Whole Exome sequencing

Single/multi-nucleotide variant (SNV/MNV) detection by whole exome sequencing (WES)
DNA was extracted from tumor material and a reference sample followed by a library prep including whole exome enrichment using the KAPA HyperExome kit (Roche). Samples were subsequently sequenced on an Illumina NovaSeq 6000 sequencer (2x 150 bp). Data was analysed based on the GATK best practices guideline (details available upon request) using reference genome GRCh38. For the genes present in the "Máxima Gene panel v.x" (for exact version of gene panel see clinical report) a mean coverage of 200X for tumor and 100X for reference was aimed for. Variants are filtered and annotated using Alissa Interpret (Agilent Technologies) focusing on variants in coding regions and 20 nucleotides of flanking intronic sequences. Variants with a variant allele frequency (VAF) lower than 5% are excluded from the analysis. Classification of variants is based on the American College of Medical Genetics (ACMG) and Association for Molecular Pathology (AMP) guidelines. Nomenclature of variants is according to the Human Genome Variation Society (HGVS) guidelines. Only clinically relevant (likely) pathogenic variants are reported.

The primary goal of this analysis is the detection of somatic variants (tumor vs. normal) in genes present in the "Máxima gene panel v.x". However, tumor-only analysis is performed for a set of genes for which all gene defects are relevant for the diagnosis and/or clinical decision making, including variants that can be present in (a mosaic state in) the reference material. Genepanels are assembles for the 3 clinical domains within the Princess Máxima Center: hemato-oncology, solid tumors and neuro-oncology (for contents genepanel, see below). In case of suspected germline variant, referral to a clinical geneticist will be advised. Carriership of pathogenic variants associated with autosomal recessive diseases will (in principle) not be reported. Incidental findings will be discussed within the incidental finding committee of the Genetics department of the University Medical Center Utrecht. The sensitivity to detect SNV's and MNV's is >95% for variants with a variant allele frequency >10%.

Single/multi-nucleotide variant (SNV/MNV) detection by whole exome sequencing (WES) is an ISO15189 accredited test: https://www.rva.nl/alle-geaccrediteerden/m325/

Copy number Variation (CNV) detection by whole exome sequencing (WES)
CNV detection from WES data was done according to GATK best practices guideline (details available upon request). An in-house panel of normals (PoN) was created from retrospective WES analyses and used for normalisation of copy ratios. Interpretation of CNV's is dependent on the copy ratio, B-allel frequency and tumor cell percentage. Only clinically relevant (likely) pathogenic CNV's are reported.

Copy number Variation (CNV) detection by whole exome sequencing (WES) is an ISO15189 accredited test: https://www.rva.nl/alle-geaccrediteerden/m325/

Máxima gene panel v2.6 (682 genes):

Gene added: PRKD1

Máxima gene panel v2.5 (681 genes):

Genes added: ACVRL1 and UBTF

Máxima gene panel v1.3 (679 genes):

A2ML1	CARD11	CTLA4	FAP	HIST1H3B	MALT1	NR3C1	PTCH1	SHOC2	TNFRSF14
ABCA4	CARS	CTNNB1	FAS	HIST1H3C	MAML2	NR4A3	PTCH2	SHROOM2	TNFRSF17
ABCB11	CASP10	CTR9	FBXO11	HIST1H4I	MAP2K1	NRAS	PTEN	SIX1	TOP1
ABCD1	CASP8	CYLD	FBXW7	HLF	MAP2K2	NSD1	PTPN1	SIX2	TP53
ABI1	CBFA2T3	DAXX	FCGR2B	HMGA1	MAP2K4	NSD2	PTPN11	SLC34A2	TPM3
ABL1	CBFB	DDB2	FCRL4	HMGA2	MAP3K1	NT5C2	PTPRD	SLC45A3	TPM4
ABL2	CBL	DDIT3	FEV	HNRNPA2B1	MAX	NTRK1	RAB27A	SMAD4	TPR
ABRAXAS1	CBLB	DDX10	FGFR1	HOOK3	MDH2	NTRK3	RABEP1	SMAD7	TRIM24
ACD	CBLC	DDX3X	FGFR1OP	HOXA11	MDM2	NUMA1	RAD50	SMAD9	TRIM27
ACKR3	CCDC6	DDX41	FGFR2	HOXA13	MDM4	NUP214	RAD51B	SMARCA4	TRIM28
ACSL3	CCNB1IP1	DDX5	FGFR3	HOXA9	MECOM	NUP98	RAD51C	SMARCB1	TRIM33
ACSL6	CCND1	DDX6	FGFR4	HOXB13	MED12	NUTM1	RAD51D	SMARCE1	TRIM37
AFDN	CCND2	DEK	FH	HOXC11	MEF2B	NUTM2A	RAF1	SMC1A	TRIP11
AFF1	CCND3	DGCR8	FHIT	HOXC13	MEN1	NUTM2B	RAG1	SMO	TRIP13
AFF3	CCNE1	DICER1	FIP1L1	HOXD13	MET	OLIG2	RAG2	SNX29	TSC1
AFF4	CD19	DIP2B	FLCN	HRAS	MFN2	OMD	RALGDS	SOCS1	TSC2
AIP	CD22	DIS3L2	FLI1	HSP90AA1	MITF	OTX2	RANBP17	SOS1	TSHR
AKAP9	CD27	DKC1	FLNA	HSP90AB1	MKL1	P2RY8	RAP1GDS1	SOX2	TTL
AKT1	CD274	DNM2	FLT1	IDH1	MLF1	PALB2	RARA	SPECC1	TYK2
AKT2	CD33	DNMT1	FLT3	IDH2	MLH1	PALLD	RASA1	SPRED1	U2AF1
AKT3	CD38	DNMT3A	FLT4	IGF2R	MLLT1	PARN	RB1	SRC	UNC13D
ALDH2	CD52	DNMT3B	FNBP1	IKZF1	MLLT10	PATZ1	RBM15	SRGAP3	USB1
ALK	CD58	DOT1L	FOXL2	IL2	MLLT11	PAX3	RBM8A	SRSF2	USH2A
AMER1	CD70	DROSHA	FOXO1	IL21R	MLLT3	PAX5	RECQL4	SRSF3	USP6
ANKRD26	CD74	DUSP10	FOXO3	IL3RA	MLLT6	PAX7	REL	SS18	USP7
APC	CD79A	EBF1	FOXO4	IL6ST	MN1	PAX8	REST	SS18L1	VHL
ARAF	CD79B	ECT2L	FOXP1	IL7R	MNX1	PBRM1	RET	SSX1	VTI1A
ARHGAP26	CDC25A	EGFR	FRG1	IRF4	MPL	PBX1	RHBDF2	SSX4	WAS
ARHGEF12	CDC73	EGLN1	FRG2	ITK	MRE11	PCM1	RHOH	STAG2	WDCP
ARID1A	CDH1	EGLN2	FSTL3	JAK1	MS4A1	PCSK7	RHPN2	STAT3	WIF1
ARID2	CDH11	EIF3H	FUBP1	JAK2	MSH2	PDCD1LG2	RIT1	STAT5A	WRAP53
ARID5B	CDK12	EIF4A2	FUS	JAK3	MSH6	PDE4DIP	RMI2	STAT5B	WRN
ARNT	CDK4	ELANE	G6PC3	JAZF1	MSI2	PDGFB	RMRP	STAT6	WT1
ASPSCR1	CDK6	ELF4	GAR1	JUN	MSN	PDGFRA	RNF213	STK11	WWTR1
ASXL1	CDKN1A	ELK4	GAS7	KAT6A	MTCP1	PDGFRB	ROR2	STX11	XPA
ASXL2	CDKN1C	ELL	GATA1	KAT6B	MTOR	PER1	ROS1	STXBP2	XPC
ATIC	CDKN2A	ELN	GATA2	KBTBD4	MUC1	PHF6	RPA1	SUFU	XPO1
ATM	CDKN2C	ELP1	GATA3	KDM5A	MUTYH	PHOX2B	RPL11	SUZ12	XRCC2
ATR	CDX2	EML4	GLI2	KDM5C	MYB	PICALM	RPL35A	SYK	YWHAE
ATRX	CEBPA	EP300	GMPS	KDM6A	MYC	PIGA	RPN1	TAF15	ZBTB16
AXIN2	CEP57	EPAS1	GNA11	KDM6B	MYCBP2	PIK3CA	RPS17	TAL1	ZBTB7A
B2M	CHCHD7	EPCAM	GNA13	KDR	MYCL	PIK3CB	RPS19	TAL2	ZIC1
BAP1	CHEK1	EPOR	GNAQ	KDSR	MYCN	PIK3CD	RPS24	TBR1	ZMYM2
BARD1	CHEK2	EPS15	GNAS	KIAA1549	MYD88	PIK3CG	RPS7	TCEA1	ZMYM3
BCL10	CHIC2	ERBB2	GOLGA5	KIF5B	MYNN	PIK3R1	RTEL1	TCF12	ZNF331
BCL11A	CHN1	ERCC1	GOPC	KIT	MYOD1	PIK3R2	RUNX1	TCF3	ZNF384
BCL11B	CIC	ERCC2	GPC3	KLF4	MYSM1	PIM1	SAMD9	TCF7L1	ZNF521
BCL2	CIITA	ERCC3	GPHN	KLF6	NACA	PINK1	SAMD9L	TCF7L2	ZNF91
BCL3	CLP1	ERCC4	GPR161	KLK2	NBN	PLAG1	SBDS	TCL1A	ZRSR2
BCL6	CLTC	ERCC5	GREM1	KMT2A	NCKIPSD	PMEL	SCG5	TEK	
BCL7A	CLTCL1	ERG	H3C1	KMT2C	NCOA1	PML	SCN9A	TENT5C	
BCL9	CNBP	ETV1	H3C10	KMT2D	NCOA2	PMS1	SDC4	TERC	
BCOR	CNOT3	ETV4	H3C11	KNL1	NCOA4	PMS2	SDHA	TERT	
BCORL1	CNTRL	ETV5	H3C12	KRAS	NDRG1	POLD1	SDHAF2	TERT_promotor	
BCR	COL1A1	ETV6	H3C13	KTN1	NF1	POLD3	SDHB	TET1	
BIRC3	COLCA2	EWSR1	H3C14	LAMA5	NF2	POLE	SDHC	TET2	
BLM	CREB1	EXT1	H3C15	LASP1	NFE2L2	POLH	SDHD	TFE3	
BMP4	CREB3L1	EXT2	H3C4	LCK	NFIB	POT1	SEPT5	TFG	
BMPR1A	CREB3L2	EZH2	H3C6	LCP1	NFKB2	POU2AF1	SEPT6	TFPT	
BRAF	CREBBP	EZR	H3C7	LHFPL6	NHP2	POU5F1	SEPT9	TFRC	
BRCA1	CRLF2	FANCA	H3C8	LIFR	NIN	PPARG	SETBP1	TGFBR1	
BRCA2	CRTC1	FANCB	H3F3A	LIG4	NKX2-1	PPM1D	SETD1B	TGFBR2	
BRD3	CRTC3	FANCC	H3F3B	LMO1	NONO	PPP2R1A	SETD2	THPO	
BRD4	CSF1R	FANCD2	HAVCR2	LMO2	NOP10	PRCC	SF3B1	THRAP3	
BRIP1	CSF2RA	FANCE	HAX1	LPP	NOS3	PRDM1	SFPQ	TINF2	
BTG1	CSF3R	FANCF	HCK	LRIG3	NOTCH1	PRDM16	SGK1	TLX1	
BTK	CSNK2B	FANCG	HDAC1	LYL1	NOTCH2	PRF1	SH2B3	TLX3	
BUB1B	CTC1	FANCI	HERPUD1	LZTR1	NOTCH3	PRKAR1A	SH2D1A	TMEM127	
CAMTA1	CTCF	FANCL	HEY1	MAF	NPAT	PRRX1	SH3GL1	TMPRSS2	
CANT1	CTDNEP1	FANCM	HIP1	MAFB	NPM1	PSIP1	SHH	TNFAIP3	

Tumor-Only gene Panels

Hemato Oncology (tumor-only) Genepanel (v24.1)

BRAF	BRCA1	BRCA2	BRIP1	CBL	CEBPA	ERCC4	ETV6	FANCA	FANCB	FANCC	FANCD2	FANCE	FANCF
FANCG	FANCI	FANCL	FBXW7	GATA2	HRAS	IKZF1	KRAS	MAP2K1	MLH1	MSH2	MSH6	MTOR	NF1
NOTCH1	NRAS	PALB2	PAX5	PMS2	PTPN11	RUNX1	SAMD9	SAMD9L	SH2B3	TCF3	TP53	TYK2	WT1

Solid Tumors (tumor-only) Genepanel (v24.1)

AKT1	AKT3	ALK	APC	BRAF	BRCA1	BRCA2	DICER1	GNA11	GNAQ	GNAS	HRAS	KRAS	MAP2K1
MLH1	MSH2	MSH6	MTOR	NF1	NF2	NRAS	PALB2	PIK3CA	PMS2	PTEN	PTPN11	RASA1	SMARCA4
SMARCB1	TP53	TSC1	TSC2	VHL									

Neuro Oncology (tumor-only) Genepanel (v24.1)

AKT1	AKT3	BRAF	BRCA1	BRCA2	DICER1	ELP1	GNA11	GNAQ	GNAS	GPR161	HRAS	KRAS	MAP2K1
MLH1	MSH2	MSH6	NF1	NF2	NRAS	PALB2	PIK3CA	PMS2	PTCH1	PTEN	PTPN11	SMARCA4	SMARCB1
SMARCE1	SUFU	TP53	TSC1	TSC2	VHL								

Archived tumor-only gene panels

Version 1.2

(49 genes)

AKT1	DICER1	MAP2K1	PIK3R2	SMARCB1
AKT3	FGFR1	MLH1	PMS2	SMARCE1
ALK	FGFR3	MSH2	PTCH1	SMO
APC	GNA11	MSH6	PTCH2	SUFU
BRAF	GNAQ	MTOR	PTEN	TP53
BRCA1	GNAS	NF1	PTPN11	TSC1
BRCA2	HRAS	NF2	RASA1	TSC2
CCND2	IDH1	NRAS	SAMD9	VHL
CDKN2A	IDH2	PALB2	SAMD9L	WT1
CDKN2B	KRAS	PIK3CA	SMARCA4	

Version 1.3 (ELP1 added)

(50 genes)

AKT1	DICER1	KRAS	PIK3CA	SMARCA4
AKT3	ELP1	MAP2K1	PIK3R2	SMARCB1
ALK	FGFR1	MLH1	PMS2	SMARCE1
APC	FGFR3	MSH2	PTCH1	SMO
BRAF	GNA11	MSH6	PTCH2	SUFU
BRCA1	GNAQ	MTOR	PTEN	TP53
BRCA2	GNAS	NF1	PTPN11	TSC1
CCND2	HRAS	NF2	RASA1	TSC2
CDKN2A	IDH1	NRAS	SAMD9	VHL
CDKN2B	IDH2	PALB2	SAMD9L	WT1

Version 1.4 (GPR161 added, PTCH2 and SMO removed)

(49 genes)

AKT1	DICER1	IDH2	PALB2	SMARCA4
AKT3	ELP1	KRAS	PIK3CA	SMARCB1
ALK	FGFR1	MAP2K1	PIK3R2	SMARCE1
APC	FGFR3	MLH1	PMS2	SUFU
BRAF	GNA11	MSH2	PTCH1	TP53
BRCA1	GNAQ	MSH6	PTEN	TSC1
BRCA2	GNAS	MTOR	PTPN11	TSC2
CCND2	GPR161	NF1	RASA1	VHL
CDKN2A	HRAS	NF2	SAMD9	WT1
CDKN2B	IDH1	NRAS	SAMD9L	