 14641020 15694340 15990872 16873482 17322918 18951090 19667065
	MAP3K5 → GAPDH_SIAH1 → GAPDH → PARP1 ⊣ PKM2 → STAT3	25391652
	IRF1 ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	22295238
	DIABLO ⊣ BIRC3 → SPHK1 → S1PR2 → LYN → STAT3	9510175
	RAD52 → RAD51 ⊣ AKT ⊣ BAD ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	10851248 10880354 11050396 11707444 12897128 14641020 15694340 15990872 16873482 17322918 18951090 19667065
	LTBR → LTBR_TRAF3 → MAP2K7 → MAPK9 ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	11062067 12169272 12566458 18570871 20679476
STAT3	FOXO3 ⊣ BIRC5 → AURKB → PKM2 → STAT3	24058770

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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
PRKCE	UBE2I → SMURF2 → TOP2A → AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	14985505 15231735 16027121 20412774 21159649 22611470 26679521 28611047
	RAD50 → RAD51 ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	10959836 14985505 15231735 16027121 20412774 21159649 22611470
	PPP4C ⊣ HDAC3 → CDKN1A ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1 → AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	11255227 14985505 15231735 16027121 20412774 21159649 22611470 22850745
	MAP3K5 → GAPDH_SIAH1 → GAPDH ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1 → AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	14985505 15231735 16027121 16474839 20412774 21159649 22611470 22850745 25391652
	SH2B1 → GRB2 → CBL → PIK3CA → PDPK1 → AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	10204582 10698680 11406619 11997436 14985505 15231735 16027121 16129412 20412774 21159649 22611470 7791764
	DIABLO ⊣ BIRC3 → SPHK1 → S1PR2 → LYN → SYK → BTK → PLCG2 → PRKCE	11226282 11507089 11788586 12093870 15184383 7500027 7896829 8058772 8137818 8197119 8395016 8598449
	RAD52 → RAD51 ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	10851248 14985505 15231735 16027121 20412774 21159649 22611470
	FANCG ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	14985505 15231735 16027121 20412774 21159649 22611470

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Indication: Acute Myeloid Leukemia(AML)

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
CSNK2A1	UBE2I → SMURF2 → TOP2A → AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	11940573 12517798 15710331 21254166 22850745 23748345 26679521 28611047 8428596
	RAD50 → RAD51 ⊣ AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	10959836 12517798 12773567 15710331 22850745 23748345 8428596
	CDKN2A → ATRIP → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	12902976 15775976 22850745 8428596
	PPP4C ⊣ HDAC3 → CDKN1A ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	11255227 22850745
	MAP3K5 → GAPDH_SIAH1 → GAPDH ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	16474839 22850745 25391652
	SH2B1 → GRB2 → CBL → PIK3CA → AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	10204582 10490823 11406619 11997436 12517798 16129412 22850745 7791764 8428596 8524815 8995358 9233773
	RAD52 → RAD51 ⊣ AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	10851248 12517798 15710331 22850745 23748345 8428596
	FANCG ⊣ AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	12517798 15710331 22850745 23748345 8428596

Cellworks
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

VENTURA™ PRECISION MEDICINE

Clinical ID: PQR8888 **Cellworks ID:** 11420 **Ref Physician:** Dr.White

Biopsy Sequence: 1 **Gender/Age:** Female / 27 **Date of Report:** May 15, 2020

Indication: Acute Myeloid Leukemia(AML)

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
MTOR	UBE2I → SMURF2 → TOP2A → AKT ⊣ AKT1S1 ⊣ MTOR	17510057 17517883 19276681 20138985 26679521 28611047
	RAD50 → RAD51 ⊣ AKT ⊣ AKT1S1 ⊣ MTOR	10959836 17510057 17517883 19276681 20138985
	PPP4C ⊣ HDAC3 → CDKN1A ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1 → AKT ⊣ AKT1S1 ⊣ MTOR	11255227 15718470 17510057 17517883 19276681 20138985 22850745
	MAP3K5 → GAPDH_SIAH1 → GAPDH → PARP1 ⊣ PKM2 ⊣ AKT1S1 ⊣ MTOR	25391652
	SH2B1 → GRB2 → CBL → PIK3CA → PDPK1 → AKT ⊣ AKT1S1 ⊣ MTOR	10204582 10698680 11406619 11997436 16129412 17510057 17517883 19276681 20138985 7791764 8524815 8995358
	MLST8 → MTOR	25906254
	IRF1 ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 ⊣ AKT1S1 ⊣ MTOR	22295238
	RAD52 → RAD51 ⊣ AKT ⊣ AKT1S1 ⊣ MTOR	10851248 17510057 17517883 19276681 20138985
	FANCG ⊣ AKT ⊣ AKT1S1 ⊣ MTOR	17510057 17517883 19276681 20138985
	FOXO3 ⊣ BIRC5 → AURKB → PKM2 ⊣ AKT1S1 ⊣ MTOR	21910584

** Assayable key kinase biomarkers identified for this patient.

Clinical ID: PQR8888 **Cellworks ID:** 11420 **Ref Physician:** Dr.White

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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: PQR8888 **Cellworks ID:** 11420 **Ref Physician:** Dr.White

Biopsy Sequence: 1 **Gender/Age:** Female / 27 **Date of Report:** May 15, 2020

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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: PQR8888 **Cellworks ID:** 11420 **Ref Physician:** Dr.White

Biopsy Sequence: 1 **Gender/Age:** Female / 27 **Date of Report:** May 15, 2020

Indication: Acute Myeloid Leukemia(AML)

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.

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