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PRECISION MEDICINE

Order ID :	11420
Clinical ID :	PQR8888
Indication :	Acute Myeloid Leukemia(AML)
Physician :	Dr. White
Patient Age :	27
Patient Gender :	Female
Patient Status :	Newly Diagnosed
Biopsy Date :	2019-10-16
Sample Type :	Whole Blood
Genomic Input :	Whole Exome Sequence
Additional Input :	NA

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

Biopsy Sequence: 1 **Gender/Age:** Female / 27 **Date of Report:** Dec 03, 2019

Indication: Acute Myeloid Leukemia(AML)

1. Drug Response Prediction

Therapies of Interest	Patient Predicted Response
AZACITIDINE	Responder
AZACITIDINE_SORAFENIB	Responder
AZACITIDINE_VENETOCLAX	Responder
CLADRIBINE_CYTARABINE_DAUNORUBICIN	Responder
CLOFARABINE_IDARUBICIN	Responder
CYCLOPHOSPHAMIDE	Responder
CYTARABINE_DAUNORUBICIN	Responder
CYTARABINE_DAUNORUBICIN_GEMTUZUMAB-OZOGAMICIN	Responder
CYTARABINE_DAUNORUBICIN_MIDOSTAURIN	Responder
CYTARABINE_ETOPOSIDE	Responder
CYTARABINE_ETOPOSIDE_MITOXANTRONE	Responder
CYTARABINE_IDARUBICIN	Responder
CYTARABINE_MITOXANTRONE	Responder
DECITABINE	Responder
DECITABINE_SORAFENIB	Responder
DECITABINE_VENETOCLAX	Responder
DOXORUBICIN	Responder
GEMTUZUMAB-OZOGAMICIN	Responder

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Therapies of Interest	Patient Predicted Response
CYTARABINE	Non-Responder
CYTARABINE_DEXAMETHASONE	Non-Responder
CYTARABINE_MIDOSTAURIN	Non-Responder
CYTARABINE_VENETOCLAX	Non-Responder
ENASIDENIB	Non-Responder
HYDROXYUREA	Non-Responder
IVOSIDENIB	Non-Responder
THIOGUANINE	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)

AKT	MTOR
CEBPA	PARP1
CHEK1	PRKCE
CSNK2A1	STAT3
H2AFX	TP53

*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									
	AKT	CEBPA	CHEK1	CSNK2A1	H2AFX	MTOR	PARP1	PRKCE	STAT3	TP53
AZACITIDINE	✓	✓	✓			✓				
AZACITIDINE_SORAFENIB	✓	✓	✓	✓		✓	✓	✓	✓	✓
AZACITIDINE_VENETOCLAX	✓	✓	✓			✓	✓	✓		
CLADRIBINE_CYTARABINE_DAUNORUBICIN	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CLOFARABINE_IDARUBICIN	✓	✓	✓	✓	✓	✓	✓	✓		✓
CYCLOPHOSPHAMIDE	✓	✓	✓	✓	✓	✓	✓	✓		✓
CYTARABINE_DAUNORUBICIN	✓	✓	✓	✓	✓	✓	✓	✓		✓
CYTARABINE_DAUNORUBICIN_GEMTUZUMAB-OZOGAMICIN	✓	✓	✓	✓	✓	✓	✓	✓		✓
CYTARABINE_DAUNORUBICIN_MIDOSTAURIN	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CYTARABINE_ETOPOSIDE	✓	✓	✓	✓	✓	✓	✓	✓		✓

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Therapies of Interest	Patient Biomarker Characteristics									
	AKT	CEBPA	CHEK1	CSNK2A1	H2AFX	MTOR	PARP1	PRKCE	STAT3	TP53
CYTARABINE_ETOPOSIDE_MITOXANTRONE	✓	✓	✓	✓	✓	✓	✓	✓		✓
CYTARABINE_IDARUBICIN	✓	✓	✓	✓	✓	✓	✓	✓		✓
CYTARABINE_MITOXANTRONE	✓		✓	✓	✓	✓		✓		✓
DECITABINE	✓	✓	✓			✓				
DECITABINE_SORAFENIB	✓	✓	✓	✓		✓	✓	✓	✓	
DECITABINE_VENETOCLAX	✓	✓	✓			✓	✓	✓		
DOXORUBICIN			✓	✓	✓	✓		✓		✓
GEMTUZUMAB-OZOGAMICIN	✓	✓	✓	✓	✓	✓	✓	✓		✓
CYTARABINE			✓							
CYTARABINE_DEXAMETHASONE	✓	✓	✓			✓		✓		
CYTARABINE_MIDOSTAURIN	✓		✓	✓		✓	✓	✓	✓	
CYTARABINE_VENETOCLAX			✓			✓	✓	✓		
ENASIDENIB										
HYDROXYUREA			✓	✓	✓	✓		✓		
IVOSIDENIB										
THIOGUANINE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

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4. Summary of Patient Genomic Profile

Input Data Type	Targeted Nucleotide Sequencing
Genetic Mutation(s)	19
Copy Number Variation(s)	261
Gene(s) Methylated	0

4.1 Detailed Information of Genomic Aberration(s) Modeled

4.1.1 Gene Mutation(s) with Gain of Function

ACTN4	CD34	CHPT1	E2F4	PHGDH	PSPH

4.1.2 Gene Mutation(s) with Loss of Function

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

4.1.3 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	

4.1.4 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	DNAJC3	DOCK2	DPPA3	DUSP1	DUSP16
DUSP9	DYNLT1	EBF1	EDNRB	ELL2	ENO2	EPS8	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	LARS	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	TBC1D4	TEAD4	TEK	THBS2	TIGAR	TKTL1
TLN1	TLX3	TNFAIP3	TNFRSF1A	TPI1	UBE2G1	UBE2R2	UGGT2
ULBP1	ULBP2	ULBP3	USP5	USP6	UTRN	VCP	VIP

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WNK1	YBX3	YWHAE	ZBTB2	ZDHHC14	ZDHHC21

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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

AZACITIDINE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	S	**AZACITIDINE** ⊣ **DNMT1** → **CPGMET** TET2 ⊣ CPGMET ⊣ PTPN6 ⊣ SRC → PIK3CA → AKT ⊣ GSK3B ⊣ AURKA → PLK1 → CANCER PROGRESSION TET2 ⊣ CPGMET ⊣ CDKN1A ⊣ CSNK2A1 → HDAC1 ⊣ RUNX3 ⊣ CANCER PROGRESSION TET2 ⊣ CPGMET ⊣ TP53 ⊣ CANCER PROGRESSION TET2 ⊣ CPGMET ⊣ CDKN1A ⊣ CSNK2A1 → AP1 → CTNNB1 → CANCER PROGRESSION	25224413 24688109 23671287 26498513 9261115 29487290 28712664 26779436 26516376 19417127 15458387 10816572 12154409 25886910 12689679 1516134 17146436 12383256 25886188 12579297 23647960 20466735 27621875 14992722

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CLADRIBINE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	S	**CLADRIBINE** → **DNA DAMAGE** TET2 ⊣ CPGMET ⊣ MLH1 → DNA REPAIR(MMR) ⊣ DNA DAMAGE	24403070 10072435 15475387 25886910 2311169 22395470 25043185

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CLOFARABINE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	S	**CLOFARABINE** → **DNA DAMAGE** TET2 ⊣ CPGMET ⊣ MLH1 → DNA REPAIR(MMR) ⊣ DNA DAMAGE	25043185 24403070 19576186 15475387 22395470 25886910 10072435

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CYCLOPHOSPHAMIDE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
RAD50	DEL	S	**CYCLOPHOSPHAMIDE** → **ICL** → **DSB** → **DNA DAMAGE** RAD50 → MRE11A-NBN-RAD50 → DNA REPAIR (HR) ⊣ DSB DNA DAMAGE	23066388 12972939 19593371
FANCG	DEL	S	**CYCLOPHOSPHAMIDE** → **ICL** → **DSB** → **DNA DAMAGE** FANCG → FA-COMPLEX → DNA REPAIR (HR) ⊣ DSB	26385482 25891850 26238431 20509860 21793181 12861027
RAD52	DEL	S	**CYCLOPHOSPHAMIDE** → **ICL** → **DSB** → **DNA DAMAGE** RAD52 → DNA REPAIR (HR) ⊣ DSB	21793181 9889125

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CYTARABINE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
NPM1	DEL	S	**CYTARABINE** → **DNA DAMAGE** NPM1 → RAD51 → DNA REPAIR (HR) ⊣ DNA DAMAGE	20713529 17549079 2311169
TET2	LOF	S	**CYTARABINE** → **DNA DAMAGE** TET2 ⊣ CPGMET ⊣ MLH1 → DNA REPAIR(MMR) ⊣ DNA DAMAGE	2311169 15475387 24403070 25886910 10072435 22395470 25043185
SLC22A4	DEL	R	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** SCL22A4 → CYTARABINE → DNA DAMAGE	28209616 2311169

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DAUNORUBICIN				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
FANCG	DEL	S	**DAUNORUBICIN** → **DNA DAMAGE** FANCG → DSB REPAIR (HR) ⊣ DNA DAMAGE	9187272 23333482 16132046
TET2	LOF	S	**DAUNORUBICIN** → **DNA DAMAGE** TET2 ⊣ CPGMET ⊣ BRCA2 → DNA REPAIR (HR) ⊣ DNA DAMAGE	23349390 2049226 25886910 22395470 15546503
SLC22A1	DEL	R	**DAUNORUBICIN** → **DNA DAMAGE** SLC22A1 → DRUG INFLUX → DNA DAMAGE	9187272 26861753

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DECITABINE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	S	**DECITABINE** ⊣ **DNMT1** → **CPGMET** TET2 ⊣ CPGMET ⊣ PTPN6 ⊣ SRC → PIK3CA → AKT → PAK1 → CANCER PROGRESSION TET2 ⊣ CPGMET ⊣ PTEN ⊣ AKT ⊣ GSK3B ⊣ GLI2 → FOXL2 → CANCER PROGRESSION TET2 ⊣ CPGMET ⊣ CDKN1A ⊣ CSNK2A1 → HDAC1 ⊣ RUNX3 ⊣ CANCER PROGRESSION TET2 ⊣ CPGMET ⊣ CDKN1A ⊣ CSNK2A1 → AP1 → CTNNB1 → CANCER PROGRESSION	23671287 25224413 20466735 27621875 26498513 28712664 14992722 9261115 12154409 25886910 12689679 1516134 17146436 12383256 25886188 24688109 12579297 23647960 11704853 14585966 15899874

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

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ENASIDENIB				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	R	**ENASIDENIB** ⊣ **mut_IDH1** → **2HG** ⊣ **TET2** TET2 ⊣ CPGMET → CANCER PROGRESSION	28193778 29339439

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ETOPOSIDE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
RAD50	DEL	S	**ETOPOSIDE** → **TOP2CC** → **DSB** → **DNA DAMAGE** RAD50 → MRE11A-NBN-RAD50 ⊣ TOP2CC	19377506 21087997 27912094 26880199 23213480 22056077
TET2	LOF	S	**ETOPOSIDE** → **DNA DAMAGE** TET2 ⊣ CPGMET ⊣ BRCA1/BRCA2 → DNA REPAIR(HR) ⊣ DNA DAMAGE	15546503 22395470 25886910 28569220 26600742
RAD52	DEL	S	**ETOPOSIDE** → **TOP2CC** → **DSB** → **DNA DAMAGE** RAD52 → DNA REPAIR (HR) ⊣ DNA DAMAGE	19377506 22056077 15941391 23213480 26880199 27912094 21087997

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GEMTUZUMAB-OZOGAMICIN				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
RAD50	DEL	S	**GEMTUZUMAB-OZOGAMICIN** → **DSB** → **DNA DAMAGE** RAD50 → MRE11-NBN-RAD50 → DSB REPAIR(HR) ⊣ DNA DAMAGE	30076173 24642965

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IDARUBICIN				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
ARID1B	DEL	S	**IDARUBICIN** → **DNA DAMAGE** ARID1B → BRG_ARID1B_BAF_COMPLEX → DNA REPAIR (NHEJ) ⊣ DNA DAMAGE	9187272 24788099
FANCG	DEL	S	**IDARUBICIN** → **DNA DAMAGE** FANCG → DSB REPAIR (HR) ⊣ DNA DAMAGE	23333482 16132046 2049226
TET2	LOF	S	**IDARUBICIN** → **DNA DAMAGE** TET2 ⊣ CPGMET ⊣ BRCA2 → DNA REPAIR(HR) ⊣ DNA DAMAGE	15546503 22395470 25886910 2049226
RAD50	DEL	S	**IDARUBICIN** → **DNA DAMAGE** RAD50 → DNA REPAIR (HR) ⊣ DNA DAMAGE	20655309 24093751 2049226

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IVOSIDENIB				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	R	**IVOSIDENIB** ⊣ **mut_IDH1** → **2HG** ⊣ **TET2** TET2 ⊣ CPGMET → CANCER PROGRESSION	30643428 29339439

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MIDOSTAURIN				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
MYB	DEL	R	**MIDOSTAURIN** ⊣ **FLT3** MYB → FLT3 → LYN → SYK → AKT → MTOR → CANCER PROGRESSION	22037378 18183025 19654408 23340802

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MITOXANTRONE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	S	**MITOXANTRONE** → **DNA DAMAGE** TET2 ⊣ CPG METHYLATION ⊣ BRCA1/BRCA2 → DNA REPAIR (HR) ⊣ DNA DAMAGE	9665145 15546503 11879553 10964110 23215809 2311171 25886910

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

Biopsy Sequence: 1 **Gender/Age:** Female / 27 **Date of Report:** Dec 03, 2019

Indication: Acute Myeloid Leukemia(AML)

SORAFENIB				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
CDKN2A	DEL	S	**SORAFENIB** ⊣ **KDR** CDKN2A ⊣ HIF1A → KDR → SRC → PIK3CA → AKT → MDM2 ⊣ TP53 ⊣ CANCER PROGRESSION	16757355 8641834 11035810 21840963 12509223 8756616 28496142 11923280
RASA1	DEL	S	**SORAFENIB** ⊣ **RAF1** RASA1 ⊣ RAS → RAF1 → MAP2K1/2 → MAPK1 → STAT3 → CANCER PROGRESSION	15466206 17505473 26993606 21858223
KRAS	DEL	R	**SORAFENIB** ⊣ **RAF1** KRAS → RAF1 → MAP2K1/2 → MAPK1 ⊣ STK11 → TP53 ⊣ CANCER PROGRESSION	23525267 29282294 15466206 21858223 29438690 17018283 22461507 15143186 25941399 17016424 30709910 10969079 17016424 19219045

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THIOGUANINE				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
TET2	LOF	R	**THIOGUANINE** → **6TG** → **TdGTP** → **MMR** → **DNA DAMAGE** TET2 ⊣ CPGMET ⊣ MLH1 → MMR	15475387 2311169 22395470 10072435 25043185 24403070 25886910

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VENETOCLAX				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
KRAS	DEL	R	**VENETOCLAX** ⊣ **BCL2** KRAS → RAF → MAP2K1 → MAPK1 → BCL2 ⊣ TP53 ⊣ CANCER PROGRESSION	29872725 23291630 16443602

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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:

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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
	CDKN2A → ATRIP → BLM ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ MDM4 → MDM2_MDM4 ⊣ TP53	10935507 11744695 14707141 14985505 15199139 15231735 15295102 15364958 15775976 15851483 16027121 16107876
	MLST8 → MTORC2 → AKT ⊣ STK11 → PRKAA1 ⊣ MDM4 → MDM2_MDM4 ⊣ TP53	10935507 11744695 12408816 14707141 14985505 15199139 15231735 15295102 15718470 15851483 16027121 16107876
	IRF1 ⊣ BCL2 ⊣ BRCA1 ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ MDM4 → MDM2_MDM4 ⊣ TP53	10935507 11744695 14707141 14985505 15199139 15231735 15295102 15509808 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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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
STAT3	RAD50 → RAD51 ⊣ AKT ⊣ BAD ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	10880354 10959836 11050396 11707444 12897128 14641020 15694340 15990872 16873482 17322918 18951090 19667065
	CDKN2A → ATRIP → BLM ⊣ AKT ⊣ BAD ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	10880354 11050396 11707444 12897128 14641020 15694340 15775976 15990872 16873482 17322918 18951090 19223555
	IFNGR1 ⊣ JAK1 → STAT3	10642538 10918587 7579387 9510175 9774693
	MAP3K5 → GAPDH_SIAH1 → GAPDH → PARP1 ⊣ PKM2 → STAT3	25391652
	MLST8 → MTORC2 → AKT ⊣ BAD ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	11707444 12408816 15694340 15990872 17322918 18030348 19446321 20705244
	IRF1 ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	22295238
	RAD52 → RAD51 ⊣ AKT ⊣ BAD ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	10851248 10880354 11050396 11707444 12897128 14641020 15694340 15990872 16873482 17322918 18951090 19667065
STAT3	LTBR → LTBR_TRAF3 → MAP2K7 → MAPK9 ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	11062067 12169272 12566458 18570871 20679476
	FANCG ⊣ AKT ⊣ BAD ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	10880354 11050396 11707444 12897128 14641020 15694340 15990872 16873482 17322918 18951090 19667065 21444773
	FOXO3 → BBC3 ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 → STAT3	14976264 15694340 17322918

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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
CEBPA	RAD50 → RAD51 ⊣ AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	10959836 14985505 15231735 16027121 18850005 20412774 21159649 22611470
	CDKN2A → ATRIP → BLM ⊣ AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	14985505 15231735 15775976 16027121 18850005 19223555 20412774 21159649 22611470
	PPP4C ⊣ HDAC3 → CDKN1A ⊣ CCNB1_CDK1 → AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	14985505 15231735 16027121 18850005 19107194 20412774 21159649 22611470
	MAP3K5 → GAPDH_SIAH1 → GAPDH ⊣ CCNB1_CDK1 → AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	14985505 15231735 16027121 16474839 18850005 19107194 20412774 21159649 22611470 25391652
	GAPDH → SIRT1 → CEBPA	18850005 20972425
	MLST8 → MTORC2 → AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	12408816 14985505 15231735 15718470 16027121 16221682 16226444 18030348 18692468 18850005 19446321 19995915
	IRF1 ⊣ BCL2 ⊣ BRCA1 ⊣ AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	14985505 15231735 16027121 18850005 20412774 21159649 21444675 22295238 22611470
	RAD52 → RAD51 ⊣ AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	10851248 14985505 15231735 16027121 18850005 20412774 21159649 22611470
	FANCG ⊣ AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	14985505 15231735 16027121 18850005 20412774 21159649 22611470
	FOXO3 → BBC3 ⊣ BCL2 ⊣ BRCA1 ⊣ AKT ⊣ STK11 → PRKAA1 → SIRT1 → CEBPA	14976264 14985505 15126506 15231735 15694340 16027121 17322918 17521387 18850005 20412774 21159649 21444675

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Indication: Acute Myeloid Leukemia(AML)

KINASE**:

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
AKT	UBE2I → PTPN11 → PIK3CA → AKT	10490823 16129412 18281483 8962143
	CDKN1B ⊣ CDK5_CDK5R1 ⊣ BECN1_PIK3C3 → WIPI1 → MAP1LC3B ⊣ TRAF6 → PIK3CA → AKT	10490823 11406619 12105209 12616480 12874320 18064631 19289601 20501938
	IFNGR1 ⊣ JAK1 → PIK3CA → AKT	10490823 11438544 18281483 19230867
	MLST8 → MTORC2 → AKT	12408816 18030348 19446321 20705244
	IRF1 → IBTK ⊣ BTK → PLCG2 → PRKCA → EZR → PIK3CA → AKT	10490823 11507089 11577348 11788586 12093870 15184383 18596081 21482705 8691147
	FOXO3 → MAP1LC3B ⊣ TRAF6 → PIK3CA → AKT	10490823 11406619 12105209 12616480 12874320 18054315 18064631 19289601

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

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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
PRKCE	UBE2I → PTPN11 → PIK3CA → PDPK1 → AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	10698680 14985505 15231735 16027121 16129412 18281483 20412774 21159649 22611470 8962143
	RAD50 → RAD51 ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	10959836 14985505 15231735 16027121 20412774 21159649 22611470
	IFNGR1 ⊣ JAK1 → IL2RB_JAK1 → JAK3 → PLCG1 → PRKCE	8598449
	MLST8 → MTORC2 → AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	12408816 14985505 15231735 15718470 16027121 16221682 16226444 18030348 18692468 19446321 19995915 20412774
	IRF1 → IBTK ⊣ BTK → PLCG2 → PRKCE	11507089 11577348 11788586 12093870 15184383 18596081 21482705 8691147
	RAD52 → RAD51 ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	10851248 14985505 15231735 16027121 20412774 21159649 22611470
	FANCG ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	14985505 15231735 16027121 20412774 21159649 22611470
	FOXO3 → BBC3 ⊣ BCL2 ⊣ BRCA1 ⊣ AKT ⊣ STK11 → PRKAA1 ⊣ PRKCE	14976264 14985505 15231735 15694340 16027121 17322918 17521387 20412774 21159649 21444675 22271894 22611470

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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
CSNK2A1	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
	MLST8 → MTORC2 → AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	12408816 12517798 15710331 15718470 16221682 16226444 18030348 19446321 19995915 22850745 22880048 23748345
	IRF1 ⊣ BCL2 ⊣ BRCA1 ⊣ AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → CSNK2A1	12517798 12773567 15710331 21444675 22295238 22850745 23748345 8428596
	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

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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
MTOR	UBE2I → PTPN11 → PIK3CA → PDPK1 → AKT ⊣ AKT1S1 ⊣ MTOR	10698680 16129412 17510057 17517883 18281483 19276681 20138985 8962143
	RAD50 → RAD51 ⊣ AKT ⊣ AKT1S1 ⊣ MTOR	10959836 17510057 17517883 19276681 20138985
	CDKN2A → ATRIP → BLM ⊣ AKT ⊣ AKT1S1 ⊣ MTOR	15775976 17510057 17517883 19223555 19276681 20138985
	PPP4C ⊣ HDAC3 → CDKN1A ⊣ CCNB1_CDK1 → AKT ⊣ AKT1S1 ⊣ MTOR	17510057 17517883 19276681 20138985
	MAP3K5 → GAPDH_SIAH1 → GAPDH → PARP1 ⊣ PKM2 ⊣ AKT1S1 ⊣ MTOR	25391652
	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 → BBC3 ⊣ BCL2 ⊣ PARP1 ⊣ PKM2 ⊣ AKT1S1 ⊣ MTOR	14976264 15694340 17322918 21910584

** 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 ('✓') 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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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.

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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.

Intended Use

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