Table S1: characteristics of the sequencing assays used with **overlapping genes marked in bold**.

Assay	Single genes analysed	Multiple genes biomarkers
Oncomine™ Focus Assay	***ABL1**, **AKT1, AKT3, ALK, APC, AR, AXL, BRAF, CCND1, CDK4, CDK6, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4**, ERG, **ESR1**, ETV1, ETV4, ETV5, **FGFR1, FGFR2, FGFR3, FGFR4, GNA11, GNAQ, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MYC, MYCN, MTOR, NRAS, NTRK1, NTRK2, NTRK3**, PDGFRA, **PIK3CA**, PPARG, **RAF1, RET, ROS1, SMO**.*	NA
Oncomine™ Comprehensive Assay Plus	*A1CF, ABCB1, **ABL1**, ABL2, ABRAXAS1, ACSM2B, ACVR1, ACVR1B, ACVR2A, ADAM18, ADAMTS12, ADAMTS2, **AKT1**, AKT2, **AKT3**, **ALK**, AMER1, ANO4, **APC**, **AR**, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ARMC4, ASXL1, ASXL2, ATM, ATP1A1, ATR, ATRX, AURKA, AURKB, AURKC, AXIN1, AXIN2, **AXL**, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BCR, BLM, BMP5, BMPR2, **BRAF**, BRCA1, BRCA2, BRINP3, BRIP1, BTK, C6, C8A, C8B, CACNA1D, CALR, CANX, CARD11, CASP8, CASR, CBFB, CBL, **CCND1**, CCND2, CCND3, CCNE1, CD163, CD274, CD276, CD79B, CDC73, CDH1, CDH10, CDK12, **CDK4, CDK6**, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CIITA, CNTN6, CNTNAP4, CNTNAP5, COL11A1, CREBBP, CSF1R, CSMD3, CTCF, CTLA4, **CTNNB1**, CTNND2, CUL1, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, CYSLTR2, DAXX, DCAF4L2, DCDC1, DDR1, **DDR2**, DDX3X, DGCR8, DICER1, DNMT3A, DOCK3, DPYD, DROSHA, DSC1, DSC3, E2F1, **EGFR**, EIF1AX, ELF3, EMSY, ENO1, EP300, EPAS1, EPCAM, EPHA2, ERAP1, ERAP2, **ERBB2, ERBB3, ERBB4**, ERCC2, ERCC4, ERCC5, ERRFI1, **ESR1**, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF7, FGF9, **FGFR1, FGFR2, FGFR3, FGFR4**, FLT3, FLT4, FOXA1, FOXL2, FOXO1, FUBP1, FYN, GALNT17, GATA2, GATA3, GLI1, GLI3, **GNA11**, GNA13, **GNAQ**, GNAS, GPR158, GPS2, GRID2, H3F3A, H3F3B, HCN1, HDAC2, HDAC9, HIF1A, HIST1H1E, HIST1H2BD, HIST1H3B, HLA-A, HLA-B, HLA-C, HNF1A, **HRAS**, ID3, **IDH1, IDH2**, IGF1R, IKBKB, IL6ST, IL7R, INPP4B, IRF4, IRS4, **JAK1, JAK2, JAK3**, KCND2, KCNH7, KCNJ5, KDM5C, KDM6A, KDR, KEAP1, KEL, KIR3DL1, **KIT**, KLF4, KLF5, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, KNSTRN, **KRAS**, KRTAP2-1, KRTAP6-2, LARP4B, LATS1, LATS2, LRRC7, MAGOH, **MAP2K1, MAP2K2**, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MARCO, MAX, MCL1, MDM2, MDM4, MECOM, MED12, MEF2B, MEN1, **MET**, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, **MTOR**, MTUS2, MUTYH, **MYC**, MYCL, **MYCN**, MYD88, MYOD1, NBN, NCOR1, NF1, NF2, NFE2L2, NLRC5, NOL4, NOTCH1, NOTCH2, NOTCH3, NOTCH4, **NRAS**, NRXN1, NSD2, NT5C2, **NTRK1, NTRK2, NTRK3**, NUP93, NYAP2, OR10G8, OR2G6, OR2L13, OR2L2, OR2L8, OR2M3, OR2T3, OR2T33, OR2T4, OR2W3, OR4A15, OR4C15, OR4C6, OR4M1, OR4M2, OR5D18, OR5F1, OR5L1, OR5L2, OR6F1, OR8H2, OR8I2, OR8U1, ORC4, PAK5, PALB2, PARP1, PARP2, PARP3, PARP4, PAX5, PBRM1, PCBP1, PCDH17, PDCD1, PDCD1LG2, PDE1A, PDE1C, **PDGFRA**, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, **PIK3CA**, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PIM1, PLCG1, PLXDC2, PMS1, PMS2, POLD1, POLE, POM121L12, POT1, PPFIA2, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPN11, PTPRD, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, **RAF1**, RARA, RASA1, RASA2, RB1, RBM10, RBP3, RECQL4, REG1A, REG1B, REG3A, REG3G, **RET**, RGS7, RHEB, RHOA, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, **ROS1**, RPA1, RPL10, RPL22, RPL5, RPS6KB1, RPTN, RPTOR, RUNDC3B, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETBP1, SETD2, SF3B1, SH3RF2, SIX1, SIX2, SLC15A2, SLC8A1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, **SMO**, SNCAIP, SOCS1, SOS1, SOX2, SOX9, SPEN, SPOP, SRC, SRSF2, STAG2, STAT1, STAT3, STAT5B, STAT6, STK11, SUFU, SYT10, SYT16, TAF1, TAP1, TAP2, TAPBP, TBX3, TCF7L2, TERT, TET2, TGFBR1, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TOP1, TOP2A, TP53, TP63, TPMT, TPP2, TPTE, TRHDE, TRIM48, TRIM51, TRRAP, TSC1, TSC2, TSHR, U2AF1, UGT1A1, USP8, USP9X, VHL, WAS, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZBTB20, ZFHX3, ZIM3, ZMYM3, ZNF217, ZNF429, ZNF479, ZNF536, ZRSR2*	• Genomic Instability Metric (GIM); • >1 mb Exonic footprint for TMB; • MSI detection. • Tumor Fraction calculation.

Table S2: classification of relevant variants in colorectal cancer according to the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT).

ESCAT evidence Tier	Clinical implication	Included variants in colorectal cancer
I: alteration-drug match is associated with improved outcome in clinical trials.	Ready for routine use	Mutations: *BRAF* V600E; *KRAS* G12C Microsatellite instability/dMMR Tumour agnostic alterations [a]
II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown.	Investigational	Mutations: *POLE* Amplifications: *ERBB2*
III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s)or with similar molecular alteration.	Hypothetical target	Mutations: *PIK3CA, ATM, AKT, FGFR, ERBB2* Amplifications: *MET* Fusions: *ALK*
IV: pre-clinical evidence of actionability.	Hypothetical target	Mutations: *BRAF* Non – V600E, *ERBB3, FBXW7, NOTCH* and *RNF43*.
V: alteration-drug match is associated with objective response, but without clinically meaningful benefit.	Combination development	ND
X: lack of evidence for actionability.	Combination development	ND

a – Tumour agnostic alterations include: NTRK 1/2/3 fusions, FGFR 1/2/3 fusions or mutations, and tumoral mutational burden high.
ND – not defined
Adapted from [1,2]