SALSA® MLPA® Probemixes for Analysis of Tumour Derived DNA

New: P376 BRCA1ness. This probemix is designed to detect BRCA1ness profile, which is present in about half of all triple negative sporadic breast cancers and is predictive for benefit from intensified chemotherapy. The following regions have been found gained in BRCA1ness profile in previous studies: 3q22-27, 6p22-23, 10p14, 12p13, 13q31-34; and the following regions are shown to be lost in previous studies: 3p21, 5q12-14, PTEN region, 12q21-23, 14q22 and 15q15 (Joose SA et al (2009) Breast Cancer Res Treat. 116:479-489). This probemix covers all of these regions. Additionally, two probes for BRCA1 and two probes for BRCA2 are included in this mix. As shown in a large collaborative study (Lips E et al, 2011, Breast Cancer Res. 13:R107), this probemix recognizes both BRCA1-mutated and sporadic tumours with BRCA1-like genomic profile. For references see: Lips E et al (2011) Breast Cancer Res. 13:R107 and Oonk A et al. Ann Oncol. 23:2301-5.

New: P417 BAP1. The BAP1 gene (3p21.1) is commonly inactivated by somatic mutations and 3p21.1 losses both in uveal melanoma and in malignant pleural mesothelioma. In addition, two recent studies have suggested that germline mutations in BAP1 predispose to melanocytic tumours and to uveal melanoma, lung carcinoma and meningioma. This probemix contains one probe for each exon of BAP1 gene (17 exons). In addition, 10 flanking probes for the BAP1 gene and also 13 reference probes are included in this probemix.

New: ME042 CIMP. Contains 29 MS-MLPA probes to detect the methylation status of promoter regions of CACNA1G, CDKN2A, CRABP1, IGF2, MLH1, NEUROG1, RUNX3 and SOCS1 genes. This mix can be used to detect methylation of these genes that are associated with the CpG Island Methylator Phenotype (CIMP). For reference see: Bruin SC et al (2011) Br J Cancer. 105:281-7.

New: ME043 Lynch syndrome. This probemix is designed for testing colorectal tumour samples to determine the methylation and copy number status of MLH1, MSH2 and CDKN2A genes and for detection of the BRAF V600E mutation. Somatic hypermethylation of MLH1 and CDKN2A gene, and/or presence of BRAF V600E mutation suggests sporadic origin of colon cancer and thereby provides an exclusion criteria for the hereditary form of colon cancer. Somatic hypermethylation of MSH2 is detected in ~24 % of Lynch tumour samples and provides a tool to identify and classify individuals with Lynch syndrome. This probemix allows molecular screening to select patients suitable for genetic counseling of Lynch syndrome. For reference see: Gausachs M et al (2012) Eur J Hum Genet. 20:762-8.

Improved: P225 PTEN. Contains 20 probes for the PTEN gene, at least two for each exon. This probemix contains also two probes for copy number detection of the pseudogene PTENP1, at 9p13.3, and five MS-MLPA probes for determination of the methylation status of shared promoter region of PTEN and KLLN genes. In addition, 9 probes for other chromosome 10 sequences are present that can help to distinguish PTEN deletions from loss of the complete 10q-arm or from chromosome 10 aneuploidy. In addition, 15 reference probes on other chromosomes are present. For references see: Aradhya S et al (2012) Genet Med 14:594-603; Pradella LM et al (2011) J Med Genet. 48:779-82; Berg M et al (2010) PLoS One.12;5:e13978; Regina S et al (2009) Clin Chem. 55:1834-42.

Improved: P335 ALL-IKZF1. This probemix contains one probe for each exon of the IKZF1 gene. In addition, it contains 7 probes for PAX5, 6 probes for ETV6, 5 probes for RB1, 4 probes for BTG1 and BTG1 downstream region, 4 probes for EBF1, 3 probes for CDKN2A/2B and 5 probes for Xp22.33 (PAR region: CRLF2, CSF2RA and IL3RA). For references see: Dorge P et al (2012) Heamatologica, in press; Krenz S et al (2012) Leukemia. doi: 10.1038/leu.2012.155; Alpar D et al (2012) Cancer Genet. 205:465-9; Waanders E et al (2012) PLoS Genet. 8:e1002533; Buitenkamp TD et al (2012) Leukemia. 26:2204-11; Palmi C et al (2012) Leukemia. 26:2245-53; Ensor HM et al (2011) Blood. 117:2129-36; Rand V et al (2011) Blood.. 117:6848-55; Simons A et al (2011) Genes Chromosomes Cancer. 50:969-81; Volejnikova J et al (2011) Haematologica. 96:1815-21; Schwab CJ et al (2010) Genes Chromosomes Cancer. 49:1104-13.

P202 IKZF1 (IKAROS). This probemix provides two probes for each exon of the IKZF1 (7p12) gene and three probes for both the IKZF2 (HELIOS, 2q34) and the IKZF3 (AIOLOS, 17q12) genes, which belong to Ikaros gene family of transcription factors and which also have important roles in the control of mature B-lymphocyte differentiation and proliferation. Four probes target the CDKN2A-CDKN2B-MIR31 genes (9p21.3), which are often deleted in acute lymphoblastic leukemia (ALL) samples and are associated with poor survival. Moreover, 4 probes target 14q32 region next to IGH region. For references see: Dorge P et al (2012) Heamatologica, in press; Alpar D et al (2012) Cancer Genet. 205:465-9; Buitenkamp TD et al (2012) Leukemia. 26:2204-11.

P377 Hematologic malignancies. This probemix is intended for screening DNA samples derived from blood or bone marrow for the most common and diagnostically relevant copy number changes associated with hematologic malignancies in combination with karyotype analysis. The targeted genes and chromosomal regions include: 2p (MYCN, ALK), 5q (MIR145, EBF1, MIR146A), 6q, 7p12 (IKZF1), 7q, 8q24 (MYC), 9p (JAK2 V617F point mutation, MTAP, CDKN2A/2B, PAX5), 10q23 (PTEN), 11q23 (ATM), 12p (ETV6), 12q, 13q (RB1, MIR15A, DLEU), 17p (TP53), 17q, Chr 18, Chr 19, 21q (RUNX1).

P078 Breast tumour. Can be used to detect copy number changes of various genes that frequently show gains or losses in breast tumours, such as ERBB2, TOP2A, PRDM14, BIRC5, MYC, ZNF703, ESR1, EGFR, FGFR1, MTDH, EMSY, CDH1, CCNE1 and CCND1. For references see: Ooi A et al (2012) J Pathol. 227:8-16; Kornegoor R et al (2012) Breast Cancer Res Treat. 135:49-58; Hlousek L et al (2012) Biotechniques. 52:316-24; Moelans CB et al (2010) Mod Pathol. 23:1029-39; Moelans CB (2010) Anal Cell Pathol. 33:13-8.

P004 ERBB2 / HER2-neu. Contains 4 probes for ERBB2 amplification detection. In addition, it contains 27 probes on chromosome 17 in order to delineate the extend of the amplification, including probes for the TOP2A gene at 60 kb telomeric of ERBB2 and probes close to the centromere. These centromeric probes can distinguish polysomy of 17 from low level amplification of only ERBB2 or only ERBB2 combined with the chromosome 17 centromeric region. Probes for the EGFR, ESR1 and BRCA2 genes are also included. For references see: Bravanccini S et al (2012) J Clin Pathol. 65:183-5; Varga Z et al (2012) Breast Cancer Res Treat. 133:929-35; Fabi et al (2011) Clin Cancer Res. 17:2055-64, Farshid G et al (2011) Diagn Mol Pathol. 20:11-7; Moelans CB et al (2010) Mod Pathol. 23:62-70; Moelans CB et al (2009) Cell Oncol. 31:1-10; te Velde EA et al (2009) Eur J Surg Oncol.35:1098-104; Moerland E et al (2006) Cell Oncol. 28:151-9.

P056 TP53. Approximately 70 % of Li-Fraumeni syndrome (LFS) cases contain germline mutations in the TP53 gene on chromosome 17p13.1. This probemix contains probes for each of the 11 exons of the TP53 gene on 17p13.1, except exon 9. Two probes are present for CHEK2 gene on chromosome 22q12.1 (second LFS locus), of which one is specific for CHEK2 1100delC mutation. Moreover, reference probes target stable chromosomal regions to allow analysis of tumour DNA as well. For references see: Gonçalves A et al (2012) BMC Cancer 12:237; Pinto EM et al (2012) Oncogene doi:10.1038/oncsis.2012.1; Magnusson S et al (2011) Fam Cancer. 11:145-55; Ruijs MW et al (2010) J Med Genet. 47:421-8; Mouchawar J et al (2010) Cancer Res. 70:4795-800; Pinto C et al (2009) Fam Cancer. 8:383-90.

P258 SMARCB1. Contains two probes for each of the nine exons of the SMARCB1 gene on 22q11. The SMARCB1 gene (also called INI1 or SNF5) is frequently deleted in malignant rhabdoid tumours. For references see: Fleming AJ et al (2012) Brain Pathol. 22:625-35; Dufour C et al (2012) Cancer. 118:3812-21; Smith MJ et al (2012) Neurogenetics.13:141-5. Epub 2012 Mar 22.Eaton KW et al (2011) Pediatric Blood Cancer. 56:7-15; Thomson TA et al (2011) Cancer Cytopathol. 25;119:49-57; Bourdeaut F et al (2011) Clin Cancer Res. 17:31-8; Jackson EM et al (2009) Clin Cancer Res. 15:1923-30; Boyd C et al (2008) Clin Genet. 74:358-66.

P315 EGFR. Contains probes for each of the 28 exons of EGFR gene. Furthermore, new update contains two point mutation specific probes for EGFR mutations T790M and L858R. For references see: Minarik M et al (2010) Eletrophoresis. 31:3518-24; Jeuken J et al (2010) Brain Pathol. 21:308-20; Jeuken J et al (2009) Brain Pathol. 19:661-671.

P323 MDM2-CDK4-HMGA2. This probemix is intended for analysis of chromosome 12 with an emphasis on the CDK4, MDM2 and HMGA2 genes. Intended use of this product is to detect amplifications of these genes in various sarcomas (e.g. liposarcomas, osteosarcomas and rhabdomyosarcomas) and in pituitary adenomas.

P370 BRAF-IDH1-IDH2 point mutations. Can be used to detect the BRAF V600E and four frequent IDH1 and IDH2 point mutations, as well as genomic duplications leading to the KIAA1549-BRAF and SRGAP3-RAF1 fusion genes. These are frequent genomic abnormalities in gliomas.

P088 Oligodendroglioma 1p-19q. Can be used to detect loss of 1p and 19q in brain tumours. Contains 15 probes on 1p, 3 probes on 1q, 2 probes on 19p, 8 probes on 19q. For references see: Sahm F et al (2012) Acta Neuropathol. 123:853-60; Mukasa A et al (2012) Cancer Sci. 103:587-92 ; Momota H et al (2011) Brain Tumor Pathol. 28:65-70; Motomura K et al (2011) Cancer. 117:1721-30; Ohka F et al (2011) PLoS One. 6:e23332. Jeuken J et al (2010) Brain Pathol. 21:308-20; Franco-Hernandez C et al (2009) Cancer Genetics and Cytogenetics. 190:93-6; Wick W. et al (2009) J Clin Oncol. 10;27:5874-80; Weller M et al (2007) Clin Cancer Res. 1;13:6933-7; Krex D. et al. (2007) Brain 130:2596-2606; Jeuken J et al (2006) J Mol Diagn. 8:433-43; Natte R et al (2005) Brain Pathol. 15:192-7.

P105 Oligodendroglioma mix 2. Can be used to detect copy number changes of PTEN, CDKN2A/B, EGFR, ERBB2 and TP53. A recent article shows the use of this product for the detection of the EGFR variant III (exon 2-7 deletion): Jeuken J et al (2009) Brain Pathol. 19:661-671. For other references see: Momota H et al (2011) Brain Tumor Pathol. 28:65-70; Jeuken J et al (2010) Brain Pathol. 19:661-71; Claes A et al (2008) Brain Pathol. 18:423-33; Franco-Hernandez C et al (2007) Int J Oncol. 30:209-15; and references for P088.

P251-P252-P253 Neuroblastoma. These three probemixes have been developed in collaboration with the SIOPEN European Neuroblastoma network to target 106 genetic loci on 19 different chromosomal arms, including MYCN/ ALK amplification, losses at 1p, 3p, 4p, 11q, and gains of 1q, 2p and 17q. For references see: Bagci O et al (2012) Cancer Lett. 317:72-7; Ambros IM et al (2011) Clin Cancer Res. 17:792-804; Combaret V et al (2011) Pediatr Blood Cancer. 56:757–61; Ambros PF et al (2009) Br J of Cancer. 100:1471-82; Villamon E et al (2008) Virchows Arch. 453:47-55.

P301-302-303 Medulloblastoma. These three probemixes cover genes / regions which are frequently altered in their copy number and are prognostically important in medulloblastomas.

P027 Uveal melanoma. Contains probes for chromosome arms 1p, 3p, 3q, 6p and 8q, which are frequently copy number altered in uveal melanomas (UM). This probemix can be used to aid the diagnosis of UM and, moreover, to better estimate the prognosis of these patients. For references see: Vaarwater J et al (2012) Melanoma Res. 22:30-7; Lake SL et al. (2012) IOVS. 53:2647-52 Lake SL et al (2011) IOVS. 52:5559-64; Damato B et al (2010) Clin Cancer Res. 16:6083-92; Lake SL et al (2010) IOVS. 51:4884-91. Damato B et al (2009) IOVS. 50:3048-55.

P037-038 CLL. These probemixes contain probes for chromosomal regions and genes that have recurrent copy number alterations in B cell CLL: 2p (MYCN, ALK, REL), 6q (AIM1, TNFAIP3, LATS1), 8q (TNFRSF10A/B, EIF3H, MYC), 9p21 (CDKN2A/B), 10q (PTEN), 11q (ATM, RDX, PP2R1B), chr. 12, 13q (RB1, DLEU1/2/7, KCNRG, MIR15A), 14q, 17p (TP53) and chr. 19. Moreover, P038 probemix contains three probes for detection of NOTCH1 P2514fs, SF3B1 K700E and MYD88 L265P mutations. For references see: Fabris S et al (2011) Genes Chr Cancer. 50:726-34; Groenen P et al (2011) J Hematopathol. 4:189-97; Abdool A et al (2010) PLoS ONE. 5:e15407; Al Zaabi EA et al (2010) J Mol Diagn. 12:197-203; Stevens-Kroef M et al (2009) Cancer Genet Cytogenet. 195:97-104; Hanlon K et al (2009) J Mol Diagn. 11:298-305; Coll-Mulet L et al (2008) Br J Haematol. 142:793-801; Santidrián AF et al (2007) Haematologica. 92:1631-8.

P040 CLL. This probemix can be used to detect copy number changes of the genes/regions that are most frequently affected in CLL: 11q (ATM), chromosome 12, 13q14 (RB1 / DLEU / MIRN15A-16) and 17p (TP53). This probemix is e.g. used to test blood donors that have a high white blood cell count for CLL abnormalities. P040 CLL contains the most relevant regions for prognosis from P037 and P038 CLL probemixes. (For references see P037-038)

P144-145 Myelodysplastic syndromes. Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by bone marrow failure. Patients with MDS have a high risk to progresses into acute myeloid leukemia. These two probemixes target several chromosomal arms (5q, 7q, 8q, 11q, 17q, 20q, 21q) that show a recurrent loss or gain in MDS patients. For reference see: Donahue AC et al (2011) Leuk Res. 35:1477-83.

P327 iAMP21. Contains 31 probes that detect chromosome 21 sequences, including several RUNX1 specific probes. Amplification of the RUNX1 gene is a recurrent chromosomal abnormality that is detected at a frequency of approximately 2 % in childhood B-lineage acute lymphoblastic leukemia (ALL).

P329 CRLF2-CSF2RA-IL3RA. Contains 35 MLPA probes in this interesting cluster of three genes in the Xp pseudosomal region (PAR1), supplemented with 11 reference probes. Deletion of IL3RA and CSF2RA activates CRLF2 by introducing a stronger promoter. Such deletions are found in 7 % of individuals with B-progenitor ALL and 53 % of individuals with ALL associated with Down's syndrome.

P146 Colon-gain. This mix contains probes for chromosome arms 8q, 13q and 20q, which show frequent copy number gains in colon cancer. For references see: Buffart TE et al (2009) Vicrows Arch. 455:213-23; Postma C et al (2005) J Pathol. 205:514-21.

P413 Colon-loss. This mix contains probes for chromosome arms 8p, 15q, 17p and 18q, which show frequent copy number losses and are of prognostic relevance in colon cancer.

P215 EXT. Contains probes for each exon of EXT1 and EXT2 gene for detection microdeletions of EXT1/2 genes, which are recurrent in both hereditary and sporadic osteochondromas. For references see: Jennes I et al (2011) BMC Medical Genetics 12:85; Stancheva-Ivanova MK et al (2011) J Inherit Metab Dis. 34:917-21; Zuntini M et al (2010) Oncogene. 29:3827-34; Jennes I et al (2008) J Mol Diagn. 10:85-92; Hameetman L et al (2007) J Natl Cancer Inst. 99:396-406; Signori E et al (2007) Genes Chromosomes Cancer. 46:470-7; Vink GR et al (2005) Eur J Hum Genet. 13:470-4.

P284 RBM14-11q13. RBM14 gene, located within the 11q13 CCND1 region, has been found to be rearranged and amplified in multiple human cancers. In several tumours the upstream silencing sequences of RBM14 appear to be lost (Sui Y et al. (2007) Oncogene 26, 822-835). This probemix contains probes for each exon of RBM14. In addition, probes are present for other 11q23 genes such as CCND1, AIP, CCS and DDB1.

P157 20q. Copy number changes in the chromosome 20q region are common in several types of cancer, including colon cancer. Among the interesting genes on 20q are: BCL2L1, AURKA, DNMT3B, SRC, MYBL2, PTPN1, ZNF217, BCAS1 and GNAS. This P157 20q region probemix contains 34 probes detecting a chromosome 20q sequence, as well as five 20p specific probes and 14 reference probes. For reference see: Wilting SM et al (2006) J Pathol. 209:220-30.

P175 Tumour-gain. Contains two probes for each gene in a selection of targets which are often gained or amplified in various tumours: MDM4, MYCN-ALK, PDGFRA, KIT, KDR, DHFR, EGFR, MET, SMO, BRAF/BRAF V600E mutation, FGFR1, MYC, ABL1, RET, CCND1, CCND2, CDK4, MDM2, AURKB, ERBB2-TOP2A, AURKA and AR. Intended as a primary test on each tumour sample, irrespective of the type of tumour. For reference see: Monticone M et al (2012) BMC Cancer. 12:358.

P294 Tumour-loss. Contains two probes for each gene / regions in a selection targets, which are frequently deleted in a wide diversity of tumours: 1p36, VHL, FHIT, APC, CDKN2A-CDKN2B, PTCH, TSC1, PTEN, WT1, BRCA2, RB1-MIR15, TSC2, TP53, NF1, BRCA1, SMAD4, STK11, FKBP8, SMARCB1 and FAM123B. Intended as a primary test on each tumour sample, irrespective of the type of tumour. For reference see: Monticone M et al (2012) BMC Cancer. 12:358.

P181-182 Centromere. Both of these two mixes contain two probes for each chromosome: one in a well characterized gene on the p-arm; and the other on the q-arm, both close to the centromere. For the acrocentric chromosomes, both probes are on the q-arm close to the centromere. These two mixes can be used separately, although using both of them allows effective cross-validation. The P181-P182 Centromere probemixes are also used to find the origin of marker chromosomes and to find the cause of spontaneous abortions. For reference: van Opstal D et al (2011) Molecular Cytogenetics. 14;4:2 (prenatal diagnostics); Chen CP et al (2010) Taiwan J Obstet Gynecol. 49:500-5.

Available soon !

P380 Wilms tumour. This probemix can be used to determine copy number status of chromosomal arms 1p, 1q, 16p and 16q, which have been found to be highly significant for prognosis in Wilms tumours, and further to determine copy number of WT1, FBXW7, FAM123B, MYCN and TP53 genes. This mix is developed in collaboration with Wilms Tumour Biology Study Committee of the International Society of Pediatric Oncology.

P383 T-ALL. This probemix contains 55 probes for 11 different chromosomal regions, which are suggested to be diagnostically and/or prognostically important in T-cell ALL including: STIL-TAL1 (1p33), LEF1 (4q25), CASP8AP2 (6q15), MYB (6q23.3), CDKN2A/B+MTAP (9p21.3), NUP214-ABL1 (9q34.1), PTEN (10q23.31), LMO1 (11p15.4), LMO2 (11p13), NF1 (17q11.2), PTPN2 (18p11.21) and PHF6 (Xq26.2).

P407 Myeloproliferative neoplasms (MPNs). This probemix contains probes for the following genes: JAK2 (V617F, E543_D544del and N542_E543del mutations), MPL (W515L mutation), IDH1 (R132S and R132C mutations), IDH2 (R140Q mutation), IKZF1, EZH2, and for FIP1L1-PDGFRA fusion detection.

P414 Myelodysplastic syndromes (MDSs). This probemix contains 44 probes for several chromosomal locations known to have a diagnostically or prognostically significant role in MDSs: 4q (TET2), 5q (MIR145, MIR146), 7q, 8q, 11q (MLL), 12p (ETV6), 17p (TP53), 20q and 21q (RUNX1). Next to this, it also contains 3 mutation specific probes for the JAK2 V617F, IDH1 R132C and IDH1 R132H mutations.

P419 Familial melanoma. This probemix contains probes for each exon of CDKN2A/B, CDK4 and also a point mutation specific probe for MITF E318K (953G>A) mutation, which has been suggested to associate with predisposition to familial melanoma.

P421-422 Malignant melanoma. These probemixes contain probes for NRAS, NOTCH2, AKT3, RAF1, MITF, KIT, GOLPH3, MET, BRAF, MYC, CDKN2A, CCND1, GAB2, CDK2, CDK4 and BCL2-genes and a mutation specific probe for the BRAF V600E mutation, for the predominant point mutations of NRAS, KIT, GNA11 and GNAQ, which are suggested to be clinically important in malignant cutaneous melanoma.

P425 Multiple myeloma. This probemix contains 42 probes for the following chromosomal regions and target genes 1p32-p21, 1q21.3 (CKS1B), 1q23.3, 5q31.3, 12p13.31, 13q14 (RB1, DLEU1, DLEU2), 16q12 (CYLD), 16q23 (WWOX), 17p13 (TP53), which are suggested to be of prognostic relevance in multiple myeloma.

In development

Products for **Cervical cancer**, **Spitzoid tumours**, **Head and neck cancers**, **Prostate cancer**, **Bladder cancer, Gastric cancer, Lung cancer**, **Follicular lymphoma, Diffuse Large B-cell lymphoma, Acute myeloid leukemia and Myelodysplastic syndromes** are in an early stage of development.

Hereditary predisposition to cancer

A large number of MLPA probemixes is available to find the cause of various genetic diseases. Among these are:

P002 BRCA1. Primary screening for deletions / duplications in BRCA1 gene.

P087 BRCA1. Can be used to confirm P002 BRCA1 results. All probes are different from the P002 probes.

P239 BRCA1 region. Probes upstream and downstream of BRCA1 gene for the further characterization of large BRCA1 deletions / duplications.

P045 BRCA2. Primary screening for deletions / duplications in the BRCA2 gene. Includes two CHEK2 probes.

P090 BRCA2. Almost identical to P045 BRCA2 but does not contain any CHEK2 probes.

P077 BRCA2. Is used to confirm P045 / P090 BRCA2 results. All probes are different from the P045 probes.

P003 MLH1-MSH2. Primary screening of these genes which cause HNPCC when defect.

P248 MLH1-MSH2. Is used to confirm P003 results. All probes are different from the P003 probes.

P008 PMS2. A new version is available which contains only PMS2 and reference probes.

P072 MSH6. Contains 15 probes for MSH6 and 3 probes for MUTYH.

P378 MUTYH. Contains 18 probes MUTYH + reference probes.

P043 APC. Contains 26 probes for APC gene + reference probes.

P016 VHL. Contains 9 probes for VHL as well as probes for flanking genes such as C3orf10.

ME024 CDKN2A / CDKN2B. Can be used to detect both deletions and duplications, as well as methylation changes in these genes. For instance in families with hereditary predisposition to melanomas.

P041-P042 ATM. Two probemixes that together cover each of the 65 ATM exons.

P081-P082 NF1. Two probemixes that together contain 55 probes for NF1 gene.

P044 NF2. Contains probes for each NF2 exon.

P122 NF1 area. Contains 28 probes for the delineation of deletions in NF1 gene region.

P056 TP53. Li-Fraumeni syndrome. Not for LOH detection: TP53 LOH cases are not due to CN change.

P225 PTEN. Contains 25 probes for PTEN gene: at least two for each exon.

P083 CDH1. Contains 17 CDH1 probes covering each CDH1 exon.

P258 SMARCB1. Contains two probes for each of the nine exons of SMARCB1 gene on 22q11.

P215 EXT1 + EXT2. Contains probes for each exon of EXT1 and EXT2 genes.

P101 STK11. Contains 13 STK11 probes covering each STK11 exon.

P158 JPS. Contains probes for each exon of BMPR1A, SMAD4 and PTEN genes.

P118 WT1. Contains at least one probe for each WT1 exon.

P067 PTCH / Gorlin. Contains probes for 23 of 24 PTCH exons.

P113 FANCB. Contains probes for each FANCB exon.
P190 CHEK2. Contains 16 probes for CHEK2 among which a 1100delC mutation specific probe.
P240 BRIP1-CHEK1. Contains probes for each exon of BRIP1 and CHEK1 genes.

MS-MLPA for the detection of aberrant methylation

ME011 MMR genes. Can be used to detect copy number changes and aberrant methylation of the MGMT, MLH1, MSH2, PMS2, MSH6, MSH3 and MLH3 genes. For references see: Gausachs M et al (2012) Eur J Hum Genet . 20:762-8; Morak M et al (2011) J Med Genet. 48:513-9; Park CK et al (2011) Neuro Oncol. 13:195-202; Guarinos C et al (2010) J Mol Diagn. 12:765-70; Shah N et al (2010) PLoS One. 6:e16146; Ligtenberg MJ et al (2009) Nat Genet. 41:112-7; Viana-Pereira M et al (2009) Neuro Oncol. 11:458-67; Gyllling AHS et al (2008) Carcinogenesis. 29:1351-9.

ME024 9p21/CDKN2A. Can be used to detect both copy number changes and aberrant methylation status of the CDKN2A($p16_{INK4A}$/$p14_{ARF}$) and CDKN2B($p15_{INK4B}$) genes. In addition, probes for CDKN2B-AS1, MTAP, MIR31 and PAX5 are included. For references see: Meijer D et al (2012) Genes Chromosomes Cancer. 51:899-909; Gardiner RB et al (2011) Pediatr Blood Cancer. 58:852-9; Cesinaro AM et al (2010) Histopathology. 57:515-27; Conway C et al (2010) Genes Chromosomes Cancer. 49:425-38; Mohseny AB et al (2010) Genes Chromosomes Cancer. 49:1095-103; Freeberg DE et al (2008) J Natl Cancer Inst. 100:784-95; Mistry SH et al (2005) Genes Chromosomes Cancer. 44:292–300.

ME001 / ME002 / ME003 / ME004 / ME046. Five different MS-MLPA probemixes to detect copy number changes, as well an aberrant methylation status of the promoter regions of a wide variety of genes. Based upon results obtained with these and other MLPA probemixes, new products for specific types of tumours can be developed by MRC-Holland in collaboration with users.

Pharmacogenetics

P103 DPYD. DPYD is the major enzyme involved in breakdown of 5-Fluorouracil, one of the most widely used drugs for cancer chemotherapy. For references see: Savva-Bordalo J et al (2010) BMC Cancer. 10:470; van Kuilenburg AB et al (2010) Hum Genet. 128:529-38; Pare L et al (2010) Br J Clin Pharmcol. 70:268-72.

P283 TPMT. Contains probes for each TPMT exon. Thiopurine S-methyltransferase (TPMT) is involved in the metabolism of thiopurine drugs. Patients that due to genetic variation lack this enzyme or have lower levels than normal, can be adversely affected if normal doses of thiopurines are prescribed.

P033 CMT. Charcot-Marie-Tooth (CMT) disease is caused in most cases by a copy number change of the PMP22 gene region and severe vincristine-induced neuropathy has been reported in CMT disease. CMT should be excluded in any patient who develops a profound, acute neuropathy following vincristine treatment, as many patients in the cases reviewed were asymptomatic and undiagnosed prior to treatment. For references see: Weterman MA et al (2010) Eur J Hum Genet.18:421-8; Stangler-Herodez S et al (2009) J Int Med Res. 37:1626-31. For references on vincristine-induced neuropathy see: Nishikawa T et al (2008) J Pediatr Hematol Oncol. 30:519-21; Chauvenet AR et al (2003) J Pediatric Hematol Oncol. 25:316-20. Other MLPA probemixes for the detection of copy number changes of genes involved in CMT are the **P129 GJB1** and the **P143 MFN2-MPZ** probemixes.

P128 Cytochrome P450. The P128 Cytochrome P-450 probemix is intended for the detection of copy number changes of several Cytochrome P450 and Glutathione S-transferase genes. It contains probes for the CYP2D6, CYP2C9, CYP2C19, CYP1B1, CYP3A4, CYP3A5, CYP2E1, CYP1A1, CYP1A2, CYP2A6, CYP2B6, GSTP1, GSTT1 and GSTM1 genes. For each gene at least two probes are present. For reference see: Scott SA et al (2012) Pharmacogenomics. 13:297-307.

In development: P344 SULT1A1. We are currently testing a probemix for the detection of copy number changes in SULT1A1. SULT1A1 is a component of a major pathway for drug metabolism in humans that show a high degree of copy number variation (Hebbering SJ et al. (2008) Cytogenet. Genome Res).

mRNA detection

R009 Inflammation. This mRNA probemix contains several probes that are specific for human mRNAs that get strongly induced through lipopolysaccharides stimulation of blood in vivo or in vitro. It contains 40 different probes, among which probes for NFKB, CCL3 (MIP1a), CCL4 (MIP1b), IL1B, IL1R1 (IL1Ra), TNFRSF1A (TNFR1), NFKBIA and IL8 mRNAs are included.

RM001 Mouse Inflammation. This mRNA probemix was designed to detect changes in the amount of transcript of multiple mouse genes that have important roles in inflammation, coagulation, cell signaling and apoptosis. Probes are present for IL4, IL6, IL10, TNF, TLR2, TLR4, TLR9, ICAM1, CXCL1, IFNG, CCL3, TFPI, F3, IL1B, PROCR, SERPINE1, PLAT, PLAUR, CD14, LY96, IRAK1, IRAK3,F2R, F2RL1, NFKBIA, NOS3, SELE, ITGA5, ITGAV, ITGB3, VCAM1, B2M,TBP,TFRC, HIF1a, MMP2, MMP9, ELA2, HP. For references see: Loubele et al (2009) J Thromb Haemost . 7:290-8; Wiersinga WJ et al (2008) Microbes Infect. 10:868-77.

RM002 Mouse Apoptosis. This mRNA probemix contains 40 different probes specific for mouse mRNAs that are important for regulation of the apoptosis pathways. Probe targets include BAX, BAK1, BCL2, BID and several BIRC mRNAs. For reference see: Wenseveen et al (2012) Blood 119:1440-9.

R011 Apoptosis mRNA. This probemix contains several probes specific for human mRNAs that are important for regulating the apoptosis pathways. The total probemix contains 42 different probes, among which probes for BAX, BAK1, BCL2, BID, BCL2L1, BOK and BBC3 (PUMA) mRNAs are present. For references see: Eldering et al (2003) Nucleic Acids Res. 1;31:e153; Hess et al (2004) Leukemia. 18:1981-8; Iglesias-Serret et al (2010) Apoptosis 15:219-29.

Development of new SALSA MLPA products & Modification of existing products

MRC-Holland is interested in the development of novel tumour specific MLPA probemixes in collaboration with laboratories and researchers world-wide. Below is some information on the way we work. In case you are interested in the co-development of new MLPA products, don not hesitate to contact us. Requests for new MLPA products and for modifications of existing products can be mailed to info@mlpa.com. Please, include details about the application and the genes of interest, such as the prevalence of the disorder, frequency of copy number changes and references to relevant publications.

Development of new SALSA MLPA products

Development of new SALSA MLPA probemixes is time-consuming and therefore expensive. For each MLPA probe we prepare a new phage M13-clone. From these clones single-stranded DNA is prepared and is digested by expensive enzymes. Design, preparation, testing and optimization of new SALSA MLPA probemixes requires several months. All costs for development of new products are paid by MRC-Holland. Once ready, new MLPA probemixes will be available at the same price as our other SALSA MLPA probemixes. Unfortunately, not all requests for new probemixes can be fulfilled. MRC-Holland scientists will critically review new "wish lists" of genes/chromosomal regions and will discuss the final content of a product with the requesting laboratories. New products can temporarily be provided exclusively to a single lab, provided that the product can be released to other labs without any restriction after a certain period.

MLPA probemixes for research

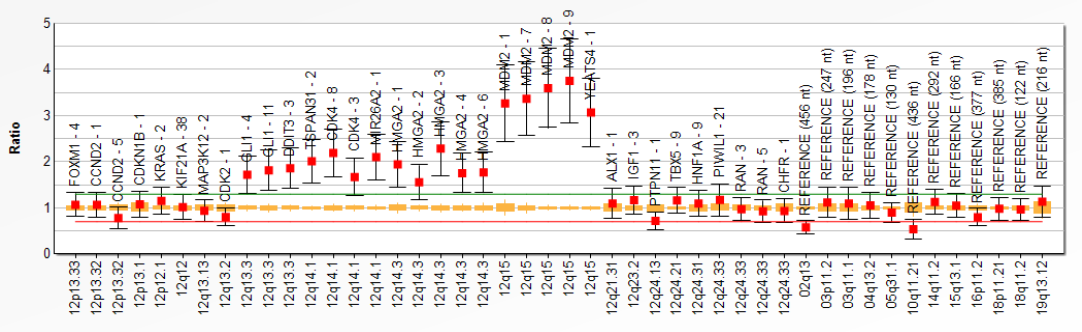
In case new MLPA probes are required for research purposes only, we recommend to design synthetic MLPA probes using the extensive Synthetic Probe Design protocol on our website www.mlpa.com → MLPA technology. Synthetic probes consist of two synthetic oligonucleotides that can be ordered from your own oligo supplier. Reagents for performing MLPA reactions, as well as reference probemixes to which your synthetic probes can be added (P200 or P300 reference probemixes) can be ordered from MRC-Holland. The advantage of synthetic MLPA probes is that the probemix will be available much sooner. The disadvantage is a lower number of probes in one probemix and the usually higher variability of synthetic probes as compared to our M13 derived probes.

Modifying existing MLPA products

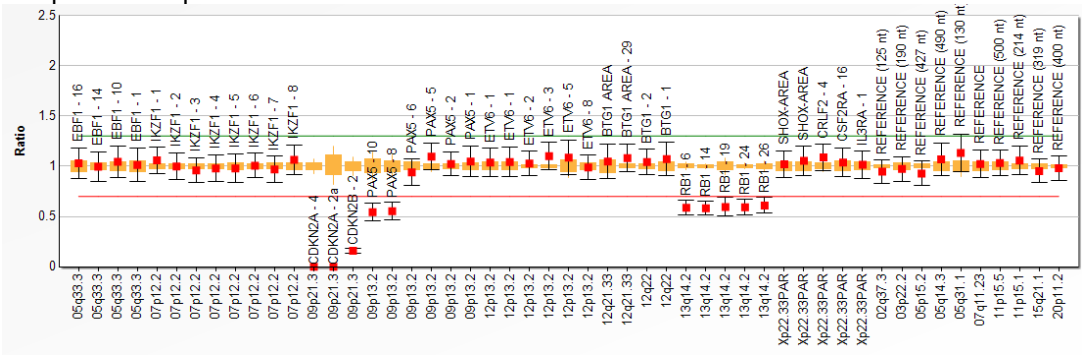
Modification of existing probemixes is often based on requests from customers. As many customers have to validate the product again when changes are made, modifications will only be made when we believe that it is an advantage for many customers. If you have suggestions to improve existing probemixes, please, inform use in detail which modifications should be made and for which reasons.

Examples of MLPA results on tumour samples

P323 CDK4-HMGA2-MDM2: Low level gain of 12q13.3-q14.3 (e.g. CDK4, HMGA2) and high level amplification of 12q15 (MDM2 and YEATS4) in liposarcoma patient sample.



P335 ALL-IKZF1: Homozygous deletion of CDKN2A/B genes and heterozygous deletions of PAX5 exons 8-10 and RB1 gene in ALL patient sample.



SALSA® MLPA® products

製造元：MRC-Holland 社
販売元：株式会社ファルコバイオシステムズ

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